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REVIEW

Maternal, Fetal, and Neonatal Outcomes of Additional Dihydroartemisinin-Piperaquine to Trimethoprim-Sulfamethoxazole in Intermittent Preventive Treatment for Malaria in HIV-Positive Pregnancies: A Systematic Review and Meta-Analysis

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Purpose: This systematic review evaluates the addition of Dihydroartemisinin-Piperaquine (DHA-PPQ) to Trimethoprim-Sulfamethoxazole (TMP-SMX) for Intermittent Preventive Treatment (IPT) in HIV-positive pregnancies, focusing on its effects on malaria infection, maternal adverse events, fetal adverse events, and birth outcomes.

Patients and Methods: Following PRISMA guidelines, we searched PubMed, Cochrane, Google Scholar, and Scopus until December 16, 2024. Out of 390 studies, three were included, assessed for bias using ROB 2.0, and analyzed with random-effects meta-analysis in RevMan 5.4.1.

Results: We analyzed three studies involving 1353 participants who received 800/160 mg of TMP-SMX, with or without 40/320 mg of DHA-PPQ administered three times. The addition of DHA-PPQ showed a non-significant trend toward lower malaria infection outcomes, including maternal parasitaemia (OR: 0.83; 95% CI [0.52, 1.33], p = 0.44) and rates of placental malaria (OR: 0.66; 95% CI [0.40, 1.08], p = 0.10). DHA-PPQ significantly lowered maternal adverse events (OR: 0.78; 95% CI [0.67, 0.91], p = 0.003), which included low hemoglobin (OR: 0.83; 95% CI [0.69, 1.00], p = 0.05), gastrointestinal events (OR: 0.66; 95% CI [0.46, 0.95], p = 0.03), neurological events (OR: 0.61; 95% CI [0.22, 1.69], p = 0.35), and skin reactions (OR: 0.40; 95% CI [0.08, 2.11], p = 0.28). No significant differences were observed in fetal adverse events (OR: 1.05; 95% CI [0.68, 1.65], p = 0.69), which comprised spontaneous abortion (OR: 1.81; 95% CI [0.60, 5.51], p = 0.30), stillbirth (OR: 1.02; 95% CI [0.55, 1.89], p = 0.95), and congenital anomalies (OR: 0.89; 95% CI [0.32, 2.47], p = 0.83). Finally, no significant effect was observed on birth outcomes (OR: 1.13; 95% CI [0.88, 1.45], p = 0.81), including low birth weight (OR: 1.15; 95% CI [0.85, 1.56], p = 0.36) and premature birth (OR: 1.08; 95% CI [0.70, 1.68], p = 0.73).

Conclusion: Additional DHA-PPQ shows promising efficacy in reducing malaria infection, a statistically significant reduction in maternal adverse events, with no significant differences in fetal and birth outcomes.

Keywords: malaria, HIV-positive pregnancies, TMP-SMX, DHA-PPQ

Introduction

Malaria remains a significant global health threat, particularly in endemic regions like sub-Saharan Africa, resulting in approximately 263 million cases and 597,000 deaths worldwide in 2023, according to the World Malaria Report.[1] In malaria-endemic regions, an estimated 25% of pregnant women are infected with malaria. Malaria during pregnancy increases the risk of severe illness in affected women due to a weakened immune system defenses.[2] This makes them three times more likely to

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develop severe malaria, with a mortality rate approaching 50%, posing serious threats to the mother.[2–5] Chemoprophylaxis has demonstrated significant effectiveness in reducing mortality and morbidity, particularly among high-risk populations.[6] The World Health Organization (WHO) emphasizes its importance by recommending intermittent preventive treatment of malaria in pregnancy (IPTp) as a key preventive measure.

IPTp involves administering antimalarial drugs at scheduled intervals during pregnancy, regardless of infection status. For malaria prevention, WHO advises at least three doses of sulfadoxine-pyrimethamine (SP) during antenatal care (ANC) visits in the second trimester (after 13 weeks of gestation) and then every four weeks until delivery, as part of routine ANC follow-up, particularly for first and second pregnancies. However, HIV-positive pregnant women are prescribed daily cotrimoxazole (trimethoprim-sulfamethoxazole or TMP-SMX) prophylaxis, as SP is contraindicated due to harmful drug interactions, leaving TMP-SMX as their sole preventive option.[6] Despite its preventive benefits, TMP-SMX is not completely safe for pregnant women. Research indicates that exposure to TMP-SMX during early pregnancy is linked to a higher risk of maternal adverse events and spontaneous abortion (SA).[7] This underscores the necessity for safer alternative regimens for malaria prevention in HIV-positive pregnant women.

Dihydroartemisinin–piperaquine (DHA–PPQ) has emerged as a potential candidate for malaria prevention. DHA–PPQ combines the rapid parasite-clearing activity of dihydroartemisinin with the long elimination half-life of piperaquine, which provides an extended post-treatment prophylactic effect against new infections.[8] Previous studies have demonstrated that repeated courses of DHA–PPQ are generally well tolerated and effective when used for intermittent preventive strategies in pregnancy and other high-risk populations.[9] These pharmacological characteristics make DHA–PPQ particularly attractive as a potential partner regimen for malaria prevention in settings where SP cannot be used.

Several clinical trials have evaluated the safety, tolerability, and efficacy of repeated doses of DHA-PPQ in the prevention and treatment of malaria among high-risk populations.[10] Thus, there is no specific meta-analysis study investigating the safety and effectiveness of DHA-PPQ in addition to TMP-SMX prophylaxis in HIV-positive pregnant women. This study aims to evaluate the efficacy of DHA-PPQ in combination with daily TMP-SMX for HIV-positive pregnant women, exploring its potential as a novel IPTp regimen to enhance maternal and neonatal outcomes.

Materials and Methods

This systematic review was conducted in accordance with the guideline recommended by the Cochrane Group and carried out following the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) statement.[11] A detailed protocol has been previously registered in PROSPERO (CRD420250653933). No amendments to the protocol were made.

Search Strategy

Four independent investigators performed literature searches through several databases, PubMed, Google Scholar, Cochrane and Scopus. The literature searches were conducted for studies published in all databases up to December 16, 2024 using several keywords and Medical Subject Headings (MeSH) terms to create the search strategy related to "Dihydroartemisinin-Piperaquine", "Trimethoprim-Sulfamethoxazole", "HIV", "Pregnancy" and their synonyms. The collected literature was screened for duplication and later divided into two groups for screening. Two and three reviewers from different groups independently assessed each group of collected literature and differences and disagreement were resolved through consensus among all authors.

Study Eligibility Criteria

In this study, the eligibility criteria used were based on the PICOS (Population, Intervention, Comparison, Outcome, Study) framework. HIV-positive pregnant women were the study population (P). The Intervention (I) was the DHA-PPQ addition to the basic IPTp using TMP-SMX. HIV-positive pregnant women given DHA-PPQ combined with TMP-SMX were compared to HIV-positive pregnant women given only TMP-SMX (C). The main outcome (O) targeted is to investigate the maternal infection, the maternal adverse event, fetal adverse event and lastly the birth outcome. Lastly, we exclusively included randomized controlled trial (RCT) studies with original quantitative data. Non-English studies or studies with irretrievable full text were excluded from this review which may result in the increase of potential source of bias.

Definitions and Outcomes

The main outcomes of this study were malaria co-infection, maternal adverse events, and birth adverse events. Malaria infection refers to the presence of malaria parasites in the mother, which can increase the risk of parasite transmission to the placenta and fetus. This parameter is measured by high parasite levels in maternal blood or known as maternal parasitemia and in placental cord or placental malaria. Maternal adverse event parameters are defined as undesirable effects resulting from additional DHA-PPQ treatment, including low hemoglobin, gastrointestinal symptoms, neurological symptoms, and skin reactions. Fetal adverse event refers to any of the complications that happen in the fetus, including spontaneous abortion, stillbirth, and congenital anomalies. Lastly, birth outcome refers to harmful outcomes that affect the neonates, such as low birth weight, and premature birth.

Data Extraction, Quality Assessment, and Data Analysis

Data screening, extraction and risk of bias assessment were conducted independently by four reviewers (AJM, CAB, EIJS, and ERS) using a pre-specified form, and discrepancies found between authors were resolved by consensus of all authors and mainly involved the fifth author (VY). The extracted data included (1) first author and publication year, (2) study design, (3) region, (4) sample size, (5) maternal age, (6) pregnancy number, (7) gestational age, and (8) control and intervention dose. The study's methodological quality and certainty of evidence were assessed using the Cochrane Risk of Bias (ROB) 2.0 tool and subsequently judged to be yielding low, moderate, or high risk of bias. All the data were dichotomous and were analyzed by pooling odds ratios (ORs) using the Mantel–Haenszel method. A meta-analysis was conducted using Review Manager v5.4.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). Heterogeneity between studies was evaluated using the chi-square test, Cochran Q-test, and I^2 statistic. A random-effects model using DerSimonian-Laird (DSL) estimator was applied due to anticipated clinical heterogeneity and subgroup analyses will be conducted if sufficient data are available. The I^2 values were categorized as follows: negligible (0–25%), low (25–50%), moderate, substantial (75%). Additionally, when the number of studies was sufficient ($n \geq 10$), potential publication bias was assessed visually by inspecting funnel plots and quantitatively using Egger's test. A p-value of <0.05 was considered statistically significant.[11]

Results

Study Selection and Characteristics

We retrieved 390 relevant articles from the included databases and removed 104 duplicates. The remaining articles were screened by title and abstract, resulting in 3 records fully assessed for eligibility. All three studies were considered suitable and were analyzed in this review (Figure 1).

The origin of our analyzed studies varies with each study being conducted in two regions, including Kenya and Malawi, Gabon and Mozambique, as well as Tororo and Uganda. Bias assessment revealed low risk of bias for every domain assessed (Figures 2 and 3), with detailed characteristics summarized in Table 1. Studies involved a total of 1.353 participants with an average maternal and gestational age of 28.80 years and 20.68 weeks, respectively. Most participants were multiparous (91.2%) while the rest were primiparous (8.2%). Control and intervention groups received specific doses of TMP-SMX (800 mg TMP and 160 mg SMX) daily, with an addition of DHA-PPQ (40 mg DHA and 320 mg PPQ) administered three times per month for the intervention group.

Outcomes

We found that specific doses of additional DHA-PPQ to TMP-SMX are associated with potential effects in the reduction of malaria infection rates and maternal adverse events. Compared to the control group, the intervention results for adverse birth events remain uncertain, showing insignificant results in each subgroup analysis conducted. In addition, restriction to the African region was noted, which may contribute to regional variations in malaria transmission intensity, drug resistance patterns, and baseline maternal health conditions.

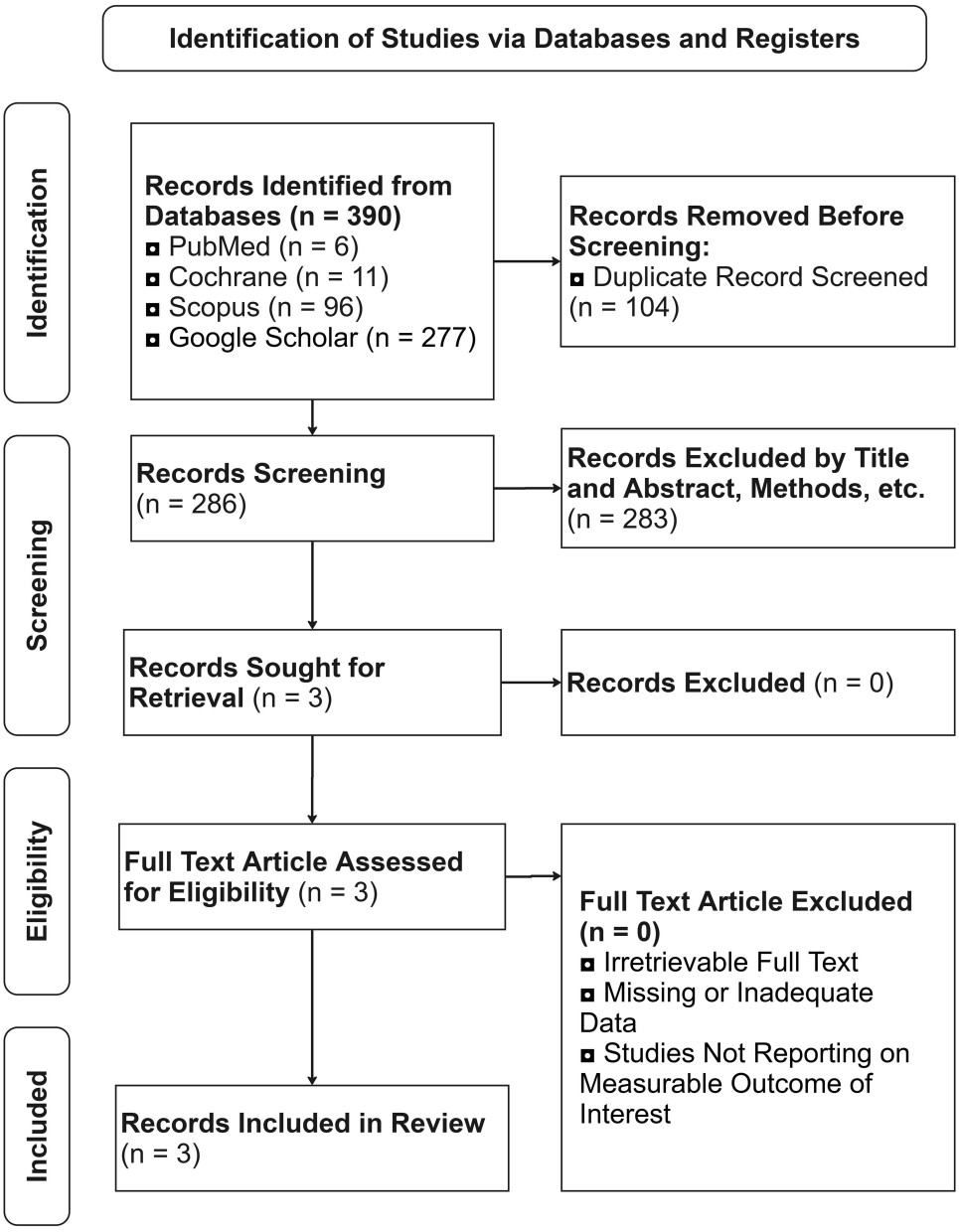

Figure 1 Diagram Flow of Literature Search and Results.

Malaria Infection

Malaria infection was assessed, including maternal parasitemia and placental malaria. All studies were included in this part. According to Figure 3, maternal parasitemia has an OR = 0.83 [95% CI: 0.52–1.33, $p = 0.44$]. The TMP-SMX + DHA-PPQ group shows a lower likelihood of maternal parasitemia compared to the TMP-SMX alone. However, this result was not statistically significant and no significant heterogeneity was observed (I^2= 18%, $p_{heterogeneity}$ = 0.29). Whereas the effect of the intervention on placental malaria is shown in Figure 4. A meta-analysis revealed that in comparison to TMP-SMX alone, those with DHA-PPQ revealed a non-significant trend toward lower placental malaria event OR = 0.66 [95% CI: 0.40–1.08, $p = 0.10$]. As an addition, this study discovered a low level of heterogeneity (I^2= 31%, $p_{heterogeneity}$ = 0.24).

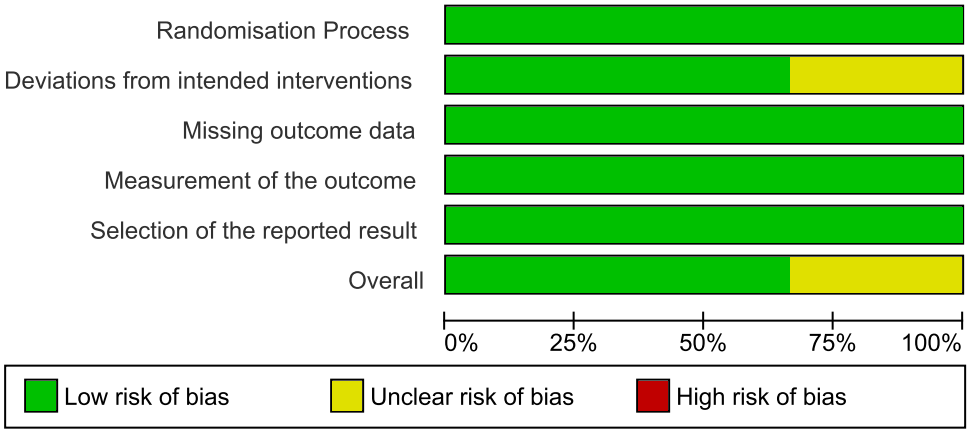

Figure 2 Risk of Bias per Study and Domain. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias.

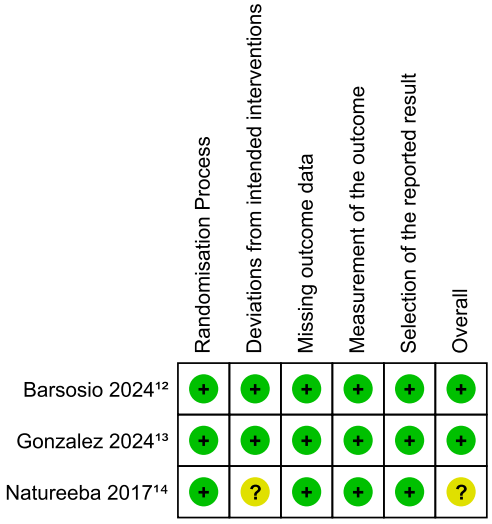

Figure 3 Summary of Risk of Bias. Green circles with a plus sign indicate low risk of bias, while yellow circles with a question mark indicate unclear risk of bias.

Maternal Adverse Events

A subgroup analysis was conducted for this parameter, encompassing low hemoglobin, gastrointestinal, neurological, and skin reactions as illustrated in Figure 5. The overall effect demonstrates statistically significant results, with an odds ratio (OR) of 0.79 [95% CI: 0.67–0.92, $p = 0.003$]. Furthermore, there was no evidence of significant heterogeneity (I^2= 1%, $p_{heterogeneity} = 0.43$). Low hemoglobin refers to a hemoglobin level below 10 g/dl. Figure 6 highlights a reduction in low hemoglobin [OR = 0.83, 95% CI: 0.69–1.00, $p = 0.05$], with the result at the threshold of statistical significance. Additionally, this study identified a low level of heterogeneity (I^2= 0%, $p_{heterogeneity} = 0.75$). Importantly, all three included studies applied the same hemoglobin cut-off (<10 g/dL), ensuring methodological consistency and strengthening the comparability of the pooled analysis. Gastrointestinal symptoms associated with this parameter included nausea, vomiting, and abdominal pain. Figure 6 show statistically significant data compared to TMP-SMX alone, with an OR of 0.66 [95% CI: 0.46–0.95, $p = 0.03$]. Moreover, the studies indicate low heterogeneity (I^2= 0%, $p_{heterogeneity} = 0.39$). Neurological adverse events in maternal subjects included headaches. Through the conducted meta-analysis on Figure 6, it was determined that, although DHA-PPQ aids in reducing the number of neurological symptoms, the result was not statistically significant, yielding an OR of 0.61 [95% CI: 0.22, 1.69, $p = 0.35$]. This meta-analysis also revealed moderate heterogeneity (I^2= 66%, $p_{heterogeneity} = 0.05$), likely driven by the distinct outcome shift in the study by Natureeba et al. This outlier effect may be related to differences in neurological symptom ascertainment methods, population

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Table 1 Characteristics of Included Studies

No	Author, Year	Study Design	Region	n		Maternal Age (Year)		Pregnancy Number (Gravidity)				Gestational Age (Weeks)		BMI (kg/m^2)		CD4+ Cell Count		Intervention Dose		Intervention Schedule	
								Primipara		Multipara											
				Study	Control	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control
1.	Barsosio, 2024[12]	Randomised, two-arm, placebo-controlled trial	Kenya and Malawi	448	456	29.2 ± 5.6	29.3 ± 5.7	32	37	416	419	22 (3.7)	22 (3.8)	24.4 (3.9)	24.2 (3.6)	–	–	(160 mg SMX, 800 mg TMP) + (3x 40 mg DHA, 320 mg PPQ)	800 mg TMP, 160 mg SMX	TMP-SMX daily + DHA-PPQ 3× monthly	Daily TMP-SMX
2.	Gonzalez, 2024[13]	Randomised, double-blinded, placebo-controlled clinical trial	Gabon and Mozambique	209	222	27.4 ± 3.5	27.4 ± 3.6	31	38	301	296	18.4 (4.7)	18.5 (4.9)	–	–	≤350: 49 (15%) >350: 188 (57%) No data: 95 (28%)[a]	≤350: 67 (20%) >350: 181 (54%) No data: 86 (26%)[a]	(160 mg SMX, 800 mg TMP) + (3x 40 mg DHA, 320 mg PPQ)	800 mg TMP, 160 mg SMX	TMP-SMX daily + DHA-PPQ 3× monthly	Daily TMP-SMX
3.	Natureeba, 2017[14]	Randomised, double-blinded, placebo-controlled trial	Tororo, Uganda	100	100	29.8 ± 6.8	30.3 ± 5.8	13	5	87	95	19.9 (4.5)	19.2 (4.1)	–	–	516 (368–660)[b]	500 (392–622)[b]	(160 mg SMX, 800 mg TMP) + (3x 40 mg DHA, 320 mg PPQ)	800 mg TMP, 160 mg SMX	TMP-SMX daily + DHA-PPQ 3× monthly	Daily TMP-SMX

Notes: [a]CD4+ T-cell count, cells per μL, n(%); [b]CD4+ T-cell count, cells/mm^3, median (IQR).
Abbreviations: TMP, trimethoprim; SMX, sulfamethoxazole; DHA, dihydroartemisinin; PPQ, piperaquine.

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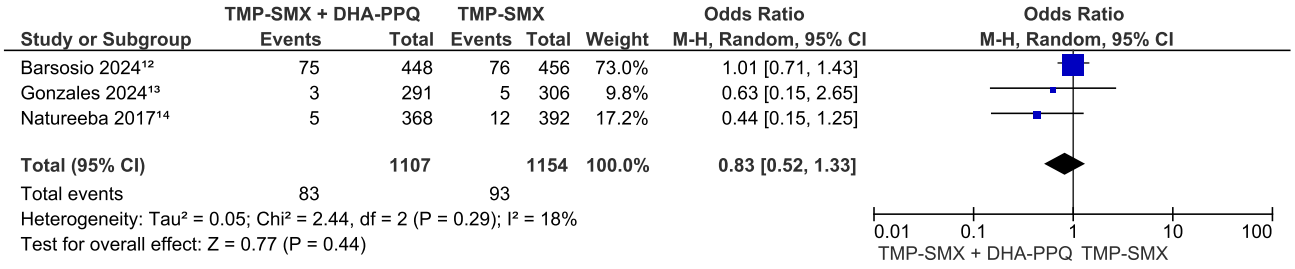

Figure 4 The Impact of Adding DHA-PPQ to TMP-SMX on Maternal Parasitemia in HIV Positive Pregnancies. Squares represent individual study effect estimates, with square size proportional to study weight. Horizontal lines indicate 95% confidence intervals, and diamonds represent pooled effect estimates.
Abbreviations: DHA-PPQ, dihydroartemisinin-piperaquine; TMP-SMX, trimethoprim-sulfamethoxazole; OR, odds ratio; CI, confidence interval; M-H, Mantel–Haenszel.

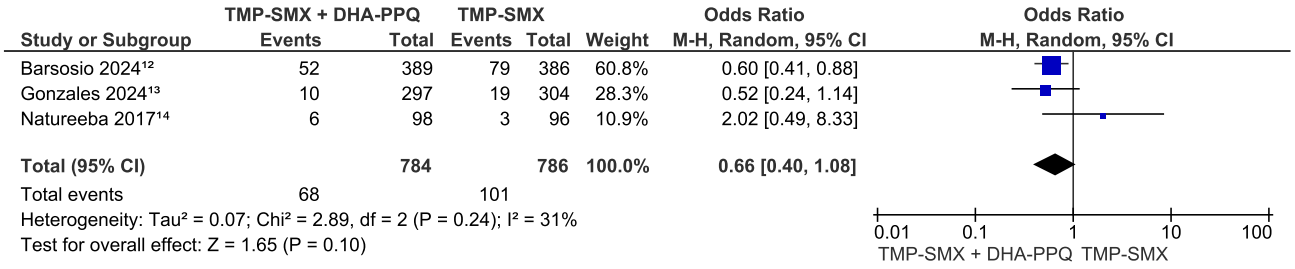

Figure 5 The Impact of Adding DHA-PPQ to TMP-SMX on Placental Malaria in HIV Positive Pregnancies. Squares represent individual study effect estimates, with square size proportional to study weight. Horizontal lines indicate 95% confidence intervals, and diamonds represent pooled effect estimates.
Abbreviations: DHA-PPQ, dihydroartemisinin-piperaquine; TMP-SMX, trimethoprim-sulfamethoxazole; OR, odds ratio; CI, confidence interval; M-H, Mantel–Haenszel.

characteristics, or local epidemiological factors, which could have influenced reporting and event detection across studies. Lastly, assessments were carried out for skin reactions, defined as itching and redness that occur on the skin following one hour after administration of the medication. Figure 6 reveals the odds ratio (OR) of 0.40 [95% CI: 0.08–2.11, p = 0.28] suggests that incorporating DHA-PPQ was associated with a non-significant reduction in skin reactions, with low heterogeneity (I^2= 0%, $p_{heterogeneity}$ = 0.79).

Fetal Adverse Events

In this parameter (Figure 7), fetal adverse events, including spontaneous abortion, stillbirth, and congenital anomalies, were analyzed. Statistically insignificant results were seen with OR = 1.05 [95% CI: 0.68–1.65, p = 0.69] without low evidence of heterogeneity (I^2=0%, $p_{heterogeneity}$ =0.69). Spontaneous abortion, defined as spontaneous pregnancy loss under the 20th week of gestation, stands as a significant adverse event in pregnant HIV-positive women. Our analysis showed statistically insignificant results with a higher number of events in the control group [OR: 1.81; 95% CI [0.60, 5.51], p = 0.30]. Results were obtained with evidence of low heterogeneity (I^2= 0%, $p_{heterogeneity}$ = 0.83) as seen in Figure 7. Stillbirth or Intrauterine Fetal Death (IUFD) is an adverse event defined as the death of a fetus after 20 weeks in the uterus. The results in Figure 7 show that through 3 studies combining DHA-PPQ with TMP-SMX gives no significant difference in reducing the numbers of stillbirths (OR: 1.02; 95% CI [0.55, 1.89], p = 0.95). In this aspect, the number of heterogeneity is low (I^2= 0%, $p_{heterogeneity}$ = 0.58). Congenital anomalies counts as several conditions of structural anomalies present at birth. These congenital anomalies result in physical, intellectual, and developmental disabilities. From three studies found, Figure 7 reveals that DHA-PPQ addition to TMP-SMX shows a non-significant possibility in reducing the number of congenital anomalies (OR: 0.89; 95% CI [0.32, 2.47], p = 0.83). Through the analysis, low heterogeneity was found (I^2= 32%, $p_{heterogeneity}$ = 0.23).

Birth Outcomes

In this parameter (Figure 8), birth outcomes, including low birth weight and premature birth, were analyzed. Statistically insignificant results were observed with an odds ratio of (OR: 1.13; 95% CI [0.88, 1.45], p = 0.81), accompanied by low evidence of heterogeneity (I^2= 0%, $p_{heterogeneity}$ = 0.68). All three studies included an analysis of low birth weight defined as

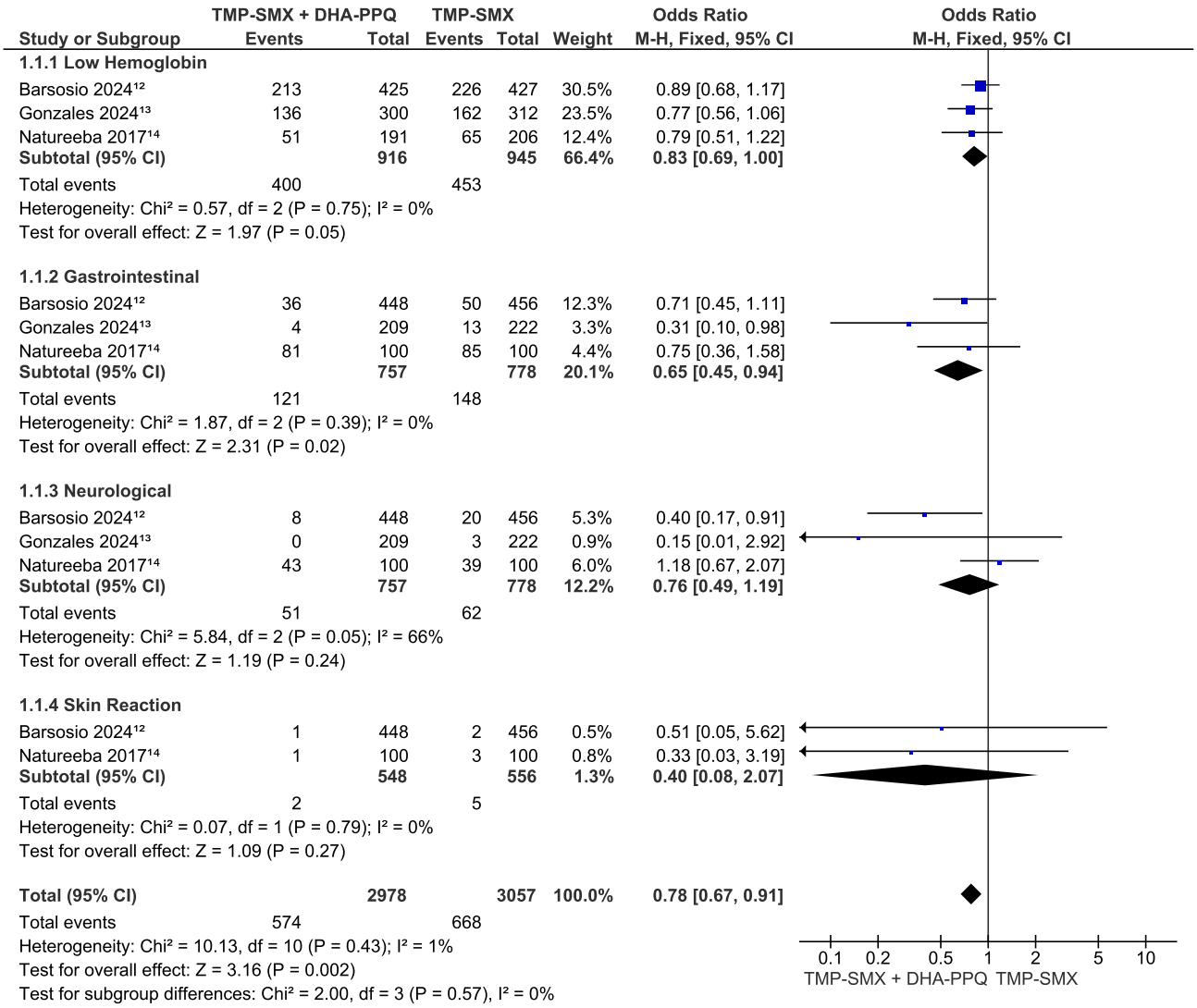

Figure 6 The Impact of Additional DHA-PPQ to TMP-SMX on Maternal Adverse Events. Subgroup analyses included low hemoglobin, gastrointestinal symptoms, neurological symptoms, and skin reactions. Squares represent individual study effect estimates, with square size proportional to study weight. Horizontal lines indicate 95% confidence intervals, and diamonds represent pooled effect estimates.
Abbreviations: DHA-PPQ, dihydroartemisinin-piperaquine; TMP-SMX, trimethoprim-sulfamethoxazole; OR, odds ratio; CI, confidence interval; M-H, Mantel–Haenszel.

less than 2500 grams. Figure 8 reveals that the occurrence of low birth weight is more likely to be higher in the TMP-SMX population alone compared to the TMP-SMX + DHA-PPQ group, with an odds ratio of (OR: 1.15; 95% CI [0.85, 1.56], $p = 0.36$), which is not statistically significant. No notable heterogeneity was identified ($I^2 = 0\%$, $p_{heterogeneity} = 0.93$). Additionally, an analysis was performed regarding premature birth parameters. Premature birth is defined as a birth occurring before 37 weeks of gestation. Figure 8 indicates that there are no significant effects associated with the addition of DHA-PPQ on premature birth events (OR: 1.08; 95% CI [0.70, 1.68], $p = 0.73$). Furthermore, low heterogeneity was identified ($I^2 = 42\%$, $p_{heterogeneity} = 0.18$).

Discussion

Principal Findings

Preventive strategies remain essential to reduce malaria-related complications in pregnancy, particularly among pregnant women living with HIV. Our meta-analysis of three included journals concluded that the administration of DHA-PPQ and TMP-SMX insignificantly lowers the risk of maternal parasitaemia (OR = 0.83, $p = 0.44$) and placental parasitaemia

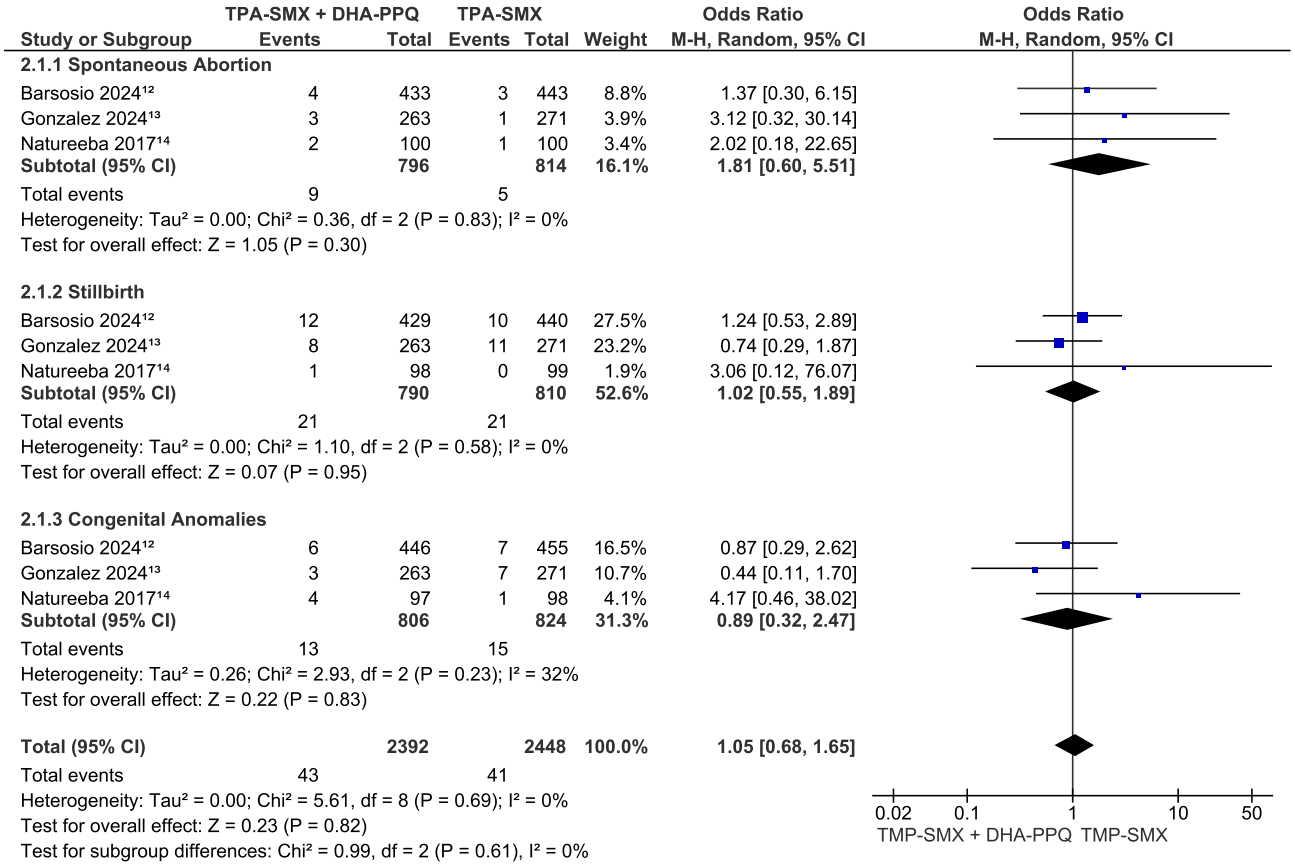

Figure 7 The Impact of Adding DHA-PPQ to TMP-SMX on Fetal Adverse Events in HIV Positive Pregnancies. Subgroup analyses included spontaneous abortion, stillbirth, and congenital anomalies. Squares represent individual study effect estimates, with square size proportional to study weight. Horizontal lines indicate 95% confidence intervals, and diamonds represent pooled effect estimates.

Abbreviations: DHA-PPQ, dihydroartemisinin-piperaquine; TMP-SMX, trimethoprim-sulfamethoxazole; OR, odds ratio; CI, confidence interval; M-H, Mantel–Haenszel.

(OR = 0.66, p = 0.10). Through the results from all included journals, the outcome for malaria infection estimated favorable significant results towards the lower risk of infection. These results went against the favorable estimated outcome caused by the lack of included studies with accumulated small sample sizes. Additionally, TMP-SMX alone was able to reduce the malaria risk by 50–70% and DHA-PPQ only adds on protection which only showed minimal differences.[3] Our meta-analysis finding of malaria infection is consistent with previous studies, which reported that the addition of DHA-PPQ or other drug regimens to daily TMP-SMX insignificantly lowers the risk of maternal parasitaemia and placental malaria.[10]

Additionally, maternal adverse events associated with the addition of DHA-PPQ have not been extensively assessed in HIV-positive pregnancies. However, in the general pregnant population, the prevalence of low hemoglobin has shown a steady decline over a five-year period, from 10.5% to 7.2%.[15] This trend is consistent with our findings, which demonstrate a reduction in maternal adverse events, particularly low hemoglobin (OR = 0.83, p = 0.05).[15] Notably, the reduction in maternal adverse events represents the most consistent finding in our analysis. When interpreted in practical terms, this reduction suggests that the addition of DHA-PPQ may modestly decrease the occurrence of treatment-related complications among pregnant women receiving malaria prophylaxis. Although the relative reduction appears moderate, even small improvements in maternal safety may be clinically meaningful in malaria-endemic settings where pregnant women, particularly those living with HIV, face a high baseline risk of anemia and other treatment-related adverse effects.

In addition, our study assessed several adverse-event parameters that have not been widely examined in previous analyses. These included gastrointestinal symptoms such as nausea, vomiting, and abdominal pain, which demonstrated a statistically significant reduction (OR = 0.66, p = 0.03). Meanwhile, neurological symptoms such as headache (OR = 0.61,

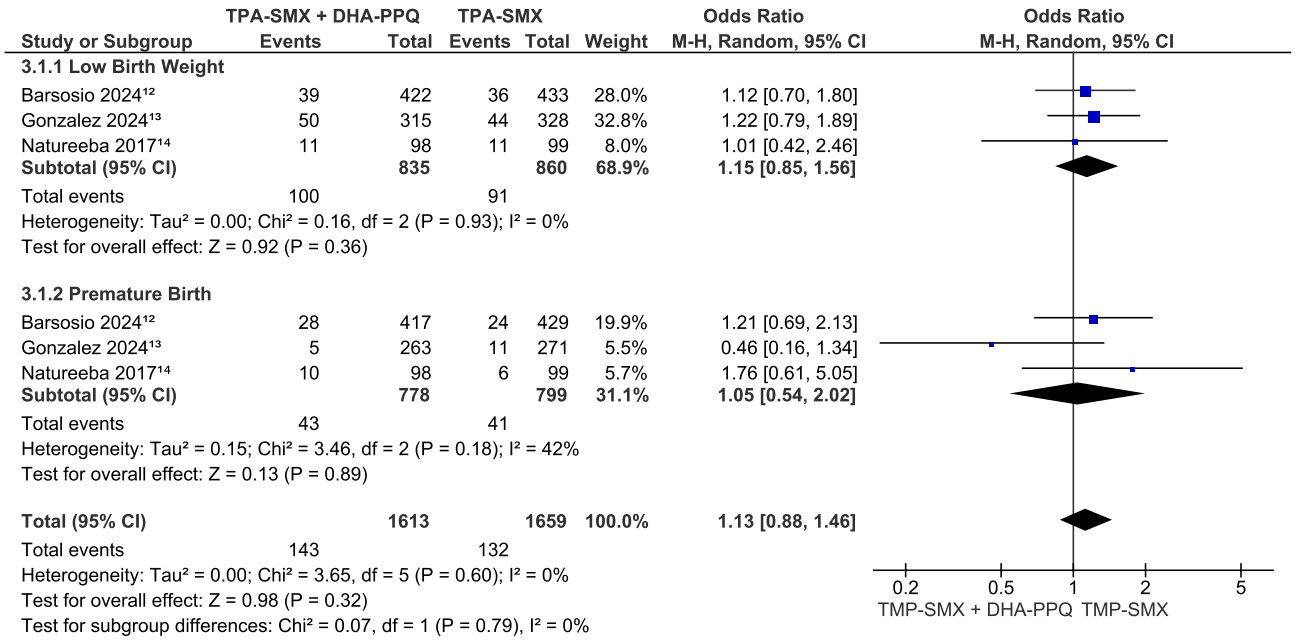

Figure 8 The Impact of Adding DHA-PPQ to TMP-SMX on Birth Outcomes Events in HIV Positive Pregnancies. Subgroup analyses included low birth weight and preterm birth. Squares represent individual study effect estimates, with square size proportional to study weight. Horizontal lines indicate 95% confidence intervals, and diamonds represent pooled effect estimates.

Abbreviations: DHA-PPQ, dihydroartemisinin-piperaquine; TMP-SMX, trimethoprim-sulfamethoxazole; OR, odds ratio; CI, confidence interval; M-H, Mantel–Haenszel.

p = 0.35) and dermatological reactions including itching and redness (OR = 0.40, p = 0.28) also showed reductions, although these were not statistically significant.

Lastly, adverse events (AEs) of malaria prevention in HIV-positive pregnant women pose significant risks to fetal health and birth outcomes. The AEs for fetal health included congenital anomalies, spontaneous abortion, and stillbirth. Previous systematic review and meta-analysis of daily cotrimoxazole prophylaxis plus another drug regimen shows no difference in stillbirth and low birth weight analysis.[16] This is similar to our meta-analysis result, whereas the risk of congenital anomalies (OR: 0.88, $p = 0.75$) is a little different from the intervention. While stillbirth (OR: 1.03, $p = 0.93$) and spontaneous abortion (OR: 1.85, $p = 0.27$) show insignificant results, with a higher number of events leaning towards the control group. Furthermore, the birth outcomes included are low birth weight and premature birth. While results of previous studies lean towards the control group, our results show a slight effect in low birth weight (OR: 1.15, and $p = 0.36$) and premature birth (OR: 1.08, $p = 0.73$).

Implications in Clinical Practice

Additional DHA-PPQ to the standard treatment of IPTp in pregnant women with positive HIV could reduce the malaria co-infection and maternal adverse events, thus leading to safer and more effective IPTp. A large-scale, multi-center randomized control trials across different regions outside Africa are needed to strengthen the generalizability of the findings.

Strength and Limitations

Although this review addresses an important finding through the additional DHA-PPQ for IPTp in pregnant women with positive HIV, the authors acknowledge that this review has some limitations. First, only 3 studies are included in the analysis, all of which originated from the African region, while authors' search was limited by language and accessibility to specific publications. Thus, the representatives of the result in the remaining regions are still questioned. Second, long-term follow-up data was not available for all included studies, thus results and analysis are limited. Third, the meta-analysis of neurological maternal adverse events shows moderate heterogeneity. However, this review provides information on treatment safety as additional information and recommendation for pregnant women with positive HIV prophylaxis guidelines. This review can help policy-makers to design and revise the new IPTp guideline for pregnant women with HIV.

Conclusion

Additional DHA-PPQ significantly reduced overall maternal adverse events for malaria prevention in HIV-positive pregnancies, and no significant differences were seen in fetal and birth outcomes. Evidence on drug efficacy in malaria prevention remains uncertain.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

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Author Contributions

Vycke Yunivita and Amanda Jessie Maharani contributed equally to this study and share first authorship. V. Yunivita contributed to study conception, literature search, data evaluation, manuscript drafting, revision, and final approval. A.J. Maharani contributed to protocol development, risk of bias assessment, data analysis, manuscript drafting, and revision. C.A. Bernadus, E.I.J. Sinaga, and E.R. Simanjuntak contributed to data collection, data analysis, and manuscript drafting. All authors made substantial contributions to the work, including the conception and design of the study, data acquisition, analysis, and interpretation. All authors participated in drafting, revising, or critically reviewing the manuscript; approved the final version to be published; agreed on the target journal; and accept accountability for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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