



Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial

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Summary

Background Late initiation of HIV antiretroviral therapy (ART) in pregnancy is associated with not achieving viral suppression before giving birth and increased mother-to-child transmission of HIV. We aimed to investigate virological suppression before giving birth with dolutegravir compared with efavirenz, when initiated during the third trimester.

Methods In this randomised, open-label trial, DolPHIN-2, we recruited 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 ART in third trimester. Participants were randomly assigned (1:1) to dolutegravir-based or efavirenz-based therapy. HIV viral load was measured 7 days and 28 days after antiretroviral initiation, at 36 weeks' gestation, and at the post-partum visit (0–14 days post partum). The primary efficacy outcome was a viral load of less than 50 copies per mL at the first post-partum visit, and the primary safety outcome was the occurrence of drug-related adverse events in mothers and infants until the post-partum visit. Longer-term follow-up of mothers and infants continues. This study is registered with ClinicalTrials.gov, NCT03249181.

Findings Between Jan 23, and Aug 15, 2018, we randomly assigned 268 mothers to dolutegravir (135) or efavirenz (133). All mothers and their infants were included in the safety analysis, and 250 mothers (125 in the dolutegravir group, 125 in the efavirenz group) and their infants in efficacy analyses, by intention-to-treat analyses. The median duration of maternal therapy at birth was 55 days (IQR 33–77). 89 (74%) of 120 in the dolutegravir group had viral loads less than 50 copies per mL, compared with 50 (43%) of 117 in the efavirenz group (risk ratio 1·64, 95% CI 1·31–2·06). 30 (22%) of 137 mothers in the dolutegravir group reported serious adverse events compared with 14 (11%) of 131 in the efavirenz group ($p=0\cdot013$), particularly surrounding pregnancy and puerperium. We found no differences in births less than 37 weeks and less than 34 weeks gestation (16·4% vs 3·3%, across both groups). Three stillbirths in the dolutegravir group and one in the efavirenz group were considered unrelated to treatment. Three infant HIV infections were detected, all in the dolutegravir group, and were considered likely to be in-utero transmissions.

Interpretation Our data support the revision to WHO guidelines recommending the transition to dolutegravir in first-line ART for all adults, regardless of pregnancy or child-bearing potential.

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Introduction

Delayed initiation of antiretroviral therapy (ART) until the third trimester of pregnancy is common in many settings where HIV is prevalent and is associated with increased mother-to-child transmission of HIV and infant mortality.^{1–3} In the Uganda Demographic Health Survey,¹ the first antenatal clinic appointment occurred at an average of 27·9 weeks; and in South Africa, 11–19% of pregnant women presented at 28 weeks gestation or later.²

Although the causes of infant HIV transmissions are multifactorial, one important factor might be the inability of existing first-line efavirenz-based therapy to suppress HIV viral load at or before labour and birth, a time when transmission risk is highest. The integrase inhibitor dolutegravir reduces HIV viral load to less than 50 copies

per mL after a median of 28 days in non-pregnant adults, compared with 84 days for efavirenz.⁴ Dolutegravir might consequently be particularly useful for women presenting late in pregnancy; however, safety and efficacy data are insufficient.

We aimed to assess whether the rapid virological decline, tolerability, and high HIV resistance barrier of dolutegravir-containing regimens⁴ conferred additional benefits to HIV-positive women initiating treatment in late pregnancy.

Methods

Study design and participants

DolPHIN-2 was a randomised, open-label trial done in South Africa and Uganda. In Cape Town, South Africa, participants were enrolled at Gugulethu Community

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Research in context

Evidence before this study

Late initiation of antiretroviral therapy in the third trimester of pregnancy is associated with a seven-times increased risk of infant HIV transmissions, and a doubling of infant mortality in the first year of life. The period of greatest risk for mother-to-child HIV transmission is during labour and delivery, and risks are highest for mothers who are not virologically suppressed at this time. We search PubMed using the search terms "HIV", "pregnancy", "initiation", "antiretroviral therapy", "Africa", for articles published from Jan 1, 1995, to Feb 10, 2020. We found that across sub-Saharan Africa, late presentation for antiretroviral therapy during pregnancy is common (up to one in five pregnancies from South Africa). Conventional (efavirenz-based) antiretroviral regimens might simply have insufficient time to suppress maternal HIV viral load quickly enough in this scenario. Newer, dolutegravir-based regimens are associated with faster declines in HIV viral load in non-pregnant adults, reaching undetectable (<50 copies per mL) viral load after a median of 28 days, compared with 84 days for efavirenz-based regimens. However, the safety and efficacy of dolutegravir in pregnancy is unknown, and randomised trial data informing selection of newer antiretroviral regimens for use in pregnant mothers are scarce. Moreover, data from a large birth registry in Botswana suggest that periconception use of dolutegravir was associated with an excess risk of neural tube defects. This safety concern has led to precautionary alerts from WHO and regulatory agencies and

the restriction of use of dolutegravir in pregnancy or women of child-bearing potential.

Added value of this study

Our study addresses an important knowledge gap around antepartum transmission of HIV in women initiating treatment late in pregnancy. Dolutegravir was associated with higher rates of viral load reduction compared with efavirenz in pregnant women. Although both regimens were well tolerated by mothers and infants, more mothers who received dolutegravir developed serious adverse events (driven mainly by prolonged pregnancies) than did those who received efavirenz.

Implications of all the available evidence

An assessment of the risks and benefits of drug use in pregnancy needs to be separately done according to trimester of exposure, especially given that the risks might be increased in early pregnancy, whereas benefits might be greater for pregnant mothers starting treatment in late pregnancy. The large differences in rates of virological suppression between dolutegravir-based and efavirenz-based regimens suggest that substantial public health benefits could accrue if dolutegravir-based therapy is widely implemented. Our data support the revision to WHO guidelines recommending the transition to dolutegravir in first-line antiretroviral therapy for all adults, regardless of pregnancy or child-bearing potential. The importance of the finding of more adverse events in mothers in the dolutegravir group is unclear and should be confirmed in other studies.

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Health Centre, following recruitment from eight primary antenatal facilities in the surrounding area. In Kampala, Uganda, participants were enrolled at the Infectious Diseases Institute, following recruitment at Kawempe Hospital (a tertiary obstetric referral unit) or eight primary antenatal facilities throughout Kampala and Wakiso District.

We enrolled participants who met all the following inclusion criteria: women aged at least 18 years with untreated but confirmed HIV infection, positive pregnancy test, estimated gestation of at least 28 weeks, and willing to provide written informed consent. We excluded individuals with any of the following: 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 randomisation; 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 and 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 receiving any drugs that significantly interact with efavirenz or dolutegravir within the preceding 2 weeks. On June 1, 2018, the protocol was amended to exclude patients with a pretreatment HIV viral load of less than 50 copies per mL.

Ethics review committees in South Africa, Uganda, and the UK approved the study. The data and safety monitoring board did a planned interim safety analysis after the first 125 mothers had given birth and were notified of all infant HIV transmissions.

A summary of the protocol is available on ClinicalTrials.gov (NCT03249181).

Randomisation and masking

Participants were randomly assigned (1:1) by the study investigators to receive efavirenz-based or dolutegravir-based regimens. Because national policy required ART to commence without delay in our study population, participants meeting eligibility criteria on the basis of history and examination (before the availability of blood results) were enrolled with block randomisation (block size of 4, stratified by country, with concealment of allocation until assignment) to commence treatment on the same day as diagnosis. Any laboratory results that

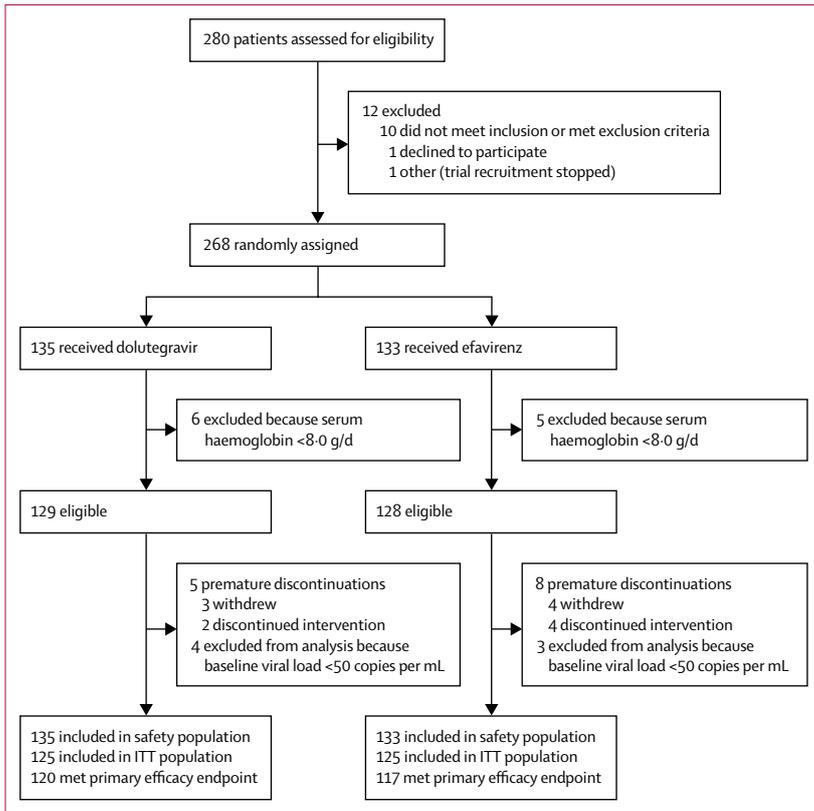


Figure 1: Trial profile
ITT=intention to treat.

See Online for appendix rendered participants ineligible led to withdrawal at confirmatory visits 7 days later.

Procedures

Ultrasound examination was done at screening or within 2 weeks of enrolment across both sites. Gestational age at screening was a best estimate based on a combination of recall of last menstrual period, pubic symphysis-fundal height, and fetal ultrasound (if done at screening). The following tests were done at screening: HIV-1 and HIV-2 antibodies, CD4 cell count, full blood count, urea concentrations, creatinine and electrolytes concentrations, bilirubin concentrations, alanine aminotransferase concentrations, and creatinine phosphokinase activity. HIV viral load and maternal safety bloods were also collected at 7 days and 28 days after antiretroviral initiation, at 36 weeks' gestation (if applicable), and at the first post-partum visit (0–14 days post partum). Study site births were attended by study staff and for offsite births the study team arranged review of mothers and infants within 14 days.

Mothers randomly assigned to the dolutegravir group received dolutegravir (50 mg) plus generic tenofovir disoproxil fumarate (300 mg) coformulated with emtricitabine (200 mg; mothers in South Africa) or lamivudine 300 mg (mothers in Uganda) once daily,

taken orally. Mothers in the efavirenz group received a generic single fixed-combination pill of efavirenz (600 mg) with tenofovir plus either emtricitabine (South Africa) or lamivudine once daily (Uganda). Each site had established protocols for supporting adherence, psychological counselling, and health advice on pregnancy and breastfeeding. Use of traditional medications, supplements, and other comedications was checked at every study visit, and drug interactions managed as appropriate. In keeping with national guidelines in South Africa and Uganda, newborn infants were prescribed nevirapine for 6 weeks.

We continue to follow up mothers and infants to 72 weeks post partum to assess the following secondary outcomes: maternal viral load response to 48 and 72 weeks (proportion with <50 and <1000 copies per mL); occurrence of infant HIV transmissions at 48 and 72 weeks; dolutegravir exposure in maternal plasma, breast milk, and infants; and virological resistance.

Outcomes

The primary efficacy outcome was HIV viral load less than 50 copies per mL at birth, and the primary safety outcome was frequency of drug-related adverse events. Secondary outcomes included viral load of less than 1000 copies per mL at birth, occurrence of mother-to-child transmission, and safety and tolerability of dolutegravir in mothers and breastfed infants (appendix p 6).

We categorised adverse events and serious adverse events according to the Medical Dictionary for Regulatory Activities,⁵ with severity classified according to the Division of AIDS Grading Scale (version 2.1, July 2017). A safety endpoint review committee (masked to allocation group) assessed all serious adverse events, stillbirths, infant deaths, and infant transmissions for associations with study medication (using the Liverpool Adverse Drug Reaction Causality Assessment Tool⁶), as well as likelihood of maternal immune reconstitution inflammatory syndrome.

Case definitions for immune reconstitution inflammatory syndrome are heavily reliant on clinical judgement, given that the symptoms are poorly defined and not specific for immune reconstitution, and the scarcity of diagnostic tests. We defined immune reconstitution inflammatory syndrome as any of the following developing within 12 weeks of treatment initiation, in the absence of an alternative diagnosis: fever and increased or new lymphadenopathy; pleural and pericardial effusions, ascites, abscess, cutaneous lesions, and new or expanding central nervous lesions; abnormal results on liver function tests or hepatitis; or atypical or exaggerated presentation of an opportunistic infection or tumour.^{7–9} Liver function abnormalities, preterm birth, pre-eclampsia, and neurological toxic effects were also identified a priori as adverse events of special interest.

For livebirths, we recorded the following infant outcomes at the post-partum visit: mode of delivery;

duration of rupture of membranes; any complications; neonatal length, weight, and head circumference; Apgar score; and evidence of intrauterine growth retardation. At the post-partum visit we used COBAS TaqMan (Roche Molecular Systems, Branchburg, NJ, USA) for HIV-1 DNA tests at the research sites.

We confirmed late preterm (<37 weeks gestation) and preterm (<34 weeks, classified as serious adverse events) births by Ballard Score¹⁰ if assessed within 7 days of birth. When any discrepancy arose, a paediatrician who was masked to treatment group assessed the infant and maternal dating assessments within 48 h of birth. We assessed congenital anomalies using the WHO protocol.¹¹ For all infant deaths, we sought consent for verbal autopsy to elucidate the cause of death.

Statistical analysis

We report a prespecified analysis of the primary efficacy outcome reached at the post-partum visit, with accompanying safety data on mother-infant pairs up to 6 weeks (plus or minus 2 weeks) post partum. We calculated sample size on the basis of clinical trial simulations (SAS version 9.3) using weighted probabilities (the weighted gestation-specific probabilities given various probabilities at various gestational ages) for achieving a viral load of less than 50 copies per mL for dolutegravir and efavirenz in treatment-naive, non-pregnant adults.⁴ Because the period of ART before birth could vary from a 1 day to 12 weeks, we estimated statistical power from simulating five different distributions of gestational age at starting treatment in the third trimester.¹² Allowing for 20% drop-out, recruitment of 250 HIV-positive women would retain at least 99% power to detect a superiority absolute difference of 28–38% between groups across all scenarios at the 5% level of significance.

Primary analyses were based on intention-to-treat. A generalised linear model for the primary endpoint analysis included treatment as a study variable, baseline viral load ($\geq 100\,000$ or $< 100\,000$ copies per mL) and baseline CD4 cell count (≥ 200 or < 200 cells per μL) as covariables, generating a risk ratio (95% CI) and risk difference (95% CI) between groups. Further covariate-adjusted generalised linear model analysis of the primary endpoint also incorporated age (younger than or equal to or older than the median), country, and gestational age (< 36 or ≥ 36 weeks) at baseline. Subgroup analysis was done for each of the five prespecified covariates (age, country [South Africa vs Uganda], viral load, CD4 cell count, and gestational age at initiation of HIV therapy). Sensitivity analysis of missing primary endpoint data was also done assuming mothers did not achieve viral loads less than 50 copies per mL, achieved viral loads less than 50 copies per mL; and did not achieve suppression in the dolutegravir group but achieved suppression in the efavirenz group.

For time-to-event analyses, we used the actual visit dates to calculate time of viral load suppression. Kaplan-Meier curves for each treatment group were

	Dolutegravir (n=125)	Efavirenz (n=125)	Total (n=250)
Age (years)	28.0 (5.3)	27.4 (5.1)	27.7 (5.2)
CD4 cell count (cells per μL)	464 (329–664)	414 (265–581)	446 (296–633)
Log ₁₀ viral load (copies per mL)	4.4 (3.6–4.7)	4.6 (3.9–4.8)	4.4 (3.8–4.8)
Estimated gestation age (weeks)	31 (29–34)	31 (29–33)	31 (29–34)
Gravidity	3 (2–4)	3 (2–4)	3 (2–4)
Previous livebirths	2 (1–3)	1 (1–2)	2 (1–3)
Primigravida	16 (13%)	14 (11%)	30 (12%)
Previous stillbirths	2 (2%)	2 (2%)	4 (2%)
Use of herbal or traditional medicine	42 (34%)	45 (36%)	87 (35%)
Use of supplements and vitamins	48 (38%)	46 (37%)	94 (38%)
Other comedications	31 (25%)	38 (30%)	69 (28%)
Tobacco consumption in pregnancy	7 (6%)	7 (6%)	14 (6%)
Alcohol consumption in pregnancy	22 (18%)	27 (22%)	49 (20%)
History of psychiatric disorders	8 (7%)	3 (2%)	11 (4%)
Weight (kg)	75.1 (16.1)	71.8 (15.6)	73.4 (16.0)
Height (cm)	157.2 (7.8)	158.0 (8.1)	157.6 (7.9)
Site			
South Africa	57 (46%)	57 (46%)	114 (46%)
Uganda	68 (54%)	68 (54%)	136 (54%)

Data are mean (SD), median (IQR), or n (%).

Table 1: Baseline demographics in the intention-to-treat population

compared by the log-rank test and hazard ratio (95% CI), calculated using the Cox regression model, with viral load and CD4-stratified covariables. Binary secondary outcomes were analysed in a similar way as the primary endpoint analysis. This trial is registered with ClinicalTrials.gov, NCT03249181.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 23, and Aug 15, 2018, we screened 280 pregnant mothers and randomly assigned 268 to treatment (figure 1; table 1). Median time on treatment until birth was 55 days (IQR 33–77) days: 52 days (31–75) in the dolutegravir group and 59 days (37–80) in the efavirenz group.

The primary endpoint of viral load less than 50 copies per mL at birth by intention-to-treat analysis was met in 89 (74.2%) of 120 mothers receiving dolutegravir, compared with 50 (42.7%) of 117 in the efavirenz group (table 2). On the basis of Kaplan-Meier analysis (figure 2), the median time to achieve viral loads less than 50 copies per mL was 28 days (95% CI 28–34) and less than 1000 copies per mL was 7 days (7–20) in the dolutegravir group and 82 days (55–97) and 23 days (21–27) in the efavirenz group.

In a covariate-adjusted analysis, the risk ratio was unaltered by maternal age, country, baseline viral load,

	Patients with events, n/N (%)		Estimate of relative risk (95% CI), p value (Dolutegravir vs efavirenz)	Estimate of risk difference (95% CI), p value (Dolutegravir vs efavirenz)	p value for interaction
	Dolutegravir	Efavirenz			
Maternal HIV viral load <50 copies per mL*	89/120 (74%)	50/117 (43%)	1.64 (1.31 to 2.06), <0.0001	29.78 (18.18 to 41.37), <0.0001	..
Maternal HIV viral load <50 copies per mL at giving birth†	1.65 (1.31 to 2.06), <0.0001	30.48 (18.97 to 41.98), <0.0001	..
Maternal HIV viral load <1000 copies per mL*	112/120 (93%)	96/117 (82%)	1.12 (1.00 to 1.25), 0.042	9.89 (0.94 to 18.84), 0.030	..
Maternal HIV viral load <1000 copies per mL at giving birth†	1.10 (0.99 to 1.23), 0.089	10.36 (0.26 to 20.47), 0.044	..
Subgroup analyses*					
Age (years)					
<28	39/54 (72%)	24/59 (41%)	1.71 (1.20 to 2.43), 0.0031	31.60 (14.56 to 48.64), 0.0003	0.87
≥28	50/66 (76%)	26/58 (45%)	1.61 (1.20 to 2.16), 0.0014	26.66 (10.49 to 42.83), 0.0012	..
Country					
South Africa	43/56 (77%)	25/55 (46%)	1.64 (1.19 to 2.25), 0.0024	30.01 (12.97 to 47.04), 0.0006	0.93
Uganda	46/64 (72%)	25/62 (40%)	1.55 (1.16 to 2.09), 0.0036	28.45 (11.18 to 45.71), 0.0012	..
Viral load at baseline (copies per mL)					
<100 000	81/103 (79%)	47/95 (50%)	1.59 (1.27 to 1.99), <0.0001	29.13 (16.34 to 41.91), <0.0001	0.27
≥100 000	8/17 (47%)	3/22 (14%)	3.41 (1.04 to 11.14), 0.042	32.93 (5.14 to 60.72), 0.020	..
CD4 count at baseline (cells per µL)					
≥200	81/107 (76%)	46/99 (47%)	1.61 (1.27 to 2.02), <0.0001	28.95 (16.48 to 41.42), <0.0001	0.60
<200	8/13 (62%)	4/18 (22%)	2.30 (0.86 to 6.15), 0.097	35.39 (3.35 to 67.43), 0.030	..
Gestational age at initiation of HIV therapy (weeks)					
<36	72/97 (74%)	46/103 (45%)	1.64 (1.29 to 2.07), <0.0001	29.80 (17.34 to 42.25), <0.0001	0.52
≥36	17/23 (74%)	4/14 (29%)	1.35 (0.79 to 2.30), 0.28	27.90 (-9.55 to 65.35), 0.14	..

*The generalised linear model had the treatment as a study variable, viral load (≥100 000 or <100 000 copies per mL) and CD4 count (≥200 or <200 cells per µL) as covariables. †The generalised linear model had the treatment as a study variable, viral load (≥100 000 or <100 000 copies per mL), CD4 count (≥200 or <200 cells per µL), age younger than or equal to or older than the median, country (South Africa or Uganda), and gestational age at enrolment (<36 or ≥36 weeks) as covariables.

Table 2: Efficacy results by generalised linear model

baseline CD4 cell count, or gestation at enrolment, with consistent between-treatment differences across these covariates and no significant interactions observed. A sensitivity analysis (appendix p 1) showed that results for the primary endpoint analyses are consistent and robust. The secondary endpoint of viral load less than 1000 copies per mL at birth was also more likely to be met in women in the dolutegravir group than in those in the efavirenz group (table 2; figure 2).

Three mother-to-child transmissions of HIV were detected, all in the dolutegravir group, and each confirmed by two to four separate HIV DNA-positive tests. The first infant tested HIV-positive at age 5 days, after 35 days of maternal dolutegravir from 32 weeks of gestation. The second infant tested HIV DNA-positive at age 3 days, after 32 days of maternal dolutegravir from 32 weeks of gestation, and the third tested positive at age 11 days, after 24 days of maternal dolutegravir from 30 weeks of gestation. The maternal viral load at the post-partum visit was less than 50 copies per mL in the first two mothers (with baseline viral loads of 48 969 copies per mL and 32 844 copies per mL), and in the third mother was 31 354 copies per mL at baseline, and 200 copies per mL at birth. We considered in-utero transmission likely, given

the early PCR-positivity of each infant, coupled with the low maternal viral loads at birth. All three mothers remained well, without signs of illness or immune reconstitution inflammatory syndrome.

Although ART was well tolerated across both groups, more mothers in the dolutegravir than in the efavirenz group reported any type of serious adverse event (table 3). This finding was driven by a higher overall frequency of pregnancy, puerperium, and perinatal events in mothers receiving dolutegravir than in those receiving efavirenz (table 3; appendix pp 2, 3), most of whom were judged to have prolonged pregnancy beyond term, with or without other conditions, which led to caesarean sections being done. Overall, 12 (9%) women had caesarean sections in the dolutegravir group and seven (9%) in the efavirenz group (of which one was in the mother who had a stillbirth in the efavirenz group). At the 28-day visit, we observed a modest increase in serum creatinine from baseline of 0.08 mg/dL in the dolutegravir group and of 0.02 mg/dL in the efavirenz group ($p < 0.0001$). Antepartum change in weight over the first 28 days of treatment did not differ between groups (data not shown).

Four stillbirths were reported: three (2.2%) in the dolutegravir group and one (<1%) in the efavirenz group.

In the dolutegravir group, the first was a macerated stillbirth at 40 weeks' gestation, judged to be related to maternal syphilis. The second was at 36 weeks' gestation following uterine rupture and haemoperitoneum, with a history of maternal syphilis. The third was a macerated stillbirth at 41 weeks' gestation to a mother with a history of intermittent fevers (onset preceding ART) and respiratory symptoms, presumptively treated for pulmonary tuberculosis, with a history of traditional medicine use and treatment for malaria at 16 weeks' gestation. The stillbirth in the efavirenz group was a post-term pregnancy at 41 weeks' gestation, with evidence of fetal distress. All four stillbirths were considered unlikely to be related to maternal antiretrovirals or immune reconstitution inflammatory syndrome.

242 livebirths (123 in the dolutegravir group and 119 in the efavirenz group) were assessed, with a median gestation at birth of 39 weeks (IQR 37·3–40·3) for both groups, and no significant difference in the proportion of preterm and late-preterm births (table 3), frequency of serious adverse events, or infant birthweights between groups. Six (3%) of 242 infant deaths were reported (four [3%] in the dolutegravir group and two [2%] in the efavirenz group; appendix p 6). Two (<1%) deaths were related to severe prematurity (a 1-day old twin born at 28 weeks' gestation in the efavirenz group, and a 19-day old infant born at 32 weeks' gestation in the dolutegravir group, whose mother had an antepartum haemorrhage). Four (2%) deaths were related to respiratory distress or asphyxia: three (2%) in the dolutegravir group (aged 2, 47, and 88 days, born at full term) and one in the efavirenz group (aged 14 days, born at 35 weeks' gestation).

Congenital disorders did not differ between groups, and comprised umbilical hernias, birth marks, skin dimples, acrochordon, heterochromia iridis, laryngomalacia, strabismus, talipes, cleft palate, and polydactyly (appendix pp 4, 5). No neural tube defects were reported.

Discussion

Women on dolutegravir-based therapy were more likely to achieve viral loads less than 50 copies per mL (or less likely to have a viral load of ≥ 50 copies per mL) at the time of giving birth compared with those taking efavirenz-based regimens, when initiated in the third trimester. These data address an important knowledge gap around antepartum transmission of HIV in women initiating treatment late in pregnancy,^{13,14} whereas other studies have assessed the use of dolutegravir earlier in pregnancy. Undisclosed ART was unlikely because we excluded mothers with a viral load of less than 50 copies per mL at baseline. Smaller differences were observed in the proportion of women achieving HIV viral load of less than 1000 copies per mL than in those achieving an HIV viral load of less than 50 copies per mL, an alternative threshold for transmission risk.¹⁵ In calculating the time from randomisation to the occurrence of achieving viral suppression, we used the visit dates at the scheduled visits at days 7 and 28. The use of this

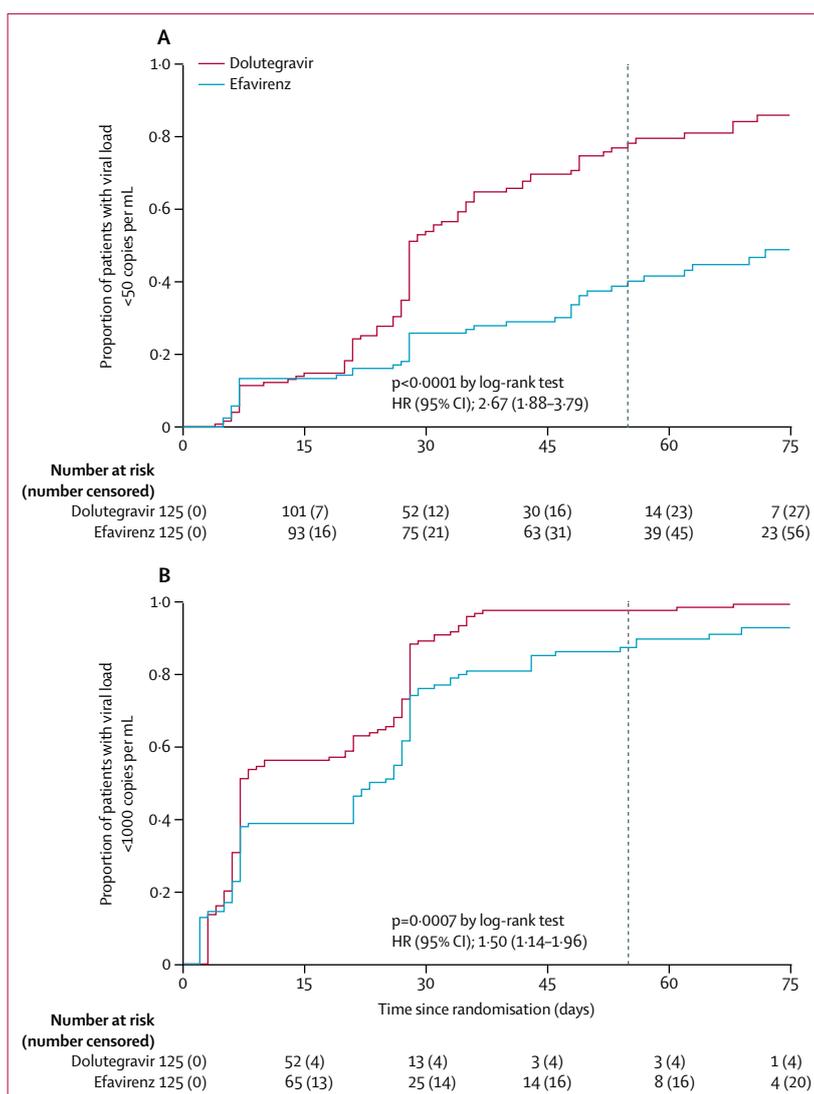


Figure 2: Proportion of patients with viral load <50 copies per mL and <1000 copies per mL following randomisation

Kaplan-Meier plots of time from randomisation to an HIV viral load of (A) <50 copies per mL and (B) <1000 copies per mL. The dashed vertical line in each plot represents the median time from randomisation to giving birth (55 days) in all patients.

algorithm might have biased the true time of viral load suppression; however, since the method was equally applied in both groups, any bias should be similar. Given that peripartum HIV transmission is strongly correlated with the prevailing maternal viral load, dolutegravir-based regimens might reduce HIV transmission around birth and potentially during breastfeeding, compared with efavirenz-based regimens in our population of pregnant mothers. The three HIV-infected infants detected were considered likely to have had in-utero infections, although peripartum transmission could not be excluded because we did not test infants within 2 days of birth. Longer-term follow-up to detect transmissions during breastfeeding is ongoing as part of this study.

	Dolutegravir	Efavirenz	Total
Mothers			
Total	137	131	268
≥1 SAE*	30 (22%)†	14 (11%)†	44 (16%)
≥1 drug-related SAE	1 (<1%)	0	1 (<1%)
≥1 IRIS-related SAE	1 (<1%)	0	1 (<1%)
System organ class			
Blood and lymphatic system disorders	2 (2%)	0	2 (<1%)
Gastrointestinal disorders	1 (<1%)	0	1 (<1%)
Infections and infestations	5 (4%)	2 (2%)	7 (3%)
Pregnancy, puerperium, and perinatal conditions excluding stillbirths	18 (13%)	10 (8%)	28 (10%)
Renal and urinary disorders	3 (2%)	0	3 (1%)
Social circumstances	1 (<1%)	0	1 (<1%)
Vascular disorders	0	1 (<1%)	1 (<1%)
Births with measurable gestational age			
Gestational age at birth, weeks‡	39 (37–41)	39 (37–40)	39 (37–40)
Late preterm (<37 weeks)	21/124 (17%)	19/120 (16%)	40/244 (16%)
Preterm (<34 weeks)	3/124 (2%)	5/120 (4%)	8/244 (3%)
Stillbirth	3/124 (2%)	1/120 (<1%)	4/244 (2%)
Infants			
Total	123	119	242
Birth weight (g)	3180 (2800–3440)	3115 (2860–3420)	3160 (2840–3440)
≥1 SAE	61 (50%)	56 (47%)	117 (48%)
Deaths	4 (3%)	2 (2%)	6 (3%)
System organ class			
Congenital, familial, and genetic disorders	67 (55%)	71 (60%)	138 (57%)
Ear and labyrinth disorders	1 (<1%)	0	1 (<1%)
Hepatobiliary disorders	1 (<1%)	0	1 (<1%)
Infections and infestations	8 (7%)	6 (5%)	14 (6%)
Injury, poisoning, and procedural complications	1 (<1%)	0	1 (<1%)
Nervous system disorders	1 (<1%)	1 (<1%)	2 (<1%)
Pregnancy, puerperium, and perinatal conditions	4 (3%)	7 (6%)	11 (5%)
Respiratory, thoracic, and mediastinal disorders	8 (7%)	4 (3%)	12 (%)

Data are n, n/N (%), n (%), or median (IQR). SAE=serious adverse event. IRIS=immune reconstitution inflammatory syndrome. *Including stillbirths. †p=0.013, χ^2 test. ‡Gestational age at birth based on best estimate using recall of last menstrual period, fundal height, and ultrasound dating, modified post partum by the Ballard score.

Table 3: SAEs and preterm births in mothers and infants

We found both dolutegravir and efavirenz to be well tolerated in mothers and infants. However, a higher proportion of mothers who received dolutegravir developed serious adverse events than did those who received efavirenz. This finding was driven by a higher overall frequency of pregnancy, puerperium, and perinatal events in mothers receiving dolutegravir (appendix p 1), most of whom were judged to have prolonged pregnancy beyond term. The significance of this finding is unclear because estimation of gestational age in late pregnancy is not always accurate. Whether our findings are replicated in other studies^{16,17} examining dolutegravir in pregnancy (eg, VESTED [NCT03048422] and the Antiviral Pregnancy Registry) will be important to examine.

For more on the Antiviral Pregnancy Registry see <http://www.apregistry.com>

The incidence of serious adverse events and treatment-related toxic effects overall was similar to previous large randomised trials in non-pregnant adults in sub-Saharan Africa.^{7,18,19}

The infant deaths, stillbirths, and infant transmissions observed attest to the poor outcomes previously reported in this group of mothers.³ Detailed examination revealed that ART or immune reconstitution inflammatory syndrome was considered unlikely to play a substantial role in any of these cases. Of the four stillbirths, two were related to obstetric complications and two to severe maternal infection. The six infant deaths were related to conditions prevalent in Uganda and South Africa, where neonatal mortality rates are four-to-nine times those of western Europe.^{20,21} We did not observe any increased risk of birth defects, although treatment was only initiated after organogenesis was completed.

Our sample size was not sufficiently large to study differences in infant transmissions, although we were powered to detect virological superiority before or at the time of birth (the best validated proxy for vertical HIV transmission). Safety follow-up of mothers and babies was limited by the short time between third trimester initiation and our primary endpoint at giving birth; however, we will continue follow-up of post-partum and infant outcomes to 72 weeks. The higher frequency of serious adverse events observed with dolutegravir should be confirmed in other studies and observational datasets, which are planned and in progress (eg, VESTED).

Policy makers weigh the risks and benefits of new treatments before data in pregnancy are available.²² A preliminary association with neural tube defects triggered precautionary measures globally, ranging widely in permissiveness for dolutegravir use in women,^{23–25} increasing the burden of health-care provision,²⁶ and delaying implementation of dolutegravir roll-out. Population modelling suggests that net population health benefits accrue when transitioning to dolutegravir, including for women of child-bearing potential.^{27,28} This benefit would hold true notwithstanding the differences in serious adverse events among mothers assigned to dolutegravir. The DolPHIN-2 results, taken together with evidence favouring dolutegravir use over efavirenz (especially in countries where HIV drug resistance is increasing²⁹), strongly support global transition to dolutegravir use in first-line ART.

Contributors

SK, DW, ML, LM, CO, and CW were involved in design of the study. SK, KB, CP, HR, AC, and CW were involved in the protocol development. All authors contributed equally to the study execution. DW, TC, CP, VW, KS, HER, and EMH contributed to the study analysis. KK, SK, LM, MT, DB, CW CO, ML were involved in writing the manuscript.

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Declaration of interests

TRM, JN, CP, KB, KS, EMH, TC, AT, JB, HR, VW, DB, DW, CW, MT, CO, AC, ML, SK, and LM report grants from Unitaid, during the conduct of the study. AC reports grants from ViiV Healthcare, MSD, Gilead, and Janssen, outside of the submitted work. ML reports grants and non-financial support from ViiV, grants and personal fees from Mylan, and grants from Janssen, outside of the submitted work. SK reports other from ViiV Healthcare, during the conduct of the study; grants from Gilead Sciences, Merck Sharp & Dohme, and Janssen; and grants and personal fees from ViiV Healthcare, outside of the submitted work. KK declares 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 (rdm@liverpool.ac.uk) 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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