

Original Article
Infectious Diseases,
Microbiology & Parasitology



Pregnancy Rates and Outcomes of HIV-Infected Women in Korea

Heun Choi ,¹ Moo Hyun Kim ,¹ Se Ju Lee ,¹ Eun Jin Kim ,² Woonji Lee ,¹ Wooyong Jeong ,¹ In Young Jung ,³ Jin Young Ahn ,¹ Su Jin Jeong ,¹ Nam Su Ku ,¹ Ji Hyeon Baek ,⁴ Young Hwa Choi ,² Hyo Youl Kim ,³ June Myung Kim ,¹ and Jun Yong Choi ,¹

¹Department of Internal Medicine and AIDS Research Institute, Yonsei University College of Medicine, Seoul, Korea

²Department of Infectious Diseases, Ajou University School of Medicine, Suwon, Korea

³Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea

⁴Department of Internal Medicine, Inha University School of Medicine, Incheon, Korea

OPEN ACCESS

Received: Apr 9, 2018

Accepted: Aug 16, 2018

Address for Correspondence:

Jun Yong Choi, MD, PhD

Division of Infectious Disease and AIDS Research Institute, Department of Internal Medicine, Yonsei University College of Medicine, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.

E-mail: SERAN@yuhs.ac

© 2018 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Heun Choi
<https://orcid.org/0000-0002-9622-9381>

Moo Hyun Kim
<https://orcid.org/0000-0003-3634-0296>

Se Ju Lee
<https://orcid.org/0000-0001-9779-5062>

Eun Jin Kim
<https://orcid.org/0000-0001-7008-0497>

Woonji Lee
<https://orcid.org/0000-0002-3431-3633>

Wooyong Jeong
<https://orcid.org/0000-0001-5138-8111>

In Young Jung
<https://orcid.org/0000-0002-2680-5224>

ABSTRACT

Background: Antepartum, intrapartum, and postpartum preventive measures with antiretroviral drugs, appropriate delivery methods, and discouraging breastfeeding significantly decrease the risk of mother-to-child transmission of human immunodeficiency virus (HIV) infection. Herein, we investigated the pregnancy outcomes in HIV-infected Korean women.

Methods: We retrospectively reviewed medical records of childbearing-age HIV-infected women between January 2005 and June 2017 at four tertiary care hospitals in Korea.







Results: Among a total of 95 HIV infected women of child-bearing age with 587.61 years of follow-up duration, 15 HIV-infected women experienced 21 pregnancies and delivered 16 infants. The pregnancy rate was 3.57 per 100 patient-years. Among the 21 pregnancies, five ended with an induced abortion, and 16 with childbirth including two preterm deliveries at 24 and 35 weeks of gestation, respectively. The two preterm infants had low birth weight and one of them died 10 days after delivery due to respiratory failure. Among the 14 full-term infants, one infant was small for gestational age. There were no HIV-infected infants.

Conclusion: The pregnancy rate of HIV-infected women in Korea is lower than that of the general population. Although several adverse pregnancy outcomes were observed, mother-to-child transmission of HIV infection was successfully prevented with effective preventive measures.

Keywords: HIV; Mother-to-Child Transmission; Pregnancy Outcomes; Pregnancy Rate

INTRODUCTION

Human immunodeficiency virus (HIV) can be transmitted from mother to child. But, with effective preventive measures including universal prenatal HIV counseling and testing, preconception care, antiretroviral prophylaxis, scheduled cesarean section delivery, and avoidance of breastfeeding, the perinatal transmission rate has decreased to < 2% among HIV-exposed infants in developed countries.¹⁻³ Even though preventive measures could significantly lower the transmission rate, HIV-infected women, particularly those with advanced disease, may have adverse pregnancy outcomes such as preterm birth, low birth weight, and neonatal

Jin Young Ahn 
<https://orcid.org/0000-0002-3740-2826>
 Su Jin Jeong 
<https://orcid.org/0000-0003-4025-4542>
 Nam Su Ku 
<https://orcid.org/0000-0002-9717-4327>
 Ji Hyeon Baek 
<https://orcid.org/0000-0002-1783-6950>
 Young Hwa Choi 
<https://orcid.org/0000-0001-5254-3101>
 Hyo Youl Kim 
<https://orcid.org/0000-0001-7827-902X>
 June Myung Kim 
<https://orcid.org/0000-0002-0337-8573>
 Jun Yong Choi 
<https://orcid.org/0000-0002-2775-3315>

Funding

This work was supported by the BioNano Health-Guard Research Center funded by the Ministry of Science, ICT, and Future Planning of Korea as a Global Frontier Project (grant H-GUARD_2013M3A6B2078953); a grant from the Ministry of Health & Welfare, Republic of Korea (grant number: H114C1324); a faculty research grant of Yonsei University College of Medicine (6-2015-0153); and the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2013R1A1A2005412).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Choi JY. Data curation: Choi H, Kim MH, Lee SJ, Kim EJ, Lee W, Jeong W, Jung IY, Ahn JY, Jeong SJ, Ku NS, Baek JH, Choi YH, Kim HY. Formal analysis: Choi H, Choi JY. Funding acquisition: Choi JY. Validation: Kim JM. Writing - original draft: Choi H, Choi JY. Writing - review & editing: Choi H, Choi JY.

death.⁴⁻⁶ Although there have been single-center studies about the prevention of mother-to-child HIV transmission and few mother-to-child transmission cases have been reported by Korea Centers for Disease Control and Prevention (KCDC), a multicenter-based study on pregnancy rate and adverse pregnancy outcomes of HIV-infected women has not been performed, yet.⁷⁻⁹ This study investigated the pregnancy rates and outcomes in HIV-infected Korean women.

METHODS

Study sites and data collection

We retrospectively reviewed medical records of childbearing-aged (18–50 years) HIV-infected women between January 2005 and June 2017 at four tertiary care hospitals: they were located at Seoul (with 2,400 beds), Suwon (with 1,000 beds), Incheon (with 900 beds) and Wonju (with 850 beds).

HIV-infected mother

Data were collected on maternal status including age, CD4⁺ cell counts, HIV viral loads, and antiretroviral treatment regimens at the time of the 3rd trimester of pregnancy; preventive measures including antepartum antiretroviral treatment, zidovudine intravenous injection during delivery, cesarean section delivery, avoidance of breastfeeding, and administration of zidovudine syrup to the newborn; and birth outcomes. The number of weeks of pregnancy was determined by examinations at the Department of Obstetrics and Gynecology of each hospital. The follow-up duration was calculated from the first date of visit to the last date of visit.

HIV-exposed infant

HIV viral load and HIV antigen/antibody for delivered children were tested within 48 hours, at one–two months, at three–six months, and at 18 months after birth. Quantitative polymerase chain reaction (PCR) assay was performed for measurement of HIV viral load.

Definition

A birth earlier than 37 weeks was considered preterm, and birth weight lower than 2,500 g was considered low birth weight. Babies with a body weight below the 10th percentile for their age and sex were considered small for gestational age.¹⁰ Neonatal death was defined as death within 28 days of life. If HIV viral loads were negative three consecutive times within six months and HIV antigen/antibody test was also negative at 18 months, the newborn was considered HIV-negative.

Ethics statement

This study was approved by the Institutional Review Board of Severance Hospital (4-2017-0556) which waived informed consent because of its retrospective design.

RESULTS

There were a total of 95 childbearing-aged HIV-infected women and the total follow-up duration was 587.61 years. The pregnancy rate was 3.57 per 100 patient-years.

Among the 15 HIV-infected women, 21 pregnancies were recorded. Five pregnancies from four HIV-infected women were terminated with induced abortions. Fourteen HIV-infected

Table 1. Maternal status and pregnancy outcomes among 21 pregnancies

Characteristics	Values
Age, yr	28.9 ± 3.4 (25–39)
Marital status, No. (%)	
Married	17 (81.0)
Never married	3 (14.3)
Separated	1 (4.8)
Pregnancy outcome, No. (%)	
Live birth	16 (76.2)
Stillbirth	0 (0)
Spontaneous abortion	0 (0)
Induced abortion ^a	5 (23.8)

Data are presented as mean ± standard deviation (range).

^aOne ectopic pregnancy was included.

women gave birth to a total of 16 children: two HIV-infected women gave birth twice during the study period. Two out of 16 children were born earlier than 37 weeks.

Table 1 shows maternal status and pregnancy outcomes among 21 pregnancies. The mean age of the mothers was 28.9 ± 3.4 (range, 25–39) years. As for marital status at the time of pregnancy, 17 (81.0%) were married, three (14.3%) were never married, and one (4.8%) was divorced. The partner's HIV status was positive in five (23.8%), negative in 12 (57.1%), and unknown in four (19.0%) pregnancies.

The median CD4⁺ T cell counts of HIV-infected women who delivered children were 507 ± 58 (110–804) cells/μL in their 3rd trimester (**Table 2**). The antepartum viral loads in 3rd trimester were suppressed (< 50 copies/mL) in 12 (75%) deliveries, two of the mothers who were unsuppressed (50–1,000 copies/mL) received antiretroviral therapy (ART) before conception and the other two mothers (10,000–100,000 copies/mL) received ART from 3rd trimester. Antepartum ART was given to all of 16 pregnancies and half of them was started

Table 2. Maternal status and preventive measures among 16 pregnancies with live birth

Characteristics	Values
Age, yr	29.5 ± 0.9 (25–39)
CD4 ⁺ T cell counts in 3rd trimester, cells/μL	507 ± 58 (110–804)
HIV viral loads in 3rd trimester, copies/mL, No. (%)	
< 50	12 (75)
50–1,000	2 (12.5)
10,000–100,000	2 (12.5)
100,000–1,000,000	0 (0)
Dates starting antiretroviral treatment, No. (%)	
Before conception	8 (50)
1st trimester	2 (12.5)
2nd trimester	3 (18.8)
3rd trimester	3 (18.8)
Antepartum antiretroviral treatment, No. (%)	
PI-based regimen	12 (75)
NNRTI-based regimen	1 (6.3)
INSTI-based regimen	1 (6.3)
Zidovudine monotherapy	1 (6.3)
Others	1 (6.3)
Intravenous zidovudine injection during delivery, No. (%)	16 (100)
Cesarean section delivery, No. (%)	15 (93.8)
Zidovudine syrup for infants, No. (%)	16 (100)

Data are presented as mean ± standard deviation (range).

PI = protease inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, INSTI = integrase strand transfer inhibitor.

Table 3. Adverse outcomes among 16 pregnancies with live birth

Adverse birth outcomes, No. of pregnancies (%)	Values
Preterm delivery ^a	2 (12.5)
Low birth weight ^a	2 (12.5)
Small for gestational age	1 (6.3)
Neonatal death ^a	1 (6.3)
Mother-to-child transmission of HIV infection	0 (0)

^aOne infant was included in each variable.

before conception. As for antepartum ART regimens, 12 (75%) received protease inhibitor (PI) based ART. One zidovudine monotherapy was given in 2005. Intravenous zidovudine was administered to all mothers during delivery. Fifteen (95%) infants were delivered by cesarean sections. Zidovudine syrup was administered for six weeks and breastfeeding was discouraged for all the infants. We followed-up 13 babies with HIV RNA PCR and antigen/antibody test until 18 months and no infant was confirmed as positive for HIV infection.

Among the 16 live births, there were three infants with adverse outcomes (**Table 3**). The three infants came from different mothers. One preterm infant was delivered by unplanned cesarean section due to vaginal bleeding at 24 weeks of gestation, with a birth weight of 870 g. His mother did not have any comorbidities except HIV infection with suppressed viral loads and CD4⁺ T cell counts of 770 cells/ μ L. The baby died 10 days after delivery due to respiratory distress. Another preterm infant was also delivered by cesarean section due to vaginal bleeding at 35 weeks of gestation. Her birth weight was 2,280 g and her mother also did not have any comorbidities except HIV infection with suppressed viral loads. Thus, these two preterm infants had low birth weights. Another infant with small for gestational age and was delivered by scheduled cesarean section at 38 weeks of gestation. Her birth weight was 2,620 g. Her mother also had no comorbidities other than HIV infection with suppressed viral loads.

DISCUSSION

HIV-infected women tend to avoid pregnancy through contraception and abstinence because of anticipated adverse outcomes such as preterm birth, low birth weight, small for gestational age, stillbirth, neonatal death, and mother-to-child transmission.^{7,11,12} However, the pregnancy rate has increased, which may be attributed to the widespread application of highly active antiretroviral therapy (HAART), which has resulted in a decrease in mother-to-child transmission.^{1,13,14} In our study population, the pregnancy rate of HIV-infected women of childbearing age was 3.57 per 100 patient-years, which was lower than the rates reported by other countries (7.4 in the United States and 7.8 in sub-Saharan Africa).^{11,14} The birth rate of child-bearing aged women (20–49 years) in the Korean general population is generally higher than HIV-infected women: 3.71 per 100 woman-years in 2005 and 4.03 per 100 woman-years in 2015, respectively.¹⁵ The pregnancy rate of the general population would be higher than the birth rate. We could not evaluate the effect of scaling up of HAART because the pregnancy rate of HIV-infected women in Korea was not previously reported. There were 16 live births and five induced abortions among 21 pregnancies. One induced abortion was therapeutic termination due to ectopic pregnancy. The induced abortion of HIV-infected women is known to be more prevalent than non-infected women,¹⁶ and our study showed a high rate (23.8%) of induced abortion among HIV-infected pregnant women in Korea. Exceeding concerns of mother-to-child transmission could give rise to the low rate of pregnancy and high rate of induced abortion.

To prevent mother-to-child transmission, antepartum, intrapartum, and postpartum preventive measures are recommended. All pregnant women are to receive HIV screening tests, ART, avoid breastfeeding, and health care providers must try to minimize exposure of the fetus to mother's blood and body fluids.^{1,2} According to our result, all mentioned preventive measures seem to be provided properly. All mothers received antepartum ART, zidovudine intravenous infusion during delivery. Furthermore, all infants received zidovudine therapy after delivery. As a result, mother-to-child transmission was not observed in this study. Two mothers with HIV RNA > 10,000 copies/mL at the 3rd trimester underwent scheduled cesarean section and their children were not infected with HIV. According to a KCDC report, there were 560 HIV-infected women in childbearing age and four mother-to-child HIV transmission cases occurred between 2005 and 2015.⁹ Considering the KCDC report and pregnancy rate among HIV-infected women from our study (3.57 per 100 patient-years), the presumptive rate of mother-to-children transmission is estimated to be 1.82% ($\frac{4}{560 \times 11 \times 0.0357} \times 100$), and it is considered to be eliminated by World Health Organization (WHO) criteria.¹⁷

A total of three (18.8%) HIV-exposed infants showed adverse outcomes: two (12.5%) preterm births, two (12.5%) low birth weight, one (6.3%) small for gestational age, and one (6.3%) neonatal death. According to a Korean study, the rate of preterm birth and low birth weight were 5.9% and 5.0%, respectively, in 2010.¹⁸ Although the rate of adverse birth outcomes was higher than that of the general population, the rates were similar to the incidence in other countries of HIV-infected women, with a preterm birth rate of 13.0% in the United Kingdom and a 23.7% preterm birth rate, an 18.4% small for gestational age rate and a 2.3% neonatal mortality rate in Botswana.^{4,12,19,20} A meta-analysis reported increased risk for preterm birth, low birth weight, small for gestational age, and stillbirth in women who have not received ART compared those who received ART.¹² Although all mothers of our study received ART, 50% of mothers started ART after conception, and 25% of mothers had unsuppressed viral loads in 3rd trimester. Fortunately, there was no adverse outcome in infants from mothers with unsuppressed viral loads in 3rd trimester in the present study. In fact, high viral load is a known risk factor for preterm birth and low birth weight.⁵ Therefore, more efforts are necessary to screen and treat HIV infection for pregnant women in order to prevent adverse birth outcomes. Several studies reported that HAART or a PI-based regimen is associated with preterm birth, and it was also reported that administration of a PI-based regimen in the first trimester increases the risk of preterm birth.^{6,20,21} Nine pregnant women who were treated with a PI-based regimen before pregnancy or during the first trimester were included in this study. Two of them (22%) had a preterm birth. Since the number of subjects was too small, we could not identify any significant association. On the other hand, there are few studies that show that ART is associated with small for gestational age.^{20,22} The association of adverse pregnancy outcomes with nevirapine has been clearly demonstrated and is now not recommended due to its toxicity.²³ In this study, no mother took nevirapine.

There are several limitations to our study. First, the small number of subjects limits the generalizability of our study, and its retrospective nature limits our ability to make any causal determinations. There could be women who were using contraceptive methods, but the relationship between contraceptive methods and outcomes could not be evaluated due to the retrospective nature of this study. In addition, induced abortion or other pregnancy outcomes might have been done in other clinics and not reported to the study hospital. So, the pregnancy rate might be underestimated and maternal mortality and complications may have been overlooked. The pregnancy rate of HIV-infected women in Korea appears to be

lower than that of the general population. Although we observed several adverse outcomes including preterm delivery, low birth weight, small for gestational age, and neonatal death, mother-to-child transmission of HIV infection was successfully prevented with effective preventive measures. Further interventions to improve pregnancy outcomes for HIV-infected women are needed.

REFERENCES

1. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiters A, Lyall H, Tookey PA. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. *AIDS* 2008;22(8):973-81.
[PUBMED](#) | [CROSSREF](#)
2. Nesheim S, Taylor A, Lampe MA, Kilmarx PH, Fitz Harris L, Whitmore S, et al. A framework for elimination of perinatal transmission of HIV in the United States. *Pediatrics* 2012;130(4):738-44.
[PUBMED](#) | [CROSSREF](#)
3. Govender T, Coovadia H. Eliminating mother to child transmission of HIV-1 and keeping mothers alive: recent progress. *J Infect* 2014;68 Suppl 1:S57-62.
[PUBMED](#) | [CROSSREF](#)
4. Brocklehurst P, French R. The association between maternal HIV infection and perinatal outcome: a systematic review of the literature and meta-analysis. *Br J Obstet Gynaecol* 1998;105(8):836-48.
[PUBMED](#) | [CROSSREF](#)
5. Kim HY, Kasonde P, Mwiya M, Thea DM, Kankasa C, Sinkala M, et al. Pregnancy loss and role of infant HIV status on perinatal mortality among HIV-infected women. *BMC Pediatr* 2012;12:138.
[PUBMED](#) | [CROSSREF](#)
6. Malaba TR, Phillips T, Le Roux S, Brittain K, Zerbe A, Petro G, et al. Antiretroviral therapy use during pregnancy and adverse birth outcomes in South African women. *Int J Epidemiol* 2017;46(5):1678-89.
[PUBMED](#) | [CROSSREF](#)
7. Seol YM, Rheu EK, Park SE, Kim GH, Lee SH, Kwak IS, et al. Prevention of Mother-to-child Transmission of HIV: experiences from an University Teaching Hospital. *Infect Chemother* 2007;39(2):95-9.
8. Park JW, Yang TW, Kim YK, Choi BM, Kim HJ, Park DW. Ten years of experience in the prevention of mother-to-child human immunodeficiency virus transmission in a university teaching hospital. *Korean J Pediatr* 2014;57(3):117-24.
[PUBMED](#) | [CROSSREF](#)
9. Korea Centers for Disease Control and Prevention. *Annual Report on the Notified HIV/AIDS in Korea 2015*. Cheongju: Korea Centers for Disease Control and Prevention; 2016.
10. Lim JS, Lim SW, Ahn JH, Song BS, Shim KS, Hwang IT. New Korean reference for birth weight by gestational age and sex: data from the Korean Statistical Information Service (2008–2012). *Ann Pediatr Endocrinol Metab* 2014;19(3):146-53.
[PUBMED](#) | [CROSSREF](#)
11. Massad LS, Springer G, Jacobson L, Watts H, Anastos K, Korn A, et al. Pregnancy rates and predictors of conception, miscarriage and abortion in US women with HIV. *AIDS* 2004;18(2):281-6.
[PUBMED](#) | [CROSSREF](#)
12. Wedi CO, Kirtley S, Hopewell S, Corrigan R, Kennedy SH, Hemelaar J. Perinatal outcomes associated with maternal HIV infection: a systematic review and meta-analysis. *Lancet HIV* 2016;3(1):e33-48.
[PUBMED](#) | [CROSSREF](#)
13. Huntington SE, Thorne C, Bansi LK, Anderson J, Newell ML, Taylor GP, et al. Predictors of pregnancy and changes in pregnancy incidence among HIV-positive women accessing HIV clinical care. *AIDS* 2013;27(1):95-103.
[PUBMED](#) | [CROSSREF](#)
14. Myer L, Carter RJ, Katyal M, Toro P, El-Sadr WM, Abrams EJ. Impact of antiretroviral therapy on incidence of pregnancy among HIV-infected women in Sub-Saharan Africa: a cohort study. *PLoS Med* 2010;7(2):e1000229.
[PUBMED](#) | [CROSSREF](#)
15. Korean Statistical Information Service. Vital statistics of Korea. http://kosis.kr/statHtml/statHtml.do?orgId=101&tblId=DT_1IN1503&conn_path=I2. Updated 2018. Accessed November 21, 2017.

16. Pilecco FB, Teixeira LB, Vigo A, Dewey ME, Knauth DR. Lifetime induced abortion: a comparison between women living and not living with HIV. *PLoS One* 2014;9(4):e95570.
[PUBMED](#) | [CROSSREF](#)
17. World Health Organization. *Global Guidance on Criteria and Processes for Validation: Elimination of Mother-To-Child Transmission of HIV and Syphilis Monitoring*. Geneva: World Health Organization; 2014.
18. Chung SH, Choi YS, Bae CW. Changes in neonatal epidemiology during the last 3 decades in Korea. *Neonatal Med* 2013;20(3):249-57.
[CROSSREF](#)
19. Short CE, Douglas M, Smith JH, Taylor GP. Preterm delivery risk in women initiating antiretroviral therapy to prevent HIV mother-to-child transmission. *HIV Med* 2014;15(4):233-8.
[PUBMED](#) | [CROSSREF](#)
20. Watts DH, Williams PL, Kacanek D, Griner R, Rich K, Hazra R, et al. Combination antiretroviral use and preterm birth. *J Infect Dis* 2013;207(4):612-21.
[PUBMED](#) | [CROSSREF](#)
21. Uthman OA, Nachega JB, Anderson J, Kanters S, Mills EJ, Renaud F, et al. Timing of initiation of antiretroviral therapy and adverse pregnancy outcomes: a systematic review and meta-analysis. *Lancet HIV* 2017;4(1):e21-30.
[PUBMED](#) | [CROSSREF](#)
22. Chen JY, Ribaud HJ, Souda S, Parekh N, Ogwu A, Lockman S, et al. Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana. *J Infect Dis* 2012;206(11):1695-705.
[PUBMED](#) | [CROSSREF](#)
23. Mugabo P, Els I, Smith J, Rabie H, Smith P, Mirochnick M, et al. Nevirapine plasma concentrations in premature infants exposed to single-dose nevirapine for prevention of mother-to-child transmission of HIV-1. *S Afr Med J* 2011;101(9):655-8.
[PUBMED](#)