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SYSTEMATIC REVIEW

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Comparison of safety and effectiveness of antiretroviral therapy regimens among pregnant women living with HIV at preconception or during pregnancy: a systematic review and network meta-analysis of randomized trials

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Abstract

Background Mother-to-child transmission is the primary cause of HIV cases among children. Antiretroviral therapy (ART) plays a critical role in preventing mother-to-child transmission and reducing HIV progression, morbidity, and mortality among mothers. However, after more than two decades of ART during pregnancy, the comparative effectiveness and safety of ART medications during pregnancy are unclear, and existing evidence is contradictory. This study aimed to assess the effectiveness and safety of different ART regimens among pregnant women living with HIV at preconception or during pregnancy.

Methods We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. We included randomized trials that enrolled pregnant women living with HIV and randomized them to receive ART for at least four weeks. Pairs of reviewers independently completed screening for eligible studies, extracted data, and assessed the risk of bias using the Cochrane risk of bias tool. Our outcomes of interest included low birth weight, stillbirth, preterm birth, mother-to-child transmission of HIV, neonatal death, and congenital anomalies. Network meta-analysis was performed using a random-effects frequentist model, and the certainty of evidence was evaluated using the GRADE approach.

Results We found 14 eligible randomized trials enrolling 9,561 pregnant women. The median duration of ART uptake ranged from 6.0 to 17.4 weeks. No treatment was statistically better than a placebo in reducing the rate of neonatal mortality, stillbirth, congenital defects, preterm birth, or low birth weight deliveries. Compared to placebo, zidovudine

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(ZDV)/lamivudine (3TC) and ZDV monotherapy likely reduce mother-to-child transmission (odds ratio (OR): 0.13; 95% CI: 0.05 to 0.31, high-certainty; and OR: 0.50; 95% CI: 0.33 to 0.74, moderate-certainty). Moderate-certainty evidence suggested that ZDV/3TC was associated with decreased odds of stillbirth (OR: 0.47; 95% CI: 0.09 to 2.60).

Conclusions Our analysis provides high- to moderate-certainty evidence that ZDV/3TC and ZDV are more effective in reducing the odds of mother-to-child transmission, with ZDV/3TC also demonstrating decreased odds of stillbirth. Notably, our findings suggest an elevated odds of stillbirth and preterm birth associated with all other ART regimens.

Keywords Infant, Pregnant women, HIV infection, Vertical transmission, Antiretroviral agents

Background

Mother-to-child transmission (MTCT) of HIV accounts for over 90% of new HIV cases among children. Untreated HIV infection during pregnancy increases the likelihood of MTCT and leads to high rates of infant morbidity and mortality [1, 2]. Each year, nearly 1.5 million women living with HIV become pregnant, predominantly in low- and middle-income countries, with sub-Saharan Africa accounting for 91% of these cases [3].

Antiretroviral therapy (ART) is crucial in reducing mothers' HIV progression and morbidity and AIDS-related mortality [4]. Over the past decade, the widespread use of ART by pregnant women has improved long-term maternal health outcomes and decreased the rate of MTCT of HIV [5]. In 2013, the World Health Organization (WHO) recommended starting ART for all pregnant women regardless of their CD4 cell count [6], and in 2016, it recommended the "treat-all" approach, so that all people living with HIV start ART promptly, regardless of their CD4 cell count [7].

While selecting ART during pregnancy, it is crucial to individualize the approach based on the patient's ART history, medication resistance test results, and other comorbidities [8]. According to the current WHO guidelines for ART during pregnancy, a dolutegravir (DTG)-based regimen combined with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone (e.g., tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) (or emtricitabine (FTC)) is recommended as the first-line ART. This recommendation is underlined by factors, such as fewer drug interactions, and higher safety, efficacy, and tolerability associated with DTG. The guideline further recommends the efavirenz (EFV)-based regimen in combination with an NRTI backbone as the alternative first-line regimen. For cases in which DTG-based regimens have failed, an alternative second-line including protease inhibitor (PI)-containing regimen (e.g., zidovudine (ZDV)/3TC/lopinavir/ritonavir (LPV/r)) is advised [9].

Although ART uptake by pregnant women living with HIV substantially reduces the MTCT rate and enhances mothers' health conditions, it would also lead to continued fetal exposure to ART regimens. Recent extensive research has delved into the association between ART and adverse prenatal outcomes, yielding a spectrum of conflicting findings. As these outcomes can occur with no detectable cause, demonstrating a causal association with medication can be challenging. Furthermore, it is essential to acknowledge that pregnant women living with HIV inherently face an elevated risk of adverse prenatal outcomes, irrespective of their ART use. However, because of the common occurrence of these outcomes, even a modest increase in the risk of experiencing adverse prenatal outcomes resulting from medication regimens have public health importance [10, 11].

After nearly 20 years of ART use during pregnancy, evidence regarding the ART comparative effectiveness is inconclusive [12]. For example, a systematic review in 2018 revealed that most ART regimens were identified with mixed evidence suggesting both harms and benefits on the risk of low birth weight (LBW) and preterm birth (PTB) [13]. Moreover, previous network meta-analysis [14] looking at the safety and effectiveness of ART during pregnancy indicated that regimens containing LPV/r were associated with a higher incidence of both LBW and PTB compared to ZDV monotherapy. However, their conclusions came burdened with significant limitations, including double counting patient data, suboptimal strategies for pooling outcome data, inadequate assessment of the risk of bias of primary studies, and lack of appraisal of the overall certainty of evidence. In addition, neither reviews included the latest ART regimen recommended by WHO containing DTG [10].

Given the existing gaps in our understanding of the safety and effectiveness of ART use during pregnancy and the limitations of previously published evidence syntheses, we have conducted a systematic review and a network meta-analysis. This innovative approach provides a comprehensive and evidence-based framework for concurrently assessing all available ART regimens for pregnant women living with HIV, at preconception or during pregnancy. By synthesizing both direct and indirect evidence across a network of studies, our study offers a meticulous perspective on the comparative effectiveness and safety of these regimens, contributing to a more informed and evidenced-based decision-making process.

Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) extension for network meta-analysis [15] and registered our protocol with PROSPERO (CRD42021261096).

Data sources and searches

We searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Web of Science, using a database-specific search, from inception until 31 July 2021. Our search included both free-text and controlled vocabulary (e.g., MeSH). We used different variations of "HIV" and "ART", and terms indicating specific adverse perinatal outcomes (e.g., PTB) (See Supplementary Appendix A for a sample search strategy). We also reviewed relevant reviews' and trials' reference list to identify additional eligible trials. Our search was limited to trials published in English.

Study selection

Pairs of reviewers independently screened titles and abstracts identified through our literature searches using the Rayyan platform (https://www.rayyan.ai). The same reviewers independently assessed the full texts of all potentially eligible articles and resolved disagreements by discussion. We included trials that enrolled pregnant women living with HIV and randomized them to any ART for at least 4 weeks compared to control/placebo (PLC) or any alternative ART and measured at least one patient-important outcome (i.e., an outcome that directly relates to the well-being and quality of life of patients) [16, 17].

We did not apply any limitations to antiretroviral drugs or combined regimens, and all types of ART regimens were deemed eligible. In accordance with the WHO guidelines, some studies have substituted 3TC to FTC, or ZDV to TDF for the management of HIV during pregnancy; Hence, in our network meta-analysis, we have amalgamated these two drugs into a single cluster [9]. Our outcomes of interest included: LBW (i.e., weight at birth < 2,500 g), stillbirth (i.e., loss of infants after 24 weeks or during labor), PTB (i.e., infants born alive before completion of 37 weeks), HIV MTCT, neonatal death (NND) (i.e., children death in the first 28 days of life) [18], and congenital anomalies (i.e., a wide range of abnormalities of body structure or function that are present at birth) [19].

Data extraction

Using standardized, pilot-tested forms, pairs of reviewers extracted the following data, independently and in duplicate: (i) Study and population characteristics (e.g., first author, publication year, country, funding source, setting, study design, sample size, mean age, mean gestational age at enrolment, lab results at the baseline, such as CD4 + count (cells per μL), viral load (log copies per mL)); (ii) Details of intervention and comparator (e.g., ART class, ART complexity (monotherapy/multiple), dose and frequency, duration of therapy); and (iii) Outcomes consist of patient-important outcomes (e.g., rate of MTCT, rate of PTB, rate of congenital anomaly, rate of NND, rate of LBW, and rate of stillbirth).

Pairs of reviewers independently assessed the risk of bias for all eligible trials using the Cochrane risk of bias tool (version 1) [20]. The following items were evaluated: random sequence generation, allocation concealment, blinding of study participants, health care providers, and outcome assessors, and incomplete outcome data reporting/missing data (20% missing data was assigned a high risk of bias), and overall bias. Studies were classified as having an overall high risk of bias when three or more items were judged to be unclear or at high risk of bias. Considering that all the outcomes of interest were objective, the absence of blinding was not a significant concern. To elaborate, we did not attribute a high risk of bias to the lack of blinding in our evaluation. This decision stems from the understanding that there is a limited risk of ascertainment bias for outcomes like MTCT, PTB, Congenital Anomaly, NND, LBW, and Stillbirth [21, 22].

Data analysis

A frequentist random-effects network meta-analysis was conducted using Stata (Stata Corp, Release 17.0). For all outcomes, we calculated the odds ratio (OR) and 95% confidence intervals (CI). Initially, for all direct comparisons when two or more trials were available, we performed conventional pairwise meta-analysis using DerSimonian–Laird random-effects model [23]. We used the I^2 statistic and visual inspection of the forest plots to assess heterogeneity in direct comparisons. We were unable to investigate publication bias due to the limited number of studies available for each outcome, which lacked statistical power [24]. We then performed a frequentist network meta-analysis to synthesize the evidence from the entire network of trials using the methodology of multivariate meta-analysis assuming a common heterogeneity parameter [25, 26]. Network coherence was assessed globally using the design-by-treatment model. We confirmed the coherence assumption locally using the side-splitting method. We estimated ranking probabilities using the surface under the cumulative ranking curve (SUCRA), mean ranks, and rankograms [27, 28].

Assessing the certainty (quality) of the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for network meta-analysis was used to assess and communicate certainty of evidence [29, 30]. In brief, for indirect evidence, we focused on the dominant lowest order loop and rated the certainty of this evidence as the lowest certainty of the contributing direct comparisons. Network estimate certainty started as the higher of the direct and indirect evidence. We considered rating down the certainty in the network estimate if there was incoherence between the indirect and direct estimates, or if there was imprecision around the treatment effect.

Results

Overall, we identified 29,687 articles through literature search, of which 26 articles represented 14 unique randomized clinical trials and 9,561 pregnant women were eligible Fig. 1. The Fowler et al. study was undertaken in two discrete intervals, with the latter period encompassing an additional experimental treatment group [31]. As a result, we have regarded these two intervals as distinct studies. Among all included trials, seven studies were conducted exclusively in Africa [32–38], one in France [39], one in Thailand [40], and the four others were multicontinental [31, 41–43]. Studies' sample sizes varied from 60 to 3,088 participants, with a median gestational age ranging from 21.2 to 36 at enrollment. Gestational age was measured using various methods, primarily the last normal menstrual period. Study characteristics are shown in Table 1 (for participants' characteristics see Supplementary Table 1). Among all included studies, seven studies defined the WHO clinical stage of HIV [31–33, 36–38, 40]; most participants were at the first stage, and AIDS-defining illnesses were rare. Overall, ten various ART regimens were investigated in trials during pregnancy with the median duration of ART uptake ranged from 6.0 weeks to 17.4 weeks [32, 43]. In terms of interventions, seven studies evaluated the safety and effectiveness of ZDV/3TC/LPV/r compared to PLC, ZDV monotherapy, LPV/r monotherapy and other combination regimens [31–33, 37–39]. Six studies evaluated the safety and effectiveness of EFV/TDF/FTC [33–35, 38, 42, 43], and the preferred first-line regimen recommended by WHO, DTG/TDF/3TC (FTC) was evaluated in three of included studies [34, 35, 43].

Risk of bias

Of the total 14 randomized controlled trials, 13 studies adequately generated their randomization sequence, and 11 were judged to be at low risk of bias for allocation concealment. Although a significant number of studies had a high risk of bias in blinding, this was not a major issue in the judgment since the outcomes of interest were not

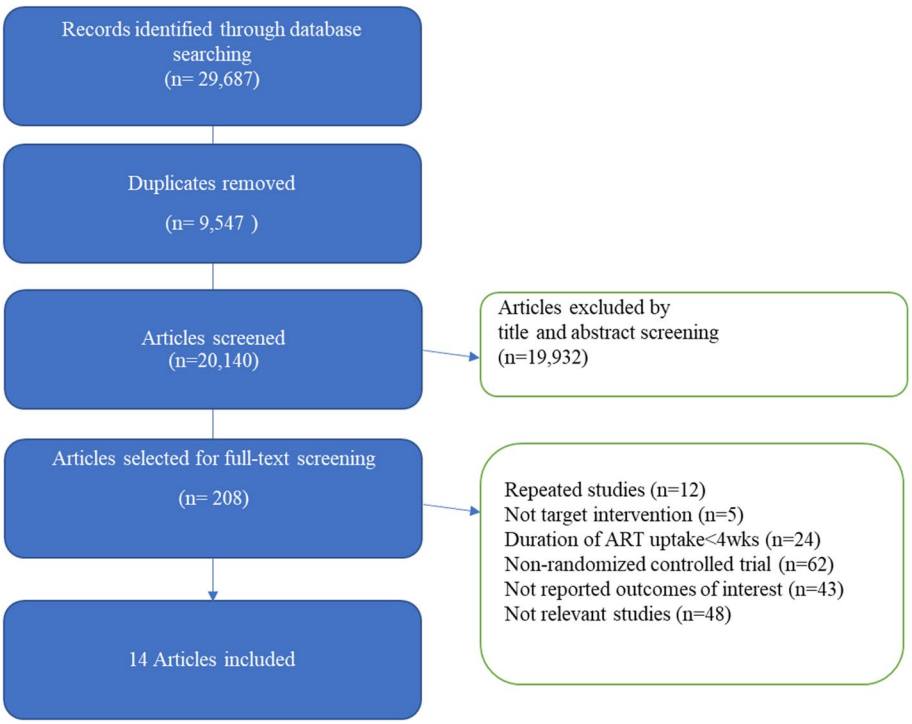

Fig. 1 Flow diagram of the study selection process

Table 1 Study characteristics included in the systematic review (*N*=14)

Study (year)	Country	Age at enrollment (Median (IQR)/ Mean (SD))	WHO clinical stage of HIV	CD4+ at enrollment (Median (IQR)/ Mean (SD) cells/ mm3)	Viral load level at enrollment (Log copies)	Intervention
Connor 1994 [41]	France, The USA	25*	-	No. with 200-500 cells:187 No. with less than 500 cells: 272	NR	1. ZDV 2. PLC
The Petra study team 2002	Uganda, Tanzania, South Africa	26 (22-30)	Stage 3 or 4: 22 (6%)	455.8 (247.7)	NR	1. ZDV/3TC 2. PLC
The Kesho Bora Study group 2010	Kenya west, South Africa	27 (24-31)	Stage 1, 2 or 3: 824 (100%)	336	4.2	1. ZDV/3TC/LPV/r 2. ZDV
Koss 2014 [33]	Uganda	29 (25-33)	Stage 1: 373 (96%)	368 (163.5)	4.2	1. ZDV/3TC/LPV/r 2. EFV/3TC/ZDV
João 2020 [42]	Argentina, Brazil, South Africa, Tanzania, Thailand, The USA	27 (22-32)	-	395 (262-574)	4.1	1. RAL/3TC/ZDV 2. EFV/3TC/ZDV
Kintu 2020 [35]	South Africa, Uganda	27.7 (5.2)	-	446 (296-633)	4.4	1. DTG/TDF/FTC (3TC) 2. EFV/TDF/FTC (3TC)
Lockman 2021 [43]	Botswana Brazil, India, South Africa, Tanzania, Thailand, Uganda The USA, Zimbabwe	26.6 (22.5-31.6)	-	466 (308-624)	3	1. DTG/TDF/FTC 2. EFV/TDF/FTC
Shapiro 2010 [37]	Bostwana	26.8 (5.94)	No AIDS defining disease	404 (297-514)	4.3	1. ZDV/3TC/ABC 2. ZDV/3TC/LPV/r
Tubiana 2013 [39]	France		-	500 (186)	3.4	1. LPV/r 2. ZDV/3TC/LPV/r
Natureeba 2014 [38]	Tororo, Uganda	29.25 (5.4)	Stage 1: 370 (95.1%) Stage 2: 18 (4.6%) Stage 3:1 (0.3%)	380.8 (162.5)	4.1	1. ZDV/3TC/LPV/r 2. EFV/TDF/FTC
Lallemant 2015 [40]	Thailand	27 (23-32)	Stage 1: 100%	453 (363-577)	4	1. ZDV 2. ZDV/LPV/r
Fowler 2016 [31]	India, Malawi, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	26 (22-30)	Stage 1: 2,981 (96.5%)	530 (436-663)	3.9	1. ZDV 2. ZDV/3TC/LPV/r 3. TDF/FTC/LPV/r
Waitt 2019 [34]	Uganda, South Africa	26 (5.75)	-	406.5 (207.2)	4.5	1. DTG/TDF/FTC 2. EFV/TDF/FTC

subjective. All the included studies were judged to be at low risk of bias regarding incomplete outcome data reporting/missing data. Conclusively, the overall risk of bias was judged to be low for 11 studies (Supplementary Fig. 1).

Effects of the interventions

Low birth weight

Findings from ten studies comprising 7,517 participants have reported LBW (See Fig. 2 for the network map). As shown in Supplementary Table 4, we did not find evidence of loop-specific incoherence. No moderate- or high-certainty evidence was found for LBW. Very low-certainty evidence suggested raltegravir (RAL)/3TC/ZDV (OR: 1.91, [95% CI: 0.76, 4.80]) and EFV/TDF/FTC (1.87, [0.93, 3.75]) were significantly associated with the increased odds of LBW compared with PLC. Other ART regimens, including ZDV/3TC/LPV/r, TDF/FTC/LPV/r, DTG/FTC/TDF, and ZDV/3TC/abacavir (ABC), were also associated with increased odds of LBW (Table 2).

Low- to very low-certainty evidence suggested that compared to PLC, ZDV (0.68, [0.44, 1.05]) and ZDV/

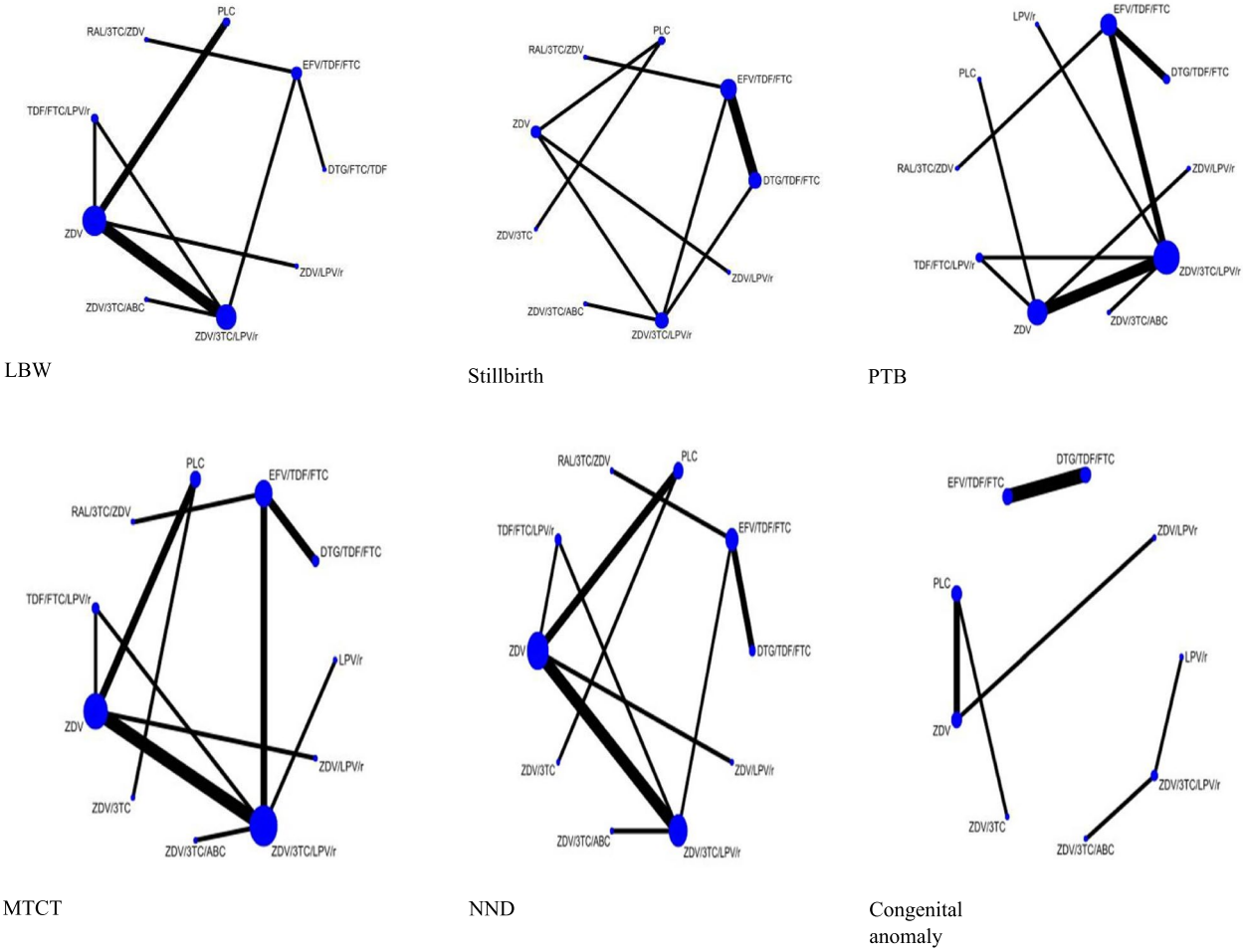

Fig. 2 Network of effects of ART on low birth weight (LBW), stillbirth, preterm birth (PTB), mother-to-child transmission (MTCT), neonatal death (NND), and congenital anomaly. The size of the nodes corresponds to the number of patients randomized to that intervention. The thickness of the lines corresponds to the number of studies for each comparison. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), raltegravir (RAL), efavirenz (EFV), dolutegravir (DTG), abacavir (ABC)

LPV/r (0.78, [0.38, 1.58]) had protective effects during pregnancy, reducing the odds of LBW (Table 2). Also, SUCRA rankings suggested ZDV had the highest probability of being the best treatment (Supplementary Table 6).

Stillbirth

Findings of eleven studies involving 5,115 participants reported the effects of ART regimens on stillbirth. Figure 2 presents the network map. No evidence of loop-specific incoherence was found (Supplementary Table 9). Moderate-certainty evidence suggested that ZDV/3TC (0.47, [0.09, 2.60]) was associated with decreased odds of stillbirth (Table 3). ZDV/3TC was also the best probable treatment in terms of stillbirth according to the SUCRA rankings (Supplementary Table 10).

Low- to very low-certainty evidence suggested that other ART regimens were significantly associated with increased odds of stillbirth. Of all, EFV/TDF/FTC (2.68, [0.07, 100.03]), ZDV (3.00, [0.12, 74.01]), and ZDV/3TC/LPV/r (3.00, [0.09, 98.86]) were probably the least harmful regimens in terms of increasing the odds of stillbirth (Table 3).

Preterm birth

The effects of ART regimens on PTB were examined in twelve studies involving 8,101 participants. Figure 2 presents the network map. No evidence of loop-specific incoherence was found (Supplementary Table 13). No moderate- or high-certainty evidence was found for PTB. Low- to very low-certainty evidence suggested that ART uptake during pregnancy is associated with elevated odds of PTB compared with PLC. ZDV/3TC/ABC (1.17, [0.49, 2.84]) and ZDV (1.27, [0.59, 2.71]) were probably the least harmful regimens in terms of PTB (Table 4). While, the SUCRA ranking

Table 2 Antiretroviral therapy network meta-analysis results on low birth weight with corresponding GRADE (the Grading of Recommendations Assessment, Development and Evaluation). Values correspond to odds ratios (95% CI) from the network meta-analysis. Odds ratios > 1 means the treatment had a higher odds of low birth weight in newborns. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), raltegravir (RAL), efavirenz (EFV), dolutegravir (DTG), abacavir (ABC)

PLC								
1.46 (0.91,2.33)	ZDV/3TC/LPV/r							
0.68 (0.44,1.05)	**0.47 (0.39,0.56)**	ZDV						
1.24 (0.69,2.23)	0.85 (0.58,1.24)	1.83 (1.23,2.71)	TDF/FTC/LPV/r					
1.91 (0.76,4.80)	1.31 (0.59,2.89)	2.82 (1.25,6.34)	1.54 (0.64,3.70)	RAL/3TC/ZDV				
0.78 (0.38,1.58)	**0.53 (0.30,0.96)**	1.14 (0.65,2.01)	0.63 (0.31,1.24)	0.41 (0.15,1.09)	ZDV/LPV/r			
1.87 (0.93,3.75)	1.28 (0.76,2.15)	2.75 (1.59,4.76)	1.51 (0.79,2.86)	0.98 (0.54,1.78)	2.41 (1.10,5.27)	EFV/TDF/FTC		
1.21 (0.49,2.95)	0.83 (0.39,1.77)	1.78 (0.81,3.88)	0.97 (0.42,2.27)	0.63 (0.28,1.43)	1.55 (0.59,4.07)	0.65 (0.37,1.13)	DTG/3TC(FTC)/TDF	
1.20 (0.62,2.32)	0.83 (0.52,1.30)	1.77 (1.08,2.90)	0.97 (0.53,1.76)	0.63 (0.25,1.57)	1.55 (0.73,3.27)	0.64 (0.32,1.28)	1.00 (0.41,2.42)	ZDV/3TC/ABC

Color description for certainty of evidence	High	Moderate	Low	Very low

Table 3 Antiretroviral therapy network meta-analysis results on stillbirth with corresponding GRADE (the Grading of Recommendations Assessment, Development and Evaluation). Values correspond to odds ratio (95% CI) from the network meta-analysis. Odds ratios > 1 means the treatment had a higher odds of stillbirth. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), raltegravir (RAL), efavirenz (EFV), dolutegravir (DTG), abacavir (ABC)

PLC								
3.00 (0.09,98.86)	ZDV/3TC/LPV/r							
4.68 (0.12,184.23)	1.56 (0.50,4.83)	ZDV/3TC/ABC						
16.96 (0.33,863.07)	5.65 (0.39,81.27)	3.63 (0.20,65.56)	ZDV/LPV/r					
0.47 (0.09,2.60)	0.16 (0.00,7.71)	0.10 (0.00,5.80)	0.03 (0.00,2.02)	ZDV/3TC				
3.00 (0.12,74.01)	1.00 (0.25,4.03)	0.64 (0.11,3.85)	0.18 (0.02,1.72)	6.34 (0.17,238.95)	ZDV			
7.88 (0.11,565.42)	2.63 (0.22,30.70)	1.68 (0.11,25.20)	0.46 (0.01,17.45)	16.65 (0.17,1655.96)	2.63 (0.16,44.31)	RAL/3TC/ZDV		
2.68 (0.07,100.03)	0.89 (0.35,2.29)	0.57 (0.13,2.49)	0.16 (0.01,2.67)	5.66 (0.10,309.16)	0.89 (0.17,4.79)	0.34 (0.04,3.30)	EFV/TDF/FTC	
5.69 (0.15,211.55)	1.90 (0.75,4.79)	1.22 (0.28,5.24)	0.34 (0.02,5.64)	12.01 (0.22,654.03)	1.90 (0.36,10.10)	0.72 (0.06,8.08)	2.12 (0.93,4.82)	DTG/TDF/3TC(FTC)/

Color description for certainty of evidence	High	Moderate	Low	Very low

Table 4 Antiretroviral therapy network meta-analysis results on preterm birth with corresponding GRADE (the Grading of Recommendations Assessment, Development and Evaluation). Values correspond to odds ratio (95% CI) from the network meta-analysis. Odds ratios > 1 means the treatment had a higher odds of preterm birth. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), raltegravir (RAL), efavirenz (EFV), dolutegravir (DTG), abacavir (ABC)

PLC									
2.08 (0.95,4.51)	ZDV/3TC/LPV/r								
1.17 (0.49,2.84)	**0.57 (0.37,0.86)**	ZDV/3TC/ABC							
1.68 (0.65,4.33)	0.81 (0.45,1.46)	1.43 (0.70,2.95)	ZDV/LPV/r						
1.27 (0.59,2.71)	**0.61 (0.52,0.72)**	1.08 (0.69,1.70)	0.75 (0.43,1.33)	ZDV					
1.89 (0.82,4.38)	0.91 (0.64,1.29)	1.61 (0.94,2.78)	1.13 (0.58,2.19)	**1.49 (1.05,2.13)**	TDF/FTC/LPV/r				
1.92 (0.68,5.42)	0.92 (0.46,1.84)	1.63 (0.73,3.66)	1.14 (0.46,2.83)	1.51 (0.74,3.08)	1.01 (0.47,2.20)	RAL/3TC/ZDV			
1.88 (0.41,8.53)	0.90 (0.25,3.32)	1.60 (0.41,6.26)	1.11 (0.27,4.65)	1.48 (0.40,5.48)	0.99 (0.26,3.81)	0.98 (0.22,4.26)	LPV/r		
1.81 (0.76,4.31)	0.87 (0.60,1.28)	1.55 (0.88,2.72)	1.08 (0.53,2.18)	1.43 (0.94,2.17)	0.96 (0.57,1.61)	0.95 (0.53,1.68)	0.97 (0.25,3.75)	EFV/TDF/FTC	
1.37 (0.52,3.61)	0.66 (0.37,1.18)	1.17 (0.57,2.38)	0.82 (0.36,1.86)	1.08 (0.59,1.97)	0.73 (0.37,1.42)	0.72 (0.35,1.47)	0.73 (0.18,3.04)	0.76 (0.49,1.16)	DTG/TDF/3TC(FTC)

Color description for certainty of evidence	High	Moderate	Low	Very low

results, suggested DTG/TDF/3TC(FTC) to be the best treatment in terms of PTB with a 47.4% probability of being the best treatment (Supplementary Table 14).

Mother-to-child transmission

The impact of ART regimens on MTCT was examined in 14 studies with a total of 8,961 participants. Figure 2 presents the network map. No evidence of loop-specific incoherence was found (Supplementary Table 17). High- to moderate-certainty evidence suggested that ZDV/3TC (0.13, [0.05, 0.31]) was probably the most effective regimen to reduce the odds of MTCT. ZDV (0.50, [0.33, 0.74]) was also effective in reducing the odds of MTCT, inferior to the most effective regimens but superior to the least effective treatment (Table 5).

Low- to very low-certainty evidence suggested RAL/3TC/ZDV (0.02, [0.00, 0.19]), LPV/r (0.04, [0.00, 0.97]), and DTG/TDF/3TC (FTC) (0.09, [0.02, 0.41]) are the most effective ART regimen in terms of reducing the odds of MTCT (Table 5). Additionally, according to SUCRA rankings, DTG/TDF/3TC (FTC) had the highest probability of being the best treatment (Supplementary Table 18).

Neonatal death

The effects of ART regimens on NND were reported in twelve studies that involved 8,551 participants. Figure 2 presents the network map. No evidence of loop-specific incoherence was found (Supplementary Table 21). No moderate- or high-certainty evidence was found for NND. Among the ART regimens with low- to very low-certainty evidence, DTG/TDF/FTC (0.33, [0.01, 10.13]) and ZDV/3TC (0.41, [0.05, 3.19]) proved to have the most significant protective effects in terms of reducing the odds of NND. RAL/3TC/ZDV and EFV/TDF/FTC also had protective effects. However, they were inferior to the most effective regimens. On the other hand, TDF/FTC/LPV/r (4.19, [0.32, 55.16]) and ZDV/LPV/r (3.67, [0.09, 155.36]) were shown to be the most harmful regimens due to the increased odds of NND (Table 6). ZDV/3TC was also the best probable treatment in terms of NND according to SUCRA rankings (Supplementary Table 22).

Congenital anomaly

The effects of ART regimens on Congenital anomalies were reported in nine studies with 3,559 participants. The network map of ART effects on congenital anomalies was not connected. Figure 2 presents the network

Table 5 Antiretroviral therapy network meta-analysis results on Mother-to-child transmission with corresponding GRADE (the Grading of Recommendations Assessment, Development and Evaluation). Values correspond to odds ratios (95% CI) from the network meta-analysis. Odds ratios< 1 means the treatment reduced the odds of mother-to-child transmission. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), raltegravir (RAL), efavirenz (EFV), dolutegravir (DTG), abacavir (ABC)

PLC										
0.21 (0.12,0.38)	ZDV/3TC/LPV/r									
0.79 (0.09,7.12)	3.66 (0.44,30.68)	ZDV/3TC/ABC								
0.27 (0.05,1.37)	1.24 (0.24,6.41)	0.34 (0.02,4.98)	ZDV/LPV/r							
0.13 (0.05,0.31)	0.60 (0.21,1.71)	0.16 (0.03,1.76)	0.48 (0.08,3.09)	ZDV/3TC						
0.50 (0.33,0.74)	**2.31 (1.52,3.50)**	0.63 (0.07,5.50)	1.85 (0.38,9.05)	3.84 (1.47,10.02)	ZDV					
0.23 (0.08,0.63)	1.05 (0.39,2.85)	0.29 (0.03,3.01)	0.85 (0.13,5.34)	1.75 (0.46,6.70)	0.46 (0.18,1.17)	TDF/FTC/LPV/r				
0.02 (0.00,0.19)	0.07 (0.01,0.84)	**0.02 (0.00,0.35)**	0.06 (0.00,1.11)	0.12 (0.01,1.73)	**0.03 (0.00,0.38)**	**0.07 (0.01,0.97)**	RAL/3TC/ZDV			
0.04 (0.00,0.97)	0.17 (0.01,4.29)	0.05 (0.00,1.61)	0.14 (0.00,5.10)	0.28 (0.01,8.41)	0.07 (0.00,1.91)	0.16 (0.01,4.73)	2.27 (0.04,127.52)	LPV/r		
0.10 (0.03,0.37)	0.48 (0.15,1.49)	**0.13 (0.02,0.86)**	0.38 (0.05,2.83)	0.79 (0.17,3.73)	**0.21 (0.06,0.70)**	0.45 (0.10,2.06)	6.37 (0.76,53.44)	2.81 (0.09,85.88)	EFV/TDF/FTC	
0.09 (0.02,0.41)	0.41 (0.10,1.69)	**0.11 (0.01,0.88)**	0.33 (0.04,2.87)	0.68 (0.12,3.96)	**0.18 (0.04,0.78)**	0.39 (0.07,2.20)	5.48 (0.56,53.82)	2.42 (0.07,81.68)	0.86 (0.37,1.98)	DTG/TDF/3TC(FTC)

Color description for certainty of evidence	High	Moderate	Low	Very low

Table 6 ART pattern network meta-analysis results on neonatal death with corresponding GRADE (the Grading of Recommendations Assessment, Development and Evaluation). Values correspond to odds ratio (95% CI) from the network meta-analysis. Odds ratios < 1 means the treatment reduced the odds of neonatal death. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r), tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), raltegravir (RAL), efavirenz (EFV), dolutegravir (DTG), abacavir (ABC)

PLC									
1.15 (0.12,10.72)	ZDV/3TC/LPV/r								
2.26 (0.06,89.65)	1.97 (0.11,36.67)	ZDV/3TC/ABC							
3.67 (0.09,155.36)	3.20 (0.10,101.01)	1.62 (0.02,149.67)	ZDV/LPV/r						
0.41 (0.05,3.19)	0.36 (0.02,7.45)	0.18 (0.00,12.32)	0.11 (0.00,8.04)	ZDV/3TC					
1.98 (0.30,12.98)	1.72 (0.52,5.71)	0.87 (0.04,20.58)	0.54 (0.02,13.70)	4.76 (0.30,76.50)	ZDV				
4.19 (0.32,55.16)	3.65 (0.57,23.49)	1.85 (0.06,59.30)	1.14 (0.03,45.09)	10.11 (0.38,270.58)	2.12 (0.37,12.11)	TDF/FTC/LPV/r			
0.56 (0.01,47.69)	0.49 (0.01,22.73)	0.25 (0.00,30.94)	0.15 (0.00,26.73)	1.36 (0.01,179.72)	0.28 (0.01,15.87)	0.13 (0.00,9.55)	RAL/3TC/ZDV		
0.58 (0.03,12.05)	0.50 (0.06,3.94)	0.26 (0.01,9.12)	0.16 (0.00,8.76)	1.39 (0.04,54.10)	0.29 (0.03,3.17)	0.14 (0.01,2.21)	1.03 (0.04,26.12)	EFV/TDF/FTC	
0.33 (0.01,10.13)	0.29 (0.02,3.79)	0.15 (0.00,7.19)	0.09 (0.00,6.70)	0.80 (0.01,42.84)	0.17 (0.01,2.88)	0.08 (0.00,1.85)	0.59 (0.02,21.24)	0.57 (0.12,2.70)	DTG/TDF/3TC(FTC)

Color description for certainty of evidence	High	Moderate	Low	Very low

map. Low- to very low-certainty evidence suggests that Moderate-certainty evidence suggested that compared to PLC, ZDV/LPV/r (1.48, [0.22, 10.01]) and ZDV (1.19, [0.63, 2.25]) increase the odds of congenital anomalies. While, Moderate-certainty evidence suggested that compared with ZDV, ZDV/LPV/r (1.25, [0.21, 7.55]) is associated with the increased odds of congenital anomalies (Table 7).

Discussion

The prevention of MTCT of HIV has been a cornerstone of global public health efforts in the fight against HIV. In this study, we conducted a comprehensive systematic review and network meta-analysis of randomized trials to provide an evidence-based perspective on the use of various ART regimens in pregnant women living with HIV. Our findings offer important insights for both clinical practice and policy-making, contributing to the ongoing discourse in the field of MTCT prevention. To our knowledge, this network meta-analysis of ART during pregnancy was the first analysis, including the WHO-recommended first-line treatment, using the GRADE approach. Consistent with previous studies, our results suggested all the ART regimens effectively reduced the odds of MTCT. However, high- to moderate-certainty evidence suggested that ZDV/3TC was the most effective regimen, followed by ZDV in reducing MTCT. We also found low-certainty evidence that DTG/TDF/3TC (FTC), RAL/3TC/ZDV, and LPV/r demonstrate notable effectiveness in reducing MTCT. Notably, our analysis revealed high- to moderate-certainty evidence suggesting that ZDV/3TC may decrease the odds of stillbirth, with pregnant women receiving ZDV/3TC exhibiting nearly half the odds of experiencing stillbirth compared to those in the PLC group.

Furthermore, our analysis found low- to very low-certainty evidence suggesting the potential superiority of other regimens, including RAL/3TC/ZDV, EFV/TDF/FTC, and DTG/TDF/3TC (FTC) concerning MTCT and NND. However, these regimens have shown contradictory effects concerning stillbirth and further research is warranted to better understand the potential advantages and harms of these regimens.

The findings regarding the impact of ART regimens on stillbirth outcomes in pregnant women living with HIV present a nuanced and somewhat unexpected picture. Moderate-certainty evidence from our analysis suggested that ZDV/3TC might be associated with decreased odds of stillbirth compared to PLC, a finding that underscores the potential importance of this specific ART regimen in mitigating adverse pregnancy outcomes. However, it is noteworthy to mention that the observed variations in stillbirth odds associated with different ART regimens may stem from multiple factors, as the etiologies of stillbirth are complicated. Previous studies have highlighted the timing of ART initiation as a crucial factor, suggesting that those on ART at preconception might face higher stillbirth odds compared to those initiating ART during pregnancy [44, 45]. The potential impact of comorbidities, such as pre-eclampsia and diabetes, on the risk of stillbirth is another critical consideration, as these conditions might influence stillbirth outcomes [44, 46]. Additionally, demographic factors, such as race and age, may contribute to variations in stillbirth rates, highlighting

Table 7 ART pattern network meta-analysis results on congenital anomaly with corresponding GRADE (the Grading of Recommendations Assessment, Development and Evaluation). Values correspond to odds ratio (95% CI) from the network meta-analysis. Odds ratios< 1 means the treatment reduced the odds of congenital anomaly. Abbreviations: Placebo (PLC), zidovudine (ZDV), lamivudine (3TC), lopinavir/ritonavir (LPV/r)

PLC			
0.95 (0.55,1.64)	ZDV/3TC		
1.19 (0.63,2.25)	1.25 (0.54,2.90)	ZDV	
1.48 (0.22,10.01)	1.56 (0.21,11.38)	1.25 (0.21,7.55)	ZDV/LPV/r

Color description for certainty of evidence	High	Moderate	Low	Very low

the consideration of these diverse factors in the analysis in future research as the body of evidence evolves [44].

Overall, our study findings revealed a heightened probability of PTB across all ART regimens. This underscores the necessity for close monitoring and management of pregnant women living with HIV to reduce the risk of PTB. Notably, in our study, DTG/TDF/FTC emerged as the most promising regimen in terms of PTB, representing a potential avenue for further investigation. Another meta-analysis found no overall increased risk of PTB with ART during pregnancy. Nevertheless, it did detect a modest elevation in prematurity risk when combination regimens were employed before or early in pregnancy. It is important to acknowledge that the majority of the studies included in this meta-analysis were cohort studies. Cohort studies are susceptible to more bias because of the absence of randomization. This lack of randomization could result in dissimilar populations, introducing potential confounding variables, such as maternal race, obstetric history, or stage of HIV [47]. Acknowledging these inherent limitations in study design is essential for a comprehensive understanding of the potential biases and generalizability of findings. Overall, the existing body of research presents conflicting results regarding maternal ART exposure and PTB [2], although many studies have indicated a higher rate of PTB in association with maternal ART exposure [2, 48].

The discussion surrounding PTB pathogenesis is inherently complicated [49]. PTB itself is a multifaceted syndrome influenced by a multitude of contributing factors, with only approximately one-fifth of cases being considered independent pathological entities based on current scientific knowledge and available data. In essence, PTB is not an isolated condition, but rather endpoint shaped by various determinants [50, 51]. Navigating this complexity is essential when considering the association between ART interventions and PTB outcomes.

Notably, we found no evidence of increased odds of PTB associated with PI when compared to other ART regimens. These results align with previous studies that failed to identify an association between different ART regimens and elevated risk of PTB [52, 53]. During the past decades, numerous studies on the association between the use of PI during pregnancy and adverse prenatal outcomes have yielded conflicting and inconsistent results. It is essential to consider that when pregnant women have symptomatic HIV, high viral loads, or low CD4 + cell counts, they are more likely to receive ART treatment, including PI [54]. Additionally, advanced HIV infection has also been associated with PTB [55, 56]. Failure to consider maternal disease-related confounders can potentially introduce bias into the estimates. Previous studies have been unable to fully account for factors related to maternal HIV stage, with most failing to consider HIV viral load, which could be a significant factor in the link between PI use and PTB [57].

Concerning LBW, our analysis revealed several noteworthy observations that except for ZDV and ZDV/LPV/r, all other available regimens suggest potential harm. Meanwhile, infants born of women living with HIV might be at higher risk of LBW because of insufficient maternal weight gain compared to those born to HIV-seronegative women [58]. According to our findings, ZDV monotherapy demonstrates a potential advantage over other combination therapies. Nonetheless, our results do not provide evidence to suggest that combination regimens inherently pose greater odds of low LBW when compared to ZDV monotherapy. It is important to note that numerous other studies have also reported no discernible association between specific ART regimens and an increased risk of LBW [48]. Despite the effects of ZDV monotherapy and combination therapy, in long-term studies, ZDV showed no benefit for maternal health and future pregnancies, leading to its exclusion from WHO guidelines [14].

Regarding congenital anomalies, the sparse evidence available made it impossible to compare the first-line regimen with PLC. As for other outcomes, we observed no consistent difference between monotherapy and combination therapy regimens. Our findings, albeit based on evidence of low- to very low-certainty, suggest that ZDV/LPV/r and ZDV are associated with increased odds of congenital anomalies compared to PLC. Furthermore, ZDV/LPV/r exhibited increased odds of congenital anomalies compared to ZDV alone. These findings emphasize the importance of a thorough risk assessment and ongoing monitoring when considering regimens that may carry a higher risk of congenital anomalies. Despite the possible increased risk of some adverse prenatal outcomes in pregnant women living with HIV on ART, the benefits of ART for both maternal health and the prevention of MTCT are well-established, making it crucial not to withhold ART due to concerns over adverse prenatal outcomes [10].

This systematic review and network meta-analysis has several strengths compared to existing reviews. First, we explored the comparative effectiveness of all currently utilized regimens during pregnancy, including studies investigating the first-line ART regimen recommended by WHO [10]. Second, we clearly defined the outcomes of interest and eligibility criteria in a pre-published protocol to prevent any classification bias. Third, we used the GRADE approach to assess the quality of evidence, which investigates the quality across each outcome and enables a systematic approach to making clinical decisions.

We, however, acknowledge the limitations of our study. First, the low number of randomized clinical trials relative to the number of comparisons is a limitation. The scarcity of evidence resulted in most of our results relying on direct comparisons, leading to low confidence in estimates for the majority of our analyses. Second, the limited evidence prevented us from stratifying the data based on various factors, such as the timing of ART initiation (before or after conception), age, race, and other social determinants of health [12]. These determinants, including economic stability, education, and access to healthcare, have been demonstrated to influence treatment adherence, durable viral suppression, and adverse perinatal outcomes [59, 60]. Third, we were unable to perform meta-regression for subgroups or sensitivity analyses due to a limited number of networks. Fourth, weincluded certain ART regimens, such as single-drug and two-drug regimens that are no longer commonly used. Fifth, networks of treatments for all outcomes were sparse and supported mostly by low- to very low-certainty evidence. Therefore, conducting further trials to examine the safety and effectiveness of different ART would be valuable in fully exploring the association between the use of these specific ART regimens and the risk of adverse prenatal outcomes.

Conclusions

In conclusion, the results of this study provide a comprehensive overview of the comparative effectiveness and safety of various ART regimens during pregnancy. Notably, the certainty of evidence ranged from high to very low, reflecting the complexities and heterogeneity inherent in the available data. While certain regimens, such as ZDV/3TC, exhibited favorable outcomes in reducing MTCT and stillbirth, they must be weighed against potential risks, including LBW and PTB. Clinicians must engage in shared decision-making with pregnant women living with HIV, considering their unique circumstances and priorities. However, as new evidence emerges and treatment guidelines evolve, ongoing research and clinical vigilance will remain paramount in the pursuit of eliminating MTCT of HIV and ensuring the health and well-being of both mothers and infants.

Abbreviations

ART	Antiretroviral therapy
MTCT	Mother-to-child transmission
WHO	World Health Organization
LBW	Low birth weight
PTB	Preterm birth
NND	Neonatal death
ZDV	Zidovudine
3TC	Lamivudine
FTC	Emtricitabine
LPV/r	Lopinavir/ritonavir
DTG	Dolutegravir
TDF	Tenofovir Disoproxil Fumarate
EFV	Efavirenz
RAL	Raltegravir
ABC	Abacavir
PLC	Placebo
OR	Odds ratio
CI	Confidence intervals
SUCRA	Surface under the cumulative ranking curve
PI	Protease inhibitors

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

FM designed the protocol, extracted and analyzed data, and wrote the main manuscript text.MK, BF, and AM reviewed and edited this work. Shahryar Moradi, Soheil Mehmandoost, and SA performed article screening, extracted data, and assessed the risk of bias.Shahrzad Motaghi designed the search strategy and performed the systematic search.BS and HS contributed equally to the methodology design, reviewing, and editing, and should be regarded as co-senior authors.All authors reviewed the manuscript.

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Competing interests

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