ORIGINAL ARTICLE

Birth Outcomes and Retention in Care among HIV-Exposed Infants at a Tertiary Care Hospital in Thailand

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Objective: To describe birth outcomes and retention in care at 6 and 18 months after birth and identify associated factors among pregnant women living with HIV and their infants.

Materials and Methods: A retrospective descriptive study was conducted at a large tertiary care center in Bangkok, Thailand. Retention in care among postpartum women living with HIV was defined as the follow-up duration after delivery at an HIV clinic. High risk of HIV vertical transmission was defined according to a standard guideline.

Results: Between January 2015 and December 2019, 153 pregnant women living with HIV with 154 live births of HIV-exposed infants were reviewed and categorized into 132 (86%) low risk and 21 (14%) high risk groups. The overall median maternal age was 31 years (IQR 26 to 35). High-risk mothers were younger at a median age of 25 years versus 32 years (p=0.009). Nineteen (12%) of the mothers experienced premature labor and 31 (20%) of the infants had low birth weight. Early infant diagnosis was completed among 143 (93%) of the HIV-exposed infants, with one child infected with HIV. Overall HIV transmission rate was 0.6% (95% CI 0.1 to 3.5). Pregnant women with detectable HIV RNA before delivery had a higher risk of low-birth-weight infants (aOR 3.19, 95% CI 1.12 to 9.04). Retention in care of postpartum women was 85.0% (95% CI 78.3 to 89.7) and 76.5% (95% CI 68.9 to 82.4), at 6 and 18 months after delivery, respectively. Mothers who initiated antiretroviral therapy (ART) before pregnancy had a higher probability of retention in care at 85.5% (95% CI 76.0 to 91.5) compared to mothers who initiated ARV during pregnancy or after delivery at 65.7% (95% CI 53.3 to 75.5, p=0.012).

Conclusion: High-risk HIV-exposed infants were at higher risk of loss in retention of care. Developing an effective program for this target population is needed.

Keywords: Birth outcomes; HIV; HIV-exposed infant; Retention

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A major route in acquired childhood human immunodeficiency virus (HIV) infection is the vertical transmission of HIV. Some studies have found that adverse birth outcomes, such as increased preterm deliveries, stillbirths, and low birth weight, occurred more frequently among HIV-exposed infants[1,2]. The meta-analysis demonstrated that maternal HIV infection is significantly associated with preterm birth, with a relative risk (RR) of 1.50, and low birth weight (RR 1.62)[3]. The overall pooled prevalence of preterm birth and low birth weight in women living with HIV was 14.1% and 13.7%, respectively[4]. Effective prevention of mother-to-child transmission (PMTCT) programs can reduce HIV vertical transmission rates and increase retention in care[5].

In Thailand, the national policy in PMTCT of HIV has been implemented to reduce the MTCT rate since year 2000 with offering a short-course zidovudine (AZT) regimen to pregnant women living with HIV. In 2004, a single-dose of nevirapine was added to the women during intrapartum period and their newborns. Since 2010, highly active antiretroviral therapy (HAART) has been given during pregnancy and continuing through the postpartum period. In 2014, Thailand began offering HAART to all people living with HIV and guidelines were modified to classify

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infants depending on their risk classification. HIV couples counseling, voluntary testing, infant HIV testing, and monitoring systems were also provided[6]. The policy also included primary prevention of HIV among women of childbearing age, prevention of unintended pregnancies in women living with HIV, prevention of vertical transmission, and provision of appropriate treatment, care, and support to women and children living with HIV and their families[7].

Thailand has greatly reduced HIV vertical transmission with the rate decreasing from 24.2% in 1994 to 1.9% in 2015 and the use of antiretroviral therapy (ART) has increased from 64.6% in 1998 to 95.6% in 2015[6]. Thailand's national AIDS strategy aims to reduce the vertical transmission rate to less than 1% by 2030 with no new perinatal HIV infection. To reach this goal, Thailand needs to encourage the prevention of HIV vertical transmission and enhance monitoring of PMTCT services. Early infant diagnosis has been implemented in Thailand since 2006, using HIV DNA polymerase chain reaction (PCR) testing to confirm HIV status[8]. Currently, data on birth outcomes in HIV-exposed infant and retention in care of postpartum women living with HIV and their infants in Thailand remain limited. The primary objective of the present study was to describe unfavorable birth outcomes such as premature delivery, low birth weight, HIV acquisition, and associated factors among HIV-exposed infants. Secondary objectives were to determine retention in HIV care among postpartum women at 6 and 18 months after delivery.

Materials and Methods

Study design

The authors conducted a retrospective descriptive study at King Chulalongkorn Memorial Hospital (KCMH), a large tertiary care center in Bangkok, Thailand that deliveries approximately 3,000 live births per year. The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB 337/64).

Study participants

Inclusion criteria were pregnant women living with HIV who visited the antenatal care clinic at KCMH between January 1, 2015 and December 31, 2019 and their infants. Cases were identified from the hospital medical database using the ICD-10 code of "R751, HIV Postpartum", "R752, HIV Pregnancy", or "Z206, Contact with and exposure to HIV" and from the database of the Department of Obstetrics Gynecology and Division of Pediatric Infectious Disease at KCMH. Infants and their mothers whose primary outcomes could not be collected from the database were excluded.

Data collection

Data was collected from hospital electronic medical records (EMR). The National AIDS Program Plus (NAP Plus) was also used to review follow-up and laboratory data of women living with HIV. Data collected included maternal data, pregnancy data, delivery outcomes, and infant data. Maternal data included demographic data, HIV status, ART use, disclosure status to husband, and postpartum follow-up. Pregnancy data included co-infection (syphilis or hepatitis B) during pregnancy, perinatal, and postpartum complications. Delivery outcomes included gestational age, mode of delivery, pregnancy outcomes such as preterm delivery, stillbirth, and abortion. Infant data included birth weight, birth defect, and HIV transmission.

Definitions

Preterm infant was defined as an infant born alive before 37 weeks of gestation. Low birth weight was defined as a birth weight of less than 2,500 grams. Stillbirth was defined as the death or loss of a baby before or during delivery. Birth asphyxia was defined as a failure to initiate spontaneous respiration and/or 1-minute Apgar score of less than 7[9].

Infants born to HIV-infected mothers were stratified according to HIV acquisition risk into low-risk and high-risk groups according to the Thai National guidelines[10]. The definition of low risk of HIV transmission includes infants whose mother received ART during pregnancy and either have documentation of undetectable plasma HIV RNA near the time of delivery or received ART for at least 12 weeks with good adherence[10]. The definition of high risk of HIV transmission includes either an infant whose mother has HIV RNA greater than 50 copies/mL near the time of delivery or received ART less than 12 weeks during antepartum or a mother has a report of poor ART adherence during pregnancy. According to Thai guidelines, low risk HIV-exposed infants received AZT 4 mg/kg twice daily for four to six weeks, while high risk HIV-exposed infants received AZT 4 mg/kg twice daily plus lamivudine 2 mg/kg twice daily and nevirapine 4 mg/kg once daily for four to six weeks.

Early infant diagnosis was performed using HIV DNA PCR for low risk HIV-exposed infants at age 1

and 2 to 4 months, and high risk HIV-exposed infants at birth, 1, 2, and 4 months. HIV antibody testing was performed at age 18 months. Definition of HIV status in infants[10] were as follows, 1) infants were categorized as not infected if they had two negative HIV DNA PCR tests with one obtained at age 1 month or later and one at age 4 months or later, and 2) infants were categorized as infected if HIV DNA PCR were positive on at least two separate occasions[11].

Retention in care among postpartum women living with HIV was defined as the duration from delivery to the last clinic visit during 18 months after delivery at any hospital. Retention in care among HIV-exposed infants was defined as completing follow-up visits to confirm HIV diagnosis at 4 months of age.

Data analysis and statistics

Continuous variables were described by mean and standard deviation (SD) or median and interquartile range (IQR). Categorical data were described using frequencies and percentages. The authors tested the association of independent variables and birth outcomes including low birth weight, preterm labor, and birth asphyxia using chi-square test or Fisher's exact test, as appropriate. Logistic regression was used to identify factors associated with attendance at follow-up clinic and retention in care of HIV-exposed infants. Kaplan-Meier survival curve analysis was used to estimate the cumulative probability of retention in care of postpartum women living with HIV. Cox regression was used to calculate the hazard ratio of risk factors on retention in care. Multicollinearity was assessed before including covariates into the multivariate model. A forward stepwise selection method was used for variable selection in the multivariate analysis. At each step the variable with the highest p-value was deleted from the subsequent model until all remaining terms were significant at p-value less than 0.10. Statistical significance was identified using a two-sided p-value less than 0.05. Statistical analysis was performed with Stata Statistical Software, version 16 (StataCorp LLC, College Station, TX, USA).

Results

One hundred fifty-three pregnant women living with HIV including 132 at low risk and 21 at high risk of transmission with 154 live birth HIV-exposed infants were reviewed. No data was excluded. Demographic and clinical characteristics are shown in Table 1 and 2. Overall, the median maternal age was 31 years (IQR 26 to 35). In the high-risk group, mothers were younger with a median age of 25 years versus 32 years (p=0.009). Among 153 pregnant women living with HIV, 97 (63%) were diagnosed with HIV infection before pregnancy. Timing of ART initiation among pregnant women living with HIV included 83 (54%) before pregnancy, 67 (44%) during pregnancy, and three (2%) during or after delivery. The most common maternal ART regimens in 109 patients (71%) were two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Pregnancy data and delivery outcomes

Syphilis and HBV co-infection were detected in nine (6%) and three (2%) of pregnant women, respectively. Pregnancy complications occurred in 25 women (16.3%), including five (3.2%) preeclampsia, four (2.6%) premature rupture of membrane, and five (3.5%) other complications. The median of CD4 closest to delivery were 463 cells/mm^3 (IQR 319 to 608). From 149 pregnant women with available data on plasma HIV RNA at near delivery, 124 (83%) reported plasma HIV RNA of less than 50 copies/mL, and 25 (17%) had median of plasma HIV RNA of 342 copies/mL (IQR 67 to 7,372). Two of the pregnant women with a history of HIV RNA below 50 copies/mL before delivery were classified in the high risk group, included one diagnosed with drug resistance and a second showed an HIV RNA of 47,948 copies/mL on the day after delivery.

Infant data and outcomes

Baseline characteristics of 154 infants, including one set of twins, were shown in Table 2. There were 133 infants (86%) in the low risk group and 21 infants (14%) in the high risk of HIV acquisition groups. The median gestational age and birth weight of all births was 38 weeks (IQR 37 to 39), and 2,945 grams (IQR 2,578 to 3,321), respectively. Overall, 19 HIV-exposed infants (12.4%) were born prematurely before 37 weeks of pregnancy. Thirty-one infants (20%) had low birth weight, and 10 infants (6.5%) experienced birth asphyxia. Of the 154 HIV-exposed infants, one died due to birth asphyxia. One hundred forty-three infants (93%) completed HIV DNA PCR testing at four months of age. Eight infants (5%) had only one negative HIV PCR test, and two infants (1%) were lost to follow up after birth. One high-risk HIV-exposed infant had positive HIV DNA PCR test at age 1 month and initiated ART promptly. The overall

Table 1. Baseline characteristics of 153 pregnant women living with HIV stratified by risk of transmission

Mothers	Total (n=153)	Low risk group (n=132)	High risk group (n=21)	p-value
Gestational age at delivery (weeks); median (IQR)	38 (37 to 39)	38 (37 to 39)	38 (37 to 39)	0.85†
Maternal age (years); median (IQR)	31 (26 to 35)	32 (27 to 36)	25 (20 to 30.5)	0.009†
Premature labor (GA <37 weeks); n (%)	19 (12.4)	16 (12.1)	3 (14.3)	0.78
Mode of delivery, cesarean section; n (%)	79 (51.7)	67 (50.8)	12 (57.1)	0.58
Received antiretroviral therapy before labor; n (%)	150 (98)	132 (100)	18 (85.7)	<0.001
ARV regimen; n (%)				
NRTI-backbone				0.27
• Zidovudine plus xTC	43 (28.7)	40 (30.3)	3 (16.7)	
• Tenofovir plus xTC	107 (71.3)	92 (69.7)	15 (83.3)	
NNRTI-based				0.17
• Efavirenz	84 (56.0)	74 (56.1)	10 (55.6)	
• Nevirapine	21 (14.0)	21 (15.9)	0 (0.0)	
• Rilpivirine	2 (1.3)	2 (1.5)	0 (0.0)	
PI-based	43 (28.7)	35 (26.5)	8 (44.4)	
Maternal HIV RNA <50 copies/mL before delivery*; n (%)	129 (86.6)	127 (97.7)	2 (10.5)	<0.001
Timing of ART initiation; n (%)				<0.001
Prior to current pregnancy	83 (54.2)	81 (61.4)	2 (9.5)	
During current pregnancy	67 (43.8)	51 (38.6)	16 (76.2)	
At delivery (no antenatal care)	1 (0.7)	-	1 (4.8)	
No ART (incidence case)	2 (1.3)	-	2 (9.5)	

xTC=lamivudine or emtricitabine; ART=antiretroviral therapy; ARV=antiretroviral; IQR=interquartile range; GA=gestational age; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor

p-value was calculated using chi-square test or Fisher's exact test as appropriate, † using unpaired t-test

* Five of pregnant women in the low risk group had no results of HIV RNA before delivery but received ART more than 12 weeks. Two of the pregnant women with a history of HIV RNA below 50 copies/mL before delivery were classified in the high risk group including that one diagnosed with drug resistance and a second who showed an HIV RNA of 47,948 copies/mL at the day after delivery.

Table 2. Baseline characteristics of 154 HIV-exposed infants stratified by risk of transmission

Infants	Total (n=154)	Low risk group (n=133)	High risk group (n=21)	p-value
Sex: male (%); n (%)	83 (53.9)	72 (54.1)	11 (52.4)	0.88
Birth weight <2,500 grams; n (%)	31 (20.1)	24 (18.0)	7 (33.3)	0.10†
Birth weight (grams); median (IQR)	2,945 (2,578 to 3,321)	2,965 (2,610 to 3,330)	2,890 (2,450 to 3,270)	1.00†
Premature infant (GA <37 weeks); n (%)	19 (12.3)	16 (12.0)	3 (14.3)	0.72
Birth asphyxia; n (%)	10 (6.5)	8 (6.0)	2 (9.5)	0.62
Neonatal ARV prophylaxis; n (%)				<0.001
AZT 4 weeks	134 (87.0)	132 (99.2)	2 (9.5)	
AZT/3TC/NVP 6 weeks	18 (11.7)	1 (0.8)	17 (81)	
No ART prophylaxis	1 (0.6)	0 (0.0)	1 (4.8)	
Other regimens: AZT/3TC+single dose NVP	1 (0.6)	0 (0.0)	1 (4.8)	

AZT=zidovudine; 3TC=lamivudine; NVP=nevirapine; ART=antiretroviral therapy; IQR=interquartile range; GA=gestational age; PI=protease inhibitor

p-value was calculated using chi-square test or Fisher's exact test as appropriate, † using unpaired t-test

transmission rate was 0.6% (95% CI 0.1 to 3.5). Low risk HIV-exposed infants had higher retention in care compared to high risk group infants with adjusted odd ratio (aOR) of 10.80 (95% CI 2.27 to 51.24). At the follow up visit of age 18 months, of the 97 infants who came to visit a tertiary care hospital, 72 infants had HIV antibody test and 64 (89%) had non-reactive and eight (11%) had inconclusive. Among the eight children with inconclusive, HIV antibody test was repeated at 3 to 6 months interval, and all showed non-reactive results.

Factors associated with birth outcomes

Associated factors with low birth weight are

Table 3. Factors associated with low birth weight in HIV-exposed infants

Characteristics	Univariate		Multivariate	
	OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value*
Maternal ARV regimen				
NRTI+NNRTI	Reference			
Others	1.97 (0.87 to 4.46)	0.11		
Initial ARV				
Before pregnancy	1.41 (0.63 to 3.16)	0.40	1.75 (0.73 to 4.18)	0.21
During or after pregnancy	Reference		Reference	
Maternal viral loads				
Detectable	2.61 (0.98 to 6.94)	0.06	3.19 (1.12 to 9.04)	0.03
Undetectable	Reference		Reference	
Risk of transmission				
Low-risk	Reference			
High-risk	2.27 (0.83 to 6.23)	0.12		
Disclosure status		0.10		
Yes	0.39 (0.13 to 1.20)			
No	Reference			

CI=confidence interval; aOR=adjusted odd ratio; ARV=antiretroviral; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor

p-values were analyzed using logistic regression. Multivariable models were developed by adjusting for covariates from forward stepwise with p<0.10 in univariable models.

shown in Table 3. Detectable maternal HIV RNA close to delivery was significantly associated with low birth weight, with aORs of 3.19 (95% CI 1.12 to 9.04). There was no significant association between maternal age, timing of ART initiation, ARV regimen, risk of HIV transmission, and disclosure status with birth outcomes.

Retention in HIV care and associated factors among postpartum women living with HIV

Among 153 postpartum women living with HIV, data were available on 148 cases with maternal follow-up visits. Retention in care of postpartum women living with HIV was 85.0% (95% CI 78.3 to 89.7) at 6 months, with all women had continued ART, and 76.5% (95% CI 68.9 to 82.4%) at 18 months after delivery, respectively. At 18 months after delivery, among 117 who received ART in the national AIDS program, 51 (48.7%) had completed CD4 testing with a median CD4 level of 573 cells/mm^3 (IQR 450 to 742). Among 49 women who had HIV RNA performed, 44 (90%) maintained undetectable HIV RNA. Maternal retention in care was found associated with timing of maternal ARV initiation. Mothers who initiated ARV before pregnancy had a higher probability of retention in care 85.5% (95% CI 76.0 to 91.5) compared to mothers who initiated ARV during pregnancy or after delivery 65.7% (95% CI 53.3 to 75.5, p=0.012) (Figure 1). There was no significant association between retention in care with other factors such as maternal age, maternal ARV regimen, and HIV RNA levels near delivery.

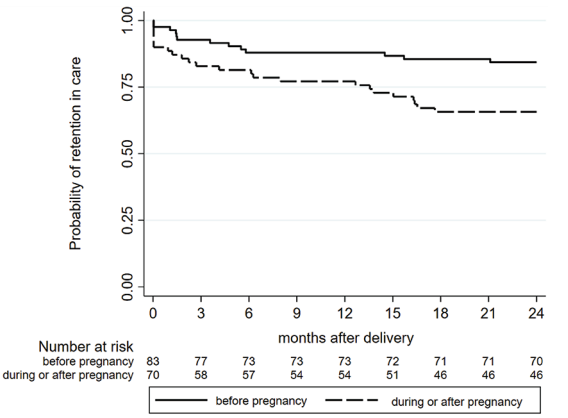

Figure 1. Cumulative probability of retention in care of women living with HIV after delivery by timing of maternal antiretroviral initiation.

Discussion

Among the present cohort, the prevalence of preterm delivery and low birth weight was comparable to the meta-analysis with rates of 12% and 20%, respectively. Infants whose mother had detectable plasma HIV RNA has 3.09 times odds of having low birth weight compared with ones whose mother had HIV RNA suppression. This emphasizes

the importance of prompt initiation of antiretroviral drug in pregnant women with a potent regimen to reduce risk of low birth weight in infants. Morever, the authors found a differential patterns of follow-up for antiretroviral treatment postpartum which mother who initiated ART during pregnancy has lower retention rate than mother who are stable on ART prior to conception with 65.7% versus 85.5%.

The prevalence of preterm delivery and low birth weight among pregnant women living with HIV was more common compared to non-HIV-infected pregnant women[3]. In the general population, the global prevalence of preterm birth ranges from 5% to 18% with the majority of the world's preterm births occur in sub-Saharan African or South Asian[12]. The prevalence of preterm birth among pregnant women living with HIV in the published studies were 8.9% in China[2], 12.5% in Korea[13], and 16% in the U.S.[14]. Regarding the prevalence of low birth weight, it ranged from 5.6% to 6.6% in the Thailand general population[15], which was lower than the present study population. The higher prevalence of low birth weight among pregnant women living with HIV were comparable with previous studies at 12.2% in China[2], 15% in the U.S.[14], and 23.4% in Nigeria[16]. In regards to associated factor with low birth weight, results from a study in China showed timing of ART initiation, maternal body mass index (BMI), and gender were associated factors[14]. In contrast, results from the present study showed only detectable maternal HIV viral load (VL) before delivery was associated with low birth weight.

Previous research on retention in care of postpartum women living with HIV in Haiti found that 69% were retained at 12 months with a decline to 59% by 24 months. ART initiation was found as an associated factor of retention in care (RR 2.1)[17]. Another important finding was that maternal age was associated with retention in care[17,18], which not found in the present study. About the follow-up in HIV-exposed infants, in the present study settings where exclusive replacement feeding with infant formula, HIV DNA PCR are tested as early infant diagnosis according to risk stratification until four months of age. This is different from the settings in Africa where breastfeeding is continued, therefore, longer follow-up among HIV-exposed infants are needed until discontinuation of breastfeeding. A study from Uganda showed the rates of loss to follow up was 29% at 6 months and increase to 48% at 18 months[19]. The level of retention may represent the effectiveness of PMTCT services. The present study found a positive correlation between the risk of transmission and retention through complete follow up. This finding has important implications for developing PMTCT services for early diagnosis of HIV-infected infants. Further study to identify additional associated factors may be helpful.

The strengths of the present study are the measurement of birth outcomes and retention in care among pregnant women living with HIV and HIV-exposed infant in tertiary care setting. The study has described associated factors including attendance at follow-up clinics and retention in care. However, there were limitations in the present study. Retrospective descriptive studies have limitations regarding data collection and the potential for bias in the selection of participants. It may not provide a complete and accurate representation of the study population. There is a possibility of incomplete or inaccurate data being collected from EMR. Last, the study only included participants from a single tertiary care center, which may limit the generalizability of the findings to other settings or populations. In conclusion, high rates of retention in HIV care were demonstrated in the present study. However, there is a need to focus on individuals at high risk of failing to complete HIV care such as pregnant women with detectable HIV VL near delivery and high-risk HIV-exposed infants.

What is already known on this topic?

Currently, PMTCT programs are more widely available and have demonstrated improvement in outcomes among HIV-exposed infants.

What does this study add?

Birth outcomes of preterm delivery and low birth weight among pregnant women living with HIV were common with a prevalence of 12% and 20%, respectively. A key factor associated with low birth weight was detectable maternal HIV VL before delivery with an aOR 3.19. Mothers who initiated ART prior to pregnancy had a higher retention rate than the ones who initiated treatment during pregnancy at 85.5% versus 65.7% (p=0.012).

Availability of data

The data used to support the findings of the present study are available upon request from the corresponding author.

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Conflicts of interest

The authors declared no conflict of interest.

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