

The Impact of ART on Stillbirth and Neonatal Death Among HIV-positive Pregnant Women — Yunnan Province, China, 2013–2022

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ABSTRACT

Introduction: This study assessed the impact of antiretroviral therapy (ART) on stillbirth and neonatal mortality and investigated associated risk factors among Human immunodeficiency virus-positive (HIV-positive) pregnant women in Yunnan, China during 2013–2022.

Methods: Data from the National Information System of Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis, and Hepatitis B Program (PMTCT) were analyzed to determine stillbirth and neonatal mortality rates. Multivariate Poisson regression was employed to identify risk factors associated with stillbirth and neonatal outcomes.

Results: Among 9,563 HIV-positive women with singleton pregnancies in Yunnan Province during 2013–2022, 9,404 (98.34%) received ART during pregnancy, while 159 (1.66%) did not. There were 9,421 live births, 76 stillbirths, and 66 neonatal deaths, yielding a stillbirth rate (SBR) of 8.07‰ and neonatal mortality rate (NMR) of 7.01 ‰. The SBR was significantly lower in pregnancies where ART was used ($P=0.033$). Univariate analysis revealed that ART ($P=0.009$), ethnicity ($P=0.012$), and antenatal care utilization ($P<0.001$) were associated with stillbirth and newborn survival. Multivariate Poisson regression identified that six or more antenatal care visits as an independent predictor of survival.

Conclusions: Stillbirth and neonatal mortality rates were elevated among mothers who did not receive ART during pregnancy compared to those who did. These findings emphasize the importance of ART during pregnancy, particularly since several mortality risk factors are amenable to intervention.

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is one of

the most critical global public health challenges, particularly threatening the health of pregnant women living with HIV and their offspring. In 2022, among the 1.2 million pregnant women living with HIV globally, approximately 82% received antiretroviral drugs to prevent mother-to-child transmission (PMTCT) of HIV (1). Without intervention, mother-to-child transmission (MTCT) of HIV occurs at rates of 15%–45% (2), but antiretroviral therapy (ART) can reduce this to less than 2% (3). Yunnan Province, which first identified HIV infection among local drug users in China, has implemented the PMTCT for HIV Program since 2003, spanning more than two decades (4). In Yunnan, ART coverage increased substantially from 75.92% in 2006 to 99.72% in 2019, corresponding with a decrease in MTCT decreased from 8.78% to 1.93% during the same period (5).

Maternal HIV infection significantly elevates the risk of intrauterine death, with rates of 7.1% among HIV-positive pregnant women compared to 2.3% among HIV-negative pregnant women (6). Additionally, maternal HIV infection increases the risks of low birth weight and preterm birth (6–7), with 13.2% of live-born infants having low birth weight and 7.4% experiencing premature birth (6). Across seven African countries, HIV infection is associated with elevated preterm birth rates of 15%–20% of all pregnancies, varying notably by ART regimen (8). In China, preterm birth rates among women living with HIV were reported at 10.70% in Hubei province (9) and 14.70% in Guangxi province (10). However, research describing neonatal outcomes among HIV-positive pregnant women in Yunnan province, which has China's highest HIV/AIDS prevalence, remains limited, and the impact of maternal ART on stillbirth and neonatal death requires further investigation in this region.

This study utilized data from the National Information System of Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis and

Hepatitis B Program to evaluate the impact of maternal ART on stillbirth and neonatal death among HIV-positive pregnant women in Yunnan.

METHODS

This study conducted a descriptive study analyzing data from the PMTCT system to evaluate the impact of maternal ART use among HIV-positive pregnant women in Yunnan Province, with data extraction performed on December 16, 2024. The study included all HIV-positive pregnant women from 2013–2022 in Yunnan Province, excluding those with multifetal pregnancies, unknown ART status, or infant deaths occurring after 28 days postpartum. The PMTCT system, established in 2007, captures comprehensive data including maternal demographics, infant characteristics, HIV transmission routes, ART regimens, and antenatal care utilization.

Our primary outcomes were stillbirth and neonatal mortality. The stillbirth rate (SBR) was defined as the number of babies born with or without signs of life at or after 28 weeks gestation per 1,000 total births. The neonatal mortality rate (NMR) was defined as deaths occurring within the first 28 days after birth per 1,000 total births.

ART during pregnancy was administered to reduce perinatal transmission. Two standardized regimens were used: the first comprised Zidovudine (AZT)–lamivudine (3TC)–lopinavir/ritonavir (LPV/r), and the second comprised of Tenofovir (TDF)–3TC–efavirenz (EFV).

Statistical analysis included descriptive statistics to characterize the study population and outcomes, stratified by maternal ART use. Chi-square tests were employed to assess differences in outcomes across education levels, marital status, ethnicity, and maternal ART use. Multivariate Poisson regression analysis was conducted to identify risk factors for stillbirth and newborn outcomes. All statistical analyses were performed using R packages *stats* and *MASS*, with statistical significance set at $P < 0.05$.

The study was exempt from ethical review by the Ethics Review Committee of the National Center for Women and Children's Health Chinese Center for Disease Control and Prevention, as the National Information System of Integrated Prevention of Mother-to-Child Transmission of HIV, Syphilis and Hepatitis B Program is a mandatory, legally supported public health surveillance system.

RESULTS

During 2013–2022, a total of 9,563 HIV-positive women pregnant with singleton pregnancies were identified in Yunnan province. The mean maternal age was 29.71 (± 5.91) years, and 7,480 (78.22%) were less than 35 years old. Educational attainment varied: 1,347 (14.09%) were illiterate, and 3,048 (31.87%) had primary education. 4,696 (49.11%) had secondary education, and 472 (4.94%) had tertiary education. ART coverage was high, with 9,404 (98.34%) women receiving treatment. Of these, 8,220 (87.41%) initiated ART before pregnancy, 599 (6.40%) during pregnancy, 78 (0.83%) during delivery, and 507 (5.39%) after delivery. Only 159 (1.66%) women did not receive ART.

Table 1 presents the demographic and clinical characteristics of the study population stratified by ART use. Marital status ($P=0.047$), educational level, parity number of children, and antenatal care visits were significantly associated with ART utilization ($P < 0.001$).

Survival of HIV-exposed Newborns

Among the study population, there were 9,421 live births, 76 stillbirths, and 66 neonatal deaths (Table 2), yielding an SBR of 8.07‰ and an NMR of 7.01‰. Poisson test analysis revealed a statistically significant difference in SBR between pregnant women who used ART and those who did not ($P=0.033$). However, no statistically significant difference was observed in NMR between these groups ($P=0.088$).

Impact on Stillbirth and Newborn Outcomes

Maternal age, marital status, education level, parity, and number of children were independently associated with newborn survival. Additionally, ART use ($P=0.009$), ethnicity ($P=0.012$), and antenatal care utilization ($P < 0.001$) had demonstrated significant associations with stillbirth and newborn survival outcomes (Table 3).

Multivariate Poisson regression analysis revealed that ART use, ethnicity, and parity were independent risk factors for stillbirth and neonatal mortality. Notably, compared to women who received no antenatal care, those who attended six or more antenatal care visits showed significantly reduced risk of stillbirth and neonatal mortality [odds ratio (OR)=0.13] (Table 4).

TABLE 1. Basic characteristics of HIV-positive pregnant women.

Characteristics	Overall, n (%)	No ART, n (%)	ART, n (%)	χ^2 , P
Age (years)				0.00, 0.979
<35	7,480 (78.22)	125 (78.62)	7,355 (78.21)	
≥35	2,083 (21.78)	34 (21.38)	2,049 (21.79)	
Ethnicity				0.02, 0.891
Han	4,670 (48.83)	79 (49.69)	4,591 (48.82)	
Other	4,893 (51.17)	80 (50.31)	4,813 (51.18)	
Marital status				0.047*
Single	591 (6.18)	13 (8.18)	578 (6.15)	
Married	8,817 (92.20)	140 (88.05)	8,677 (92.27)	
Divorced/widowed	155 (1.62)	6 (3.77)	149 (1.58)	
Level of education				20.42, <0.001
Illiterate	1,347 (14.09)	32 (20.13)	1,315 (13.98)	
Primary	3,048 (31.87)	68 (42.77)	2,980 (31.69)	
Secondary	4,696 (49.11)	57 (35.85)	4,639 (49.33)	
Tertiary	472 (4.94)	2 (1.26)	470 (5.00)	
Parity				14.39, <0.001
Primiparity	3,178 (33.23)	30 (18.87)	3,148 (33.48)	
≥1	6,385 (66.77)	129 (81.13)	6,256 (66.52)	
No. of child				19.98, <0.001
0	3,486 (36.45)	36 (22.64)	3,450 (36.69)	
1	3,965 (41.46)	68 (42.77)	3,897 (41.44)	
≥2	2,112 (22.09)	55 (34.59)	2,057 (21.87)	
Antenatal care visits				828.89, <0.001
0	516 (5.42)	89 (55.97)	427 (4.54)	
1–5	4,151 (43.41)	57 (35.85)	4,094 (43.53)	
≥6	4,896 (51.20)	13 (8.18)	4,883 (51.92)	
Total	9,563 (100.00)	159 (100.00)	9,404 (100.00)	

Abbreviation: ART=antiretroviral therapy.

* Fisher's exact test.

TABLE 2. Impact of ART on stillbirth and newborn outcomes.

Characteristics	Overall	No Maternal ART	Maternal ART	P
Live births	9,421	152	9,269	
SBR (‰)	76 (8.07)	4 (26.32)	72 (7.77)	0.033
NMR (‰)	66 (7.01)	3 (19.74)	63 (6.80)	0.088

Abbreviation: ART=antiretroviral therapy; SBR=stillbirth rate; NMR=neonatal mortality rate.

DISCUSSION

The health outcomes of infants born to HIV-infected mothers are crucial for promoting newborn health and evaluating mother-to-child transmission prevention efforts. Our analysis of surveillance data examined the impact of maternal ART use during pregnancy on adverse pregnancy and newborn

outcomes among women living with HIV. In accordance with China's technical guidelines for PMTCT of HIV, Syphilis, and Hepatitis B, newborns have not yet received an HIV diagnosis. Our study primarily evaluated two major health conditions: stillbirth as an adverse pregnancy outcome and neonatal death (within 28 days of birth) as an adverse newborn outcome. This study found significantly

TABLE 3. Independent associations with stillbirth and newborn outcomes and relevant factors.

Characteristics	Live births, <i>n</i> (%)	Death, <i>n</i> (%)	χ^2 , <i>P</i>
ART			0.009
No	152 (1.61)	7 (4.93)	
Yes	9,269 (98.39)	135 (95.07)	
Age (years)			0.82, 0.364
<35	7,364 (78.17)	116 (81.69)	
≥35	2,057 (21.83)	26 (18.31)	
Ethnicity			6.30, 0.012
Han	4,616 (49.00)	54 (38.03)	
Other	4,805 (51.00)	88 (61.97)	
Marital status			0.133*
Single	586 (6.22)	5 (3.52)	
Married	8,680 (92.13)	137 (96.48)	
Divorced/widowed	155 (1.65)	0 (0.00)	
Level of education			7.10, 0.069
Illiterate	1,319 (14.00)	28 (19.72)	
Primary	3,002 (31.86)	46 (32.39)	
Secondary	4,630 (49.15)	66 (46.48)	
Tertiary	470 (4.99)	2 (1.41)	
Parity			0.71, 0.400
Primiparity	3,136 (33.29)	42 (29.58)	
≥1	6,285 (66.71)	100 (70.42)	
No. of child			3.97, 0.137
0	3,437 (36.48)	49 (34.51)	
1	3,913 (41.53)	52 (36.62)	
≥2	2,071 (21.98)	41 (28.87)	
Antenatal care visits			84.05, <0.001
0	497 (5.28)	19 (13.38)	
1–5	4,048 (42.97)	103 (72.54)	
≥6	4,876 (51.76)	20 (14.08)	
Total	9,421 (100.00)	142 (100.00)	

Abbreviation: ART=antiretroviral therapy.

* Fisher's exact test.

higher stillbirth rates among mothers who did not use ART during pregnancy compared to those who did, highlighting the critical importance of ART adherence in this vulnerable population.

Neonatal mortality serves as a crucial indicator of maternal and child health. Yunnan province has a substantial population of HIV-positive pregnant women, with both crude HIV-positivity rates and the proportion of subsequent pregnancies among HIV-positive women showing consistent annual increases between 2006 and 2019 (11). Consequently, the number of infants born to mothers living with HIV is

projected to rise. Previous research has demonstrated that HIV-exposed but uninfected infants, compared to HIV-unexposed infants, experience poorer health outcomes and may face impaired physical and neurological development (12–13). These findings underscore the need for enhanced neonatal healthcare and the development of targeted interventions to improve child health outcomes.

Our findings suggest that HIV exposure may increase the probability of stillbirth in pregnancies of women living with HIV. Comparative data from India showed a significantly higher SBR among HIV-

TABLE 4. Risk factors of stillbirth and the outcomes of newborn by multivariate Poisson regression.

Characteristics	Estimate (95% CI)	OR (95% CI)	SE	Z value	P
Intercept	-3.11 (-3.99, -2.40)	0.04 (0.02, 0.09)	0.40	-7.74	<0.001
ART					
No	Reference		Reference	Reference	
Yes	-0.48 (-1.30, 0.42)	0.62 (0.29, 1.52)	0.42	-1.16	0.247
Ethnicity					
Han	Reference		Reference	Reference	
Others	0.30 (-0.03, 0.65)	1.35 (0.97, 1.91)	0.17	1.75	0.081
Antenatal care visits					
0	Reference		Reference	Reference	
1-5	-0.29 (-0.79, 0.27)	0.75 (0.45, 1.30)	0.27	-1.09	0.274
≥6	-2.06 (-2.72, -1.39)	0.13 (0.07, 0.25)	0.34	-6.13	<0.001

Abbreviation: CI=confidence intervals; OR=odds ratio; SE=standard error; ART=antiretroviral therapy.

infected women (26.7‰, 93/3,478) compared to the national average (5‰) (14). Similarly, in Zambia, a stillbirth rate of 26 per 1,000 live births was reported among 1,229 HIV-infected pregnant women (15). While our study revealed lower stillbirth rates among HIV-infected women (8.07‰) compared to these international studies, the statistically significant difference in stillbirth rates between ART users (26.32‰) and non-users (7.77‰) remained.

Notably, multivariable Poisson regression analysis did not identify ART use as independently associated with adverse pregnancy outcomes. The discrepancy between chi-square testing and multivariable regression results may be attributed to several factors. First, the single stillbirth case among pregnant women who did not use ART could represent a random occurrence. Second, when controlling for ethnicity, parity, and antenatal care visits in the multivariable Poisson regression, the differences in SBR and NMR between ART users and non-users became non-significant at certain variable levels. The regression results demonstrated that women with six or more antenatal care visits had a lower risk of adverse pregnancy outcomes compared to those without any visits, emphasizing the importance of regular antenatal care.

Our study has limitations. As a descriptive analysis focusing solely on mortality, we did not examine other health aspects of infants born to HIV-positive women. There is an urgent need for in-depth analysis of specific causes of death and comprehensive evaluation of health conditions beyond survival. Future research should prioritize both psychological and physiological studies in this population.

The stillbirth and neonatal mortality rates were

significantly higher among HIV-positive mothers who did not receive ART during pregnancy compared to those who received ART. Healthcare interventions for HIV-positive pregnant women warrant increased attention to ensure universal ART coverage and to address modifiable risk factors associated with stillbirth and neonatal mortality through targeted preventive measures.

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