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META-ANALYSIS: THE EFFECT OF HIV/AIDS IN PREGNANT WOMEN AGAINST THE INCIDENCE OF LOW BIRTH WEIGHT AND PRETERM BIRTH

Neti Husaeni*, Cusmarih
Bachelor of Midwifery, STIKES Abdi Nusantara, Jl. Swadaya No. 7, Jatibening, Pd. Gede, Bekasi, West Java 17412, Indonesia
*netihuseni@gmail.com

ABSTRACT

Pregnancy poses a major challenge to immune system regulation. Immune function is suppressed in both HIV-infected and non-HIV-infected women. Transmission of the virus has also been reported to occur between mothers to fetuses. So that HIV infection can reduce the quality of pregnancy outcomes such as low birth weight babies (low birth weight) and premature birth (preterm) The purpose of this meta-analysis is to estimate the strength of the effect of HIV infection on the incidence of low birth weight babies and preterm delivery. This study is a *systematic review* and meta-analysis. Primary data is retrieved through the electronic databases PubMed, Science Direct, Web of Science, Springer Link and Cochrane Database. search keywords "HIV AND AIDS", "HIV AND *pregnancy", "HIV AND* pregnancy *AND adjusted odds ratio",* and "HIV AND Pregnancy AND adjusted odds ratio". Articles taken between 2013-2023. Statistical analysis was performed using the RevMan 5.3 application. 6 articles qualified quantitatively for analysis. women who have HIV infection during pregnancy can increase the risk of giving birth to babies with low birth weight 3.32 times and statistically significant Odds Ratio (OR 3.32; 95% CI: 2.24 – 4.93; p value < 0.001). Results also reported women who have HIV infection during pregnancy were 4.79 times more likely to giving before the due date (premature) than women who were not infected with HIV during pregnancy and had a statistically significant odds ratio (OR 4.79; 95% CI: 2.50 – 9.19; p value 0.008). HIV infection in pregnancy can increase the risk of low birth weight babies and premature birth

Keywords: human immuno deficiency virus; low birth weight; premature birth

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a virus that attacks the human immune system and causes a set of symptoms of disease due to HIV infection, namely Acquired Immune Deficiency Syndrome (AIDS). HIV is found in blood and genital fluids that are transmitted through sexual intercourse, blood transfusions, use of HIV-infected syringes, organ transplants, and mother-to-fetus transmission. (Karimy, 2018) Pregnancy is a major challenge for the regulation of the immune system. Immune function is suppressed in both HIV-infected and non-HIV-infected women. During pregnancy there is a decrease in immunoglobulin, a decrease in the number of complements, and a decrease in cellular immunity. The prevalence of pregnancy will make the progress of HIV in pregnancy worse. (Malaba, 2021)

In a French study grouping 57 pregnant women with HIV and 114 pregnant women without HIV infection and followed for 61 months, there was no significant difference in progressivity12. The Swiss study grouped 32 HIV in pregnancy and 416 non-pregnant HIV in age and CD4 counts followed for 4.8 years to conceive and 3.6 years for control13. The results showed no difference in disease progression and average age of death, unless there was already an infection such as bacterial pneumony.13 The maternal fetal immune response in pregnancy is influenced by the thymus as the central tolerance and T reg (T regulator) as the regulator of peripheral tolerance. The size and

structure of the thymus shrinks during pregnancy, but its size and function will return to normal after postpartum.(Savira, 2017)

At least T reg in pregnancy triggers abortion, stillbirth, low birth weight, preterm labor. The balance of Th1 and Th2 is an important thing to achieve in maintaining a pregnancy. HIV infection leads to decreased CD4 and Th2 counts, and decreased activation of other immune cells. Studies comparing the use of HAART have shown significant differences in immunological profiles.15 The process of systemic immunological regulation changes during pregnancy. (Kala, 2020) Studies in mice have shown an increase in T reg since early pregnancy triggered by paternal antigens. Pregnancy failure can also occur in the absence of this T reg. Human studies have shown the same; a lack of T reg in the decidual layer can induce abortion, preeclampsia, and infertility (Savira 2017).

In HIV negative T reg expands early in pregnancy and decreases even lower after postpartum. Unlike HIV infection, the T reg does not change until the second trimenter. Tregs in HIV infection accumulate in lymphoid tissue and in postpartum the T reg count is higher in HIV infected patients compared to those who are HIV negative (Savira 2017). Information on how influential HIV is on the incidence of low birth weight and preterm delivery is still very diverse, so generalization through meta-analyses would be very useful in detecting and performing care, however. Indonesian researchers are still unable to conduct studies on the impact and effect of HIV / AIDS infection on the incidence of low birth weight and preterm delivery. Based on this background, researchers are interested in conducting a meta-analysis of the impact of HIV/AIDS on low birth weight and preterm delivery.

METHOD

The research design is a meta-analysis conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).(Moher, 2015)The database search is conducted from April 2023. PubMed, Science Direct, Web of Science, Springer Link and Cochrane Database. By using the search keywords *"HIV AND AIDS"*, *"HIV AND pregnancy"*, *"HIV AND pregnancy AND adjusted odds ratio", and "HIV AND Pregnancy AND adjusted odds ratio"*. In addition to determining keywords, article searches are carried out by determining eligibility criteria defined using the PICO model, namely: Population: Pregnant women. Intervention: Exposure to HIV. Comparison: Not exposed to HIV. Outcome: BBLR and preterm deliveryArticles that do not fall into qualitative criteria, will mostly be discussed in this article and used as a source of literature. all articles will be quantitatively analyzed using Review Manager (RevMan) 5.3.Full paper published in English or Indonesian. Published from 2013 to 2023. Report complete analysis results including *adjusted risk ratio, confident interval,* and *p-value.* The article was analyzed by multivariate analysis reported in the closeness of the odds ratio relationship.

RESULTS AND DISCUSSION

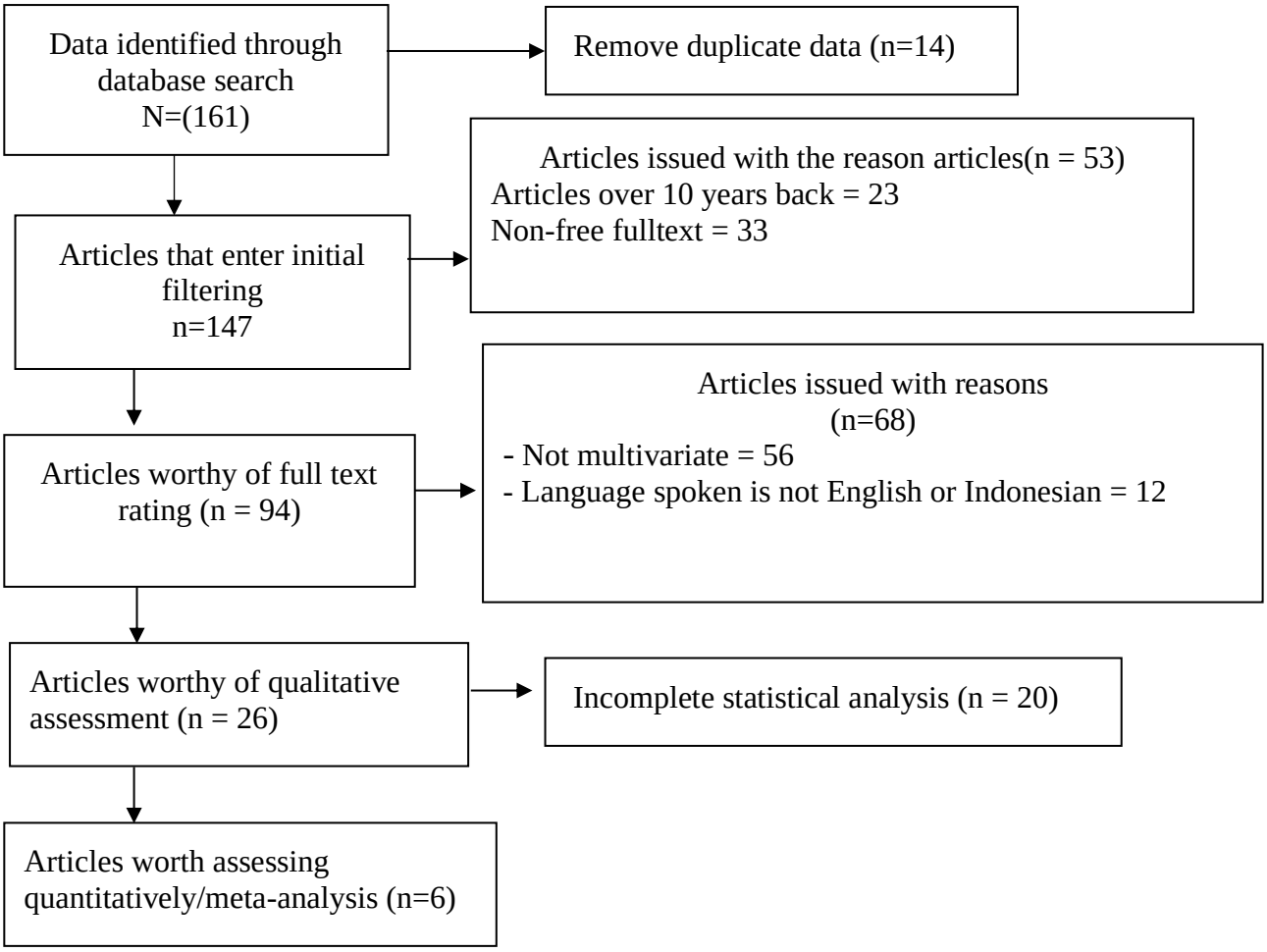

Figure 1. Research and data search flow based on PRISMA guidelines

Table 1.
Summary of quantitatively qualified research articles

Author	Subject and location	Result
(Rough, 2018) Birth Outcomes for Pregnant Women with HIV Using Tenofovir–Emtricitabine	There were 4646 birth outcomes included mother–infant pairs enrolled from April 1, 2007, through March 1, 2016, in the Dynamic cohort of the SMARTT study, which enrolled women with HIV infection and their infants at 23 or more weeks of gestation through 1 week after delivery. United state of America	As compared with women receiving ZDV–3TC–LPV/r, women receiving TDF–FTC–LPV/R had a similar risk of preterm birth (risk ratio, 0.90; 95% confidence interval [CI], 0.60 to 1.33) and low birth weight (risk ratio, 1.13; 95% CI, 0.78 to 1.64). As compared to women receiving TDF–FTC–ATV/r, women receiving TDF–FTC–LPV/R had a similar or slightly higher risk of preterm

Author	Subject and location	Result
		birth (risk ratio, 1.14; 95% CI, 0.75 to 1.72) and low birth weight (risk ratio, 1.45; 95% CI, 0.96 to 2.17). There were no significant differences between regimens in the risk of very preterm birth or very low birth weight.
(Ajibola, 2018) HIV Exposure and Formula Feeding Predict Under-2 Mortality in HIV-Uninfected Children, Botswana	HIV-infected and HIV-uninfected mothers and their children in the prospective observational Tshipidi study at 2 sites (1 city and 1 village) in Botswana from May 2010-July 2012. Live-born children and their mothers were followed for 24 months postpartum.	893 live-born HIV-uninfected children (436 HEU, 457 HIV-unexposed) were followed. HIV-infected mothers had a median CD4 count of 410 cells/mm3, 32% took 3-drug antiretroviral
(Cambrea, 2023) Fetal Growth Restriction and Clinical Parameters of Newborns from HIV-Infected Romanian Women	During the study period, between 2008 and 2019, 408 HIV-positive pregnant women were monitored, of whom 244 mothers were from HIV-AIDS Constanta, RC, and 164 mothers were from HIV-AIDS Craiova, RC. The population study consisted of participants > 18 years, with a singleton pregnancy. Exclusion criteria included pre-existing hypertension, diabetes, renal, autoimmune, active opportunistic infection for HIV-positive women, morbid obesity, or drug use.	Interestingly, our results showed that in Craiova, RC, there was a chance of 2.16 to find an HIV-negative newborn with an HC < 10th percentile and a 2.54 chance to find an HIV-negative newborn with a BL < 10th percentile compared to Constanta, RC, without any significant differences. On the contrary, Constanta, RC, represented a higher risk of death (i.e., 3.049 times, p = 0.0470) for HIV-positive newborns compared to Craiova, RC.
(Li, 2020) Maternal HIV infection and risk of adverse pregnancy outcomes in Hunan province, China A prospective cohort study	This prospective cohort study was carried out among 483 HIV-infected pregnant women and 966 HIV-uninfected pregnant women. The HIV-infected and HIV-uninfected women were enrolled from midwifery hospitals in Hunan province between October 2014 and September 2017	The incidences of stillbirth (3.9% vs 1.1%), preterm birth (PTB) (8.9% vs 3.7%), low birth weight (LBW) (12.2% vs 3.1%) and small for gestational age (SGA) (21.3% vs 7.0%) were higher in HIV-infected women than HIV-uninfected women, with adjusted ORs of 2.77 (95%CI: 1.24–6.17), 2.37 (95%CI: 1.44–3.89), 4.20

Author	Subject and location	Result
		(95%CI: 2.59–6.82) and 3.26 (95%CI: 3.26–4.64), respectively.
(Tukei, 2020) 24-Month HIV-free survival among HIV-exposed Infants in Lesotho: the PEAWIL cohort study	a prospective observational cohort study that enrolled 653 HIV-positive and 941 HIV-negative pregnant women. Twenty-seven HIV-negative women acquired HIV during follow-up and their infants for 24 months after delivery. Participant recruitment started in June 2014 and follow-up ended in September 2018. Trained nurses collected study information through patient interviews and chart abstraction at enrolment and every three to six months thereafter.	T he risk of HIV transmission from HIV-positive mothers to their infants by 24 months of age was 2.9% (95% CI: 1.8 to 4.7). The estimated 24-month mortality rate among HEIs was 6.0% (95% CI: 4.4 to 8.2) compared to 3.8% (95% CI: 2.6 to 5.3) among HUIs (Log-rank p = 0.065). HIV-free survival at 24 months was 91.8% (95% CI: 89.2 to 93.7). Lower maternal age and birth weight were independently associated with increased HIV infection or death of infants.
(VENKATESH, 2019) Association between HIV antiretroviral therapy and preterm birth based on antenatal ultrasound gestational age determination: a comparative analysis	The PROMISE trial recruited pregnant women with HIV infection at 14 sites across eastern and southern Africa and India. The trial compared open-label strategies and included sequential randomizations for antenatal antiretroviral regimens	Women receiving ZDV- and TDF-based ART had significantly higher odds of PTB<37 by ultrasound compared to ZDV alone (AORs: 1.68; 95% CI: 1.10 to 2.57, and 2.71; 95% CI: 1.39 to 5.29), as well as for PTB<34 weeks. These results held for ultrasounds performed<24 weeks, and were generally consistent with prior analyses from the PROMISE trial using the NBS.

Forest Plot Analysis

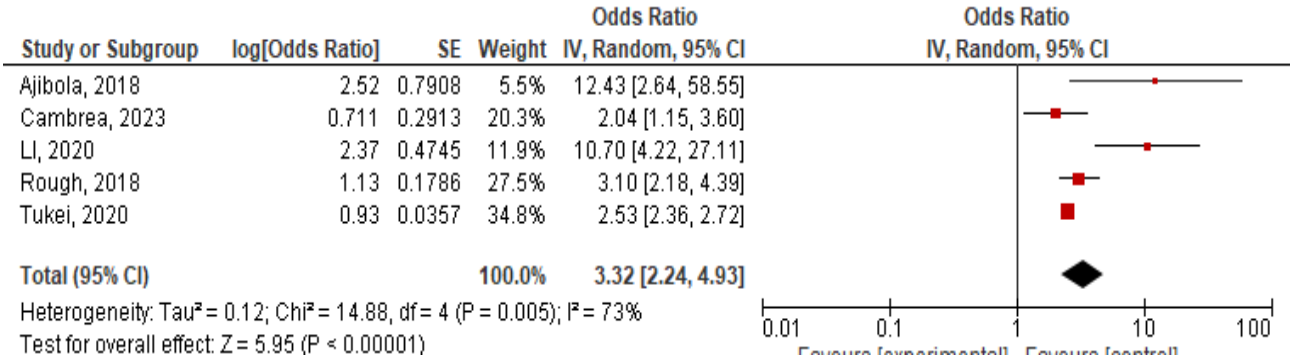

Figure 1. Forest plot analysis of the effect of HIV infection on low birth weight infants

Based on the results of the forest plot analysis in figure 1 above, it can be seen that women who experience HIV infection during pregnancy are at risk of giving birth to babies with low birth weight 3.32 times compared to women who are not infected with HIV during pregnancy, and statistically significant Odds Ratio (OR 3.32; 95% CI: 2.24 – 4.93; p value < 0.001).

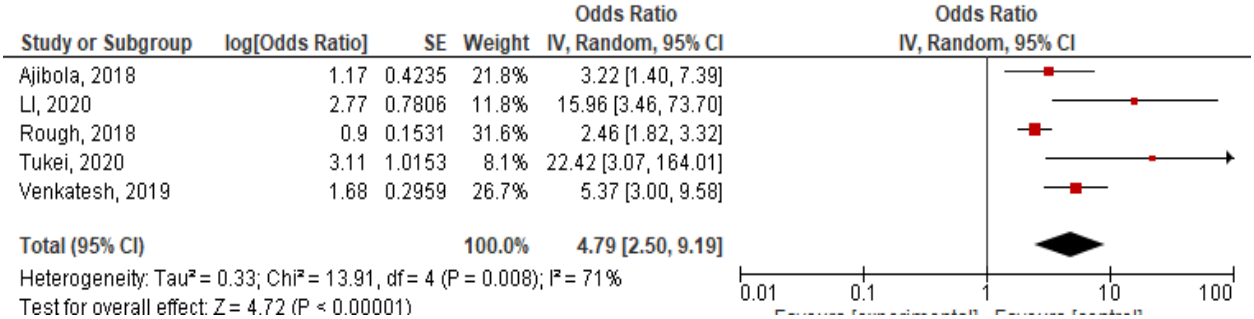

Figure 2. Forest plot analysis of the effect of HIV infection on low birth weight infants

Based on the results of the forest plot analysis in figure 2 above, it can be seen that women who experience HIV infection during pregnancy are at risk of giving birth early or preterm 4.79 times compared to women who are not infected with HIV during pregnancy and statistically significant Odds Ratio (OR 4.79; 95% CI: 2.50 – 9.19; p value 0.008).

These results are consistent with studies conducted by which reported that women were infected with HIV and received (Kala, 2020)Treatment *Lopinavir-cART* is also associated with selective depletion of UNK cells, decreased migration of trophoblasts and damaged placentation. Lopinavir-associated decidualization defects are associated with decreased transcription factor expression *STAT3*, which is known to regulate decidualization, initiation of periconception of lopinavir-cART, but not darunavir-cART, causes maturation of the damaged endometrium of the uterus, causing disturbances in the remodeling of the spiral arteries and placentation, thus contributing to poor birth outcomes.

Quality of pregnancy outcomes associated with use *Anti Retroviral Therapy* (ART), in HIV patients receiving ART have reported lower cases of low birth weight and premature weight. Low CD4 cell levels are one of the main factors in inhibiting fetal development and spreading HIV infection and causing prematurity. This is because the amount of virus that is not controlled when a mother has HIV / AIDS will cause chronic immune activation and high cytokine levels, thus making the

intrauterine environment less favorable for fetal growth. Conversely, preterm labor may be more associated with acute changes that occur in the mother during pregnancy such as tuberculosis infection that causes severe coughing and continuous suppression of the mother's abdomen.(Malaba, 2021; Zash, 2016)

A number of studies have reported an association between prematurity and a higher risk of HIV infection in labor with gestational ages between 32 weeks and 35 weeks; in fact, case reports of extreme prematurity (births under 32 weeks) are associated with a transmission rate of HIV/AIDS infection of 31%. A study that reported an association between HIV infection in infants and low birth weight has also been described in the United States. (Zash, 2016) However, the majority of women in all of these studies did not receive ART. In a multivariate analysis of risk factors for perinatal transmission, low birth weight and gestational age were no longer significantly associated with perinatal transmission when the model or patient received ART during pregnancy (Romlah, 2020).

CONCLUSION

HIV infection in pregnancy can increase the risk of low birth weight babies and premature birth.

REFERENCES

Karimy, M. &. Z. I., 2018. Predictors of HIV-preventive behavior changes among HIV-infected patients in Iran: Application of the extended health belief model. *International Journal of High Risk Behaviors and Addiction,* 7(4).

Savira, M., 2017. Imunologi Human Immunodeficiency Virus (HIV) dalam Kehamilan. *Jurnal Ilmu Kedokteran,* 8(1), pp. 1-10.

Kala, S. e. a., 2020. Periconceptional exposure to lopinavir, but not darunavir, impairs decidualization: A potential mechanism leading to poor birth outcomes in HIV-positive pregnancies. *Human Reproduction,* 35(8), p. 1781–1796.

Malaba, T. e. a., 2021. Cohort profile: Prematurity Immunology in Mothers living with HIV and their infants Study (PIMS). *BMJ Open,* 11(9).

Moher, D. e. a., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. pp. 1-9.

Rough, K. S. I. G. R. W. P. L. H.-D. S. H. Y. C. E. G. .. &. P. K., 2018. Birth outcomes for pregnant women with HIV using tenofovir–Emtricitabine. *New England Journal of Medicine,* 378(17), pp. 1593-1603.

Ajibola, G. L. J. M. G. K. v. W. E. M. T. P. C. .. &. L. S., 2018. HIV exposure and formula feeding predict under-2 mortality in HIV-uninfected children, Botswana. *The Journal of pediatrics,* Volume 203, pp. 68-75.

Cambrea, S. C. D. E. P. L. C. M. C. M. G. C. P. L. .. &. D. F., 2023. Fetal Growth Restriction and Clinical Parameters of Newborns from HIV-Infected Romanian Women. *Medicina,* 59(1), p. 111.

Li, H. L. J. T. D. H. G. Z. J. X. J. .. &. Z. G., 2020. Maternal HIV infection and risk of adverse pregnancy outcomes in Hunan province, China: a prospective cohort study. *Medicine,* 99(8).

Tukei, V. J. M. R. G. M. M. T. A. M. M. I. A. .. &. G. L., 2020. 24-Month HIV-free survival among HIV-exposed Infants in Lesotho: the PEAWIL cohort study. *Journal of the International AIDS Society,* 23(12), p. e25648.

VENKATESH, K. K. F. M. F. T. M. D. S. N. A. I. K. N. C. .. &. B. H. C., 2019. Association between HIV antiretroviral therapy and preterm birth based on antenatal ultrasound gestational age determination: a comparative analysis. *AIDS (London, England),* 33(15), p. 2403.

Zash, R. e. a., 2016. Reassuring birth outcomes with tenofovir/emtricitabine/efavirenz used for prevention of mother-to-child transmission of HIV in Botswana. *In Journal of Acquired Immune Deficiency Syndromes,* p. 428–436.

Romlah, S. P. R. &. H. I., 2020. Human Immunodeficiency Virus (Hiv) pada Bayi Baru Lahir Ditinjau dari Berbagai Literatur. *Edu Dharma Journal: Jurnal penelitian dan pengabdian masyarakat,* 4(2), p. 78.