

Analysis of Factors of Incompliance To Breastfeeding in Hepatitis B Virus-Infected Mothers Taking Nucleos(t)ide Analogs During Pregnancy for Prevention of Mother-To-Child Transmission

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Research article

Keywords: Chronic hepatitis B, nucleos(t)ide analogs, breastfeeding, patient's compliance

Posted Date: January 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-143445/v1>

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Version of Record: A version of this preprint was published at BMC Pregnancy and Childbirth on August 12th, 2021. See the published version at <https://doi.org/10.1186/s12884-021-04020-z>.

Abstract

Background: We encourage Hepatitis B virus-infected mothers to breastfeed postpartum, even when continuing pregnancy category B nucleos(t)ide analogs treatment. However, a large proportion of the Hepatitis B virus-infected mothers were not compliance to the breastfeeding recommendation. This study aimed to investigate the causes and influencing factors of incompliance to breastfeeding recommendation in Hepatitis B virus-infected mothers receiving nucleos(t)ide analogs treatment during pregnancy for preventing mother-to-child transmission.

Methods: A total of 155 mothers with chronic hepatitis B receiving nucleos(t)ide analogs treatment for preventing mother-to-child transmission during the late gestational period were included and divided into the exclusive breastfeeding (n=63), mixed feeding (n=34), and artificial feeding (n=58) groups according to the feeding types postpartum. Independent variables associated with feeding types were analyzed by logistic regression analysis.

Results: Compared to the breastfeeding and mixed feeding groups, the artificial feeding group had significantly higher parity, later postpartum timing of stopping nucleos(t)ide analogs treatment, and lower proportion of having knowledge of nucleos(t)ide analogs medications (all $P < 0.05$). In addition, multivariate logistic regression analysis confirmed that higher parity, later postpartum timing of stopping nucleos(t)ide analogs treatment, and lacking knowledge of medication were independent factors associated with incompliance to breastfeeding.

Conclusion: Hepatitis B virus-infected mothers with later postpartum timing of stopping nucleos(t)ide analogs treatment and less knowledge of medication were more likely to incompliance to breastfeeding recommendation. Strengthening health education may be an important method to improve compliance to breastfeeding.

Background

Hepatitis B virus (HBV) infects more than 2 billion people worldwide [1]. According to the World Health Organization (WHO), 257 million people were estimated to be chronically infected with HBV in 2015 worldwide [2], including 65 million women of childbearing age [3]. Chronic hepatitis B (CHB) resulted in 60% and 80% of cases of cirrhosis and hepatocellular carcinomas (HCCs) in Chinese patients, respectively [4].

Mother-to-child transmission (MTCT) is the major route of hepatitis B virus spread, accounting for nearly half of global chronic infections [5]. The active-passive immunization combining hepatitis B vaccines with hepatitis B immunoglobulin (HBIG) can effectively prevent about 90% of the MTCT of HBV [6]. However, there is still a small portion of newborns encountering the failure of active-passive immunoprophylaxis in preventing MTCT [7]. Clinical studies in recent years have confirmed that nucleos(t)ide analogs (NAs) treatment, such as tenofovir disoproxil fumarate (TDF) and telbivudine (LDT), in the second and third trimesters of pregnancy can effectively reduce the MTCT of HBV [8–11]. As a result, the guidelines set by

several liver disease associations, including the Asian Pacific Association for the Study of the Liver (APASL) [12], the European Association for the Study of the Liver (EASL) [13], the National Institute for Health and Care Excellence (NICE) [14] and the American Association for the Study of Liver Diseases (AASLD) [15] all recommend high viral load CHB pregnant women who lying in the immune tolerance period to receive pregnancy category B NAs (such as TDF and LDT [16]) during the second and third trimesters to reduce the MTCT rate.

Currently, however, there is no consensus on whether HBV-infected mothers receiving pregnancy category B NAs treatment should breastfeed or not. In the US [17] and European guidelines [13], breastfeeding is not recommended for HBV-infected mothers on TDF treatment. Nevertheless, in the WHO guidelines [18] and Asian-Pacific clinical practice guidelines [12], no clear instructions were given about breastfeeding by HBV-infected mothers with TDF treatment. The 2015 Chinese guideline by the Hepatology Branch of Chinese Medical Association [19] did not recommend breastfeeding for mothers who need to continue pregnancy category B drugs postpartum. In the 2019 Chinese guidelines [31], breastfeeding is no longer opposed for HBV-infected mothers receiving NAs for preventing MTCT during the gestational period, but breastfeeding is still not explicitly recommended.

It has been reported that breastfed infants have extremely lower TDF exposure than those in exposed the fetuses and children receiving tenofovir treatment [20–22]. TDF and LDT belong to pregnancy Category B medications, and TDF has low potential toxicity in breastmilk. Therefore, we believe that HBV-infected mothers on NAs treatment should be not a contraindication for breastfeeding. Hence, in clinical practice, we recommend HBV-infected mothers to breastfeed postpartum, even when continuing pregnancy category B NAs treatment. We intend to use the clinical practice to prove the safety of breastfeeding. However, during the follow-up, it was found that a significant portion of the HBV-infected mothers not compliance to the breastfeeding recommendation, but adopted artificial feeding. Therefore, the purpose of this study was to investigate the causes and influencing factors of incompliance to breastfeeding in HBV-infected mothers receiving NAs treatment during pregnancy for preventing MTCT.

Methods

Study design and subjects

This was a retrospective survey. From January 2017 to August 2019, in the Department of Infectious Disease of the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. A total of 155 CHB mothers with high viremia and lying in the immune-tolerant phase receiving NAs treatment for preventing MTCT during the gestational period were included. The inclusion criteria were: 1) age between 18 to 45 years; 2) detectable HBsAg at the screening visit and at least 6 months prior; 3) positivity for serum HBeAg, an HBV DNA level above 10^6 IU/ml, and an ALT level below the upper limit of normal (ULN; 40U/L). The exclusion criteria were: 1) coinfection with hepatitis A, C, D, or E virus or human immunodeficiency virus; 2) previous AVT for HBV infection (except for antivirals administered to prevent MTCT during a previous pregnancy and discontinued more than 6 months before the current pregnancy);

3) concurrent treatment with cytotoxic drugs, immune modulators, glucocorticoids or nephrotoxic drugs; 4) clinical signs of threatened miscarriage in early pregnancy; 5) evidence of hepatocellular carcinoma or cirrhosis; 6) evidence of fetal deformity by 3-dimensional ultrasound examination; 7) history of congenital malformation or congenital genetic disease in a previous pregnancy; 8) HBV infection of the husband.

This study was approved by the institutional review board of our hospital. Written informed consent was obtained from each subject.

Data collection

Subject's demographic and clinical characteristics were collected from medical records of the subjects. We collected data in the form of questionnaires. Patients meeting the inclusion criteria would sign the informed consent form when taking NAs for preventing MTCT in the prenatal period, and they will be formally included in the group during the return visit after delivery. Meanwhile, they will be given questionnaires and telephone communication form for long-term post-natal follow-up, each of which is required to be true and reliable.

Patient's knowledge of medication (LDT/TDF) were evaluated by a specialist doctor using a self-designed scale that consisted of several questions about mother-to-child transmission of LDT / TDF drugs.

Statistical analysis

Continuous data were indicated with mean \pm standard deviation (SD). For the comparisons between two groups, the student's independent t-test or Mann-Whitney U test (if normality was not assumed) was used. Categorical data were indicated with number and percentage (%), and the distribution would be tested with the Chi-square test or Fisher's exact test (if any expected value ≤ 5 was observed). One-way ANOVA was used for the means among groups (over 2 groups) and Fisher's LSD test was used as post-hoc comparisons. Kruskal-Wallis would be used as a replacement if normality was not assumed. To investigate the associations between independent variables and feeding types, the univariate and multivariate logistic regression models were used. The variables which reached $P < 0.10$ in the comparisons of mean differences would be analyzed using logistic regression models. The significant variables ($P < 0.05$) in the multivariate model would be recognized as associated factors to feeding types. ROC analysis was used to investigate the diagnostic efficacy of continuous variable to dichotomous outcomes. A $P < 0.05$ would be recognized as reaching the significance of each test, two-tailed. All analyses were performed using IBM SPSS Version 25 (SPSS Statistics V25, IBM Corporation, Somers, New York).

Results

Subject's demographic and clinical characteristics

A total of 155 CHB mothers (mean age=29.50±3.55 years) receiving NAs treatment for preventing MTCT during the gestational period were included. Participant's demographic and clinical characteristics were summarized in Table 1. NAs antiviral treatment included LDT (n=131, 84.52%) and TDF (n=24, 15.48%). The mean gestational period was 39.92±2.41 weeks. The delivery methods included vaginal (n=114, 73.55%) and cesarean section deliveries (n=41, 26.45%).

According to the feeding types postpartum, the subjects were divided into three groups: exclusive breastfeeding (n=63, 40.65%), mixed feeding (n=34, 21.94%), and artificial feeding (n=58, 37.41%) groups. The majority of subjects (n=111, 71.61%) had their first parity. It was found that subjects with higher parity would be more likely to use artificial feeding (P=0.003). Participants in the mixed feeding group had the highest gestational week and normal viral load rate (both P<0.05). The later the postpartum timing of stopping NAs treatment, the greater the possibility of using artificial feeding (P=0.022). Participants who had more knowledge of medication (LDT/TDF) were more likely to have breastfeeding (P<0.001). The exclusive breastfeeding group had significantly higher breastfeeding months than mixed feeding group (P<0.001).

Participant's clinical characteristics between groups with or without breastfeeding

Participants were further dichotomously separated into groups with or without breastfeeding (mixed feeding includes breastfeeding). As indicated in Table 2, the significances were similar to Table 1. The artificial feeding group had significantly higher parity, later postpartum timing of stopping NAs treatment, and fewer rate of knowing the knowledge of medication (all P<0.05).

Independent variables associated with feeding types

To further investigate the independent variables associated with feeding types (with or without breastfeeding), logistic regression analysis was performed. The variables reaching P<0.10 in Table 2 would be entered into univariate and multivariate logistic regression models, including educational level, parity, postpartum timing of stopping NAs treatment, infant birth bodyweight, and knowledge of medication.

As shown in Table 3, the independent factors associated with feeding types were parity, postpartum timing of stopping NAs treatment, and knowledge of medication (all P<0.01). These results suggested that subjects with higher parity, later postpartum timing of stopping NAs treatment, and less knowledge of medication were more likely to use artificial feeding.

Discussion

The issue of breastfeeding by HBV-positive mothers has attracted more and more attention. Previous studies demonstrate that breastfeeding by HBV-infected mothers is safe and does not increase the risk of MTCT if the newborns have received active-passive immunoprophylaxis [23, 24], including HBeAg⁺ CHB mothers [25]. Although a previous study has shown that HBsAg, HBeAg, and HBV DNA may be presented

in breastmilk [26] but generally cannot enter the infant blood through the internal barrier of the intestinal mucosa. Only when mucosal permeability is increased due to complications or injuries, the virus has the opportunity to synthesize and enters the infant blood [27]. Therefore, guidelines have suggested that breastfeeding should be encouraged for infants undergoing the standard passive-active immunoprophylaxis [6, 28, 29]. However, there is no consensus on whether HBV-infected mothers receiving pregnancy category B NAs treatment should breastfeed. The 2015 Chinese guideline [19] did not recommend breastfeeding for mothers who need to continue pregnancy category B drugs postpartum.

Based on the notions that TDF and LDT belong to pregnancy Category B medications, and TDF has low potential toxicity in breastmilk [20–22], we encourage HBV-infected mothers to breastfeed postpartum, even when continuing pregnancy category B NAs treatment. However, a large proportion of the HBV-infected mothers were not compliance to the breastfeeding recommendation. In the current study, of the 155 pregnant CHB women receiving NAs treatment during the gestational period, only 40.65% of cases underwent exclusive breastfeeding. In this study, we investigated the causes of incompliance to breastfeeding in HBV-infected mothers receiving NAs treatment during pregnancy for preventing MTCT. Our results showed that the artificial feeding group had significantly higher parity than the breastfeeding and mixed feeding groups and multivariate logistic regression analysis showed that higher parity was the independent factor associated with artificial feeding. This observation is inconsistent with previous reports that higher parity children are more likely to be breastfed [30]. However, we did not survey the feeding habits of prior parity in those with multiple parities. Therefore, the clinical meaning of this phenomenon is limited.

Among the 110 cases of stopping NAs treatment at the delivery day in this study, 45.45% and 25.45% of cases adopted exclusive breastfeeding and mixed feeding, respectively; only 29.02% used artificial feeding. However, of the 20 continuing NAs treatment after delivery, 70.00% of the cases used artificial feeding. On the other hand, among the 120 cases with the knowledge of medication (LDT/TDF), 71.67% of cases adopted breastfeeding or mixed feeding, while 28.33% of cases used artificial feeding. By contrast, in 32 cases without the knowledge of medication, 68.75% of the cases used artificial feeding. In addition, multivariate logistic regression analysis confirmed that both postpartum timing of stopping NAs treatment and knowledge of medication were independent factors associated with incompliance to breastfeeding. The association between later postpartum timing of stopping NAs treatment and artificial feeding should be attributed to concerning the drugs remaining in breastmilk may have an adverse effect on breastfed infants. However, the previous study shows that breastfed infants have a blood TDF concentration of only 2%–4% of maternal blood [21], so breastfed infants have lower TDF exposure than those in exposed the fetuses [20, 21]. Recently, Hu et al. have compared the dosage levels of TDF exposure in fetuses, breastfed infants, and children receiving tenofovir treatment. Their results reveal that the daily TDF dose ingested from breastmilk represented only 0.01–0.04% of the proposed pediatric therapeutic daily dose for children receiving TDF treatment and 0.5%–16% of those in exposed the fetuses [22]. These findings suggested that TDF has low potential toxicity in breastmilk. In fact, concerning later postpartum timing of stopping NAs treatment may harm infants is the same as a lack of knowledge of these NAs. It is worth to mentioned that even the healthcare workers may not have

systematic and comprehensive knowledge about HBV MTCT [31]. Therefore, making a health education leaflet to explain the low concentration of category B pregnancy drugs LDT / TDF in breastmilk may be an important method to improve compliance to breastfeeding in HBV-infected mothers receiving NAs treatment during pregnancy.

Our findings could provide a reference for revising the guidelines to recommend breastfeeding for HBV-infected mothers receiving pregnancy category B NAs treatment. In the least Chinese guidelines for the prevention and control of mother-to-child transmission of hepatitis B virus (2019 edition) [32], breastfeeding is no longer opposed for HBV-infected mothers receiving NAs treatment during pregnancy, but breastfeeding is still not explicitly recommended.

There are still some limitations to this study. First, this is a retrospective study with a relatively small sample size. In addition, we did not survey the feeding habits of prior parity in those with multiple parities. In the future, a prospective large trial should be conducted to validate the findings of this study.

Conclusions

In summary, our findings suggested that HBV-infected mothers with later postpartum timing of stopping NAs treatment and less knowledge of medication were more likely to in compliance to breastfeeding. Strengthening health education may be an important method to improve compliance to breastfeeding.

Abbreviations

HBV: Hepatitis B virus; WHO: World Health Organization; CHB: Chronic hepatitis B HCCs: hepatocellular carcinomas; MTCT: Mother-to-child transmission; HBIG: hepatitis B immunoglobulin; TDF: tenofovir disoproxil fumarate; LDT: telbivudine; AASLD: American Association for the Study of Liver Diseases; SD: standard deviation

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of the Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from each subject.

Consent for publication

Written informed consent was obtained from each subject for the publication of this study.

Availability of data and materials

All the data and materials have been presented in the main paper.

Competing interests

The authors declare that they have no conflict of interest.

Funding

This study was funded by the Science and Technology Fund of Guangdong Province (2014A020212483).

Authors' contributions

Lixin Xiao and Kai Feng carried out the study and drafted the manuscript. Kai Feng and Zhi-shuo Mo collected data and performed data analyses. Chao-shuang Lin contributed to the study design, data analyses, and critical revision of the manuscript, as well as communication with the journal. All authors had access to the study data and reviewed and approved the final manuscript. Lixin Xiao and Kai Feng contributed equally to this work and share first authorship.

Acknowledgements

None declared.

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Tables

Table 1. Clinical characteristics among different feeding types

Parameters	N	Exclusive breastfeeding (n=63)	Mixed feeding (n=34)	Artificial feeding (n=58)	All (n=155)	P
Age, year	155	29.08±3.30	27.88±2.96	29.50±3.55	28.97±3.36	0.079
Educational level						0.233
Junior and senior high	31	8 (25.81%)	6 (19.35%)	17 (54.84%)	-	
Undergraduate	108	47 (43.52%)	25 (23.15%)	36 (33.33%)	-	
Graduate and above	16	8 (50.00%)	3 (18.75%)	5 (31.25%)	-	
Work status						0.933
Unemployed	42	17 (40.48%)	9 (21.43%)	16 (38.10%)	-	
Part-time or freelance	14	7 (50.00%)	2 (14.29%)	5 (35.71%)	-	
Full-time	99	39 (39.39%)	23 (23.23%)	37 (37.37%)	-	
Parity	155	1.16±0.41	1.26±0.45	1.45±0.50	1.29±0.47	0.003
Delivery method						0.366
Vaginal	114	48 (42.11%)	27 (23.68%)	39 (34.21%)	-	
Cesarean section	41	15 (36.59%)	7 (17.07%)	19 (46.34%)	-	
Medication						0.361
LDT	131	52 (39.69%)	27 (20.61%)	52 (39.69%)	-	
TDF	24	11 (45.83%)	7 (29.17%)	6 (25.00%)	-	
Gestational timing of anti-viral therapy	155	25.19±4.17	24.18±4.07	24.67±2.96	24.77±3.73	0.430
Postpartum timing of stopping NAs treatment						0.022
Delivery day	110	50 (45.45%)	28 (25.45%)	32 (29.09%)	-	
1 month	3	1 (33.33%)	2 (66.67%)	0 (0.00%)	-	
1.5 months	18	6 (33.33%)	2 (11.11%)	10 (55.56%)	-	
2 months	1	1 (100.00%)	0 (0.00%)	0 (0.00%)	-	

3 months	1	1 (100.00%)	0 (0.00%)	0 (0.00%)	-	
6 months	1	0 (0.00%)	0 (0.00%)	1 (100.00%)	-	
9 months	1	0 (0.00%)	0 (0.00%)	1 (100.00%)	-	
Never	20	4 (20.00%)	2 (10.00%)	14 (70.00%)	-	
Postpartum liver function						0.158
Normal	94	39 (41.49%)	22 (23.40%)	33 (35.11%)	-	
Index rising	23	9 (39.13%)	2 (8.70%)	12 (52.17%)	-	
Postpartum viral load						0.028
Normal	54	18 (33.33%)	19 (35.19%)	17 (31.48%)	-	
Abnormal	79	35 (44.30%)	12 (15.19%)	32 (40.51%)	-	
Infant gender						0.524
Male	78	34 (43.59%)	18 (23.08%)	26 (33.33%)	-	
Female	76	28 (36.84%)	16 (21.05%)	32 (42.11%)	-	
Vaccination on time						0.405
No	1	1 (100.00%)	0 (0.00%)	0 (0.00%)	-	
Yes	154	62 (40.26%)	34 (22.08%)	58 (37.66%)	-	
Successful hepatitis B vaccination						0.054
No	5	0 (0.00%)	1 (20.00%)	4 (80.00%)	-	
Yes	142	59 (41.55%)	30 (21.13%)	53 (37.32%)	-	
Breastfeeding months	-	9.16±4.38	5.56±3.64	-	7.92±4.47	<0.001
Breastfeeding with wounds						0.314
No	57	38 (66.67%)	19 (33.33%)	0 (0.00%)	-	

Yes	32	19 (59.38%)	12 (37.50%)	1 (3.13%)	-	
Decision of feeding method						0.319
Both parents	85	36 (42.35%)	20 (23.53%)	29 (34.12%)	-	
Physician	39	19 (48.72%)	6 (15.38%)	14 (35.90%)	-	
Mother alone	31	8 (25.81%)	8 (25.81%)	15 (48.39%)	-	
Infant birth body weight, kg	155	4.22±1.65	4.02±1.43	3.71±1.38	3.99±1.51	0.179
Infant birth body length, cm	155	48.94±3.42	49.82±2.39	49.40±2.09	49.31±2.76	0.315
Child with unusually healthy issue						0.791
No	143	59 (41.26%)	31 (21.68%)	53 (37.06%)	-	
Yes	4	1 (25.00%)	1 (25.00%)	2 (50.00%)	-	
Knowledge of medication (LDT/TDF)						<0.001
No	32	4 (12.50%)	6 (18.75%)	22 (68.75%)	-	
Yes	120	58 (48.33%)	28 (23.33%)	34 (28.33%)	-	
Child with unusual height or weight						0.382
No	149	61 (40.94%)	33 (22.15%)	55 (36.91%)	-	
Yes	3	1 (33.33%)	0 (0.00%)	2 (66.67%)	-	

Table 2. Clinical characteristics between groups with or without breastfeeding

Parameters	N	Breast and mixed feeding (n=97)	Artificial feeding (n=58)	All (n=155)	P
Age, year	-	28.66±3.22	29.50±3.55	28.97±3.36	0.133
Educational level					0.080
Junior and senior high	31	14 (45.16%)	17 (54.84%)	-	
Undergraduate	108	72 (66.67%)	36 (33.33%)	-	
Graduate and above	16	11 (68.75%)	5 (31.25%)	-	
Work status					0.987
Unemployed	42	26 (61.90%)	16 (38.10%)	-	
Part-time or freelance	14	9 (64.29%)	5 (35.71%)	-	
Full-time	99	62 (62.63%)	37 (37.37%)	-	
Parity	-	1.20±0.42	1.45±0.50	1.29±0.47	0.001
Gestational weeks	-	40.04±2.50	39.72±2.24	39.92±2.41	0.429
Delivery method					0.169
Vaginal	114	75 (65.79%)	39 (34.21%)	-	
Cesarean section	41	22 (53.66%)	19 (46.34%)	-	
Medication					0.171
LDT	131	79 (60.31%)	52 (39.69%)	-	
TDF	24	18 (75.00%)	6 (25.00%)	-	
Gestational timing of anti-viral therapy	-	24.84±4.14	24.67±2.96	24.77±3.73	0.794
Postpartum timing of stopping NAs treatment					0.002
Delivery day	110	78 (70.91%)	32 (29.09%)	-	
1 month	3	3 (100.00%)	0 (0.00%)	-	
1.5 months	18	8 (44.44%)	10 (55.56%)	-	
2 months	1	1 (100.00%)	0 (0.00%)	-	
3 months	1	1 (100.00%)	0 (0.00%)	-	
6 months	1	0 (0.00%)	1 (100.00%)	-	
9 months	1	0 (0.00%)	1 (100.00%)	-	
Never	20	6 (30.00%)	14 (70.00%)	-	

Postpartum liver function					0.132
Normal	94	61 (64.89%)	33 (35.11%)	-	
Index rising	23	11 (47.83%)	12 (52.17%)	-	
Postpartum viral load					0.289
Normal	54	37 (68.52%)	17 (31.48%)	-	
Abnormal	79	47 (59.49%)	32 (40.51%)	-	
Infant gender					0.261
Male	78	52 (66.67%)	26 (33.33%)	-	
Female	76	44 (57.89%)	32 (42.11%)	-	
Vaccination on time					1.000
No	1	1 (100.00%)	0 (0.00%)	-	
Yes	154	96 (62.34%)	58 (37.66%)	-	
Successful hepatitis B vaccination					0.145
No	5	1 (20.00%)	4 (80.00%)	-	
Yes	142	89 (62.68%)	53 (37.32%)	-	
Breastfeeding months	-	7.92±4.47	-	7.92±4.47	-
Breastfeeding with wounds					0.768
No	57	57 (100.00%)	0 (0.00%)	-	
Yes	32	31 (96.88%)	1 (3.13%)	-	
Decision of feeding method					0.363
Both parents	85	56 (65.88%)	29 (34.12%)	-	
Physician	39	25 (64.10%)	14 (35.90%)	-	
Mother alone	31	16 (51.61%)	15 (48.39%)	-	
Infant birth body weight, kg	-	4.15±1.57	3.71±1.38	3.99±1.51	0.080
Infant birth body length, cm	-	49.26±3.11	49.40±2.09	49.31±2.76	0.760
Child with unusually healthy issue					0.997
No	143	90 (62.94%)	53 (37.06%)	-	
Yes	4	2 (50.00%)	2 (50.00%)	-	

Knowledge of medication (LDT/TDF)					<0.001
No	32	10 (31.25%)	22 (68.75%)	-	
Yes	120	86 (71.67%)	34 (28.33%)	-	
Child with unusual height or weight					0.651
No	149	94 (63.09%)	55 (36.91%)	-	
Yes	3	1 (33.33%)	2 (66.67%)	-	

Table 3. Associations between independent variables to groups with or without breastfeeding

Parameters	Univariate		Multivariate	
	OR (95%)	P	OR (95%)	P
Educational level		0.087		0.177
Junior and senior high	ref.	-	ref.	-
Undergraduate	0.41 (0.18 to 0.93)	0.032	0.43 (0.17 to 1.10)	0.077
Graduate and above	0.37 (0.10 to 1.34)	0.130	0.34 (0.07 to 1.65)	0.179
Parity	3.12 (1.54 to 6.33)	0.002	3.21 (1.42 to 7.23)	0.005
Postpartum timing of stopping NAs treatment, levels	1.30 (1.13 to 1.51)	<0.001	1.36 (1.15 to 1.62)	<0.001
Infant birth body weight, kg	0.81 (0.64 to 1.03)	0.083	0.82 (0.62 to 1.09)	0.174
Knowledge of medication (LDT/TDF)				
No	ref.	-	ref.	-
yes	0.18 (0.08 to 0.42)	<0.001	0.22 (0.09 to 0.56)	0.001