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The Characteristics of Neonatal Outcomes of HIV-Infected Mothers with the Use of Antiretrovirals (ARVS)

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Abstract---Objective: The purpose of the scoping review is to find out the characteristics of neonatal outcomes of HIV-infected mothers with antiretroviral use. Design: Writing a scoping review following the writing rules of PRISMA ScR. Method: The results of the review show that there are 10 articles obtained from the search process through the Proquest, Pubmed, Science Direct, and Google Scholar databases. As well as following the criteria for inclusion and exclusion. Results: This review raises the theme of outcomes from HIV pregnant women with antiretroviral use before conception and after conception. The administration of ARVs in pregnancy causes various kinds of neonatal outcomes, namely babies born normally, babies with lightweight, babies born prematurely, abortions, IUFD and babies infected with HIV. It was concluded that there is an impact of giving ARVs to pregnant women, but prevention of vertical transmission by taking ARVs immediately and routinely is better done to reduce the incidence of HIV transmission. Conclusion: Factors causing babies born with BBLR, premature, IUFD, and abortion are not necessarily due to factors of ARV use in pregnant women. Other factors cause poor output, namely due to the high maternal CD4 factor and low maternal viral load, thus the administration of ARVs during pregnancy is still given for prevention from mother to baby and increased morbidity rates in mothers and transmission in babies.

Keywords---antiretrovirals, HIV, neonatal, scoping review.

Introduction

An estimated 8604 HIV-infected babies are born each year. The estimated costs incurred to treat and treat HIV-infected babies are around Rp 42 billion every year. This fee is used for the procurement of antiretrovirals (ARVs) consumed by HIV-infected babies for the rest of their lives and is at risk for orphaning babies born to mothers with HIV/AIDS (Sitohang, 2020). More than 90% of HIV-infected babies are infected by their mothers during pregnancy. Transmission can occur during pregnancy, during childbirth and breastfeeding. Prevention of Mother to Child HIV Transmission (PMTCT) or known as Prevention of HIV Transmission from Mother to Child (PPIA) is a very effective measure in preventing such transmission.

Mothers or babies infected with HIV/AIDS have a high chance of contributing to the mortality rate. Maternal and infant mortality rates are a determination of the level of public health degrees in a country (Sitohang, 2020). When the mother already knows that she is pregnant, there is a policy to examine the health facility 1, one of which is the VCT examination. Following the standard, all pregnant women with HIV are given ARV therapy, without having to check the viral load and CD4 amount first, because the pregnancy itself is already an indication of the administration of an ARV that is continued for life (Beyrer et al., 2012; Kasim & Kurniati, 2023).

Research Methods

The type of study to be used is scoping review. Studies related to neonatal external results will be reviewed including the method of sampling, the variables contained in the article to be taken, and the results of the study (Lockwood et al., 2019; Maramba et al., 2019). The stages in conducting a scoping review are the focus of the review, using the PEOs (Problem, Exposure, outcome and study design) framework, identifying relevant studies, describing the process, identifying literature with PRISMA flowchart, data extraction and mapping or scoping (Arksey & O'Malley, 2005 in (Nurhayati et al., 2020)), as follows:

1. Identifying scoping review questions

Identify core concepts, and gaps in reviewing and as a source of evidence to inform policies and practices in the use of ARVs while pregnant. The question of the review is what are the characteristics of neonatal outcomes of HIV-infected mothers with the use of antiretrovirals?

The development of the review, using the steps of the search strategy begins with the search for research using the population, exposure, outcome, and study design (PEOs) framework (Vickery et al., 2020) in managing and solving the focus of the review.

Population	Exposure	Outcome	Study Design
Pregnant woman	Art	Baby with HIV	Any article related to pregnant women with HIV
Pregnancy woman	Arv	Premature birth	
	Antiretrovirals	Mature Birth	
		Dead birth BBLR	

2. Identifying Relevant Studies

a. Database

The databases taken are Pubmed, Science Direct, Google Scholar and Proquest.

b. Grey literature

Grey literature used is the World Health Organization (WHO), the American College of Obstetricians and Gynecologists (ACOG) and the United Nations Programme on HIV and AIDS (UNAIDS).

After that establish the criteria for inclusion and exclusion in the selection of study articles. The following are the exclusion and inclusion criteria in research studies:

Inclusion Criteria	Exclusion Criteria
a. Free full text	a. Review of the article
b. Original Research	b. Opinion articles
c. Articles published in English and Indonesian	
d. Articles discussing HIV pregnant women taking ARVs	
e. Published 2018-2021	

PRISMA is a Preferred Reporting Item for Systemic reviews and Meta-Analyses developed to assist authors in reporting on Systematic Reviews (SR) and Meta-Analyses (MA). PRISMA is considered appropriate to use because its use can improve the quality of publication reporting results (Page et al., 2021).

After obtaining sufficient evidence, a critical appraisal was carried out using a form from the Joanna Briggs Institute (JBI) to assess the quality of the evidence. The data selected are following the criteria that have been determined by the researcher. Here are the stages of data filtering:

c. Charting Data

No.	Title/Author/ Year/Grade	Data Collection	Result
1.	Relationship of Antiretroviral (ARV) Use with Neonatal Externals in mothers infected with Human Immunodeficiency Virus (HIV) (Apriyani et al., 2018)	HIV-infected mothers used antiretrovirals totalling 24 (33%) and those not taking antiretrovirals totalling 49 (67%).	There is a relationship between pregnant women taking ARVs with prematurity and there is no relationship between mothers taking ARVs with the incidence of IUFD, as fiction and IUGR.
2.	Effects of Antiretroviral Therapy and HIV Exposure in Utero on Adverse Pregnancy and Infant Outcomes: A Prospective Cohort Study in Guangzhou, China (HU et al., 2019)	Data grouped by antiretroviral user and not ARV user	Adverse pregnancy outcomes occurred in 202 (35.1%) women infected with HIV and 121 (31.3%) of the resulting output showed adverse effects on early growth at 4 weeks of age. Adverse pregnancy outcomes such as spontaneous abortion, ectopic pregnancy, stillbirths, infant mortality and perinatal HIV infection were higher among women who did not receive an ARV, compared to those treated with cART or mono/double ARVs (P <0.05). However, women treated with cART have higher levels of SGA, compared to untreated women (P <0.05).
3.	Risk Factors for Adverse Birth Outcomes in the PROMISE 1077BF/1077FF Trial (Sebikari et al., 2019)	Results of treatment with inhibitor-based antiretroviral (ART) treatment (PI (ARM Band ARM C)) and ZDV-based ones only.	PI-based ART given during PMTCT among HIV-infected women, remains a risk factor for low-birth-weight outcomes and premature birth.
4.	Adverse Pregnancy Outcomes Among Women Who Conceive Antiretroviral Therapy (Hoffman et al., 2019)	Data are grouped randomly on mothers who resumed ARV and terminated ARVs	Women who were randomized to continue art who later became pregnant were more likely to have spontaneous abortions or stillbirths, compared to women who were randomized to stop ART; However, the findings did not remain significant
5.	Association between HIV antiretroviral therapy and preterm birth based on antenatal ultrasound gestational age determination: a comparative analysis (Venkatesh et al., 2019)	The data is grouped into 3. That is - ZDV only - ZDV-based ART - TDF-based ART	Among the 720 pregnant women assessed, PTB (Preterm Birth) <37 weeks was 15.4% based on NBS (New Born Screening/TBJ) and 18.3% with ultrasound. NBS was specific but insensitive to PTB <37 weeks (92.0% and 48.5%). Women who received ZDV and TDF-based ART had a significantly higher chance of PTB<37 Viewed when ultrasound compared to ZDV alone
6.	Transmission of Hiv Infection in Infants from Mothers	The data were grouped on the final results of pregnant women with	HIV transmission in infants is higher if the mother takes an ARV for less than 6 months, other factors are also

	Hiv Positive Patients Born in Hospitals Hajj Adam Malik Medan from 2009 – 2017 (Hasibuan et al., 2019)	ARV consumption < 6 months, > 6 months and those who did not consume ARVs	affected, namely KPD, CD4 <350 and giving birth to pervaginam.
7.	Pregnancy Outcomes of Women Conceiving Antiretroviral Therapy (ART) Compared to Those Commenced on ART During Pregnancy (Theron et al., 2021)	The data were grouped on women who continued ART until the next pregnancy without breastfeeding in their first pregnancy and the group stopped ART while pregnant and breastfeeding and continued ART when they were finished breastfeeding	There is a higher risk in mothers who consume ART before conception with low birth, abortion, and IUFD.
8.	Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DoIPHIN-1 study) (Waitt et al., 2019)	Hiv RNA suppression <50 coffee/mL is twice as fast as DTG compared to EFV. DTG has the potential to reduce the risk of vertical transmission in mothers who start treatment at the end of pregnancy	The administration of ARVs in the 3rd trimester of pregnancy influences the transmission of mother to baby
9.	Pregnancy Profile and Infant Outcomes Among HIV Infected Women Who Delivered in Cipto Mangunkusumo Hospital (Indarti et al., 2020)	Almost all babies received ARV prophylaxis (97.9%) and formula feeding. HIV PCR was examined in 16 infants at the age of 6 weeks and in 13 infants at the age of 6 months. There was 1 baby with viral load results >400 who immediately referred to the Pediatric HIV clinic	Administration of ARVs in early pregnancy significantly reduces transmission vertically
10.	Timing of initiation of antiretroviral therapy and risk of preterm birth in studies of HIV-infected pregnant women: the role of selection bias (Stoner et al., 2018)	There is an increased risk of 1.10 in women with ARV given before conception	Premature births are higher in women with ARV use before conception

d. Mapping/ Scoping

1) Characteristics of Geography

The results of article reviews obtained from several countries are Indonesia 3 articles, China 1 article, Africa 3 articles, India 3 articles, Zambia 2 articles, South Malawi 1 article, Tanzania 1 article, Uganda 1 article, Zimbabwe 1 article, California 1 article, and South Africa 1. All articles obtained are using quantitative research studies.

- 2) Characteristics of the type of study
From as many as 10 selected articles, the results were obtained that the study used the Randomize Control Trial study of as many as 3 articles, the Randomize Control Trial study was 6 articles, the crosssectional study was 2 articles, and the cohort study was 2 articles.
- 3) Thematic
The results of the review found several results that are following the focus of the review, namely as follows:

Theme	Sub Themes	Article
Granting of an ARV before conception	a. Premature	a. A10, A5
	b. BBLR	b. A7
	c. Abortus	c. A2, A4, A7
	d. IUFD	d. A2, A4, A7
	e. Pregnant Ectopic	e. A2
	f. HIV-infected	f. A2
	g. Babies born normally	g. A9
Granting of ARVs after conception	a. HIV-infected	a. A6, A8
	b. BBLR	b. A3
	c. Premature	c. A3

Results and Discussion

Pregnancy in mothers with HIV is particularly susceptible to transmission or other risk factors to the fetus. When a person is declared HIV, especially in pregnant women, the level of pain is carried out by taking an ARV (Engels et al., 2002; Alter, 2006). However, in consuming ARVs in pregnant women, there are also no risks in the results of fetal output in mothers with ARV consumption. The following are the results of the review obtained regarding the results of neonatal output in HIV-pregnant women with ARV constituencies (Wen et al., 2004; Yu et al., 2020).

1. Granting ARVs Before Conception

Antiretroviral administration is recommended for all people with HIV, regardless of the amount of CD4 or the stage of the disease. This includes pregnant or lactating women. However, several studies have shown a disadvantage in the use of ARVs before pregnancy (Theron et al., 2021). Here are some conception results from the use of ARVs in HIV mothers before conception.

a. Premature

According to the review, it was stated that among the 720 pregnant women who were rated as premature birth (<37 weeks) were at a higher risk of 15.4% (if examined with ultrasound) and 18.3% higher (if done by pregnancy screening). And ZDV and TDF-based ART administration have a higher chance of experiencing premature birth (Venkatesh et al., 2019). Another study stated that the preterm birth rate was higher among 267 women in the PI ARV group than in the 263 women in the NRTti group. PI-based ARVs are more significant for premature birth. Because in the study after 1 month of administration of ARV type PI, the mother had a lower BMI than the NRT type, although it did not occur directly in premature babies. Although it is higher to produce premature babies, it does not increase infant hospitalizations or increase mortality (Powis et al., 2011). Early use of ARVs can also increase the risk of premature, especially before conception (Stoner et al., 2018). Factors such as the type of ARV and the time of initial administration of the ARV are one of the causes of the baby being born prematurely.

b. BBLR

There are research results on women who continue to ARV after their first pregnancy resulting in a higher risk of low birth weight for subsequent pregnancies (Theron et al., 2021). However, in other studies, it is explained that the factor of BBLR is not when the mother is exposed to an ARV or not, but when the mother's viral load is high and CD4 is low. This is precisely the factor causing pregnant women with HIV to give birth to BBLR or premature (Gibango et al., 2018).

c. Abortus

According to the review, there is an influence on pregnant women with ARVs that make the baby with poor growth at the beginning of pregnancy, which in the study mentioned a gestational age of 4 weeks. Resulting in adverse pregnancies such as spontaneous abortions, ectopic and stillbirth pregnancies than mothers without the use of ARVs in their pregnancies (HU et al., 2019). Another article experimented with and stated the results that women given ARVs (continuing ARVs) were more likely to occur spontaneous abortions or stillbirths compared to women who discontinued using ARVs while pregnant. However, the study is still not significant, further research must still be carried out. Other studies have shown that low CD4 counts and high viral loads can be triggers for abortion rates and infant mortality. So it is not only due to the factor of using antiretrovirals alone (Soubeiga et al., 2018).

d. IUFD

As mentioned earlier, there are adverse outcomes when administering ARVs at the time before conception, which shows an unfavourable effect on early growth. One of the results of her pregnancy was stillbirth (HU et al., 2019). Babies born to HIV-infected women have a higher risk of developing BBLR and are born prematurely and are at risk of a high mortality rate. Because women with HIV are very inclined in influencing the health of their babies (Jao et al., 2017). According to the review, there are adverse pregnancy outcomes for women with ARV therapy compared to women who stop ARVs during pregnancy, that is, the presence of stillbirth in the fetus. HIV infection in mothers receiving antiretroviral therapy has been linked to adverse pregnancy outcomes such as premature birth, low birth weight (BBLR), and stillbirth. Premature birth is the number two cause of death in the world in children under five years of age (Hasibuan et al., 2019).

e. Pregnant Ectopic

There are several articles mentioning that the consumption of ARVs before conception causes ectopic pregnancy. The review of the study stated that the results of pregnancy in the administration of ARVs before conception were normal live births, live births followed by neonatal death (≤ 28 days), ectopic pregnancy, spontaneous abortion and induction abortion and stillbirth (Theron et al., 2021). Ectopic pregnancy is associated with the weight gain of the ARV recipient's mother which can cause disruptions in the hormones that cause ectopic pregnancies. These results are supported by research that states that at the beginning of the pandemic, PLHIV was at risk of losing subcutaneous fat (lipoatrophy) causing the development of newer antiretroviral agents, so researchers added an inhibitor-based regimen that can cause an increase in obesity rates and can be at risk of ectopic pregnancy in pregnant women (Koethe et al., 2020).

f. HIV-infected

The administration of ARVs to pregnant women with HIV strongly emphasizes the occurrence of vertical transmission. But it is also inseparable that it can still be transmitted from mother to fetus. Research states that perinatal are more likely to be infected with HIV compared to those who do not receive ARVs. However, the level of maternal nutrition degree is higher than that of mothers who do not receive ARVs (HU et al., 2019). HIV transmission is not necessarily because the mother uses an ARV. There are many factors that a baby can contract HIV, one of which is if the birth is spontaneous, the occurrence of KPD and the mother's CD4 rate is < 350 (Hasibuan et al., 2019).

g. Normal Birth baby

The study conducted by Indarti et al. (2020), stated that giving ARVs at the beginning of pregnancy can significantly reduce the risk of infection from mother to baby vertically. Another study stated that the administration of ART before pregnancy and during pregnancy had a low prevalence of MTCT (Mother to Child Transmission) compared to mothers who did not receive ARVs during pregnancy (Agabu et al., 2020). So that the factor of giving ARVs from the beginning of administration and routine administration is very influential in preventing vertical transmission.

2. Granting of ARVs after conception

When compared to women who start antiretrovirals at the end of pregnancy, the conception results are more minimalist in the risk of problems in the baby but do not regulate the level of viral load of PLHIV which can increase more rapidly because it is not suppressed the increase (Esté & Cihlar, 2010; Wimalasundera et al., 2002).

a. HIV-infected

According to the review of the article states that the baby of an HIV-infected mother is very likely to be infected with HIV, especially if the mother takes an ARV for less than 6 months which can cause the amount of CD4 <350 which causes the infection rate to be higher (Hasibuan et al., 2019). Other factors cause the baby to become infected with HIV from the mother, namely the presence of KPD and the delivery of pervaginam. Research on pervaginam delivery by mothers with HIV can be considered if the number of viral loads ≤ 1000 at the time before delivery. However, if you find a mother who irregularly consumes an ARV and the number of viral loads > 1000, then an SC plan is carried out 2 weeks before HPL (ACOG, 2018). The type of ARV used can also have an effect. Research shows that the use of DTG-type ARVs faster reduces the risk of HIV 2x faster than EFV ARV types (Waitt et al., 2019). So that many factors cause the transmission of HIV transmission from mother to baby.

b. BBLR

The review obtained from the results of the study by Apriyani et al. (2018), stated that there was a meaningful relationship between pregnant women who took ARVs with premature events and BBLR. A cohort study conducted by a study in South Africa stated that babies born to mothers who used ARVs had a relatively low birth weight than babies who were not exposed to HIV and ARV (Nyemba et al., 2021).

h. Premature

According to the review, there are premature pregnancy results from two types of antiretrovirals (based on PI and ZDV) which have more influence, namely PI-type ARVs given after conception (Sebikari et al., 2019). However, in other studies, it is stated that PI-type ARVs are actually at lower risk of impact compared to other types of ARVs. PI-based ART during pregnancy is not associated with a significantly increased risk of BBLR or premature birth (Szyld et al., 2006; Twabi et al., 2020).

The downside of this scoping is that there is still a need for further research on the exact impact of ARVs on pregnancy. Because there is still a gap between pregnant women with ARV consumption which causes pain rates and HIV pregnant women without any morbidity rates when consuming ARVs. So the use of ARV for pregnant women has not been maximized.

Conclusions and Suggestions

The results of the study were 84 babies born to 79 women, there were 5 babies with HIV-positive results. And of the five babies came from mothers who did not take ARVs during pregnancy (Levin et al., 2017). So, it can be concluded that giving ARVs to pregnant women does have a lot of impact on the results of HIV mothers' output with ARV consumption. Moreover, there is another risk of routine use before conception (Theron et al., 2021). However, it is very better to prevent HIV from mother to baby. Therefore, regular use of ARVs in pregnant women with HIV is very mandatory by knowing the impact that will occur if it is irregular in consuming it. The provision of ARVs to pregnant women is useful as a preventive measure in increasing the number of pain and death caused by HIV, so it is mandatory for pregnant women who already know their HIV to take regular ARVs and still maintain a balance of body mass index to prevent the existence of BBLR, premature birth, IUFD can be inherited. The factors causing babies born with BBLR, premature, IUFD, and abortion is not necessarily due to factors of ARV use in pregnant women. Other factors cause poor output, namely due to the high maternal CD4 factor and low maternal viral load, thus the administration of ARVs during pregnancy is still given for prevention from mother to baby and increased morbidity rates in mothers and transmission in babies. Several factors cause mothers to be irregular in taking ARVs, namely knowledge and support from the closest people (Di et al., 2019).

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