

Original Article

Characteristics of HIV-positive pregnant women and HIV- and antiretroviral therapy-exposed fetuses: A case-control study

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Abstract

Introduction: This study determined risk factors, obstetric comorbidities, and fetal conditions among HIV-positive mothers to improve their maternal care.

Methodology: This retrospective case-control study included HIV-positive pregnant women 18 years of age or older and age-, parity-, and delivery method-matched HIV-negative controls between 2011 and 2018. Those who had stillbirth were excluded. Baseline demographics, labor process, CD4 count, plasma HIV viral load, and antiretroviral therapy (ART) regimen were recorded. Fetal conditions were recorded as well.

Results: Forty HIV-positive women (45 parities; 22 via NSD, 23 via C/S) were included, with 45 HIV-negative parities as controls. Twenty-nine (72.5%) HIV-positive women had illicit drug use. In the HIV-positive group, 17% received ART prior to first perinatal visit, and 75.6% reached viral suppression pre-delivery. Zidovudine and ritonavir-boosted lopinavir were the majorly prescribed ART. Mild perineal lacerations via NSD were observed in HIV-positive women. Fetal body weight was lower in HIV- and ART-exposed fetuses (2665 vs 3010 g, $p < 0.001$). Preterm delivery PTB (28.9% vs 8.9%, $p = 0.015$) and small-for gestational age SGA (28.9% vs 8.8%, $p = 0.003$) rates were higher in the HIV-positive group. There was no vertical transmission of HIV.

Conclusions: HIV-positive women tend to deliver fetuses with low body weight and have higher SGA and PTB rates. Given that most women received zidovudine and protease inhibitors, benefits of newer agents for HIV-positive pregnancies should be studied.

Key words: Pregnancy; fetus; HIV; AIDS; antiretroviral therapy.

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Introduction

Worldwide human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) epidemics has resulted in 35 million deaths for the past 35 years [1], and there are approximately 36.7 million people living with HIV (0.8% of the global adult population aged 15–49 years) in 2016 [2], with more than half of them being women. New HIV infection rates are declining because of global efforts to strengthen HIV prevention and treatment programs, and especially, in children aged 15 years of age or younger, infections have declined to 47% since 2010 owing to the provision of antiretroviral therapy (ART) to pregnant women, increasing from 47% [38%–55%] to 76% [60%–88%] over the same period. Nowadays, an estimated 240,000 children acquired HIV infection per

year, majorly through mother-to-child transmission (MTCT) [1,2].

Prevention of MTCT (PMTCT) programs provided ART to HIV-positive pregnant women, effectively reducing MTCT to < 2% [3], and also supported women by providing services, including appropriate contraceptive use, proper infant feeding methods, early infant diagnosis, and lifelong ART [4]. Evaluation of PMTCT programs estimated that 1.4 million HIV infections among children had been averted between 2010 and 2018 [5].

By the end of 2018, Taiwan had less than 37,000 reported cases living with HIV. Among them, 2000 cases were women, with 45% being injection drug users and 53% being heterosexual [6]. According to the Taiwan Centers for Disease Control PMTCT programs,

HIV screening of all pregnant women during prenatal examination had been implemented since 2005. By 2017, coverage of HIV screening was 98.6% [6]. Unfortunately, 17 children with HIV infections were diagnosed between 2005 and 2018 [6]. In our hospital, most of the mothers of MTCT cases missed their prenatal examination owing to illicit intravenous drug use or homelessness.

Small-for-gestational age (SGA), preterm birth (PTB), or low birth weight (LBW) in HIV-positive women is widely observed in several cohort studies [7-12]. The possible risk factors for SGA include Hepatitis B infection and ART initiation later than 14 weeks gestation. In a Malawian observational cohort, ART use reduced SGA rate, but it is still higher than that of HIV-negative individuals. Apart from the HIV infection itself [13], ART exposure also poses a risk for SGA in HIV-exposed fetus. Several observational studies reported that ART use, especially protease inhibitors, is related to SGA or intrauterine growth restriction (IUGR) [11,12,14,15].

From 2011 to 2018, more than 50 HIV-positive pregnant women were followed up at Taoyuan General Hospital; of these, 45 delivered their babies. To the best of our knowledge, no studies have compared these obstetric and fetal complications between HIV-positive and -negative pregnant women in the Asia-Pacific region. Thus, we aimed to determine the characteristics, obstetric morbidities, and fetal conditions and complications of pregnant women with HIV infection, and to compare these to those of HIV-negative controls to improve their maternal care.

Methodology

Subjects

This case-control observational study was conducted at Taoyuan General Hospital (TYGH), a 1,000-bed hospital located in northern Taiwan (Figure 1). There are more than 2,000 cases with HIV infection who visit the outpatient clinics regularly. This study was approved by the institutional review board of TYGH (IRB No. TYGH107081). The inclusion criteria of the case group were as follows: HIV-positive pregnant women 18 years of age or older, and delivered at TYGH between 1 January 2011 and 15 December 2018. In the case group, women with multiple deliveries in our hospital were included only once in the transmission categories, but all the other characteristics were collected and calculated per delivery. Women who were in the prenatal care program in the hospital but delivered outside the hospital were not included in the case group, but the babies born were included in the

Figure 1. The map of Taiwan and location of Taoyuan City.



Source: Google Maps. Google, inc.

fetal analysis. Women who had stillbirth were excluded from the analysis. The control group were retrospectively selected randomly from HIV-negative mothers who delivered at TYGH, matched by maternal age (± 5 years), parity (nulligravida or multigravida before this delivery), and delivery methods [normal spontaneous delivery (NSD) or cesarean section (C/S)]. Similar to the case group, for those who were in the prenatal care program in the hospital but delivered outside the hospital were excluded, but their babies were included in the fetal analysis. Gestational age was calculated since the last menstrual period (LMP).

Analysis of obstetric characteristics and fetal conditions

The demographic characteristics, including age, parities, body mass index (BMI) on the first visit, blood pressure on the first visit, comorbidities, hemograms, modes of deliveries, and obstetric complications, were recorded. For pregnant women with HIV infection, transmission categories, CD4+ T cell counts, plasma HIV viral loads, ARTs, time of ART initiation, and regimens of protease inhibitors (PIs), non-nucleos(t)ide reverse transcriptase inhibitors (NNRTIs), and integrase inhibitors (IIs) were also documented. The labor processes of NSD, the operative times for C/S, and total blood loss were recorded for both groups. The differences in the abovementioned characteristics between women with HIV infection and their matched controls were analyzed. Missing data were recorded in the result tables.

Records of birth conditions, including gestational ages at birth, body weight at birth, and Apgar score at 1 and 5 minutes, of the fetuses delivered from both groups were also reviewed. Preterm birth was defined as a birth of an infant less than 37 weeks of gestational age. SGA was defined as < 10% of birth weight for gestational age. The differences of the abovementioned

characteristics between HIV- and ART-exposed fetus and non-exposed controls were also analyzed.

Statistical analysis

Demographic data were presented as median (interquartile range, IQR) for continuous variables and percentiles for discrete variables. Chi-square and

Table 1. Baseline demographics of HIV-positive and HIV-negative pregnant women who delivered between 2011 and 2018 in Taoyuan, Taiwan.

	Women with HIV N = 45	Women without HIV N = 45	p-value
Age (median, IQR)	32.1 (28.9-35.6)	33.3 (30.9-35.2)	0.390
Parity (n, %)			
Primigravida	11 (24.4)	11 (24.4)	-
Multigravida	34 (75.6)	34 (75.6)	-
Body mass index, kg/m ² , (median, IQR)	24.79 (22.99-28.29)	26.39 (24.8-31.22)	0.093
Systolic blood pressure, mmHg (median, IQR)	125 (119-135)	126 (115-135)	0.861
Diastolic blood pressure, mmHg (median, IQR)	77 (68-86)	78 (72-85)	0.159
Comorbidities (n, %)			
Hypertension	0	0	-
Diabetes mellitus	0	0	-
HBsAg positive	7 (17.5)	2 (4.4)*	0.231
HCVAb positive	19 (47.5)	NC	-
Syphilis	0	0	-
Anti-retroviral therapy			
Gestational age when ART was initiated, weeks (median, IQR)	13 (10.3-21)	NC	-
ART started before pregnancy (n,%)	8 (17.8)	NC	-
ART started at 12-14 weeks of pregnancy (n,%)	14 (31.1)	NC	-
ART started after 28 weeks of pregnancy (n,%)	3 (6.7)	NC	-
Transmission categories			
Illicit drug use (n,%)	29 (72.5)	NA	-
Heterosexual sex (n,%)	11 (27.5)	NA	-
Regimen of ART			
Zidovudine-containing (n,%)	38 (84.4)	NC	-
NNRTI-based (n,%)	3 (6.7)	NC	-
PI-based (n,%)	37 (82.2)	NC	-
II-based (n,%)	5 (11.1)	NC	-
CD4+ T cell counts on the 1 st prenatal examination			
< 200 cells/uL (n,%)	3 (6.7)	NC	-
≥ 200 to < 500 cells/uL (n,%)	27 (60)	NC	-
≥ 500 cells/uL (n,%)	15 (33.3)	NC	-
Plasma HIV viral load (PVL)			
Log ₁₀ PVL copies/mL on 1 st prenatal exam (mean ± SD)*	3.22 ± 1.15	NC	-
PVL < 1000 copies/mL on first prenatal exam (n,%)	14 (31.1)	NC	-
PVL < 50 copies/mL on first prenatal exam (n,%)	10 (22.2)	NC	-
PVL < 1000 copies/mL before delivery (n,%)	42 (93.3)	NC	-
PVL < 50 copies/mL before delivery (n,%)	34 (75.6)	NC	-
Mode of delivery			
Normal spontaneous delivery	22	22	-
Cesarean section	23	23	-
Obstetric complications			
PROM (n,%)	3 (6.7)	1 (2.2)	0.306
Preterm labor (n,%)	13 (28.9)	4 (8.9)	0.015
Prolonged labor (n,%)	1 (2.2)	4 (8.9)	0.167
(Pre)eclampsia (n,%)	1 (2.2)	2 (4.4)	0.557

IQR: interquartile range; NC: not checked; NNRTI: non-nucleos(t)ide reverse transcriptase inhibitor; II: Integrase inhibitor; PI: Protease inhibitor; PROM: premature rupture of membrane; SD: standard deviation; HIV, human immunodeficiency virus; *Seven data were missing.

Mann-Whitney U tests were used to compare the categorical and continuous variables, respectively.

Covariates with $p < 0.3$ in the univariate analyses were included in the multivariate logistic regression analyses to determine the covariates predicting SGA in HIV-and ART-exposed fetuses. The odds ratio (OR) and 95% confidence interval (CI) were estimated, and $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using Stata Statistical Software: Release 14 (StataCorp LLC. 2017, College Station, TX).

Results

Subjects and demographics

During the study period, 40 HIV-positive pregnant women, with 45 parities, delivered at our hospital. There were 3 HIV-positive women who had 2 parities and 1 had 3 parities during the study period. The mean age was 32.1 and 33.3 years respectively for HIV-positive and HIV-negative women. Eleven women were primigravida in both groups. In the HIV-positive group, 7 were HBsAg-positive, whereas only 2 were HBsAg-positive in the HIV-negative group. HCV antibody seropositivity was observed in 19 HIV-positive women. Contrarily, in the HIV-negative controls, the HCV antibody status was not available because HCV antibody testing is not included in the national perinatal program. Regarding HIV acquisition, 29 (72.5%) HIV-positive women were illicit drug users, whereas 11 (27.5%) were engaged in heterosexual sex. The mean \log_{10} HIV viral load during the first perinatal visit was 3.22; 22% of the patients were viral-suppressed ($1 < 50$ copies/mL during the first visit) (Table 1).

Viral suppression and ART

Among them, 17% of the HIV-positive pregnant women were on ART before prenatal care; of these, 31% and 22% achieved viral suppression ($< 1,000$ and < 50 copies/mL, respectively) at the first prenatal examination, and 93.3% and 75.6% achieved viral suppression ($< 1,000$ and < 50 copies/mL, respectively) during deliveries (Table 1).

Regarding ART, most of the HIV-positive women (84%, 38 cases) received zidovudine (AZT), lamivudine, and boosted PI (37 cases of lopinavir; 1 case of atazanavir). In particular, 4 cases had taken dolutegravir before April 2018 without knowledge of neural tubal defects.¹⁵ During deliveries, 5 parities (11.1%) underwent intravenous zidovudine infusion due to detectable viral load peri-partum (Table 1).

Delivery and birth outcomes

Finally, 22 and 23 parities underwent NSD and C/S, respectively. Regarding the reasons for C/S, nine was due to previous C/S, 8 was due to patients' own decision, 3 due to premature rupture of membrane, 1 due to breech presentation, 1 due to prolonged labor, and 1 due to preeclampsia. There was no maternal mortality in our study (Table 2).

Compared to controls, women with HIV who underwent NSD had lower hemoglobin level (11.4 vs 12 g/dL, $p = 0.005$), but this was not observed in HIV women who underwent C/S (11 vs 11 g/dL, $p = 0.333$). Perineal laceration of the HIV women who underwent NSD was milder than that of controls who underwent NSD (4.5% vs 27.2% of 1st degree laceration, $p = 0.005$), although some data were missing. Other parameters, including BMI, blood pressure, white cell count, platelet count, time of NSD labor process,

Table 2. Comparison of normal spontaneous delivery and cesarean section between HIV-positive and HIV-negative pregnant women in Taoyuan, Taiwan.

	Women with HIV N = 45	Women without HIV N = 45	p value
Normal spontaneous delivery (n = 22 vs 22)			
Labor process			
Time of first stage, minutes (median, IQR)	123 (95-170)	60 (51-193)	0.451
Time of second stage, minutes (median, IQR)	9 (5-36)	13 (3-19)	0.535
Time of third stage, minutes (median IQR)	4 (4-10)	5 (4-8)	0.293
Blood loss, mL (median IQR)	175 (125-300)	150 (100-200)	0.071
Perineal laceration*			
First degree (n,%)	6 (27.2)	1 (4.5)	0.005
Second degree (n,%)	10 (45.5)	17 (77.3)	0.008
Third degree (n,%)	0 (0.0)	1 (4.5)	0.288
Cesarean section (n=23 vs 23)			
Operative time, minutes (median, IQR)	85 (70-95)	100 (80-105)	0.372
Blood loss, mL (median, IQR)	500 (400-800)	600 (550-900)	0.227

IQR: interquartile range; NC: not checked; HIV, human immunodeficiency virus; *Data were missing.

Table 3. Comparison of the fetal conditions between HIV- and ART-exposed fetuses and the controls.

	HIV-and ART-exposed fetus N = 45	Non-exposed fetus N = 45	P
APGAR score at 1 minute after delivery (median, IQR)	8 (8-8)	8 (8-8)	-
APGAR score at 5 minutes after delivery (n,%)	9 (9-9)	9 (9-9)	-
Gestational age at birth, weeks (median, IQR)	37.7 (36.6-38.9)	39 (37.9-39.4)	0.007
Body weight at birth, g (median, IQR)	2,665 (2,360-2,975)	3,010 (2,840-3,365)	< 0.001
Bilirubin on day1, mg/dL (median, IQR)	10.1 (6.3-12.7)	8.8 (8.1-11.6)	0.867
Percentage of premature birth (n,%)	13 (28.9)	4 (8.9)	0.015
Percentage of SGA (%; n/N)	28.9 (13/45)	8.8 (3/34)	0.003

ART: antiretroviral therapy; SGA: small for gestational age; HIV, human immunodeficiency virus.

operative time for C/S, and blood loss, were not statistically significant between the HIV-positive and HIV-negative women (Table 2).

There were 45 HIV- and ART-exposed fetuses analyzed. Among them, 6.7% were exposed to NNRTI, 82.2% to PI (97.2% used ritonavir-boosted lopinavir), and 84.4% to AZT intrauterine. After birth, all were administered oral AZT solution for 6 weeks, and none developed MTCT. Among the women who were taking PI, 28.9% had premature birth and 29.7% had SGA fetus. There were no congenital defects, including neural tubal defects (Table 3).

Compared to the non-exposed fetuses, HIV- and ART-exposed fetuses had SGA at birth (37.7 weeks vs 39 weeks, $p = 0.007$) and lower body weight (2,665 grams vs 3,010 grams, $p < 0.001$). The rates of SGA were also higher in the HIV- and ART-exposed fetuses (28.9% vs 8.8%, $p = 0.003$) (Table 3).

Multivariate logistic regression analysis showed that BMI, blood pressure, HBsAg carriage, anti-HCV seropositivity, history of illicit drug use, CD4 count (either stratified by 200 cumm/m³ or 350 cumm/m³), exposure of zidovudine, or HIV viral load (stratified by 200 copies/mL), were not significant predisposing factors for SGA among HIV- and ART-exposed fetus (Table 4).

Discussion

This is the first study in the Asia-Pacific region that compared the obstetric complications between women

with and without HIV and showed that HIV-positive mothers tended to have PTD and SGA infants. In our study, Taiwanese women with HIV infection had a trend of preterm deliveries and SGA infants. Studies from the United States revealed increased preterm labor and low birth weight rates in HIV-positive women, who are mostly African American, which is similar to our observation [13]. The retrospective cohort in the United States involving 183 HIV-positive pregnant women reported that SGA rates were associated with HIV severity (determined by CD4 count), but not ART regimens. Moreover, sociodemographic and behavior characteristics also contributed to SGA outcomes. In their cohort, higher SGA rates were associated with smoking. Compared with our study, the case group were mostly women with incarceration due to illicit drug use, and the proportion of smokers is higher than the control group. Otherwise, rates of stillbirth and abnormal Apgar scores were similar between ART-exposed and non-exposed fetuses.

Regarding the parameters of HIV-positive mothers, we observed lower hemoglobin levels in HIV-positive women who delivered via NSD than in HIV-negative individuals who delivered via NSD as well, but such difference was not observed between HIV-positive and -negative women who delivered via C/S. Most of our patients were taking zidovudine as their NRTI backbone, which is the possible etiology of anemia [16]. Another cohort study in Brazil revealed the relation between anemia and co-infection, along

Table 4. Risk factors of SGA among ART- and HIV-exposed fetuses.

Risk factors	Univariate analysis		Multivariate analysis	
	OR (CI)	p value	OR (CI)	p value
HBsAg seropositivity	0.30 (0.03-2.8)	0.297	0.16 (0.02-1.83)	0.144
HCVAb seropositivity	1.49 (0.39-5.65)	0.560		
BMI < 23 kg/m ²	0.19 (0.21-1.68)	0.136	0.19 (0.20-1.74)	0.143
PVL > 50 copies/mL before delivery	2.32 (0.58-9.36)	0.237	2.74 (0.56-13.28)	0.208
Exposure to zidovudine	0.74 (0.15-3.54)	0.707		
Exposure to protease inhibitors	0.68 (0.17-2.68)	0.586		
Illicit drug use	1.13 (0.28-4.48)	0.867		

ART: antiretroviral therapy; SGA: small for gestational age; HIV, human immunodeficiency virus.

with initiation of ART during pregnancy [17]. In our study, nearly half of the HIV-positive women had co-infection with HCV, and most of them were receiving ART during pregnancy. Theoretically, anemia should be observed in all HIV-positive women who were taking zidovudine, given that more than 90% of women were taking zidovudine as the backbone in either the NSD subgroup or C/S subgroup, which is suggested in the WHO guidelines in 2010 [18]. The small sample size should be taken into account in our observational results.

For women with HIV infection and had NSD in this study, perineal laceration was milder than that of their matched controls. The possible etiology is the small fetal size in HIV-positive women (in the subgroup analysis with NSD, median fetus body weight is 2,463 g in HIV-positive women, whereas it was 2,985 g in HIV-negative women; $p = < 0.001$). Perineal laceration was seldom mentioned in the literature. Milder degree of perineal laceration may indicate a lower rate of maternal complications such as wound infection owing to perineal laceration, but regarding the fetal complications, higher rates of SGA and preterm birth pose higher risk of fetal complications.

Regarding the SGA rate, HIV infection itself and ART both contributed to a higher SGA rate [11,19]. Among the ART regimens, one mouse-based model revealed that PI will affect the IUFG by decreasing the progesterone level, which leads to fetal growth restriction [14]. No previous study has mentioned about PI being related to prematurity, but other researchers explained that advanced stages of AIDS and maternal high viral loads may be the causes for receiving the PI-based therapy. In Taiwan CDC guidelines, zidovudine/lamivudine plus ritonavir-boosted PI is still considered as the first-line regimen in pregnant HIV individuals due to the toxicity of NNRTI until the introduction of integrase inhibitor (INSTIs) [15]. Even in recent guidelines, the use of INSTIs in pregnancy with HIV infection is still controversial due to the possible adverse effect of neural tube defects of dolutegravir. Therefore, most of our patients in the case group had PI-based regimen.

This study has several limitations of this study. First, this is a retrospective observational study with a small sample size and incomplete data. Until now, this is the first study focusing on the obstetric and fetal complications of HIV-positive pregnant women in Taiwan. Second, although most of the pregnant women with HIV infection had maximally achieved viral suppression during delivery, there were still a high number of women undergoing C/S. Data from the

National Health Insurance showed that approximately 35% of Taiwanese pregnant women choose C/S, rather than NSD [20], and a similar rate was observed in women with HIV infection.

Conclusion

Women with HIV infection in this study tend to be anemic and have preterm deliveries and SGA infants. Larger studies are needed to stratify the risks of SGA in this patient cohort. Moreover, as ART has remarkably progressed these years, benefits of newer agents for HIV-positive pregnancies should be studied.

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References

1. World Health Organization (2015) Progress report 2011: Global HIV/AIDS response. Available: https://www.who.int/hiv/pub/progress_report2011/en/. Accessed 22 May 2019.
2. World Health Organization (2018) Global health observatory data. Available: <https://www.who.int/gho/hiv/en/>. Accessed 22 May 2019.
3. Minkoff H (2003) Human immunodeficiency virus infection in pregnancy. *Obstet Gynecol* 101: 797-810.
4. World Health Organization (2010) PMTCT strategic vision 2010-2015: Prevention mother-to-child transmission of HIV to reach UNGASS and millennium development goals. Available: https://www.who.int/hiv/pub/mtct/strategic_vision.pdf. Accessed 22 May 2019.
5. UNAIDS (2018) Miles to go-closing gaps, breaking barriers, righting injustices. Available: <https://www.unaids.org/en/resources/documents/2018/global-aids-update>. Accessed 22 May 2019.
6. Taiwan Centers for Disease Control (2019) Epidemics of HIV/AIDS in Taiwan, 2018. Available: https://www.cdc.gov.tw/En/Category/ListContent/bg0g_VU_Ysrgkes_KRUDgQ?uaid=CqNo313w78G1fWhz429xDA. Accessed 22 May 2019.
7. Ategeka J, Wasswa R, Olwoch P, Kakuru A, Natureeba P, Muehlenbachs A, Kanya MR, Dorsey G, Rizzuto G (2019) The prevalence of histologic acute chorioamnionitis among HIV infected pregnant women in Uganda and its association with adverse birth outcomes. *PLoS One* 14: e0215058.
8. Malaba TR, Newell ML, Madlala H, Perez A, Gray C, Myer L (2018) Methods of gestational age assessment influence the observed association between antiretroviral therapy exposure, preterm delivery, and small-for-gestational age infants: A prospective study in Cape Town, South Africa. *Ann Epidemiol* 28: 893-900.
9. Li HX, Zheng JF, Huang GW, Xiao J, Wang H, Yang M, Feng N (2018) Prevalence and associated risk factors on preterm birth, low birth weight, and small for gestational age among

- HIV-infected pregnant women in Hunan province, 2011-2017. *Zhonghua Liu Xing Bing Xue Za Zhi* 39: 1368-1374.
10. Dadabhai S, Gadama L, Chamanga R, Kawalazira R, Katumbi C, Makanani B, Dula D, Hua N, Lau B, Mallewa M, Taha TE (2019) Pregnancy outcomes in the era of universal antiretroviral treatment in Sub-Saharan Africa (POISE Study). *J Acquir Immune Defic Syndr* 80: 7-14.
 11. Snijdewind IJM, Smit C, Godfried MH, Bakker R, Nellen JFJB, Jaddoe VWV, van Leeuwen E, Reiss P, Steegers EAP, van der Ende ME (2018) Preconception use of cART by HIV-positive pregnant women increases the risk of infants being born small for gestational age. *PLoS One* 13: e0191389.
 12. Watts DH, Williams PL, Kacaneck D, Griner R, Rich K, Hazra R, Mofenson LM, Mendez HA, Pediatric HIV/AIDS Cohort Study (2013) Combination antiretroviral use and preterm birth. *J Infect Dis* 207: 612-621.
 13. Aaron E, Bonacquisti A, Mathew L, Alleyne G, Bamford LP, Culhane JF (2012) Small-for-gestational-age births in pregnant women with HIV, due to severity of HIV disease, not antiretroviral therapy. *Infect Dis Obstet Gynecol* 2012: 135030.
 14. Papp E, Mohammadi H, Loutfy MR, Yudin MH, Murphy KE, Walmsley SL, Shah R, MacGillivray J, Silverman M, Serghides L (2015) HIV protease inhibitor use during pregnancy is associated with decreased progesterone levels, suggesting a potential mechanism contributing to fetal growth restriction. *J Infect Dis* 211: 10-18.
 15. Dugdale CM, Ciaranello AL, Bekker LG, Stern ME, Myer L, Wood R, Sax PE, Abrams EJ, Freedberg KA, Walensky RP (2019) Risks and benefits of dolutegravir- and efavirenz-based strategies for South African women with HIV of child-bearing potential: A modeling study. *Ann Intern Med* 170: 614-625.
 16. Rachlis A and Fanning MM (1993) Zidovudine toxicity. Clinical features and management. *Drug Saf* 8: 312-320.
 17. Delicio AM, Lajos GJ, Amaral E, Lopes F, Cavichioli F, Myioshi I, Milanez H (2018) Adverse effects of antiretroviral therapy in pregnant women infected with HIV in Brazil from 2000 to 2015: A cohort study. *BMC Infect Dis* 18: 485.
 18. World Health Organization (2010) Antiretroviral drugs for treating pregnancy women and preventing HIV infection in infants. Available: <https://www.who.int/hiv/pub/mtct/antiretroviral2010/en/>. Accessed 22 May 2019.
 19. Delicio AM, Lajos GJ, Amaral E, Cavichioli F, Polydoro M, Milanez H (2018) Adverse effects in children exposed to maternal HIV and antiretroviral therapy during pregnancy in Brazil: A cohort study. *Reprod Health* 15: 76.
 20. Health Promotion Administration and Ministry of Health and Welfare. Available: <https://www.mohw.gov.tw/dl-13409-e69c4fde=886b-457b-aalb-55541a488dcl.html>. Accessed 22 May 2019.

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