Thai Journal of Obstetrics and Gynaecology
April 2015, Vol. 23, pp. 68-75

OBSTETRICS

Comparison of Preterm Delivery Rates between HIV-infected Pregnant Women Receiving Highly Active Antiretroviral Therapy (HAART) Containing Protease Inhibitors (PIs) and HIV-infected Pregnant Women Receiving Zidovudine Monotherapy

Bongkot Chakornbandit, MD*,
Fuanglada Tongprasert, MD*.

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand*

ABSTRACT

Objective: To compare the preterm delivery rates between pregnant women receiving HAART containing protease inhibitors (HAART-PIs) and zidovudine monotherapy (ZDVm) during pregnancy.

Materials and Methods: A retrospective study was conducted in antiretroviral-naïve HIV-infected pregnant women who received antiretroviral drugs during pregnancy at least 4 weeks and delivered in Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand between January 2002 and December 2013. Preterm delivery rates were compared between HAART-PIs and ZDVm groups.

Results: Of the 166 pregnant women who received antiretroviral drugs, 24 (14.5%) pregnant women delivered before 37 completed weeks. The incidence of preterm delivery was higher in the HAART-PIs group (82 cases) than in the ZDVm group (84 cases), but the difference was not significant (18.3% vs. 10.7%, p = 0.17).

Conclusion: The almost twofold incidence of preterm delivery rate was observed in those pregnancy women who received HAART-PIs; however, it was not significantly different from the rate among those who received ZDVm.

Keywords: HIV, HAART, zidovudine, preterm delivery, protease inhibitors

Correspondence to: *Fuanglada Tongprasert, MD., Department of Obstetrics and Gynecology Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand*
Phone: +66-53-945552 Fax: +66-53-946112 E-mail: fuanglada.t@cmu.ac.th

Introduction

To maximize maternal health and prevent HIV transmission to the newborn, the use of antiretroviral drug (ARV) in all HIV-infected pregnant women during

pregnancy is recommended[1]. In a setting of universal prenatal HIV testing and counseling, highly active antiretroviral therapy (HAART), and elective cesarean delivery and breastfeeding avoidance, the rate of HIV mother-to-child transmission (MTCT) is less than 1%[2]. HAART — or the antiretroviral drug combinations of two nucleoside reverse transcriptase inhibitors (NRTIs) — plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), has been shown to effectively reduce the risk of vertical transmission by adequate viral suppression in pregnant women[1]. HAART (mostly containing PIs) was widely in use to prevent MTCT instead of zidovudine monotherapy in the last decade. However, adverse pregnancy outcomes associated with the use of these drugs still need to be addressed and dealt with. Preterm delivery is the complication of the highest concern, although the mechanism remains unclear[3]. There have been reports, by many studies, of increased rates of prematurity, with odd ratios (OR) in the range of 1.6–2.6 in pregnancy receiving HAART containing PIs compared with monotherapy or no therapy[4-8]. However, some studies, including the meta-analysis and the systematic review, did not confirm this association[9-14].

This study aimed to compare the preterm delivery rates between HIV-infected pregnant women receiving HAART containing PIs and HIV-infected pregnant women receiving zidovudine monotherapy during pregnancy in a single center cohort of Thai pregnant women with HIV infection.

Materials and Methods

A retrospective study was conducted at Maharaj Nakorn Chiang Mai Hospital, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, with the approval of the Research Ethics Committee, using a database of HIV-infected pregnant women who received antenatal care at the hospital between January 2002 and December 2013. The eligibility criteria included the following: (1) naïve HIV-infected pregnant women; (2) received HAART containing PIs or zidovudine monotherapy during pregnancy; and (3) at least 4 weeks of drug exposure. The exclusion criteria included the following: (1) multiple pregnancies; (2) preterm delivery indicated or caused by medical, surgical, or obstetric complications; (3) fetal chromosomal abnormalities or structural anomalies; and (4) failure of ARV drug adherence. The sample size was calculated based on the preterm delivery rate of 23.9% among pregnant women receiving zidovudine monotherapy in a previous study[5]. Eighty-three pregnant women were needed in each treatment group for a 0.05 two-sided type 1 error with 0.9 powers.

HAART containing PIs regimen (HAART-PIs) is defined by at least three drug combinations of two NRTIs (e.g., zidovudine, lamivudine, stavudine, tenofovir, emtricitabine) plus one PI (e.g., lopinavir/ritonavir, atazanavir, indinavir, darunavir). Zidovudine monotherapy (ZDVm) is defined as using zidovudine in a dose of 500–600 mg/day. Preterm delivery is defined as a delivery that takes place before 37 weeks of gestation. Gestational age is based on a certain last menstrual period or early fetal biometry either by crown-rump length in the first trimester or by biparietal diameter in the second trimester.

The patient demographic data, obstetric and medical history, antenatal complications, pre-pregnancy body mass index (BMI), CD4 cell counts before drugs exposure and before delivery, hemoglobin levels before drugs exposure, gestational age at the beginning of ARV drugs, HIV RNA viral load before delivery, route of delivery, gestational age and birth weight at delivery, APGAR score at 1-minute and 5-minute, and neonatal status of HIV infection were obtained from the database and the medical records.

Statistical analysis

All of the statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL). The demographic characteristics were described and compared between the HAART-PIs and the ZDVm groups using the independent samples t-test, the Mann-Whitney U test, and the Chi-square test. The categorical data were presented as frequencies (%), and the continuous data were presented as mean and standard deviation (SD) or median and interquartile range (IQR). The preterm delivery rates were compared between the

two groups using the Chi-square test or the Fisher's exact test. A multivariate logistic regression was used to obtain the odds ratios (OR) and 95% confidence intervals (CI) for potential risk factors that were identified in the univariate analysis. A $p < 0.05$ was considered statistically significant.

Results

During the twelve-year study period, 169 naïve HIV-infected pregnant women received HAART-PIs or ZDVm during pregnancy. Two pregnant women were excluded from the study because they had less than 4 weeks of drugs exposure. Medical history details indicated that preterm delivery was induced in one pregnant woman at 36 weeks of gestation due to the diagnosis of severe preeclampsia, and she was also excluded from the analysis. Of the remaining 166 cases, 82 cases (49.4%) received the HAART-PIs regimen and 84 cases (50.6%) received the ZDVm regimen. In the HAART-PIs group, the antiretroviral drug combinations were zidovudine plus lamivudine plus lopinavir/ritonavir (74 cases), lamivudine plus stavudine plus lopinavir/ritonavir (3 cases), lamivudine plus tenofovir plus lopinavir/ritonavir (3 cases), lamivudine plus stavudine plus atazanavir (1 case), and tenofovir plus emtricitabine plus atazanavir (1 case).

As presented in Table 1, the baseline characteristics of the study population were not significantly different between the HAART-PIs group and the ZDVm group, except for the gestational age at the beginning of the ARV drugs, the duration of the drug exposure, HIV RNA before delivery and gestational diabetes. The medical complication found in the HAART-PIs group was chronic hypertension (1 case). The medical complications found in the ZDVm group were asymptomatic prolapsed mitral valve post repair (1 case) and asymptomatic hypothyroidism (1 case). The obstetric complication found in both the HAART-PIs group and the ZDVm group was IUGR (4 cases in each group). Gestational diabetes was diagnosed in 12 cases in the HAART-PIs group and in 2 cases in the ZDVm group.

The hemoglobin levels and the anemia rate before the exposure to the drugs were similar in both the groups. Maternal anemia is defined as a hemoglobin level of less than 11.0 g/dL in the first or the third trimester, or a hemoglobin level of less than 10.5 g/dL in the second trimester. The HIV RNA viral load before the drug exposure was not routinely evaluated, but the HIV RNA viral load and the $CD4^+$ cell counts after the drug exposure or before the delivery were usually performed at the same time. The average gestational age of the investigation was 35.1 ± 2.2 weeks of gestation; however, some patients who delivered prematurely did not take these blood tests. The HIV RNA viral load of more than 1000 copies/mL was the cut-off level that offered the choice for the pregnant women to deliver by cesarean section. Those pregnant women with HIV RNA viral load of less than 1000 copies/mL received counseling for spontaneous vaginal delivery if they did not have any indication for cesarean section. After birth, the HIV DNA PCR was tested in the infant at 1 month and 4 months. An infant was defined as HIV-infected upon testing positive for HIV DNA PCR in both the tests. An infant who had negative HIV DNA PCR in both the tests was also confirmed as such by HIV antibody and HIV DNA PCR at 18 months. The route of delivery and the other pregnancy outcomes are demonstrated in Table 2.

Table 1. Baseline Characteristics of HIV-infected Pregnant Women Receiving HAART-PIs or ZDVm Regimens.

Baseline characteristics	Total (166 cases)	HAART-PIs (82 cases)	ZDVm (84 cases)	P
Maternal age (years, mean ± SD)	28.0±5.2	28.5±5.9	27.5±4.4	0.19
Nulliparity (%)	36.1	35.4	36.9	0.84
• Previous abortion rate (n, %)	57 (34.3)	25 (30.5)	32 (38.1)	0.30
• Previous preterm delivery rate (n, %)	5 (3.0)	4 (4.9)	1 (1.2)	0.21#
Hb pre-ARV exposure (g/dL, mean ± SD)	11.0±1.2	11.2±1.2	10.9±1.1	0.14
• Pre-ARV exposure anemia rate (n, %)	65 (39.2)	29 (35.4)	36 (42.9)	0.32
$CD4^+$ cell count pre-ARV exposure (cells/mm^3, mean ± SD)	404.1±185.9	409.2±189.5	395.3±181.1	0.69
CD4+cell count before delivery (cells/mm^3, mean ± SD)	477.8±184.5	489.2±190.9	460.3±134.5	0.12
HIV RNA before delivery (copies/mL, median, and 25^{th}, 75^{th} percentile)	166.5 (40.0, 400.0)	46.0 (40.0, 400.0)	3668.5 (400.0, 15466.0)	< 0.001*
GA at the beginning of ARV (weeks, median, and 25^{th}, 75^{th} percentile)	19.5 (14.0, 28.0)	16.0 (14.0, 21.8)	28.0 (27.0, 28.0)	< 0.001*
Duration of ARV (weeks, median, and 25^{th}, 75^{th} percentile)	18.0 (11.8, 24.0)	20.1 (14.5, 24.0)	11.0 (10.0, 12.0)	< 0.001*
Pre-pregnancy BMI (kg/m^2, mean ± SD)	21.3±2.9	21.6±3.1	21.1±2.8	0.31
• Underweight; BMI < 18.5 kg/m^2 (n, %)				
• Overweight; BMI > 25.0 kg/m^2 (n, %)				
Gestational diabetes (n, %)	14 (8.4)	12 (14.6)	2 (2.4)	0.005#
Medical complications (n, %)	3 (1.8)	1 (1.2)	2 (2.4)	0.57
Obstetric complications (n, %)	8 (4.8)	4 (4.9)	4 (4.8)	1.00#

Note: Hb = hemoglobin; g/dL = gram per deciliter; cells/mm3 = cells per cubic millimeter; copies/mL = copies per milliliter; GA = gestational age; ARV = antiretroviral drug; BMI = body mass index; SD = standard deviation.
*Mann-Whitney U Test.
#Fisher's Exact Test.

Table 2. Pregnancy Outcomes of HIV-infected Pregnant Women Receiving HAART-PIs or ZDVm Regimens.

Pregnancy outcomes	Total (166 cases)	HAART-PIs (82 cases)	ZDVm (84 cases)	P
GA at delivery (weeks, mean ± SD)	38.0±1.7	37.9±2.0	38.1±1.4	0.44
• Delivery at GA < 37 weeks (n, %)	24 (14.5)	15 (18.3)	9 (10.7)	0.17
• Delivery at GA < 34 weeks (n, %)	2 (1.2)	2 (2.4)	0 (0)	0.24#
Birth weight (g, mean ± SD)	2904.5±413.5	2826.3±421.5	2,980.7±393.3	0.02
• Low birth weight (n, %)	23 (13.9)	14 (17.1)	9 (10.7)	0.24
Route of delivery				
• ND (n, %)	89 (53.6)	54 (65.9)	35 (41.7)	0.002
• Elective CS (n, %)	42 (25.3)	12 (14.6)	30 (35.7)	0.002
• Emergency CS (n, %)	34 (20.5)	15 (18.3)	19 (22.6)	0.49
• VE, FE, BA (n, %)	1 (0.6)	1 (1.2)	0 (0)	0.49#
APGAR score at 1-minute < 7 (n, %)	19 (11.4)	10 (12.2)	9 (10.7)	0.76
APGAR score at 5-minute < 7 (n, %)	0 (0)	0 (0)	0 (0)	-
HIV-infected infant (n, %)	2 (1.3)	0 (0)	2 (2.4)	0.50#

Note: GA = gestational age; g = gram; ND = normal delivery; CS = cesarean section; VE = vacuum extraction; FE = forceps extraction; BA = breech assisted delivery; SD = standard deviation.
#Fisher's Exact Test.

Discussion

A potent combination antiretroviral (ARV) regimen is strongly recommended for all HIV-infected pregnant women to reduce the risk of mother-to-child transmission (MTCT)[1]. Two-NRTIs backbone plus NNRTI or PI regimens have been demonstrated in clinical trials to have higher rates of viral suppression and acceptable side effects in the mother, the fetus, and the newborn[1]. PI regimens, that is, atazanavir with ritonavir boosting (ATV/r) and lopinavir with ritonavir boosting (LPV/r), are preferable for starting the course in the first trimester due to potential fetal teratogenicity concern from the NNRTI regimens, efavirenz (EFV)[1]. Although it is generally safe and is now a standard care, the association between these PI regimens as part of HAART in pregnant women and the risk of preterm delivery is still controversial[6, 9, 15-17]. The mechanisms supporting the occurrence of preterm birth caused by PI regimens are not well explained. One hypothesis is that the interaction between ritonavir and adrenal enzymes could induce spontaneous preterm birth through maternal and fetal adrenal axis[7]. Another explanation is that the influence of these drugs on the T-helper 1/T-helper 2 cytokine shift has been shown to affect the duration of pregnancy in women with a history of recurrent pregnancy losses[11].

Numerous studies have investigated the relationship between PIs use during pregnancy and prematurity with conflicting results[4-14]. Most of the studies reported an increased risk of preterm delivery upon using HAART with PIs in comparison with no therapy or zidovudine monotherapy or HAART without PIs[4-8]. The incidence of preterm births in pregnant women receiving HAART with PI regimens has been found to be in the range of 14.7–36.6% and the adjusted odd ratio to be in the range of 1.6–2.6[4-8]. However, evidences from a meta-analysis and a systematic review study indicated that PI regimens were not significantly associated with an increased risk of prematurity[9, 11]. Similarly, in our study, it was found that the use of HAART with PIs during pregnancy was not associated with a statistically significant increase in the risk of

preterm delivery. However, the incidence of preterm births in our population receiving PI regimens was 18.3%, which was not very different from the findings obtained in the previous studies[6, 10, 12]. Upon comparing with the 10.7% incidence rate of preterm births in those receiving zidovudine monotherapy, pregnant women receiving HAART with PIs were found to have almost twofold risk of prematurity and the rate was observed to be quite higher than the 12% incidence of preterm births in the general population in Thailand[18]. The detection of this tendency may be helpful in counseling those HIV-infected pregnant women who are treated with PIs containing regimens for MTCT prevention.

The use of a variety of doses of the PIs regimen in the different studies, especially LPV/r, may have resulted in some inconsistencies in the data interpretation. An increased dose of LPV/r, of 533/100 mg or 600/150 mg, twice daily has been suggested by some investigators to increase maternal plasma concentrations during the third trimester[19, 20]. Despite the fact that, in one study[7], these higher LPV/r doses were reported to be related to prematurity, a systematic review did not find any signs of this association when compared with the standard LPV/r dose[11]. In the present study, most pregnant women undergoing HAART with PI regimens received a fixed-standard dose of LPV/r 400/100 mg twice daily in all the trimesters.

The important limitation of this study was the small number of cases in both the groups as well as the preterm index cases. This may have limited the power to detect significant differences in some variables. However, our findings present the pregnancy outcomes of HIV-infected pregnant women who receive HAART in this era, which is different from the zidovudine monotherapy scenario in the last decade. Superior viral suppression, absence of cases of HIV-infected infants from vertical transmission, and lower cesarean delivery rates were also demonstrated in the HAART with the PIs group— all of which resulted in better maternal and fetal health.

Conclusions

The preterm delivery rate in HIV-infected pregnant women who received HAART with PI regimens was not significantly different from those who received zidovudine monotherapy. However, an increased incidence of preterm delivery rate of 18.3% was found, which was almost twofold higher than the rate among those who received ZDVm. These pregnant women should be counseled regarding the risks of preterm birth in order that they gain access to close monitoring, early detection, and proper management.

Acknowledgment

The authors would like to thank Ms. Atcharawan Sansupa for her contribution as the research assistant nurse in this study. The authors report no conflict of interest.

References

1. Panel on treatment of HIV-infected pregnant women and prevention of perinatal transmission. Recommendation for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. [cited 2014 Jun 22]; Available from: http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf.
2. Townsend CL, Cortina-Borja M, Peckham CS, de Ruiter 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;22:973-81.
3. 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;15:233-8.
4. European Collaborative Study et al. Combination antiretroviral therapy and duration of pregnancy. AIDS 2000;14:2913-20.
5. Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ. Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth? J Infect Dis 2006;193:1195-201.
6. Powis KM, Kitch D, Ogwu A, Hughes MD, Lockman S, Leidner J, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. J Infect Dis 2011;204:506-14.
7. Sibiude J, Warszawski J, Tubiana R, Dollfus C, Faye A, Rouzioux C, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost? Clin Infect Dis 2012;54:1348-60.
8. Watts DH, Williams PL, Kacanek D, Griner R, Rich K, Hazra R, et al. Combination antiretroviral use and preterm birth. J Infect Dis 2013;207:612-21.

9. Kourtis AP, Schmid CH, Jamieson DJ, Lau J. Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis. AIDS 2007;21:607-15.
10. Morris AB, Cu-Uvin S, Harwell JI, Garb J, Zorrilla C, Vajaranant M, et al. Multicenter review of protease inhibitors in 89 pregnancies. J Acquir Immune Defic Syndr 2000;25:306-11.
11. Pasley MV, Martinez M, Hermes A, d'Amico R, Nilius A. Safety and efficacy of lopinavir/ritonavir during pregnancy: a systematic review. AIDS Rev 2013;15:38-48.
12. Patel K, Shapiro DE, Brogly SB, Livingston EG, Stek AM, Bardeguez AD, et al. Prenatal protease inhibitor use and risk of preterm birth among HIV-infected women initiating antiretroviral drugs during pregnancy. J Infect Dis 2010;201:1035-44.
13. Szyld EG, Warley EM, Freimanis L, Gonin R, Cahn PE, Calvet GA, et al. Maternal antiretroviral drugs during pregnancy and infant low birth weight and preterm birth. AIDS 2006;20:2345-53.
14. Townsend C, Schulte J, Thorne C, Dominguez KI, Tookey PA, Cortina-Borja M, et al. Antiretroviral therapy and preterm delivery-a pooled analysis of data from the United States and Europe. BJOG 2010;117:1399-410.
15. Townsend CL, Cortina-Borja M, Peckham CS, Tookey PA. Response to Kourtis et al. 'Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis'. AIDS 2007;21:1831-2.
16. Patel D, Thorne C, Newell ML. Response to Kourtis et al. 'Use of antiretroviral therapy in pregnant HIV-infected women and the risk of premature delivery: a meta-analysis'. AIDS 2007;21:1656-7.
17. Kourtis AP, Fowler MG. Antiretroviral use during pregnancy and risk of preterm delivery: more questions than answers. J Infect Dis 2011;204:493-4.
18. Country data and rankings for preterm birth data EMBARGO until May 2nd 2012. Born too Soon: The Global Action Report on Preterm Birth [cited 2014 July 08]; Available from: http://www.who.int/pmnch/media/news/2012/201204_borntoosoon_countryranking.pdf.
19. Mirochnick M, Best BM, Stek AM, Capparelli E, Hu C, Burchett SK, et al. Lopinavir exposure with an increased dose during pregnancy. J Acquir Immune Defic Syndr 2008;49:485-91.
20. Best BM, Stek AM, Mirochnick M, Hu C, Li H, Burchett SK, et al. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. J Acquir Immune Defic Syndr 2010;54:381-8.

การศึกษาเปรียบเทียบอัตราการคลอดก่อนกำหนดในสตรีตั้งครรภ์ติดเชื้อเอชไอวีระหว่างกลุ่มที่ได้รับยาต้านไวรัสที่มี protease inhibitors เป็นส่วนประกอบ และกลุ่มที่ได้รับยาต้านไวรัส zidovudine ชนิดเดียว

บงกช ชาครบัณฑิต, เฟื่องลดา ทองประเสริฐ

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราการคลอดก่อนกำหนดจากการใช้ยาต้านไวรัสในสตรีตั้งครรภ์ติดเชื้อเอชไอวีในกรณีที่ได้รับยาต้านไวรัสชนิดรวมกันหลายตัวที่มี protease inhibitors เป็นส่วนประกอบ และกลุ่มที่ได้รับยาต้านไวรัส zidovudine ชนิดเดียว*

วัสดุและกระบวนการ: *การศึกษาเชิงวิเคราะห์ชนิดโคฮอร์ตแบบย้อนหลังจากเวชระเบียนของสตรีตั้งครรภ์ติดเชื้อเอชไอวีที่มารับการฝากครรภ์ที่โรงพยาบาลมหาราชนครเชียงใหม่ตั้งแต่เดือนมกราคม พ.ศ. 2545 ถึงเดือนธันวาคม พ.ศ. 2556 โดยเก็บข้อมูลลักษณะพื้นฐานและผลลัพธ์การตั้งครรภ์ของสตรีตั้งครรภ์กลุ่มที่ได้รับยาต้านไวรัสชนิดที่มี protease inhibitors เป็นส่วนประกอบ และนำมาเปรียบเทียบกับสตรีตั้งครรภ์กลุ่มที่ได้รับยาต้านไวรัส zidovudine ชนิดเดียว*

ผลการศึกษา: *จากสตรีตั้งครรภ์จำนวนทั้งหมด 166 ราย พบว่าอัตราการคลอดก่อนกำหนดโดยรวมเท่ากับร้อยละ 14.5 กลุ่มที่ได้รับยาต้านไวรัสชนิดที่มี protease inhibitors เป็นส่วนประกอบจำนวน 82 รายมีอัตราการคลอดก่อนกำหนดร้อยละ 18.3 มากกว่ากลุ่มที่ได้รับยาต้านไวรัส zidovudine ชนิดเดียวจำนวน 84 รายซึ่งมีอัตราการคลอดก่อนกำหนดร้อยละ 10.7 แต่ไม่มีนัยสำคัญทางสถิติ (ค่า p = 0.17)*

สรุป: *สตรีตั้งครรภ์ติดเชื้อเอชไอวีที่ได้รับยาต้านไวรัสชนิดที่มี protease inhibitors เป็นส่วนประกอบมีอัตราการคลอดก่อนกำหนดสูงเกือบสองเท่ามากกว่าสตรีตั้งครรภ์ที่ได้รับยาต้านไวรัส zidovudine ชนิดเดียว*