

Assessing the effectiveness of prevention of mother-to-child HIV transmission

R.M. Khamidulina^{1*}, M.G. Katyagina², I.S. Zolotova², L.E. Ziganshina¹

¹Kazan State Medical University, Kazan, Russia;

²Republican Center for the Prevention and Control of AIDS
and Infectious Diseases, Yoshkar-Ola, Russia

Abstract

Aim. To analyze the outcomes of a set of interventions to prevent vertical transmission of the human immunodeficiency virus (HIV) in the Republic of Mari El.

Methods. A retrospective analysis of temporary registration forms “Notifications of the termination of pregnancy in an HIV-infected woman” and “Notifications of a newborn born by an HIV-infected mother”, case histories and outpatient medical records of HIV-infected women who gave birth in 2000–2018 was carried out. The study included all children born in the Republic of Mari El to HIV-positive women registered with the Republican Center for the Prevention and Control of AIDS and Infectious Diseases, as well as children whose HIV status is detected after birth as a result of epidemiological investigations. The assessment of the risks of transmission as an outcome of the three-step preventive interventions has been carried out. A comparative analysis of the results of perinatal prevention of HIV transmission in the Republic of Mari El and other regions of the Russian Federation was performed.

Results. A total of 299 HIV-infected pregnant women and 368 children born to these women during the study period were registered in the region; 63 (21.7%) of these women had more than one child. Over the entire study period, 18 (4.8%) children with confirmed HIV infection were registered. The most common factor associated with infant HIV infection is late maternal HIV diagnosis: (1) several years after childbirth in the absence of antiretroviral (ARV) prophylaxis and the infants were breastfeeding (11 cases, 64.7%); (2) during or shortly after childbirth, when the patient did not receive entire three-step antiretroviral prophylaxis during pregnancy and childbirth (6 cases, 29.4%); (3) in the third trimester of pregnancy (1 case, 5.5%). An important limitation for the successful prevention of vertical transmission of HIV was the lack of routine HIV testing, which is required by women and their partners before and at various stages during pregnancy. A single case of self-infection indicates the need to introduce preventive measures from early adolescence among children.

Conclusion. Due to the late maternal HIV diagnosis, during or after delivery, HIV transmission events occurred either with limited or no limited antiretroviral prophylaxis.

Keywords: HIV-infection, antiretroviral therapy, pregnancy, prevention of perinatal transmission.

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Background. According to the official worldwide data of the World Health Organization (WHO), at the end of 2019, approximately 38 million people were infected by human immunodeficiency virus (HIV), of which 1.8 million were children aged < 14 years. Moreover, of 1.7 million people with HIV infection in 2019, 48% were women aged >15 years. In addition, >60% of new HIV infections worldwide are registered in populations aged 15–49 years. In 2019, life-long antiretroviral therapy (AVRT) was given in 68% of all adults and in 53% of children with HIV infection [1,2]. In Russia, according to the official data of WHO as of Decem-

ber 31, 2017, approximately 1 million people were infected with HIV [3].

According to the Federal Service for Surveillance of Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) as of December 31, 2018, 1,329,331 citizens of the Russian Federation have HIV infection, of which 472,405 (35.5%) were women and 795,256 (59.8%) were men. Moreover, 72% of individuals with HIV infection are aged 20–40 years [4].

When a significant proportion of HIV infection was identified in individuals of working and reproductive age, the focus is on effective prevention of

vertical transmission of HIV infection from the mother to her child.

Preventive measures for HIV transmission from the mother to her child are carried out using three stages of ARVT [5,6]; HIV can be transmitted at any of these stages: antepartum (transplacental during pregnancy, through the amniotic membranes and amniotic fluid, and during diagnostic invasive procedures), intrapartum (during childbirth), and postpartum (during breastfeeding). The risk of transmission can be virtually eliminated if the mother and her baby received ARVT drugs on time during pregnancy and breastfeeding [7]. The timing of ARVT prescription is dependent on the disease stage, viral load, and level of CD4 lymphocytes to achieve an undetectable viral load before delivery, as it is the most important factor that affects the likelihood of HIV transmission from the mother to her child [8].

In 2014, HIV and Reproductive Health and Research Departments of WHO, in collaboration with other international organizations, published guidelines on global processes and criteria for the elimination of mother-to-child transmission of HIV and syphilis which aim to eliminate this type of HIV transmission [9]. With the complex of measures taken in 2018, the frequency of perinatal HIV transmission in the Russian Federation was 1.5% [10].

Aim. This study aimed to analyze the outcomes of preventive measures for vertical transmission of HIV from the mother to her child in the Republic of Mari El, an administrative region of the Russian Federation.

Materials and methods. This study analyzed retrospectively 359 cases, as recorded “On the termination of pregnancy in an HIV-infected woman” Form No. 313/y and “On a newborn born by an HIV-infected mother” Form No. 309/y, which register cases of children born in the territory of Mari El in 2000–2018, to assess the vertical transmission of HIV in women with HIV infection who presented for regular medical checkup in the State Budgetary Institution of the Republic of Mari El Republican Center for the Prevention and Control of AIDS and Infectious Diseases and those without regular medical checkup.

In this study, case histories of children whose positive infectious status was detected after birth at different time periods as a result of ongoing epidemiological investigations (from age 1 to 13 years) were evaluated. The primary outcome was the child’s HIV-positive status, which was determined after chemoprophylaxis. Dichotomous data (with chemoprophylaxis/without chemoprophylaxis) were pooled, dichotomous outcomes were analyzed, and results were presented as the risk ratio

(95% confidence interval) of having an HIV-infected child.

Calculations were performed using Cochrane Collaboration Certified Review Manager 5.4.1 (RevMan) software. HIV infection was diagnosed based on the results of enzyme immunoassay and immune blotting by the clinical diagnostic laboratory of the AIDS Center of the Republic of Mari El. Disease stage was determined based on the clinical manifestations and results of laboratory tests in accordance with the Annex “Clinical classification of HIV infection” and instructions for filling out the annual form of state federal statistical observation No. 61 “Information on the patient populations with HIV infection,” approved by Order No. 166 dated March 17, 2006, of the Ministry of Health and Social Development of Russia [11, 12].

Moreover, this study used the information provided in annual federal reporting forms No. 61 “Information on the contingents of patients with the disease caused by the human immunodeficiency virus (HIV),” which was approved by the order of Rosstat dated December 30, 2015, No. Statistical Surveillance in Healthcare for 2014–2018, presented by the State Budgetary Institution of the Republic of Mari El Republican Center for the Prevention and Control of AIDS and Infectious Diseases, which provided accurate information about the patient population.

In addition, information bulletins “HIV infection” of the Federal Scientific and Methodological Center for the Prevention and Control of AIDS were used to provide a complete description of patients with HIV infection during the study period.

Furthermore, for a detailed analysis of the ARVT regimen as part of the ongoing prevention of mother-to-child transmission of HIV infection from 2000 to 2018, we performed a retrospective analysis of 150 case histories of patients who underwent regular medical checkup at the State Budgetary Institution of the Republic of Mari El Republican Center for the Prevention and Control of AIDS and Infectious Diseases Forms No. 025/y approved by Order No. 834n dated December 15, 2014, “On approval of unified forms of medical documentation used in medical organizations providing medical care on an outpatient basis and procedures for filling them out” of the Ministry of Health of the Russian Federation.

We also performed a comparative analysis of the indicator “Coverage of mother and child pairs with chemoprophylaxis for HIV infection” as a target indicator of subprogram 4 “Maternal and child health” of the program approved by Decree No. 294 dated April 15, 2014, of the Government of the Russian Federation “On approval of the state

program of the Russian Federation Healthcare Development.”

Descriptive statistics were performed in the distribution of patients by age, indicators of mean values, ratio of different groups of patients, indicators of coverage with chemoprophylaxis, analysis of ART regimens, as well as minimum and maximum values. Data were processed using the Microsoft Office software package.

Results. As of December 31, 2018, a total of 2,181 residents had HIV infections in the Republic of Mari El. Of the 682,333 total populations in the region, 1331 people underwent medical checkup at the end of the year, of which 685 were men and 646 women (51.46%/48.53%), while 63 (9.7%) patients who had a positive HIV status were first identified when undergoing pregnancy checkup. The number of patients receiving ARVT is 914.

The average age of patients with HIV infection and receiving ART was 37 ± 0.3 years (range, 0–67) years, and patients aged 31–40 years make up more than half of all registered HIV-infected cases in the republic (54% of the total number of patients).

With a high rate of morbidity in women, an increase in the number of deliveries was noted in patients with HIV infection. Table 1 shows the dynamics of the number of pregnant women with HIV infection in the Republic of Mari El for the period from 2015 to 2018, which shows an increase in the number of women who had full-term pregnancy and delivery. The average age of parturient women was 28 ± 0.38 (range, 16–51) years.

In the Republic of Mari El, for the period from January 01, 2000, to December 31, 2018, 368 children born to 299 women with HIV infection underwent regular medical checkup for perinatal HIV contact, of which 63 (21.7%) patients had repeated deliveries. As of December 31, 2018, 18 children with confirmed HIV-positive status were registered at the dispensary, 17 of them after perinatal contact, and one case was a result of unprotected sex. An increase in the number of deliveries in pregnant women with HIV infection was recorded during the study interval: from isolated cases in 2003 up to 38 cases of successful delivery in 2018.

For the 2000–2018 period, the overall rate of chemoprophylaxis coverage in the Republic of Mari El was 95.1%. Thus, the coverage rate in 2018 was 97.3%, which exceeded the expected rates for “coverage of mother and child pairs” of 85.8% in 2018 and expected coverage of 85.9% in 2020. The rate of vertical transmission of HIV without preventive measures ranged from 10% to 40%, of which 15%–30% accounted for the transplacental route of transmission (intrauterine), 50%–75% of

Table 1. Number of pregnant women with HIV infection in the Republic of Mari El from 2000 to 2018

Parameters	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Total number of residents with HIV infection	14	195	298	340	477	526	569	610	690	784	1018	1101	1222	1348	1505	1471	1785	2009	2258
Proportion of women, %	—	26.2	—	—	—	37.5	—	—	—	48.5	52	58	50	49	50	50.2	49.9	48.9	48.5
Number of pregnant women with HIV infection	—	—	—	—	—	22	—	—	31	—	—	—	—	—	52	50	47	61	64
Number of female patients with HIV infection who had full-term pregnancy and childbirth during the reporting year	2	1	9	6	12	11	9	23	16	22	23	20	15	23	38	33	28	30	38

Table 2. Coverage rates of chemoprophylaxis in women with HIV infection in the Republic of Mari El from 2000 to 2018

Types of chemoprophylaxis	Stages of its conduction	Number of deliveries in women with HIV infection, abs. (%)	Number of children born with HIV infection, abs. (%)
One stage, total	—	17 (4.6)	2 (11.8)
	Antepartum	3	0
	Intrapartum	4	1
	Postpartum	10	1
Two stages, total	—	22 (5.9)	4 (23.5)
	Antepartum + intrapartum	4	0
	Antepartum + postpartum	2	0
	Antepartum + postpartum	16	4
Three stages	Antepartum + intrapartum + postpartum	311 (84.5)	1 (5.9)
Chemoprophylaxis not performed		16 (4.3)	9 (52.9)
No data on whether chemoprophylaxis was performed		2 (0.5)	1 (5.9)
Total		368 (100)	17 (100)

Table 3. Ratio of infection risks at different stages of prevention in the Republic of Mari El from 2000 to 2018

Types of chemoprophylaxis	Number of mother–child pairs	Number of children with HIV infection	Relative risk of infection (95% confidence interval)	p
One stage, total	17	2	0.32 (0.06; 1.57)	0.16
Two stages, total	22	4	0.46 (0.13; 1.68)	0.24
Three stages, total	311	1	0.01 (0.00; 0.08)	<0.0001
Total	357	7	0.13 (0.02; 1.06)	0.06

cases occurred during childbirth, 10%–20% were transmitted through breastfeeding [13].

Indicators of chemoprophylaxis carried out in the region are presented in Table 2.

To assess outcomes, Cochrane Collaboration's Review Manager 5.4.1 (RevMan) software resource was used to calculate the risk ratio for child infection.

Different numbers of infected children were registered at each stage of prevention. In accordance with our sample, the risk ratio of having an HIV-infected child for a mother–child pair who has undergone different stages of chemoprophylaxis is presented in Table 3.

Considering the sample size of mother–child pairs, the risk of infection significantly reduced when three-stage prophylaxis was carried out, with a hazard ratio of 0.01 and 95% confidence interval of 0.00–0.08. In our sample, only one child of 311 mother–child pairs had HIV infection and was registered after all stages of perinatal prophylaxis because of late diagnosis and ART was initiated at the end of pregnancy. A higher risk of infection (0.46) was recorded during two-stage prophylaxis compared with one stage prophylaxis because a large number of women were in labor in this group and a large number of patients received chemopro-

phylaxis only at the last stages (intrapartum and postnatal; Table 2). We did not include cases of infection of children among patients of these groups who received antenatal chemoprophylaxis.

We conducted a detailed analysis of the treatment regimen of 150 patients who received ARVT as prevention of mother-to-child HIV infection transmission and found that 78% (n = 117) of treatments were given at different stages of pregnancy and 22% (n = 33) were prescribed prior to pregnancy.

Prescribed ARVT regimens are presented in Table 4.

As shown in Table 3, the most commonly prescribed treatment regimens included two nucleoside reverse transcriptase inhibitors in combination with a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor: zidovudine + lamivudine + lopinavir/ritonavir (AZT + 3TC + LPN/r), tenofovir + lamivudine + lopinavir/ritonavir (TDF + 3TC + LPN/r), and abacavir + lamivudine + lopinavir/ritonavir (ABC + 3TC + LPN/r).

For moderate anemia, an alternative treatment regimen of phosphazide + lamivudine + lopinavir/ritonavir (PhAZT + 3TC + LPN/r) was prescribed in accordance with the clinical guidelines of the Ministry of Health of the Russian Federa-

Table 4. Schemes for antiretroviral perinatal prevention of mother-to-child HIV transmission in the Republic of Mari El from 2000 to 2018 (n = 150)

ARVT scheme	Abbreviation*	Number of prescriptions, n (%)
2 NRTI + PI	3TC+LPV/r+ZDV	77 (51.3)
	3TC+LPV/r+TDF	28 (18.7)
	3TC+LPV/r+PhAZT	23 (15.3)
	3TC+LPV/r+ABC	5 (3.3)
2 NRTI + NNRTI	3TC+EFV+TDF	4 (2.7)
	3TC+NVP+ZDV	3 (3.0)
	3TC+EFV+d4T	2 (1.3)
	3TC+EFV+ZDV	2 (1.3)
	3TC+ATV+ZDV	1 (0.7)
	DTG+EFV+ZDV	1 (0.7)
NRTI	ZDV	2 (1.3)
2 NRTI + 2 PI	3TC+DRV+RTV+ABC	1 (0.7)
	3TC+FPV+RTV+ABC	1 (0.7)

Note: ARVT, antiretroviral therapy; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; * drug abbreviations have been brought in line with the WHO Model List of Essential Medicines [14]: ZDV, zidovudine; 3TC, lamivudine; LPV/r, lopinavir/r; TDF, tenofovir; PhAZT, phosphazide; ABC, abacavir; EFV, efavirenz; d4T, stavudine; NVP, nevirapine; DRV, darunavir; RTV, ritonavir; DTG, dolutegravir; ATV, atazanavir.

tion KR411 “HIV infection: prevention of perinatal transmission of human immunodeficiency virus.” In 8.7% of chemoprophylaxis cases (n = 13), the AZT + 3TC + LPN/r regimen was the only regimen being prescribed before or during pregnancy at different periods and was not changed because of associated side effects or ineffectiveness.

Children are infected perinatally in 94.4% of cases (17 of 18). A three-stage course of chemoprophylaxis was not administered to a mother–child pair due to the following reasons:

- In 10 (58.9%) children, the diagnosis was made a few years after birth, during an epidemiological investigation, or when the mother’s subsequent pregnancy was registered.

- In 6 (35.3%) children, mothers were not registered in the dispensary and did not receive prophylaxis during pregnancy, so the HIV-positive status of the women was established shortly before or during childbirth or shortly after childbirth.

- In 1 (5.8%) child, perinatal infection occurred after all preventive measures were performed to the mother, presumably due to the late initiation of AVRT drugs at 36 weeks of gestation.

Discussion. Therapy with antiretroviral drugs reduces (stops) the transmission of the virus and disease progression and increases the life expectancy of people with HIV infection [1, 15, 16]. Analysis of barriers to successful prevention of vertical transmission of HIV infection in other regions of the Russian Federation allowed comparison of the statistical results of activities carried out in the regions at different periods of time.

The results of a retrospective study in the Republic of North Ossetia-Alania for the period from 1998 to 2017 demonstrated that 74% of pregnant women with HIV infection received three-stage perinatal prophylaxis. As of January 1, 2017, the dispensary register of the Republic of North Ossetia-Alania included 13 children who acquired HIV infection through the perinatal route, 12 of whom did not receive chemoprophylaxis at any stage. In 46.15% of cases, mothers did not undergo regular medical checkup and did not receive prophylaxis during pregnancy, cases of concealment of pregnancy and refusal of therapy for religious reasons were recorded, and in 1 (7.7%) child, perinatal infection occurred presumably in utero after all preventive measures were taken [17].

As regards the coverage rates for chemoprophylaxis in the Ulyanovsk region of the Volga Federal District of the Russian Federation, chemoprophylaxis was administered during pregnancy in 95.1% in 2018 and in 88.4% of cases in 2017, while coverage during delivery remained at a high level at 93.5 and 93.4%, respectively [18].

Moreover, analysis of the causes of HIV infection in children in the Ulyanovsk region showed the following [19]:

- In 34.5% of cases, pregnant women received ARVT but presumably had low adherence to therapy.

- In 33% of cases, a woman’s HIV-positive status was later established at a period of 30–33 weeks.

- In 32.5% of cases, women knew about their status but deliberately hid, so they were not monitored in the antenatal clinic and AIDS center.

Our results for the Republic of Mari El are comparable with the results of studies conducted in other regions of the Russian Federation, showing an increase in the number of children born to seronegative and unexamined women during pregnancy with a high viral load before childbirth [20–22]. In the present study, most of the children in the Republic of Mari El were identified during epidemiological investigations performed several years after birth.

Despite the annual improvement in values, the main reasons for perinatal infection of children in

the region remain the insufficient level of coverage with regular testing of women and their sexual partners and untimely access to medical care, especially in groups with low social status. Thus, the coverage of population testing for HIV infection in 2018 in the Republic of Mari El was 19.4%, and the average value for the Volga Federal District was 25.1% [23].

From our point of view, the general barriers to successful perinatal prevention include late diagnosis of HIV infection in a woman and/or spouse/partner, infection of a woman after childbirth, postnatal infection of a child, diagnosis of HIV infection in late pregnancy and late initiation of ARVT, and non-adherence to the ARVT regimen due to the low adherence of patients to treatment for various reasons (such as personal convictions, religious reasons, and pressure from the environment/relatives).

Given the current situation, to improve timely diagnosis at early stages, it is necessary to strengthen investigations aimed at raising awareness, social involvement, and responsibility of the population as well as raising awareness among physicians of antenatal clinics and maternity hospitals about the need to counsel women on HIV and perinatal prevention. In addition, pregnant women and their partners should have access to regular testing with the same frequency at all stages of possible transmission of HIV infection from the mother to her child, including during the period of maternal/parent seronegativity: before pregnancy, during pregnancy, and during breastfeeding. The self-infection in an adolescent patient implies the need to introduce preventive and educational measures from earlier adolescence (10–14 years) among children.

CONCLUSIONS

1. Since 2000 in the Republic of Mari El, an increase in HIV infection has been recorded in women of working age and childbearing age, that is, from isolated cases to 1,095 cases in 2018. Since 2014, there has been an increase in the number of pregnant women with HIV infection who have full-term pregnancies and delivery (from 23 in 2013, up to 38 deliveries in 2014).

2. When assessing the outcomes of preventive measures, most cases of infection in children were related to late diagnosis of HIV infection in the mother, late onset, or lack of chemoprophylaxis during pregnancy.

3. The risk of infection is the smallest (risk ratio, 0.01; 95% confidence interval 0.00–0.08, $p < 0.0001$) during three-stage prophylaxis.

4. The most commonly prescribed treatment regimens were two nucleoside reverse transcrip-

tase inhibitors in combination with protease inhibitors: AZT + 3TC + LPN/r and TDF + 3TC + LPN/r. These regimens were also the only regimens throughout pregnancy.

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