Switch to long-acting cabotegravir and rilpivirine in virologically-suppressed adults with HIV in Africa (CARES): week 48 results from a randomised, multicentre, open-label, noninferiority trial.

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ABSTRACT (word count maximum 250: current: 250)

Background

Long-acting injectable cabotegravir and rilpivirine is licensed for individualised treatment of HIV-1 infection in resource-rich settings. Additional evidence is required to support use in African treatment programmes where demographic factors, viral subtypes, prior treatment, and delivery and monitoring approaches differ.

Methods

Sub-Saharan African participants with viral load below 50 copies/ml on oral therapy and no history of virological failure were randomised (web-based, permuted blocks) to receive cabotegravir (600mg) and rilpivirine (900mg) by intramuscular injection every 8 weeks; or continue oral therapy. Viral load was monitored every 24 weeks. The primary outcome was week 48 viral load below 50 copies/ml, assessed with the Food and Drug Administration snapshot algorithm (non-inferiority margin 10%) in the intention-to-treat exposed population. PACTR number, 202104874490818.

Findings

We enrolled 512 participants (58% female; 74% prior NNRTI exposure). Week 48 viral load was below 50 copies/ml in 246/255 (96%) participants in the long-acting therapy group and 250/257 (97%) in the oral therapy group (difference -0.8 %; 95% confidence interval [CI], −3.7 to 2.3), demonstrating non-inferiority (confirmed in per-protocol analysis). Two participants had virological failure in the long-acting therapy group, both with drug resistance; none in the oral therapy group. Adverse events of grade 3 or greater severity occurred in 24 (9%) on long-acting therapy and 10 (4%) on oral therapy; one participant discontinued long-acting therapy (for injection-site reaction).

Interpretation

Long-acting therapy had non-inferior efficacy compared to oral therapy with a good safety profile and may be considered for African treatment programmes.

Funding

Janssen

RESEARCH IN CONTEXT (word count maximum 500: current: 329)

Evidence before this study

Long-acting injectable therapy with cabotegravir and rilpivirine is a recommended option for individualized treatment of human immunodeficiency virus type 1 (HIV-1) infection in resource-rich settings, based on several randomised controlled trials demonstrating non-inferiority against various oral regimens. However, additional evidence is needed to evaluate the role of long-acting therapy in the public health approach in Africa. We searched PubMed, with no start date or language restrictions, using the search terms “cabotegravir” and “rilpivirine” and “randomised trial” for articles published until 25 February 2024. We identified no trials that compared long-acting therapy with the WHO-recommended treatment regimen of tenofovir, lamivudine and dolutegravir; or that administered long-acting therapy with sparse viral load and safety monitoring; or that evaluated long-acting therapy in a trial population representative of those receiving treatment under the public health approach in Africa.

Added value of this study

This trial demonstrated that switching to long-acting therapy maintained high levels of viral suppression that were non-inferior to continuing an oral regimen that comprised mainly the combination of tenofovir, lamivudine and dolutegravir; with low risk of virological failure with resistance; and with few treatment-related severe adverse events, or treatment-limiting adverse events. In addition to being the first trial to directly compare long-acting therapy with the WHO-recommended treatment regimen, this trial is the first to evaluate long-acting therapy administered with WHO-recommended sparse viral load and safety monitoring and to do so in a population comprising a majority of Black women; with extensive prior exposure to NNRTI-based regimens, and with viral subtypes that are typical of people receiving treatment Africa.

Implications of all the evidence

This trial, taken in context with previous evidence generated from trials done mainly in resource-rich settings, demonstrates that long-acting therapy may be considered as an option for treatment programmes in Africa. Careful evaluation of risks and benefits for people and programmes will determine whether, and to what extent, long-acting therapy ultimately finds a place in the public-health approach to HIV treatment in Africa.

INTRODUCTION

Antiretroviral therapy for human immunodeficiency virus (HIV) infection is delivered globally mainly using the World Health Organisation (WHO)-recommended public-health approach, comprising a small number of standardized regimens and simplified monitoring and care.[1] The current standard first-line regimen comprises a combination of three drugs taken as daily oral therapy; tenofovir and lamivudine (nucleoside reverse-transcriptase inhibitors, NRTIs); and dolutegravir (an integrase strand-transfer inhibitor).[2] This regimen demonstrated good viral suppression in African trials, irrespective of pre-existing drug resistance.[3-5] The previously-recommended first-line standard treatment in the public health approach was a non-NRTI (NNRTI)-containing regimen, which was used almost universally but had a high risk of developing drug resistance during periods of non-adherence or at other times when viral replication was not fully controlled. Treatment programmes have recently switched most people from NNRTI-containing regimens to the new standard regimen; including some with occult virological failure and archived NNRTI mutations.[2,6]

Trials done mainly in North America and Europe, enrolling people with viral suppression on various oral regimens, have shown that switching to a two-drug regimen of cabotegravir (an integrase inhibitor) and rilpivirine (an NNRTI) given by intramuscular injection once every 4 or 8 weeks, maintains viral suppression and increases treatment satisfaction.[7-10] This is one of the recommended individualised treatment options for virologically-suppressed people in treatment guidelines for these settings, with the exception of those with hepatitis B virus (HBV) infection who need to maintain NRTIs in their regimen for activity against both infections.[11,12] HIV treatment guidelines recommend an HIV viral load test to be done within 4-8 weeks after switch to long-acting therapy;[11-13] and 8-weekly thereafter.[13]

Long-acting therapy may be a valuable alternative to standard oral treatment in treatment programmes in Africa, but evidence is currently limited. The previous trials done in North America and Europe generally have low representation of women; Black participants; people with extensive prior exposure to NNRTI-containing regimens (and archived NNRTI resistance); and viral subtypes common in Africa. No trials have compared long-acting therapy to the

current WHO-recommended oral regimen and used sparse viral load and safety monitoring typical of the public-health approach. We conducted a trial under such conditions to determine whether switching to long-acting therapy with injections every 8 weeks is non-inferior to daily oral therapy in Africa.

METHODS

Trial design and oversight

The Cabotegravir and Rilpivirine Efficacy and Safety (CARES) Trial is a prospective, multicentre, randomized, open-label, non-inferiority, 96-week trial comparing switching to long-acting therapy - injections of cabotegravir and rilpivirine every 8 weeks - to maintaining daily oral therapy in adult participants with established virological suppression managed in sub-Saharan Africa (figure 1). Data on the primary outcome (week 48 viral load below 50 copies/ml) are presented here, with safety data and participant-reported outcomes.

The trial was designed by academic investigators in the trial team and by Janssen. The Joint Clinical Research Centre (JCRC), Uganda coordinates the trial and is legal sponsor. An independent trial steering committee provides oversight. An independent data and safety monitoring committee reviews safety and interim efficacy data. National and local ethics committees and regulatory agencies approved the trial. Participants provided written informed consent. Authors vouch for the accuracy and completeness of data and fidelity to the protocol.

Trial population

Participants were eligible for inclusion if they were at least 18 years of age; had taken a regimen of tenofovir, lamivudine (or emtricitabine) and either dolutegravir, efavirenz or nevirapine for at least six months continuously before screening; and had viral load below 50 copies/mL at screening and at 4-6 months before screening.

The main exclusion criteria were having two consecutive viral load tests of at least 50 copies/ml in the 12 months prior to screening; history of virological failure (two consecutive viral load tests of at least 200 copies/ml) at any time; pregnancy; or evidence of current or past hepatitis B virus infection with either positive hepatitis B surface antigen or antibodies against hepatitis B core antigen (anti-HBc). Complete eligibility criteria are listed in the appendix p5-8.

Randomisation and masking

Participants were randomly assigned (1:1 ratio) to long-acting or oral therapy. Randomization was done using a Web-based system, pre-programmed with a computer-generated

randomization list; used random permuted blocks; and was stratified by the third-drug class (integrase inhibitor or NNRTI) at screening. Randomisation was performed by the study coordinator at each site, who could access the next number on the system but not the whole list.

The trial management team did not have access to aggregate unmasked data except for serious adverse events and pregnancy reports. The trial statistician had access to unmasked data through formal request to the data management group when required for study analyses. Treatment allocation was not masked to site staff and participants.

Treatment

For the first 4 weeks after randomization, participants assigned to long-acting therapy were given the choice to take daily oral therapy with 30mg of cabotegravir and 25mg of rilpivirine (to assess tolerability) or continue their current regimen. At weeks 4, 8, 16, 24, 32, 40 and 48, within a 7-day window from the scheduled date, participants received 600mg of cabotegravir and 900mg of rilpivirine by injection into the gluteus muscle. Oral cabotegravir and rilpivirine were available to bridge periods where the participant could not attend for injection within the window. Participants assigned to oral therapy took the WHO-recommended first-line regimen of 300mg of tenofovir, 300mg of lamivudine and 50mg of dolutegravir, once daily by mouth as a fixed-dose combination; or other regimens with dolutegravir or efavirenz in combination with NRTIs at the standard doses recommended in treatment guidelines.

Assessments and Outcomes

Visits in the long-acting therapy group were at weeks 4 and 8, then every 8 weeks to week 48, coinciding with scheduled injections; and in the oral therapy group at week 12, then every 12 weeks to week 48. Assessments at each visit included adherence (oral therapy) assessed by pill count and participant interview in the event of discrepancies; injection-site reactions (long-acting therapy); and adverse events. Standard safety blood tests (full blood count, sodium, potassium, creatinine, glucose, ALT, bilirubin, and alkaline phosphatase) were done at weeks 4 and 8 (long-acting therapy), 12 (oral therapy), 24 and 48 (both groups); plasma lipid profile at week 24; urine pregnancy tests at all visits in women of child-bearing potential. Adverse events were graded using standard criteria.[14]

CD4 and viral load were measured at weeks 24 and 48. Viral load testing was repeated after an interval of 4-6 weeks following a result at or above 200 copies/ml (long-acting group); or after an interval of 10-16 weeks following a result at or above 1000 copies/ml (oral treatment group; higher threshold and longer re-test interval allow for adherence counselling, following WHO guidelines).[2] Genotypic resistance testing was performed (centralised in WHO-accredited laboratories) if the re-test viral load remained above the treatment-specific threshold. Genotypic resistance testing, together with determination of viral subtype, was also performed on archived proviral DNA extracted from peripheral blood mononuclear cells stored at baseline in all participants. DNA extraction and sequencing were done retrospectively in batches when participants had completed at least 48 weeks of trial follow-up; results were returned to clinicians upon request at the end of trial follow-up. Viral subtype, resistance mutations and drug susceptibility were determined using the Los Alamos National Laboratory Panel, IAS-USA 2023 list, and Stanford algorithm respectively.

Quality of life was assessed with the MOS-HIV questionnaire and treatment satisfaction with HIV Treatment Satisfaction Questionnaire (HIVTSQ), change version; both at week 48.[15,16]

The primary outcome was a viral load below 50 copies/ml at week 48, determined using a modified Food and Drug Administration (FDA) snapshot algorithm. The modification specified that temporary changes in regimen for no more than 31 days; use of oral bridging cabotegravir and rilpivirine with later return to injectible therapy; and within-class changes within the oral therapy group should not count as treatment switch.[17] This outcome of viral suppression was chosen as the primary outcome, in preference to the outcome of viral non-suppression (viral load of at least 50 copies/ml) recommended by the FDA for switch studies, because it aligns more closely with programmatic goals for HIV treatment and with the trial objective to provide relevant data on effectiveness of long-acting therapy under conditions of the public health approach in Africa. The key secondary outcome was confirmed virological failure (two consecutive values of at least 200 copies/ml) by week 48. Additional pre-specified secondary outcomes were viral non-suppression (at or above 50 copies/ml); viral suppression below 200 copies/ml; and confirmed virological failure with new genotypic drug resistance mutation by week 48, all reported here. Prespecified other (exploratory) outcomes reported here are treatment adherence; change from baseline to week 48 in CD4 cell count, quality of life,

treatment satisfaction, BMI and selected laboratory parameters; incident (from baseline to week 48) grade 3 or higher adverse events, serious adverse events, HIV disease progression events, injection site reactions, and events leading to discontinuation of treatment between baseline and week 48. We also report incident obesity and hypertension to week 48 that were done as post-hoc analyses.

Further details regarding the conduct of the trial are provided in the protocol. -**Statistical analysis**

The primary outcome was analysed in the intention-to-treat exposed population (all those who received a dose of assigned intervention). The between group difference was estimated using the Cochran- Mantel-Haenszel weighted Miettinen and Nurminen Method, adjusting for third drug class (INSTI or NNRTI) at screening. Noninferiority of long-acting therapy could be concluded if the lower limit of the two-sided 95% confidence interval for the difference between groups in the proportion of participants with viral load below 50 copies/ml at week 48 was above -10 percentage points. This margin is consistent with the range (10-12%) used for judging non-inferiority for the outcome of virological suppression (whether as primary or secondary outcome) in treatment trials done in the African programme setting, and in previous long-acting trials. [3-5,7,9,10]

Sensitivity analyses were performed using a model adjusting for site, gender and third-drug class; using a per-protocol population (excluding those who withdrew; had an injection more than 14 days from the scheduled date; or missed oral treatment for more than 7 days at one or more visits); and with the use of complete cases. The key secondary outcome of confirmed virological failure was also analysed for non-inferiority in the intention-to-treat population, following a hierarchical approach conditional on demonstration of non-inferiority on the primary outcome.

We estimated the sample size based on consideration of both the primary and the key secondary outcome. For the primary outcome, we assumed that 94% of participants in each group would have viral load below 50 copies/ml at week 48 (based on previous 8-weekly long-acting trials);[8] with 10% noninferiority margin, 5% two-sided significance level, and 90% power we calculated that 238 participants (119 per group) were required to show noninferiority. For

the key secondary outcome, we assumed that 1.7% would have confirmed virological failure in both arms (based on previous 8-weekly long-acting trials);[18] with a hierarchical testing procedure, 4% non-inferiority margin, 5% two-sided significance level and 85% power, we calculated that 512 participants (256 per group) were required to show non-inferiority. We selected the larger of these two sample sizes to give adequate power for both analyses and to provide a substantive body of safety data that might give more confidence for adoption of long-acting therapy in the public health approach. The power to show non-inferiority for the primary outcome with the stated parameters was close to 100%.

Secondary and other analyses are described in the statistical analysis plan. All analyses were performed with the use of Stata software version 16.1 (StataCorp), except for the estimate of difference in proportions for the efficacy analysis that was performed in R version 4.3.3.

Role of the funding source

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

RESULTS

A total of 1039 participants were screened and 512 were randomly assigned at 8 sites in Uganda, Kenya and South Africa between 1 September 2021 to 31 August 2022 (figure 2; appendix p 9). All participants took at least one dose of the randomly-assigned study medication and were included in the intention-to-treat exposed population. Four (1%) of 512 withdrew from follow-up before week 48 (figure 2). Baseline characteristics were similar between randomised groups and broadly representative of people receiving HIV treatment in sub-Saharan Africa: of the 512 participants, 295 (58%) were female, 108 (21%) had obesity, and 380 (74%) had prior NNRTI exposure. Of those with a sequence available from DNA in peripheral blood mononuclear cells stored at baseline, 234 (57%) of 414 had subtype A1 virus, 51 (14%) of 377 had archived rilpivirine resistance mutations, and 29 (16%) of 180 had archived cabotegravir resistance mutations (table 1; appendix p 10-15).

In the long-acting therapy group, 214 (84%) of 255 participants took oral rilpivirine and cabotegravir for 4 weeks before first injection; 211 (83%) received all scheduled injections within the protocol-mandated 7-day window; nine (4%) had one injection administered more than 14 days after the scheduled date (appendix p 26; all nine had viral load below 50 copies/ml at weeks 24 and 48; no participant had more than one injection delayed by more than 14 days); two (1%) took oral bridging therapy for 8 weeks when overseas travel prevented return to the site; one (<1%) changed from long-acting to standard oral treatment. In the oral therapy group, 239 (93.0%) of 257 participants took tenofovir, lamivudine and dolutegravir (appendix p 15); 16 (6%) missed more than 7 days of treatment at one or more visits (there were no missed doses at 94% of participant visits); five (2%) changed oral drugs in the regimen (table 3).

In the intention-to-treat exposed population, viral load below 50 copies/ml was found in 246 (96%) of 255 participants (96%) in the long-acting therapy group and 250 (97%) of 257 in the oral therapy group (difference -0.8 percentage points; 95% confidence interval [CI], −3.7 to 2.3), meeting the pre-specified non-inferiority criterion (table 2). Findings were generally similar across subgroups (appendix p 27). Non-inferiority was also shown in sensitivity analyses including the per-protocol population; and in secondary analyses including outcomes of viral

non-suppression (at or above 50 copies/ml) and suppression below 200 copies/ml. Long-acting therapy was also non-inferior to oral therapy on the key secondary outcome of confirmed virological failure (table 2). There was no difference in CD4 cell count change between baseline and week 48 in long-acting and oral therapy groups (p=0.15).

Two participants on long-acting therapy were considered to have confirmed virological failure. Of these, one participant (subtype A1; no baseline rilpivirine resistance mutations; L74M polymorphism conferring potential low-level resistance to cabotegravir; not obese) had confirmed virological failure at week 48; with mutations conferring intermediate-level resistance to rilpivirine (V108I, E138K) and intermediate-level resistance to cabotegravir (E92E/V, N155H and L74M; potential low-level resistance to dolutegravir; table 2). The participant was switched to the standard oral regimen of tenofovir, lamivudine and dolutegravir and achieved viral re-suppression. The second participant (subtype D; baseline mutations conferring low-level resistance to rilpivirine [K103N/S, E138A]; no baseline cabotegravir resistance mutations; not obese) had viral load of 44,984 copies/ml at week 48 but died before confirmatory viral load test could be performed (cause of death was unrelated to HIV; and occurred after the end of the week 48 visit window so not reported as a death in the follow-up period to week 48; table 2). Mutations conferring high-level resistance to rilpivirine (K103N/S, V106V/A, E138A, M230M/L) and high-level resistance to cabotegravir (G118R; high-level resistance to dolutegravir) were found at week 48 (table 2). The level of viraemia and accompanying resistance profile were considered to have precluded re-suppression on long-acting therapy, if a confirmatory viral load had been performed. Neither participant missed or delayed injections beyond the 7-day scheduled window. No participants in the oral therapy group had confirmed virological failure.

Adverse events of grade 3 or greater severity occurred in 24 (9%) participants on long-acting therapy and 10 (4%) on oral therapy (difference 5.5%, 95%CI 1.2 to 9.8%); 3 and 2 events respectively were considered related to study drug (table 3; appendix p 16). Serious adverse events occurred in three participants on long-acting therapy and five on oral therapy; none were considered related to study drug (table 3; appendix p 17-18). Injection-site reactions were reported by 188 (74%) participants on long-acting therapy; mostly pain and of grade 1-2 severity (appendix p 19). Only one (injection-site nodule) was grade 3; and one (injection-site

sterile abscess) led to treatment discontinuation (table 3). The common non-injection site reactions affected a similar proportion of participants in each group, apart from increased cholesterol that occurred more frequently in the long-acting therapy group (table 3).

More women on long-acting therapy than on oral therapy developed new obesity at week 48 (13 [14%] versus 5 [5%] respectively; P=0.02) and started antihypertensive medication (appendix p 20-21 and p 28). Blood lipids increased more in the long-acting group, in both sexes (appendix p 22).

Six women became pregnant during period up to 48 weeks: two in the long-acting group (one healthy live birth; one miscarriage) and four in the oral therapy group (three healthy live births; one elective abortion).

Overall quality of life was high and similar between groups (appendix p 23-24). Treatment satisfaction score increased more from baseline to week 48 in the long-acting therapy group compared with the oral therapy group (adjusted mean difference 10.4 points; 95% CI 8.7 to 12.2) (appendix p 25).

DISCUSSION

We found that switching to long-acting therapy with cabotegravir and rilpivirine injections every 8 weeks was non-inferior to continuing daily oral therapy. Virological suppression was maintained in over 96%, exceeding the 95% target considered necessary to reduce HIV population incidence.[19] These findings are consistent with previous trials of long-acting treatment,[7-10] but provide new evidence essential for evaluating the role of this intervention in African treatment programs.

Firstly, the trial population was representative of those on treatment in Africa, with the majority being women and having prior exposure to NNRTI-containing regimens. The proportion of participants with archived rilpivirine resistance mutations at baseline was higher than in previous long-acting therapy trials, but consistent with extensive NNRTI treatment history in this setting. A previous pooled analysis of long-acting therapy trials identified a strong association between the presence of archived rilpivirine resistance mutations prior to start of long-acting therapy and the risk of subsequent virological failure on this regimen. Our finding of a low rate of virological failure despite the high proportion of participants with prior NNRTI exposure and baseline resistance mutations provides important reassurance that extensive programmatic use of NNRTIs in the past does not preclude consideration of future use of long-acting therapy as an option for the public health approach.

The previous pooled analysis also identified virus subtype A6 or A1 as a risk factor for virological failure, although it was later recognized that most of the cases driving this association were subtype A6 virus (from Russia).[20] Virological failure was observed in people with subtype A1 virus, raising the possibility that the risk might also extend to that subtype, although the population with subtype A1 in that pooled analysis (total of 19) was too small to be conclusive.[20] As subtype A1 is the commonest subtype in East Africa (found in 57% of participants in our study population) this represented a potential risk for the use of long-acting therapy in Africa that was essential to assess in this trial. Our findings indicate that the substantive risk of virological failure does not extend to people with subtype A1 (nor indeed to subtype C or D virus, also well represented, for whom data were limited prior to this trial); and

lend support to the published model suggesting that risk of failure is largely confined to subtype A6. Obesity, common in this African population, may also increase the risk of virological failure in combination with other factors. [20] Overall, the low virological failure rates (below 1%) indicate that, despite the major differences between this population and that of previous studies including several putative risk factors for virological failure, there appears to be no diminution of efficacy of long-acting therapy in this African population. CD4 cell counts were high at trial entry, reflecting the long period of prior treatment and were maintained throughout follow-up in the two groups, equally, as expected given the high proportion with viral suppression.

Secondly, almost all participants in the oral therapy group received the WHO-recommended standard regimen of dolutegravir, tenofovir and lamivudine, permitting efficacy and safety comparisons of long-acting therapy that are relevant for the public-health approach; whereas only a minority (0-2%) were taking this standard oral regimen in previous trials.[7-10] Thirdly, treatment was delivered using infrequent (6-monthly) viral load and safety monitoring, allowing assessment of risks associated with relatively late detection of treatment failure or toxicity that often occurs in treatment programmes.

Establishing non-inferior efficacy is an essential prerequisite to considering long-acting therapy for use in the public-health approach. However, evaluation of the advantages and disadvantages compared to oral therapy - both from the perspective of people requiring HIV treatment and the perspective of treatment programmes – is required to determine its role. Long-acting therapy was well tolerated, as in all previous trials, with only one grade 3 injection-site reaction and one adverse event leading to treatment discontinuation. Increased BMI observed in women on long-acting therapy may represent integrase inhibitor-associated weight gain, enhanced in Black women;[21,22] combined with removal of weight-suppressive effects of tenofovir.[23] This has not been noted in previous trials of long-acting therapy, possibly as a result of the paucity of female enrollment. There were no reports of abnormal fat deposition (lipodystrophy); the distribution of fat will be investigated further in a body composition substudy which is ongoing. Increased lipid levels also likely represent reversal of lipid-lowering effects of tenofovir.[24] Longer-term consequences for cardiovascular disease risk of switching from oral to long-acting therapy in the public-health approach are important to consider given

the large cardiovascular disease burden in Africa.[25]

The risk of drug resistance is a critical consideration in selecting regimens for programmatic use. Our finding of only two cases of new cabotegravir resistance (below 1%), despite relatively high levels of baseline NNRTI resistance, is reassuring. The impact of cabotegravir resistance on future treatment options is mitigated by the preservation of dolutegravir susceptibility in some with treatment failure (as we observed in one case);[8,10] and by the availability of a subsequent effective treatment option in the public-health approach (tenofovir, lamivudine and ritonavir-boosted darunavir) that would achieve viral re-suppression irrespective of resistance from prior treatment failure.[5]

The risk of re-activation of HBV infection on switch to long-acting therapy (which lacks activity against this virus), can be averted by testing for hepatitis B surface antigen before switch. We also excluded people with antibodies against hepatitis B core antigen (anti-HBc), which indicates past HBV exposure, common in Africa;[26] and this was the dominant cause of screen failure in this trial. However, recent observational data from a cohort of over 7,000 people with anti-HBc and without surface antigen who switched to antiretroviral regimens without HBV activity showed an overall HBV reactivation risk of 1.6% (further reduced in those with positive hepatitis B surface antibody [anti-HBs]).[27] In a small cohort study of people with anti-HBc switched to long-acting therapy, the three people who reactivated had low-level HBV viraemia with normal liver function tests and either resuppressed with switch back to a tenofovir-containing regimen or were considered stable and observed.[28] Overall, the data suggest that long-acting therapy could reasonably be used in those with anti-HBc, with additional clinical HBV monitoring. Testing for anti-HBs prior to switch and giving HBV vaccination for those who lack antibody may further mitigate risk of reactivation.

The main advantage of long-acting therapy for people living with HIV appears to be increased treatment satisfaction, observed in this and all previous trials. This is driven by increased convenience (not needing to carry, or remember to take, daily pills); and by reduced fear of disclosure (upon discovery of pills),[9] which is also a major consideration in sub-Saharan Africa. From a programme perspective, long-acting therapy provides a unique opportunity to maintain very high population levels of viral suppression, without dependence on individuals to adhere to

daily pill consumption – which is uncertain and difficult for programmes to monitor and support remotely. In contrast, attendance at injection visits provides certainty of drug dosing and can be directly tracked and supported. We found high adherence to the injection schedule, suggesting feasibility for African programmes; albeit with additional trial resources supporting visit attendance including travel reimbursement costs for all participant visits and additional staff resources available to remind participants of forthcoming appointments. Although such resources may be more limited when treatment is delivered outside a clinical trial, more modest and targeted support may suffice – when combined with the higher levels of treatment satisfaction that we observed on long-acting therapy – to maintain high motivation and attendance rates for injections. Implementation studies will be needed to determine the best approach in individual settings. Health economic analyses are underway to evaluate resource use and costs.

The main limitation of this trial is use of open-label treatment, but blinding would have required both placebo injections and pills, decreasing feasibility and preventing meaningful assessment of participant perceptions; the high retention rate and laboratory-based primary outcome reduce likelihood of substantial bias in assessment of efficacy outcomes. We did not include participants in West Africa, where viral subtypes differ from those in our trial, but the characteristics of the study population and approach to treatment delivery - following the WHO public health approach - are likely to ensure broad generalisability to African treatment programmes. The primary analysis of efficacy and safety after 48 weeks, as presented here, is over a relatively short period given that this therapy may be used for many years. Ongoing trial follow-up to week 96 will assess durability of long-acting therapy, but previous trials have found few people have confirmed virological failure after the first 48 weeks.[18,29,30]

In summary, this trial provides critical evidence for the efficacy, safety, acceptability and potential feasibility of switching from standard oral therapy to long-acting therapy in the public-health approach; the essential first step for considering possible use of long-acting therapy in treatment programmes. Careful evaluation of risks and benefits for individuals and for programmes will determine whether long-acting therapy – a potential paradigm shift for HIV treatment – ultimately finds a place in the public-health approach to HIV treatment in Africa.

Contributors

CK, VVE, PM, FAB and NIP designed the study. CK, IM, KO, CO and NIP coordinated the study. SS, HM, GA, FC, AS, JK, RS, LN, KM, AK and CW enrolled participants into the study. CO and JM accessed and verified the data and did the statistical analysis. All authors interpreted data. NIP wrote the first version of the report; and made the final independent decision to submit for publication. All authors provided input into the report and approved the final version of the report.

Declaration of interests

CK reports funding paid to institution and donation of drugs to institution from Janssen for the work reported in this manuscript. SS reports funding paid to institution and personal fees for speaking at symposia from Janssen and donation of drugs to institution from ViiV, all outside the work reported in this manuscript. FC reports funding paid to institution and donation of drugs to institution from Janssen and funding paid to institution from ViiV, Gilead, Wellcome Trust and the National Institute of Health Research UK outside the work reported in this manuscript; and unpaid role as Chair of Steering Committee for an investigator-initiated long-acting implementation trial. KM reports personal fees for speaking at symposia from Janssen outside of the work reported in this manuscript. VvE is an employee of Johnson and Johnson and holds stock options of Johnson and Johnson; and a patent related to rilpivirine. PM was an employee of Janssen at the time of trial design; and then an employee of ViiV during the time of trial conduct and manuscript submission; and holds stock from GSK as an employee of ViiV. FAB is an employee of Johnson and Johnson and holds stock options of Johnson and Johnson. NIP reports grants paid to institution, donation of drugs to institution and personal fees for speaking at symposia from Janssen outside the work reported in this manuscript; and is the Chief Investigator on a trial with funding paid to institution by the European Union for testing anti-tuberculosis drug combinations based on the drug ganfeborole, owned by GSK. IKM, JM, HM, GA, AS, JK, RS, LN, KO, CO, AK, and CW declare no competing interests.

Data sharing

Anonymised individual participant data and study documents can be requested from the corresponding author and will be made available from 12 months after publication of this paper, subject to approval of the Trial Steering Committee

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TABLES

Table 1 Baseline characteristics of participants*

Characteristic	Long-acting therapy (n=255)	Oral therapy (n=257)	Overall (N=512)
Female sex – no (%) †	146 (57)	149 (58)	295 (58)
Median age (IQR) – yr	43 (36-51)	42 (35-49)	42 (35-51)
Age group – no (%)			
18-34 yr	52 (20)	63 (25)	115 (22)
35-49 yr	127 (50)	130 (51)	257 (50)
≥50 yr	76 (30)	64 (25)	140 (27)
Country of residence – no (%)			
Uganda	121 (47)	123 (48)	244 (48)
Kenya	78 (31)	84 (33)	162 (32)
South Africa	56 (22)	50 (19)	106 (21)
Black race – no (%)	254 (100)	256 (100)	510 (100)
Median body mass index (IQR) - kg/m^2 ‡	25.4 (21.5-29.5)	25.8 (22.3-29.0)	25.5 (21.9-29.2)
Obesity - no (%) ‡	57 (22)	51 (20)	108 (21)
Median CD4+ cell count (IQR) - per mm^3	702 (513-882)	725 (561-898)	707 (536-888)
HIV-1 viral load ≥ 50 copies/ml – no (%) §	5 (2)	10 (4)	15 (3)
Viral subtype A1 - no (%) ¶	119/213 (56)	115/201 (57)	234/414 (57)
Rilpivirine resistance mutations -no (%) ‖	25/200 (12)	26/177 (15)	51/377 (14)
Rilpivirine intermediate/high-level resistance -no (%) **	17/200 (8)	21/177 (12)	38/377 (10)
Cabotegravir resistance mutations -no (%) ‖	15/95 (16)	14/85 (16)	29/180 (16)
Cabotegravir intermediate/high-level resistance - no (%) **	10/95 (11)	5/85 (6)	15/180 (8)
Median time on first-line ART (IQR) – years	8 (4-13)	7 (4-13)	8 (4-13)
Prior exposure to NNRTI – no (%)	189 (74)	191 (74)	380 (74)
Regimen at trial entry (screening) - no (%)			
Integrase inhibitor-containing regimen	231 (91)	240 (93)	471 (92)
NNRTI-containing regimen	24 (9)	17 (7)	41 (8)

* Table shows characteristics for the intention-to-treat exposed population. IQR denotes interquartile range. NNRTI denotes non-nucleoside reverse transcriptase inhibitor

† Sex was as assigned at birth. Information on gender identity was not collected.

‡ Body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. Obesity is defined as BMI ≥30kg/m^2.

§ Viral load range 52 to 2855 copies/ml at baseline (all had viral load < 50 copies/ml at screening).

¶ Sequencing performed on archived viral DNA extracted from peripheral blood mononuclear cells stored at baseline. Subtype determined by comparison of sequence to the Los Alamos National Laboratory HIV sequence database; primary determination made from reverse transcriptase sequence, and integrase

sequence where reverse transcriptase not available. No subtype A6 was identified.

‖ Resistance mutations listed in the 2022 edition of the IAS-USA drug resistance mutations list

** Susceptibility determined using Stanford risk algorithm

Table 2 Main efficacy outcomes at week 48*

Outcome	Long-acting therapy (n=255)	Oral therapy (n=257)	Difference (95% CI) † *Percentage points*
Primary outcome			
HIV-1 viral load level – no. (%)			
< 50 copies/ml	246 (96)	250 (97)	-0.8 (-3.7 to 2.3)
≥ 50 copies/ml ‡	7 (3)	5 (2)	0.8 (-1.8 to 3.4)
No virological data §	2 (1)	2 (1)	-
Primary outcome, sensitivity analyses			
HIV-1 viral load level – no. (%)			
< 50 copies/ml (additional adjustment) ¶	96	97	- 0.9 (-4.1 to 2.2)
< 50 copies/ml (per protocol) ‖	237/244 (97)	234/239 (98)	-0.8 (-3.7 to 1.9)
< 50 copies/ml (complete case)	246/253 (97)	250/255 (98)	-0.8 (-3.4 to 1.8)
Secondary and other efficacy outcomes			
HIV-1 viral load < 200 copies/ml – no. (%)	250 (98)	252 (98)	-0.01 (-2.4 to 2.4)
Confirmed virological failure - no. (%) **	2 (1)	0	0.8 (-0.7 to 2.8)
Confirmed virological failure (per protocol) – no (%) **	2 (1)	0	•
Confirmed virological failure with ≥1 major acquired resistance mutation – no (%) ††	2 (1)	0	•
Change from baseline in CD4+ cell count- cells/mm^3 ‡‡	-13 ± 203	13 ± 206	-26 (-62 to 9)

* HIV-1 denotes human immunodeficiency type 1. Plus-minus values are means ± SD.
All analyses of viral load suppression above or below threshold use the FDA snapshot algorithm and are done in the intention-to-treat exposed population, except where stated. Analyses of confirmed virological failure are done in the intention-to-treat exposed population unless otherwise stated. Analysis of change in CD4 count use complete case analysis. The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects on secondary and other efficacy outcomes.

† Estimates of difference and 95%CI for primary and secondary virological outcomes used the Cochran-Mantel-Haenszel weighted Miettinen and Nurminen Method, adjusting for third drug class (INSTI or NNRTI) at screening; except for sensitivity analysis (additional adjustment) that used modified Poisson regression with unbiased sandwich estimate of variance; and except for analysis of confirmed virological failure for which no adjustment for third drug class was performed. Estimate of difference and 95%CI for CD4 count change used Student's t-test.

‡ All VL values ≥ 50 copies/ml had a value in window (none were due to switches for lack of efficacy or withdrawal).

§ The 4 participants with no virological data in window withdrew before week 48 for reasons other than adverse events.

¶ Adjusted for third drug class (INSTI or NNRTI) at screening, site and sex.

‖ The per-protocol population excludes 2 participants in each group who withdrew from trial follow-up; 9 in the long-acting group with injection more than 14 days after the target date; and 16 in the oral treatment group who missed more than 7 days of treatment at one or more visits.

** Confirmed virological failure is defined as 2 consecutive viral load values $\geq$ 200 copies/ml. One of the two participants in the long-acting group had a viral load of 44,984 copies/ml at week 48 that could not be confirmed (participant died 9 days after the visit, before viral load test could be repeated, following an operation for strangulated umbilical hernia). The level of viraemia and accompanying resistance profile were considered to have precluded re-suppression on long-acting therapy, if a confirmatory viral load had been performed.

†† The participant with confirmed virological failure had no mutations conferring rilpivirine resistance and an L74M polymorphism conferring potential low-level resistance to cabotegravir at baseline; and mutations conferring intermediate-level resistance to rilpivirine (V108I and E138K) and high-level resistance to cabotegravir (E92E/V, N155H and L74M; potential low-level resistance to dolutegravir) at week 48. The participant with a single high viral load had virus with resistance mutations conferring low-level resistance to rilpivirine (K103N/S, E138A) and no mutations conferring resistance to cabotegravir at baseline; and mutations conferring high-level resistance to rilpivirine (K103N/S, V106V/A, E138A, M230M/L) and high-level resistance to cabotegravir (G118R; high-level resistance to dolutegravir) at week 48.

‡‡ CD4+ cell count data were available for 508 participants; missing values were due to withdrawal (2 in each group). P value = 0.15 for difference between arms.

Table 3 Adverse events occurring between baseline and week 48 *

	Long-acting therapy (n=255)	Oral therapy (n=257)	Difference (95% CI) †
Participants with at least one adverse event grade ≥ 3 - no (%)			
Any	24 (9)	10 (4)	5.5 (1.2 to 9.8)
Related to study drug ‡	3 (1)	2 (1)	0.4 (-1.3 to 2.1)
Participants with at least one serious adverse event - no (%)			
Any	3 (1)	5 (2)	-0.8 (-2.9 to 1.4)
Related to study drug	0	0	•
Participants with at least one adverse event of any grade - no (%)			
Any	217 (85)	172 (67)	18.2 (10.9 to 25.4)
Leading to study drug discontinuation §	1 (<1)	3 (1)	-0.8 (-2.3 to 0.7)
Excluding injection-site reactions	181 (71)	172 (67)	4.1 (-4.0 to 12.1)
Injection-site reactions	188 (74)	0	-
Common non-injection site reaction adverse events (≥ 5% participants in either group) – no (%)			
Clinical			
Upper respiratory tract infection	33 (13)	31 (12)	-
Hypertension	25 (10)	17 (7)	-
Urinary tract infection	18 (7)	16 (6)	-
Malaria	17 (7)	6 (2)	-
Laboratory			
Hyponatraemia	27 (11)	25 (10)	-
Increased cholesterol ¶	34 (13)	9 (4)	-
Increased triglycerides	15 (6)	9 (4)	-

*Table shows number of participants with at least one adverse event in each event category.

† Estimates of difference and 95%CI used the normal approximation to the binomial method.

‡ Grade ≥ 3 adverse events considered related to study drug were injection-site nodule, increased LDL cholesterol and proteinuria, each in one participant in the long-acting group; and decreased estimated glomerular filtration rate (eGFR) and increased blood glucose, each in one participant in the standard oral therapy group.

§ Adverse events leading to study drug discontinuation were injection-site sterile abscess in one participant in the long-acting treatment group (switched to standard oral treatment); increased blood glucose (switched dolutegravir to efavirenz), osteoporosis (switched tenofovir to abacavir) and decreased eGFR (switched tenofovir to abacavir) each in one participant in the standard oral therapy group. In addition, 2 participants in the standard oral therapy group with low eGFR at baseline switched tenofovir to abacavir during follow-up to prevent further decline in eGFR.

¶ An additional 4 participants in the long-acting group and 2 participants in the oral therapy group had increased LDL reported (with total cholesterol not tested or not elevated).

LEGENDS TO FIGURES

Figure 1 Trial Design

TDF=tenofovir. 3TC=lamivudine. FTC=emtricitabine. DTG=dolutegravir. NVP=nevirapine. EFV=efavirenz. CAB=cabotegravir. RPV=rilpivirine. LA=long-acting therapy group. OT=oral therapy group. PBMC=peripheral blood mononuclear cells.

*For the first four weeks after randomization, participants assigned to the long-acting therapy group were given the choice to switch to daily oral therapy with 30mg of cabotegravir and 25mg of rilpivirine or to continue their current oral regimen.

Figure 2 Trial profile

HBsAg=hepatitis B virus surface antigen. Anti-HBc=antibody against hepatitis B virus core antigen.