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Incidence of neonatal sepsis among HIV exposed neonates of mothers on integrase strand transfer inhibitors in sub-Saharan Africa: a systematic review and meta-analysis

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Abstract

Introduction Human immunodeficiency virus (HIV)-exposed infants face elevated risks of neonatal sepsis, influenced by maternal antiretroviral therapy (ART) regimens. Dolutegravir (DTG), a widely used integrase transfer inhibitor (INSTI), and the preferred first line drugs for management of HIV in pregnancy, has shown potential adverse effects such as hyperglycaemia, which may impact neonatal outcomes including risk of neonatal sepsis. We estimated the pooled incidence of neonatal sepsis among neonates exposed to INSTIs *in utero* compared to non-INSTIs-based ART regimens.

Methods and analysis A systematic review and meta-analysis were conducted following written as per the PRISMA guidelines. Databases including PubMed/MEDLINE, Embase, Cochrane Library, CINAHL, Global Health and Global Index Medicus were searched for studies published between January 2013 and September 2025. Eligible studies included clinical trials and cohort studies comparing INSTI-based ART regimens with non-INSTI regimens among pregnant women living with HIV. Data were extracted using Covidence software, Cochrane risk of bias (RoB) and Newcastle-Ottawa Scale (NOS) were used to assessed for quality of randomised clinical trials and observational studies, respectively. The certainty of the evidence was assessed using the Grading, Recommendation, Assessment, Development and Evaluation (GRADE) framework.

Results A total of 714 studies were identified and screened based on their titles and abstracts, of which 63 articles underwent full-text review. Ultimately, four studies, comprising 7,636 participants, met the predefined eligibility criteria and were included in the analysis. The pooled odds ratio (OR) for neonatal sepsis among infants exposed to INSTIs was 0.44 (95% confidence interval [CI]: 0.15–1.30, $p=0.137$). The test for subgroup difference was not significant ($p=0.358$): the pooled OR for dolutegravir was 0.27 (95% CI 0.06–1.23, $p=0.090$) and for the single raltegravir study was 0.73 (95% CI 0.16–3.30, $p=0.681$).

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Conclusion INSTI-based ART was not associated with a significant difference in neonatal sepsis risk compared with non-INSTI regimens. However, the low number of events limited the precision of the estimates, highlighting the need for further research.

Registration This review has been registered with the PROSPERO at https://www.crd.york.ac.uk/PROSPERO/view/CRD420251178411, registration number CRD420251178411,

Keywords Newborn infection, Dolutegravir, Raltegravir, HIV-exposed infants, Antiretroviral therapy

Background

Low- and middle-income countries (LMICs) suffer a significant burden of neonatal deaths with sub-Saharan Africa registering a staggering one million of these deaths in 2022, despite the global decline from 2.9 to 2.3 million between 2015 and 2022 [1]. The highest burden is in Eastern Africa, with a pooled prevalence of 42% compared to 36% in the sub-Saharan African region [2] and is attributable to causes such as prematurity, birth asphyxia [1], and neonatal sepsis [3]. Identifiable risk factors for neonatal sepsis include prematurity, small for gestational age, absence of or suboptimal breastfeeding, maternal deaths, poverty [4, 5] and exposure to human immunodeficiency virus (HIV) [6]. Exposure to altered HIV viral proteins, glycoproteins, maternal pro-inflammatory state and immune compromise, antiretroviral therapy (ART) and other drugs in utero and in breast milk have been highlighted as risk factors for neonatal sepsis unique to HIV-exposed neonates [4]. Until mid-2019, when the World Health Organization (WHO) updated its guidelines by replacing tenofovir triple combination with dolutegravir, a second generation integrase strand transfer inhibitor (INSTI), tenofovir disoproxil fumarate, lamivudine, and efavirenz (TDF + 3TC + EFV) has for more than two decades been the standard of care for pregnant women with HIV in most LMICs [7]. Currently, dolutegravir is the preferred drug of choice among women of reproductive age including pregnant women living with HIV [8]. Despites the known benefits of ART in reducing risk of vertical transmission of HIV, ART and other drugs in utero and breast milk have been highlighted as risk factors of neonatal sepsis unique to HIV-exposed neonates [4, 6]. Since dolutegravir -based ART regimens are the main first-line treatment options for person with HIV (PWH), including pregnant women, because of their efficacy, tolerability, high resistance barrier, and low cost [9, 10], yet dolutegravir has been associated with adverse events, such as hyperglycaemia and new-onset diabetes mellitus [11, 12] which potentially increase the risk of sepsis in both mothers and babies. High incidence of dolutegravir -associated hyperglycaemia has been reported in Uganda with about 40.1% of patients having to change their regimens due to new onset hyperglycaemia [11].

Doluravir-induced maternal hyperglycaemia could adversely impact both maternal and foetal outcomes [13]. Dolutegravir is associated with increased foetal and maternal peripartum complications [9, 13] including neonatal sepsis [13]. Neonatal hyper- or hypoglycaemia is associated with an increased risk of sepsis with poor outcome including death [14]. There is scanty evidence regarding transplacental transfer of INSTIs, especially dolutegravir with limited metabolism through the foetal uridine diphosphate glucuronosyl transferase activity leading to comparable plasma dolutegravir levels in both the mothers and the foetus [15] and prolonged long half-life [16]. These may then lead to foetal hyperglycaemia. The impact of ART factors, especially dolutegravir-induced maternal hyperglycaemia, in modulating risks to neonatal sepsis remain incompletely understood in these settings, despite the high burden of neonatal sepsis in LMICs.

In this systematic review and meta-analysis we estimated the pooled incidence of neonatal sepsis and risk factors among neonates exposed to INSTIs *in utero* compared to non-INSTI-based ARV regimens. The review question was "In sub-Saharan Africa, does maternal use of INSTI-based ART regimen for HIV treatment during pregnancy increase or decrease the risk of neonatal sepsis in HIV-exposed newborns compared with non-INSTI-based regimens?".

Methods

Study design

This systematic review and meta-analysis paper was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [17], and the search protocol registered with PROSPERO, CRD420251178411,

Search strategy

With the help of a qualified medical librarian, studies published from 1st January 2013 to 21st September 2025 were searched from 6 databases; PubMed/MEDLINE, Embase, Global Health, CINAHL, Global Index Medicus, and Cochrane Library. The 2013 dateline was chosen based on the Food and Drug Administration approval dates for clinical use of dolutegravir. Observational cohort studies, clinical trials and quasi-experimental

studies were included. Technical reports, thesis, research protocols, book reviews, qualitative and mixed methods, conference proceedings, commentaries, blog posts, and other kinds of grey publications were excluded.

An example of search strategy for Ovid MEDLINE is neonatal sepsis (sepsis or bloodstream infection* or neonatal infection* or bacteraemia or septicaemia or systemic infection*) OR (neonate* or newborn* or infant* or perinatal or baby or babies) AND (HIV exposure or maternal HIV or HIV positive or HIV infected, or HIV exposed or HIV seropositive).

For Embase: ((sepsis OR bloodstream infection* OR neonatal infection* OR bacteraemia or septicaemia OR systemic infection*) OR 2 Neonatal Sepsis/ OR (neonate* or newborn* or infant* or perinatal or baby or babies) Infant, Newborn)) AND ((HIV exposure or maternal HIV or HIV positive or HIV infected, or HIV exposed or HIV seropositive) OR Infections)).

For COCHRANE: ((sepsis or bloodstream infection* or neonatal infection* or bacteraemia or septicaemia or systemic infection*)) OR MeSH descriptor AND [Neonatal Sepsis] explode all trees ((neonate* or newborn* or infant* or perinatal or baby or babies)): MeSH descriptor: [Infant, Newborn] explode all trees AND ((HIV exposure or maternal HIV or HIV positive or HIV infected or HIV exposed or HIV seropositive)) OR [HIV Infections] explode all trees.

For CINAHL: ((MH "Neonatal Sepsis") OR ((sepsis or bloodstream infection* or neonatal infection* or bacteremia or septicemia or systemic infection*)) AND ((MH "Infant, Newborn") OR ((neonate* or newborn* or infant* or perinatal or baby or babies))) AND ((HIV exposure or maternal HIV or HIV positive or HIV infected or HIV exposed or HIV seropositive)) OR (MH "HIV Infections"))

For Global Health: [All: neonatal sepsis] AND [All: maternal HIV]; [All: sepsis] AND [All: HIV exposure] AND [All: neonat*]; [All: sepsis] AND [All: HIV exposure] AND [All: infant*].

For Global Health Medicus: (sepsis) AND (HIV exposure) AND (neonat*).

Study selection criteria

Duplicate studies were identified and removed using Covidence software by PFP. Titles and abstracts were primarily screened independently by PFP and IP to exclude those not related to this study. After the initial screening, full texts of potentially eligible studies were retrieved and examined for eligibility. Studies that were observational cohort studies, clinical trials and quasi-experimental studies were included. Those that were published before 2013, did not have the outcome of interest, evaluated other interventions, lacked full texts, did not meet design criteria, or had the wrong population were excluded (Fig. 1). Any discrepancies between the reviewers were discussed and resolved through consensus.

Data extraction

Two reviewers (PFP and IP) independently extracted data from the four included studies using a standardized data extraction form. The entire process was managed using Covidence. Reviewers independently screened and charted the data based on the predefined extraction form created for the purpose of this study, which included study characteristics, population details, ART regimen components, and specific neonatal outcomes. Any discrepancies or conflicts encountered during the extraction process were resolved by consensus between the two reviewers. Once consensus was reached and the data were finalized, the complete dataset was exported from Covidence to a Microsoft Excel 2021 spreadsheet for statistical analysis.

Quality assessment

The methodological quality and risk of bias for all included studies were assessed. For the randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 (RoB 2) tool was employed. This tool evaluated bias across five key domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. For the observational cohort study, the Newcastle-Ottawa Scale (NOS) was used. The NOS was applied to assess the quality of the study based on three categories: the selection of the study cohorts, the comparability of the cohorts, and the ascertainment of the outcome. Two reviewers (PFP and IP) independently conducted the quality assessments. Any discrepancies were resolved through discussion. The findings from the quality assessment were used to contextualize the evidence.

Assessment of certainty of evidence

We assessed the certainty of the body of evidence for each primary outcome (neonatal sepsis and all-cause neonatal mortality) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [18]. The evidence was evaluated across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. RCTs started as high-certainty evidence, while the observational study started as low-certainty evidence. However, given that the high-quality observational study [19] included in this review showed results consistent with the RCTs and had a low risk of bias (NOS score 9/9), it was evaluated alongside the RCTs as part of the overall body of evidence. We downgraded the certainty rating by one or two levels depending on the severity of limitations in any of the five

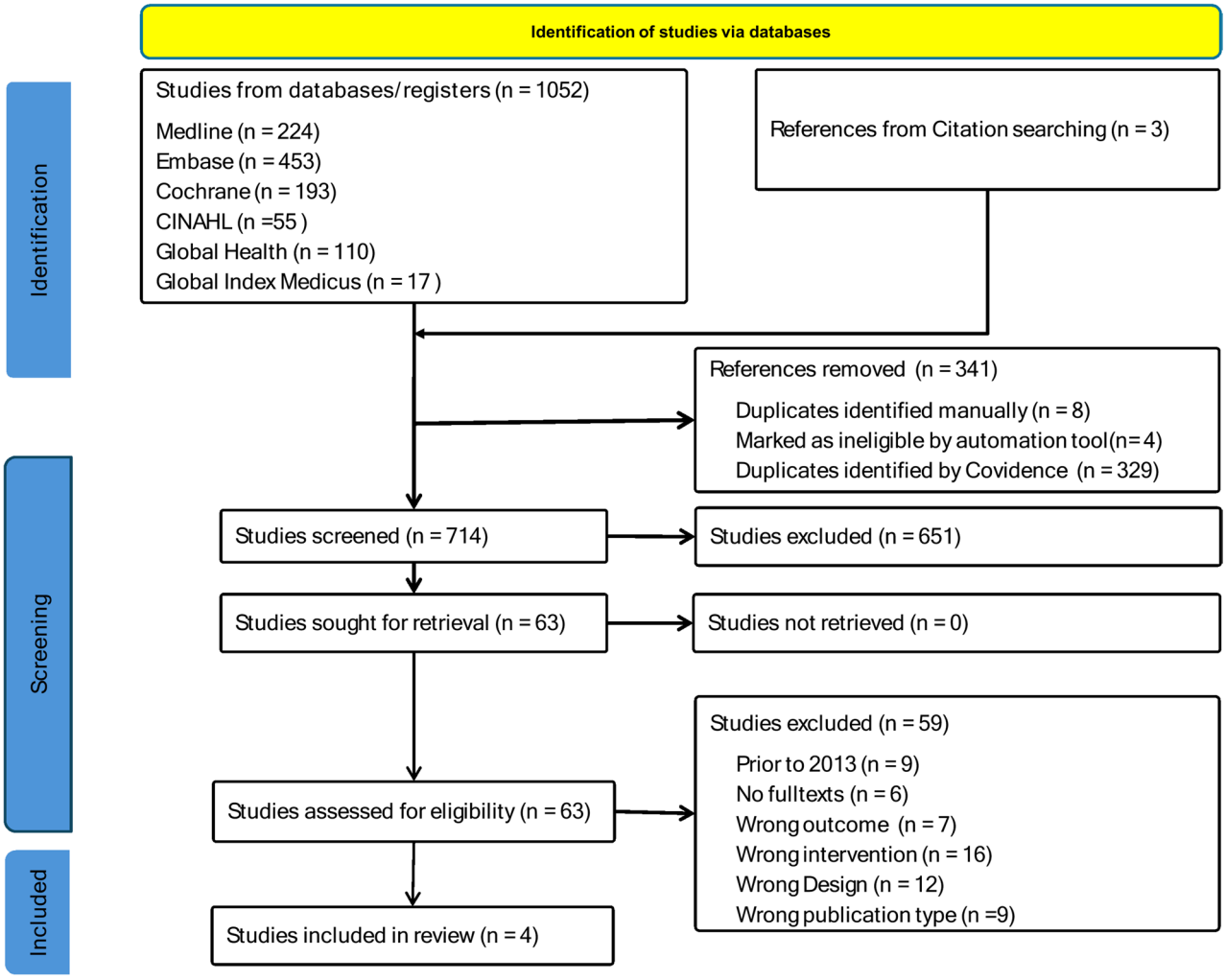

Fig. 1 PRISMA flow diagram showing the article screening process

domains. The certainty of evidence was assessed using the GRADE approach described by Balshem et al. (2011) [20], with overall certainty categorized as high, moderate, low, or very low based on considerations of risk of bias, imprecision, inconsistency, indirectness, and publication bias. A GRADE Evidence Profile was generated to present the summary of findings and the certainty of evidence.

Statistical analysis

Descriptive accounts of the included studies were first synthesized and tabulated. This summary included study characteristics (author, year, study design, and country), population details (number of participants in each arm), and the specific ART regimens compared (integrase inhibitor-based vs. non- dolutegravir -based). Key outcomes, including the prevalence of neonatal sepsis, sepsis-related mortality, and all-cause neonatal mortality, were extracted and presented in a summary table to map the existing evidence.

A meta-analysis was conducted to estimate the pooled odds ratio (OR) for the association between INSTI use (dolutegravir or raltegravir) and the specified outcome across the studies. The inverse variance method was applied using a random-effects model to account for potential variability across studies. Between-study heterogeneity was quantified using the tau-squared (τ^2) statistic, the I^2 index, and Cochran's Q test. The τ^2 value was estimated through the restricted maximum-likelihood approach, while its 95% confidence interval was derived using the Q-profile method. When zero events were reported in a study arm, a continuity correction of 0.5 was applied to stabilize variance estimates. Subgroup analyses were performed by drug type (dolutegravir vs. raltegravir) to explore possible effect modification. To assess robustness, we performed leave-one-out analyses, repeated the meta-analysis restricted to the randomised controlled trials, varied the continuity correction applied to zero-event arms (0.5, 0.1, and 0.01), and re-estimated the pooled odds ratio (OR) using the Peto and

Mantel-Haenszel methods, which do not require a fixed continuity correction. Statistical significance was defined at $p < 0.05$, and results were displayed using forest plots showing study-specific and pooled ORs with corresponding 95% confidence intervals (CI). All analyses were performed using R (meta package), and the random-effects model was selected given the potential clinical and methodological diversity among the included studies.

Results

Study selection

A total of 1052 articles identified through the search process were retrieved from the six electronic databases (PubMed/MEDLINE, Embase, Cochrane, CINAHL, Global Health and Global Index Medicus) and an additional 3 were identified through citation list searches. The complete search strategies used for each of these databases can be found in the additional files. After the initial removal of duplicates, 714 records remained for title and abstract screening. After the initial screening of titles and abstracts, 651 articles were considered not eligible for further review, leaving 63 studies for full-text retrieval. After detailed review, 59 studies were excluded for various reasons (Fig. 1). Ultimately, four studies [21, 19, 22, 23] met all inclusion criteria and were included in the final review.

Study characteristics

All four studies were multicenter and three were clinical trials while one was a cohort study. They had a combined sample size of 7,636 participants (2,497 in experimental and 5,139 in control arms) (Table 1**).** The studies were primarily conducted in sub-Saharan Africa, with additional sites in South and North America and Asia including a total 286 (3.8%) of all the recruited participants. All compared the safety and efficacy of dolutegravir or raltegravir–based ART regimens with efavirenz–based or other non- dolutegravir /raltegravir regimens among pregnant women living with HIV.

Quality assessment results

The methodological quality of the four included studies was assessed. The observational study scored 9/9 on the NOS, indicating very good quality and low risk of bias (Table 2**).** The three RCTs were evaluated with the Cochrane RoB 2 tool and rated as having "some concerns," mainly due to their open-label design. All RCTs showed low risk of bias in randomization, outcome measurement, and reporting, as primary outcomes were objective. Overall, the evidence was of moderate to high quality (Table 3**).**

Table 1 Comprehensive summary of findings from included studies

Data Point	IMPAACT 2010 / VESTED	Tsepamo Study	DolPHIN-2 Trial	NICHD P1081 Trial
First Author, Year	Lockman, 2021(21)	Zash, 2018(19)	Kintu, 2020(22)	Joao, 2020(23)
Study Design	Phase 3 randomized controlled trial	Observational cohort	Randomized controlled trial	Phase 4 randomized controlled trial
Country/Countries	Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, Zimbabwe, USA	Botswana	South Africa, Uganda	Argentina, Botswana, Brazil, Peru, South Africa, Thailand, USA
Participants (Infants)	DTG Arm: 415 Non-DTG Arm: 202	DTG Arm: 1729 Non-DTG Arm: 4593	DTG Arm: 137 Non-DTG Arm: 133	RAL Arm: 216 Non-RAL Arm: 211
Maternal ART Initiation	14–28 weeks gestation	During pregnancy	≥ 28 weeks gestation	20–37 weeks gestation
INSTI-based Regimen	(1) DTG + TAF/FTC (2) DTG + TDF/FTC	DTG + TDF/FTC	DTG + TDF + FTC (or 3TC)	Raltegravir (RAL)-based ART
Non-INSTI-based Regimen	Efavirenz (EFV) + TDF/FTC	EFV + TDF/FTC	EFV + TDF + FTC (or 3TC)	EFV-based ART
Prevalence of Neonatal Sepsis (DTG/Integrase Arm)	0% (0/415) (as cause of death)	0.06% (1/1729) (as cause of death)	0% (0/137) (as serious adverse event)	1.4% (3/216) (as serious adverse event)
Prevalence of Neonatal Sepsis (Non-DTG Arm)	1.5% (3/202) (as cause of death)	0.09% (4/4593) (as cause of death)	1.5% (2/133) (as serious adverse event)	1.9% (4/211) (as serious adverse event)
Sepsis-Related Mortality (DTG/Integrase Arm)	0 deaths	1 death	0 deaths	0 deaths
Sepsis-Related Mortality (Non-DTG Arm)	3 deaths	4 deaths	0 deaths	1 death
All-Cause Neonatal Mortality (DTG/Integrase Arm)	Combined: 6 deaths (1.4%)	21 deaths (1.2%)	3 deaths (2.2%)	3 deaths (1.4%)
All-Cause Neonatal Mortality (Non-DTG Arm)	11 deaths (5.4%)	56 deaths (1.2%)	1 death (0.8%)	6 deaths (2.8%)

Table 2 Quality assessment of observational study (Newcastle-Ottawa scale; Study) Zash et al. (2018), Tsepamo Study [19]

Domain	Item	Star Awarded (★)	Rationale
Selection	1. Representativeness of the Exposed Cohort	★	The study is a national birth outcomes surveillance program, capturing ~ 45% of all births in Botswana, making it highly representative.
	2. Selection of the Non-Exposed Cohort	★	The non-INSTI (EFV) cohort was drawn from the same surveillance program in the same facilities, just prior to the national guideline change.
	3. Ascertainment of Exposure	★	ART regimens were abstracted from obstetric records by trained research assistants.
	4. Outcome Not Present at Start	★	The outcomes (neonatal death, sepsis) occurred after the exposure (maternal ART).
Comparability	1. Comparability of Cohorts	★★	The analysis was adjusted for key confounders, including maternal age, gravidity, and education, controlling for the most important factors.
Outcome	1. Assessment of Outcome	★	Outcomes (neonatal death, cause of death) were determined from abstracted obstetric records and reviewed.
	2. Follow-up Long Enough	★	Follow-up was sufficient to capture all neonatal outcomes (death within 28 days).
	3. Adequacy of Follow-up	★	As a surveillance study of delivery records, follow-up for the primary neonatal outcomes was complete.
Total Score		**9 Stars (Very Good Quality)**	

Outcomes

Prevalence of neonatal sepsis and all cause neonatal mortality

Across the included studies, the prevalence of neonatal sepsis varied and was reported either as a cause of neonatal death [19, 21] or as a serious adverse event [22, 23] rather than as a separate outcome. In the non-INSTI-based arms, the reported prevalence ranged from 0.09% to 1.9%. Sepsis accounted for neonatal deaths in three of the four studies. In contrast, the INSTI arms generally showed lower rates, ranging from 0% to 1.4%. Notably, no cases of neonatal sepsis were observed in the dolutegravir arms of the IMPAACT 2010/VESTED and DolPHIN-2 trials. Sepsis-related mortality was also uncommon in these groups, with only one death due to sepsis reported across all INSTI arms (Table 1).

All-cause neonatal mortality

The IMPAACT 2010/VESTED trial reported a higher all-cause neonatal mortality rate in the EFV arm (5.4%) compared with the combined dolutegravir arms (1.4%). Similarly, both the DolPHIN-2 and NICHD P1081 trials showed lower mortality in the dolutegravir or raltegravir arms (2.2% and 1.4%, respectively) relative to the efavirenz arms (0.8% and 2.8%), though these differences were not statistically significant. In contrast, the Tsepamo study reported identical mortality rates (1.2%) across both groups (Table 1).

Pathogens and risk factors

None of the included studies provided detailed information on the specific pathogens responsible for neonatal sepsis, nor did they systematically assess differences in maternal or neonatal risk factors between ART regimens. Neonatal sepsis was therefore primarily reported within the context of safety and mortality outcomes, limiting further interpretation of etiological patterns or mechanisms.

Metanalysis

A total of four studies involving 7,636 participants (2,497 in experimental and 5,139 in control arms) were included in the analysis, reporting 17 total cases of neonatal sepsis across treatment groups. Individual study ORs ranged from 0.07 (95% CI: 0.00–1.33) in the IMPAACT 2010 trial to 0.73 (95% CI: 0.16–3.30) in the NICHD P1081 study (Fig. 2).

The pooled random-effects estimate indicated an overall OR of 0.44 (95% CI: 0.15–1.30, $p = 0.137$), suggesting a non-significant reduction in the odds of neonatal sepsis among participants receiving INSTI compared with control ART regimens ($z = -1.49$, $p = 0.137$). Heterogeneity across studies was low ($I^2 = 0.0\%$, $\tau^2 = 0.00$), with the Q-test for heterogeneity showing no significant variation between studies ($Q = 2.36$, $df = 3$, $p = 0.501$), supporting the appropriateness of the pooled model.

In subgroup analyses, studies evaluating dolutegravir ($k = 3$) produced a pooled OR of 0.27 (95% CI: 0.06–1.23, $p = 0.090$) with negligible heterogeneity ($I^2 = 0\%$), while the single raltegravir study yielded an OR of 0.73 (95% CI: 0.16–3.30, $p = 0.681$). The test for subgroup differences

Table 3 Quality assessment of randomized controlled trials (Cochrane RoB 2)

Study	Domain 1: Randomization Process	Domain 2: Deviations from Intervention	Domain 3: Missing Outcome Data	Domain 4: Measurement of Outcome	Domain 5: Selection of Reported Result	Overall Risk of Bias
Lockman, 2021 (IMPAACT 2010)	Low Risk (Central computerized randomization; permuted blocks; baseline characteristics similar)	Some Concerns (Open-label design; participants and staff were unmasked. However, analysis was intention-to-treat.)	Low Risk (High follow-up rate of 92% for infants; missing data unlikely to be biased.)	Low Risk (Outcomes like death and sepsis are objective and unlikely to be influenced by lack of blinding.)	Low Risk (Trial was registered; pre-specified outcomes were reported.)	Some Concerns (Mainly due to open-label design)
Kintu, 2020 (DolPHIN-2)	Low Risk (Central web-based randomization; permuted blocks; baseline characteristics balanced.)	Some Concerns (Open-label design. However, analysis was intention-to-treat.)	Low Risk (High completion rate of 93%; low loss to follow-up.)	Low Risk (Safety Endpoint Review Committee was blinded to allocation, mitigating the open-label design for outcomes.)	Low Risk (Trial was registered; pre-specified outcomes were reported.)	Some Concerns (Mainly due to open-label design)
Joao, 2020 (NICHD P1081)	Low Risk (Web-based randomization; permuted blocks; baseline characteristics similar.)	Some Concerns (Open-label design. However, analysis was intention-to-treat.)	Low Risk (Loss to follow-up was low and balanced between groups (9–10%).)	Low Risk (Outcomes like sepsis and death are objective and unlikely to be influenced by lack of blinding.)	Low Risk (Trial was registered; pre-specified outcomes were reported.)	Some Concerns (Mainly due to open-label design)

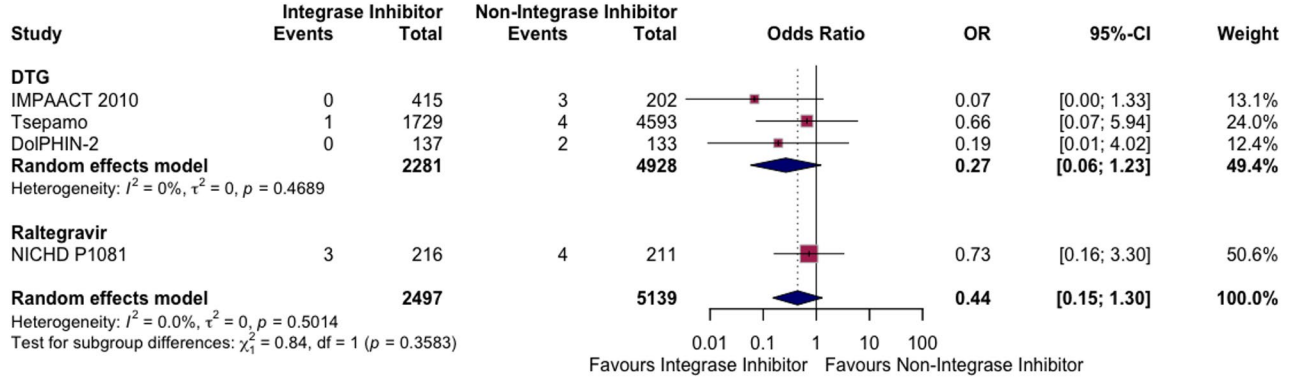

Fig. 2 The forest plot showing effect estimates of neonatal sepsis across studies

was not statistically significant (Q = 0.84, *df* = 1, *p* = 0.358), indicating no evidence of differential effects between the two drug subgroups.

The forest plot (Fig. 2) visually demonstrated consistent directionality of effect estimates across studies, with all point estimates favouring INSTI but with wide confidence intervals reflecting limited event rates.

The pooled estimate was consistent in direction but sensitive in magnitude to the handling of sparse and zero-event data. In leave-one-out analysis the pooled OR ranged from 0.27 (95% CI 0.06 to 1.23) to 0.59 (95% CI 0.19 to 1.86), and every iteration remained non-significant with unchanged heterogeneity (I^2 = 0%). Restricting the analysis to the three randomised controlled trials produced a comparable estimate (OR 0.39, 95% CI 0.11 to 1.34, *p* = 0.134). Because two of the four studies reported no sepsis events in the INSTI arm, we varied the continuity correction and found the pooled OR moved toward the null as the correction was reduced (OR 0.56, *p* = 0.341 at 0.1; OR 0.68, *p* = 0.537 at 0.01). Rare-event methods that avoid a fixed correction gave a somewhat lower estimate (Peto OR 0.36, 95% CI 0.13 to 0.98; Mantel-Haenszel OR 0.36, 95% CI 0.12 to 1.08), although the Peto method is biased when arm sizes are markedly unequal, as here, so its narrower interval should not be read as evidence of a protective effect.

Certainty of evidence

The certainty of the evidence for the neonatal sepsis is summarized **in** Table 4. For neonatal sepsis, the certainty of the evidence was rated as low. While the risk of bias was not serious (objective outcomes in open-label trials) and there was no inconsistency (I^2 = 0%) or indirectness, the evidence was downgraded by two levels for very serious imprecision. This was due to the extremely low number of events (*n* = 17 total across all studies) and a wide 95% CI (OR 0.44; 95% CI 0.15–1.30) that crossed the line of no effect and included potential for both appreciable benefit and harm.

Table 4 GRADE Evidence Profile for INSTI-based vs. non-INSTI-based ART in Pregnant Women Living with HIV

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**INSTI**	**Non-INSTI**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Neonatal Sepsis (follow up: birth to 28 days)												
4	Randomized trials [a]	Not serious	Not serious	Not serious	Very serious [b]	None	2,497	5,139	**OR 0.44** (0.15 to 1.30)	**2 fewer** per 1,000 (from 3 fewer to 1 more)	⨁⨁◯◯ **LOW**	CRITICAL
All-Cause Neonatal Mortality (follow up: birth to 28 days)												
4	Randomized trials [a]	Not serious	Not serious	Not serious	Serious [c]	None	2,497	5,139	**OR 0.84** (0.59 to 1.19)	**2 fewer** per 1,000 (from 5 fewer to 2 more)	⨁⨁⨁◯ **MODERATE**	CRITICAL

a. The body of evidence includes three RCTs and one high-quality observational study (Tsepamo) [19]. The observational study showed consistent results with the RCTs and had low risk of bias, so it was pooled with the RCTs. The starting certainty was based on the RCTs

b. Downgraded two levels for very serious imprecision due to very low event rate n = 17 total) and wide CI crossing the line of no effect

c. Downgraded one level for serious imprecision as the 95% CI crosses the line of no effect

For all-cause neonatal mortality, the certainty of the evidence was rated as moderate. The evidence was downgraded by one level for serious imprecision because the 95% CI (OR 0.84; 95% CI 0.59–1.19) crossed the line of no effect, although the sample size was large ($n = 7{,}636$).

Discussion

To our knowledge, this is the first systematic review to assess neonatal sepsis prevalence among HIV-exposed infants exposed in utero to INSTI- versus non-INSTI-based antiretroviral regimens in sub-Saharan Africa. Overall, no statistically significant difference in the risk of neonatal sepsis was observed between INSTI-based and non-INSTI ART regimens. Although the point estimate favoured INSTI-based regimens, the limited number of events and wide confidence intervals that included the null value preclude firm conclusions regarding any potential benefit. Given the limited number of outcome events and the resulting imprecision of the effect estimates, further evaluation in larger datasets is needed. There was also no statistically significant difference between dolutegravir and raltegravir in the subgroup analysis, although this comparison was constrained by the inclusion of only one raltegravir study.

The differences in how neonatal sepsis was defined and reported across studies may have introduced outcome heterogeneity and potential misclassification, as cases were identified either through cause-of-death classification or serious adverse event reporting. Consequently, the pooled estimate should be interpreted with caution because variations in outcome ascertainment may have influenced the observed association between INSTI exposure and neonatal sepsis.

Several studies have demonstrated a relative protective role of INSTI in neonatal sepsis. In a Spanish cohort [24], INSTI has been shown more effective than non-INSTI regimens in achieving virological suppression and in the restoration on the maternal microbiome composition. Recent studies have shown normalization of neonatal microbiome in both HIV exposed and unexposed infants especially for those whose mother has been on ART for a longer period compared to those newly diagnosed with HIV [25]. The restoration among mothers has been seen to be significant among those on INSTI [25]. PI-based fixed dose regimens such as ATV has been linked to cases of neonatal hypoglycaemia including neonatal sepsis [26]. Although bictegravir, a second generation INSTI, has been implicated in an increased risk of respiratory tract infections among children and teenagers aged 6 to 18 years [27] data are still limited in the neonatal population. In one study, the rates of culture positive neonatal sepsis among HIV exposed uninfected infants whose mothers were on ART were lower than in HIV unexposed infants, although the authors attributed this to the widespread use of cotrimoxazole in their study population [28]. Despite the many improvements in neonatal outcomes as a result of ART, HIV exposed infants are still at a greater odds of neonatal admissions and deaths compared to the unexposed infants [29].

HIV-exposed infants have lower birthweight compared to HIV-unexposed infants, even in the absence of neonatal HIV infection, suggesting an impact of maternal HIV infection and *in* utero foetal exposure [30]. Preterm and very preterm births, which have comparatively low birthweights, are more prevalent among HIV exposed yet they are at a high risk of developing neonatal sepsis and resulting in neonatal deaths [31]. In 2020, more than 180,000 cases of low, very low birth weight, and small for gestational age in LMICs, predominantly in SSA, was attributed to HIV and ARVs, of which the majority were receiving combination preconception ARTs [30]. Comparatively, INSTIs have been shown to be associated with lower rates (4.3%) of low birthweight compared to NNRTIs (19.8%) and PI based ART(18.9%) [30]. Although these factors were not evaluated in the current study, future research is warranted to investigate whether the type of maternal antiretroviral regimen influences birthweight outcomes and subsequent risk of neonatal sepsis.

All-cause neonatal mortality was numerically lower in the INSTI groups than in the non-INSTI groups in three of the four studies, with the exception of the Tsepamo study, although this difference was not statistically significant and the wide confidence intervals indicate considerable uncertainty around the effect estimate. These observations should therefore be regarded as hypothesis-generating and warrant further evaluation in larger, adequately powered datasets.

Although the pooled estimates did not demonstrate a statistically significant association between INSTI exposure and all-cause mortality, the direction of effect observed in most included studies warrants further investigation in larger, adequately powered cohorts. Any potential differences may be related to the favorable safety profile and effective virologic suppression associated with INSTI-based regimens, as reported in a retrospective cohort study from Spain involving raltegravir and dolutegravir [24]. Furthermore, the accumulating evidence supporting the safety and efficacy of INSTIs during pregnancy has contributed to their incorporation into contemporary HIV treatment guidelines, including the 2025 CDC recommendations that identify bictegravir-based regimens as preferred treatment options during pregnancy [8]. Collectively, these findings contribute to the growing body of evidence on the safety of INSTIs, which have become cornerstone agents in HIV treatment because of their potency, tolerability, and high barrier to resistance [32].

Strength and limitations

Our study provides a thorough analysis of neonatal sepsis among HIV exposed infants whose mothers are on dolutegravir and raltegravir based regiments compared to HIV exposed neonates whose mothers are not on INSTI-based regiments in sub-Saharan Africa and other LMICs by synthesizing data from four studies, providing a clear contextual perspective. Utilizing rigorous statistical methods, we enhanced reliability by minimizing bias and assessing heterogeneity. Our study was conducted according to Cochrane guidelines with exposures and outcomes clearly predefined to minimize misclassification bias and promote consistency across studies. Subgroup analyses and multiple sensitivity analyses confirmed the consistent direction of effect, although the magnitude of the pooled estimate depended on the analytic handling of the sparse, zero-event data. This systematic review and meta-analysis should be interpreted in consideration of the following limitations. Based on the GRADE assessment, the certainty of the evidence for neonatal sepsis was low, primarily due to very serious imprecision. The data were limited to only four studies with a pooled sample of 7,636 participants and only 17 total cases of neonatal sepsis. This resulted in large confidence intervals lending external validity. Neonatal sepsis was therefore primarily reported within the context of safety and mortality outcomes, limiting further interpretation of etiological patterns or mechanisms. None of the included studies provided detailed information on the specific pathogens responsible for neonatal sepsis, nor did they systematically assess differences in maternal or neonatal risk factors between ART regimens. This systematic review and meta-analysis have a limitation in that it only included quantitative observational studies published in English, which may have overlooked significant research published in other languages. Although the majority of the participants were from sub-Saharan Africa, about of 3.8% (286) of the total 7,636 participants were from other countries including Brazil, Thailand, Argentina, United States, and India with differing contextual care. Specifically, one of the RCTs, the NICHD P1081 Trial, an open labelled study, had about 34.6% of participants from sub-Saharan Africa, and the rest from other regions. These differences could have affected the interpretation of the findings in this metanalysis.

Conclusions

In conclusion, no statistically significant difference in neonatal sepsis risk was demonstrated between INSTI-based ART regimens, particularly dolutegravir, and non-INSTI regimens. However, the low statistical power of the study limits definitive conclusions regarding potential differences between treatment groups. These findings emphasize the need for further large-scale studies to validate the role of INSTIs on neonatal sepsis and to explore underlying mechanisms, including maternal glycaemic control and microbiome modulation.

Author contributions

PFP, conceived the idea, PFP, drafted the protocol and manuscript; DHH, JN, FB supervised the process, critically reviewed the protocol and manuscript. BM retrieve the articles PFP, IP, Extracted the Data. RN, VO, BM critically reviewed the draft manuscript. All authors approved manuscript and shall be accountable for all the aspects of it.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This systematic review and meta-analysis utilized data from publicly available published studies; therefore, ethical approval was not required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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