# 72 weeks post-partum follow-up of dolutegravir versus efavirenz initiated in late pregnancy (DolPHIN-2): an open-label, randomised controlled study

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## Summary

**Background** Late initiation of antiretrovirals in pregnancy is associated with increased risk of perinatal transmission and higher infant mortality. We report the final 72-week postpartum results for efficacy and safety of dolutegravir-based compared with efavirenz-based regimens in mothers and infants.

**Methods** DolPHIN-2 was a randomised, open-label trial. Pregnant women in South Africa and Uganda aged at least 18 years, with untreated but confirmed HIV infection and an estimated gestation of at least 28 weeks, initiating antiretroviral therapy in third trimester were eligible for inclusion. Eligible women were randomly assigned (1:1) to receive either dolutegravir-based (50 mg dolutegravir, 300 mg tenofovir disoproxil fumarate, and either 200 mg emtricitabine in South Africa or 300 mg lamivudine in Uganda) or efavirenz-based (fixed dose combination 600 mg tenofovir disoproxil fumarate plus either emtricitabine in South Africa or lamivudine in Uganda) therapy. The primary efficacy outcome was the time to a viral load of less than 50 copies per mL measured at 6, 12, 24, 48, and 72 weeks postpartum with a Cox model adjusting for viral load and CD4 cell count. Safety endpoints were summarised by the number of women and infants with events. This trial is registered with ClinicalTrials.gov, NCT03249181.

**Findings** Between Jan 23 and Aug 15, 2018, 280 women were screened for inclusion, of whom 268 (96%) women were randomly assigned: 133 (50%) to the efavirenz group and 135 (50%) to the dolutegravir group. 250 (93%; 125 [50%] in the efavirenz group and 125 [50%] in the dolutegravir group) women were included in the intention-to-treat analysis of efficacy. Median time to viral load of less than 50 copies per mL was 4·1 weeks (IQR 4·0–5·1) in the dolutegravir group compared with 12·1 weeks (10·7–13·3) in the efavirenz group (adjusted hazard ratio [HR] 1·93 [95% CI 1·5–2·5]). At 72 weeks postpartum, 116 (93%) mothers in the dolutegravir group and 114 (91%) in the efavirenz group had a viral load of less than 50 copies per mL. Of 57 (21%) mothers with a severe adverse event, three (2%) in the dolutegravir group and five (4%) in the efavirenz group were related to the drug (dolutegravir drug-related events were one woman each with suicidal ideation, suicide attempt, herpes zoster meningitis; efavirenz drug-related events were one woman each with suicide attempt and liver cirrhosis, and three people with drug-induced liver injury). Of 136 (56%) infants in whom severe adverse events were recorded, none were related to the study drugs. In addition to the three infant HIV infections detected at birth in the dolutegravir group that have been previously reported, an additional transmission in the efavirenz group occurred during breastfeeding despite optimal maternal viral suppression and serial negative infant tests in the first year of life.

**Interpretation** Dolutegravir was safe and well tolerated, supporting updated WHO treatment recommendations in pregnant and breastfeeding women. Infant HIV transmissions can occur during breastfeeding despite persistently undetectable maternal viral load highlighting the need for continued infant testing.

**Funding** Unitaid.



## Introduction

Elimination of perinatal transmission of HIV remains a key global health priority. Safe and effective antiretroviral drugs during pregnancy and breastfeeding are crucial to achieve this aim. In sub-Saharan Africa, approximately one in five pregnant women with HIV are diagnosed late or access antenatal care late in pregnancy annually.[1] Late diagnosis leads to delayed initiation of antiretroviral therapy (ART) and is associated with a seven-times higher perinatal transmission risk and a two-times higher infant mortality risk in the first year of life.[1] Maternal HIV viral load is directly associated with perinatal transmission, consequently antiretroviral drugs, such as dolutegravir, which cause a rapid decline in viral load, offer more

## Research in context

### Evidence before this study

In 2018, WHO published interim guidelines recommending a transition from use of efavirenz in first-line regimens to dolutegravir-containing regimens, with a cautionary note highlighting the scarcity of definitive evidence of safe use in pregnancy. Only now are data emerging from two randomised trials assessing dolutegravir in pregnant women. We searched PubMed from the inception of the database to Jan 4, 2022, using the search terms "HIV", "pregnancy", "initiation", "antiretroviral therapy", and "Africa". Alongside our previous report of findings from the DolPHIN-2 trial, the VESTED trial was the only other to evaluate dolutegravir in pregnant women living with HIV initiating therapy between 14 and 28 weeks of gestation. Although both studies differed in time of initiation of antiretroviral therapy, study design, primary endpoints, and geographical region, dolutegravir was well tolerated by participants in both studies. In our interim analysis of the DolPHIN-2 trial, dolutegravir was associated with superior virological suppression at the time of birth which is commonly used as a proxy for risk of intrapartum perinatal transmission of HIV. However, although the occurrence of serious adverse events remained low, we observed a statistically higher incidence of serious adverse events in the dolutegravir group, mainly driven by prolonged pregnancies. Moreover, all three infant transmissions diagnosed around the time of birth were in the dolutegravir group.

### Added value of this study

Longer term follow-up to establish continued benefit, safety, and tolerability in mothers and infants is required. Here we report long-term (72 weeks postpartum) data confirming the efficacy and safety of both efavirenz-based and dolutegravir-based regimens when initiated in late pregnancy. Evidence for superiority of viral load suppression with dolutegravir is confirmed with most differences occurring early on (eg, at birth), whereas by 72 weeks postpartum overall rates of viral load suppression were similar. These add to the growing body of evidence from longer term follow-up for safety and efficacy of first-line use of dolutegravir in pregnancy, with detailed monitoring of mothers and their infants.

### Implications of all the available evidence

Evaluation of risks versus benefit continue to strongly favour use of dolutegravir over efavirenz in pregnant women, especially if antiretroviral therapy is initiated in the third trimester. Longer term follow-up (to 72 weeks postpartum) of mothers and infants provides reassurance of drug safety and efficacy. However, the detailed documentation of late postpartum HIV infection of an infant yields more evidence that undetectable maternal viral load during breastfeeding does not entirely eliminate the risk of perinatal transmission of HIV.

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opportunities for maternal viral load suppression in pregnancy, addressing a key gap in elimination of perinatal transmission. Updated WHO treatment guidelines in 2019 recommended dolutegravir-containing regimens as the preferred first-line and second-line treatments for pregnant women and those of childbearing potential.[2] These updated guidelines are supported by our previous interim analysis in women initiating ART late in pregnancy, which confirmed that dolutegravir was associated with superior responses (viral load <50 copies per mL) when women gave birth,[3] and by recent similar findings in mothers treated much earlier in pregnancy from the VESTED trial.[4] Despite these new data, longer-term safety and efficacy data (beyond the immediate postpartum period) on the use of dolutegravir in pregnant and breastfeeding women remain scarce.

We aimed to assess the efficacy (viral load <50 copies per mL) and safety (occurrence of maternal and infant drug-associated serious adverse events) of dolutegravir-containing and efavirenz-containing regimens in women initiating ART late in pregnancy and continuing treatment in the postpartum period up to 72 weeks.

## Methods

### Study design and participants

DolPHIN-2 (NCT03249181) is an open-label, phase 4 randomised trial done in Cape Town, South Africa, and Kampala, Uganda, with 268 pregnant mothers initiating ART in the third trimester, as previously described.[3] Pregnant women aged 18 years or older with untreated but confirmed HIV infection with an estimated gestation of 28 weeks or more were eligible for inclusion. Women who had received ART in the preceding year or ever received integrase inhibitors, documented virological failure of a non-nucleoside-containing antiretroviral regimen, previous efavirenz toxic events or other clinical history that would preclude random assignment, estimated glomerular filtration rate less than 50 mL/min, haemoglobin less than 8·0 g/dL, decompensated liver disease or alanine aminotransferase more than five times the upper limit of normal (ULN), or alanine aminotransferase more than three times ULN, bilirubin more than two times ULN (with >35% direct bilirubin), severe pre-eclampsia, a medical, psychiatric, or obstetric condition that might affect participation in the study, or had received any drugs that significantly interact with efavirenz or dolutegravir in the 2 weeks preceding enrolment were excluded. On June 1, 2018, the protocol was amended to exclude patients with a pretreatment HIV viral load of less than 50 copies per mL (appendix p 24). In South Africa, eligible women were recruited from eight primary antenatal facilities in Cape Town and were enrolled at Gugulethu Community Health Centre, Cape Town. In Uganda, eligible women were recruited from eight primary antenatal facilities in Kampala and

See Online for appendix

Wakiso District, and they were enrolled at Kawempe Hospital, Kampala.

Ethics committee approval was obtained in South Africa, Uganda, and the UK. All participating women provided written informed consent at enrolment and affirmation of consent after giving birth for continued participation. The Independent Data and Safety Monitoring Board met regularly and did two planned analyses: an interim analysis after the first 125 women gave birth and the final analysis after all women had completed their final visit at week 72.

### Randomisation and masking

Eligible women were randomly assigned (1:1) with block randomisation (block size of 4, stratified by country with concealment of allocation until assignment) to initiate ART with efavirenz 600 mg per day (standard of care at the time) or dolutegravir 50 mg per day, in combination with tenofovir disoproxil fumarate plus either lamivudine in Uganda or emtricitabine in South Africa taken orally once daily and followed up until 72 weeks postpartum.[3] All participants and staff were not masked to treatment allocation.

Given the need to start treatment as soon as possible, mothers meeting eligibility criteria other than laboratory investigations were enrolled at the screening visit and initiated ART on the same day. At the confirmatory study visit 7 days later, participants who were deemed ineligible on the basis of screening laboratory assessments were switched to efavirenz-based regimens if allocated to the dolutegravir group and transferred to routine care services.

### Procedures

Screening evaluations to determine eligibility included HIV and ART and medical history, gestational age assessment, vital sign measurement, urinalysis, and blood draw for laboratory investigations. Gestational age was based on the most reliable estimate available by either fetal ultrasound, symphysis-fundal height, or last menstrual period. Throughout the study, data were collected from measurement of vital signs, clinical examinations, laboratory assessments, and multiple questionnaires. Study procedures during pregnancy and when giving birth, which have previously been described,[3] focused on primary outcomes, while study procedures at the postpartum visits (6, 12, 24, 48, and 72 weeks) focused on secondary outcomes and safety endpoints and included maternal and infant assessments.

For the **protocol synopsis** see https://clinicaltrials.gov/ct2/show/NCT03249181

Follow-up laboratory assessments were done at each visit from the maternal safety bloods using maternal blood samples and included urea, creatinine, electrolytes, bilirubin, and alanine aminotransferase concentrations; creatinine phosphokinase activity; and full blood count. At the 6 weeks postpartum visit infant tests included creatinine, alanine aminotransferase, bilirubin, and glucose concentrations. Maternal plasma viral load was measured at all postpartum visits and breastmilk viral load was measured at visits until weaning occurred. Maternal weight was measured using standardised procedures at all postpartum visits. Additionally, at these visits comedications, including traditional medicines and supplements, were also checked and any drug interactions managed as appropriate. Hyperglycaemia was assessed on fasted blood samples at 48 and 72 weeks. Across both sites, all participants received ongoing adherence counselling and support. Additionally, participants with poor adherence and those with detectable viral load (>75 copies per mL in Uganda and >1000 copies per mL in South Africa) were followed up and received intensive adherence counselling. Women were classified as having protocol defined virological failure if they either did not have a viral load of less than 50 copies per mL by 24 weeks postpartum or were virological responders (viral load <50 copies per mL) who subsequently rebounded with two confirmed elevations in the viral load to more than 1000 copies per mL. Additionally, a safety and endpoint review committee reviewed every case of suspected virological failure (blinded to allocation), and mothers for whom treatment was deemed to be clinically failing (eg, low-grade virological rebound) who did not meet protocol definitions of virological failure were reclassified as failing therapy.

Site specific psychological counselling for risk of anxiety or depression took place and advice on contraceptives and infant feeding was given. After giving birth, pregnancy screening occurred at all postpartum visits with women counselled about contraception and encouraged to use their preferred method of contraception with the importance of good adherence highlighted. Women with a subsequent pregnancy had study medication withdrawn and were transitioned to their national treatment programme. However, these pregnant women could elect to remain in the study, with active follow-up and data entered in the Antiretroviral Pregnancy Registry. For full details regarding study conduct, the protocol synopsis is available online and the full protocol is included in the appendix (pp 2–133).

### Outcomes

The primary outcome of the study was a viral load of less than 50 copies at delivery. The focus of this analysis was on the prespecified secondary outcomes of efficacy, specifically maternal viral load response, and occurence of perinatal transmission (including additional perinatal transmission) up to 72 weeks postpartum. Maternal viral load response was measured as time from randomisation to first viral load suppression (<50 copies per mL and <1000 copies per mL) event, and occurrence of virological failures.

Additionally, we report safety endpoints, which include safety and tolerability of dolutegravir in women and their breastfed infants and the occurrence of maternal and infant drug related adverse events and serious adverse events. The severity of the adverse

events and serious adverse events that occurred were graded according to the Division of AIDS criteria: mild (grade 1), moderate (grade 2), severe or medically significant (grade 3), life threatening (grade 4), and death (grade 5); we report grade 3 or worse events.[5] All serious adverse events were reviewed by a masked Safety Endpoint Review Committee, using the Liverpool Causality Assessment Tool,[6] to assess whether each event was associated with the study medication. The maternal adverse events of interest identified a priori included liver abnormalities, suicidal ideation, BMI and bodyweight changes, and glycosuria; infant events included hyperglycaemia and HIV infection.

### Statistical analysis

Our sample size calculations are previously published[3] and were designed to yield 99% or more power to detect a superiority absolute difference of 28–38% between the two treatment groups across five simulated distributions of gestational age (within the third trimester) at a 5% level of significance. Analyses were done with SAS (version 9.4). Determination of efficacy was based on the intention-to-treat (ITT) population, which consisted of all eligible participants who consented to be included excluding those withdrawn post-screening due to ineligibility. Efficacy was evaluated using time-to-event analyses, which determined the median time to achieve viral suppression (viral load <50 and <1000 copies per mL) from the time of randomisation. Observations were censored at the timepoints at which the last available viral load of ≥50 copies per mL or ≥1000 copies per mL was available. Kaplan-Meier curves for each treatment group were compared by the log-rank test and hazard ratio (95% CI), calculated using the Cox regression model with treatment as the study variable and viral load (≥100 000 copies per mL or <100 000 copies per mL) and CD4 cell count (≥200 cells per μL or <200 cells per μL) as covariables. Viral load rebound was not considered for the time-to-event analysis. The proportionality assumption was tested based on scaled Schoenfeld residuals. Subgroup analyses were done for each country (South Africa *vs* Uganda). Safety endpoints were evaluated in the safety population, which included all randomly assigned women who receive at least one dose or partial dose of study medication and their infants. Women who were initially randomly assigned but were deemed ineligible after laboratory tests at day 7 and women who switched treatment regimens outside of the study and were no longer receiving study medication were included in the safety population. Safety endpoints were summarised by the number of women and infants with events. For the postpartum weight change analysis, a linear mixed-effects model was used, with random intercepts fitted for postpartum maternal weights. p values less than 0·05 were considered statistically significant. This trial is registered with ClinicalTrials.gov, NCT03249181.

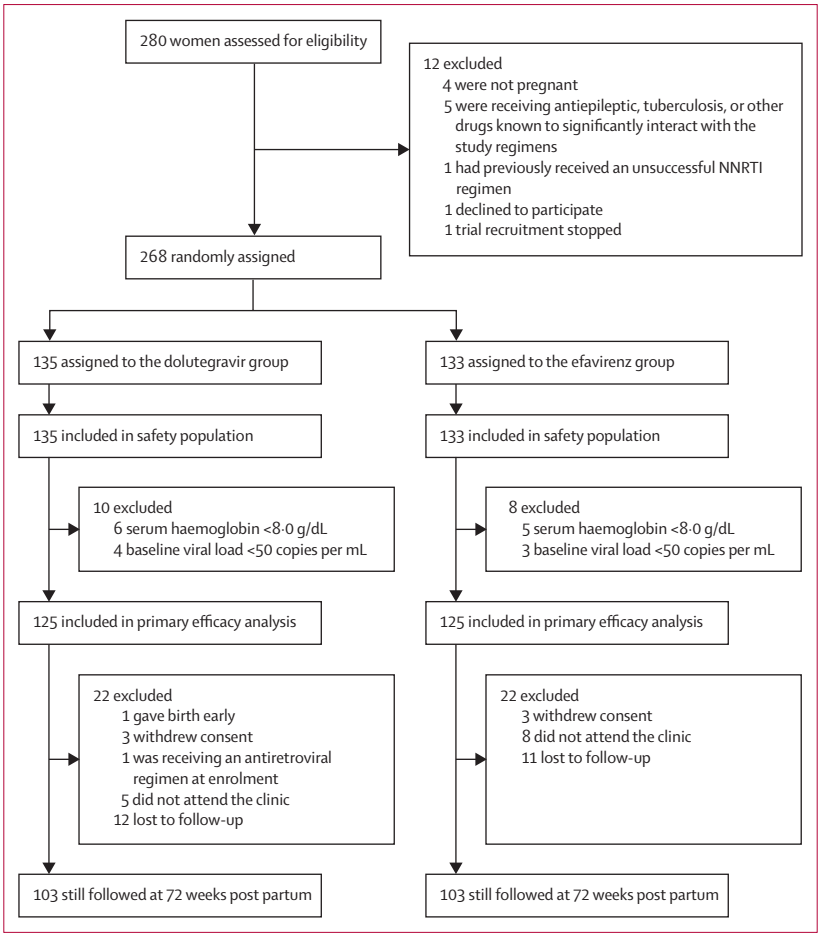


***Figure 1:*** **Trial profile**
NNRTI=Non-nucleoside reverse transcriptase inhibitor.

### Role of the funding source

The study funder had no role in study design, data collection, data analysis, interpretation, or writing of the report which remains the responsibility of the DolPHIN-2 trial management group, accountable to the Trial Steering Committee.

## Results

Between Jan 23 and Aug 15, 2018, 280 pregnant women screened for inclusion, of whom 268 (96%) women were randomly assigned (135 [50%] to the dolutegravir group and 133 [50%] to the efavirenz group), received at least one dose of their assigned regimen, and were included in the safety analysis. 18 (7%) women (ten [7%] from the dolutegravir group and eight [6%] from the efavirenz group) were excluded from the intention-to-treat analysis: 11 women had less than 8·0 g/dL serum haemoglobin and seven women had a viral load less than 50 copies per mL at baseline (figure 1). As a result, 250 (89%) of the 280 women screened (125 [50%] in the dolutegravir group and 125 [50%] in the efavirenz group) formed the intention-to-treat population for efficacy.

| | Total (n=268) | Dolutegravir group (n=135) | Efavirenz group (n=133) |
|---|---|---|---|
| Study site (%) | | | |
| South Africa | 129 (48%) | 65 (48%) | 64 (48%) |
| Uganda | 139 (52%) | 70 (52%) | 69 (52%) |
| Age, years | | | |
| <24 | 58 (22%) | 26 (19%) | 32 (24%) |
| 25–29 | 113 (42%) | 52 (39%) | 61 (46%) |
| >30 | 97 (36%) | 57 (42%) | 40 (30%) |
| Median age | 28 (24–31) | 28 (24–32) | 27 (24–30) |
| Gestational age, weeks | 31 (29–34) | 31 (29–34) | 31 (28–33) |
| Number of pregnancies (%) | | | |
| 1 | 32 (12%) | 18 (13%) | 14 (11%) |
| 2 | 76 (28%) | 33 (24%) | 43 (32%) |
| ≥3 | 160 (60%) | 84 (62%) | 76 (57%) |
| Median | 3 (2–4) | 3 (2–4) | 3 (2–4) |
| Previous pregnancy loss* | 52 (22%) | 21 (18%) | 31 (26%) |
| Bodyweight, kg | 73 (16) | 75 (16) | 71 (16) |
| BMI, kg/m | | | |
| Normal (<24·9) | 73 (27%) | 33 (24%) | 40 (30%) |
| Overweight (25·0–29·9) | 86 (32%) | 40 (30%) | 46 (35%) |
| Obese (>30·0) | 109 (41%) | 62 (46%) | 47 (35%) |
| Mean (SD) | 30 (7) | 30 (7) | 28·68 (7) |
| Median (IQR) | 27·91 (24·65–32·87) | 29·22 (25·15–33·79) | 26·96 (24·42–31·09) |
| CD4 count, cells per µL | 446 (288–633) | 465 (325–668) | 412 (268–566) |
| HIV-1 RNA, copies per mL | | | |
| <100 000 | 222 (83%) | 114 (84%) | 108 (81%) |
| 100 001–500 000 | 39 (15%) | 20 (15%) | 19 (14%) |
| >500 000 | 7 (3%) | 1 (1%) | 6 (5%) |
| Median | 27 655 (5258–61 171) | 22 895 (3461–55 624) | 34 647 (7978–68 058) |
| Baseline $\log_{10}$ viral load, copies/mL | 4·36 (3·54–4·75) | 4·54 (3·90–4·83) | 4·44 (3·72–4·79) |
| Haemoglobin, g/dL | | | |
| Normal (≥11·0) | 119 (44%) | 61 (45%) | 58 (44%) |
| Mild anaemia (9–10·9) | 123 (46%) | 60 (44%) | 63 (47%) |
| Moderate anaemia (7–8·9) | 22 (8%) | 11 (8%) | 11 (8%) |
| Severe anaemia (<7) | 4 (1%) | 3 (2%) | 1 (1%) |
| Mean | 11 (2) | 11 (2) | 11 (2) |
| Renal function, creatinine clearance (mg/L) | 0·52 (0·09) | 0·53 (0·10) | 0·52 (0·08) |
| Alanine aminotransferase concentration, IU/L | 10 (8–13) | 9·5 (8–13) | 10 (8–13) |
| Positive urine glucose | 3 (2·22) | 2 (1·50) | 5 (1·87) |
| Medication use | | | |
| Herbal or traditional | 90 (34%) | 44 (33%) | 46 (35%) |
| Supplements and vitamins | 98 (37%) | 50 (37%) | 48 (36%) |
| Other comedications | 71 (26%) | 32 (24%) | 39 (29%) |
| Substance use in pregnancy | | | |
| Tobacco | 14 (5%) | 7 (5%) | 7 (5%) |
| Alcohol | 51 (19%) | 24 (18%) | 27 (20%) |
| History of psychiatric disorders | 11 (4) | 8 (6) | 3 (2) |

Data are mean (SD), median (IQR), or n (%). *In women with at least one previous pregnancy.

*Table 1:* **Baseline demographics in the safety population**

At baseline (third trimester), median weight was 71 kg (IQR 61–83) with no differences observed between the study groups (table 1). However, differences were observed by site, with a higher median baseline weight in South Africa (80 kg; 69–92) compared with Uganda (65 kg; 58–75). The mean pregnancy BMI was 30 kg/m², with a higher proportion of women in the dolutegravir group (62 [46%]) classified as obese compared with the efavirenz group (47 [35%]). At baseline, the HIV disease status differed between groups: a higher median CD4 cell count was reported in the dolutegravir group (465 cells per µL [IQR 325–668]) than the efavirenz group (412 cells per µL [268–556]). Overall, 46 (18%) women had a viral load of at least 100 000 copies per mL; more women in the efavirenz group (six women) had a viral load of more than 500 000 copies per mL compared with the dolutegravir group (one woman). Renal function, alanine aminotransferase concentration, and the proportion of women with positive urine glucose were similar across treatment groups. Traditional medicines and supplement use did not differ between groups; however, a higher frequency of other comedication use was reported in the efavirenz group (table 1).

At 72 weeks postpartum, 116 (93%) of 125 women in the dolutegravir group and 114 (91%) of 125 women in the efavirenz group had a viral load less than 50 copies per mL (primary endpoint). However, the median time to viral load suppression was significantly shorter in the dolutegravir group (median time 4·1 weeks [IQR 4·0–5·1]) compared with the efavirenz group (12·1 weeks [10·7–13·3]; adjusted hazard ratio [HR] 1·9 [95% CI 1·5–2·5]; figure 2A).

A similar pattern of virological response was observed for viral load of less than 1000 copies per mL endpoint, with a median time to suppression of 1·0 weeks (IQR 1·0–2·9) in the dolutegravir group compared with 3·7 weeks (3·0–4·0) in the efavirenz group (adjusted HR 1·8 [95% CI 1·4–2·4]; figure 2B). For both viral load suppression endpoints, similar findings were observed when stratified by site.

At 48 weeks postpartum, the median CD4 cell count in the dolutegravir group was slightly, but not significantly, higher than in the efavirenz group (704 cells per µL [IQR 500–976] in the dolutegravir group *vs* 642 cells per µL [433–904]; p=0·85), which can be explained by the differences observed at baseline. However, the median change from baseline was similar in both groups with an increase of 189 cells per µL (IQR 103–388) in the dolutegravir group and 203 cells per µL (120–352) in the efavirenz group.

There was a low rate of discontinuations and switches for any cause (virological failure, clinical failure, and adverse events). Eight (6%) women in the dolutegravir group and 12 (10%) women in the efavirenz group had virological failure (as defined by the protocol). Six (5%) women in the dolutegravir group and eight (6%) women in the efavirenz group were classified as having

virological failure on the basis of a viral load of less than 50 copies per mL not being reported by 24 weeks postpartum. Two (2%) women in the dolutegravir group and four (3%) in the efavirenz were classified as having virological failure because they had a previously suppressed viral load which then rebounded (>1000 copies per mL). Clinical failure was judged by the Safety and Endpoint Review Committee to have occurred in an additional 12 (10%) women in the dolutegravir group and ten (8%) women in the efavirenz group. These included women with persistent low level viraemia and those who rebounded without two consecutive viral loads of more than 1000 copies per mL, including a viral load of more than 1000 copies per mL at the last study visit. There was a low proportion of women discontinuing their assigned trial regimen: four (3%) in the efavirenz group and four (3%) in dolutegravir group. Two women discontinued efavirenz because of treatment-limiting toxicity (both related to liver dysfunction). No women discontinued in the dolutegravir group due to toxicity.

Four cases of infant transmission were detected. Three transmissions in the dolutegravir group that were detected at birth and judged to be in-utero transmissions as a result of PCR positivity at an early timepoint postpartum were reported previously.[3] An additional infant transmission occurred in the efavirenz group despite optimal maternal suppression (as judged by viral load <50 copies per mL) at 12, 24, 48, and 72 weeks postpartum. The infant tested positive at 72 weeks (confirmed by separate HIV DNA positive tests), after testing HIV DNA negative at birth, and 6 weeks, and 12 weeks postpartum. Infant visits at 24 or 48 weeks were missed; however, subsequent analysis of stored specimens were negative. The mother attended these visits and was HIV DNA undetectable. Both mother and infant had subtype D with viral genotypes susceptible to non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, and protease inhibitors. Sequencing of maternal and infant virus revealed no evidence of drug resistance in reverse transcriptase and protease genes. 18 polymorphisms (departure from HXB2 consensus) not associated with resistance were observed in virus recovered from the infant at the time of diagnosis. Exactly the same mutations were detected in the maternal plasma sample at baseline with an additional mixed call at position 232 of reverse transcriptase; these matching mutations confirmed that this was a linked transmission. There was no history of surrogate breastfeeding. The infant was exclusively breastfed until 24 weeks followed by mixed feeding; breastfeeding stopped at 48 weeks postpartum. No history of maternal mastitis was recorded throughout the postpartum period.

By 72 weeks postpartum, 57 (21%) of 268 women had had any type of serious adverse events during pregnancy and the postpartum period (table 2); 21 (7%) women had events in the postpartum period (table 2). No maternal deaths occurred. 49 (18%) women had grade 3 or worse serious adverse events in both pregnancy and the postpartum period. 19 (7%) women had grade 3 or worse adverse events only during postpartum period (table 2). Most events were related to pregnancy complications, investigations, and infections. Serious adverse events were reported by 33 (24%) of 135 women in the dolutegravir group and 24 (18%) of 133 women in the efavirenz group. This finding was largely driven by a higher frequency of pregnancy, puerperium, and perinatal conditions in the dolutegravir group primarily linked to prolonged pregnancy and pre-eclampsia.[3] Following causality assessments, eight (3%) women were deemed to have had adverse events associated with the study medication. Three (2%) women in the dolutegravir group and five (4%) of women in the efavirenz group had drug-related adverse events.

Overall, 136 (56%) of 242 infants had a serious adverse event. 11 (5%) of the 242 infants died (eight [7%] of 121 infants in the dolutegravir group and three [2%] of 121 infants in the efavirenz group). Six deaths were previously reported;[3] the deaths were associated with severe prematurity and respiratory distress or asphyxia. The five additional deaths (four [3%] in the dolutegravir

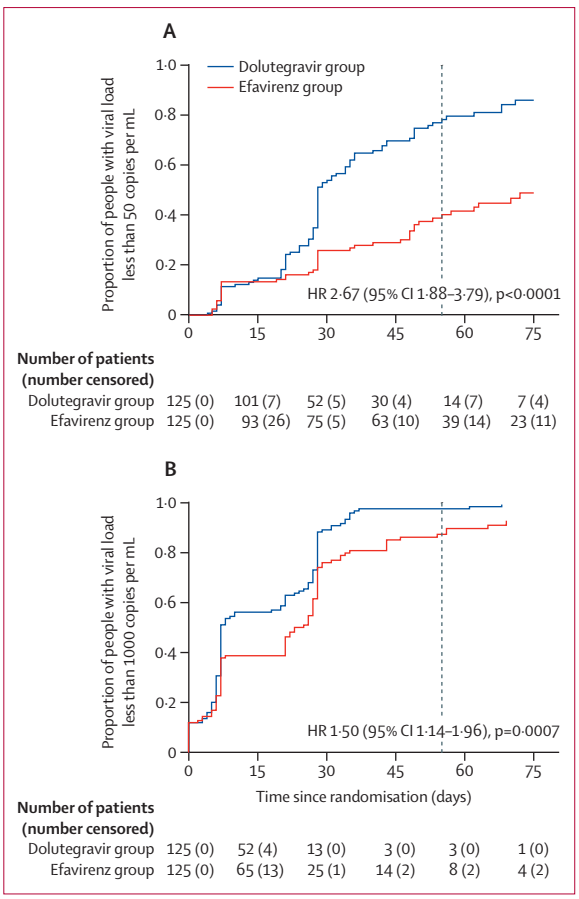


***Figure 2:*** **Kaplan-Meier plot of time from randomisation to a viral load of <50 (A) and <1000 copies per mL (B)**
HR=hazard ratio.

| | Total | Dolutegravir group | Efavirenz group |
|---|---|---|---|
| **Mothers** | | | |
| Number of mothers | 268 | 135 | 133 |
| Serious adverse events | | | |
| Overall (pregnancy and postpartum events) | | | |
| 1 or more serious adverse event | 57 (21%) | 33 (24%) | 24 (18%) |
| Serious adverse event grade ≥3 | 49 (18%) | 28 (21%) | 21 (16%) |
| 1 or more drug related serious adverse event | 8 (3%) | 3 (2%) | 5 (4%) |
| Deaths | 0 | 0 | 0 |
| Postpartum events | | | |
| 1 or more serious adverse event | 21 (8%) | 9 (7%) | 12 (9%) |
| Serious adverse event grade ≥3 | 19 (7%) | 8 (6%) | 11 (8%) |
| 1 or more drug related serious adverse event | 7 (3%) | 2 (2%) | 5 (4%) |
| System organ class | | | |
| Blood and lymphatic system disorders | 3 (1%) | 2 (2%) | 1 (1%) |
| Gastrointestinal disorders | 1 (<1%) | 1 (1%) | 0 |
| Infections and infestations | 11 (4%) | 7 (5%) | 4 (3%) |
| Pregnancy, puerperium, and perinatal conditions excluding stillbirths | 24 (9%) | 15 (11%) | 9 (7%) |
| Renal and urinary disorders | 3 (1%) | 2 (2%) | 0 |
| Vascular disorders | 1 (<1%) | 0 | 1 (1%) |
| **Infants** | | | |
| Number of infants | 242 | 121 | 121 |
| Serious adverse events | | | |
| 1 or more serious adverse event | 136 (56%) | 73 (60%) | 63 (52%) |
| Serious adverse event grade ≥3 | 60 (25%) | 32 (26%) | 28 (23%) |
| 1 or more drug related serious adverse event | 0 | 0 | 0 |
| Deaths | 11 (5%) | 8 (7%) | 3 (2%) |
| System organ class | | | |
| Congenital, familial, and genetic disorders | 98 (40%) | 48 (40%) | 50 (41%) |
| Ear and labyrinth disorders | 2 (1%) | 2 (2%) | 0 |
| Hepatobiliary disorders | 1 (<1%) | 1 (1%) | 0 |
| Infections and infestations | 36 (15%) | 18 (15%) | 18 (15%) |
| Injury, poisoning, and procedural complications | 4 (2%) | 3 (3%) | 1 (1%) |
| Nervous system disorders | 4 (2%) | 3 (3%) | 1 (1%) |
| Respiratory, thoracic, and mediastinal disorders | 19 (8%) | 12 (10%) | 7 (6%) |

*Table 2:* **Serious adverse events**

group and one [1%] in the efavirenz group), were caused by infections, respiratory disorders, and general disorders. In addition to these deaths, 60 (25%) infants had grade 3 or worse adverse events (table 2). The high frequency of these events were primarily driven by congenital disorders (umbilical hernia and birth marks). None of the infant events were deemed to be drug related.

When adjusted for study site, women in the dolutegravir group weighed more on average than women in the efavirenz arm (figure 3). The mean change in maternal weight from delivery to 72 weeks postpartum was –1·16 kg (SD 6·69); women in the dolutegravir group lost less weight (–0·67 kg; SD 7·53) than women in the efavirenz group (–1·59 kg; SD 5·91; appendix p 136). Additionally, differences were observed by country: women in South Africa weighed more than women in Uganda (figure 3). Similar findings were observed for BMI (appendix p 136). No other major safety concerns were observed with no significant differences between the two treatment groups in incidence of maternal glycosuria, infant hyperglycaemia, or proportion of women with anxiety and depression.

Despite encouraging contraceptive use following the index pregnancy, 18 subsequent pregnancies were reported, and of these 12 women provided consent for follow-up of the subsequent pregnancy (four [3%] women in the dolutegravir group and eight [6%] in the efavirenz group). All women in the dolutegravir group were switched to receive efavirenz when the subsequent pregnancy was confirmed. Two pregnancies in the dolutegravir group and three in the efavirenz group resulted in pregnancy loss and seven live births.

## Discussion

In the DolPHIN-2 trial, we evaluated the safety and efficacy of dolutegravir-based and efavirenz-based regimens when initiated in the third trimester of pregnancy. Women randomly assigned to the dolutegravir group had viral suppression after ART initiation more quickly than those in the efavirenz group, with virological suppression maintained throughout the breastfeeding period. These results support updated WHO recommendations for HIV treatment in pregnant women and contribute to the growing evidence of the safety and efficacy of dolutegravir in pregnancy and the breastfeeding period.

Despite significant differences in the time to achieve an undetectable viral load, we found both regimens had similar long-term virological efficacy, with more than 90% of women reported to have viral suppression by 72 weeks postpartum. Similar findings have been reported for non-pregnant adults.[7] Benefits of both regimens were maintained in long-term follow-up resulting in sustained viral suppression including in the efavirenz group, for which concerns have been raised about increasing levels of non-nucleoside reverse transcriptase resistance.[2] In our study, mothers in the dolutegravir group had a superior virological response during the first few weeks of therapy where appreciable differences were observed,[3] consistent with findings from other randomised studies in non-pregnant adults.[8,9]

In our study, maternal dolutegravir-based and efavirenz-based regimens were both safe and well tolerated in mothers and their infants. The overall incidence of serious adverse events was similar to previous randomised trials in similar settings in sub-Saharan Africa.[10,11] Similar to our primary endpoint analysis, overall we observed differences in adverse events by treatment group, with a higher proportion of serious adverse events in the dolutegravir group. However, this difference was primarily driven by pregnancy, puerperium, and perinatal events, which have been previously reported.[3] At 6 weeks postpartum, women in the dolutegravir group had double the number of

events compared with women in the efavirenz group; however, by 72 weeks postpartum the difference between the two groups was smaller because after delivery there was a reversal with fewer events in the dolutegravir group than in the efavirenz group. Our results at time of birth differ to those reported in the VESTED trial,[4] in which no differences were observed between the dolutegravir and efavirenz treatment groups. This is possibly due to differences in the study populations: women in our study were recruited late in pregnancy (>28 weeks); therefore, they were probably at a higher risk of adverse pregnancy outcomes compared with women included in the VESTED trial, who presented earlier in pregnancy (14–28 weeks gestation).[12–14]

Of the four cases of perinatal transmission, three were previously reported as in-utero transmissions on the basis of PCR positivity at 3, 5, and 11 days.[3] In the VESTED trial,[4] infant transmissions were also observed in the dolutegravir group and determined to be in-utero transmissions.[4] We reported an additional infant transmission in the efavirenz group occurring between 12 and 72 weeks of age. This was despite repeated and durable plasma viral load suppression in the mother; transmission is most probably associated with breastfeeding. The risk of late postnatal perinatal transmission has been shown to be higher in women breastfeeding beyond 6 months, particularly when viral load remains unsuppressed.[15] Even though breastfeeding continued until 12 months postpartum, there was optimal maternal suppression throughout the breastfeeding period. An undetectable viral load during breastfeeding greatly reduces perinatal transmission risk; however, it does not completely eliminate this possibility because of differences in HIV dynamics and viral load between breastmilk and plasma.[16] Perinatal transmission has been shown in previous studies done in similar settings in which perinatal transmission during breastfeeding was observed despite undetectable breastmilk HIV viral load.[17] Additionally, there is another report of transmission at the closest timepoint to which both plasma and breastmilk viral load were undetectable.[15] More investigations are underway to characterise breastmilk viral loads in this mother to determine if there were discordant virological responses with maternal plasma viral load. An alternative explanation could be the presence of persistent cell-associated HIV viral reservoirs in breastmilk not eliminated by ART because of the differences between blood and breastmilk cells.[18]

Alongside the widespread use of dolutegravir there have been reports of hyperglycaemia, greater weight gain, treatment emergent obesity with adults initiating dolutegravir compared with those initiating efavirenz.[19–21] There has also been some suggestion of heterogeneity of effects across populations, especially in non-pregnant women who showed large increases in fat mass in the ADVANCE trial.[20] We found that at 72 weeks postpartum, no differences were observed between maternal glycosuria or infant hyperglycaemia by treatment group;

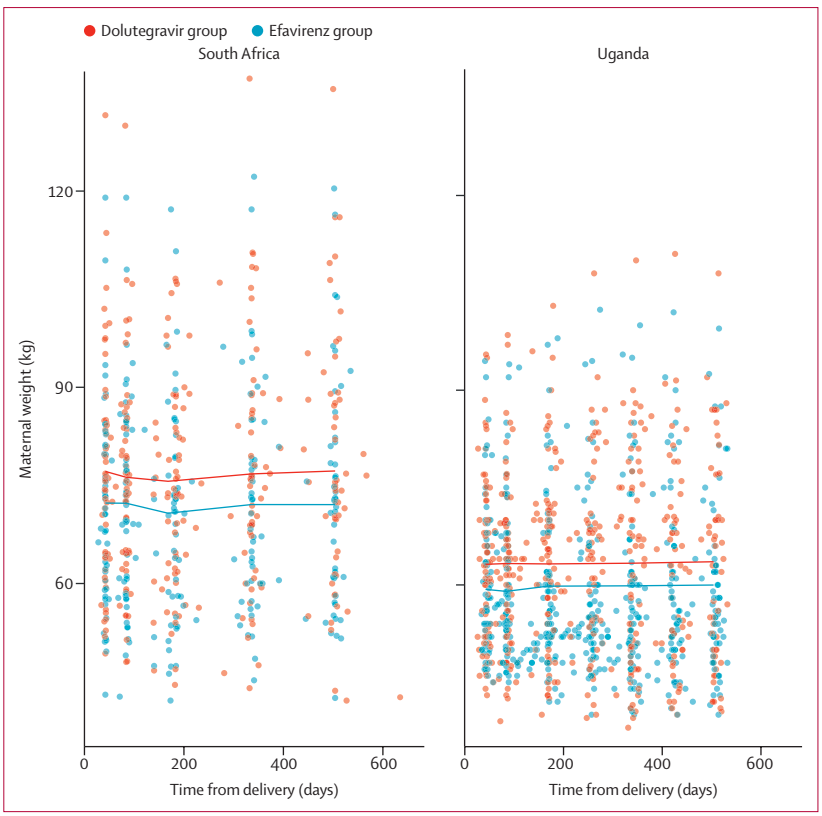


*Figure 3:* **Mean predicted postpartum weight**

however, we did find that women in the dolutegravir group had higher bodyweight than those in the efavirenz group, which is probably driven in part by differences in postpartum weight changes. Women on dolutegravir retained more weight postpartum than those on efavirenz, which is consistent with data from an observational cohort in Botswana that found that dolutegravir was associated with persistently higher weight in the post-partum period than efavirenz.[22] Differences in weight retention in women across our two sites were reported; women in South Africa had higher weight retention, which points to potential regional differences that require more investigation with studies from different settings with longer follow-up periods and standardised end-points. Excess weight retention in women postpartum is particularly concerning because it is preferentially deposited in central rather than peripheral sites, increasing the risk of cardiometabolic conditions.[23,24] Mechanisms underlying potential dolutegravir-associated weight gain and retention are currently unclear; a proposed direct mechanism includes an effect on adipogenesis and gut microbiome disturbance.[25] Indirect pathways through reduced side-effects of newer anti-retrovirals have been suggested; however, sensitivity analyses from the ADVANCE trial,[20] which eliminated some of these adverse effects, did not find any weight gain differences.[20] Data on the effect of dolutegravir on

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gestational weight gain and postpartum weight retention are emerging, but more mechanistic studies are required because dolutegravir will be a mainstay in treatment of HIV in pregnant women and women of childbearing age. Additional qualitative studies are in progress to evaluate how postpartum weight gain is perceived by mothers, and its potential effect on adherence.

Our findings support updated WHO treatment recommendations in pregnant and breastfeeding women. Dolutegravir was found to exhibit superior virological efficacy with rapid viral suppression following initiation, and to be safe and well tolerated throughout the breastfeeding period. The infant HIV infection in the efavirenz group highlights the potential for transmission during breastfeeding despite evidence of virological suppression. An extended phase of follow-up of our cohort is in progress, as with other cohorts evaluating dolutegravir use as first-line therapy in sub-Saharan Africa, to look for longer-term toxicity in this population.[19,20] Long-term follow-up of exposed infants will also be necessary to add to the evidence of dolutegravir safety. As dolutegravir use increases, enhanced pharmacovigilance systems will be required that can better capture safety data routinely.

### The DolPHIN-2 Study Team

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### Contributors

SK, DW, ML, LM, CO, CW, and MT designed the study. SK, KB, HR, AC, and CW developed the protocol. TRM, IN, KK, AC, TC, HR, LR, JR, L-AS, MM, KB, KS, AT, HT, EMH, JC, N-CH, DB, DW, JB, YA, SB, CW, MT, CO, ML, LM, and SK contributed equally to study completion. DW, TC, LR, JR, and HR did the analysis. DW and TC verified the data. TRM, SK, LM, MT, DB, CW, CO, and ML wrote the manuscript. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

### Declaration of interests

DB, DW, ML, LM, MT, and SK report grants from Unitaid during the study. DB reports grants from ViiV Healthcare, Merck, and Gilead; consulting fees from Merck; and personal fees from Pfizer, ViiV Healthcare, outside of the submitted work. SK reports consulting fees from ViiV Healthcare, Merck, and Thera Technologies and personal fees from ViiV Healthcare and Merck outside of the submitted work. ML reports a grant and personal fees from Janssen outside of the submitted work. All other authors report no competing interests.

### Data sharing

We adhere to the principles of the UK Concordat on Open Research Data, which recognises that research data should wherever possible be made openly available for use by others in a manner consistent with relevant legal, ethical, disciplinary, and regulatory frameworks and norms, and with due regard to the cost involved. Our data will be assigned a DOI through deposition in the University of Liverpool Research Data Catalogue and shared under a data transfer agreement (or equivalent; eg, as part of a research collaboration agreement or confidentiality disclosure agreement), with all originating DolPHIN-2 data remaining the property of the University of Liverpool.

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