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Raltegravir versus efavirenz in antiretroviral-naive pregnant women living with HIV (NICHD P1081): an open-label, randomised, controlled, phase 4 trial

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Summary

Background Although antiretroviral regimens containing integrase inhibitors rapidly suppress HIV viral load in non-pregnant adults, few published data from randomised controlled trials have compared the safety and efficacy of any integrase inhibitor to efavirenz when initiated during pregnancy. We compared safety and efficacy of antiretroviral therapy with either raltegravir or efavirenz in late pregnancy.

Methods An open-label, randomised controlled trial was done at 19 hospitals and clinics in Argentina, Brazil, South Africa, Tanzania, Thailand, and the USA. Antiretroviral-naive pregnant women (20–<37 weeks gestation) living with HIV were assigned to antiretroviral regimens containing either raltegravir (400 mg twice daily) or efavirenz (600 mg each night) plus lamivudine 150 mg and zidovudine 300 mg twice daily (or approved alternative backbone regimen), using a web-based, permuted-block randomisation stratified by gestational age and backbone regimen. The primary efficacy outcome was plasma HIV viral load below 200 copies per mL at (or near) delivery. The primary efficacy analysis included all women with a viral load measurement at (or near) delivery who had viral load of at least 200 copies per mL before treatment and no genotypic resistance to any study drugs; secondary analyses eliminated these exclusion criteria. The primary safety analyses included all women who received study drug, and their infants. This trial is registered with Clinicaltrials.gov, number NCT01618305.

Findings From Sep 5, 2013, to Dec 11, 2018, 408 women were enrolled (206 raltegravir, 202 efavirenz) and 394 delivered on-study (200 raltegravir, 194 efavirenz); 307 were included in the primary efficacy analysis (153 raltegravir, 154 efavirenz). 144 (94%) women in the raltegravir group and 129 (84%) in the efavirenz group met the primary efficacy outcome (absolute difference 10%, 95% CI 3–18; p=0·0015); the difference primarily occurred among women enrolling later in pregnancy (interaction p=0·040). Frequencies of severe or life-threatening adverse events were similar among mothers (30% in each group; 61 raltegravir, 59 efavirenz) and infants (25% in each group; 50 raltegravir, 48 efavirenz), with no treatment-related deaths.

Interpretation Our findings support major guidelines. The integrase inhibitor dolutegravir is currently a preferred regimen for the prevention of perinatal HIV transmission with raltegravir recommended as a preferred or alternative integrase inhibitor for pregnant women living with HIV.

Funding Eunice Kennedy Shriver National Institute of Child Health and Human Development and National Institute of Allergy and Infectious Diseases.

Introduction

In 2018, an estimated 1·3 million pregnant women living with HIV worldwide required antiretrovirals both for their own health and to prevent transmission of HIV to their infants.[1] Strategies for prevention of perinatal transmission of HIV prioritise antiretroviral therapy (ART) during pregnancy to rapidly achieve HIV viral load suppression sustained until delivery.[2] Because the risk of perinatal transmission is greatly affected by the timing of ART initiation,[3] women who present late in pregnancy need potent ART to suppress viral load quickly and minimise the risk of HIV transmission.

The non-nucleoside reverse transcriptase inhibitor efavirenz has been extensively studied in non-pregnant adults and has been shown to effectively reduce HIV RNA viral load. Raltegravir is an integrase inhibitor, a newer class of antiretrovirals that have been shown to be potent antiretrovirals and to rapidly reduce HIV viral load in non-pregnant adults who are treatment-naive and those who are treatment experienced with triple-class resistant virus. Integrase inhibitors have also been examined in preclinical, phase 1, and phase 3 studies in adult patients and have been generally well tolerated. Pregnant women living with HIV, especially those

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Research in context

Evidence before this study

We searched PubMed, ClinicalTrials.gov, Web of Knowledge, and abstracts of the Conference on Retroviruses and Opportunistic Infections and International AIDS Society for publications on clinical trials of integrase strand transferase inhibitors in pregnancy that were published between Nov 1, 2009, and Nov 1, 2019. We used the keywords "raltegravir" and "pregnancy" and searched for articles in English, French, and Portuguese. We found two randomised controlled trials supporting the use of integrase inhibitors during pregnancy. The Dolphin-2 trial compared efavirenz with dolutegravir in late-presenting pregnant women. The safety analysis included 268 women and the efficacy analysis 237. The trial found that virological response defined as the percentage of women with less than 50 copies per mL was 72% in the dolutegravir group versus 43% in the efavirenz group. Trial NCT01854762 randomly assigned 17 late-presenting pregnant women to raltegravir-based regimens and 16 to lopinavir-based regimens. Participants in the raltegravir group achieved significantly greater virological response within 2 weeks of enrollment (77% *vs* 25%). These trials suggest that integrase inhibitors could be a good option for women living with HIV who present late in pregnancy.

Added value of this study

We compared two potent HIV treatment regimens, one with raltegravir and the other with efavirenz, for pregnant women who start prenatal care late in the second or third trimester, between 20 weeks and 36 weeks of pregnancy. The aim was to compare how well the regimens reduced the plasma HIV viral load by delivery, how safe the regimen was, and how well women tolerated the regimens. 94% of women who took the HIV regimen that included raltegravir had undetectable viral load by delivery, whereas 84% of women who took the HIV regimen that included efavirenz were undetectable by delivery.

Implications of all the available evidence

In this study, all participants' genotypic resistance testing was done at screening and antiretroviral therapy (ART)-experienced women were excluded. However, participants in the Dolphin-2 trial were permitted to have taken ART more than 12 months before enrolment and resistance testing was not done. Despite these differences, both studies found that integrase inhibitors were potent and well tolerated, with low HIV vertical transmission. Similar to NCT01854762, in this study raltegravir was more potent than the comparator regime. However, NCT01854762 compared raltegravir and lopinavir, whereas we compared raltegravir and efavirenz, and had a larger sample size.

presenting for care late in pregnancy, could potentially benefit from effective and well tolerated integrase inhibitor-based ART regimens that produce more rapid viral load suppression, potentially reducing the risk of vertical transmission of HIV to their infants.

Although integrase inhibitors have become first-line antiretroviral therapy for non-pregnant adults, few large randomised controlled studies have compared the safety and efficacy during pregnancy of integrase inhibitor-based ART with the first-line efavirenz-based ART regimen,[4–6] which was recommended for pregnant women by WHO at the time the study was completed. We aimed was to compare the ability of two triple-antiretroviral regimens (one containing efavirenz and the other raltegravir) begun at or after 20 weeks of gestation to achieve a viral load of less than 200 copies per mL at the time of delivery in treatment-naive pregnant women living with HIV and to compare the safety and tolerability of the two regimens.

Methods

Study design and participants

NICHD P1081 was a phase 4, multicentre, open-label, randomised controlled trial comparing the virological response, safety, and tolerability of raltegravir, the first licensed integrase inhibitor, with efavirenz, a non-nucleoside reverse transcriptase inhibitor in combination with two nucleoside reverse tra nscriptase inhibitors in ART-naive pregnant women initiating ART from 20 to 36 weeks gestation. The trial enrolled participants at 19 clinic and hospital sites in Argentina (two), Brazil (seven), South Africa (one), Tanzania (one), Thailand (three), and the USA (five).

P1081 was originally developed by the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) as a three-arm randomised trial (raltegravir-based *vs* efavirenz-based *vs* lopinavir and ritonavir-based ART) for women at 28–<37 weeks gestation, and began enrolment on Sep 5, 2013, but was closed to accrual on Dec 2, 2014, due to slow enrolment. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Allergy and Infectious Diseases (NIAID) assumed responsibility for the trial, which was modified to a two-arm trial (raltegravir ART *vs* efavirenz ART) with a smaller sample size and inclusion of data from the 14 IMPAACT P1081 participants in the two continuing groups in final study analyses. The six women in the lopinavir and ritonavir group continued scheduled study evaluations up to 6 months postpartum but were excluded from all data analyses. Enrolment resumed in July, 2015, was expanded to include women at 20–<37 weeks gestation on Aug 1, 2016, after 22% of the target sample was enrolled, and was completed on Feb 28, 2018.

Pregnant women living with HIV infection with gestational age of 20–<37 weeks (determined by last menstrual period or ultrasound) who were ART-naive or who had received short-course zidovudine (maximum of 8 weeks) in previous pregnancies to prevent perinatal transmission of HIV were eligible for enrolment. Pregnant women living with HIV who were referred to HIV care clinics and hospitals and met the inclusion criteria were offered participation in the study.

Participants were required to be of the legal age of consent as defined by the country of the specific study site. Principal inclusion criteria were naivety to ART or receipt of ART with short course zidovudine (maximum of 8 weeks) for prevention of perinatal HIV transmission in previous pregnancies, documentation of HIV-1 infection defined as positive results from two samples collected at different time points, viable pregnancy with gestational age of 20–36 weeks based upon last menstrual period or ultrasound, and intent to continue pregnancy.

Exclusion criteria were active labour, use of ART during current pregnancy, chemotherapy for active malignancy, HIV genotypic resistance to efavirenz or raltegravir or to nucleoside reverse transcriptase inhibitors that were included in the antiretroviral regimens, serious active opportunistic infection, known allergy or sensitivity to any study drugs or their formulations or sulfonamide allergy, haemoglobin grade 3 or higher, absolute neutrophil count grade 2 or higher, alanine transaminase or aspartate transaminase grade 2 or higher, serum creatinine grade 1 or higher, or platelet count grade 3 or higher within 30 days of enrolment, evidence of pre-eclampsia, and receipt of disallowed medications per protocol. The complete list of inclusion and exclusion criteria is provided in the appendix (p 1).

All versions of the trial protocol and amendments were approved by the institutional review boards or regulatory entities of each site or country. Pregnant women who agreed to participate gave oral and written, informed consent.

Randomisation and masking

Participants were randomly assigned to either raltegravir-based ART or efavirenz-based ART. The web-based, central computer randomisation system used permuted block allocation (block size 4) with stratification by gestational age at enrolment (20–<28 weeks, 28–<31 weeks, 31–<34 weeks, and 34–<37 weeks) and nucleoside reverse transcriptase inhibitor backbone (lamivudine and zidovudine or alternative, locally-supplied nucleoside reverse transcriptase inhibitor regimen), and dynamic balancing by study site.[7] The participants, site staff, and the statisticians who analysed the data were not masked to group assignment.

Procedures

At an initial screening visit, clinical case history, confirmatory HIV testing, and specimen for HIV-1 genotypic resistance testing were obtained. Women were randomly assigned to receive raltegravir 400 mg twice a day or efavirenz 600 mg each night in addition to lamivudine 150 mg and zidovudine 300 mg twice a day (or an alternative, locally supplied nucleoside reverse transcriptase inhibitor regimen) from study entry until delivery. Resistance testing results were not required for enrolment or initiation of assigned study drugs; once resistance testing results became available, clinicians could modify ART if resistance was identified, and women with resistance to any study antiretroviral were excluded from the primary efficacy analysis. Maternal evaluations at study visits (screening, entry, weeks 1, 2, and 4, and every 2 weeks until delivery, then weeks 2, 6, 16, and 24 postpartum) included an interval medical history, physical examination, haematology and chemistry tests, HIV RT-PCR, and CD4 T-cell count. Infant evaluations at study visits (birth and weeks 2, 16, and 24) included clinical history, physical examinations, haematological and chemistry laboratory evaluations, and HIV nucleic acid testing. Women who had virological failure and HIV-infected infants had additional HIV resistance testing. Participants were followed until 24 weeks postpartum.

Women enrolled to NICHD P1081 had HIV RNA viral load measurements done using Abbott (Lake Forest, IL) Real Time assays, with a lower limit of quantification of either 20 copies per mL or 40 copies per mL. The 14 women enrolled under IMPAACT P1081 who were eligible for inclusion in final analyses might have had their viral load measured using local assays obtained as part of standard of care with a lower limit of quantification of 200 copies per mL or lower.

All participating sites and testing labs complied with the IMPAACT Division of AIDS Manual of Procedures. Per the Manual, genotyping and viral load assessments were done at Virology Quality Assurance-certified (non-US sites) or Clinical Laboratory Improvement Amendments-certified (US sites) laboratories. HIV testing laboratories and haematology and chemistry testing laboratories were required to maintain College of American Pathologist certification. Immunology testing, such as CD4 T-cell counts, was done at laboratories monitored by the Division of AIDS Immunology Quality Assurance Program. In addition to required certification, sites and laboratories storing peripheral blood mononuclear cells were tested quarterly to evaluate their reliability in cryopreservation.

Outcomes

The primary efficacy outcome measure was maternal plasma HIV-1 RNA viral load of less than 200 copies per mL at or near (within 21 days before) delivery. The primary safety outcome measure for women and infants was a new grade 3 or 4 adverse event (including a sign or symptom, diagnosis, or haematology or chemistry event) according to the Division of AIDS Table for Grading the

	Efavirenz (N=202)	Raltegravir (N=206)	Total (N=408)
Age (years)	25 (22–31)	27 (23–32)	27 (22–32)
Race or ethnicity			
Asian or Pacific Islander	24/200 (12%)	23/205 (11%)	47/405 (12%)
Black, not Hispanic	74/200 (37%)	72/205 (35%)	146/405 (36%)
Hispanic, Latino	101/200 (51%)	108/205 (53%)	209/405 (52%)
White, not Hispanic	1/200 (1%)	2/205 (1%)	3/405 (1%)
HIV-1 RNA viral load (log_{10} copies per mL)	4·1 (3·4–4·5)	4·1 (3·3–4·6)	4·1 (3·4–4·6)
Absolute CD4 count (cells per μL)	408 (289–602)	389·5 (240–567)	395 (262–574)
NRTI background regimen			
Lamivudine and zidovudine	170 (84%)	171 (83%)	341 (84%)
Emtricitabine and tenofovir disoproxil fumarate	31 (15%)	33 (16%)	64 (16%)
Lamivudine and tenofovir disoproxil fumarate	1 (<1%)	2 (1%)	3 (1%)
Gestational age (weeks)	27 (23–31)	28 (22–31)	27 (23–31)
20–<28	102 (50%)	103 (50%)	205 (50%)
28–<37	100 (50%)	103 (50%)	203 (50%)
Genotypic resistance results*			
Reverse transcriptase resistance mutation	14/187 (7%)	21/197 (11%)	35/384 (9%)
Integrase inhibitor resistance mutation	0/190 (0%)	0/192 (0%)	0/382 (0%)
Incomplete genotypic resistance results	21/202 (10%)	17/206 (8%)	38/408 (9%)

Data are n (%), n/N (%), or median (IQR). The baseline values are those observed or measured closest to (and on or before) the date of randomisation. *Genotypic resistance testing for each woman was done on a sample taken during the screening visit. Although results from this testing were not available until after entry (ie, randomisation), these results measured resistance before randomisation. 38 women had incomplete resistance results; 12 were missing reverse transcriptase results (three in the raltegravir group and nine in the efavirenz group), 14 were missing integrase results (eight in the raltegravir group and six in the efavirenz group), and 12 were missing both results (six in each group).

Table 1: **Baseline characteristics**

Severity of Adult and Pediatric Adverse Events (version 2.0, November, 2014).[8] New adverse events were defined as those that occurred on or after randomisation, or if present at baseline, adverse events that increased in grade. The primary tolerability outcome measure was remaining on randomised study treatment (raltegravir or efavirenz) up to delivery.

Secondary efficacy outcome measures included maternal HIV viral load of less than the assay's lower-limit-of-quantification at or near delivery and a composite efficacy-tolerability outcome. This composite outcome consisted of a rapid, sustained viral load decrease, defined as achieving a prespecified minimum drop in plasma HIV-1 RNA by week 2 (≥2·0 log_{10} decrease from entry or <200 copies per mL) and maintaining less than 1000 copies per mL until delivery (among women who delivered after 28 days on study), and remaining on randomised study treatment up to delivery (appendix p 57).

Adverse pregnancy outcome measures included stillbirth, low (<2500 g) and extremely low (<1500 g) birthweight, preterm (<37 weeks) and extremely preterm (<34 weeks) delivery, and major congenital anomaly. All reported congenital anomalies were reviewed centrally and classified as major, minor, or not a defect on the basis of the Metropolitan Atlanta Congenital Defects Program.[9] Infants were classified centrally as HIV-infected if they had at least two positive HIV nucleic acid test results from different samples and HIV-uninfected if they had at least two negative HIV nucleic acid test results at 6 weeks, 16 weeks, or 24 weeks postpartum, and no positive result at any week.

Statistical analysis

The target sample size of 334 evaluable women provided 80% power to detect a difference in response proportions of 75% versus 60% with a two-sided type I error rate of 0·05 and allowing for two interim efficacy analyses. Assuming 5% of women were non-evaluable, and 10% were excluded due to genotypic resistance, target enrolment was 394 women (197 per group).

Women eligible for the primary efficacy analysis were those who had a valid viral load result at or near delivery; per Data and Safety Monitoring Board recommendation, evaluable women were those who had plasma HIV-1 RNA viral load of 200 copies per mL or more at screening or entry. The efficacy analysis was done in three ways. The primary analysis excluded women who had genotypic resistance to, or incomplete resistance results for, any study drugs at screening. A secondary efficacy analysis included all evaluable women, regardless of genotypic resistance status at screening. A sensitivity efficacy analysis included all eligible women, regardless of genotypic resistance status or screening or entry viral load.

Prespecified sensitivity analyses were also done to assess the potential effect of missing data on the results of the aforementioned efficacy analyses. These analyses were planned to be done in two ways: as an extreme worst-case analysis, assuming a missing viral load at delivery would show a successful or unsuccessful viral load decrease in a way that would minimise the difference between groups, and a more plausible analysis assuming a missing viral load would show a successful viral load decrease with probability equal to the estimated probability of achieving the target viral load among women in the same group who had a viral load at delivery. However, because the worst-case analysis showed similar response proportions to the primary efficacy analysis, the more plausible analysis was not needed and not done.

Women who received at least one dose of study drug (and their infants) were evaluable for the safety and tolerability analyses.

All primary statistical comparisons (efficacy, safety, and tolerability) were done by Cochran-Mantel-Haenszel test stratified by gestational age at enrolment (but not nucleoside reverse transcriptase inhibitor backbone). We calculated Wald CIs (with continuity correction) for the difference in response proportions. Subgroup analyses were done to assess the heterogeneity of treatment effects on the primary efficacy comparison with respect to gestational age stratum at entry, with

interaction testing done by logistic regression. A post-hoc interval-censored analysis based on non-parametric survival analysis for interval-censored data[10] compared time to virological suppression using a generalised log-rank test and a hazard ratio (HR) with 95% CI from an interval-censored proportional hazards model. This analysis included all women who received at least one dose of study drug and had a viral load of at least 200 copies per mL at screening or entry (ie, did not have the event at baseline). Subgroup analyses were again done to investigate whether the treatment effect differed by gestational age stratum, with interaction testing done with an interval-censored proportional hazards model. The exact date of virological suppression during pregnancy was interval-censored because it occurred in the interval between two viral load measurements (the last measurement of ≥200 copies per mL and the first measurement of <200 copies per mL). An interval-censored survival plot shows the estimated cumulative probability of achieving virological suppression according to number of weeks since randomisation, with dotted lines indicating intervals where probability estimates are undefined.[11] Approximate numbers of women at risk and censored at each timepoint were calculated using Kaplan-Meier analysis. Comparisons of pregnancy outcomes and infant infections were done by use of Fisher's exact test.

The trial was monitored semi-annually by the US NIAID Division of AIDS multinational Data and Safety Monitoring Board which reviewed study conduct and safety at each meeting and reviewed two interim efficacy analyses. Because interim efficacy analyses used the conservative Haybittle-Peto stopping boundary (p<0·001), no adjustment for alpha spending was done in the final analysis, and a nominal two-sided p value of less than 0·05 was considered statistically significant. Analyses were done with SAS version 9.4.

Further details are provided in the statistical analysis plan (for access to the plan, see the Data Sharing Statement at the end of the manuscript).

The trial is registered with ClinicalTrials.gov, number NCT01618305.

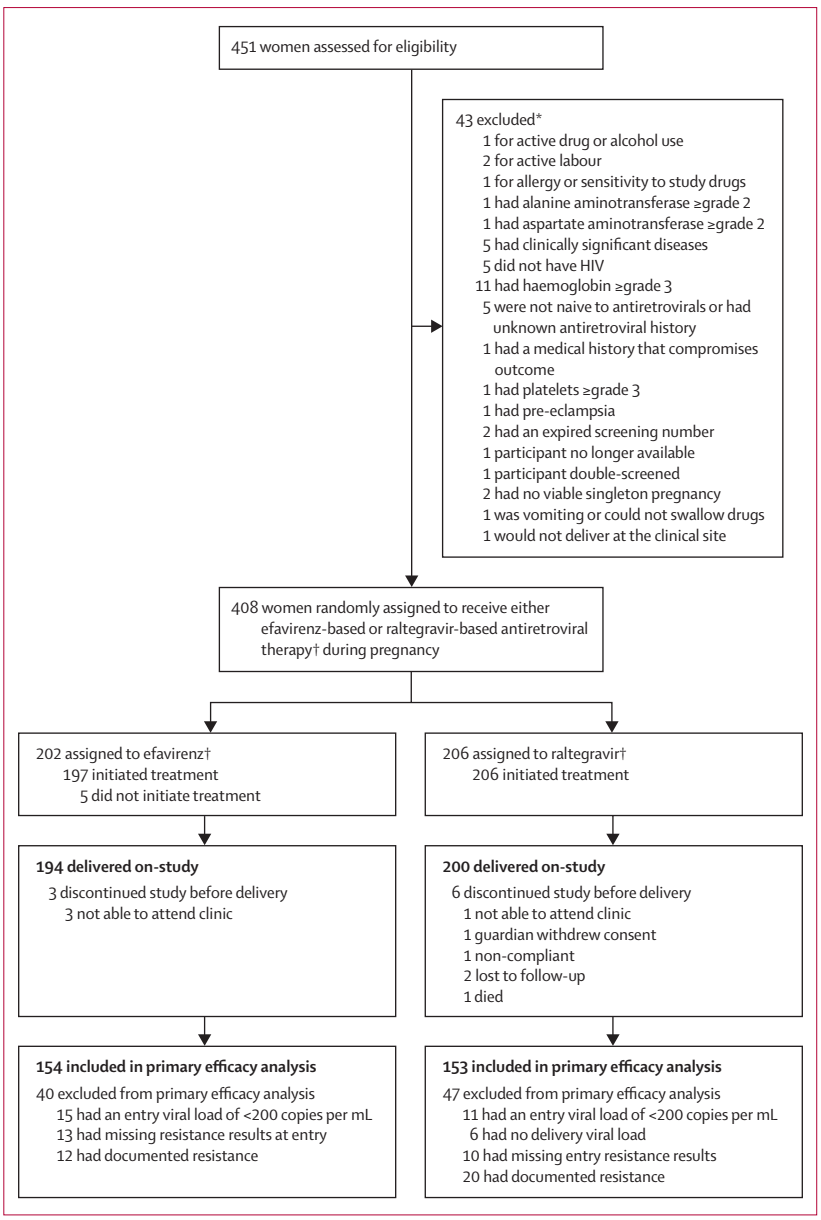

Figure 1: **Study profile**

*Screening information was only available for women enrolled under NICHD P1081 (version 3 of the protocol). Among the 408 women who enrolled, 394 were enrolled under NICHD P1081. †Antiretroviral therapy consisted of efavirenz or raltegravir (whichever was assigned) plus two nucleoside reverse transcriptase inhibitors; women were stratified by whether they would receive lamivudine and zidovudine or two alternative, locally supplied nucleoside reverse transcriptase inhibitors.

Role of the funding source

Staff of NICHD, which provided the funding for the protocol, were full study team members involved in study design, data collection, data analysis, data interpretation, and writing of the report. Companies that supplied study drug (Merck Company, Bristol Myers-Squibb, and ViiV Healthcare) 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

From Sep 5, 2013, to Feb 28, 2018, 408 pregnant women were enrolled at sites in Argentina (N=20), Brazil (N=190), South Africa (N=60), Tanzania (N=84), Thailand (N=47), and the USA (N=7). 206 were assigned to raltegravir and 202 to efavirenz. 205 (50%) enrolled at 20–<28 weeks gestation and 203 (50%) at 28–<37 weeks gestation. Baseline characteristics were well balanced between groups (table 1). Of the 408 women enrolled, 14 withdrew before delivery. Of the 394 on study at delivery, 368 (94%) had either a screening or entry plasma HIV-1 RNA viral load of at least 200 copies per mL and were thus eligible

	Efavirenz, n/N (%)	Raltegravir, n/N (%)	Absolute difference (95% CI)	p value*	Interaction p value†
Primary: viral load <200 copies per mL at delivery					
Overall	129/154 (84%)	144/153 (94%)	10% (3 to 18%)	0·0015	0·040
20–<28 weeks gestation	74/76 (97%)	68/71 (96%)	–2% (–9 to 6%)	..	..
28–<37 weeks gestation	55/78 (71%)	76/82 (93%)	22% (9 to 35%)	..	..
Secondary: viral load less than the lower limit of quantification at delivery	90/154 (58%)	131/153 (86%)	27% (17 to 37%)	<0·0001	..
Composite: rapid, sustained viral load decrease plus tolerability					
Overall	84/133 (63%)	124/139 (89%)	26% (16 to 36%)	<0·0001	..
Rapid viral load decrease	93/133 (70%)	129/139 (93%)	23% (13 to 33%)	..	..
Sustained viral load decrease	118/124 (95%)	121/127 (95%)	0% (–6 to 6%)	..	..
Remained on study treatment until delivery	129/133 (97%)	134/139 (96%)	–1% (–6 to 4%)	..	..

Although 307 women were included in the primary efficacy analysis, the window for an evaluable delivery viral load was larger (from 21 days before delivery to delivery). The composite efficacy analysis required a week 2 viral load, and the window for an evaluable Week 2 viral load was smaller (day 11–17). Therefore, fewer women had an evaluable week 2 viral load than had a delivery viral load. A small number of women who delivered after 28 days on study treatment were also excluded because they did not have any viral up to delivery. *Calculated via Cochran-Mantel-Haenszel test stratified by gestational age (20–<28 weeks, 28–<31 weeks, 31–<34, and 34–<37 weeks) at entry. †Calculated by logistic regression. Gestational age strata were combined due to small sample size and low event rates in the later gestational age strata; two strata (20–<28 weeks and 28–<37 weeks) were considered in interaction testing.

Table 2: **Efficacy outcomes**

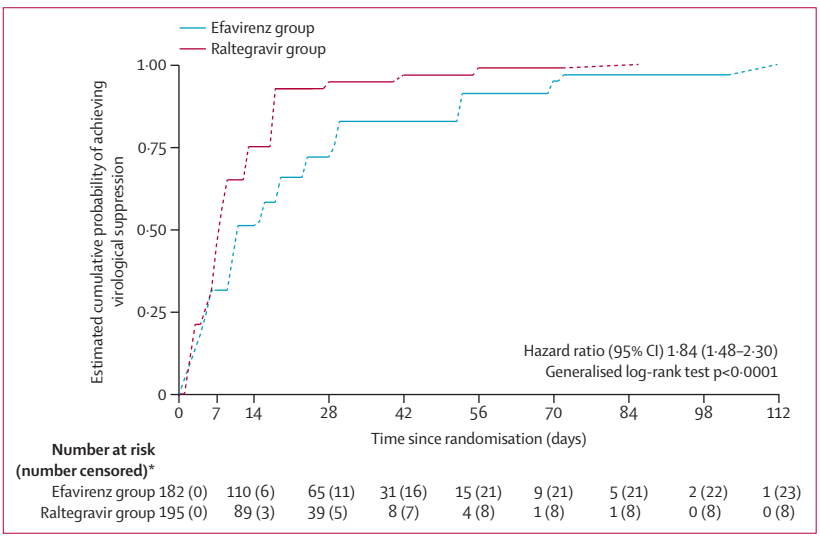

Figure 2: **Estimated cumulative probability of virological suppression by time since randomisation**
This interval-censored survival plot shows the estimated cumulative probability of achieving virological suppression according to number of weeks since randomization, based on non-parametric survival analysis for interval-censored time-to-event data. Virological suppression was defined as having an HIV-1 RNA plasma viral load of less than 200 copies per mL. Dotted lines indicate intervals where probability estimates are undefined (unlike Kaplan-Meier survival plots, which are continuous step functions). Interval censoring was used, because the exact date of virological suppression is not known; however, the date is known to be in the interval between the last viral load measurement of 200 copies per mL or more and the first one of less than 200 copies per mL. Participants who did not achieve virological suppression by delivery were censored at their delivery date (or their off-study date if they discontinued study participation before delivery). Participants were considered at risk at a timepoint if they were on study, had not yet delivered, and had not yet had an observed viral load of less than 200 copies per mL.

for the primary efficacy analysis. Among eligible women, 307 had complete genotypic resistance results documenting no resistance to study drug and were evaluable for the primary efficacy analysis. Baseline characteristics were generally well balanced between evaluable and non-evaluable women, except those that differed by design due to criteria for evaluability (eg, HIV-1 RNA viral load, genotypic resistance status), and race or ethnicity. Baseline characteristics by evaluability status are shown in the appendix (p 2).

370 (91%) of the 408 women enrolled had complete genotypic resistance results, and an additional 26 (6%) women had partially complete results. Among those with resistance results at screening, 35 (9%) of 384 women had genotypic resistance to reverse transcriptase inhibitors and none had resistance to integrase inhibitors. Among the 408 women enrolled, five (all assigned to efavirenz) withdrew before initiating study treatment and were excluded from all post-baseline analyses. Nine additional women (three assigned to efavirenz and six assigned to raltegravir) withdrew before delivery and were excluded from the primary efficacy analysis and analyses of pregnancy outcomes (figure 1).

In the primary efficacy analysis (table 2), the proportion of women with a viral load of less than 200 copies per mL at or near delivery was significantly larger in the raltegravir group (144 [94%] of 153) than the efavirenz group (129 [84%] of 154; absolute difference 10%, 95% CI 3–18; p=0·0015). The treatment effect differed significantly by gestational age at entry (interaction p=0·040). Women in each group who enrolled at 20–<28 weeks gestation had similar response proportions for the primary efficacy outcome, whereas among those who enrolled at 28–<37 weeks gestation, 76 (93%) of 82 in the raltegravir group achieved a delivery viral load of less than 200 copies per mL compared with 55 (71%) of 78 in the efavirenz group. The results were consistent in both secondary and sensitivity analyses of the primary efficacy outcome measure (appendix p 3). Additionally, similar response proportions were observed in a prespecified worst-case sensitivity analysis (data not shown).

Results were similar for the secondary efficacy outcome measures. The proportion of women who achieved a viral

load below the local assay lower-limit-of-quantification at or near delivery was significantly higher in the raltegravir group (131 [86%] of 153) than the efavirenz group (90 [58%]of 154; p<0·0001). Similarly, the proportion of women who had a successful composite efficacy-tolerability outcome was significantly higher in the raltegravir group (124 [89%] of 139) than the efavirenz group (84 [63%] of 133; p<0·0001), primarily because a larger proportion (129 [93%] of 139 *vs* 93 [70%] of 133) had a rapid viral load decrease. Results were consistent in all secondary and sensitivity analyses of both the secondary and composite efficacy outcome measures (p<0·0001 for all; appendix p 3). Overall, six women in the efavirenz group and four women in the raltegravir group had a viral load of less than 200 copies per mL at some point before delivery but then had viral rebound by the time of delivery.

In a post-hoc analysis of time to virological suppression (figure 2), time to first viral load of less than 200 copies per mL in pregnancy was shorter in the raltegravir group than the efavirenz group (HR 1·84, 95% CI 1·48–2·30; p<0·0001). In subgroup analyses, time to virological suppression was shorter in the raltegravir group in both subgroups of gestational age at enrolment (20–<28 weeks gestation HR 1·52, 95% CI 1·13 to 2·07; 28–<37 weeks gestation HR 2·25, 95% CI 1·62–3·13; appendix pp 6–7). The magnitude of the difference in time to virological suppression between groups was larger among women enrolled from 28–<37 weeks gestation (interaction p=0·052).

Among the 403 women who initiated study treatment, 397 (99%) received their first dose within 1 day of randomisation (all 403 received it within 1 week). Tolerability was high in both groups; 96% of women (199 [97%] of 206 in the raltegravir group *vs* 188 [95%] of 197 in the efavirenz group; p=0·56) stayed on assigned treatment up to delivery. The time on assigned treatment until delivery was similar between treatment groups, ranging from 1 day to 22 weeks (median 11·3 weeks, IQR 6·9–15·6).

Similar proportions of women in both groups had at least one new grade 3 or 4 adverse event (59 of 197 in the efavirenz group *vs* 61 of 206 in the raltegravir group; p=0·91; table 3). There were no substantial differences between the groups with respect to specific adverse events (appendix p 4). The most common laboratory adverse events were abnormal haematology values (46 of 403; 11%), primarily abnormal haemoglobin values. Similar proportions of women had a new grade 3 or 4 clinical diagnosis in both groups, and each diagnosis was infrequently observed (≤2% for all). When grouped by body system, the most common diagnoses were cardiovascular (hypertension in pregnancy or pre-eclampsia) and haematological.

Of the 394 women who remained on study until delivery, 390 (99%) had livebirths and four (1%) had stillbirths (one in the efavirenz group and three in the raltegravir group; table 3). One mother who had discordant outcomes (one intrauterine fetal demise at 18 weeks gestation and one livebirth on-study) was considered to have had a livebirth singleton pregnancy, because the intrauterine fetal demise occurred before study entry and initiation of study treatment. The proportion of stillbirths did not significantly differ between groups (Fisher's exact p=0·62).

There were three pairs of liveborn twins, making a total of 393 livebirth infants delivered on-study. There were no

	Efavirenz (N=197)	Raltegravir (N=206)	Total (N=403)	p value*
Maternal adverse events				
Any grade ≥3	59 (30%)	61 (30%)	120 (30%)	0·91
Grade ≥3 sign or symptom	14 (7%)	11 (5%)	25 (6%)	..
Grade ≥3 lab adverse event	34 (17%)	33 (16%)	67 (17%)	..
Haematological	22 (11%)	24 (12%)	46 (11%)	..
Chemistry	13 (7%)	9 (4%)	22 (5%)	..
Grade ≥3 diagnoses	31 (16%)	34 (17%)	65 (16%)	..
Deaths (any reason)	0 (0%)	1 (<1%)†	1 (<1%)	..
Adverse pregnancy outcomes				
Stillbirth	1/194 (1%)	3/200 (2%)‡	4/394 (1%)	0·62
Preterm birth (<37 weeks)§	20/190 (11%)	24/195 (12%)	44/385 (11%)	0·63
Extremely preterm birth (<34 weeks)¶	6/169 4%)	4/171 (2%)	10/340 (3%)	0·54
Low birthweight (<2500 g)	24/193 (12%)	25/197 (13%)	49/390 (13%)	>0·99
Extremely low birthweight (<1500 g)	0/193 (0%)	1/197 (1%)	1/390 (<0·5%)	>0·99
HIV transmissions				
HIV-infected infant‖	6/184 (3%)	1/190 (1%)	..	0·064

Data are n (%) or n/N (%). *The p value for the primary safety comparisons (proportion that experienced any grade 3 or higher adverse event) was calculated by Cochran Mantel Haenszel test stratified by gestational age at entry. p values for comparisons of adverse pregnancy outcomes and HIV transmissions were calculated by Fisher's Exact test. †The maternal death was ruled a murder, attributed by the reporting site as unrelated to study treatment or conduct. The primary cause of death was liver rupture due to trauma. ‡One woman in the raltegravir group had discordant outcomes. Because one of the outcomes occurred before study entry (intra-uterine fetal demise), only the outcome for the infant who was delivered on-study (livebirth) is included. §This analysis excluded four stillbirths (one in the efavirenz group and three in the raltegravir group) and five liveborn infants with no gestational age at delivery recorded (three in the efavirenz group and two in the raltegravir group). ¶In addition to the exclusions in the preterm birth analysis, this analysis excluded 45 infants born to women who enrolled at 34 weeks gestation or greater. ‖Excluded infants (ten in the efavirenz group and 9 in the raltegravir group) had no positive HIV-infection test result, but also did not have sufficient negative test results to meet the definition of HIV-uninfected.

Table 3: **Maternal adverse events and pregnancy outcomes**

	Efavirenz (N=194)	Raltegravir (N=199)	Total (N=393)	p value*
Any grade ≥3 adverse event	48 (25%)	50 (25%)	98 (25%)	0·94
Grade ≥3 sign or symptom	15 (8%)	15 (8%)	30 (8%)	..
Grade ≥3 lab adverse event	22 (11%)	17 (9%)	39 (10%)	..
Haematological	13 (7%)	6 (3%)	19 (5%)	..
Chemistry	11 (6%)	11 (6%)	22 (6%)	..
Grade ≥3 diagnosis	32 (16%)	34 (17%)	66 (17%)	..
Deaths (any reason)†	1 (1%)	1 (1%)	2 (1%)	..

Data are n (%). *The p value for the primary safety comparisons (proportion that experienced any grade 3 or higher adverse event) was calculated by Cochran Mantel Haenszel test stratified by gestational age at entry. p values for comparisons of adverse pregnancy outcomes and HIV transmissions were calculated by Fisher's Exact test. †Both infant deaths were attributed by the reporting site as not related to study treatment or conduct. The primary causes of death were neonatal necrotising enterocolitis (efavirenz group) and presumed sudden infant death syndrome (raltegravir group).

Table 4: **Infant adverse events**

significant differences between groups in the proportions of infants with (extremely) preterm or (extremely) low birthweight (20 [11%] of 190 for efavirenz and 24 [12%] of 195 for raltegravir; p>0·5 for all; table 3).

The proportion of infants who had at least one new grade 3 or 4 adverse event did not differ between groups (48 of 194 in the efavirenz group *vs* 50 of 199 in the raltegravir group; p=0·94; table 4). There were also no substantial differences in the proportions of infants who had individual adverse events (appendix p 5). Congenital anomalies were infrequently observed and were balanced between groups.

Seven (1·9%, 95% CI 0·8–3·8) infants had HIV infections, one (0·5%, 95% CI <0·1 to 2·9) in the raltegravir group and six (3·3%, 95% CI 1·2 to 7·0) in the efavirenz group (absolute difference –2·7%, 95% CI –5·5 to <0·1; p=0·064). Each HIV-infected infant had their first positive HIV test within 48 h of birth, suggesting all infections occurred in utero, and all infected infants were born to mothers who enrolled at 28–<37 weeks gestation.

Discussion

In this study, the proportion of ART-naive pregnant women living with HIV infection with a viral load of less than 200 copies per mL at or near delivery was significantly greater in the raltegravir group than the efavirenz group, primarily among those enrolling in the third trimester. Both regimens were safe and well tolerated. A larger difference was observed when comparing virological suppression below the local assay lower limit of quantification. In a composite analysis of efficacy and tolerability, the difference in outcomes between raltegravir and efavirenz was even more pronounced and was driven by the faster viral load reduction with raltegravir.

Integrase inhibitors are potent, well tolerated antiretrovirals that are recommended as first-line ART regimens in non-pregnant adults living with HIV.[12] The integrase inhibitors raltegravir and dolutegravir are also recommended as preferred regimens for use during pregnancy by the US Perinatal HIV Guidelines Panel due to their efficacy, tolerance, and pharmacokinetic profiles.

The Dolphin-2 trial compared efavirenz with dolutegravir in late-presenting pregnant women.[6,13] The safety analysis included 268 women and the efficacy analysis 237. Virological response defined as the percentage of women with less than 50 copies per mL was 72% in the dolutegravir group versus 43% in the efavirenz group. P1081 data are in keeping with what is known from the Dolphin trial, with both trials showing that pregnant women receiving an integrase inhibitor had a better viral load response than those receiving efavirenz.

Another open-label trial involving late-presenting pregnant women comparing raltegravir and lopinavir and ritonavir found that, of 33 patients in total, 76·5% in the raltegravir group and 25% in the lopinavir and ritonavir group achieved virological suppression at delivery[16]. Observational real-life studies have reported rates of virological suppression ranging from 70% to 86% among women who received raltegravir during pregnancy. These studies, which included participants with considerable variability in the length of ART exposure, observed a rapid decline in concentrations of plasma HIV RNA among women receiving raltegravir, and a large proportion quickly achieved suppression of HIV replication.[9,14] In our population, a larger proportion of women receiving raltegravir had a 2·0-log decrease by week 2 compared with those receiving efavirenz, which is consistent with previous observational studies.[15–18]

These results should be considered in the context of ART resistance profiles, which can vary significantly by country or region. 9% of women enrolling in our study had at least one resistance mutation to non-nucleoside reverse transcriptase inhibitors or nucleoside reverse transcriptase inhibitors. In a cohort of ART-naive pregnant women in Brazil, the proportions of resistance to non-nucleoside reverse transcriptase inhibitors was 9% and to nucleoside reverse transcriptase inhibitors was 21%.[19] Our study found no resistance to integrase inhibitors at study entry, consistent with an observational study done in the USA in 2010–16 that reported very low rates of resistance to integrase inhibitors (0·2%) in ART-naive non-pregnant adults.[20] Treatment for late presenting pregnant women living with HIV in regions with comparatively high rates of non-nucleoside reverse transcriptase inhibitor resistance should prioritise integrase inhibitors including raltegravir, particularly when genotype test results cannot be obtained rapidly, because genotypic resistance to integrase inhibitors before treatment is uncommon.

Pregnancy outcomes in this study were consistent with previous studies of initiation of other antiretroviral regimens in pregnancy. 11–12% of women in our study had preterm deliveries, lower than the reported proportion of preterm deliveries of 18% among ART-exposed pregnant women and their infants in Botswana and of 20% in NISDI studies in Latin America, but similar to results reported in a trial in HIV-exposed infants whose mothers did not receive ART.[21–23] The proportion of infants with low birthweights was 13% in our study, similar to the proportion (14%) reported in HIV-exposed infants at similar sites.[24] The most common comorbidity among infants was congenital syphilis (6% in both groups). A study done at similar sites in Africa and Brazil found that 9·3% of infants whose mothers did not receive prenatal care had syphilis.[21]

As in our study, most retrospective studies have reported no difference in adverse events between integrase inhibitor and non-nucleoside reverse transcriptase inhibitor use in pregnancy.[22] One previous study in non-pregnant adults reported higher rates of adverse events in those taking efavirenz compared with raltegravir.[4] Few adverse events occurred in infants in our study, consistent with the results of observational studies that have reported few adverse events in infants whose mothers used raltegravir.[9,15]

Although the HIV perinatal transmission rate was not significantly different between treatment groups in our study, substantially fewer infants were infected in the raltegravir group compared with the efavirenz group (p=0·064). Previous studies have shown that elevated viral load and late presentation to antenatal care are major causes of perinatal transmission.[25,26] Integrase inhibitors, such as raltegravir, might be useful in rapidly reducing high viral load, and ultimately an effective option for prevention of mother to child transmission,[27] but ideally the diagnosis and the treatment cascade should begin before conception.

However, one of the limitations of this study was that it was underpowered to detect a difference in the HIV perinatal transmission rate between study groups. The proportion of infected infants in the raltegravir group was very low (0·5%) and was comparable to results in previous observational studies.[9,14,15,17] Limitations of the study also include our use of a lamivudine and zidovudine nucleoside reverse transcriptase inhibitor backbone, which might not be applicable to clinical practice.

Another limitation is that a fixed dose combination was not used in the trial, which could have led to increased attribution and reporting of specific toxicities in a treatment group. We attempted to minimise these biases by setting up stringent criteria for toxicity management, participant management, including regimen modification, treatment discontinuation, and inadequate virological response.

A strength of this study is the high quality and completeness of data. Around 96% of women who initiated treatment remained on study drug until delivery, and 96% of infants completed all protocol requirements. This high completion rate permitted evaluation of safety in a large, representative group of mothers and infants.

In this multicentre randomised controlled trial comparing an integrase inhibitor with efavirenz in pregnant women living with HIV, the rate of suppression at delivery was higher with raltegravir, and raltegravir was shown to be a potent and well tolerated antiretroviral. These results support the use of raltegravir in pregnant women who present late for care, particularly those initiating treatment after 28 weeks of gestation.

Declaration of interests

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Data sharing statement

Individual participant data will be available (including data dictionaries). Individual participant data that underlie the results reported in this article will be shared after de-identification (text, tables, figures, and appendices). The study protocol (including sample informed consent form) and statistical analysis plan will also be available. The data will be available beginning 9 months following article publication and will be shared with researchers whose proposed use is approved by the NICHD Data and Specimen Hub (DASH) Data Access Committee as scientifically and ethically appropriate and does not conflict with constraints or informed consent limitations and will be made available for analyses required to achieve aims in the approved proposal. To gain access, data requestors will need to create a free NICHD DASH account, submit a data access proposal, and if approved, sign a data access agreement. Information regarding creating a NICHD DASH account and accessing data may be found on the NICHD DASH website. The authors assume responsibility for the accuracy and completeness of the data, as well as the fidelity of the trial to the protocol. Upon acceptance, the protocol will be made available online as per *The Lancet HIV* guidelines, via the NICHD DASH portal.

For the **NICHD DASH** website see https://dash.nichd.nih.gov/

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