Integrase versus protease inhibitor therapy in advanced HIV disease (LAPTOP): a multicountry, randomised, open-label, non-inferiority trial

*Georg M N Behrens, Lambert Assoumou, Geoffroy Liegeon, Andrea Antinori, Rafael Micán, Francesco G Genderini, Frank A Post, Jürgen K Rockstroh, Lisa Hamzah, Pere Domingo, Adrian Curran, Monserrat Laguno, Carl Fletcher, Jack Moody, Anton Pozniak, on behalf of the NEAT-ID Foundation and LAPTOP Study Team**

Summary

Background To date, clinical trials have been underpowered to assess which antiretrovirals perform best in people with advanced HIV disease. We aimed to investigate the efficacy and safety of an integrase inhibitor-containing versus a boosted protease inhibitor-containing regimen for this population.

Methods In this open-label, multicentre, non-inferiority trial in seven European countries (Spain, France, Italy, Germany, Belgium, Ireland, and the UK), therapy-naive adults with advanced HIV disease were randomly allocated (1:1) to receive either bictegravir, emtricitabine, and tenofovir alafenamide (integrase inhibitor group) or darunavir, cobicistat, emtricitabine, and tenofovir alafenamide (boosted protease inhibitor group) for 48 weeks. Randomisation was computer generated in permuted blocks within strata with block sizes of four and stratified by country and baseline CD4 cell count. The primary composite outcome (time to first occurrence of specified virological or clinical events) and its components were evaluated by Kaplan–Meier and Cox regression analyses in both modified intention-to-treat (mITT) and per-protocol populations. The mITT population included all randomly allocated participants who received at least one dose of the study drug, whereas the per-protocol population excluded those who received incorrect treatment. Non-inferiority of the integrase inhibitor-based regimen versus the boosted protease inhibitor-containing regimen was declared if the upper limit of the 95% CI of the hazard ratio (HR) for the primary composite endpoint was less than 1·606, corresponding to a 12% difference in the cumulative probability of the composite primary endpoint. Adverse events, a secondary endpoint, were recorded at eight visits in all participants. This trial is registered with ClinicalTrials.gov, NCT03696160, and is completed.

Findings Between May 13, 2019, and June 26, 2023, 222 people were randomly assigned to the integrase inhibitor group and 225 to the boosted protease inhibitor group. Of these 447 recruited participants, 442 (99%) participants with a median CD4 count of 41 cells per µL (IQR 17–79) received at least one dose. 358 (81%) of the 442 treated participants self-reported as male and 84 (19%) female, and 276 (62%) were of White ethnicity, 83 (19%) Black, and 83 (19%) other. In the mITT analysis, the 48-week composite primary outcome event occurred in 49 (22%) of 220 participants in the integrase inhibitor group versus 70 (32%) of 222 participants in the boosted protease inhibitor group (adjusted HR 0·70 [95% CI 0·48–1·00]; non-inferiority shown). The per-protocol analysis gave a similar estimated adjusted HR of 0·69 (0·48–1·00; non-inferiority shown). By mITT, drug-related adverse events (grade ≥2) occurred in 16 (7%) of 220 participants in the integrase inhibitor group versus 32 (14%) of 222 in the boosted protease inhibitor group (p=0·043). The rates of serious adverse events or adverse events leading to study discontinuation did not differ between groups. 12 deaths occurred during the study (nine in the integrase inhibitor group and three in the boosted protease inhibitor group), not related to the study drugs.

Interpretation In people with advanced HIV disease, bictegravir, emtricitabine, and tenofovir alafenamide was shown to be non-inferior to darunavir, cobicistat, emtricitabine, and tenofovir alafenamide and resulted in fewer adverse events, supporting its use as a preferred first-line antiretroviral regimen in this vulnerable population.

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Introduction

In 2023, an estimated 39·9 million people were living with HIV.[1] Late presentation (defined as CD4 count of less than 350 cells per µL) and advanced HIV disease (CD4 count <200 cells per µL or AIDS-defining illness at presentation), terms originally developed to improve surveillance and satisfy public health needs,[2] remain common, with late presentation affecting approximately 50% and advanced HIV disease approximately 30% of individuals diagnosed with HIV globally.[3–6] These late presentations, referred to hereon as people with advanced HIV disease, are linked to markedly higher mortality, increased health-care burdens,

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*Members listed at the end of the Article

Department of Rheumatology and Immunology, Hannover Medical School, Hanover, Germany (Prof G M N Behrens MD); **Centre for Individualized Infection Medicine, HZI–Hannover Medical School, Hanover, Germany** (Prof G M N Behrens); **German Centre for Infection Research Partner Site Hannover–Braunschweig, Hanover, Germany** (Prof G M N Behrens); **Sorbonne University, Inserm, Pierre Louis Institute of Epidemiology and Public Health, Paris, France** (Prof L Assoumou PhD); **Paris Cité University and Sorbonne University, Paris, France** (G Liegeon MD); **Department of Infectious and Tropical Diseases, Saint-Louis and Lariboisière Hospital, Paris, France** (G Liegeon); **Clinical and Research Department, IRCCS Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, Italy** (Prof A Antinori PhD); **Infectious Diseases Unit, La Paz University Hospital, Madrid, Spain** (R Micán MD); **Infectious Diseases Department, Saint-Pierre University Hospital, Brussels, Belgium** (F G Genderini MD); **Department of Sexual Health and HIV, Kings College Hospital NHS Foundation Trust, London, UK** (Prof F A Post PhD); **Department of Internal Medicine, University Hospital Bonn, Bonn, Germany** (Prof J K Rockstroh MD); **Department of Clinical Infection, St George's Hospital, London, UK** (L Hamzah PhD); **Infectious Diseases Unit, Hospital de la Santa Creu i Sant**

Pau, Barcelona, Spain (P Domingo PhD); **Department of Infectious Diseases, Vall d'Hebron University Hospital, Barcelona, Spain** (A Curran PhD); **Infectious Diseases Service, Hospital Clinic de Barcelona, Barcelona, Spain** (M Laguno PhD); **Research Organisation (KC), London, UK** (C Fletcher BSc, J Moody BSc); **Chelsea and Westminster Hospital, London, UK** (Prof A Pozniak MD); **London School of Hygiene & Tropical Medicine, London, UK** (Prof A Pozniak)

Correspondence to: Georg M N Behrens, Department of Rheumatology and Immunology, Hannover Medical School, Hanover 30625, Germany
behrens.georg@mh-hannover.de

Research in context

Evidence before this study

Approximately 50% of people with HIV are diagnosed late (CD4 count <350 cells per µL) and 30% are diagnosed with advanced HIV disease (CD4 count <200 cells per µL). Advanced HIV disease is associated with higher mortality and increased health-care burden. Pivotal randomised trials of first-line antiretroviral therapy have included only small proportions of people with HIV and CD4 counts less than 200 cells per µL, skewing efficacy data towards healthier populations. Previous trials have shown beneficial effects of early antiretroviral therapy initiation, whereas intensification with additional agents has shown no benefit. We searched PubMed for articles published from database inception to July 15, 2025, with no language restrictions and the terms "advanced HIV disease" OR "late presenter" AND "randomized trial" OR "CD4 <200" AND "trial". We identified one randomised comparative trial on first-line triple antiretroviral therapy, which was prematurely stopped due to incomplete enrolment. Evidence on which antiretrovirals perform best in people with advanced HIV disease remains largely retrospective and based on cohort studies.

Added value of this study

This large, prospective, randomised comparison of an integrase inhibitor-based regimen (bictegravir, emtricitabine, and tenofovir alafenamide) versus a boosted protease inhibitor-based regimen (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide) in treatment-naive adults with advanced HIV disease shows non-inferiority of the bictegravir-containing regimen, with superior virological efficacy and fewer adverse events. This trial is the first to directly compare first-line triple antiretroviral therapy regimens specifically in people with advanced HIV disease with respect to virological efficacy, immune recovery, and adverse events. The key strengths of the trial include the sufficient statistical power and inclusion of people with advanced HIV disease from 56 sites in seven European countries, enhancing generalisability. Despite a high risk for disease progression, we observed no significant differences between groups for AIDS-defining events, serious non-AIDS-defining events, or deaths related to HIV, AIDS-related illness, opportunistic infections, or bacterial infections. This finding highlights the value of rigorous clinical endpoint assessment, which is typically absent in retrospective studies.

Implications of all the available evidence

This trial supports high genetic resistance barrier integrase inhibitor-based regimens as the preferred first-line therapy in advanced HIV disease, consistent with global antiretroviral therapy trends. Taken together with previous data, the study provides high-level evidence on antiretroviral performance in people with advanced HIV disease and adds substantially to findings from previous observational or uncontrolled studies. Although we compared two single-tablet regimens with identical reverse transcriptase inhibitor backbones, our results are probably relevant to other first-line, triple-drug regimens containing dolutegravir in people with advanced HIV disease and could potentially inform global treatment guidelines for this vulnerable population.

and poorer long-term prognosis,[7] prompting calls to treat advanced HIV as a neglected condition.[8]

Only a small fraction (circa 10%) of participants in pivotal randomised trials for current first-line antiretroviral treatments had CD4 counts lower than 200 cells per µL,[9–11] skewing efficacy data towards healthier populations and better outcomes. To date, no large randomised controlled trial has compared first-line antiretroviral therapy regimens specifically in people with advanced HIV disease for non-inferiority, virological efficacy, immune recovery, or adverse events.[12–14] Previous trials have shown beneficial effects of early antiretroviral therapy initiation,[15–17] whereas intensification with additional agents showed no benefit.[18,19] Regimens with rilpivirine or dual therapies have low efficacy in advanced disease and are not recommended by the European AIDS Clinical Society or US Department of Health and Human Services guidelines.[20]

For the **European AIDS Clinical Society 2025 guidelines** see https://eacs.sanfordguide.com/

A boosted protease inhibitor-based regimen is an option with a high genetic barrier to resistance development for treatment of advanced HIV disease, especially when genotypic testing is unavailable. Currently, integrase inhibitors with a high genetic barrier to resistance, a favourable safety profile, and rapid viral suppression are a preferred option. However, evidence from advanced HIV populations remains mostly retrospective.[21–25] We conducted a prospective comparison of an integrase inhibitor-based regimen (bictegravir, emtricitabine, and tenofovir alafenamide once daily) versus a boosted protease inhibitor-containing regimen (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide once daily) in treatment-naive adults with advanced HIV disease. The primary objective was to show the non-inferiority of the integrase inhibitor-based regimen versus the boosted protease inhibitor-containing regimen in this population. Secondary objectives were to investigate the immunological and virological response, tolerability, resistance development, discontinuation of therapy due to tolerability, quality of life, and immune reconstitution inflammatory syndrome (IRIS) incidence.

Methods

Study design and participants

The Late Presenter Treatment Optimisation (LAPTOP) study was an investigator-initiated, open-label, randomised, multicentre, non-inferiority trial at 56 sites within the NEAT ID Network in seven countries (Spain, France, Italy, Germany, Belgium, Ireland, and the UK). Eligible

participants were self-reported as antiretroviral therapy naive, were aged 18 years and older, and had documented, untreated HIV-1 infection with either: AIDS-defining illness[26] at any CD4 cell count; a severe bacterial infection with a CD4 count less than 200 cells per µL within 28 days before study entry; a CD4 count less than 100 cells per µL within 28 days before study entry; or current treatment for opportunistic infections. Study participants needed to have an entry HIV viral load of more than 1000 copies per mL and the ability to take oral medications. Exclusion criteria were defined as: any therapeutic antiretroviral that was commenced less than 2 weeks before screening and that was taken for more than 48 h; systemic cancer chemotherapy within 30 days before study entry, or current treatment for cancer (with the exception of Kaposi's sarcoma or lymphoma); current or anticipated use of contraindicated medications or anticipated systemic chemotherapy during study enrolment; known resistance to the components of study medications; history or symptoms of advanced renal or hepatic impairment; current drug or alcohol use that, in the opinion of the investigator, would cause interference with the study; cryptococcal meningitis or active tuberculosis or current or expected treatment requiring rifampicin or rifabutin; history or presence of allergy to the study drugs or their components, or drugs of their class; using any concomitant therapy that was disallowed as per the product labelling for the study drugs; any investigational drug within 30 days before study drug administration; severe (Child–Pugh class C) hepatic impairment; and women who were pregnant, breastfeeding, or planned to become pregnant or breastfeed during the study (appendix p 5).

The trial was conducted in accordance with Good Clinical Practice and the ethical principles of the Declaration of Helsinki. The trial protocol was reviewed and approved by national, regional, and investigational site ethics committees (UK—West Midlands Edgbaston Research Ethics Committee, 18/WM/0352; Spain—Comite de Etica de la Investigacion con Medicamentos del Hospital Universitario La Paz, 5307; France—Comité de Protection des Personnes SUD-EST II, 2019–38, 19.04.01.62440; Belgium—Centrale Ethische Commissie Universitair Ziekenhuis Antwerpen, 19/27/32; Italy—Comitato Etico Dell'Istituto Nazionale per le Malattie Infettive "Lazzaro Spallanzani" IRCCS, 197; Germany—Medizinische Hochschule Hannover Ethikkommission, 8448_AMG_2019; Ireland—Mater Misericordiae University Hospital Institutional Review Board, 1/478/87), and all participants provided written informed consent. This trial is registered at ClincalTrials.gov, NCT03696160.

Randomisation and masking

Participants were randomly allocated (1:1) to the bictegravir, emtricitabine, and tenofovir alafenamide group (integrase inhibitor group) or to the darunavir, cobicistat, emtricitabine, and tenofovir alafenamide group (boosted protease inhibitor group). Randomisation was computer generated in permuted blocks within strata with block sizes of four and stratified by country and baseline CD4 cell count (<50, 50–199, or ≥200 cells per µL). The randomisation list was generated by an independent statistician who was not part of the study team. Randomisation was done at the baseline visit (date of study treatment initiation). This study was open label; therefore, all investigators, site pharmacists, study nurses, and participants were unmasked and aware of the treatment allocation throughout the study.

Procedures

Participants in the integrase inhibitor group received one combined bictegravir 50 mg plus emtricitabine 200 mg plus tenofovir alafenamide 25 mg tablet taken orally once daily for up to 48 weeks. Participants in the boosted protease inhibitor group received one combined darunavir 800 mg plus cobicistat 150 mg plus emtricitabine 200 mg plus tenofovir alafenamide 10 mg tablet taken orally once daily for up to 48 weeks. Participants were assessed at screening, baseline, and weeks 4, 8, 12, 24, 36, and 48, and at a follow-up visit 30 days following the week 48 visit. At screening, participants underwent laboratory assessments, including viral load testing and resistance testing (the result of the last resistance test carried out before giving written informed consent could be used, if applicable, to avoid repetitive resistance testing in individuals who were therapy naive). Resistance mutation results were not required to be available before the start of therapy. Routine investigations at baseline and treatment visits included HIV-1 RNA testing, CD4 cell counts, CD8 cell counts, haematology tests (including haemoglobin, white blood cell with differential, and platelet counts), biochemistry tests (including sodium, potassium, creatinine, phosphorus, albumin, glucose, alanine transaminase, aspartate aminotransferase, alkaline phosphatase, total and indirect bilirubin, total cholesterol, HDL and LDL, and triglyceride measurements), a quality-of-life questionnaire (EuroQoL EQ-5D-3L), the HIV Symptom Index–Symptom Distress Module, urine sample testing (for haematuria, proteinuria, glycosuria, leukocytes, nitrites, and pregnancy testing in women of child-bearing potential), and assessment for adverse events. Adherence during the trial was monitored by participant questioning regarding missed tablets at the week 12, 24, 36, and 48 visits. Participants were free to withdraw from the study at any time. In addition, the investigator could decide, for reasons of medical prudence, to stop the study medication (eg, due to low efficacy). Participants who discontinued study medication were followed up at an early termination visit and encouraged to attend study visits up until week 48 to continue follow-up despite discontinuing. More details are provided in the study protocol (appendix pp 133–219).

See Online for appendix

Outcomes

The primary outcome was the first occurrence of the composite primary endpoint, comprised of virological

failure or clinically relevant adverse outcomes. Virological failure was defined as an insufficient virological response (defined as either an HIV-1 RNA reduction of less than 1 log_{10} copies per mL at week 12 or a viral load of more than 50 HIV-1 RNA copies per mL at week 48) or viral rebound (defined as a rebound of HIV-1 RNA viral load to >200 copies per mL after having reached HIV-1 RNA viral load <50 copies per mL, or a rebound of HIV RNA viral load by >1 log_{10} copies per mL from the nadir value for participants whose viral load had never been suppressed below 50 copies per mL). Clinically relevant adverse outcomes were death related to HIV, AIDS-defining illness, opportunistic infection or severe bacterial infection, or complications of therapy including IRIS; any new or recurrent AIDS-defining event on or after 28 days of therapy; any new serious non-AIDS-defining event documented by the endpoint review committee (including severe bacterial infection, end-stage liver disease, renal failure, cardiovascular event, and malignant disease not related to AIDS-defining illness); or clinically relevant adverse events of any grade or IRIS that required treatment interruption (lasting >5 days) of integrase inhibitor or boosted protease inhibitor therapy within the first 48 weeks after randomisation. We considered clinical endpoints only if confirmed by an independent clinical endpoint review committee. A data safety monitoring board regularly monitored the main safety and efficacy outcome measures and the overall conduct of the trial.

Secondary outcomes were cumulative incidence of the composite primary endpoint at week 48; proportion of participants with HIV-RNA viral load of less than 50 copies per mL at weeks 24, 36, and 48; HIV-1 drug resistance at confirmed virological failure; time to reach a CD4 count of more than 200 per µL (first measurement); proportion of participants with CD4 cell counts less than 200 µL and less than 350 µL at weeks 4, 8, 12, 24, 36, and 48; CD4:CD8 ratio at weeks 4, 8, 12, 24, 36, and 48; incidence of IRIS in the two groups up to week 48; incidence and duration of hospitalisation or rate of relapse of specific opportunistic infection or bacterial infection up to week 48; number and proportion of participants with grade 2, 3, and 4 adverse events, treatment-related adverse events, adverse events leading to study drug discontinuation, and death up to week 48; antiretroviral therapy and opportunistic or bacterial infection treatment changes and dose modifications due to toxicities and drug–drug interactions with antiretroviral therapy, and IRIS up to week 48; health-care resource use, including total inpatient days and emergency room visits up to week 48; quality of life and functional status outcomes, including participant-reported outcomes (the HIV Symptom Index and EuroQol EQ-5D-3L) from baseline to week 48; and discontinuation or modification of study medication due to insufficient virological response, resistance mutations at baseline, or resistance mutation development before week 48.

Statistical analysis

In the ANRS 146 OPTIMAL trial,[19] 12·2% of people with advanced HIV disease in the boosted protease inhibitor group experienced severe morbidity annually, including new adverse events, HIV-related conditions, serious non-AIDS-defining events, IRIS, or death. Similarly, in the IMEA 040 DATA study, virological failure at week 48 was observed in 20% of individuals receiving darunavir and ritonavir.[14,19] Accounting for participants meeting multiple endpoints, we assumed that 25% of participants would meet the composite primary endpoint at week 48 in the boosted protease inhibitor group and 23% in the integrase inhibitor group. These assumptions were derived from the hypothesis that the integrase inhibitor-based regimen would be non-inferior to the boosted protease inhibitor-based regimen, with a potential for slight improvement. A total of 404 individuals (202 per group) would provide at least 80% power to detect a non-inferiority margin of 1·606 in the hazard ratio (HR), corresponding to a 12% difference in the cumulative probability of failure rate, with a two-tailed α of 0·05. The group size was increased to 220 per group to account for potential loss to follow-up.

Baseline characteristics were summarised for the overall cohort and by treatment group, using median (IQR) or mean (SD) for continuous variables and frequencies with percentages for categorical variables. Subgroup analyses (modified intention-to-treat [mITT] population) assessed the consistency of treatment effects across demographic and clinical variables (eg, age, smoking status, and CD4 cell count), using unadjusted Cox models with interaction terms to evaluate heterogeneity. In addition, additive interaction was assessed by calculating the relative excess risk due to interaction along with its 95% CI, which was estimated using bootstrap resampling. Due to low enrolment from Ireland, data from the UK and Ireland were analysed as a combined group.

Primary endpoint analyses were conducted using both mITT and per-protocol populations. The mITT population included all randomly allocated participants who received at least one dose of the study drug, whereas the per-protocol population excluded those who received incorrect treatment since baseline and censored data after treatment discontinuation. Kaplan–Meier analysis was used to estimate the probability of reaching the primary composite endpoint (virological or clinical event) at week 48. Between-group comparisons were made using a Cox proportional hazards model adjusted for stratification factors (country or region and baseline CD4 count <50 cells per µL or ≥50 cells per µL). The proportional hazards assumption was assessed using both graphical methods (specifically Schoenfeld residual plots) and a formal statistical test based on these residuals. Non-inferiority of the integrase inhibitor-based regimen to the boosted protease inhibitor-containing regimen was concluded if the upper bound of the 95% CI of the adjusted HR was less

than 1·606 in both mITT and per-protocol analyses. A secondary superiority analysis of the integrase-based regimen was also planned to detect a 50% reduction in HR (ie, HR 0·5) after non-inferiority had been established and would test the null hypothesis (HR=1·0) against a two-sided alternative (HR≠1·0).

Secondary outcomes were analysed in the mITT population. Two-sided p values less than 0·05 were considered statistically significant. Viral suppression (<50 copies per mL) at week 48 was assessed using the US Food and Drug Administration Snapshot algorithm and compared between groups via a modified Poisson regression model for binary outcome with robust SEs adjusted for stratification factors. We carried out post-hoc subgroup analyses in the mITT population to assess the consistency of virological success rates across key baseline characteristics: the presence or absence of resistance mutations, CD4 count (<50 *vs* ≥50 cells per µL), and viral load (<100 000, 100 000–500 000, or >500 000 copies per mL). CD4 count trajectories (<200 cells per µL and <350 cells per µL) were analysed over time using generalised estimating equations. An independent covariance structure, binomial distribution, log link function, and cluster-robust standard errors were specified to estimate the relative risk (RR). The models included treatment group, time (modelled as a categorical variable), and the interaction between treatment group and time. Time to a CD4 count of more than 200 cells per µL was assessed using Kaplan–Meier analysis and Cox models. The event time was assigned to the visit date when a CD4 count of more than 200 cells per µL was first recorded. We conducted a sensitivity analysis using an interval-censored method to account for the exact event time occurring between study visits. Changes in continuous outcomes from baseline to week 48 were analysed using mixed-effects models, and changes in binary outcomes were analysed using generalised estimating equations. Adverse events (grade ≥2), serious adverse events, adverse events leading to treatment discontinuations, drug-related adverse events, drug-related adverse events leading to treatment discontinuation, and deaths were summarised as frequencies and incidence rates per 100 person-years. Group comparisons were made using Poisson regression models, with negative binomial regression used in cases of substantial overdispersion. IRIS events and hospitalisations were evaluated using Kaplan–Meier analysis and Cox models. Health-care use and emergency department visits were compared using logistic regression, adjusted for stratification factors. Handling of missing data is described in the appendix (p 6). Analyses were done using IBM SPSS Statistics software (version 28) and SAS software (version 9.4).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 13, 2019, and June 26, 2023, 475 individuals were screened for eligibility, of whom 447 (94%) were randomly assigned to a treatment group. The per-protocol analysis set included 441 participants (219 in the integrase inhibitor group and 222 in the boosted protease

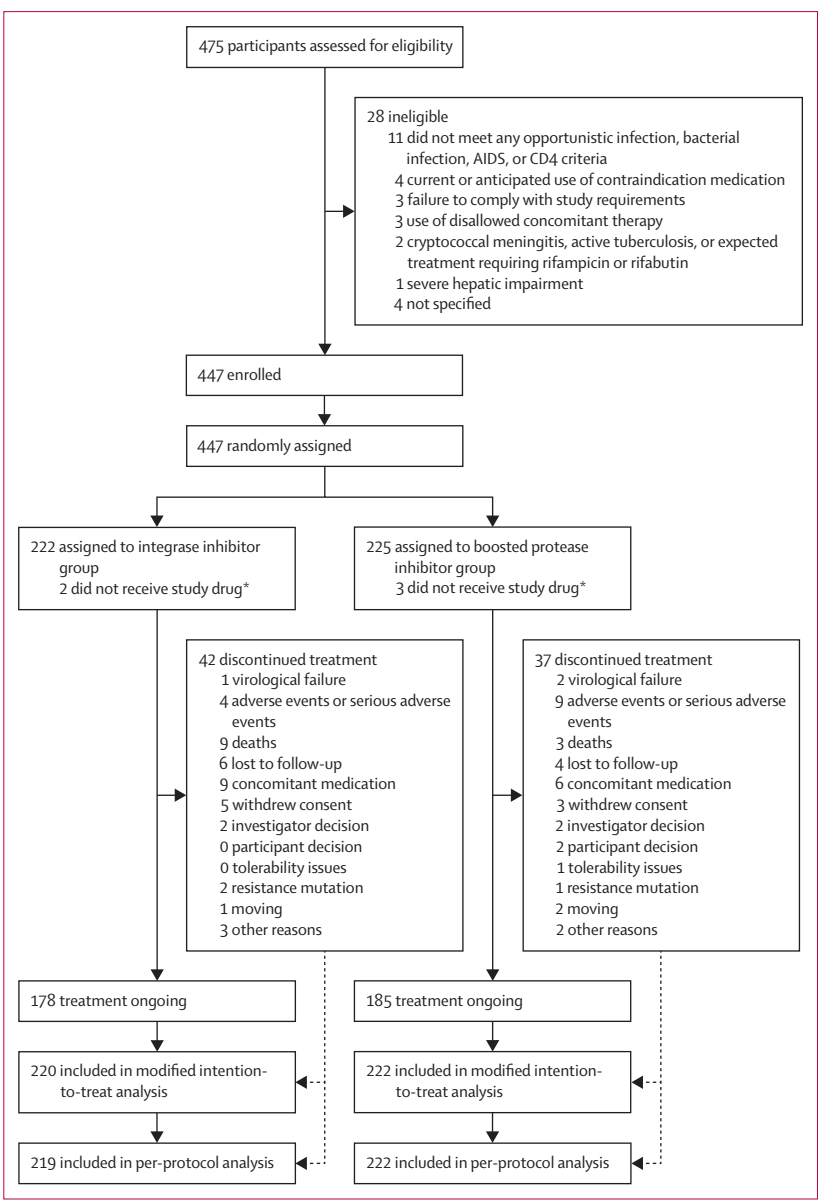

Figure 1: **Trial profile**

One participant in the integrase inhibitor group did not receive the correct treatment since baseline, discontinued the study on day 58, and was therefore excluded from the per-protocol analysis. For all other participants who discontinued the study, data were censored at the time of discontinuation for the per-protocol analysis. One participant in each group discontinued antiretroviral therapy due to resistance testing results potentially compromising nucleoside reverse transcriptase inhibitors, which became available after randomisation, but remained in the study and was included in the modified intention-to-treat analysis. One participant in the integrase inhibitor group without baseline resistance mutations against the assigned antiretroviral therapy changed therapy and discontinued the study because of detection of resistance mutations against nucleoside reverse transcriptase inhibitors and integrase inhibitors at week 8 without protocol-defined virological failure. *These participants were excluded from the modified intention-to-treat population.

inhibitor group). Two of 222 participants randomly assigned to the integrase inhibitor group and three of 225 randomly assigned to the boosted protease inhibitor group did not receive the study drug, resulting in an mITT analysis set of 442 participants. 178 (81%) of 222 participants in the integrase inhibitor group and 185 (83%) of 225 participants in the boosted protease inhibitor group continued treatment at week 48 (figure 1).

The 442 participants in the mITT population were well matched for baseline characteristics with a median age of 43 years (IQR 35–53), sex self-reported as 358 (81%) male and 84 (19%) female, and 276 (62%) of White ethnicity (table 1). At enrolment, 379 (86%) participants had a CD4 count of fewer than 100 cells per µL and 197 (45%) had a viral load of more than 500 000 HIV-1 RNA copies per mL. 27 (6%) participants had high-level or intermediate-level resistance to antiretrovirals at baseline, primarily to non-nucleoside reverse transcriptase inhibitors (appendix p 8). Three participants had an M184V mutation conferring high-level resistance to emtricitabine and none had a

	Integrase inhibitor group (n=220)	Boosted protease inhibitor group (n=222)
Age, years		
Median	44 (36–54)	42 (34–51)
Mean	45 (12)	43 (11)
Sex		
Male	180 (82%)	178 (80%)
Female	40 (18%)	44 (20%)
Child-bearing potential	19/40 (48%)	31/44 (71%)
Ethnicity		
White	140 (64%)	136 (61%)
Black	43 (20%)	40 (18%)
Other	37 (17%)	46 (21%)
Participating countries		
UK	45 (20%)	42 (19%)
Spain	61 (28%)	61 (27%)
France	30 (14%)	32 (14%)
Belgium	17 (8%)	17 (8%)
Italy	28 (13%)	30 (14%)
Germany	37 (17%)	38 (17%)
Ireland	2 (1%)	2 (1%)
BMI, kg/m²*		
Median	22·3 (19·8–24·3)	22·2 (19·9–24·8)
Mean	22·5 (3·9)	22·4 (3·9)
Weight, kg†		
Median	66·8 (59·5–75·0)	68·3 (57·1–75·4)
Mean	67·6 (12·7)	67·1 (13·0)
Alcohol intake, yes	81 (37%)	77 (35%)
Smoking status		
Never smoked	117 (53%)	113 (51%)
Current smoker	59 (27%)	69 (31%)
Ex-smoker	43 (20%)	40 (18%)
Unknown	1 (<1%)	0
Recreational drug use	22 (10%)	21 (9%)
Positive hepatitis B surface antigen	8 (4%)	10 (5%)
Positive hepatitis C virus antibody	10 (5%)	8 (4%)
Positive tuberculosis interferon-γ release assay result	0	1 (<1%)
AIDS-defining event	130 (59%)	129 (58%)
Severe bacterial infection	18 (8%)	12 (5%)
Currently treated opportunistic infection	39 (18%)	31 (14%)
Time from HIV diagnosis to treatment initiation, days‡	19 (12–30)	17 (13–29)
(Continued from previous column)		
HIV RNA, log_{10} copies per mL		
Median	5·6 (5·2–6·0)	5·6 (5·2–6·0)
Mean	5·6 (0·7)	5·6 (0·6)
<100 000	37 (17%)	41 (18%)
100 000–500 000	89 (40%)	78 (35%)
>500 000	94 (43%)	103 (46%)
CD4 count, cells per µL		
Median	41 (16–81)	41 (19–78)
Mean	57·8 (58·5)	57·6 (60·7)
<50	127 (58%)	127 (57%)
50–99	60 (27%)	65 (29%)
100–199	27 (12%)	24 (11%)
≥200	6 (3%)	6 (3%)
CD4, %§		
Median	4·9% (2·1–8·6)	5·0% (2·6–8·1)
Mean	6·1% (4·8)	6·5% (7·0)
CD8 count, cells per µL¶		
Median	440 (306–779)	490 (281–710)
Mean	652 (663)	567 (433)
CD8, %‖		
Median	66·1% (55·5–74·8)	63·8% (53·2–72·3)
Mean	63·4% (15·1)	62·3% (13·7)
CD4:CD8 ratio¶		
Median	0·1 (0–0·1)	0·1 (0–0·1)
Mean	0·5 (5·1)	0·6 (4·3)
High-level or intermediate resistance to antiretrovirals	15/205 (7%)	12/214 (6%)

(Table 1 continues in next column)

Data are median (IQR), mean (SD), n (%), or n/N (%). *n=216 in the integrase inhibitor group and 222 in the boosted protease inhibitor group. †n=218 in the integrase inhibitor group and 222 in the boosted protease inhibitor group. ‡n=208 in the integrase inhibitor group and 210 in the boosted protease inhibitor group. §n=219 in the integrase inhibitor group and 222 in the boosted protease inhibitor group. ¶n=217 in the integrase inhibitor group and 221 in the boosted protease inhibitor group. ‖n=212 in the integrase inhibitor group and 216 in the boosted protease inhibitor group.

Table 1: **Baseline characteristics of the study population**

high-level resistance mutation against darunavir or bictegravir. Resistance mutation data, which became available after randomisation, prompted change of the assigned HIV therapy in one participant in each group.

In mITT analyses, the primary composite outcome event occurred in 49 (22%) of 220 participants in the integrase inhibitor group versus 70 (32%) of 222 participants in the boosted protease inhibitor group by week 48 (adjusted HR [aHR] 0·70 [95% CI 0·48–1·00]; p=0·052, non-inferiority shown; table 2, figure 2A). Non-inferiority was concluded on the basis of the upper bound of the 95% CI (1·00) lying below the predefined margin of 1·606. The p value of 0·052 is related to the secondary superiority analysis. The per-protocol analysis gave a similar estimated aHR of 0·69 (0·48–1·00) and treatment effects did not vary significantly between subgroups of trial participants (appendix p 9). The analysis of additive interaction showed similar results (appendix p 10). The Kaplan–Meier estimate for virological failure due to insufficient virological response was significantly lower in the integrase inhibitor versus boosted protease inhibitor group (HR 0·53 [95% CI 0·32–0·88]; p=0·014); however, viral rebound and other clinical outcomes were similar between groups (table 2, appendix pp 27–32). No resistance mutation development was reported in people with protocol-defined virological failure.

Participants in the integrase inhibitor group were more likely to reach an HIV viral load of less than 50 copies per mL at week 4 (35 [16%] of 220 *vs* three [1%] of 222; adjusted RR [aRR] 11·64 [95% CI 3·63–37·28], p<0·0001), week 8 (76 [35%] *vs* 16 [7%]; aRR 4·79 [2·91–7·89], p<0·0001), and week 12 (101 [46%] *vs* 38 [17%]; aRR 2·67 [1·94–3·68], p<0·0001) than those in the boosted protease inhibitor treatment group (appendix p 11). Figure 2B shows virological outcomes at week 48, where 151 (69%) in the integrase inhibitor group versus 136 (61%) in the boosted protease inhibitor group had an HIV-RNA viral load of less than 50 copies per mL. Among the 27 participants with high-level or intermediate-level resistance mutations to antiretroviral drugs detected at baseline, three had viral loads of more than 50 copies per mL at week 48. Most individuals with detectable HIV-RNA had viral loads of 200 copies per mL or less, and the evolution of HIV-RNA in all participants with detectable HIV-RNA at week 48 is shown in the appendix (p 32).

The proportion of people with CD4 counts of fewer than 200 cells per µL decreased from 211 (96%) of 220 to 64 (36%) of 179 in the integrase inhibitor group (risk ratio 0·37 [95% CI 0·31–0·45]) and from 214 (96%) of 222 to 65 (35%) of 186 in the boosted protease inhibitor group (risk ratio 0·37 [0·30–0·44]) between baseline and week 48 (p=0·90; appendix p 12). Among those people with CD4 counts of 200 cells per µL or lower at baseline, the proportion who reached a CD4 count of more than 200 cells per µL did not differ between the integrase

	Modified intention-to-treat analysis				Per-protocol analysis			
	Integrase inhibitor group (n=220)	Boosted protease inhibitor group (n=222)	aHR	p value	Integrase inhibitor group (n=219)	Boosted protease inhibitor group (n=222)	aHR	p value
Primary composite endpoint	49 (22%)	70 (32%)	0·70 (0·48–1·00)	0·052	48 (22%)	69 (31%)	0·69 (0·48–1·00)	0·051
Virological failure	25 (11%)	46 (21%)	0·54 (0·33–0·88)	0·013	25 (11%)	46 (21%)	0·54 (0·33–0·88)	0·013
Insufficient virological response*	23 (10%)	43 (19%)	0·53 (0·32–0·88)	0·014	23 (10%)	43 (19%)	0·53 (0·32–0·88)	0·014
Viral rebound†	2 (1%)	3 (1%)	0·69 (0·12–4·15)	0·69	2 (1%)	3 (1%)	0·69 (0·12–4·15)	0·69
Clinical events	25 (11%)	26 (12%)	0·99 (0·57–1·72)	0·97	24 (11%)	25 (11%)	0·99 (0·56–1·73)	0·97
Any new or recurrent AIDS-defining event on or after 28 days of therapy	7 (3%)	15 (7%)	0·48 (0·20–1·19)	0·11	7 (3%)	14 (6%)	0·52 (0·21–1·29)	0·16
Serious adverse events due to non-AIDS-defining events	11 (5%)	5 (2%)	2·32 (0·81–6·68)	0·12	10 (5%)	5 (2%)	2·09 (0·72–6·13)	0·18
Adverse events leading to antiretroviral therapy interruption‡	1 (<1%)	7 (3%)	0·15 (0·02–1·18)	0·071	1 (<1%)	7 (3%)	0·15 (0·02–1·19)	0·072
Death related to HIV, AIDS-defining conditions, opportunistic infection, or bacterial infection	7 (3%)	3 (1%)	2·41 (0·62–9·33)	0·20	7 (3%)	3 (1%)	2·42 (0·63–9·35)	0·20

Data are n (%), aHR (95% CI), or p value. *HIV-1 RNA reduction less than 1 log_{10} copies per mL at week 12 or viral load more than 50 HIV-1 RNA copies per mL at week 48. †Confirmed rebound of HIV-1 RNA to more than 200 copies per mL after having reached less than 50 copies per mL, or confirmed rebound of HIV RNA by more than 1 log_{10} copies per mL from the nadir value for participants whose viral load has never been suppressed below 50 copies per mL. ‡Antiretroviral therapy interruption for more than 5 days, if not continued by alternative integrase or protease inhibitor according to randomisation. aHR=adjusted hazard ratio.

Table 2: **Primary composite endpoint and its components**

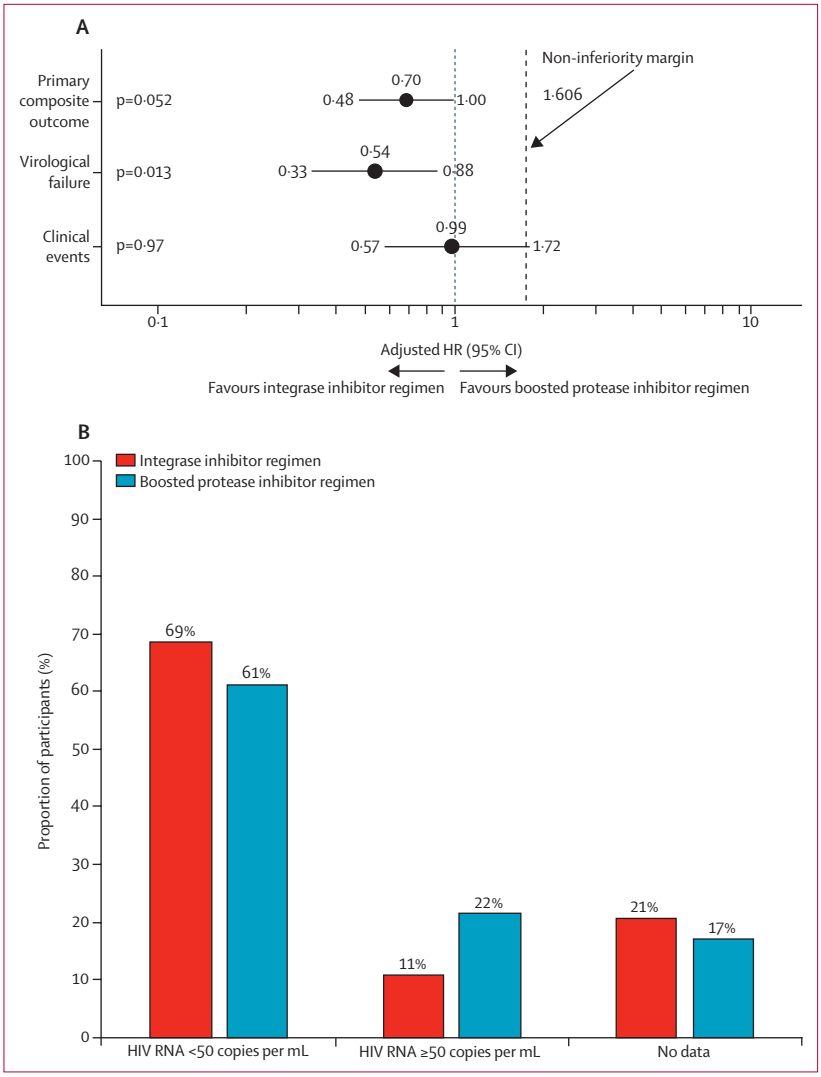

Figure 2: **Adjusted HRs for the primary composite outcome and its two main components (A) and virological outcomes at week 48 (B) in the modified intention-to-treat analysis set**
HR=hazard ratio.

inhibitor and boosted protease inhibitor groups (149 [70%] of 212 *vs* 142 [66%] of 215; aHR 1·12 [95% CI 0·89–1·41], p=0·34; appendix p 33). A sensitivity analysis using interval-censored data confirmed this result (aHR 1·12 [95% CI 0·89–1·42], p=0·33). At week 12, the risk ratio for remaining at a CD4 count of fewer than 350 cells per µL was significantly higher in the boosted protease inhibitor group than in the integrase inhibitor group (risk ratio 0·88 [95% CI 0·83–0·93] *vs* 0·94 [95% CI 0·91–0·98], p=0·041; appendix p 12; for more secondary outcomes see appendix pp 13–14).

The mean CD4 count increased by 216 cells per µL (SE 9·1) from 63 cells per µL (9·2) to 279 cells per µL (9·8) in the integrase inhibitor group and by 194 cells per µL (9·0) from 62 cells per µL (9·2) to 256 cells per µL (9·6) in the boosted protease inhibitor group between baseline and week 48 (appendix p 34); no significant difference in CD4 cell counts was noted between treatment groups (p=0·085). Bodyweight increased by a mean 10·9 kg from a mean 67·4 kg (SD 12·8) with no differences between the two groups (appendix p 15).

In total, by mITT, 435 adverse events of grade 2 or higher occurred in 124 participants in the integrase inhibitor group, and 548 adverse events occurred in 139 participants in the boosted protease inhibitor group (table 3). The incidence rate of any adverse events (grade ≥2) was 18% lower in the integrase inhibitor group (220·7 per 100 person-years) compared with the boosted protease inhibitor group (264·7 per 100 person-years; adjusted incidence rate ratio [aIRR] 0·82 [95% CI 0·73–0·93], p=0·0024). Drug-related adverse events (grade ≥2) occurred in 16 (7%) of 220 participants in the integrase inhibitor group versus 32 (14%) of 222 in the boosted protease inhibitor group, representing a 39% reduction in the integrase inhibitor group (aIRR 0·61 [0·38–0·98], p=0·043; mostly grade 2). The rates of serious adverse events or adverse events leading to study discontinuation did not differ between groups (12 [5%] participants in each group).

12 people died during the study period. The median time to death for the nine participants who died in the integrase inhibitor group was 29 days (IQR 20–44), and reported reasons for death included two IRIS, three respiratory failure (pneumocystis pneumonia and bacterial pneumonia), two cardiac arrest, one sepsis, and one distributive shock. The median time to death for the three participants who died in the boosted protease inhibitor group was 114 days (25–136), and reasons for death included two respiratory failure (mpox and pulmonary fibrosis) and one B-cell lymphoma. All deaths were considered unrelated to the study treatment.

Post-hoc analyses found that baseline resistance had no statistically significant effect on reaching an HIV RNA viral load of less than 50 copies per mL at week 48. Virological treatment responses in both groups at week 48 were similar when stratified by baseline CD4 cell counts or HIV RNA viral load (appendix p 26).

Discussion

In therapy-naive people with advanced HIV disease, the integrase inhibitor regimen was non-inferior to the boosted protease inhibitor regimen, had a 30% lower risk for the primary composite endpoint, had a better virological response at week 48, and had fewer overall adverse events. The risk reduction with the integrase inhibitor regimen did not reach the predefined 50% risk reduction for superiority, and the p value was not conventionally significant. This was the first large randomised controlled trial to adequately compare antiretroviral therapy strategies for this highly prevalent population.[4–5] The study provides high-level evidence and adds substantially to data from previous observational or uncontrolled studies. Studies found that early treatment

	Integrase inhibitor group (n=220, 197·2 person-years)			Boosted protease inhibitor group (n=222, 207·0 person-years)			Adjusted incidence rate ratio (95% CI)	p value
	Events, n	Participants, n (%)	Incidence rate per 100 person-years	Events, n	Participants, n (%)	Incidence rate per 100 person-years		
Any adverse events (grade ≥2)	435	124 (56%)	220·7	548	139 (63%)	264·7	0·82 (0·73–0·93)	0·0024
Grade 2	338	111 (50%)	171·5	442	127 (57%)	213·5	0·79 (0·69–0·91)	0·0013
Grade 3	68	37 (17%)	34·5	85	46 (21%)	41·1	0·83 (0·60–1·14)	0·26
Grade 4	29	18 (8%)	14·7	21	13 (6%)	10·1	1·42 (0·81–2·49)	0·22
Grade 3 or 4	97	47 (21%)	49·2	106	52 (23%)	51·2	0·95 (0·72–1·25)	0·71
Drug-related grade ≥2 adverse events	27	16 (7%)	13·7	45	32 (14%)	21·7	0·61 (0·38–0·98)	0·043
Drug-related grade 3–4 adverse events	5	3 (1%)	2·5	5	4 (2%)	2·4	0·99 (0·29–3·44)	0·99
DRESS syndrome (rash)	0	0	..	1	1 (<1%)	..	..	..
IRIS	0	0	..	3	2 (1%)	..	..	..
IRIS-Kaposi's sarcoma	1	1 (<1%)	..	0	0	..	..	..
PML-IRIS requiring hospitalisation	1	1 (<1%)	..	0	0	..	..	..
Progressive rash	0	0	..	1	1 (<1%)	..	..	..
Transaminitis	1	1 (<1%)	..	0	0	..	..	..
Worsening symptoms of PML	1	1 (<1%)	..	0	0	..	..	..
Alteration of general state	1	1 (<1%)	..	0	0	..	..	..
Adverse events leading to study discontinuation	25	16 (7%)	12·7	25	18 (8%)	12·1	1·03 (0·59–1·79)	0·92
Drug-related adverse events leading to study discontinuation	11	7 (3%)	5·6	15	11 (5%)	7·2	0·77 (0·32–1·79)	0·52
Serious adverse events	84	48 (22%)	42·6	85	52 (23%)	41·1	1·03 (0·77–1·40)	0·83
Death*	9	9 (4%)	4·6	3	3 (1%)	1·5	3·22 (0·87–11·9)	0·079

DRESS=drug reaction with eosinophilia and systemic symptoms. IRIS=immune reconstitution inflammatory syndrome. PML=progressive multifocal leukoencephalopathy. *Reasons for death included IRIS (n=2), respiratory failure (pneumocystis pneumonia, bacterial pneumonia, mpox, or pulmonary fibrosis; n=5), cardiac arrest (n=2), B-cell lymphoma (n=1), sepsis (n=1), and distributive shock (n=1).

Table 3: **Adverse events in the modified intention-to-treat analysis set**

in people with advanced HIV disease is preferred,[17] with some exceptions.[27,28] Enhanced prophylaxis plus antiviral therapy for advanced HIV in Africa has been shown to reduce mortality,[29] but strategies using therapy intensification with raltegravir or maraviroc have provided no benefit.[18,19]

Although smaller randomised trials with modest statistical power have investigated antiretroviral therapy in advanced HIV disease,[12–14] available data comparing high-resistance-barrier integrase and protease inhibitors come from retrospective studies. These studies suggest longer durability of integrase inhibitor-based regimens[23] and a 50% reduction in a composite endpoint of advanced complications of HIV, serious non-AIDS-defining events, virological failure, and treatment discontinuation.[24] Some data suggest that bictegravir, emtricitabine, and tenofovir alafenamide leads to more favourable outcomes than either boosted darunavir-containing or dolutegravir-containing regimens,[30] whereas others do not.[23] In line with our findings, studies of integrase inhibitors have shown earlier viral suppression and immune reconstitution.[21]

Although we compared two single-tablet regimens with identical reverse transcriptase inhibitor backbones, our results are likely to be relevant to other first-line triple-drug regimens containing dolutegravir in people with advanced HIV disease and could potentially inform global treatment guidelines. Despite a high risk for disease progression—259 (59%) of 442 participants had AIDS-defining conditions and 12 people died during the study—we observed no significant differences between the groups in terms of AIDS-defining events, serious non-AIDS-defining events, or deaths related to HIV, AIDS-related illness, opportunistic infection, or bacterial infections.[24,25] This finding highlights the value of rigorous clinical endpoint assessment, which is typically absent in retrospective studies. Although numbers of deaths were numerically higher in the integrase inhibitor group, causes of death mostly reflected fatal outcomes of clinical conditions often observed in advanced HIV disease.

Recently diagnosed people with advanced HIV disease are ideal candidates for rapid antiretroviral therapy initiation to improve opportunistic disease outcomes, restrict viral replication, and minimise immunodeficiency duration. Our protocol allowed rapid initiation without requiring resistance data at baseline. Concurrent to declining resistance in Europe,[31] resistance mutations at baseline were found in only 27 (6%) of 419 participants—mainly against non-nucleoside reverse transcriptase inhibitors—and just 17 (2%) had mutations against components of the trial regimens. Although resistance testing remains ideal, our data suggest that it might not be essential before starting antiretroviral therapy in people with advanced HIV disease and that high-barrier regimens (dolutegravir, bictegravir, or boosted darunavir) are appropriate when genotypic data are not available or delayed. No acquired resistance mutations in people with protocol-defined virological failure were detected during the trial, confirming the robustness of both regimens. Next-generation sequencing at failure and baseline is ongoing to validate this finding.

Treatment failure was primarily due to insufficient virological response at week 48. HIV-RNA viral loads of more than 50 copies per mL or more than 200 copies per mL were numerically more frequent in the boosted protease inhibitor group and remained detectable in many cases at follow-up. However, low-level viraemia at week 48 does not necessarily predict future rebound or resistance development on darunavir, cobicistat, emtricitabine, and tenofovir alafenamide. A longer follow-up might have reduced observed differences. Nonetheless, virological suppression rates of 50 copies per mL or less at week 48 (151 [69%] of 220 participants in the mITT population receiving the integrase inhibitor regimen *vs* 136 [61%] of 222 receiving the boosted protease inhibitor regimen) were markedly lower than in first-line trials in populations with less advanced HIV[10,32] or retrospective data for people with advanced HIV.[22] The high proportion of missing data at week 48 was mainly due to deaths and adverse event-related discontinuations. Differences in discontinuations have also been observed in trials of darunavir and dolutegravir in individuals with higher CD4 cell counts.[32] In our study, regimens were safe and well tolerated with high adherence. Moderate adverse events and drug-related events were less frequent in the integrase inhibitor group. The exclusion of participants with tuberculosis minimised rifampicin interactions with darunavir, cobicistat, emtricitabine, and tenofovir alafenamide and probably reduced drug-related discontinuations. The greater potential for clinically relevant drug interactions in the CYP3A inhibitor-containing treatment group was the reason for the open-label study design.

Weight gain in people with HIV is multifactorial. Greater increases have been observed with dolutegravir, bictegravir, and tenofovir alafenamide.[33] LAPTOP is the first direct comparison of a single-boosted protease inhibitor versus integrase inhibitor regimen with identical reverse transcriptase inhibitors, which do not attenuate weight gain. Baseline BMI was lower than in other trials,[10,11] but weight gain was more pronounced. Because advanced HIV is associated with weight loss, the gains observed are likely to reflect reversal of disease-associated wasting, reducing or masking any potential direct drug-specific effects in the short term. Alternatively, our study results question assumptions regarding an association between integrase inhibitors and excessive weight gain.[33]

Rapid viral decline with the integrase inhibitor-based regimen between weeks 4 and 12 could be clinically meaningful, potentially reducing complications and transmission, and accelerating immune recovery. This finding aligns with previous findings showing superior early virological responses of integrase inhibitors over protease inhibitors.[32] A Dutch study reported increased IRIS risk with integrase inhibitors in people with advanced HIV disease,[34] but no link to mortality or hospitalisation. A meta-analysis found no significant effect of dolutegravir on IRIS,[35] and randomised trials found no difference in IRIS incidence between regimens with and without integrase inhibitors in advanced HIV disease populations.[18] In our study, IRIS incidence was low (15 [3%] of 442 participants) and similar between groups. Excluding people with cryptococcal meningitis or tuberculosis—both known IRIS risk factors—is likely to have contributed to this finding. These results support current guidelines recommending immediate antiretroviral therapy in people with advanced HIV, regardless of regimen.[20]

A key strength of the LAPTOP trial is its inclusion of people with advanced HIV disease from 56 sites in seven European countries, enhancing generalisability. However, our results might not fully reflect populations in settings with different opportunistic disease burdens, and study enrolment was delayed due to the COVID-19 pandemic. Similar safety and discontinuation rates support feasibility of both regimens. Bictegravir, emtricitabine, and tenofovir alafenamide could offer practical advantages—once-daily dosing, fewer drug interactions, and food-independent administration—that improve early phase adherence. Limitations include: the open-label design, which might bias adverse event reporting, although objective endpoints were adjudicated; modest follow-up, restricting long-term conclusions; and exclusion of tuberculosis and cryptococcal meningitis cases, which restricts applicability in those groups. It is important to consider that bictegravir, emtricitabine, and tenofovir alafenamide is mainly used in high-income settings as a first-line option. Cost and access issues also restrict generalisability in resource-limited settings, although the study findings are likely to extend to dolutegravir-based regimens combined with tenofovir disoproxil fumarate and emtricitabine used in those regions.

In conclusion, the bictegravir regimen was non-inferior to the boosted darunavir regimen, with better week 48 virological outcomes and fewer adverse events in people

with advanced HIV disease. These findings support high-barrier integrase inhibitor-based regimens as preferred evidence-based first-line therapy in advanced HIV disease, in line with global antiretroviral therapy trends.

LAPTOP Study Team
Andrea Antinori, Cristina Gómez Ayerbe, Georg M N Behrens, Phil Bright, Mar Masia Canuto, Antonella Castagna, Aoife Cotter, Alberto Díaz De Santiago, Pere Domingo, Adrian Curran, Julie Fox, Lucio J Garcia-Fraile, Francesco G Genderini, Andrea Giacomelli, Juan Gonzalez, Giovanni Guaraldi, Lisa Hamzah, Elbushra Herieka, Guillen Sirera Jiménez, Margaret A Johnson, Christine Katlama, Stephen Kegg, Chris Kenyon, Hernando Knobel, Karine Lacombe, Montserrat Laguno, Clara Lehmann, Pierre Leroy, Alain Makinson, Patrick Mallon, Giulia Marchetti, Rob Miller, Jean-Michel Molina, Roya Movahedi, Chloe Meave Orkin, Federico Pulido Ortega, Jose L Casado Osorio, Patrick Philibert, Joaquín Portilla, Frank A Post, Francois Raffi, Jose Ramon Blanco Ramos, Iain Reeves, Jürgen Rockstroh, Karen Rogstad, Maria Saumoy, Guido Schäfer, Sarah Schoeman, Christoph D Spinner, Christoph Stephan, Janina Trauth, Andrew P Ustianowski, Linos Vandekerckhove, Alan Winston.

NEAT-ID Foundation
Georg M N Behrens, Brenda Crabtree, Nikos Dedes, Carlo Giaquinto, Beatriz Grinsztejn, Esteban Martinez, Jean-Michel Molina, Anton Pozniak, Jürgen K Rockstroh, Francois Venter.

Contributors
GMNB, LA, and AP contributed to the conception of the study and trial design. GMNB, GL, AA, RM, FGG, FAP, JKR, LH, PD, AC, and ML recruited participants and acquired data. CF and JM performed data collection and data curation. LA performed the statistical analysis. GMNB and AP wrote the first draft. All authors contributed to drafting and revising the work for intellectual context and approved the manuscript. All authors had access to the raw data and JM, LA, AP, and GMNB verified the data. 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
GMNB reports honoraria for speaking at educational events or consulting from Gilead, ViiV Healthcare, MSD, and Pfizer. AP reports grants, contracts, or honoraria for speaking at educational events from Gilead and Janssen. AA reports honoraria for consulting from AstraZeneca, Bavarian Nordic, Gilead, GSK, Janssen, Merck, Pfizer, and ViiV Healthcare. RM reports honoraria for consulting from and participation on advisory boards for Gilead, J&J, and ViiV Healthcare. FAP reports grants, contracts, or honoraria for speaking at educational events from Gilead, ViiV Healthcare, MSD, and Immunocore. JKR reports grants, contracts, or honoraria for speaking at educational events from, consulting for, and participation on advisory boards for Gilead, Boehringer, MSD, ViiV Healthcare, AbbVie, Janssen, Berlin Cures, and the European AIDS Clinical Society. PD reports honoraria for speaking at educational events from and participation on advisory boards for Gilead, ViiV Healthcare, Janssen, Merck, Theratechnologies, and Ferrer International. AC reports grants, contracts, or honoraria for speaking at educational events from Gilead, ViiV Healthcare, J&J, and MSD. All other authors declare no competing interests.

Data sharing
The protocol, consent form, statistical analysis plan, and other relevant trial materials are available in the appendix (pp 39–304). The trial steering committee will facilitate the use of the trial data and approval will not be unreasonably withheld, providing the committee are satisfied that any proposed publication is of high quality, honours the commitment made to the trial participants in the consent documentation and ethics approval, and is compliant with the relevant legal and regulatory requirements. All requests should be made to the corresponding author.

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