European Journal of Medical and Health Sciences
www.ejmed.org

Aterm Pregnant Women with Human Immunodeficiency Virus Infection Which Receive Antiretroviral Therapy Combination of Nucleoside Analogue Reverse Transcriptase Inhibitor as A Risk Factor of High Expression of Apoptosis Including Factors

I Gusti Made Kusuma Widnyana, I Wayan Artana Putra, Tjok. G. A. Suwardewa, Putu Doster Mahayasa, I Made Darmayasa, and I Gde Sastra Winata

ABSTRACT

Aim: **To determine whether term pregnant women with human immunodeficiency virus infection who received antiretroviral therapy had high Caspase-3 expression in the placenta.**

Methods: **This cross-sectional analytical study was conducted at Sanglah General Hospital, Denpasar, and educational network hospitals. Subjects collected were termed pregnant women with HIV (+) who received antiretroviral therapy (ART) 6 months as a risk group and pregnant women with HIV (-) as a non-risk group. AIF expression was assessed by immunohistochemical examination of placental tissue. The AIF expression cut-off value was determined by constructing a receiver operating characteristics (ROC) curve. The chi-square test assessed the difference in proportion by displaying the prevalence ratio (RP) results. The significance of this study was p<0.05.**

Results: **40 pregnant women were included in the risk and no-risk groups. There was no difference in age, gestational age, parity and BMI in the two groups. The mean AIF expression was significantly higher in the group with HIV (+) (162±52.5) than HIV (-) (126.75±61.4), p-value = 0.003. The cut-off value of AIF expression was 112.50, with a sensitivity of 80% and a specificity of 45%. After classification, a significantly higher proportion of AIF expression was found in the HIV (+) group (42.5%) than in the HIV (-) group (27.5%) with p=0.038. Pregnant women with HIV (+) and receiving antiretroviral therapy for six months had a 4.6 times higher chance of having a high AIF prevalence than pregnant women who were not infected with HIV (RP=4.63; 95% CI=1.023 – 21.004).**

Conclusion: **Term pregnant women with HIV infection who received antiretroviral therapy had high AIF expression in the placenta.**

Keywords: AIF expression, antiretroviral therapy, human immunodeficiency virus, term pregnancy.

Submitted : April 9, 2022

Published : May 17, 2022

ISSN: 2593-8339

DOI: 10.24018/ejmed.2022.4.3.1325

I. G. M. K. Widnyana
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
(e-mail: drkusumawidnyana@gmail.com)
I. W. A. Putra*
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
T. G. A. Suwardewa
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
P. D. Mahayasa
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
I. M. Darmayasa
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.
I. G. S. Winata
Department of Obstetrics and Gynecology, Medical Faculty of Udayana University/Sanglah Hospital, Indonesia.

****Corresponding Author***

I. Introduction

Human immunodeficiency virus (HIV) is a virus that destroys the system immunity body by infecting and destroying CD4 cells. HIV is transmitted through the exchange of natural fluid body, and way most common transmission is with connection sexual. Contact blood to blood, like through needle injection or transfusion blood can also transmit HIV. Almost 25 years since antiretroviral therapy (ART) first appeared to prevent HIV transmission from mother to baby, 76% of mothers who live pregnant with HIV (more than 1 million women) received ART every year. HIV during pregnancy is one contributor to the number of

Dead Mothers highest in several world regions [1]. An infected mother can also transmit HIV to the baby they good During pregnancy, birth, and breast feeding [2].

A longitudinal study in 8 mothers city provinces in Indonesia from 2003-to 2009 found HIV prevalence in pregnant mothers increases every year. From 2003-to 2006, the prevalence was found by 0.36%. Furthermore, in 2008 it was prevalent at 0.52%, and in 2009 at 0.54%. The prevalence found decreased in 2010 that is by 0.25% [3]. Another study at Sanglah Hospital, Denpasar, found 42 mothers pregnant receiving service prevention mother-child transmission (PMTCT) in the period 2013-to 2014 [4].

Guidelines clinical the latest in Indonesia as stated in Minister of Health Regulation no. 87 the year 2014 recommend giving ART to mother pregnant miss from clinical-stage suffered HIV infection. However, the use of ART in pregnancy is lately linked with enhancement risk of preterm delivery. A review of References systematic 2015 sums up findings related to this and finds that the use of ART during pregnancy Upgrades the risk heavy born low (LBW) and underweight for age gestation [5]. One mechanism that explains the happening effect side is the consequence of toxicity from ART itself and how ART can trigger tissue apoptosis placenta. ART is known to own nature toxic and increase oxidative stress. ROS are molecules that can damage mitochondria. Damage membrane mitochondria could start release apoptotic factors that are in it, such as Bcl-2, caspase, and apoptosis-inducing factor (AIF), and lead to apoptosis or Dead mobile network placenta [6]. HIV infection and treatment antiretroviral therapy (ART) have a cause-effect side in pregnancy even though it can press the viral load and CD4 increases. Still available other problems resulting from HIV infection and suspected antiretroviral therapy impact the occurrence of placental apoptosis, one of which is marked by the rise in AIF. The apoptotic placenta is one mechanism happening outside pregnancy that is not wanted as preterm delivery and intrauterine growth restriction (IUGR) [7]. Apoptosis involves some good protein in track depending on caspase and tracks caspase free. One of the related proteins is AIF, whose sum is increased and assigned activation of the apoptotic process. Amount HIV- infected cells are relatively low compared with total CD4 cells undergoing apoptosis. This thing believed that happening drop in CD4 cells during HIV infection is the consequence of happening induction of bystander apoptosis. AIF alone is a protein that triggers Dead mobile with the method enter the nucleus or cell nucleus and starting the process of condensation chromatin and DNA fragmentation [8]. As a result, an increase in AIF expression can become a marker of the occurrence of apoptosis and ART toxicity. Although ART toxicity to mitochondria and their associations with the risk of preterm labor has long been known, the potential of AIF as one of the marker toxicities it's on the placenta still needs investigation more continued.

II. Discussion

This study uses the normality test, Shapiro Wilk, with results analysis showing that the distribution of distributed variables is not normal (p-value < 0.05). Because of that, the characteristic sample of the research is analyzed using the Mann-Whitney test. Characteristics sample in the study could be seen in Table I that, results in analysis to a distinctive sample of them age mother, age pregnancy, BMI and parity-based on group Mother pregnant term without HIV infection and mother pregnant aterm infected with HIV get ART treatment six months show that no there is the difference significant (p > 0.05).

The normality test of the data with the Shapiro- Wilk test shows distributed AIF expression is not normal (p-value < 0.05). A bivariate test is done with a parametric test using the Mann-Whitney test. The analysis could see in Table II.

TABLE I: CHARACTERISTICS SAMPLE BASED ON MOTHER'S AGE, GESTATIONAL AGE, BMI AND PARITY

Characteristic	Without HIV	HIV with ART 6 months	P-value
Maternal age	27.35±5.42	29.40±4.09	0.052
Gestational age	37.85±0.81	37.70±0.65	0.598
BMI	21.55±1.37	20.92±1.65	0.137
Parity	0.95±1.05	1.45±1.14	0.208

TABLE II: CHARACTERISTICS SAMPLE BASED ON MOTHER'S AGE, GESTATIONAL AGE, BMI AND PARITY

Variable	Without HIV	HIV with ART 6 months	P-value
AIF expression Mean (±SD)	126.75±61.4	162±52.5	0.003

Analysis results show a lower average AIF expression between Mother pregnant term infected with HIV getting ART treatment for six months and an aterm mother pregnant without HIV infection. The average AIF expression is significantly higher in the placenta. Mother pregnant aterm infected with HIV get ART treatment for six months is by 162±52.5 compared to with Mother pregnant term without HIV infection was 126.75±61.4. Determination of the cut-off value of AIF expression in the study, we use curve Receiver Operating Characteristics (ROC). ROC curve becomes reference mark limit predictor in mother pregnant, where all AIF expression data will be input to a ROC curve, data is processed and determined cut off value for AIF expression

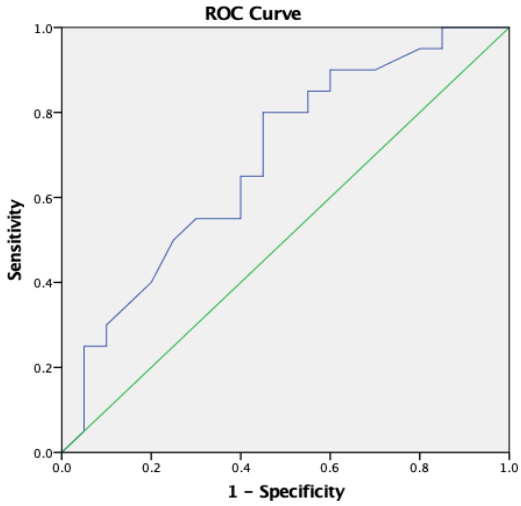

Fig. 1. ROC diagram of aif expression and status of term pregnant women.

From the calculation of the ROC curve, we get the cut-off value of the AIF level is 112.50 pg /ml, with a sensitivity of 80%, specificity of 45%, and the importance of the area under the curve (AUC) was 0.688 (95% CI 0.522 – 0.853, p-value <0.042).

TABLE III: MATERNAL PREVALENCE RATIO ATERM TO ENHANCEMENT AIF EXPRESION

AIF expression	Pregnant Mother Aterm				P R	95% CI	*p*
	Without HIV infection (n = 20)	%	HIV infection with ART 6 months (n = 20)	%			
Low	9	22.5	3	7.5	4.636	1.023- 21.004	0.0 38
High	11	27.5	17	42.5			

Based on results analysis in Table III found that aterm mother's pregnant with placental AIF expression tall and mothers pregnant time infected with HIV get ART treatment for six months there is as many as 17 people (42.5%) while Aterm pregnant woman without HIV infection as many as 11 people (27.5%). Placental AIF expression is low most in aterm mothers pregnant without HIV infection, as many as nine people (22.5%) while mothers pregnant term infected with HIV got ART treatment for six months as many as three people (7.5%). Based on analysis results statistics, Chi-square found p-value = 0.038, so it could conclude that there is meaningful relationship between placental AIF expression to mother with aterm pregnancy

Based on the analysis of the results is known that the characteristics sample of them age mother, gestational age, BMI, and several parities in mother pregnant term without HIV infection and mother with aterm pregnancy infected with HIV get ART treatment six months in the study this no own difference meaningful characteristics statistically and can compare.

Average age Mother pregnant term infected with HIV get ART treatment six months as big as 29.40 years. When compared with the average mother with aterm pregnancy without HIV infection, the average higher is 27.35 years. Analysis result age Mother study shows results no significant difference (p=0.052). That indicates that all mothers are entitled to get married and get descendants. Become HIV-positive mother no reduce correct. However, Mother with HIV infection is recommended obtained ART therapy that can give impact significant on their health during pregnant [9]. Study this take sample mother pregnant with age from 21 years and less of 31 years. That thing supported from prevalence data HIV infection in Indonesia is mostly in the group age young around 21-28 years old about 3% compared age elder [10].

Results data research on samples found that average mothers who are not infected with HIV were 37.85 weeks, and the mean age HIV - infected mothers who get ART therapy was 37.70 weeks. Analysis result obtained p-value = 0.598 so that no difference means at age pregnancy. Research results are in line with research conducted in Africa in 2016 that Mother 49% of pregnant women infected with HIV experienced incident labor < 37 weeks [11].

Research results on the number of parities obtained average Mother pregnant term infected with HIV get ART treatment six months of 1.45 and mother pregnant term without HIV infection by 0.95. The analysis results of the different tests obtained a p-value = 0.208. An aterm pregnancy mother without HIV infection and an aterm pregnancy mother infected with HIV get ART treatment for six months to show no difference means. Different from the results of research in Tanzania that explains that mothers pregnant who are not infected with HIV (40%) give birth compared to Mother infected pregnant women (5.7%). Group Mother HIV - infected pregnant women who do not treat, own more risk high. Approximately 7.4% (95% CI 6.7–8.1%) of mothers pregnant infected with HIV, with enhancement possibility of infection with more parity high compared with mothers pregnant that is not infected with HIV [12].

Research by [13] showed that placental apoptosis in the second and third trimesters was higher than in the first trimester, and apoptosis in the third trimester was also higher than in the second trimester. Mitochondria abnormal placenta and disorders from function placenta often occur in mothers who experience HIV infection receiving combination ART. AIF was initially found as a factor inducer of apoptosis [13]. Many theory report different levels of the evidence enhancement toxicity mitochondria and, in some cases maternal, fetal, and placental apoptosis.

Analysis results show lower average AIF expression significantly higher in the placenta. Mother pregnant term infected with HIV gets ART treatment for six months that, is by 162±52.5 compared with Mother pregnant term without HIV ie of 126.75±61.4. Calculation result ROC curve in research this obtained mark AIF cut-off level of 112.50 pg/ml, with sensitivity by 80%, specificity of 45%. The area under the curve (AUC) value was 0.688 (95% CI 0.522 – 0.853, p-value <0.042). Based on analysis results statistics, Chi-square found mark p = 0.038, which could conclude a meaningful relationship among AIF expression against Mother pregnant term infected with HIV get ART treatment six months. Analysis results more carry on obtained ratio prevalence of 4.636 (RP>1). This shows that ART therapy becomes a factor risk happening enhancement AIF expression in mothers pregnant. Opportunity value obtained from results analysis bivariate of 4.6 (95% CI: 1.023-21.004) means by mean high AIF expression in mothers HIV - infected pregnant and getting ART therapy has 4.6 times more chance big than Mother pregnant that is not infected with HIV.

A study conducted in Spain found results same research study. Research the show results existence correlation is positive at the limited significance observed in mothers pregnant infected with HIV. They are taking ART, and the mother is pregnant and not infected compared with NRTI treatment (p=0.044). So that could be concluded by significant use of ART in mothers expectant which HIV infection increases incident adverse perinatal outcomes in pregnancy because existence dependency development of apoptosis in NRTI toxicity [14].

Apoptosis-inducing factor (AIF) is proapoptotic, released by the mitochondria. The translocation to the cell nucleus causes irreversible DNA damage and apoptosis. ROS can also Act as a caspase-independent trigger of apoptosis; ROS mediates activation of poly- ADP- ribose polymerase-1 (PARP-1) [15]. Research conducted by [6] shows that Mother HIV - infected pregnant women show noticeable improvement, though no significant 100% increase in

apoptosis compared to healthy mothers. Mothers exposed to NRTIs showed content more mtDNA low (39.20% ± 2.78%) than women who don't infect. HIV infection itself is linked with drop content mtDNA and changes morphology and function of mitochondria. Several severe cases lead to clinical events. Various side effects in people with HIV infection receiving therapy NRTI-based have been suspected to be related to dropping function mitochondria. Zidovudine, didanosine, zalcitabine, and stavudine development programs need subtraction doses because of suspected toxicity associated with impact drugs on mitochondria [16]. Based on the data and discussion above, we could conclude that ART therapy for six months is a risk factor for increased AIF expression in pregnant women with HIV.

III. Conclusion

Based on the data and discussion above, it can be concluded that ART therapy for 6 months or more is a risk factor for increased AIF expression in term pregnant women.

References

[1] Stover J, Glaubius R, Teng Y, et al. Modeling the epidemiological impact of the UNAIDS 2025 targets to end AIDS as a public health threat by 2030. *PLoS Med.* 2021; 18(10): e1003831.
[2] Abrams EJ, Mofenson LM, Pozniak A, Lockman S, Colbers A, Belew Y, et al. Enhanced and Timely Investigation of ARVs for Use in Pregnant Women. *J Acquir Immune Defic Syndr.* 2021; 86(5): 607-615.
[3] Badru O, Dairo MD, Oladokun RE. Quality of Life of HIV Infected Children Attending the Antiretroviral Clinic, University College Hospital, Ibadan. *West Afr J Med.* 2020; 37(5): 521-527.
[4] Ekouevi DK, Stringer E, Coetzee D, Tih P, Creek T, Stinson K, et al. Health facility characteristics and their relationship to coverage of PMTCT of HIV services across four African countries: the PEARL study. *PLoS One.* 2012; 7(1): e29823.
[5] Alemu FM, Yalew AW, Fantahun M, Ashu EE. Antiretroviral Therapy and Pregnancy Outcomes in Developing Countries: A Systematic Review. *International Journal of MCH and AIDS.* 2015; 3(1): 31–43.
[6] Hernandez S, Moren C, Lopez M, Coll O, Cardellach F, Gratacos E, et al. Perinatal outcomes, mitochondrial toxicity and apoptosis in HIV-treated pregnant women and in-utero-exposed newborn. *Aids.* 2012; 26(4): 419-428.
[7] Gurugubelli Krishna R, Vishnu Bhat B. Molecular mechanisms of intrauterine growth restriction. *J Matern Fetal Neonatal Med.* 2018; 31(19): 2634-2640.
[8] Hangen E, Blomgren K, Bénit P, Kroemer G, Modjtahedi N. Life with or without AIF. *Trends in Biochemical Sciences.* 2010; 35(5): 278-287.
[9] Dadhwal V, Sharma A, Khoiwal K, Deka D, Sarkar P, Vanamail P. Pregnancy Outcomes in HIV-Infected Women: Experience from a Tertiary Care Center in India. *Int J MCH AIDS.* 2017; 6(1): 75-81.
[10] Wang N, Yuan Z, Niu W, Li Q, Guo J. Synthetic biology approach for the development of conditionally replicating HIV-1 vaccine. *J Chem Technol Biotechnol.* 2017; 92(3): 455-462.
[11] Heyderman RS, Madhi SA, French N, Cutland C, Ngwira B, Kayambo D, et al. Group B streptococcus vaccination in pregnant women with or without HIV in Africa: A non-randomised phase 2, open-label, multicentre trial. *The Lancet Infectious Diseases,* 2016; 16(5): 546–555.
[12] Habib NA, Daltveit AK, Bergsjø P, Shao J, Oneko O, Lie RT. Maternal HIV Status and Pregnancy Outcomes in Northeastern Tanzania: A Registry-Based Study. *BJOG: An International Journal of Obstetrics and Gynaecology.* 2008; 115(5): 616–624.
[13] Sevrioukova IF. Apoptosis-Inducing Factor: Structure, Function, and Redox Regulation. Antioxidants & Redox Signaling. 2011.
[14] Guitart Mampel M, Hernandez AS, Moren C, Catalan-Garcia M, Tobias E, Gonzalez-Casacuberta I, et al. Imbalance in Mitochondrial Dynamics and Apoptosis in Pregnancies Among HIV-Infected Women on HAART with Obstetric Complications. *The Journal of Antimicrobial Chemotherapy*. 2017; 72(9): 2578–2586.
[15] Artana Putra IW, Suwiyoga K. Provision of combined antiretroviral therapy in HIV-positive pregnant women and the increased risk of apoptosis-related intra-uterine growth restriction. *HIV and AIDS Review.* 2019; 18(1): 1–6.
[16] Cossarizza A, Moyle G. Antiretroviral Nucleoside and Nucleotide Analogues and Mitochondria. *Aids*. 2004; 18(2): 137–151.