

## ORIGINAL ARTICLE

# Pregnancy Profile and Infant Outcomes Among HIV Infected Women Who Delivered in Cipto Mangunkusumo Hospital

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## ABSTRAK

**Latar belakang:** infeksi HIV pada kehamilan merupakan masalah besar untuk masa depan bangsa. Virus ini dapat ditularkan ke bayi melalui kehamilan, persalinan dan selama menyusui yang memerlukan deteksi dan intervensi dini. Tujuan dari penelitian ini adalah untuk menggambarkan proses pencegahan penularan di antara pasien kami. **Metode:** ini adalah studi kohort retrospektif penularan vertikal HIV. Kriteria inklusi adalah wanita hamil dengan infeksi HIV yang menjalani perawatan antenatal di Rumah Sakit Cipto Mangunkusumo dari Januari 2013 hingga Desember 2018. Data diambil dari rekam medis, registrasi HIV dan hasil laboratorium. Data yang dimasukkan adalah demografi, risiko infeksi, data obstetri, cara persalinan, riwayat ARV, riwayat laboratorium pada ibu dan bayi. Data disajikan sebagai data deskriptif. **Hasil:** terdapat 138 wanita hamil HIV dimasukkan sebagai subyek penelitian. Sebagian besar wanita berusia 25-29 tahun (39,85%), sebagai ibu rumah tangga (41,30%), dengan riwayat lebih dari satu pasangan seksual (50,73%). Subjek sebagian besar multigravida (77,5%), kunjungan pertama ke RSCM pada trimester ketiga (98,6%), dengan riwayat perawatan antenatal >4 kali (48,6%), janin tunggal (99,3%), dan disampaikan oleh C-section (84,1%). Diagnosis HIV dilakukan selama kehamilan (73,53%), dan sudah memakai antiretroviral (ARV) selama lebih dari 6 bulan (50,7%). Didapatkan data CD4 pada 78% peserta (24% peserta dengan <200 sel/mL) dan 84% data viral load (36% dengan viral load >200). Sekitar 72,5% bayi yang lahir dengan berat lahir 2500-3500g. Hampir semua bayi menerima profilaksis ARV (97,9%) dan pemberian susu formula. PCR HIV diperiksa pada 16 bayi pada usia 6 minggu dan pada 13 bayi di usia 6 bulan. Ada 1 bayi dengan hasil viral load >400 yang segera merujuk ke klinik HIV Pediatrik. Analisis bivariat menunjukkan korelasi yang signifikan antara konsumsi ARV ibu dan hasil bayi saat lahir ( $P=0,05$ ). Tingkat CD4 ibu tidak berkorelasi secara signifikan dengan status virologi neonatal ( $P=0,12$ ). **Kesimpulan:** diagnosis HIV pada wanita hamil adalah penting, karena pemberian ARV pada awal kehamilan secara signifikan mengurangi penularan vertikal. Protokol profilaksis ARV penting untuk mencegah infeksi HIV pada bayi.

**Kata kunci:** HIV dalam kehamilan, luaran obstetrik, luaran bayi.

## ABSTRACT

**Background:** HIV infection in pregnancy is a big concern for the future of our nation. The virus can be transmitted to the baby through pregnancy, childbirth and during breastfeeding which rendering to early detection and intervention. The aim of this study was to describe the transmission prevention cascade among our patient. **Methods:**

*this was a retrospective cohort study of HIV vertical transmission. The inclusion criteria was pregnant women with HIV infection who have antenatal care in Cipto Mangunkusumo Hospital from January 2013 up to December 2018. Data was retrieved from medical record, HIV registry and laboratory results. The included data were demographic, risk of infection, obstetrical data, mode of delivery, ARV history, laboratory history in mother and infant. Data was presented as descriptive. Results: there was 138 HIV pregnant women included as study subjects. Most women were at 25-29 years old (39.85%), as housewife (41.30%), with history of more than one sexual partners (50.73%). The subjects was mostly multigravida (77.5%), first visit to RSCM in third trimester (98.6%), with history of antenatal care >4 times (48.6%), singleton fetus (99.3%), and delivered by C-section (84.1%). HIV diagnosis was done during pregnancy (73.53%), and already on antiretroviral (ARV) for more than 6 months (50.7%). There was 78% subjects with CD4 (24% subjects with <200 cells/mL) and 84% with viral load data (36% with viral load >200 copies/uL). Around 72.5% infants born with birth weight 2500-3500g. Almost all infant received ARV prophylaxis (97.9%) and formula feeding. PCR HIV was examined on 16 infant on 6 weeks of age and 13 on 6 month age. There was 1 infant with viral load results >400 copies/ml which immediately referred to Pediatric HIV clinic. Bivariate analysis showed significant correlation between maternal ARV consumption and infant result at birth (P=0.05). Maternal CD4 level was not significantly correlate with neonatal virology status (P=0.12). Conclusion: HIV diagnosis in pregnant women is important, since ARV administration on early pregnancy significantly reduce vertical transmission. ARV prophylaxis protocols is important to prevent HIV infection on infant.*

**Keywords:** HIV in pregnancy, obstetric outcome, infant outcome.

## INTRODUCTION

Human Immunodeficiency Virus (HIV)/ Acquired Immune Deficiency Syndrome (AIDS) is one of the world's growing and increasing health problems. As many as 36.7 million people live with HIV with 1.5 million deaths due to AIDS based on data until the end of 2015.<sup>1</sup> The incidence pregnant women with HIV in Asia was around 77,000 in the end of 2015.<sup>2</sup> In Indonesia, the total number of pregnant women living with HIV was 2955 in 2018.

HIV infection in pregnancy has become the most common problem in some developing countries. It has major implication for the management of pregnancy and birth.<sup>3,4</sup> The program to prevent transmission of HIV infection from mother to child (PMTCT) in Indonesia has included HIV screening as one of the standard examinations during antenatal care which widely applied in the last 5 year.<sup>5</sup> There were more than 15 million pregnant women with HIV infection in developing countries and more than 500,000 infected babies born HIV every year. Based on previous studies, it was found that 2.5% of 21,103 pregnant women diagnosed with HIV positive in 2011 in Indonesia.<sup>6</sup> Interventions to prevent HIV transmission from mother to infant are needed so as not to increase the number of HIV-infected children. Possible interventions

are achievable by preventing HIV infection in women-child-bearing age, managing pregnant women with HIV infection with antiretroviral (ARV) to achieve reduction of viral load, minimizing fetal exposure to blood and body fluids during delivery, and optimizing the health of neonates born to mothers with HIV infection. This study is about pregnant women with HIV infection and the outcomes on infants in tertiary referral hospital.

## METHODS

This was a retrospective cohort study. The population of the study were all pregnant and in labor women with HIV infection at RSUPN Cipto Mangunkusumo Jakarta from January 2013 up to December 2018. The inclusion criteria was pregnant women with HIV infection who have antenatal care, delivery and follow up in Cipto Mangunkusumo Hospital. Total sampling was used. This study has been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia (reference number: 0035/UN2.F1/ETIK/2019).

Typically patients referred to our hospital due to their obstetric problem and/or their HIV status. The obstetric care coordinated with HIV integrated service especially for HIV and comorbidity and ARV treatment. Once the

patients gave birth to their infants, they will be followed up in obstetry clinic and pediatric clinic. Most of the time they use our service up to 6 month and they transferred back to other health care near their home. Infant diagnosis was a challenge since it was not part of PMTCT service covered by government until 2017.

Data was retrieved from medical record, HIV registry and laboratory results. Maternal demographic status including age, education, employment, and number of sexual partner. The obstetric status including the parity, gestational age at admission, number of fetus, frequency of antenatal care, and delivery method. HIV status of mother including known HIV status before pregnancy, ARV consumption, CD4 level, viral load level, and the present of opportunistic infection. Status of the baby including birth weight, use of ARV prophylaxis, and infant result which was determined by at least 2 PCR RNA results on 6-8 weeks of age and on 6 month of age.

Collected data was presented as distribution and displayed in tables as number and percentages.

## RESULTS

There was a total of 138 subjects who were under Cipto Mangunkusumo Hospital care from January 2013 to December 2018. Demographic data shows that most women were at 20-35 years old (n=108, 78.3%). Fifty-eight pregnant women work as housewife (42%), 24 subjects (17.4%) work as employee and 8 subjects (5.8%) work as entrepreneur. Seventy subjects (50.7%) were on second or more marriage, 65 subjects (47.1%) married one time only, and one pregnant woman has no marriage status. Number of sexual partners was not available since it was not part of data collected on medical record.

On the obstetric status, most subjects have a history of multigravida more than 2 (n=107, 77.5%). They usually came at third trimester (n=136, 98.6%), with singleton fetus (n=137, 99.3%), already have ANC more than 4 times (n=67, 48.6%), and delivered by C-section (n=116, 84.1%). Detailed data on distribution of maternal obstetric status can be seen on **Table 1**.

Almost all (93%) diagnosed prenatally

**Table 1.** Distribution of maternal characteristics (2013-2018) (N=138).

Characteristic of Subjects	n (%)
Age of subjects	
- < 20 years	10 (7.2)
- 20-35 years	108 (78.3)
- >35 years	20 (14.5)
Employment	
- Housewife	58 (42.0)
- Employee	24 (17.4)
- Entrepreneur	8 (5.8)
- No data	48 (34.8)
Number of Marriage	
- One	65 (47.1)
- More than one	70 (50.7)
- Unmarried	1 (0.7)
- No data	2 (1.5)
Gravida	
- 1	31 (22.5)
- ≥2	107 (77.5)
Gestational age at delivery	
- Trimester 2	2 (1.4)
- Trimester 3	136 (98.6)
Fetus	
- Singleton	137 (99.3)
- Multi fetus	1 (0.7)
History of Ante Natal Care	
- No data	45 (32.6)
- ANC 1-3 times	26 (18.8)
- ANC ≥ 4 times	67 (48.6)
Delivery method	
- Vaginal delivery	22 (15.9)
- Cesarean section	116 (84.1)
Intrapartum complications	
- Premature rupture of membrane	34 (24.7)
- Preeclampsia	8 (5.8)
- No complication	96 (69.5)

(40%) and intranatal (83 cases, 53%). did not received HIV diagnosis prenatally. Ten subjects (7.3%) were diagnosed during delivery which were seen as diagnosis missed opportunity. However around 51% subjects had already on ARV for more than 6 months while the rest were less than 6 months.

There were 10 subjects with opportunistic condition. According to HIV-WHO disease stage 3-4, there was 5 with lung tuberculosis, 3 with oral candidiasis, and 1 with CMV infection.

On the other hand, there was 1 patient with Molluscum Contagiosum which categorized as HIV- WHO disease stage 1-2. There were 10 subjects with co-infection, consisted of 8 with hepatitis (B or C) and 2 subjects with condyloma acuminata. Unfortunately, data of maternal CD4 and viral load were mostly (78% and 84%) unavailable. Distribution of maternal HIV status can be seen on **Table 2**.

**Table 2.** Distribution of HIV status of the mother (2013 – 2018) (N=138)

Characteristic of Subjects	n (%)
HIV diagnosis	
- Before Pregnancy	83 (60.1)
- During pregnancy	45 (32.6)
- At Delivery	10 (7.3)
Mother's ARV	
- No ARV	32 (23.2)
- ARV <6 months	26 (18.8)
- ARV >6 months	70 (50.7)
- N/A	10 (7.3)
The last CD4 level	
- < 200sel/uL	8 (5.8)
- 200-500 sel/uL	20 (14.5)
- ≥ 500sel/UI	2 (1.5)
- N/A	108 (78.2)
The last viral load level	
- < 50 copies/mL	14 (10.2)
- 50-400 copies/mL	2 (1.4)
- 401-1000 copies/mL	0 (0.0)
- >1000 copies/mL	6 (4.3)
- N/A	116 (84.1)
WHO HIV stage	
- Stage 1-2	129 (93.4)
- Stage 3-4	9 (6.6)

Most babies born with birth weight 2500-3500 gr (n=100; 72.5%) and received ARV prophylaxis (n=135; 98%).

There was small number of pregnancy with HIV during 2013-2018; it was 1.4% in 2013, 1.3% in 2014, 1.1% in 2015, 1.6% in 2016, 1.3% in 2017, and 1.5% in 2018 among all pregnant patients in Cipto Mangunkusumo Hospital. Unfortunately we do not have infant data from 2013-2015. Therefore, we analyzed 66 infants result only from 2016-2018. There were 24 babies with viral load results at 6 weeks and 1

baby with viral load above 40 copies/mL. At 6 months of age, viral load on all the babies were undetected. Distribution of baby status can be seen on **Table 3 and 4**.

**Table 3.** Description and outcome of baby (2013-2018) (N=138)

Characteristic of Subjects	n (%)
Birth weight	
- < 1000 g	1 (0.7)
- 1000 to <1500 g	3 (2.2)
- 1500 to <2500 g	24 (17.4)
- 2500 to <3500 g	100 (72.5)
- ≥ 3500 g	10 (7.2)
Baby's ARV	
- No data	3 (2.2)
- Yes	135 (97.8)
- No	0 (0.0)

**Table 4.** Baby's viral load examination (2016-2018) (N=66).

Variables	n (%)
Baby's VL examination at 6 weeks	
- No data	42 (63.6)
- Undetected	23 (35.0)
- Detected (> 40 copies/mL)	1 (1.4)
Baby's VL examination at 6 months	
- No data	49 (74.2)
- Undetected	17 (25.8)
- Detected (> 40 copies/mL)	0 (0.0)

Bivariate analysis revealed no significant correlation between maternal ARV consumption and neonatal virology result at 6 weeks ( $P=0.077$ ) and at 6 months ( $p=0.795$ ). Maternal CD4 level was not significantly correlate with neonatal virology status at 6 weeks ( $P=0.784$ ) and 6 months ( $p=0.671$ ).

## DISCUSSION

This is the first study that try to explain the cascade of HIV transmission from mother to child who use care from intranatal through post natal in Cipto Mangunkusumo Hospital. During study time there was 138 pregnant patients with HIV, which use obstetry care in RSCM. They were mostly at 20-24 years old, which is similar to any HIV worldwide epidemy.<sup>1,2</sup> According to UNAIDS, there was approximately 36.7 million



people infected with HIV, among which 26% of new infections occurred in women aged 15-25 years old.

Women education plays an important risk in HIV infection, according to WHO that woman has less access to education and lack of employment opportunity have higher probability for HIV infection.<sup>2</sup> Around 50.8% women who live with HIV in USA were also not graduate from high school.<sup>3</sup> Unfortunately there was no data on subjects education in our study. The majority of our subjects were housewife (41.3%). This is similar with study on 109 patients with HIV, which 17% were women; 45% were unemployed.<sup>4</sup>

History of more than one sexual partner (50.73%) reflected in our data in which more than half were on their second marriage. This finding was similar with data from a research in Russia, among 758 HIV cases there were 73.9% with multi partners.<sup>5</sup> Marital relationships does not translate into less risk of HIV infection. Yang in Cambodia, shown that HIV transmission within marital relationships have increased, this was transmission from HIV-positive men to their HIV-negative spouses. Plausible factors influencing inter-spousal HIV transmission were a hierarchical male dominated society, husbands' involvement with sex workers, cultural values concerning the ideal Khmer woman and unprotected sex between an HIV infected husband and his uninfected wife.<sup>6</sup>

Our study presented a higher distribution of multigravity (77.5%), similar to a larger study in Malawi with 87.3% (2426) with >2 pregnancies. Compared with another study, a surveillance study in the United Kingdom and Ireland showed 65.7% (n:144) multigravity.<sup>7,8</sup> This numbers were associated with conception rates, which were influenced by sexual activity, procreational intent, fertility, and access to and use of contraception. A higher rate of conception rate, likely reflecting on perceived improvement in HIV treatment and vertical transmission risk.

In our study, 99.3% of our subjects were pregnant with single fetus. This result is comparable with other studies. Kreitchmann R et al in a cohort study in Latin America and the Caribbean shows 96.7% (n=1483) single

fetus pregnancy.<sup>6</sup> From another study, lower transmission rates area also seen in twin's deliveries compared with single deliveries, with twice as likely not to be infected than single born infant (OR = 0.5% CI 0.378-0.85 p=0.007), based on study by Nkenfou CN et al.<sup>9</sup> It is speculated that more care is given in multiple pregnancies. This occurs in their study, that more women with multiple pregnancy underwent prevention of mother-to-child transmission than women with single pregnancy (p=0.02).<sup>9</sup> However a more recent study concludes that twin pregnancies had lower risk of HIV transmission, provided that the mother is on highly active antiretroviral therapy (HAART) or has received effective ARV treatment in the antenatal period.<sup>10,11</sup>

Our study shows sufficient ANC visits (48.6%). ANC can be a media to ensure that pregnant mothers received ARV to their HIV condition, as a prophylaxis to mother-to-child transmission. Mothers who did not take prophylaxis during ANC were three times more likely to transmit HIV to their children compared to those who took the prophylaxis during ANC. (AOR: 3.1; 95% CI: 1.3, 0.9). Lack of prophylaxis may increase viral load and its chance to transmit HIV to their children. ANC visits itself were not statistically significant.<sup>12</sup> Our study shows higher number of ANC visits (>4 ANC visits, 48.6%, n: 67), though not significantly higher compared to less ANC visits number.

A study by UNAIDS in 2013 showed that 54% pregnant women in low and middle-income countries did not had routine HIV tests during ANC, which is an important step to prevent HIV transmission.<sup>13</sup> Therefore, in Indonesia itself, there was a low coverage of pregnant women living with HIV accessing antiretroviral medicines. Even so there is an increase from 9% in 2010 to 21% in 2016.<sup>2</sup> Which may explain, even though the HIV mothers conducts frequent ANC visits, it is not a guarantee to receiving HIV prophylaxis.

Delivery method in our study were dominated by cesarean section (84.1%, n:116), similar to a study in a tertiary care in India 91.5% mothers delivered by cesarean sections.<sup>13</sup> The mothers were counseled about the benefits and risks of the

delivery types. The majority opted for cesarean delivery to prevent perinatal transmission.<sup>14</sup> However, the total number of cesarean delivery among pregnant women with HIV in Japan and Korea relatively small with 9 pregnant women in Japan for 3 years and 15 pregnant women for 12 years.

In this study, HIV status of patients (53%) was unknown before pregnancy. This is because the HIV test has not been carried out simultaneously for screening before pregnancy in Indonesia. Data from UNAIDS obtained in 2016, around 40% of individuals living with HIV globally do not know their HIV status.<sup>2</sup> In 2013, 54% of pregnant women in low- and middle-income countries did not get an HIV test done.<sup>15</sup> Costa et al.<sup>16</sup> reported routine HIV screening during pregnancy was effective and recommended for preventing universal mother-infant transmission ( $p < 0.001$ ). But in reality many hospitals and primary health care have not implemented the program HIV screening in pregnant women is an effort to detect HIV in pregnant women.

As there was only 50.7% patients having ARV more than 6 months though almost 93% patients was diagnosed HIV before and after pregnancy, we assumed that diagnosis of HIV was not early in pregnancy or if done early did not automatically followed by having ARV. Ten patients (7.3%) also was diagnosed at delivery that translated as failure of HIV screening before pregnancy (as premarital screening) and during pregnancy (as 1st trimester screening). This could be a failure of a national program for 1st trimester screening for HIV infection in Indonesia. This could occur also because there was a not financial coverage for HIV infection screening.<sup>17</sup>

Our finding shows that ART was given more than 6 months before delivery (50%). This is similar with previous research at the Haji Adam Malik General Hospital Medan in 2012-2016 based on the duration of antiretroviral (ARV) use, the highest was found in the duration of  $>1$  year as many as 44 people (97.8%) and followed by a duration of  $<6$  months as many as 1 person (2.2%). Then HIV / AIDS pregnant women with duration of 6-12 months antiretroviral use and HIV / AIDS pregnant women who have never

taken antiretroviral drugs each have the same number of respondents as many as 0 people (0%).<sup>18</sup>

One consideration is to allow pregnant patients with HIV, among others, if the immune system is good enough, CD4 above 500.<sup>19</sup> In a previous study at the Medan Malik Haji General Hospital in Medan 2012-2016, it was found that HIV / AIDS pregnant women with a CD4 count  $<350 / \text{mm}^3$  were 22 people (48.9%). In HIV / AIDS pregnant women with a CD4 count of  $>350 / \text{mm}^3$  as many as 17 people (37.8%), and in medical records that have no data obtained as many as 6 people (13.3%).<sup>18</sup> Other studies at Midwifery Poly Sanglah Hospital Denpasar, July 2013 - June 2014, there were 25 patients who had  $\text{CD4} > 200 \text{ cells} / \text{mm}^3$  (59.5%).<sup>10</sup> In the study in RSCM in 2013-2018, it was found that HIV / AIDS pregnant women with a CD4 count  $<200 \text{ cell/uL}$  were 8 people (8%). In HIV/ AIDS pregnant women with a CD4 count of 200-500 cell/uL were 20 people (14%). In HIV/ AIDS pregnant women with a CD4 count of  $>500 \text{ cell/uL}$  were 2 cases (1%) and 108 cases (78%) cannot be counted.

Considerations to allow pregnant people with HIV include: if the immune system is good enough, viral load is minimal / undetectable (less than 1000 copies / ml).<sup>9</sup> In this study, patients with viral load level  $<50 \text{ copies} / \text{ml}$  were recorded as many as 14 patients (10%), viral load level 50-400 copies / ml as many as 2 patients (1%), and not counted as many as 116 (84%).

In our study, opportunistic infections occurred only in 20 patients (14%). HIV / AIDS is characterized as a severe immunosuppressive disease that is often associated with opportunistic infections.<sup>11</sup> Previous research at the Dr. Wahidin Sudirohusodo Hospital in Makassar during May 2011 - April 2012 shows that out of 172 cases of HIV-AIDS, 121 people (70%) suffered from opportunistic infections.<sup>12</sup> The incidence of non-opportunistic infections is lower than the incidence of opportunistic infections at Cipto Mangunkusumo Hospital, Jakarta.

In our study, 72.5% babies were born with birth weight 2500-3500 gr. This result is similar with the study by Ahmudu.<sup>21</sup> in Nigeria, which found that 81% babies born from HIV positive

mothers have birth weight more than 2500 gr. Based on study by European Collaborative Study,<sup>22</sup> neither birth weight and height was associated with HIV infection status in neonates.

ARV prophylaxis was administered on 135 babies (97.8%). There was no available data on 3 babies (2.2%), which could be because the babies were premature with neonatal problems that prohibited oral intake in the first 72 hour. According to our protocol, ARV prophylaxis is mandatory to all babies born from mother with HIV infection. This protocol is similar to WHO recommendation that a short duration of antiretroviral prophylaxis (for 4-6 weeks) is indicated for infant born to HIV infected women receiving ART, to further reduce peripartum and postpartum HIV transmission, in addition to the protection received from the mother's ARV regimen.<sup>2</sup> Regardless of infant feeding choice, infant prophylaxis provides added protection from early postpartum transmission, particularly in situations where women have started ART late in pregnancy, have less than optimal adherence to ART and have not achieved full viral suppression. Through this study, we also found there was 1 baby with positive viral load at 6 weeks age and no baby with positive viral load at 6 months age. This success story was consistent with WHO recommendation about HIV prophylaxis for babies delivered by mother with HIV infection.<sup>2</sup>

Bivariate analysis showed that antiretroviral therapy during pregnancy was associated with neonatal virology status even though with not significant result statistically. This result similar with meta-analysis from Cochrane.<sup>23</sup> A regimen combining triple antiretrovirals is most effective for preventing transmission of HIV from mothers to babies. Short courses of antiretroviral drugs are also effective for reducing mother-to-child transmission of HIV and are not associated with any safety concerns in the short-term.

## CONCLUSION

HIV screening in pregnant women is important and should be performed prenatally or during early pregnancy, in order to apply ARV prevention in mother, safe infant delivery, prophylaxis ARV in infant and negative

transmission results which we showed in this study. Our study showed that in those with completed data, prevention of transmission HIV can be done successfully. Support to completeness of PMTCT should be part of program covered by government.

## CONFLICT OF INTEREST

There is no conflict of interest in this article

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