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PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION: FROM THE FIRST STAGES TO THE POSSIBILITY OF ELIMINATION

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▪ Despite the success in reducing mother-to-child HIV transmission rate worldwide, the problem of perinatal HIV transmission is still relevant. Sexual activity nowadays is the predominant way of transmission, therefore the number of HIV cases among women growths. This leads to an increased number of pregnancies and childbirth in HIV-infected women. Better preventive treatment has decreased the transmission risk to 1% or less. Despite this, the Russian Federation is still not among the countries where the elimination of mother-to-child transmission has been recorded. This review article focuses on the main stages of mother-to-child transmission prevention from the time that no antiretroviral therapy was available to the current stage, when highly active antiretroviral therapy is used during pregnancy, childbirth and for the treatment of newborns. The research provides a comparative analysis of modern national and international clinical recommendations for the prevention of mother-to-child HIV transmission.

▪ **Keywords:** HIV-infected pregnant women; mother-to-child HIV transmission prevention; mother-to-child HIV transmission rate.

ПРОФИЛАКТИКА ПЕРИНАТАЛЬНОЙ ПЕРЕДАЧИ ВИРУСА ИММУНОДЕФИЦИТА ЧЕЛОВЕКА: ОТ ПЕРВЫХ ШАГОВ ДО ВОЗМОЖНОСТИ ЭЛИМИНАЦИИ

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▪ Несмотря на значительный успех в снижении частоты перинатальной передачи ВИЧ-инфекции в мире, эта проблема не теряет своей актуальности. В настоящее время в связи с преобладанием полового пути заражения ежегодно увеличивается доля женщин в структуре новых случаев ВИЧ-инфицирования, что обусловливает рост числа беременностей и родов у ВИЧ-инфицированных женщин. Совершенствование мер в области профилактики перинатальной передачи ВИЧ привело к снижению риска заражения до 1 % и менее. Несмотря на это, Российская Федерация не входит в ряд стран, где зафиксирована элиминация перинатального инфицирования. В обзоре изложены основные этапы профилактики перинатальной передачи ВИЧ от периода, когда не были доступны антиретровирусные препараты, и до современного этапа применения высокоактивной антиретровирусной терапии при беременности, в родах и новорожденным. Проведен сравнительный анализ современных национальных и международных клинических рекомендаций по профилактике перинатальной передачи ВИЧ-инфекции.

▪ **Ключевые слова:** ВИЧ-инфицированные беременные; профилактика перинатальной передачи ВИЧ; частота перинатальной передачи ВИЧ.

Gender characteristics in the Human immunodeficiency virus epidemic

Human immunodeficiency virus (HIV) infection is a chronic infectious disease that is characterized by a polymorphic clinical presentation, resulting in the development of acquired immunodeficiency syndrome (AIDS), gradual suppression of the immune system, and development of opportunistic infections and tumors [1, 2].

In the early years of the epidemic, HIV infection mainly affected young men who used narcotic drugs intravenously or had sexual intercourse with men without using barrier contraception [3]. The active involvement of women in the HIV epidemic was associated with an increase in the proportion of heterosexual transmission [4, 5]. In 2010, more than 50% of HIV infection cases accounted for women with an uneven distribution in the world. For instance, women accounted for 60% of all HIV-infected people in sub-Saharan Africa, 35% in Latin America, and 50% in the Caribbean [5]. In 2018, 37.9 million people globally were living with HIV, and 49.6% of them were women aged 15 years and over, and 4.5% were children under the age of 15 years [6, 7].

The involvement of women in the epidemic is due to not only an increase in the frequency of the genital transmission of infection but also anatomical and biological aspects, namely, a larger mucous membrane surface area of the lower genital tract, a higher concentration of HIV in the semen of an infected partner than in cervico-vaginal secretions, and an increase of susceptibility to infection during menstruation and in phase 1 of the menstrual cycle. During sexual intercourse, the risk of HIV transmission from men to women is twice than from women to men [8]. Social factors play an important role in the infection of women with HIV, as women are more often economically dependent, subjected to violence, have unprotected sexual intercourse more often, have several partners, and consider sex for money, narcotic drugs, food, or dwelling [9]. The increase in the number of HIV-infected women of fertile age is steadily increasing the number of their pregnancies and childbirth [10, 11].

The global trends of the epidemic process, characterized by an increase in the proportion of women in the structure of HIV-infected patients, have been noted in Russia for the last few years, as with an increase in the frequency of heterosexual transmission of HIV, the number of seropositive women is increasing. In 2018, 41% of HIV-infected people in the Russian Federation were women [12]. In St. Petersburg, 59,077 cases of HIV infection were detected for the entire monitoring period at the beginning of 2020 [13]. The gender distribution of HIV-infected residents has not always been the same, as men predominated among all HIV cases recorded since 1987, but since 2002, there has been a tendency toward an increase in the proportion of women. In 2000, the proportion of women among all detected new cases of HIV infection among city residents was 26%, and it has increased to more than 40% since 2015 [14, 15]. Among female patients first identified in St. Petersburg in 2019, women of fertile age (15–49 years old) prevail (80.9%) [16].

The annual increase in the number of HIV-infected women of reproductive age is accompanied by a consistently high number of deliveries in this group of patients in St. Petersburg (Fig. 1). The number of births in HIV-infected women is 0.8%–0.9% of the total number of births in the city in different years.

The incidence of perinatal HIV transmission is about 1.5% in the Russian Federation and 1.3% in St. Petersburg, which is higher compared with countries where mother-to-child HIV transmission has been eliminated. Cuba was the first country to receive a World Health Organization (WHO) certificate for the elimination of the vertical route of HIV transmission in 2015; Armenia, Belarus, and Moldova received it in 2016, and six more countries in the Caribbean region received it in 2017 [17]. The registered cases of perinatal HIV infection in the Russian Federation necessitate continuous improvement of measures aimed at reducing perinatal HIV transmission, obstetric complications, and maternal and infant mortality incidence in this group of patients.

In 1985, the Centers for Disease Control and Prevention in the USA reported that 76% of children with confirmed HIV-positive status had a common infection factor, namely, an HIV-infected mother or a mother in a group infection risk. Thus, the perinatal route of HIV infection was confirmed, and its frequency reached 65% [18]. Considering the high frequency of perinatal infection transmission, the lack of

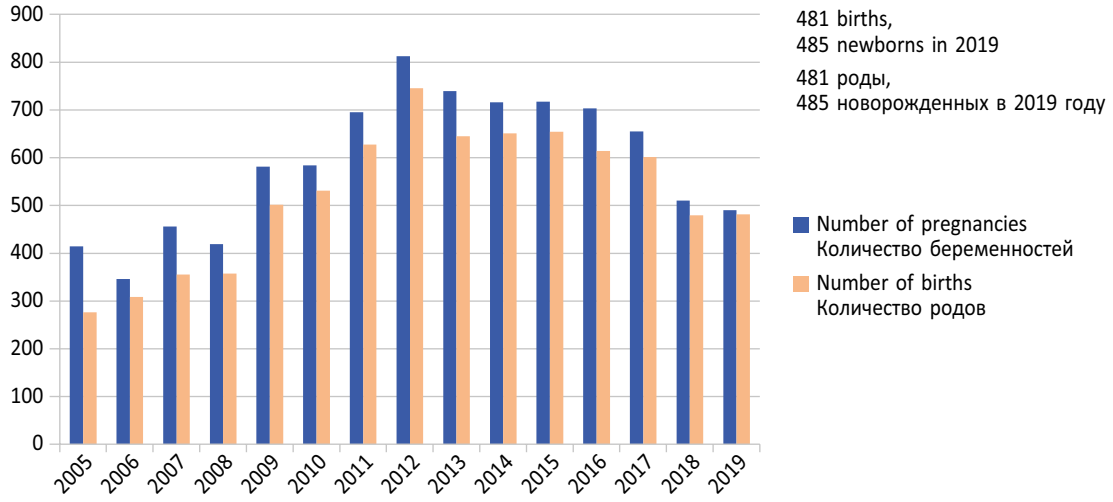

Fig. 1. Number of pregnancies and childbirth in HIV-infected women in Saint Petersburg, Russia in 2005-2019

Рис. 1. Динамика количества беременностей и родов у ВИЧ-инфицированных женщин в Санкт-Петербурге в 2005–2019 гг.

specific HIV treatment, and the high mortality rate of children from AIDS in the first 2 years of life, all HIV-infected women of reproductive age were recommended to use reliable methods of contraception and termination in the case of pregnancy [19].

In 1987, it was revealed that breastfeeding by an HIV-positive mother increases the risk of infection in a child by 14%. Therefore, it was recommended to feed children born to infected mothers with breast milk substitutes from birth [20]. In 1989, researchers published data that HIV transmission can occur antenatally, during childbirth, and through breast milk with a 20%–60% probability [21]. In the same year, it was reported that all children born to HIV-infected mothers have maternal antibodies, so a positive enzyme-linked immunosorbent assay does not imply that the child is infected [22].

In 1992, American researchers revealed that HIV does not penetrate through the intact placental barrier [23]. Factors that increase the frequency of perinatal HIV transmission have been described, including a high HIV RNA level in the mother's blood, immunodeficiency and opportunistic infections in a pregnant woman, vaginal delivery compared with cesarean section, and long period without amniotic fluid [24].

Antiretroviral drugs (ARVs) as a method for preventing mother-to-child HIV transmission were first recommended in 1994 after successful completion of a randomized clinical trial under ACTG protocol No. 076 in the USA and France. The treatment regimen included daily oral administration of zidovudine (ZDV) to a pregnant woman from week 14–34 of gestation to delivery. Intravenous administration of ZDV during labor and oral administration to the newborn during the first 6 weeks of life were also recommended. This preventive regimen has reduced the frequency of perinatal transmission to 8.3% [25]. However, for countries with limited resources, PACTG 076 was expensive and inaccessible. In response, several studies have been conducted in Thailand, sub-Saharan Africa, and other low-income countries using more simplified regimens [26, 27]. These included a study in Tanzania, South Africa, and Uganda (Petra) to evaluate the safety and efficacy of three short courses of combined ZDV and lamivudine regimens. In this study, the importance of starting antiretroviral therapy (ARVT) during pregnancy was established compared with ARVT only in childbirth and mandatory ARVT for the newborn. ZDV was the only drug that completely suppressed viral replication, but because of the inconvenience of the regimen (the drug intake is six times a day), the rapid development of resistance, and many side effects, it became necessary to search for new regimens for preventing perinatal HIV transmission [28].

In 1997, recommendations were published in the United States for the use of highly active antiretroviral therapy (HAART) combination regimens in pregnancy, including protease inhibitor

drugs. The use of combined HAART regimens during pregnancy reduced the level of perinatal transmission to 4% or less [29].

An important issue was the gestational age to start ARVs. Randomized trials have revealed that women who received ARVs throughout pregnancy did not have vertical transmission of HIV compared with women who received treatment only in the third trimester, and the incidence of HIV infection in their children was 3.6% [29]. The European National Study on HIV infection in pregnant women and children revealed that every additional week of antenatal use of a combination of three HAART drugs correlates with a 10% decrease in risk of transmission [30]. Russian researchers have shown the dependence of the frequency of perinatal HIV transmission on the initiation time of ARV treatment (Fig. 2) [31].

In the Russian Federation, the prevention of perinatal transmission of HIV infection has been performed since 2001 in accordance with the decree of the Moscow City Government, dated July 31, 2001, No. 699 "On urgent measures to combat HIV infection" and the order of the Moscow Healthcare Committee, dated May 15, 2001, No. 199 "On organization of measures to prevent perinatal transmission of HIV infection in health care facilities of the Moscow Healthcare Committee." Since 2003, the prevention of perinatal transmission of HIV infection has been implemented in all regions of the Russian Federation in accordance with the order of the Ministry of Health of Russia, dated December 19, 2003, No. 606 "On approval of instructions for the prevention of mother-to-child transmission of HIV infection and a sample of informed consent for chemoprophylaxis of HIV infections." ZDV and Viramune were recommended from week 28 of pregnancy, and intravenous administration of ZDV or oral administration of Viramune were recommended during childbirth.

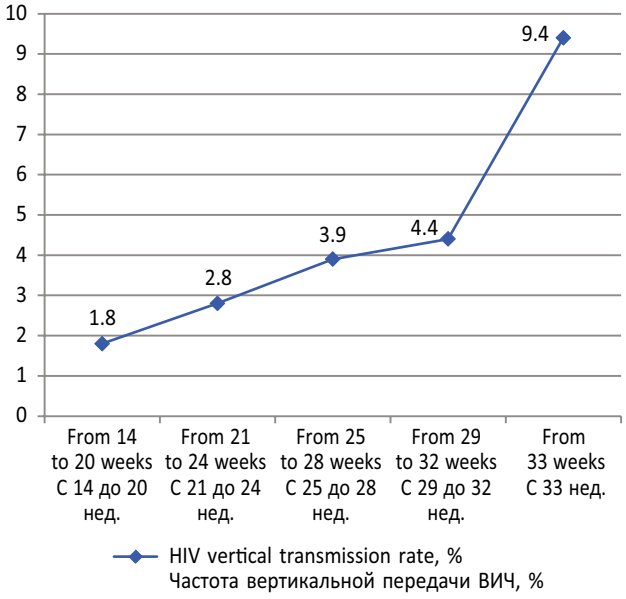

Fig. 2. Mother-to-child HIV transmission rate by timing of initiation of antiretroviral therapy during pregnancy

Рис. 2. Частота перинатальной передачи ВИЧ в зависимости от срока начала высокоактивной антиретровирусной терапии при беременности

In 2002–2005, slightly more than half of the mother–child couples (56%) received three-stage chemoprophylaxis, which reduced perinatal HIV transmission in the country from 20% to 10% [32]. Three-component chemoprophylaxis in Russia was started in 2009 in accordance with national clinical guidelines [33]. Currently, in the Russian Federation, HAART is recommended to start at the stage of pregnancy planning to achieve virological and immunological efficacy at the time of conception or, if a woman did not receive HAART before pregnancy, as soon as possible after the end of the first trimester [34].

In 2014, the European protocols for treating HIV infection recommended for the first time the use of an extended prophylaxis regimen in pregnancy using an integrase inhibitor (II) as component 4 of an ARVT regimen. An extended regimen was proposed to prescribe to HIV-infected women to rapidly reduce the viral load in the blood by the time of delivery with a detectable viral load in the blood in the third trimester of pregnancy [35]. Before this, the virological and immunological efficacy of II in the nonpregnant state was proven in several studies, where after 10 days of treatment, the initial level of HIV-1 RNA decreased by 2 $\log_{10}$ copies/mL [36]. In the BENCHMRK studies, at week 48 of using II, not only a rapid decrease in viral load but also a significant increase in the number of CD4 lymphocytes was noted [37]. The analysis of the concentration of II in the mother's blood plasma and umbilical cord blood revealed that the drug penetrates the placental barrier well and, accordingly, reduces the risk of intrauterine infection of the fetus [38]. When using II as part of an extended regimen for

preventing perinatal HIV transmission during pregnancy, no embryotoxic effect of the drug was noted, which is indicated in the International Registry for the Use of Antiretroviral Drugs in Pregnancy [39]. This registry is constantly updated with data on pregnancy outcomes and the absence or presence of malformations in newborns when using ARVs by their mothers throughout pregnancy, including the first trimester.

To assess congenital abnormalities, it is necessary to obtain data on at least 200 children born to HIV-infected mothers who received ARVs in the first trimester of pregnancy. The data analysis established that the risk of congenital abnormalities in children from HIV-infected mothers was 2.2 times higher than that of the general population. (The frequency of congenital abnormalities in the population was about 3%.) When 1000 newborns or more were evaluated, the risk of congenital abnormalities was five times higher than the general population. The II group drugs as component 4 of the ARVT regimen have been proven safe to the fetus, so the incidence of congenital malformations in newborns with the use of II (raltegravir [RAL]) was 2.72 with 20,372 available cases [39]. Adverse effects in newborns in case of II intake by the mother within the therapy regimen during pregnancy were noted in 14% of cases, including the birth weight did not correspond to the gestational age, and in isolated cases, leukopenia and neutropenia were revealed in newborns. These disorders were resolved spontaneously and were not clinically significant [16, 38].

In the national clinical guidelines, it was only in 2015 when the use of component 4 of ARVT, II, was recommended at 32 weeks of gestation and more and a viral load of more than 100,000 copies/mL [34]. Since every fourth HIV-infected pregnant woman in Russia has a preterm birth [12], an extended prophylaxis regimen starting from week 32 of pregnancy and only with an HIV RNA level of more than 100,000 copies/mL did not reduce the viral load before childbirth, especially if it occurred preterm.

Currently, there are no restrictions in the Russian Federation on the provision of chemoprophylaxis to HIV-infected pregnant women, puerperas, and newborns [34]. When HIV-infected women contact the AIDS Center at any stage of pregnancy or are planning it, the examinations, specialist consultations, prescription, and provision of an effective HAART regimen are performed free of charge.

National and international clinical guidelines for preventing perinatal HIV transmission are updated regularly based on the results of evidence-based studies in this field [34, 40–44].

Current recommendations for preventing perinatal HIV transmission

Prevention of perinatal HIV transmission during pregnancy

The only generally accepted method for preventing perinatal HIV transmission during pregnancy is the regular intake of ARVs no later than the start of the second trimester of pregnancy. According to national guidelines, if an HIV-infected woman received well-tolerated, virologically, and immunologically effective HAART before pregnancy, and the drugs included in it did not have embryotoxic or teratogenic effects, then HAART should be continued throughout pregnancy [34]. If an HIV-infected woman did not receive HAART at the time of conception, then the decision on the timing of its initiation is made after receiving the clinical and laboratory test results. Thus, if a pregnant woman has laboratory (HIV RNA level greater than 100,000 copies/mL or CD4 count lower than 350 cells/μL) and/or clinical (acute stage of HIV infection and manifestations of secondary diseases at stage IV or V of the disease according to the classification by Pokrovsky, 1989) indications, the ARVs are started without waiting for the onset of the second trimester (Table) [34, 41].

In the absence of indications for the immediate start of taking ARVs, it is recommended to start prophylaxis of perinatal transmission after the end of the first trimester (from week 14). If an HIV-infected pregnant woman seeks medical help during the second trimester of pregnancy (up to week 28), then ARVT is prescribed after receiving the laboratory test results (HIV RNA level, CD4 lymphocytes count, and clinical and biochemical blood tests). When an HIV-infected pregnant woman seeks medical help in the third trimester or when HIV infection is detected after week 28, ARVT is started immediately on the day

of visiting a doctor, without waiting for the test results. After receiving them, the ARV regimen can be corrected. When the HIV RNA level is more than 100,000 copies/mL, the regimen must be supplemented with component 4 to quickly reduce the viral load (Table) [34].

The WHO recommends starting ARVs for all HIV-infected pregnant women diagnosed with uterine progressive pregnancy, regardless of the clinical disease stage and CD4 cell count, and continuing treatment lifelong (Table) [42].

According to the recommendations of the British HIV Association, the recommended gestational age to start the intake of ARVs is determined by the viral load of a pregnant woman, so it should be started as early as possible during pregnancy for HIV-infected women with a viral load greater than 100,000 copies/mL and no later the onset of the second trimester (week 14) of pregnancy for women with a viral load lower than 30,000 copies/mL. If the HIV RNA level is less than 30,000 copies/mL, ARVT can be started in the second trimester but no later than week 24 of pregnancy. When a woman seeks medical help later than week 28 of pregnancy, a four-component regimen is recommended, including II (Table) [43].

The European AIDS Clinical Society guidelines indicate that HAART should be started at

National and international recommendations for the prevention of mother-to-child HIV transmission
Национальные и международные рекомендации по проведению профилактики перинатальной передачи ВИЧ

Indicator	EACS, 2019	DHHS, 2019	BHIVA, 2019	WHO, 2016	National clinical recommendations, 2017
Time to start HAART	When HIV is detected/during pregnancy planning	When HIV is detected/during pregnancy planning	When HIV is detected/ during pregnancy planning	When HIV is detected/during pregnancy planning	When HIV is detected/during pregnancy planning
When pregnancy occurs without the use of HAART	As early as possible, no later than week 14 of pregnancy	Immediately upon the detection of uterine pregnancy, regardless of the HIV RNA and CD4 lymphocyte levels	In trimester 2, but no later than week 24, if HIV RNA <30,000 copies/mL; starting from week 14 in case of 30–100,000 copies/mL; during trimester 1 of pregnancy in case >100,000 copies/mL	Immediately upon the detection of uterine pregnancy, regardless of the HIV RNA and CD4 lymphocyte levels	Immediately if HIV RNA >100,000 copies/mL or CD4 <350 cells/μL; or starting from week 14 in other cases
Start ARVT at the end of trimester 2 or in trimester 3 of pregnancy	Immediately, add II (dolutegravir/raltegravir)				Immediately, add II if HIV RNA >100,000 copies/mL
ARVT is performed during labor	With HIV RNA >50 copies/mL at weeks 34–36 of gestation	With HIV RNA >1000 copies/mL at weeks 34–36 of gestation	With HIV RNA >50 copies/mL at weeks 34–36 of gestation		
Cesarean section for epidemiological indications	With HIV RNA >50 copies/mL at weeks 34–36, or unknown RNA of HIV	With HIV RNA >1000 copies/mL at weeks 34–36, or unknown RNA of HIV	With HIV RNA >400 copies/mL at weeks 34–36, or unknown RNA of HIV	With HIV RNA >1000 copies/mL at weeks 34–36, or unknown RNA of HIV	With HIV RNA >1000 copies/mL at weeks 34–36, or unknown RNA of HIV or unknown RNA of HIV
Breastfeeding	Not recommended				
Breastfeeding	Not recommended				

N o t e. HAART, highly active antiretroviral therapy; ARVT, antiretroviral therapy; II, integrase inhibitors; HIV, human immunodeficiency virus; EACS, European AIDS Clinical Society; DHHS, Department for Health and Human Services; BHIVA, British HIV Association; WHO, World Health Organization.

the pregnancy planning stage. If pregnancy occurs in the absence of treatment, it is strongly recommended to start it as early as possible, regardless of the HIV RNA level and CD4 lymphocyte count [44]. If the follow-up of women starts at the end of the second or third trimester of pregnancy, it is suggested to start HAART immediately, without waiting for the examination results, and to consider adding II (RAL or dolutegravir) as component 4 to achieve undetectable HIV RNA levels by the end of the third trimester. An HIV RNA level less than 50 copies/mL is considered an undetectable HIV RNA level in the European region. If an undetectable HIV RNA level is not reached in the third trimester, a resistance test should be performed, and the possibility of adding a drug from the II group to the HAART regimen should be considered (Table).

In the USA, the most recent changes to the recommendations of the Department for Health and Human Services for preventing perinatal HIV transmission were made at the end of 2019 [40]. HIV-infected women are advised to start taking ARVs as early as possible when they become pregnant, if they have not received treatment before (Table).

Choosing a method of delivery in HIV-infected women and perinatal transmission of HIV during labor

According to the current national clinical guidelines, ARV treatment during childbirth is recommended for all HIV-infected and pregnant women with a high risk of infection (intravenous narcotic drug use during pregnancy and sexual intercourse with an HIV-infected partner with high or unknown HIV RNA levels). The decision on the method of delivery is made depending on the HIV RNA level at 34–36 weeks of pregnancy, value of HIV RNA at this time, adherence to treatment, and presence of obstetric and/or somatic indications if choosing surgery. Cesarean section for epidemiological indications is recommended for HIV-infected women who have HIV RNA levels of 1000 copies/mL or greater or HIV RNA unknown at 34–36 weeks. Delivery is performed at week 38–39. In the absence of obstetric and epidemiological indications, vaginal delivery should be performed. All obstetric manipulations that can lead to nonintegrity of the baby's skin during childbirth (perineotomy/episiotomy, amniotomy, forcep application, vacuum-assisted delivery, and invasive fetal monitoring) must be strictly justified, since they increase the risk of infection of the fetus with HIV.

In various recommendations, a different number of copies of the virus in a milliliter of a pregnant woman's blood is taken as a safe "undetectable" level of HIV RNA, for example, it is less than 1000 copies/mL in the American and WHO recommendations, less than 400 copies/mL in the British recommendations, and 50 copies/mL or less in the European recommendations. If the threshold has been exceeded during the examination for HIV viral load in a pregnant woman at 34–36 weeks, preference is given to delivery by cesarean section to reduce the risk of fetal infection. In childbirth, it is possible to skip ARVT if HIV RNA has reached an undetectable level by 34–36 weeks (Table) [34, 40–44].

Conclusion

The steady increase in the proportion of women of fertile age in the HIV epidemic, increase in the number of pregnancies and childbirth in this group, and lack of elimination of perinatal HIV transmission necessitate further study of this issue. Since the beginning of the registration of cases of perinatal infection of children, numerous studies have been conducted globally that proved that the only way to prevent transmission of HIV infection from mother to fetus is the intake of ARVs by a pregnant woman with control of HIV viral load throughout pregnancy and before childbirth. The use of various ARVs, their combination, and the term of starting ARVT have changed over time based on the results of evidence-based scientific research. Perinatal transmission of HIV was possible to eliminate in several countries, but the frequency of perinatal transmission remains above 1% in the overwhelming number of countries, including the Russian Federation. The main reasons for perinatal infection of children are the spread of HIV dissidence, insufficient population coverage of HIV testing (including women at the stage of pregravid preparation, pregnant women, and their sexual partners), preservation of the proportion of HIV-infected pregnant women who actively use narcotic drugs, reduced motivation for medical supervision, birth of a healthy child,

and in some countries, cases of sexual violence and gender or racial inequality. Not only obstetricians-gynecologists should be involved in providing care to HIV-infected pregnant women but also infectious disease specialists, psychologists, and narcologists to increase adherence to ARVs and monitor the effectiveness of measures aimed at the birth of healthy children.

At this stage, new ARVs are being actively studied and introduced, which are used in regimens for preventing perinatal HIV transmission. These drugs must meet safety criteria for both the fetus at all stages of its development and the pregnant woman, have high virological and immunological efficacy, penetrate well through the fetoplacental barrier, be easy to take, and have minimal side effects. As the evidence base about a particular drug is accumulated, changes are made to the clinical recommendations for preventing perinatal HIV transmission aimed at eliminating perinatal infection.

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