













# Factors Influencing HIV Infection in Children Born to HIV-Infected Mothers in Turkey

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**Background:** Human immunodeficiency virus (HIV) is still a challenge for children. About 15 to 45% of the HIV positive pregnant women can transmit the virus to their children during pregnancy, delivery and/or breastfeeding. The risk of transmission can be decreased by several measures.

**Aims:** To identify factors associated with HIV infection in children born to HIV-infected mothers.

**Study Design:** A multi-center retrospective cohort study.

**Methods:** A ten-year retrospective cohort study in five dedicated HIV centers was conducted. The 325 women in our cohort were between the ages of 18 and 45. During the study period, 44 (13.5%) of these

women gave birth and 51 babies were born. Of the 51 infants, 7 (13.7%) were HIV/AIDS positive.

**Results:** Among the factors studied, breastfeeding, having a HIV-positive sibling and being on antiretroviral treatment during pregnancy and detectable HIV-RNA during delivery were found statistically significant. A multivariable logistic regression analysis showed that being on antiretroviral treatment during pregnancy is the most important predictor of mother-to-child transmission.

**Conclusion:** Mother-to-child transmission appears to be an important route of HIV transmission in Turkey. Lack of antiretroviral treatment during pregnancy appears to be a key factor in transmission.



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Received: February 06, 2023 Accepted: June 05, 2023 Available Online Date: September 07, 2023 • DOI: 10.4274/balkanmedj.galenos.2023.2023-3-12

Available at [www.balkanmedicaljournal.org](http://www.balkanmedicaljournal.org)

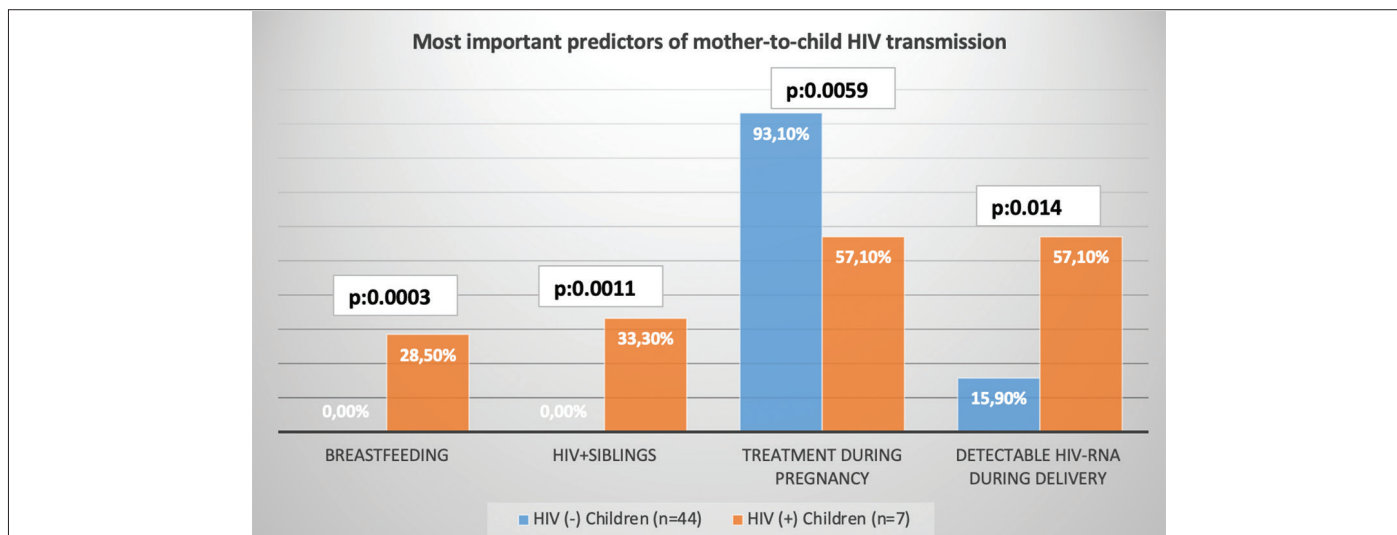
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Cite this article as:

Zerdali E, Mete B, Altuntaş Aydın Ö, Gündüz A, Yılmaz Nakir İ, Bolukçu S, Kumbasar Karaosmanoğlu H, Sevgi DY, Koç MM, Tabak F. Factors Influencing HIV Infection in Children Born to HIV-Infected Mothers in Turkey. *Balkan Med J.*; 2023; 40(5):367-72.

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## GRAPHICAL ABSTRACT



## INTRODUCTION

According to The Joint United Nations Program on HIV/AIDS (UNAIDS), 37.7 million people worldwide were infected with the human immunodeficiency virus (HIV) in 2020. Among them, 1.7 million were children, and 150,000 children were newly infected with HIV in 2020.<sup>1</sup>

HIV infection can be transmitted from mother to child during pregnancy, delivery, and/or breastfeeding.<sup>2</sup> Current evidence suggests that HIV can infect the placenta, and the risk of transplacental transmission increases toward the end of pregnancy.<sup>3,4</sup> During labor and birth, transmission occurs not only through direct exposure of the infant to infected maternal blood and genital secretions but also through ascending infection (i.e., from the vagina and cervix to the fetus) and viral absorption in the fetal-neonatal gastrointestinal tract.<sup>5</sup> Finally, breastfeeding has increased the risk of virus transmission to infants by 7-12%.<sup>6</sup> All of these stages that may result in virus transmission to infants can be prevented with effective measures, including the control of viral replication with antiretroviral treatment (ART).

Without intervention, 15-45% of HIV-infected pregnant women can transmit the virus to their children.<sup>7</sup> Mother-to-child transmission (MTCT) accounts for more than 90 new HIV infections in children.<sup>8</sup> Antenatal HIV screening, ART for the mother, prophylaxis for the infant, and withholding breastfeeding can significantly reduce the transmission rate. However, although transmission methods to infants are being investigated and effective measures are being developed, pediatric HIV infection remains a challenging public health concern. According to UNAIDS, 4,000 new HIV infections occur daily, with children accounting for 10%. In 2020, there were 680,000 AIDS-related deaths, and 99,000 were children (< 15 years old).<sup>1</sup>

Although the HIV prevalence in Turkey is low, there has been an increase in newly diagnosed HIV/AIDS cases reported to the Ministry of Health of Turkey.<sup>9</sup> Pregnant women are routinely

screened for HIV, and treatment, and prophylaxis are covered. Physicians continue to report HIV-infected infants born to HIV/AIDS-positive mothers. Despite standard recommendations to prevent MTCT, many demographic, and sociologic features and practices influence the transmission dynamics. The exact situation of MTCT is unknown. Therefore, we aimed to determine the factors associated with HIV infection in children born to HIV-infected mothers. The findings of this study are expected to contribute to implementing strategies to reduce HIV transmission to children from infected mothers.

## MATERIALS AND METHODS

## Study Design

The present study was a retrospective cohort study.

## Setting

The study was conducted at five HIV treatment centers in İstanbul. Using patient charts, a 10-yr retrospective cohort study design was used on mothers living with HIV/AIDS and their infants.

## Participants

From January 2011 to March 2021, all mothers with HIV/AIDS in five HIV centers were recorded.

One hundred forty-four (9.9%) of the 4,423 patients in our cohort were female. Three hundred twenty-five (7.3%) of these women were between the ages of 18 and 45 yr. Forty-four (13.5%) gave birth.

## Inclusion Criteria

All women with a current or previous positive test of reoxyribonucleic acid-polymerase chain reaction test (RNA-PCR) test were included. Those with a child or children under the age of 18 months old were included in the study.

### Exclusion Criteria

Women who did not respond to follow-up were excluded. Infants/children without confirmed results and at least 18 months of follow-up were excluded from the study. The pair (both mother and infant) data were excluded if the mother's or infant's data were missing.

### The Study Procedure

Requests for the study were addressed to five dedicated HIV centers (two university hospitals and three education and training hospitals), and all were approved. The study protocol was provided, and all was confirmed. Each hospital directory approved the protocol and permitted sharing of medical records between HIV-infected mothers and their children. Each center received a Microsoft Excel spreadsheet. This sheet contains data on mother and child pairs. After 3 months, the centers sent the sheet.

### Statistical analysis

The data were uploaded to SPSS software (version 17) for analysis. The data were examined for any inconsistencies, missing values, or outliers. After reviewing the data in the source, necessary corrections were made. Descriptive statistics were used, and the results were presented as mean  $\pm$  standard deviation. Continuous and categorical variables between HIV-infected and non-HIV-infected groups (mothers or infants) were compared using the Student's t-test and chi-square test (Fisher's exact test). The association between the variables was determined using multivariate logistic regression analysis with a confidence interval of 95%. Variables with a *p* value of  $< 0.25$  in bivariate analysis were included in multivariate analysis. Variables with a *p* value of  $< 0.05$  in multivariate analysis were accepted as associated with the outcome.

### Ethics

The study was approved by the Committee of Ethics of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (83045809-604.01.02).

Two outliers (mother's age at delivery) were identified as data entry errors and corrected. Three missing data of detectable HIV-RNA on conception were imputed using before and after results. There were no inconsistencies found.

### RESULTS

During the 10-yr study period, 51 infants were born to 44 HIV/AIDS-positive mothers: one mother gave birth three times, and five mothers gave birth twice (Table 1). Thus, the HIV-infected children group included seven HIV-infected children from six mothers, and the non-HIV-infected children group included 44 non-HIV-infected children from 38 mothers. During the study's 10-yr period, seven (13.7%) of 51 infants born to mothers living with HIV/AIDS were HIV positive.

The mean age of women was  $30.96 \pm 4.8$  yr (at the time of birth) and  $35.05 \pm 5.2$  yr (at the time of study analysis). Breastfeeding, having an HIV-infected sibling, lack of ART during pregnancy, and detectable HIV-RNA during delivery were statistically significant among the factors studied (Table 1). The parameters of mother's age at delivery, breastfeeding, gravidity, HIV + siblings, treatment during pregnancy, prophylaxis after birth, detectable HIV-RNA on conception, and detectable HIV-RNA during delivery were added to the multivariable logistic regression analysis, which revealed that lack of ART during pregnancy is the most important predictor of MTCT (adjusted odds ratio, 3.8; 95% confidence interval, 1.143-8.342).

**TABLE 1.** Characteristics of Non-HIV-infected and HIV-infected Infants and Their Mothers.

	Non-HIV-infected children (n = 38) <sup>a</sup>	HIV-infected children (n = 6) <sup>b</sup>	<i>p</i>
Mother's age on delivery (yr, mean $\pm$ standard deviation)	31.1 sd=4.9	29.7 $\pm$ 2.6	0.22
Mother's education (illiterate/primary/secondary/higher/unknown)	1/13/12/6/6 (3%/34%/31%/16%/16%)	1/2/2/0/1 (17%/33%/33%/0%/17%)	0.75
Father's anti-HIV test (positive/negative/unknown)	25/16/3 (57%/36%/7%)	4/2/1 (57%/29%/14%)	0.77
Mode of delivery	Normal: 12 (27%), cesarean: 32 (73%)	Normal: 3 (43%), cesarean: 4 (57%)	0.40
Breastfeeding	0/44 (0%)	2/7 (29%)	0.0003
Gravidity	1.57 $\pm$ 0.79	2.02 $\pm$ 0.93	0.23
HIV + siblings	0/14 (0%)	1/3 (33%)	0.0011
Treatment during pregnancy	41/44 (93%)	4/7 (57%)	0.0059
Prophylaxis after birth	44/44 (100%)	5/6 (83%)	0.13
Detectable HIV-RNA on conception	20/44 (46%)	4/7 (57%)	0.33
Detectable HIV-RNA during delivery	7/44 (16%)	4/7 (57%)	0.014
Time of detection of HIV of mother	Antenatal: 26 (59%), during pregnancy: 15 (34%), during birth: 3 (7%)	Antenatal: 5 (72%), during pregnancy: 1 (14%), during birth: 1 (14%)	0.51

<sup>a</sup>Eight mothers and 44 children, <sup>b</sup>Six mothers and seven children, HIV, human immunodeficiency virus.

ART was used during pregnancy by 41 of 44 women in the non-HIV-infected children group and four of seven women in the HIV-infected children group ( $p < 0.01$ ). The most widely used treatment was a combination of tenofovir disoproxil fumarate, emtricitabine, and raltegravir, which was used in 30 of 41 non-HIV-infected children group and all four HIV-infected children group (Table 2).

After-birth prophylaxis includes oral zidovudine given to infants for 6 weeks at comparable rates (Table 2).

**DISCUSSION**

In our study, the MTCT of HIV was 13.7% in a 10-yr cohort. This result represents a significantly high transmission rate and a challenge to HIV care in our society. The study sites include tertiary HIV care centers in the country’s biggest city, revealing gaps in the HIV care continuum even at specialized centers. The study showed a high MTCT rate (13.5%) in Turkey. Considering that the World Health Organization’s (WHO) elimination target for the non-breastfeeding population is < 2%, the rate in our country’s HIV centers is far from local and global targets. The study shows shortcomings in diagnosing HIV infection before delivery and providing the mother with effective treatment (undetectable RNA).

According to our study, a lack of ART during pregnancy is the key predictor of MTCT. A previous case-control study revealed that effective control of viral load with antiretroviral (ARV) is associated with a lower risk of MTCT of HIV-1.<sup>10</sup> After adjusting for viral load, CD4(+) T-cell count, and ARV therapy initiation time, the only factor identified to be independently associated with MTCT of HIV was viral load. Between 2010 and 2019, treatment coverage during pregnancy increased from 33% to 70% in sub-Saharan Africa, whereas the MTCT of HIV reduced from 27.2% to 16.9%.<sup>11</sup> In the same study, a subgroup analysis revealed that higher rates of ARV coverage and lower rates of MTCT were recorded in upper-middle-income groups. Maternal viral load and CD4 cell count were shown to affect MTCT rates in HIV-2, which has lower MTCT rates than HIV-1.<sup>12</sup> A meta-analysis found that ART is a safe and effective strategy for sustaining maternal virologic suppression, reducing infant mortality, and lowering rates of MTCT in HIV-infected pregnant women.<sup>13</sup> In our cohort, while detectable HIV-RNA was comparable between groups during conception (20/44 vs. 4/7,  $p = 0.33$ ), it was significantly lower in the non-HIV-infected children group during delivery (7/44 vs. 4/7,  $p = 0.014$ ). Thus, maintaining an effective ART appeared to decrease the MTCT of HIV.

While no mothers in the non-HIV-infected children group breastfed, two of seven in the HIV-infected children group did. Breastfeeding has been shown to increase the risk of perinatal MTCT. Although maternal ART use significantly reduces the risk, the Center for Disease Control and Prevention and the American Academy of Pediatrics suggest that mothers with HIV/AIDS avoid breastfeeding their infants, regardless of ART and maternal viral load.<sup>14</sup> On the other hand, in resource-limited settings, the WHO<sup>15</sup> recommends that mothers living with HIV/AIDS breastfeed exclusively during the first 6 months and continue breastfeeding for at least 12 months of life, with the addition of complementary foods (WHO). The Turkish HIV Diagnosis and Treatment Guideline by the Ministry of Health of Turkey recommend that mothers with HIV/AIDS avoid breastfeeding.<sup>16</sup>

The mode of delivery can affect the MTCT rate. The cesarean section before labor and membrane rupture (so-called elective cesarean section [ECS]) has been suggested to decrease MTCT rates. A Cochrane review 2005 showed that ECS is an effective measure for preventing MTCT in HIV-1-infected women who are not on ARV or taking only zidovudine.<sup>17</sup> This report also emphasized that the risk of MTCT varies depending on the mode of delivery in HIV-infected women with low viral loads. Accordingly, in our study, the mode of delivery was not shown to be a factor affecting the rate of MTCT. The predominant effect of viral load/maternal ART probably offsets the effects of other factors, including the mode of delivery.

Having an HIV-infected sibling appears to be a significant factor for MTCT. Although it represents one case in the HIV-infected children group, it emphasizes the role of the mother’s adherence to the measures to prevent MTCT.

Although prophylaxis was provided to five infants in the HIV-infected children group, it appeared ineffective. This unsatisfactory result may be attributed to a combination of variables, including a lack of treatment during pregnancy ( $n = 3$ ), breastfeeding ( $n = 2$ ), ineffective viral suppression (detectable HIV-RNA during delivery,  $n = 3$ ), and probably other factors that did not achieve statistical significance.

While the number of newly diagnosed cases in Turkey has consistently increased, it has decreased in the last 2 years (Figure 1). This recent decrease can be attributed to the COVID-19 pandemic<sup>18</sup> and maybe temporal. The disease burden increases

**TABLE 2.** Treatment During Pregnancy.

	Non-HIV-infected children ( $n = 38^*$ )	HIV-infected children ( $n = 6^{**}$ )	<i>p</i>
Treatment during pregnancy	41/44 (93%)	4/7 (57%)	0.0059
Drugs used	TDF + FTC + RAL: 30 (73%) 3TC + ZDV + LPV/r: 5 (12%) TDF + FTC + LPV/r: 2 (5%) TDF + FTC + DRV/r: 2 (5%) TDF + FTC + DTG/TDF + FTC + RAL: 1 (2.5%) TDF + FTC + EVG/c: 1 (2.5%)	TDF + FTC + RAL: 4 (100%)	

3TC, lamivudine; DRV, darunavir; DTG, dolutegravir; EVG/c, elvitegravir/cobicistat; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; RAL, raltegravir; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine.

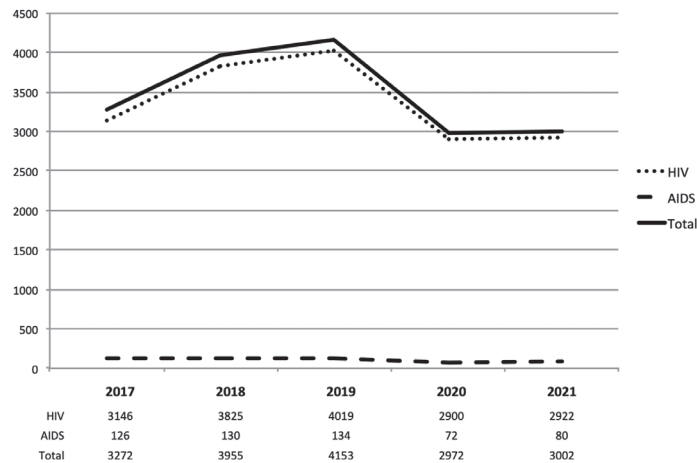


FIG 1. HIV and AIDS cases by years reported to the Ministry of Health of Turkey.

with time. HIV treatment and prophylaxis are covered by social security. All pregnant women are routinely screened for hepatitis B, hepatitis C, and HIV. Seropositive and seronegative women with a seropositive spouse are informed about the risk of infection and how to protect the child. In Turkey, 72-74% of all HIV patients were estimated to be diagnosed, 92% were on ARV therapy and 70% achieved viral suppression.<sup>19</sup> These numbers do not include pregnant women. Because HIV screening is routine, the gaps in providing ARV therapy and achieving viral suppression are estimated.

The limitation of this study is that the study design is a retrospective cohort, and some details could not have been obtained. Mothers with HIV-infected children may have presented clinical care more frequently than mothers with non-HIV-infected children. Because lost follow-up cases were excluded from the study, the MTCT values may be overestimated. The second limitation is that although prophylaxis for children born to HIV-infected mothers is well reported, prophylaxis for the mother, particularly in the HIV-infected children group, is not described, which may affect the MTCT rate. Another limitation of the study is its small sample size. A study with a larger sample size may clearly define the factors influencing MTCT.

MTCT appears to be a considerable way of HIV transmission in Turkey. Detecting HIV-infected mothers, initiating ARV therapy, and counseling mothers to sustain adherence appear to be the key factors in decreasing MTCT.

**Acknowledgments:** The authors would like to thank Rukiye Zenginol for her contributions to data management. The authors also acknowledge all healthcare professionals who have contributed to the care of their patients.

**Ethics Committee Approval:** The study was approved by the Committee of Ethics of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (83045809-604.01.02).

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Authorship Contributions:** Concept- E.Z., İ.Y.N., F.T., Design- E.Z., B.M.,

Ö.A.A., F.T., Data Collection or Processing- E.Z., B.M., Ö.A.A., A.G., İ.Y.N., S.B., H.K.K., D.Y.S., M.M.K., F.T., Analysis or Interpretation- E.Z., B.M., Ö.A.A., A.G., İ.Y.N., H.K.K., F.T., Literature Search- E.Z., B.M., Ö.A.A., A.G., İ.Y.N., S.B., D.Y.S., M.M.K., Writing- E.Z., B.M., Ö.A.A., A.G., İ.Y.N.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Funding:** The authors declared that this study received no financial support

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