Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial

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Summary

Background Doubts exist regarding optimal second-line treatment options for HIV-1-infected patients in resource-limited settings. We assessed safety and efficacy of dolutegravir compared with ritonavir-boosted lopinavir, plus two nucleoside reverse transcriptase inhibitors (NRTIs) in adults in whom previous first-line antiretroviral therapy with a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two NRTIs has failed.

Methods DAWNING is a phase 3b, open-label, parallel-group, non-inferiority, active-controlled trial done at 58 sites in 13 countries. Eligible adults were aged at least 18 years and, during at least 6 months of treatment with a first-line treatment containing an NNRTI and two NRTIs, had virological failure (confirmed HIV-1 RNA ≥400 copies per mL). Participants were randomly assigned by a central randomisation system to receive oral dolutegravir (50 mg once daily) or ritonavir-boosted lopinavir (800 mg lopinavir plus 200 mg ritonavir once daily or 400 mg plus 100 mg twice daily), plus two investigator-selected NRTIs (at least one fully active based on resistance testing at screening). The primary outcome was the proportion of participants achieving viral suppression (defined as plasma HIV-1 RNA <50 copies per mL) at week 48 using the snapshot algorithm and a non-inferiority margin of –12%. The primary analysis was done in an intention-to-treat-exposed (ITT-E) population of participants who received at least one dose of study medication, according to original group assignment. Safety was analysed in all participants who received at least one dose of study drug, according to which drug was received. The study was registered at ClinicalTrials.gov, number NCT02227238, and viiv-studyregister.com, number 200304.

Findings Between Dec 11, 2014, and June 27, 2016, 968 adults were screened and 627 were randomly assigned to the dolutegravir group (n=312) or the ritonavir-boosted lopinavir group (n=315). Three patients in the ritonavir-boosted lopinavir group did not receive study medication and so 624 were included in the ITT-E population. At week 48, 261 (84%) of 312 participants in the dolutegravir group achieved viral suppression compared with 219 (70%) of 312 in the ritonavir-boosted lopinavir group (adjusted difference 13·8%; 95% CI 7·3–20·3). Non-inferiority was achieved on the basis of the 95% CI of the adjusted treatment difference having a lower bound greater than –12% (prespecified non-inferiority margin). Because the lower bound of the 95% CI is greater than zero (7·3%), superiority of dolutegravir was also concluded (p<0·0001). The safety profile for dolutegravir was favourable compared with that of ritonavir-boosted lopinavir. More grade 2–4 drug-related adverse events occurred with ritonavir-boosted lopinavir than dolutegravir (44 [14%] of 310 with ritonavir-boosted lopinavir *vs* 11 [4%] of 314 with dolutegravir), mainly driven by gastrointestinal disorders.

Interpretation When administered with two NRTIs, dolutegravir was superior to ritonavir-boosted lopinavir at 48 weeks and can be considered a suitable option for second-line treatment.

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Introduction

Access to antiretroviral therapy (ART) in low-income and middle-income countries has increased over the past decade. In mid-2017, 20·9 million people living with HIV were receiving ART worldwide;[1] thus, the need for second-line treatment is increasing, particularly in low-resource settings such as sub-Saharan Africa.[2] Until 2018, WHO recommended a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with atazanavir plus ritonavir or ritonavir-boosted lopinavir for second-line therapy after virological failure on a non-NRTI (NNRTI)-based first-line regimen.[3,4] Various studies have assessed alternative second-line regimens; however, evidence supporting any particular

Research in context

Evidence before this study

We searched PubMed for clinical trial publications, cohort studies, and review articles using combinations, abbreviations, and variations of the search terms "HIV", "antiretroviral therapy", "dolutegravir", "integrase strand transfer inhibitor", "nucleoside reverse transcriptase inhibitor", "lopinavir", "protease inhibitor", and "second-line therapy". General internet searches were used to acquire relevant practice guidelines, prescribing inserts, and publications related to patient-reported outcomes instruments from governmental, non-governmental, and corporate organisations. Searches were done from Jan 5, 2018, to April 25, 2018. Materials used to develop the study background were published from 1988 to 2018. We identified few studies that focused on options for second-line therapy for treatment of HIV-1 infection, and most assessed nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimens. Until recently, ritonavir-boosted protease inhibitors were the basis for WHO recommendations for second-line treatment of HIV-1 infection after failure on a non-nucleoside reverse transcriptase inhibitor-based first-line regimen, but these drugs are associated with lipid and gastrointestinal side-effects and bone, renal, and cardiovascular toxicities. Dolutegravir is an integrase strand transfer inhibitor approved for treatment of HIV-1 in previously treated and untreated patients. Extensive clinical trial data support the virological efficacy of dolutegravir, its favourable safety profile, and its high barrier to drug resistance. These characteristics suggest that dolutegravir might have a use as a core drug for second-line treatment regimens.

Added value of this study

The DAWNING study showed that dolutegravir was superior to the protease inhibitor ritonavir-boosted lopinavir in terms of virological suppression at week 48 when either drug was administered in regimens containing two NRTIs to patients in whom first-line treatment had failed. These clinical outcomes support dolutegravir as an option for second-line therapy in patients in whom treatment has failed, especially in low-resource settings where WHO's public health approach is crucial in formulating treatment regimens.

Implications of all the available evidence

Data on viable options for second-line treatment of HIV-1 infection are scarce, and patients would benefit from the availability of drugs that offer favourable efficacy, safety, and resistance profiles compared with the recommended drugs. WHO uses a public health approach to formulate their recommendations for therapy, taking into consideration factors such as cost and ease of use, as well as clinical efficacy and safety. These considerations are intended to ensure that recommended drugs are accessible and amenable to high levels of medication adherence in low-resource settings. The DAWNING study provides important information to help guide second-line treatment decisions in low-resource settings. In its 2018 interim guidance, WHO recommends dolutegravir plus two NRTIs as a preferred second-line regimen for patients whose non-dolutegravir-based first-line regimen is not effective, including women and adolescent girls of childbearing potential using consistent and reliable contraception who are fully informed of the benefits and risks of dolutegravir.

second-line ART, especially outside the paradigm of boosted protease inhibitors as the core drug, has been scarce.[5]

Associations between protease inhibitors and increased risks of bone mineral density loss,[6] cardiovascular disease,[7] and renal impairment, when combined with tenofovir disoproxil fumarate,[8] suggest challenges for long-term safety and tolerability. Gastrointestinal adverse events occur more frequently with ritonavir-boosted lopinavir-containing ART than with other regimens.[9] Data on alternative treatment options are needed for people living with HIV who have virological failure with first-line ART. Dolutegravir is an integrase strand transfer inhibitor (INSTI) approved for treatment-naive and previously treated patients with HIV-1 infection worldwide,[10] with more than a million patient-years of cumulative exposure to dolutegravir (unpublished data, 2018). Several phase 3 trials analysing dolutegravir have demonstrated non-inferior or superior virological efficacy and low proportions of treatment failures compared with drugs in the INSTI,[11,12] NNRTI,[13] and protease inhibitor[14,15] classes. The safety profile of dolutegravir is consistent among phase 3 trials, with few serious adverse events or adverse events leading to discontinuation.[11–15] Treatment-emergent resistance has not been reported in any treatment-naive participant who received dolutegravir plus two NRTIs in phase 3 trials,[12–15] demonstrating dolutegravir's high barrier to resistance. In the SAILING study,[11] which enrolled previously treated participants who had a viral load of HIV-1 RNA of at least 400 copies per mL and resistance to at least two ART classes while on non-INSTI-based therapy, significantly fewer participants had virological failure with treatment-emergent INSTI resistance of those treated with dolutegravir than of those treated with raltegravir. In a post-hoc analysis of SAILING, no protocol-defined virological failures were observed among participants treated with dolutegravir plus two NRTIs (n=32), even though 12 of those participants received a regimen with only one fully active NRTI.[16]

Here, we report week 48 results of the DAWNING study, which is assessing safety and efficacy of dolutegravir

compared with ritonavir-boosted lopinavir, each with two NRTIs, in adults who have had virological failure on first-line ART consisting of an NNRTI plus two NRTIs.

Methods

Study design

DAWNING is an open-label, multinational, multicentre, parallel-group, non-inferiority, randomised, active-controlled, phase 3b trial done at 58 sites in Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russia, South Africa, Thailand, and Ukraine. The study was conducted in compliance with local regulatory requirements and with approval from national, regional, or investigational centre ethics committees or institutional review boards in accordance with the 2008 Declaration of Helsinki and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use's guideline for Good Clinical Practice. Written informed consent was obtained from each participant before study initiation.

Participants

Eligible participants were aged at least 18 years with HIV-1 infection who, during at least 6 months of treatment with a first-line regimen of one NNRTI plus two NRTIs, had virological failure (HIV-1 RNA ≥400 copies per mL on two consecutive visits ≥7 days apart). All participants were protease inhibitor and INSTI naive and received an investigator-selected dual NRTI background regimen for second-line treatment, including at least one fully active NRTI based on genotypic resistance testing at screening. NRTIs showing no evidence of genotypic resistance at screening were considered fully active. One change in NRTIs was allowed for management of drug toxicity, provided that at least one fully active NRTI was retained. Switch from lamivudine to emtricitabine or vice versa was not considered a background NRTI change. Switch from lopinavir 800 mg plus ritonavir 200 mg once daily to lopinavir 400 mg plus ritonavir 100 mg twice daily or vice versa was allowed.

Participants with chronic hepatitis B virus infection and evidence of HIV resistance to lamivudine (eg, Met184Val) could receive lamivudine as a third NRTI. Participants with previous exposure to any INSTIs or protease inhibitors; an HIV-1 immunotherapeutic vaccine within 90 days of screening; or radiation therapy, cytotoxic chemotherapy, or systemically administered immunomodulators within 28 days of screening were excluded. Other exclusion criteria were any active Centers for Disease Control and Prevention (CDC) category C disease;[17] severe hepatic impairment; unstable liver disease, cirrhosis, or biliary abnormalities; anticipated need for hepatitis C virus therapy during the study; allergy or intolerance to study drugs or components; ongoing malignancy; and patients with risk of suicide as per investigator's judgment. All eligibility criteria are listed in the appendix.

Randomisation and masking

Participants meeting eligibility criteria were centrally randomised 1:1 to either the dolutegravir group or the ritonavir-boosted lopinavir group. This was an open-label study and did not include masking procedures. The randomisation schedule, including stratification for baseline plasma HIV-1 RNA (≤100 000 *vs* >100 000 copies per mL) and number of fully active NRTIs in the background regimen (fewer than two *vs* two) at baseline, was generated using validated randomisation software, RandAll NG, version 1.3.3.

Procedures

Patients received an investigator-selected background therapy of two NRTIs (including ≥1 fully active) and those in the dolutegravir group received 50 mg dolutegravir once daily whereas those in the ritonavir-boosted lopinavir group received 800 mg lopinavir with 200 mg ritonavir once daily or 400 mg lopinavir with 100 mg ritonavir twice daily, at the investigator's discretion. The treatment was received for 48 weeks plus a 4-week treatment extension. All reported laboratory and safety assessments were done at baseline and at weeks 4, 8, 16, 24, 36, 48, and 52 except fasting lipids and glucose, which were done at baseline and weeks 16, 24, and 48. HIV-1 RNA was retested at week 52 in participants who had detectable viral load (≥50 copies per mL) at week 48 in accordance with the US Food and Drug Administration (FDA) snapshot algorithm.[18] After successful completion of week 52, patients in the dolutegravir group continue to have access to dolutegravir until locally available and are followed up every 12 weeks thereafter. Participants in the ritonavir-boosted lopinavir group completed the study at the week 52 visit unless they were switched to dolutegravir plus two NRTIs. Plasma HIV-1 RNA was quantified using the Abbott RealTime HIV-1 Viral Load assay (lower limit of detection 40 copies per mL; Abbott Molecular, Des Plaines, IL, USA) at each assessment. During screening, protease and reverse transcriptase resistance assays were performed on participant plasma samples to establish eligibility and aid in background NRTI selection (Q² Solutions, Valencia, CA, USA).

Participants met the criteria for confirmed virological withdrawal if they had, on two consecutive tests, a plasma HIV-1 RNA decrease of less than one $\log_{10}$ copies per mL by week 16 (unless <400 copies per mL); or plasma HIV-1 RNA of at least 400 copies per mL after confirmed HIV-1 RNA less than 400 copies per mL; or plasma HIV-1 RNA of at least 400 copies per mL at week 24 or later. These participants were withdrawn from the study but could continue receiving the study drug at the investigator's discretion until results of genotypic and phenotypic resistance testing were available (usually about 1 month); they were included in the intention-to-treat-exposed (ITT-E) population. Monogram Biosciences (San Francisco, CA, USA) did genotypic and phenotypic resistance testing using the PhenoSense GT assay for

See Online for appendix

protease and reverse transcriptase for all baseline samples. For patients meeting criteria for confirmed virological withdrawal, baseline samples and the first sample of the two required to meet confirmed virological withdrawal criteria were tested for protease and reverse transcriptase and for the integrase genotype and phenotype using PhenoSense Integrase and GenoSure (Monogram Biosciences). If the PhenoSense GT plus Integrase assay was unsuccessful, an alternative PhenoSense GT and Integrase assay was used.

Adverse events were evaluated and graded at all study visits according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events, version 1.0.[19] The electronic Columbia-Suicide Severity Rating Scale was used to monitor suicidal ideation and behaviour, with treatment-emergent events recorded as adverse events.

For the **Columbia-Suicide Severity Rating Scale** see https://cssrs.columbia.edu/

Outcomes

The primary efficacy outcome was the proportion of participants achieving viral suppression (defined as plasma HIV-1 RNA of less than 50 copies per mL) at week 48 using the FDA snapshot algorithm.[18] Secondary outcomes were the proportion of participants achieving viral suppression at week 24 and the proportion with less than 400 copies per mL at weeks 24 and 48 (FDA snapshot); changes from baseline in CD4 cell counts at weeks 24 and 48; incidence of disease progression (HIV-associated conditions, AIDS, and death) at any time during the randomised phase of the study; proportion of patients without virological or tolerability failure by weeks 24 and 48 (results not reported here); incidence of treatment-emergent genotypic and phenotypic resistance to dolutegravir, ritonavir-boosted lopinavir, and investigator-selected background therapy in participants with confirmed virological failure; time to viral suppression; treatment satisfaction, patient-reported adherence, and gastrointestinal symptom rating score; and the effects of dolutegravir and ritonavir-boosted lopinavir on fasting lipids over time. Safety was monitored by incidence and severity of adverse events and clinical laboratory evaluations.

Statistical analysis

Assuming a 70% response rate in the dolutegravir group, the study required at least 306 evaluable participants per group for 90% power with a 12% non-inferiority margin and a one-sided 2·5% significance level.

The DAWNING study was designed to establish whether the antiviral effect of dolutegravir plus two NRTIs is non-inferior to ritonavir-boosted lopinavir plus two NRTIs at week 48 in the ITT-E population. For the primary comparison, we did a stratified analysis using Cochran-Mantel-Haenszel weights, adjusting for baseline plasma HIV-1 RNA (≤100 000 *vs* >100 000 copies per mL) and number of fully active NRTIs in the background regimen (fewer than two *vs* two) at baseline, to provide adjusted estimates of the difference in the number of responders between the dolutegravir group and the ritonavir-boosted lopinavir group. Analyses of the primary outcome were done for prespecified subgroups, which were age (<35 years, 35 years to <50 years, and ≥50 years), sex (female and male), African American or African heritage (yes and no), white (yes and no), HIV-1 subtype (B, C, complex, A1, AE, and other; appendix), baseline viral load (>100 000 and ≤100 000 copies per mL), baseline CD4 count (<200 cells per µL, 200 to <350 cells per µL, and ≥350 cells per µL), CDC category (A, B, and C; appendix), and number of fully active NRTIs (two and fewer than two). Stratification by WHO-recommended second-line background NRTIs (yes and no) was also included post-hoc.

Changes in LDL cholesterol and ratio of total cholesterol to HDL cholesterol were analysed using analysis of variance, adjusting for plasma HIV-1 RNA, fully active NRTIs, age, and cholesterol levels at baseline. Multiple imputation using a missing-at-random algorithm was the primary method for handling missing data in the cholesterol analysis.

Post-hoc efficacy analyses were done at week 48 on whether WHO-recommended second-line NRTIs were chosen according to participants' first-line NRTIs per WHO 2016 guidelines.[3] Recommended second-line NRTIs were defined as follows: tenofovir disoproxil fumarate plus emtricitabine or lamivudine when first-line therapy included zidovudine or stavudine plus lamivudine; and zidovudine plus lamivudine when first-line therapy included tenofovir disoproxil fumarate plus emtricitabine or lamivudine.[3]

The primary analysis was done in the ITT-E population of all participants who received at least one dose of study medication and also in the per-protocol population; safety was assessed in the same population. In the ITT-E analysis, participants were included in the treatment group to which they were randomised; in the safety analysis, participants were grouped according to treatment received. The per-protocol population consisted of participants who met eligibility criteria and had no major protocol deviations that could have affected the assessment of antiviral activity, including those known to have had less than 90% adherence to study medication. We used SAS, version 9.4, within a Linux environment, for statistical analyses.

Non-inferiority was concluded if the lower bound of a two-sided 95% CI for the difference in proportion of patients achieving viral suppression (dolutegravir group minus ritonavir-boosted lopinavir group) in the ITT-E population at week 48 was greater than –12%. If non-inferiority was achieved in both the ITT-E and per-protocol populations, superiority would be assessed in the ITT-E population and concluded if the lower end of the 95% CI for the treatment difference from the primary analysis was greater than 0%.

An independent data monitoring committee (IDMC) provided external review of efficacy and safety data. DAWNING is registered with ClinicalTrials.gov (NCT02227238).

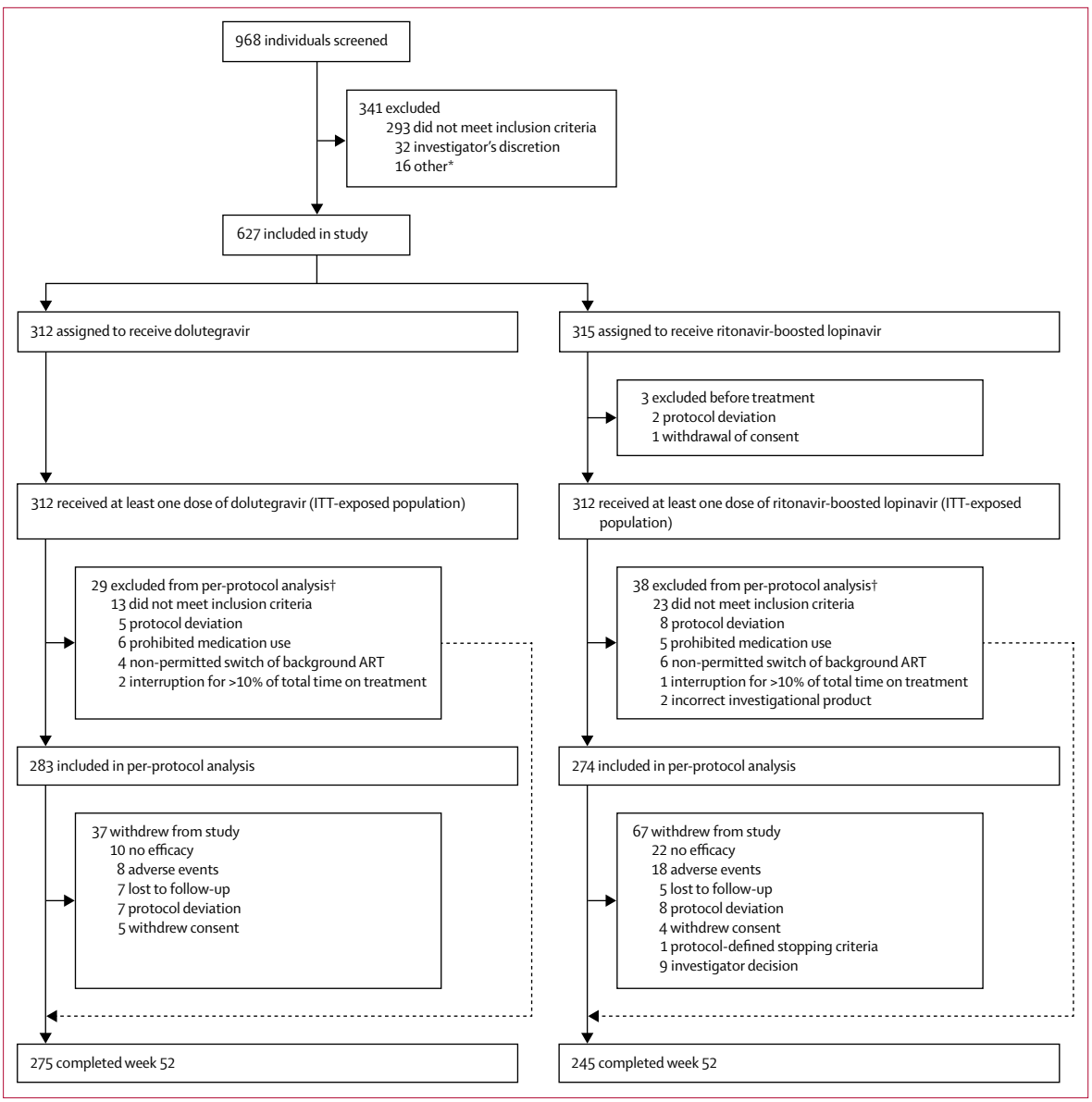

Figure 1: **Trial profile**
ART=antiretroviral therapy. ITT=intention-to-treat. *Other reasons participants were not included accounted for less than 1% of participants screened (six withdrew consent, five for multiple reasons, four were lost to follow-up, and one because of an adverse event). †Participants could have had more than one protocol deviation leading to exclusion from the per-protocol population.

Role of the funding source
The funder of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to the data and the corresponding author had final responsibility for the decision to submit for publication.

Results
Participants were recruited between Dec 11, 2014, and June 27, 2016. The last participant completed 52 weeks of treatment on Aug 2, 2017. Of 968 people screened, 627 were randomly assigned to the dolutegravir group (n=312) or the ritonavir-boosted lopinavir group (n=315). Three patients in the ritonavir-boosted lopinavir group did not receive study medication and so 624 were included in the ITT-E population (figure 1). Two participants assigned to ritonavir-boosted lopinavir incorrectly received dolutegravir instead and so were included in the dolutegravir group for safety analyses. More participants withdrew from the ritonavir-boosted lopinavir group (n=67) than the dolutegravir group (n=37), resulting in 245 patients in the ritonavir-boosted lopinavir group and 275 in the dolutegravir group completing the study

	Dolutegravir (n=312)	Ritonavir-boosted lopinavir (n=312)
Age, years		
Mean (SD)	37·5 (9·1)	38·7 (9·4)
Range	19–64	18–72
Sex		
Women	116 (37%)	103 (33%)
Men	196 (63%)	209 (67%)
Ethnicity		
Hispanic or Latino	105 (34%)	109 (35%)
Not Hispanic or Latino	207 (66%)	203 (65%)
Race		
African American or African heritage	130 (42%)	112 (36%)
American Indian or Alaskan native	42 (13%)	53 (17%)
White	90 (29%)	90 (29%)
Asian	50 (16%)	56 (18%)
Mixed race	0	1 (<1%)
Hepatitis status		
Hepatitis B only	10 (3%)	13 (4%)
Hepatitis C only	22 (7%)	22 (7%)
Hepatitis B and C	3 (<1%)	3 (<1%)
CDC category[17]		
A	147 (47%)	158 (51%)
B	58 (19%)	59 (19%)
C: AIDS	107 (34%)	95 (30%)
HIV-1 RNA		
Mean (SD), $\log_{10}$ copies per mL	4·2 (0·9)	4·2 (0·9)
<400 copies per mL	11 (4%)	9 (3%)
400 to <1000 copies per mL	23 (7%)	18 (6%)
1000 to <10 000 copies per mL	88 (28%)	103 (33%)
10 000 to <50 000 copies per mL	93 (30%)	85 (27%)
50 000 to ≤100 000 copies per mL	27 (9%)	34 (11%)
>100 000 copies per mL	70 (22%)	63 (20%)
CD4 cell count*		
Mean (SD), $\log_{10}$ cells per µL	2·1 (0·5)	2·2 (0·4)
≥200 cells per µL	146 (47%)	160 (51%)
<200 cells per µL	166 (53%)	151 (48%)
Duration of previous ART		
Median (IQR), weeks	86·4 (48·4–230·9)	90·9 (45·0–199·5)
Previous non-NRTI therapy		
Efavirenz	242 (78%)	242 (78%)
Nevirapine	70 (22%)	69 (22%)
Rilpivirine	0	1 (<1%)

(Table 1 continues on next page)

through week 52. Most withdrawals were because of virological failure or adverse events (figure 1). The per-protocol population included 283 participants in the dolutegravir group and 274 participants in the ritonavir-boosted lopinavir group. The most frequent reasons for exclusion from the per-protocol analysis were deviations from inclusion or exclusion criteria, protocol deviation, use of prohibited medication, and non-permitted switch of background ART. Three participants were excluded from the per-protocol analysis because of study drug interruption for more than 10% of total time on treatment.

Participant demographics were well balanced across treatment groups (table 1). Because of broad geographical participation, the population was diverse in race, sex, and HIV-1 subtype (185 participants [30%] were subtype B, 150 [24%] were subtype C, 86 [14%] were subtype AE, 69 [11%] were complex subtype, and 56 [9%] were subtype A1). About a third of participants had a history of AIDS (CDC category C[17] at baseline) and about half had a CD4 cell count of less than 200 cells per µL. Overall, 318 (51%) of 624 participants had had a first-line regimen of efavirenz plus tenofovir disoproxil fumarate with emtricitabine or lamivudine, and 484 (78%) had had any combination that included efavirenz. Most participants had mutations associated with two-class resistance against NNRTIs and NRTIs (273 [88%] of 312 in the dolutegravir group and 271 [87%] of 312 in the ritonavir-boosted lopinavir group). All participants had at least one active NRTI in their background regimen based on screening resistance test results, and treatment groups were balanced in baseline genotypic and phenotypic susceptibility scores (table 1). Met184Val/Ile substitutions were present alone or with additional NRTI mutations in 513 (82%) of 624 participants.

A greater proportion of participants receiving dolutegravir achieved viral suppression (HIV-1 RNA <50 copies per mL) at week 48 than in the ritonavir-boosted lopinavir group. In the ITT-E population, 261 (84%) of 312 participants assigned to dolutegravir achieved viral suppression at week 48 compared with 219 (70%) of 312 participants assigned to ritonavir-boosted lopinavir (table 2). Adjusted treatment difference was estimated to be 13·8% (95% CI 7·3–20·3; p<0·0001), with the lower bound of the 95% CI greater than 0%. The primary endpoint of non-inferiority was achieved on the basis of the 95% CI of the adjusted treatment difference having a lower bound greater than –12% (prespecified non-inferiority margin). Results at week 48 were consistent with those at week 24, at which point viral suppression had been achieved by 257 (82%) of 312 participants in the dolutegravir group and 215 (69%) in the ritonavir-boosted lopinavir group (adjusted treatment difference 13·8%, 95% CI 7·3–20·3; p<0·0001).

The study protocol was modified on April 19, 2017, when an IDMC did an ad-hoc review of efficacy and safety data up to week 24, revealing a significant difference in viral suppression between the dolutegravir and ritonavir-boosted lopinavir groups. Based on the IDMC's recommendation to discontinue the ritonavir-boosted lopinavir group, the protocol was amended to allow participants to switch to dolutegravir if considered appropriate by the investigator. The third planned IDMC analysis at week 24 was not done. The timing of this change had minimal effect on the primary endpoint; all participants on ritonavir-boosted lopinavir who switched to dolutegravir after local approval of the protocol

amendment or who discontinued because of the IDMC recommendation had a week 48 viral load measurement that contributed to the primary endpoint. On the basis of the IDMC recommendation, nine patients in the ritonavir-boosted lopinavir group were withdrawn early and 12 switched to dolutegravir.

Results of the per-protocol analysis were consistent with those of the ITT-E population. 246 (87%) of 283 participants in the dolutegravir group and 204 (74%) of 274 in the ritonavir-boosted lopinavir group achieved viral suppression at week 48 (adjusted treatment difference 12·3%, 95% CI 5·8–18·7). Because the ITT-E and per-protocol analyses both showed non-inferiority, superiority of dolutegravir over ritonavir-boosted lopinavir was assessed and confirmed at week 48 (p<0·0001). Subgroup analyses were consistent with overall efficacy results (figure 2). Although in participants with baseline viral load of 100 000 copies per mL or less the dolutegravir group had a greater proportion of participants (216 [89%] of 242) achieving viral suppression at week 48 than the ritonavir-boosted lopinavir group (178 [71%] of 249), similar proportions between the groups were recorded in participants with baseline viral load greater than 100 000 copies per mL (45 [64%] of 70 in the dolutegravir group and 41 [65%] of 63 in the ritonavir-boosted lopinavir group). Notably, the number of participants with viral load greater than 100 000 copies per mL was small (133 [21%] of 624).

Median time to viral suppression was significantly shorter in the dolutegravir group (29·0 days, IQR 29·0–57·0) than in the ritonavir-boosted lopinavir group (111·0 days, IQR 35·0–167·0; p<0·0001). At week 4, 207 (66%) of 312 participants receiving dolutegravir achieved viral suppression compared with 80 (26%) of 312 receiving ritonavir-boosted lopinavir (figure 3). At week 48, 273 (88%) participants receiving dolutegravir achieved HIV-1 RNA less than 400 copies per mL compared with 241 (77%) receiving ritonavir-boosted lopinavir. At week 24, 280 (90%) participants receiving dolutegravir achieved HIV-1 RNA less than 400 copies per mL compared with 263 (84%) receiving ritonavir-boosted lopinavir. Median increase in CD4 counts at week 48 was similar between groups (120·0 cells per µL [IQR 63·0–204·0] in the dolutegravir group and 118·0 cells per µL [66·0–191·0] in the ritonavir-boosted lopinavir group). Median increase in CD4 counts at week 24 was also similar between groups (84·0 cells per µL [31·0–146·0] in the dolutegravir group and 82·0 cells per µL [31·0–146·0] in the ritonavir-boosted lopinavir group). Reports of progression to CDC category C (AIDS)[17] or death up to week 48 were low and similar between groups: seven (2%) participants in the dolutegravir group, including two deaths, and seven (2%) in the ritonavir-boosted lopinavir group, including three deaths.

During the randomised phase, by week 52, fewer participants receiving dolutegravir (11 [4%] of 314) met criteria for confirmed virological withdrawal than those receiving ritonavir-boosted lopinavir (30 [10%] of 310). All 11 participants who met virological withdrawal criteria and received dolutegravir (including one who was randomised to ritonavir-boosted lopinavir, but received dolutegravir instead, and was included in the ritonavir-boosted lopinavir group in the ITT-E analysis) had the same phenotypic

	Dolutegravir (n=312)	Ritonavir-boosted lopinavir (n=312)
(Continued from previous page)		
Previous NRTI therapy		
Lamivudine	219 (70%)	215 (69%)
Tenofovir disoproxil fumarate	181 (58%)	186 (60%)
Emtricitabine	92 (29%)	95 (30%)
Zidovudine	89 (29%)	89 (29%)
Abacavir	27 (9%)	26 (8%)
Stavudine	15 (5%)	9 (3%)
Didanosine	1 (<1%)	3 (<1%)
NRTI background in second-line regimen		
Zidovudine plus lamivudine	132 (42%)	121 (39%)
Tenofovir disoproxil fumarate plus lamivudine or emtricitabine	128 (41%)	134 (43%)
Tenofovir disoproxil fumarate plus zidovudine	36 (12%)	41 (13%)
Abacavir plus lamivudine	7 (2%)	7 (2%)
Other	9 (3%)	9 (3%)
Stanford baseline genotypic susceptibility scores to background ART		
0 to <1	30 (10%)	36 (12%)
1 to <2	221 (71%)	212 (68%)
2	61 (20%)	64 (21%)
>2	0	0
Baseline phenotypic susceptibility scores to background ART		
0	3 (<1%)	6 (2%)
1	223 (71%)	204 (65%)
2	69 (22%)	81 (26%)
>2	0	0
Data not available†	17 (5%)	21 (7%)
Resistance mutations by drug class		
NRTI mutations‡		
Lys65Arg	95 (30%)	92 (29%)
Lys70Glu	33 (11%)	37 (12%)
Met184Val/Ile only	77 (25%)	85 (27%)
Met184Val/Ile with any other major NRTI mutation	184 (59%)	167 (54%)
Other major NRTI mutation	90 (29%)	88 (28%)
Thymidine analogue mutations	71 (23%)	81 (26%)
NNRTI mutations		
One major mutation	68 (22%)	62 (20%)
Two or more major mutations	230 (74%)	233 (75%)
Any major mutation with no NRTI mutation	24 (8%)	23 (7%)
No major mutations	14 (4%)	17 (5%)

Data are n (%) or median (IQR) unless otherwise stated. ART=antiretroviral therapy. CDC=US Centers for Disease Control and Prevention. NNRTI=non-NRTI. NRTI=nucleoside reverse transcriptase inhibitor. *One patient in the ritonavir-boosted lopinavir group did not have a baseline CD4 cell count. †Phenotypic susceptibility score total is <100% because the necessary phenotypic data were not available for some participants with failed Monogram resistance testing, which is needed to generate those scores. ‡No participants had NRTI mutations at codons 69 or 151.

Table 1: **Demographics and baseline characteristics**

resistance results at baseline and at confirmed virological withdrawal visits. Two (18%) of the 11 participants had an at least 13-fold change in susceptibility to dolutegravir (Monogram's upper clinical cutoff) through week 52 and were therefore established to have treatment-emergent phenotypic resistance to dolutegravir. Genotypic resistance results showed that one of these two participants, who had HIV-1 subtype B, had emergent INSTI (Gly118Arg) and NRTI (Asp67Asn) resistance substitutions. This participant received a background regimen of emtricitabine and tenofovir disoproxil fumarate; however, the Asp67Asn substitution is treatment emergent for stavudine and zidovudine, not the regimen received.[20] The other participant had HIV-1 subtype C and had only INSTI substitutions His51His/Tyr; Gly118Arg; Glu138Glu/Lys; and Arg263Arg/Lys. In comparison, of the 30 participants receiving ritonavir-boosted lopinavir and meeting confirmed virological withdrawal criteria, three (10%) had emergent NRTI mutations. The Lys70Lys/Arg and Met184Val substitutions emerged in one participant receiving a background regimen of tenofovir disoproxil fumarate and lamivudine. The Lys219Lys/Gln substitution emerged in a participant receiving zidovudine and

	Dolutegravir (n=312)	Ritonavir-boosted lopinavir (n=312)
Response	261 (84%)	219 (70%)
Non-response	30 (10%)	68 (22%)
Did not achieve <50 copies per mL by week 48	18 (6%)	34 (11%)
Discontinued because of no efficacy before reaching <50 copies per mL	6 (2%)	20 (6%)
Discontinued for other reason when not at <50 copies per mL	2 (1%)	7 (2%)
Change in antiretroviral therapy	4 (1%)	7 (2%)
No data available	21 (7%)	25 (8%)
Discontinued because of adverse event or death	7 (2%)	17 (5%)
Discontinued for other reasons	12 (4%)	6 (2%)
Missing data but still on study	2 (1%)	2 (1%)

Table 2: **Primary outcome results at week 48**

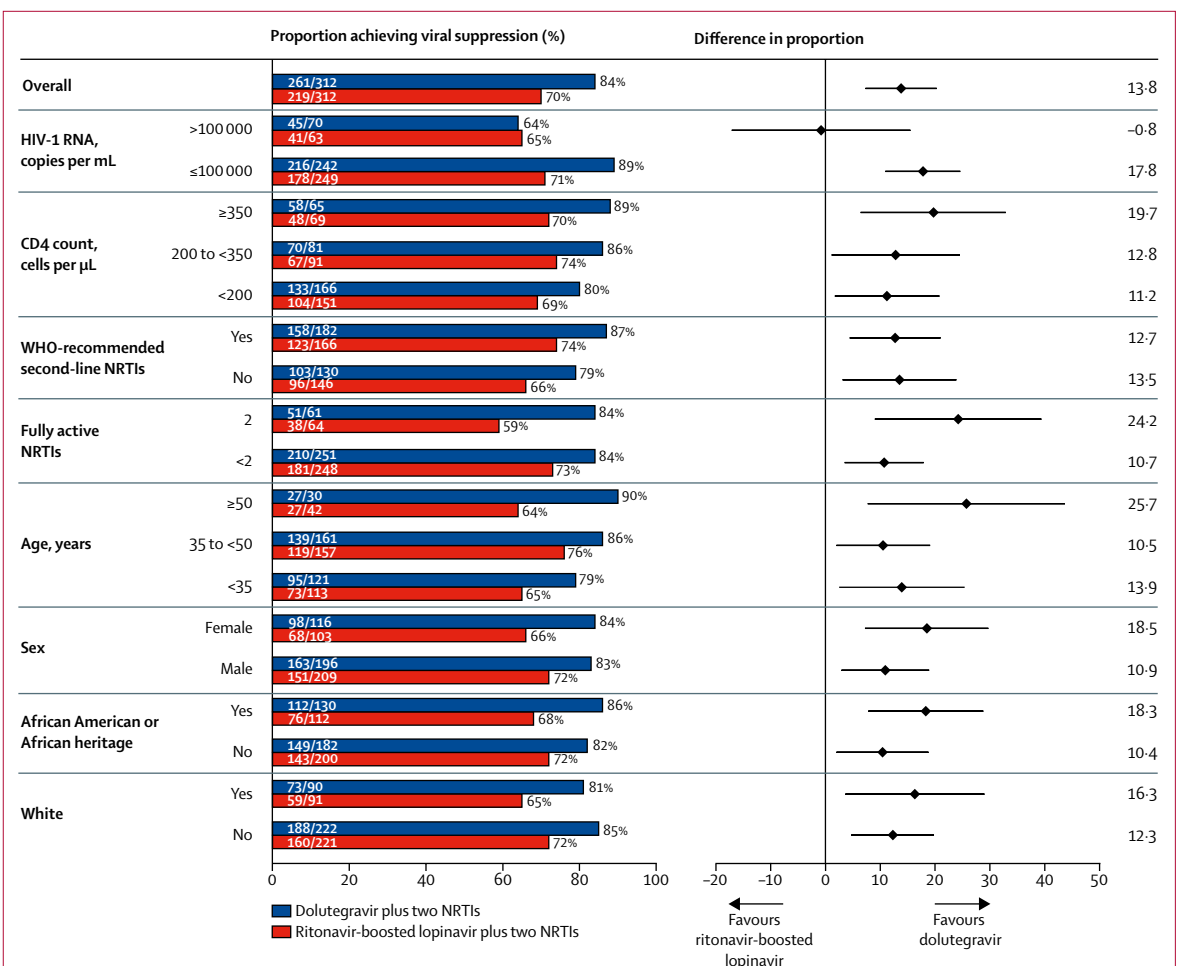

Figure 2: **Subgroup analysis of participants achieving viral suppression at week 48**
Analysis is in the intention-to-treat-exposed population. Viral suppression is defined as plasma HIV-1 RNA less than 50 copies per mL. Diamonds show treatment differences (adjusted for overall difference; unadjusted for subgroup differences) and bars show 95% CI. NRTI=nucleoside reverse transcriptase inhibitor.

lamivudine, and Lys70Lys/Gln/Arg and Lys219Lys/Glu emerged in another participant receiving this same background regimen. No participant developed treatment-emergent phenotypic resistance to protease inhibitors.

The safety profile of dolutegravir plus two NRTIs through the randomised phase was generally favourable compared with that of ritonavir-boosted lopinavir plus two NRTIs, with more adverse events in the ritonavir-boosted lopinavir group (table 3). The most common adverse events were diarrhoea (28 [9%] of 314 in those receiving dolutegravir *vs* 105 [34%] of 310 in those receiving ritonavir-boosted lopinavir), upper respiratory tract infection (45 [14%] *vs* 43 [14%]), and headache (25 [8%] *vs* 17 [5%]; table 3). Grades 2–4 treatment-related adverse events occurred in 11 (4%, dolutegravir group) versus 44 (14%, ritonavir-boosted lopinavir group) of participants, with the difference driven by gastrointestinal disorders in the ritonavir-boosted lopinavir group. Eight (3%) participants receiving dolutegravir reported adverse events leading to discontinuation compared with 18 (6%) receiving ritonavir-boosted lopinavir. Eight (3%) participants withdrew from the ritonavir-boosted lopinavir group because of gastrointestinal adverse events; six (2%) of these participants reported diarrhoea. Anaemia led to two (1%) withdrawals of those receiving dolutegravir and four (1%) of those receiving ritonavir-boosted lopinavir; most participants who had anaemia were also taking zidovudine, which is known to be associated with anaemia. All other adverse events leading to withdrawal were reported in less than 1% of participants (table 3).

Psychiatric adverse events were reported in 19 (6%) participants receiving dolutegravir and 17 (5%) receiving ritonavir-boosted lopinavir; none led to study withdrawal. Some participants who reported psychiatric adverse events had a history of psychiatric disorders at baseline. Insomnia was the most common psychiatric adverse event in both groups (eight [3%] receiving dolutegravir and seven [2%] receiving ritonavir-boosted lopinavir). Five participants had drug-related psychiatric adverse events, three (1%) receiving dolutegravir (insomnia, anxiety, and mental disorder caused by a general medical condition, one each) and two (1%) receiving ritonavir-boosted lopinavir (both insomnia). Grade 3 psychiatric adverse events (depression, which was also considered a serious adverse event, and suicidal ideation) occurred in two participants, both of whom were receiving dolutegravir. Neither adverse event was considered treatment related. No grade 4 psychiatric adverse events were reported.

Numbers of serious adverse events were similar across treatment groups (20 [6%] receiving dolutegravir and 20 [6%] receiving ritonavir-boosted lopinavir). Five deaths occurred through the randomised phase: two (1%) in those receiving dolutegravir (pneumonia; immune reconstitution inflammatory syndrome [IRIS]-associated tuberculosis) and three (1%) in those receiving ritonavir-boosted lopinavir (pneumonia; IRIS, cerebral toxoplasmosis, and Epstein-Barr virus infection; encephalitis and IRIS). Of the five fatal adverse events, two were considered treatment related (one participant with IRIS-associated tuberculosis in the dolutegravir group and one with encephalitis and IRIS in the ritonavir-boosted lopinavir group).

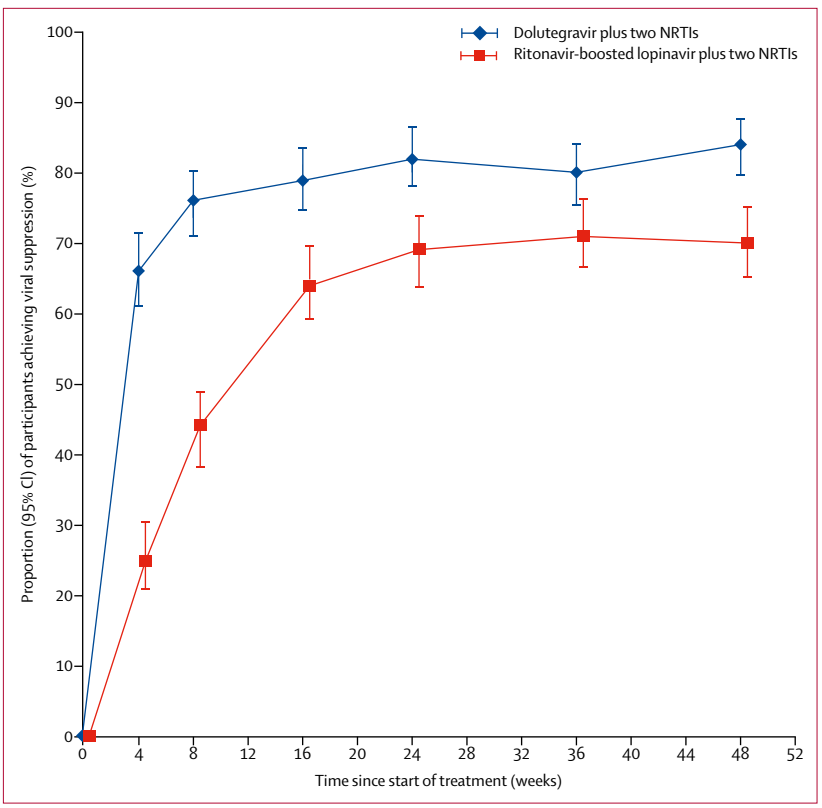

Figure 3: **Participants achieving viral suppression over the course of the study**
Analysis is in the intention-to-treat-exposed population. Viral suppression is defined as plasma HIV-1 RNA less than 50 copies per mL. NRTI=nucleoside reverse transcriptase inhibitor.

Compliance concerns related to unreported adverse events and concomitant medications were raised at the Kenyan site after completion of the week 48 primary analysis. The Kenyan regulatory authority was notified, and additional analyses were done to estimate the effect on study results. The Good Clinical Practice concerns were not considered a serious breach or considered to have significantly affected overall study data integrity. Furthermore, there was no evidence of participant safety being compromised.

The 292 participants with available cholesterol data in the ritonavir-boosted lopinavir group had significantly greater adjusted mean change from baseline in fasting LDL cholesterol (0·1350, SE 0·042) compared with the 303 participants with available data in the dolutegravir group (–0·012, 0·039; n=303; p=0·0100; appendix). Five (2%) of 314 participants receiving dolutegravir and 20 (6%) of 310 receiving ritonavir-boosted lopinavir had an at least grade 2 increase in calculated LDL cholesterol versus baseline. A statistically significant difference was

	Dolutegravir (n=314)	Ritonavir-boosted lopinavir (n=310)
All adverse events	223 (71%)	244 (79%)
≥5% in either group		
Diarrhoea	28 (9%)	105 (34%)
Upper respiratory tract infection	45 (14%)	43 (14%)
Headache	25 (8%)	17 (5%)
Nausea	10 (3%)	30 (10%)
Lower respiratory tract infection	13 (4%)	14 (5%)
Anaemia	11 (4%)	15 (5%)
Vomiting	5 (2%)	21 (7%)
Psychiatric adverse events	19 (6%)	17 (5%)
Adverse events leading to discontinuation		
Any	8 (3%)	18 (6%)
≥1% in either group		
Anaemia	2 (1%)	4 (1%)
Diarrhoea	0	6 (2%)
Treatment-related adverse events		
Any grade	50 (16%)	119 (38%)
Grades 2–4	11 (4%)	44 (14%)
≥2% in either group		
Diarrhoea	1 (<1%)	23 (7%)
Nausea	0	6 (2%)
Serious adverse events		
Any	20 (6%)	20 (6%)
In more than one participant		
Pneumonia	3 (1%)	5 (2%)
Cerebral toxoplasmosis	1 (<1%)	2 (1%)
Anaemia	2 (1%)	2 (1%)
Headache	1 (<1%)	1 (<1%)
Immune reconstitution inflammatory syndrome	0	2 (1%)
Treatment-related	3 (1%)	2 (1%)
Fatal	2 (1%)*	3 (1%)†

Data are n (%). Two participants received dolutegravir plus two NRTIs instead of ritonavir-boosted lopinavir plus two NRTIs. IRIS=immune reconstitution inflammatory syndrome. NRTI=nucleoside reverse transcriptase inhibitor. *One participant with grade 3 IRIS-associated tuberculosis, considered related to study treatment; and one participant with grade 4 pneumonia that was not considered related to study treatment. †One participant with grade 4 pneumonia that was not considered related to study treatment; one participant with grade 4 meningoencephalitis and grade 4 IRIS, both considered related to study treatment; and one participant with grade 4 Epstein-Barr virus infection, grade 4 toxoplasmic encephalitis, and grade 4 IRIS, none of which were considered related to study treatment.

***Table 3*: Summary of adverse events through the randomised phase**

also observed in the mean change from baseline in the ratio of fasting total cholesterol to HDL cholesterol, with a decrease in the 306 patients receiving dolutegravir (–0·084, SE 0·069) versus an increase in the 295 receiving ritonavir-boosted lopinavir (0·275, 0·073; p=0·0004; appendix).

Compared with baseline values, mean serum creatinine concentrations increased by 12·48 µmol/L (SD 8·84; n=256) at week 48 in the dolutegravir group from a baseline of 66·34 µmol/L (15·08; n=314) compared with 5·84 µmol/L (13·48; n=235) in the ritonavir-boosted lopinavir group from a baseline of 66·88 µmol/L (16·03; n=310). Nine (3%) participants receiving dolutegravir and six (2%) receiving ritonavir-boosted lopinavir had increases in alanine aminotransferase to at least three times the upper limit of normal; none were considered related to the study drug.

Treatment satisfaction, assessed by the HIV Treatment Satisfaction Questionnaire, improved after initiation of dolutegravir (appendix). Using the Morisky Medication Adherence Scale, a larger proportion of participants receiving dolutegravir reported high adherence at week 48 than those receiving ritonavir-boosted lopinavir, and participants receiving dolutegravir reported fewer gastrointestinal symptoms than those receiving ritonavir-boosted lopinavir, as assessed by the Gastrointestinal Symptom Rating Scale (appendix).

Discussion

The DAWNING study demonstrates that dolutegravir plus two NRTIs is superior to ritonavir-boosted lopinavir plus two NRTIs after 48 weeks of treatment in adults with virological failure after first-line NNRTI-based ART. The difference was primarily driven by fewer non-responders in the dolutegravir group. The per-protocol analysis at week 48 supported the ITT-E results, and overall efficacy was consistent across the subgroups defined by number of fully active NRTIs and CD4 cell counts. Most participants were receiving fewer than two fully active background NRTIs, and in this subgroup, a larger proportion of patients achieved viral suppression in both treatment groups than in the corresponding group of those with two fully active NRTIs. This finding is consistent with previous trials of second-line ART demonstrating high proportions of patients with virological failure among those without or with few resistance mutations.[21,22] One possible explanation is that patients who have virological failure after first-line regimens and have few or no resistance mutations are more likely to have had challenges with adherence and associated lower selective pressure for resistance.[21,22]

Previous studies examined the use of ritonavir-boosted lopinavir in combination with raltegravir after first-line treatment failure.[23,24] In the SECOND-LINE study,[23] ritonavir-boosted lopinavir with raltegravir was non-inferior to ritonavir-boosted lopinavir with NRTIs, with 223 (83%) of 270 in the raltegravir group versus 219 (81%) of 271 in the NRTI group achieving viral loads less than 200 copies per mL at week 48. Results for outcomes based on proportion of patients achieving HIV-1 RNA less than 50 copies per mL at 48 weeks[23] are generally similar to those in our study. The EARNEST study[24] compared three regimens, including ritonavir-boosted lopinavir with NRTIs, raltegravir with a protease inhibitor, and protease inhibitor monotherapy after induction with raltegravir. Raltegravir with a protease inhibitor was non-inferior to

ritonavir-boosted lopinavir with NRTIs, with disease control achieved by 277 (imputed mean; 64%) of 433 participants with raltegravir plus a protease inhibitor versus 255 (60%) of 426 with ritonavir-boosted lopinavir plus NRTIs, achieving a composite endpoint indicative of good HIV-1 infection control. Both regimens were superior to the protease inhibitor monotherapy group.[24] DAWNING is the first major study supporting the use of a non-boosted protease inhibitor-based regimen for second-line ART.

In our study, fewer virological withdrawals occurred in the dolutegravir group than in the ritonavir-boosted lopinavir group. Two participants with NRTI resistance mutations at baseline (Lys70Glu plus Met184Val or Met184Val plus Lys219Lys/Glu) in the dolutegravir group, who had received lamivudine and zidovudine or emtricitabine and tenofovir disoproxil fumarate as background drugs, had treatment-emergent Gly118Arg resistance mutations in the integrase gene at the time of virological withdrawal. The Gly118Arg mutation has previously been associated with impaired integrase strand transfer activity and low-level reduction of dolutegravir susceptibility.[25] In our study, the Gly118Arg mutation occurred with a thymidine analogue mutation (Asp67Asn) in reverse transcriptase in one participant and with His51His/Tyr, Glu138Glu/Lys, and Arg263Arg/Lys substitutions in integrase in another participant. In the presence of Gly118Arg, the His51Tyr and Glu138Lys substitutions might partly restore integrase function, and in-vitro studies suggest that, for Gly118Arg and Glu138Lys, susceptibility to dolutegravir is similar to that of wild type. However, Gly118Arg and His51Tyr together are associated with reduced dolutegravir susceptibility, similar to that of Gly118Arg alone.[25] The presence of Gly118Arg in two of our participants who had confirmed virological withdrawal was associated with an at least 13-fold change in susceptibility to dolutegravir, which is clinically significant.

Surveillance of ART programmes and ongoing real-world evidence cohorts in low-resource settings will be important to explore the effect of dolutegravir and the roll-out of tenofovir disoproxil fumarate–lamivudine–dolutegravir in these settings, including monitoring of treatment failures and surveillance of emerging resistance to dolutegravir.

Safety data for dolutegravir during the randomised phase of our study were consistent with previous dolutegravir studies.[11,12,14,15] Dolutegravir was associated with fewer adverse events overall, treatment-related adverse events, and adverse events leading to withdrawal than was ritonavir-boosted lopinavir, suggesting greater overall tolerability. This difference was mainly driven by fewer gastrointestinal adverse events with dolutegravir than with ritonavir-boosted lopinavir, which has been associated with increased diarrhoea, nausea, and vomiting. Rates of psychiatric adverse events (eg, insomnia, depression, and anxiety) were similar between groups, consistent with a pooled analysis of five phase 3 studies showing no meaningful difference in the frequency of psychiatric adverse events between participants treated with dolutegravir and the comparator group in each study.[26]

Changes in the fasting serum lipid profile over 48 weeks of treatment favoured dolutegravir, with decreases associated with dolutegravir for fasting LDL cholesterol and total cholesterol to HDL cholesterol ratio versus increases with ritonavir-boosted lopinavir. These differences are consistent with lipid biomarker analyses from previous studies.[12,14,15]

Preliminary results from a birth outcomes surveillance study done in Botswana indicate a higher-than-expected incidence of neural tube defects in infants born to women exposed to dolutegravir at the time of conception.[27] This potential safety issue is being investigated further.

This analysis of the DAWNING study has potential limitations. Resistance testing at screening somewhat limits the applicability to low-resource settings where testing is not routinely done to guide second-line therapy. However, of all participants screened, only 8% failed screening because they had no active NRTI available, suggesting that the DAWNING population is generally representative of the population in low-resource settings. Furthermore, results from subgroup analyses comparing participants who received or did not receive WHO-recommended second-line background drugs were consistent with overall efficacy results, demonstrating superior efficacy of dolutegravir over ritonavir-boosted lopinavir in each group. The study conclusions are also limited by use of ritonavir-boosted lopinavir, an older antiretroviral drug than dolutegravir, as a comparator because of the frequent reports of gastrointestinal toxicity with this drug.[9] However, ritonavir-boosted lopinavir was a WHO-recommended option for second-line ART, and its widespread availability across study regions supported its use as a comparator. Another limitation is the open-label design, which might have resulted in bias in the perceptions of both physicians and participants. It would have been logistically challenging to implement masking because of the potential for once-daily or twice-daily dosing of ritonavir-boosted lopinavir and the various options for background NRTIs selected by the investigator on the basis of screening resistance test results.

This 48-week analysis of the DAWNING study supports the use of dolutegravir plus two NRTIs as protease inhibitor-sparing second-line ART in patients with virological failure after a first-line ART regimen and informs the potential use of this strategy in low-income and middle-income settings. WHO recommends dolutegravir in combination with an optimised NRTI background regimen as a preferred second-line regimen for patients whose non-dolutegravir-based first-line regimen is not effective.[4]

Contributors

MA, FZ, JS, DB, MU, MCN, MG, and KS participated in the conceptualisation of the studies. JS, JH, MU, MCN, and YP curated data. MA, JS, DB, JH, MU, MCN, YP, MG, and KS were involved with formal data analysis. MA, DB, MG, and KS were involved in funding acquisition. RK, JL, FZ, JAH, EM, MHL, PC, and CB were study investigators. MA, JS, DB, JH, MU, MCN, MG, and KS were involved in

developing the methods. MA, JS, DB JH, MU, MCN, YP, MG, and KS were involved in project administration and supervision. MG and KS were responsible for study resources. JH and MU handled software and program development and validation. All authors participated in the drafting and review of the manuscript.

Declaration of interests

MA, JS, DB, MU, MCN, YP, MG, and KS are employees of ViiV Healthcare and own stock in GlaxoSmithKline (GSK). JAH reports personal fees from GSK Peru and Pharmaceutical Product Development (PPD) during the conduct of the study and personal fees from PPD outside of the submitted work. MHL reports grants from GSK during the conduct of the study and grants from GSK, Merck, AbbVie, and Gador outside of the submitted work. PC reports grants from the National Institute of Allergy and Infectious Diseases, GSK, Gilead, and Merck Sharp & Dohme. JH is an employee of and owns stock in GSK. All other authors declare no competing interests.

Data sharing

For **individual participant data and study documents** see https://www.clinicalstudydatarequest.com/

Anonymised individual participant data and study documents can be requested for further research from ClinicalStudyDataRequest.com.

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