INFEKCIJA VIRUSOM HUMANE IMUNODEFICIJENCIJE U TRUDNOĆI

PREGLEDNI RAD

REVIEW ARTICLE

HUMAN IMUNODEFICIENCY VIRUS INFECTION IN PREGNANCY

Radmila Sparić[1,2], Aleksandra Pavić[2], Luka Andrić[1], Aleksa Novković[2], Đina Tomašević[3], Slađana Pavić[4]

[1] Univerzitetski klinički centar Srbije, Klinika za ginekologiju i akušerstvo, Beograd, Srbija

[2] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija

[3] Opšta bolnica Čačak, Odeljenje opšte i dečije hirurgije, Čačak, Srbija

[4] Opšta bolnica Užice, Odeljenje infektivnih i tropskih bolesti, Užice, Srbija

[1] *University Clinical Center of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia*

[2] *University of Belgrade, Faculty of Medicine, Belgrade, Serbia*

[3] *General Hospital Čačak, Department of General Surgery and Pediatric Surgery, Čačak, Serbia*

[4] *General Hospital Užice, Department of Infectious and Tropical Diseases, Užice, Serbia*

SAŽETAK

HIV infekcija predstavlja jedan od najvećih globalnih izazova javnog zdravlja, posebno kod žena u reproduktivnom periodu. U 2020. godini, u svetu je bilo 1,3 miliona trudnica sa HIV-om. Nelečena HIV infekcija u trudnoći nosi povećani rizik od maternalnog i perinatalnog morbiditeta i mortaliteta. Perinatalna transmisija HIV-a podrazumeva prenos virusa sa majke na dete tokom trudnoće, porođaja, ili tokom dojenja. Cilj ovog rada je prikaz najnovijih informacija o dijagnostici, lečenju i praćenju trudnoće kod trudnica pozitivnih na HIV, uz osvrt na vreme i način završavanja trudnoće radi prevencije transmisije virusa sa majke na fetus.

Osnovni ciljevi praćenja i lečenja HIV infekcije u trudnoći su: prevencija prenosa virusa na fetus, očuvanje zdravlja majke i stvaranje uslova za bezbedan porođaj. Cilj terapije je da održi najmanji nivo virusa u krvi, posebno u vreme porođaja, kako bi se smanjio rizik od vertikalnog prenosa.

Preporučljivo je započeti lečenje HIV infekcije pre trudnoće. Takođe, neophodna je redovna kontrola serumskog nivoa virusa, broja CD4+ limfocita, krvne slike, kao i obavljanje testova funkcije jetre i bubrega.

Izbor vremena i načina završavanja trudnoće ne bi trebalo da se razlikuje kod trudnica sa niskim nivoom virusa u serumu u odnosu na zdrave trudnice, dok kod trudnica sa visokim nivoom virusa, trudnoću treba završiti elektivnim carskim rezom.

HIV infekcija utiče i na trudnicu i na fetus, te je važno antenatalno, intrapartalno i postporođajno praćenje. Odluka o terapiji, kao i o vremenu i načinu porođaja, treba da bude individualna, a donosi se u skladu sa serumskim nivoom virusa, kliničkom slikom HIV infekcije majke i stanjem fetusa.

Ključne reči: trudnoća, porođaj, HIV

ABSTRACT

HIV infection represents one of the major global public health challenges, especially among women of reproductive age. In 2020, there were 1.3 million pregnant women infected with HIV worldwide. Untreated HIV infection in pregnancy carries an increased risk of maternal and perinatal morbidity and mortality. Perinatal transmission of HIV refers to the transmission of the virus from mother to child during pregnancy, childbirth, or puerperium. The aim of this paper is to present the up-to-date information on diagnosis, treatment, and monitoring of pregnancy in HIV-positive women, with reference to the time and mode of delivery, in order to prevent the transmission of the virus from mother to fetus.

The main goals of monitoring and treating HIV infection during pregnancy are the following: preventing the transmission of the virus to the fetus, preserving the mother's health, and providing conditions for a safe delivery. The goal of treatment is to maintain the lowest level of the virus in the blood, especially at the time of delivery, in order to reduce the risk of vertical transmission.

It is recommended to start treatment of HIV infection before pregnancy. Also, regular monitoring of the viral load, the CD4+ lymphocyte count, and blood count, as well as performing liver and kidney function tests, is necessary.

The choice of the time and mode of delivery should not differ in pregnant women with a low viral load, as compared to healthy pregnant women, while in pregnant women with a high viral load, the pregnancy should be ended with elective caesarean section.

HIV infection affects both the pregnant woman and the fetus. Therefore, antenatal, intrapartum, and postpartum monitoring is important. The decision on therapy, as well as the time and mode of delivery, should be individual, and made in accordance with the viral load, the clinical presentation of HIV infection of the mother, and the condition of the fetus.

Key words: pregnancy, delivery, HIV

Autor za korespondenciju:
Radmila Sparić
Klinika za ginekologiju i akušerstvo, Univerzitetski klinički centar Srbije
Koste Todorovića 26, 11000 Beograd, Srbija
Elektronska adresa: radmila@rcub.bg.ac.rs

Corresponding author:
Radmila Sparić
Clinic for Gynecology and Obstetrics, University Clinical Center of Serbia
26 Dr Koste Todorovića Street, 11000 Belgrade, Serbia
E-mail: radmila@rcub.bg.ac.rs

Primljeno • *Received*: February 4, 2023; **Revidirano • *Revised*:** April 26, 2023; **Prihvaćeno • *Accepted*:** May 9, 2023; ***Online first*:** June 25, 2023

DOI: 10.5937/smclk4-42665

UVOD

Prvi bolesnici sa sindromom stečene imunodeficijencije (engl. *acquired immune deficiency syndrome - AIDS*) opisani su 1981. godine, a nakon dve godine, identifikovan je i uzročnik bolesti - humani imunodeficijentni virus (HIV) [1]. Krajem 2020. godine, u svetu je HIV-om bilo inficirano oko 37,7 miliona ljudi, od čega 36 miliona odraslih osoba, a 1,7 miliona dece mlađe od 14 godina. Ženska populacija činila je 53% inficiranih. Tokom 2020. godine, registrovano je 1,5 miliona novoobolelih i 680.000 preminulih [2]. Imajući ovo u vidu, jasno je da HIV infekcija predstavlja jedan od najvećih globalnih izazova javnog zdravlja, posebno kod žena u reproduktivnom periodu.

Perinatalna transmisija HIV-a podrazumeva prenos virusa sa majke na dete tokom trudnoće, porođaja ili tokom dojenja. Nelečena HIV infekcija u trudnoći povezana je sa nepovoljnim ishodima trudnoće, kao što su prevremeni porođaj, mala porođajna težina novorođenčeta i mrtvorođenost [3].

U 2020. godini, u svetu je bilo 1,3 miliona trudnica sa HIV-om. Antiretrovirusnu terapiju, kao prevenciju prenosa virusa na fetus, koristilo je 85% trudnica [4]. Upravo zahvaljujući primeni terapije, prenos HIV-a sa majke na dete, tokom 2018. godine, bio je prisutan kod manje od 1% novorođenčadi [5]. Osim uticaja na fetus, HIV ima i značajan uticaj na zdravlje i kvalitet života trudnice. Opisane su česte depresivne epizode i suicidalne ideje kod trudnica inficiranih HIV-om, posebno onih kojima je infekcija dijagnostikovana nakon začeća. Oko 60% trudnica kojima je HIV dijagnostikovan tokom trudnoće, pokazalo je znakove somatske bolesti [6].

Centar za kontrolu bolesti u Atlanti ističe društvene i ekonomske faktore kao najvažnije za bezbedno planiranje i praćenje trudnoće žena sa HIV-om [5].

EPIDEMIOLOGIJA I ETIOLOGIJA HIV INFEKCIJE

Globalna prevalencija HIV-a u adultnoj populaciji, u 2020. godini, bila je 0,7% [2]. Najveći broj ljudi sa HIV infekcijom živi na afričkom kontinentu (preko 25,3 miliona), zatim u Aziji (5,8 miliona), zapadnoj i centralnoj Evropi (2,2 miliona) i Latinskoj Americi (2,1 milion) [2].

Četvrtinu inficiranih osoba u subsaharskoj Africi čini ženska populacija uzrasta 15 – 25 godina. Približno jedna trećina (35%) žena u svetu je izložena fizičkom/seksualnom nasilju, što u nekim regionima povećava verovatnoću prenosa infekcije HIV-om. Najčešći put prenosa virusa je preko krvi i obično se na taj način inficiraju intravenski uživaoci droga. Polni put prenosa dominira kod transrodnih osoba, žena koje pružaju seksualne usluge i mlađih homoseksualaca [2]. Moguć je i prenos virusa sa majke na dete, takozvana vertikal-

INTRODUCTION

The first patients with acquired immune deficiency syndrome (AIDS) were described in 1981, and two years later, the cause of the disease was identified - human immunodeficiency virus (HIV) [1]. At the end of 2020, around 37.7 million people were infected with HIV worldwide, of whom 36 million were adults, and 1.7 million were children under the age of 14. Females made up 53% of the infected population. In 2020, 1.5 million new cases and 680,000 deaths were registered [2]. With this in mind, it is clear that HIV infection represents one of the greatest global public health challenges, especially among women of reproductive age.

Perinatal transmission of HIV refers to the transmission of the virus from mother to child during pregnancy, childbirth or breastfeeding. Untreated HIV infection in pregnancy is associated with adverse pregnancy outcomes, such as preterm birth, low birth weight, and stillbirth [3].

In 2020, there were 1.3 million pregnant women with HIV worldwide. A total of 85% of pregnant women used antiretroviral therapy to prevent virus transmission to the fetus [4]. It is owing to the administration of therapy that the transmission of HIV from mother to child was present in less than 1% of newborns, in 2018 [5]. In addition to affecting the fetus, HIV also has a significant impact on the health and quality of life of pregnant women. Frequent depressive episodes and suicidal ideas have been described in HIV-infected pregnant women, especially in those whose infection was diagnosed after conception. About 60% of pregnant women diagnosed with HIV during pregnancy showed signs of somatic disease [6].

The Atlanta Center for Disease Control highlights social and economic factors as the most important for safe pregnancy planning and monitoring the pregnancy of women with HIV [5].

EPIDEMIOLOGY AND ETIOLOGY OF HIV INFECTION

The global prevalence of HIV in the adult population, in 2020, was 0.7% [2]. The largest number of people with HIV infection live in Africa (over 25.3 million), followed by Asia (5.8 million), Western and Central Europe (2.2 million) and Latin America (2.1 million) [2].

A quarter of the infected persons in sub-Saharan Africa are in the female population aged 15 – 25 years. Approximately one-third (35%) of women in the world are exposed to physical/sexual violence, which in some regions increases the likelihood of HIV transmission. The most common route of transmission of the virus is by blood, and intravenous drug users are usually

na transmisija. Kod odsustva antiretrovirusne terapije, do prenosa HIV-a sa majke na dete tokom trudnoće, porođaja, ili perioda dojenja, dolazi u oko 15 – 45% slučajeva [4].

Virus je detektovan u skoro svim telesnim sekretima i ekskretima (krvi, pljuvački, suzama, cerebrospinalnoj tečnosti, ejakulatu). U organizam domaćina ulazi kroz mukozne membrane. HIV se ne prenosi vazduhom, vodom, komarcima ili drugim insektima, pljuvačkom ili suzama koji nisu pomešani sa serumom inficirane osobe, socijalnim kontaktima (rukovanjem, grljenjem, poljupcem, korišćenjem zajedničkog posuđa i slično) [4].

Zahvaljujući lipoproteinskom omotaču, HIV je izuzetno osetljiv na rastvarače masti, deterdžente, kiseline i baze, kao i temperaturu od preko 60 °C, u trajanju dužem od 30 minuta. Otporan je na uobičajene doze zračenja (ultravioletno, rentgen, gama), pa se za inaktivaciju virusa na ovaj način moraju koristiti veće doze uz kraće rastojanje od izvora zračenja [7]. Virus se može održati u krvi u špricevima na sobnoj temperaturi do 42 dana, a u obdukcionoj krvi i cerebrospinalnoj tečnosti do 11 dana [8, 9]. Međutim, virus nije detektovan u plodovoj vodi žena koje su koristile antiretrovirusnu terapiju [10].

Virus sličan virusu HIV-a, iz iste porodice i potporodice, otkriven je kod makaki majmuna. Zbog toga se veruje da HIV vodi poreklo od primata sa kojih je početkom 20. veka prešao na ljude [11]. Prema morfologiji, fizičkim, hemijskim i biološkim osobinama, HIV pripada porodici *Retroviridae*, potporodica *Lentivirinae* (spori virusi). Na osnovu genetskih razlika virusa, postoje tri glavne grupe (M, N i O). Preko 90% HIV infekcija potiče iz grupe M, koju čini devet podtipova virusa. Podtip B je najčešće prisutan u zemljama zapadne Evrope i Amerike [12]. HIV ima dva serološka tipa: 1 i 2. HIV 1 je češće prenosiv, agresivniji je u ranoj fazi bolesti i češće se prenosi sa majke na dete [13].

PATOGENEZA HIV INFEKCIJE

Patogenezu HIV infekcije uslovljava fenotip virusa, kao i receptori/koreceptori koji omogućavaju ulazak virusa u ćelije domaćina. HIV primarno inficira CD4+ T limfocite, za koje se vezuju proteini omotača virusa gp 120 i gp 41. Ostale ćelije podložne infekciji HIV-om su hematopoetske (makrofagi, monociti, dendritske ćelije, fetalni timociti i ćelije timusnog epitela, B limfociti, megakariociti, ćelije prirodne ubice, matične ćelije), ćelije centralnog nervnog sistema (mikroglijalne ćelije, astrociti, oligodendrociti, endotelne kapilarne ćelije), ćelije epitela kolona, Kupferove ćelije jetre, sincicijalne ćelije i trofoblastne placentarne ćelije [14]. Za ulazak virusa u ćeliju, neophodni su koreceptori koji zavise od vrste ćelija. Dva glavna hemokinska koreceptora su

infected that way. Sexual transmission predominates in transgender persons, female sex workers, and younger homosexuals [2]. Transmission of the virus from mother to child, the so-called vertical transmission, is also possible. Without antiretroviral therapy, transmission of HIV from mother to child during pregnancy, childbirth, or breastfeeding occurs in about 15 – 45% of cases [4].

The virus was detected in almost all bodily secretions and excretions (blood, saliva, tears, cerebrospinal fluid, ejaculate). It enters the host organism through mucous membranes. HIV is not transmitted through air, water, mosquitoes or other insects, saliva or tears that are not mixed with the serum of an infected person, or social contacts (handshakes, hugs, kisses, sharing dishes, etc.) [4].

Owing to its lipoprotein envelope, HIV is extremely sensitive to fat solvents, detergents, acids and bases, as well as exposure to temperatures of above 60 °C lasting more than 30 minutes. It is resistant to the usual doses of radiation (ultraviolet, X-ray, gamma), so in order to inactivate the virus in this way, higher doses must be used with a shorter distance from the radiation source [7]. The virus can survive in blood in syringes, at room temperature, for up to 42 days, and in post-mortem blood and cerebrospinal fluid for up to 11 days [8, 9]. However, the virus has not been detected in amniotic fluid of pregnant women who were on antiretroviral therapy [10].

A virus similar to HIV, belonging to the same family and subfamily, was discovered in macaque monkeys. Therefore, it is believed that HIV originated from primates, from which it passed on to humans at the beginning of the 20th century [11]. According to its morphology, physical, chemical and biological properties, HIV belongs to the family *Retroviridae*, subfamily *Lentivirinae* (slow viruses). Based on the genetic differences of the viruses, there are three main groups (M, N and O). Over 90% of HIV infections originate from group M, which consists of nine subtypes of the virus. Subtype B is most often present in the countries of Western Europe and America [12]. HIV has two serological types: 1 and 2. HIV 1 is more frequently transmissible, is more aggressive in the early stages of the disease, and is more often transmitted from mother to child [13].

PATHOGENESIS OF HIV INFECTION

The pathogenesis of HIV infection is determined by the phenotype of the virus, as well as by the receptors/coreceptors that allow the virus to enter host cells. HIV primarily infects CD4+ T lymphocytes, to which the viral envelope proteins gp 120 and gp 41 bind. Other cells susceptible to HIV infection are hematopoietic (macrophages, monocytes, dendritic cells, fetal thymocytes

CCR5 i CKSCR4. Njih imaju krvni i tkivni makrofagi, dendritske ćelije i T limfociti [15]. Najveći rezervoari HIV-a su tkivni makrofagi. Mogu se naći u mozgu, plućima, limfnim žlezdama, koži i koštanoj srži inficiranih osoba. Monociti i makrofagi su glavni posrednici u širenju virusa kroz tkiva. Nakon što virus uđe u organizam domaćina, dolazi do brze replikacije virusa, što utiče na aktivaciju CD8+ T limfocita koji uništavaju ćelije inficirane HIV-om. Dobar odgovor CD8+ T limfocita povezan je sa sporijom progresijom oboljenja [16]. U hroničnoj fazi bolesti postoji kontinuirana replikacija virusa i posledična generalizovana imunološka aktivacija u kojoj važnu ulogu imaju i proinflamatorni citokini [17]. Citokini poreklom iz makrofaga doprinose progresiji bolesti [18].

Humoralni odgovor na HIV infekciju ostvaruju prvenstveno neutrališuća antitela vezujući virus i sprečavajući ga da inficira ciljne ćelije. Neutrališuća antitela se vezuju za inficirane ćelije i pokreću efektorske ćelije, koje indukuju citolizu ili apoptozu inficiranih ćelija [19].

Veruje se da koreceptor CCR3 ima ulogu u ulasku virusa u fetalne ćelije [20]. Glavnu ulogu u prenosu HIV-a sa majke na fetus ima placenta. Virus može inficirati endotelne placentarne ćelije, Hofbauerove makrofagne ćelije, trofoblaste i ćelije terminalnih horionskih resica. Ćelije placente produkuju različite solubilne faktore koji utiču na dalju replikaciju HIV-a [21].

KLINIČKA SLIKA HIV INFEKCIJE

Klinička slika HIV infekcije može biti različita, od asimptomatske do postojanja teških oportunističkih infekcija. Oportunističke infekcije su infekcije koje se javljaju kod imunodeficijentnih osoba, kakve su osobe inficirane HIV-om, a ispoljavaju se češće, ili su teže od uobičajenih. Svetska zdravstvena organizacija je rangirala kliničku sliku infekcije HIV-om u četiri stadijuma. Prvi stadijum čini asimptomatska infekcija ili generalizovana limfadenopatija duža od 6 meseci. U drugom stadijumu su prisutni blagi simptomi poput gubitka u težini od manje od 10%, rekurentne respiratorne infekcije i niz kožnih oboljenja. Treći stadijum karakterišu umereni simptomi kao što su veći gubitak telesne težine, dugotrajna neobjašnjiva dijareja, plućna tuberkuloza, teške sistemske bakterijske infekcije i ozbiljne mukokutane promene. Bolesnici u četvrtom stadijumu imaju teške simptome raznih bolesti koje definišu *AIDS* (pneumocistična pneumonija, teška bakterijska pneumonija, ekstrapulmonalna tuberkuloza, HIV encefalopatija, hronična toksoplazmoza, orolabijalni herpes, Kapošijev sarkom). Pored toga, i druge teške ili protrahovane infekcije treba da podstaknu na dijagnostiku HIV-a [22].

Žene zaražene HIV-om češće imaju patološke promene grlića materice izazvane humanim papiloma vi-

and thymic epithelial cells, B lymphocytes, megakaryocytes, natural killer cells, stem cells), cells of the central nervous system (microglial cells, astrocytes, oligodendrocytes, endothelial capillary cells), colonic epithelial cells, liver Kupffer cells, syncytial cells and trophoblastic placental cells [14]. For the entry of the virus into the cell, co-receptors that depend on the type of cells are necessary. The two main chemokine coreceptors are CCR5 and CKSCR4. Blood and tissue macrophages, dendritic cells, and T lymphocytes have these receptors [15]. The largest reservoirs of HIV are tissue macrophages. They can be found in the brain, lungs, lymph glands, skin, and bone marrow of infected individuals. Monocytes and macrophages are the main mediators in the spread of viruses through tissues. After the virus enters the host's organism, rapid replication of the virus occurs, which affects the activation of CD8+ T lymphocytes that destroy HIV-infected cells. A good CD8+ T lymphocyte response is associated with slower disease progression [16]. In the chronic phase of the disease, there is continuous replication of the virus and consequent generalized immune activation in which proinflammatory cytokines also play an important role [17]. Macrophage-derived cytokines contribute to disease progression [18].

Humoral response to HIV infection is achieved primarily by neutralizing antibodies, which bind the virus and prevent it from infecting target cells. Neutralizing antibodies bind to infected cells and trigger effector cells, which induce cytolysis or apoptosis of infected cells [19].

The CCR3 co-receptor is believed to play a role in viral entry into fetal cells [20]. The placenta plays a key role in the transmission of HIV from mother to fetus. The virus can infect placental endothelial cells, Hofbauer macrophage cells, trophoblasts, and terminal chorionic villus cells. Placental cells produce various soluble factors that influence further HIV replication [21].

CLINICAL PRESENTATION OF HIV INFECTION

The clinical presentation of HIV infection can vary, from asymptomatic to the presence of severe opportunistic infections. Opportunistic infections are infections that occur in immunodeficient persons, such as persons infected with HIV, and they manifest more often or are more severe than usual infections. The World Health Organization categorized the clinical presentation of HIV infection into four stages. The first stage consists of asymptomatic infection or generalized lymphadenopathy lasting longer than six months. In the second stage, mild symptoms, such as weight loss of less than 10%, recurrent respiratory infections, and a number of skin diseases are present. The third stage is characterized by moderate symptoms such as greater weight loss, prolonged unexplained diarrhea, pulmonary tuberculosis,

rusom, vaginalnu kandidijazu i pelvičnu inflamatornu bolest. HIV infekcija takođe negativno utiče na plodnost [23].

UTICAJ HIV-A NA MAJKU I FETUS

U oblastima gde su lošiji ekonomski uslovi, tuberkuloza je najčešća oportunistička infekcija kod trudnica sa HIV-om [24]. Osim tuberkuloze, tokom trudnoće i puerperijuma, česte su i pneumonija izazvana gljivicom *Pneumocystis Jirovecii* i parazitarne infekcije [11]. Opisan je negativni uticaj HIV-a na učestalost i tok mnogih infekcija u trudnoći, kao što su genitalni herpes, infekcija humanim papiloma virusom, vulvovaginalna kandidijaza, bakterijska vaginoza, sifilis, trihomonijaza, toksoplazmoza, malarija, infekcija virusima hepatitisa B i C, kao i citomegalovirusom. Trudnice inficirane HIV-om takođe imaju i češće infekcije urinarnog trakta i bakterijske pneumonije [11].

Uticaj HIV-a na fetus zavisi od stadijuma HIV infekcije majke, koncentracije virusne ribonukleinske kiseline (RNK) u plazmi i broja CD4+ T limfocita majke, kao i vremena pucanja plodovih ovojaka. Ukoliko majka ima pridružene i druge polno prenosive bolesti, povećana je genitalna sekrecija HIV-a [23].

U Tabeli 1 prikazani su faktori rizika vertikalnog prenosa HIV-a tokom trudnoće, porođaja i puerperijuma [25].

Komplikacije trudnoće u slučaju infekcije HIV-om uključuju povećanje perinatalnog morbiditeta i mortaliteta, i to: češće spontane pobačaje, horioamnionitis, severe systemic bacterial infections, and severe mucocutaneous lesions. Patients in the fourth stage have severe symptoms of various diseases that define AIDS (pneumocystis pneumonia, severe bacterial pneumonia, extrapulmonary tuberculosis, HIV encephalopathy, chronic toxoplasmosis, orolabial herpes, Kaposi's sarcoma). In addition, other severe or protracted infections should prompt preforming diagnostics for HIV [22].

Women infected with HIV more often have pathological changes of the cervix caused by the human papillomavirus, vaginal candidiasis, and pelvic inflammatory disease. HIV infection also negatively affects fertility [23].

THE IMPACT OF HIV ON THE MOTHER AND FETUS

In areas with poorer economic conditions, tuberculosis is the most common opportunistic infection in pregnant women with HIV [24]. In addition to tuberculosis, pneumonia caused by the fungus *Pneumocystis Jirovecii* and parasitic infections are common during pregnancy and the puerperium [11]. The negative impact of HIV on the frequency and course of many infections in pregnancy, such as genital herpes, human papillomavirus infection, vulvovaginal candidiasis, bacterial vaginosis, syphilis, trichomoniasis, toxoplasmosis, malaria, hepatitis B and C virus infection, as well as cytomegalovirus. HIV-infected pregnant women also have more frequent urinary tract infections and bacterial pneumonia [11].

Tabela 1. Faktori rizika za vertikalni prenos HIV-a [25].

Table 1. Factors associated with risk of perinatal HIV transmission [25].

Faktori rizika za vertikalni prenos HIV-a / *Factors associated with risk of perinatal HIV transmission*		
Pre porođaja / *Ante-partum*	**Tokom porođaja / *Intra-partum***	**Posle porođaja / *Post-partum***
Visoka viremija majke / *High maternal plasma HIV-1 viral load*	Cervikovaginalni nivo HIV-a / *Maternal cervicovaginal HIV-1 levels*	Dojenje / *Breastfeeding*
Smanjen broj CD4+ T limfocita majke / *Decreased maternal CD4⁺ T-lymphocyte count*	Način porođaja / *Mode of delivery*	
Progresija infekcije majke/ *Progression of maternal infection*	Prolongirana ruptura plodovih ovojaka/ *Prolonged membrane rupture*	
Deficijencija vitamina A / *Vitamin A deficiency*	Prevremeni porođaj / *Premature delivery*	
Korišćenje psihoaktivnih supstanci / *Use of illicit drugs*	Promene vaginalne sluznice/ *Vaginal mucosa alterations*	
Amniocenteza, posebno u trećem trimestru / *Amniocentesis, especially in the third trimester*	Episiotomija / *Episiotomy*	
Nedijagnostikovana ili kasno dijagnostikovana infekcija / *Undiagnosed and delayed diagnosis of infection*	Invazivne fetalne procedure / *Invasive fetal procedures*	
Nedostatak zdravstvene nege / *Absence of medical care*		

intrauterini zastoj u rastu ploda, malu telesnu težinu deteta na rođenju i mrtvorođenost [26].

Smatra se da trudnoća ne utiče negativno na tok HIV infekcije, u smislu progresije bolesti, ili kraćeg preživljavanja majke. Dijagnostikovane su stabilne vrednosti virusne RNK tokom trudnoće, ali je moguće smanjenje broja CD4+ T limfocita, što je objašnjavano hemodilucijom, a ne realnim smanjenjem broja krvnih ćelija [27]. Podaci se odnose na razvijene zemlje, dok je u nerazvijenim zemljama, posebno u subsaharskoj Africi, uočen značajan morbiditet i mortalitet kod majki inficiranih HIV-om, i to ne samo u periodima kada je antiretrovirusna terapija bila mnogo manje dostupna [3,28].

DIJAGNOSTIKA HIV INFEKCIJE U TRUDNOĆI

Dijagnoza HIV infekcije može se postaviti indirektno - detekcijom anti-HIV antitela. HIV specifična serumska antitela IgG klase dokazuju se enzimski povezanim imunosorbentnim testom (engl. *enzyme-linked immunosorbent assay - ELISA*). Neophodna je potvrdna analiza *Western blot* tehnikom. Prvi testovi za detekciju anti-HIV antitela su se pojavili 1984. godine, a od 1985. godine je uvedeno obavezno testiranje krvi koja se koristi za transfuziju na HIV [29]. Postoje i brzi testovi za dokazivanje anti-HIV antitela, koji imaju visoku specifičnost i senzitivnost, i najčešće se koriste za dijagnostiku infekcije tokom porođaja žena sa nepoznatim HIV statusom.

Testovima za dokazivanje čestica virusa dokazuju se proteinske čestice, npr. p 41, ili virusni genetski materijal.

Virusne nukleinske kiseline (ribonukleinska - RNK ili provirusna dezoksiribonukleinska - DNK) se dokazuju polimeraznom lančanom reakcijom (engl. *polymerase chain reaction - PCR*). Postoji vremenski period („period prozora“) između izlaganja HIV-u i pozitivnog testa, jer je potrebno vreme da se virus u domaćinu dovoljno replikuje, ili da domaćin napravi imunološki odgovor na infekciju koji bi bio detektovan. Kod detektovanja anti-HIV antitela najnovijom generacijom testova, ovaj period iznosi 11 dana. Slično je i prilikom korišćenja *PCR* metode pri kojoj „period prozora“ iznosi 12 dana [30]. Kod novorođenčadi HIV-om inficiranih majki, anti-HIV antitela poreklom od majke mogu se održavati do osamnaestog meseca života, pa se njihovim određivanjem u tom periodu ne može isključiti infekcija.

PRAĆENJE I LEČENJE HIV INFEKCIJE U TRUDNOĆI

Neophodno je pratiti trudnice inficirane HIV-om zbog moguće progresije HIV infekcije i zbog uticaja primenjene antiretrovirusne terapije. Za procenu stadijuma HIV infekcije u trudnoći, koriste se metode fizikalnog

The impact of HIV on the fetus depends on the stage of HIV infection in the mother, the concentration of viral ribonucleic acid (RNA) in the plasma and the number of CD4+ T lymphocytes of the mother, as well as the time of rupture of the fetal membranes. If the mother has associated and other sexually transmitted diseases, the genital secretion of HIV is increased [23].

Pregnancy complications in case of HIV infection include an increase in perinatal morbidity and mortality, namely: more frequent miscarriages, chorioamnionitis, intrauterine growth retardation, low birth weight and stillbirth [26].

It is considered that pregnancy does not negatively affect the course of HIV infection, in terms of disease progression, or shorter survival of the mother. Stable values of viral RNA during pregnancy have been diagnosed, but a decrease in the number of CD4+ T lymphocytes is possible, which has been explained by hemodilution rather than by a real decrease in the number of blood cells [27]. The data refer to developed countries, while in underdeveloped countries, especially in sub-Saharan Africa, significant morbidity and mortality have been observed in HIV-infected mothers, and not only in time periods when antiretroviral therapy was less available [3,28].

DIAGNOSTICS OF HIV INFECTION IN PREGNANCY

The diagnosis of HIV infection can be made indirectly – by detecting anti-HIV antibodies. HIV-specific IgG class serum antibodies are proven by enzyme-linked immunosorbent assay (ELISA). Confirmation by Western blot analysis is necessary. The first tests for the detection of anti-HIV antibodies appeared in 1984, and since 1985, mandatory testing of blood used for transfusion for HIV has been in place [29]. There are also rapid tests for proving anti-HIV antibodies, which have high specificity and sensitivity, and are most often used to diagnose infection during childbirth in women with unknown HIV status.

Tests for proving virus particles are used to confirm the presence of protein particles, e.g., p 41, or viral genetic material.

Viral nucleic acids (ribonucleic – RNA or proviral deoxyribonucleic – DNA) are proven by polymerase chain reaction (PCR). There is a period of time (the window period) between exposure to HIV and a positive test, because it takes time for the virus to sufficiently replicate in the host, or for the host to initiate an immune response to the infection that can be detected. When detecting anti-HIV antibodies with latest generation tests, this period is 11 days. It is similar when the PCR method is applied, where the window period is 12 days [30]. In infants of HIV-infected mothers, anti-HIV anti-

pregleda uz upotrebu različitih mikrobioloških metoda za dokazivanje oportunističkih infekcija. Osim toga, koriste se hematološki (kompletna krvna slika, retikulociti, serumsko gvožđe), biohemijski (testovi za ispitivanje funkcije bubrega, jetre, pankreasa) i imunološki testovi (broj CD4+ T limfocita). Stadijumi HIV infekcije se, pored kliničkih pokazatelja, određuju na osnovu broja CD4+ T limfocita. Progresiju bolesti prati pad broja ovih ćelija. S druge strane, njihovo povećanje je pokazatelj imunske rekonstitucije tokom primene antiretrovirusne terapije. Trudnice sa novootkrivenom HIV infekcijom ne zahtevaju dodatna ispitivanja, osim onih koja se rutinski sprovode. Važno je praćenje serumskog nivoa virusa, najmanje jednom u svakom trimestru i neposredno pre porođaja [31].

U cilju smanjenja rizika od prenosa virusa sa majke na fetus, poželjno je lečenje HIV infekcije započeti pre planirane trudnoće [5]. S obzirom da se antiretrovirusni lekovi eliminišu preko jetre i bubrega, potrebno je trudnicama tokom lečenja pratiti funkcije ovih organa. Jedan od neželjenih efekata terapije može biti supresija koštane srži, pa je neophodno redovno praćenje krvne slike [32]. Antiretrovirusna terapija se prilagođava genotipu HIV-a, koji se određuje pre započinjanja terapije. Kao i kod ostalih osoba inficiranih HIV-om, i trudnicama se određuje prisustvo hepatotropnih virusa B i C [32]. Tabela 2 prikazuje protokol praćenja trudnica sa HIV infekcijom [30].

Kod trudnoća sa rizikom od postojanja hromozomskih aberacija fetusa treba primeniti neinvazivne skrining testove [32]. Ukoliko nisu neophodni, sve invazivne testove treba odložiti do postizanja nivoa virusa <50 kopija HIV RNK/ml seruma. Ukoliko je invazivna dijagnostika ipak neophodna, potrebno je 2 – 4 h pre izvođenja dati antivirusnu terapiju [32]. Podaci iz literature ukazuju da majčina antitela mogu perzistirati do osamnaestog meseca života, tako da njihovo određivanje u tom periodu ne može isključiti infekciju.

bodies originating from the mother can persist until the eighteenth month of life, so their determination during that period cannot rule out infection.

FOLLOW-UP AND TREATMENT OF HIV INFECTION IN PREGNANCY

Follow-up of pregnant women infected with HIV is necessary because of the possible progression of HIV infection and because of the effect of the applied antiretroviral therapy. To assess the stage of HIV infection in pregnancy, physical examination methods and various microbiological methods are applied, so as to verify opportunistic infections. In addition, hematological (complete blood count, reticulocytes, serum iron), biochemical (tests for kidney, liver, pancreatic function), and immunological tests (number of CD4+ T lymphocytes) are used. The stages of HIV infection, in addition to clinical indicators, are determined based on the number of CD4+ T lymphocytes. The progression of the disease is accompanied by a decrease in the number of these cells. On the other hand, their increase is an indicator of immune reconstitution during the administration of antiretroviral therapy. Pregnant women with newly discovered HIV infection do not require additional tests, except those that are routinely performed. It is important to monitor the HIV viral load, at least once in each trimester and immediately before delivery [31].

In order to reduce the risk of transmission of the virus from the mother to the fetus, it is preferable to start the treatment of HIV infection before the planned pregnancy [5]. Considering that antiretroviral drugs are eliminated through the liver and kidneys, it is necessary for the function of these organs to be monitored in pregnant women during treatment. One of

Tabela 2. Praćenje HIV infekcije u trudnoći [30]].

Table 2. Follow-up of HIV infection in pregnancy [30]

	Interval / *Interval*	**Razlog / *Reason***
Nivo virusa u krvi / *Viral load*	Svake 2 – 4 sedmice na početku terapije, kasnije ređe / *Every 2–4 weeks, on initiation of treatment, and less frequently, later*	Napredak i efikasnost praćenja / *Progress and efficacy of management*
Testovi funkcije jetre i bubrega / *Liver and kidney function tests*	Svake sedmice na početku terapije, kasnije ređe, ukoliko su stabilne / *Weekly, at onset of treatment, and less frequently, when stable*	Detekcija ranog oštećenja jetre i bubrega uzrokovanog terapijom / *Detection of early drug induced liver of kidney damage*
Kompletna krvna slika / *Full blood count*	Svakog meseca, sa fokusom na vrednost hemoglobina i trombocita / *Monthly (with a focus on the hemoglobin level and platelet count)*	Supresija koštane srži uzrokovana terapijom / *Treatment induced bone marrow suppression*
Broj CD4+ T ćelija / *CD4+ T cell count*	Svaka tri meseca / *Every three months*	Progresija bolesti / *Disease progression*

ture ukazuju na to da je amniocenteza bezbedna kod žena koje uzimaju antiretrovirusnu terapiju [33].

Jedini antiretrovirusni lek zvanično dozvoljen za upotrebu u trudnoći je zidovudin u trećem trimestru. Međutim, postoji globalni konsenzus da žene koje su lečene pre trudnoće terapiju treba da nastave i tokom trudnoće, i dalje doživotno. Lekovi se mogu promeniti u odnosu na prethodno započetu terapiju, u zavisnosti od njihove farmakokinetike u trudnoći [31]. Cilj terapije je da održi najmanji nivo virusa u krvi, posebno u vreme porođaja, kako bi se smanjio rizik od vertikalnog prenosa. Svetska zdravstvena organizacija preporučuje da sve trudnice i dojilje sa HIV-om, bez obzira na nivo virusa, broj CD4+ T limfocita i klinički stadijum infekcije, treba da se leče [34]. Preporučuje se da se lečenje trudnica koje pre trudnoće nisu lečene antiretrovirusnom terapiju započne u ranom drugom trimestru trudnoće [31]. Izbor lekova zavisi od njihove toksičnosti, dužine lečenja, rezistencije virusa i prisustva komorbiditeta. Treba obratiti pažnju i na učestalost doziranja i interakcije sa drugim lekovima. Od velike važnosti je da lek prolazi placentarnu barijeru i da može da obezbedi pre-ekspozicionu profilaksu [31].

Toksičnost antiretrovirusnih lekova je česta. Obično se manifestuje anemijom, mitohondrijalnim poremećajima (miopatija, periferna neuropatija, kardiomiopatija), hiperlipidemijom, insulinskom rezistencijom. Dijagnostikovani su i poremećaji koštanih struktura (osteopenija, osteoporoza) i kožne promene [35, 36]. Uprkos velikoj učestalosti neželjenih efekata antiretrovirusne terapije uočenih kod trudnica, nije bilo težih efekata. Od lekova novije generacije se očekuje bolja efikasnost i značajno povoljniji profil podnošljivosti [37].

Teratogeni efekti antiretrovirusne terapije i dalje su predmet ispitivanja, posebno zbog sinteze novih lekova. Potencijalni uticaj na fetus zavisi od samog leka, doziranja, gestacijske starosti fetusa u trenutku izlaganja leku, dužine terapije, te interakcije leka sa drugim agensima kojima je fetus izložen. Dostupne informacije se baziraju na *in vitro* i *in vivo* testovima na životinjama, ali prediktivna vrednost takvih testova u humanoj populaciji nije poznata [38]. Na osnovu podataka iz američkog Nacionalnog vodiča može se izvesti zaključak da je 1,5 puta češća pojava urođenih malformacija kod novorođenčadi čije su majke u prvom trimestru uzimale antiretrovirusnu terapiju. Ograničavajući faktor u ovom istraživanju je bio taj što je uzorak obuhvatio svega 1.000 novorođenčadi [38]. Uloga antiretrovirusne terapije u nastanku urođenih malformacija ostaje kontroverzna. Najčešće se pominju urođene mane genitourinarnog i kardiovaskularnog sistema [39]. U nekoliko studija o urođenim

the side effects of the therapy can be bone marrow suppression, so regular monitoring of the blood count is also necessary [32]. Antiretroviral therapy is adapted to the HIV genotype, which is determined before starting therapy. As with other HIV-infected persons, the presence of hepatotropic viruses B and C is also investigated in pregnant women [32]. Table 2 shows the follow-up protocol for pregnant women with HIV infection [30].

Non-invasive screening tests should be used in pregnancies with risk of fetal chromosomal aberrations [32]. If not necessary, all invasive tests should be delayed until the viral load is < 50 copies of HIV RNA/ml of serum. If invasive diagnostics is still necessary, antiviral therapy must be administered 2 – 4 hours before the procedure [32]. Data from literature indicate that amniocentesis is safe in women taking antiretroviral therapy [33].

The only antiretroviral drug officially approved for use in pregnancy is zidovudine, which can be used in the third trimester. However, there is a global consensus that women who have been treated before pregnancy should continue the treatment during pregnancy and for life. Drugs can be changed in relation to previous treatment, depending on their pharmacokinetics in pregnancy [31]. The goal of therapy is to maintain the lowest possible viral load, especially at the time of delivery, in order to reduce the risk of vertical transmission. The World Health Organization recommends that all pregnant and breastfeeding women with HIV, regardless of the viral load, CD4+ T lymphocyte count, and clinical stage of infection, should be treated [34]. It is recommended that the treatment of pregnant women who were not treated with antiretroviral therapy before pregnancy should be started in the early second trimester of pregnancy [31]. The choice of drugs depends on their toxicity, the length of treatment, the resistance of the virus, and the presence of comorbidities. Attention should also be paid to the frequency of dosing and interactions with other drugs. It is of great importance that the drug can cross the placental barrier and provide pre-exposure prophylaxis [31].

Toxicity of antiretroviral drugs is common. It usually manifests as anemia, mitochondrial disorders (myopathy, peripheral neuropathy, cardiomyopathy), hyperlipidemia, insulin resistance. Bone structure disorders (osteopenia, osteoporosis) and skin lesions have also been registered [35,36]. Despite the high frequency of side effects of antiretroviral therapy observed in pregnant women, there have been no severe side effects registered. Newer generation drugs are expected to have better efficacy and a significantly more favorable tolerability profile [37].

anomalijama kod fetusa i novorođenčadi žena koje su primale različite retrovirusne lekove, nije uočena razlika u odnosu na izloženost lekovima u prvom i kasnijim trimestrima [40 – 42].

PORODAJ TRUDNICA INFICIRANIH HIV-OM

Cilj antiretrovirusne terapije u trudnoći je da u vreme porođaja serumski nivo HIV-a bude što je moguće niži. Ukoliko je taj nivo < 50 kopija HIV RNK/ml krvi u 36. nedelji trudnoće i u odsustvu akušerskih kontraindikacija, poželjna opcija je vaginalni porođaj. Ukoliko je u serumu trudnice 400 kopija HIV RNK/ml u 36. nedelji, porođaj treba sprovesti elektivnim carskim rezom. Za žene sa virusnim opterećenjem od 50 – 399 kopija HIV RNK/ml, treba razmotriti carski rez uzimajući u obzir praćenje virusnog nivoa tokom cele trudnoće, dužinu lečenja, akušerske faktore i mišljenje trudnice. Takođe, važan je i zaključak dosadašnjih istraživanja da je rizik od vertikalnog prenosa HIV-a duplo veći pri vaginalnom porođaju u odnosu na carski rez [31,43]. Radi smanjenja verovatnoće prenosa virusa tokom carskog reza, preporučuje se njegovo izvođenje između 38. i 39. nedelje gestacije [44].

Ukoliko se HIV-om inficirana trudnica porađa vaginalno, porođaj treba da bude, ukoliko je moguće, sproveden po protokolu za trudnice koje nisu inficirane HIV-om. Ranije preporuke o izbegavanju amniotomije, instrumentalnog porođaja, epiziotomije i uzorkovanja fetalne krvi, nisu više prihvaćene zbog primene antivirusne terapije koja je umnogome smanjila rizik od vertikalnog prenosa virusa [5]. Podaci pokazuju da korišćenje instrumenata pri porođaju nije rizično za prenos infekcije kako se ranije mislilo. Izbor vrste operativnog porođaja uvek treba da obezbedi najmanju traumu fetusa [45]. Nakon rupture plodovih ovojaka, porođaj treba završiti u roku od 24 h. Postoje podaci u literaturi da tokom tog vremenskog perioda ne postoji povećan rizik od transmisije virusa [46].

U cilju smanjenja rizika od prenosa HIV-a sa majke na novorođenče tokom samog porođaja, ispitivana je primena odloženog podvezivanja pupčane vrpce novorođenčeta, jedan do tri minuta, kao mogući faktor rizika [47]. Odloženo podvezivanje pupčane vrpce je metoda kojom se smanjuje rizik od anemije kod novorođenčeta [48]. Podaci iz literature nisu pokazali da odlaganje podvezivanja pupčane vrpce povećava mogućnost prenošenja HIV-a sa majke na novorođenče. Zbog dokazanih prednosti odlaganja podvezivanja pupčanika od jednog do tri minuta, preporučuje se da se ovo primeni i pri porođaju žena koje žive sa HIV-om, ili žena sa nepoznatim HIV statusom [47].

The teratogenic effects of antiretroviral therapy are still the subject of investigation, especially due to the development of new drugs. The potential impact on the fetus depends on the drug itself, the dosage, the gestational age of the fetus at the time of exposure to the drug, the length of therapy, and the interaction of the drug with other agents to which the fetus is exposed. Available information is based on in vitro and in vivo animal tests, but the predictive value of such tests in the human population is unknown [38]. Based on the data from the American National Guide, it can be concluded that the occurrence of congenital malformations is 1.5 times more frequent in newborns whose mothers took antiretroviral therapy in the first trimester. A limiting factor in this study was that the sample included only 1,000 infants [38]. The role of antiretroviral therapy in the development of congenital malformations remains controversial. Birth defects of the genitourinary and cardiovascular systems are most often mentioned [39]. In several studies of congenital anomalies in fetuses and infants of women receiving different antiretroviral drugs, no difference was observed in relation to drug exposure in the first and subsequent trimesters [40–42].

DELIVERY IN HIV INFECTED WOMEN

The goal of antiretroviral therapy during pregnancy is to keep the HIV viral load as low as possible at the time of delivery. If the level is < 50 copies of HIV RNA/ml of blood in the 36th week of pregnancy and if there are no obstetric contraindications, vaginal delivery is the preferred option. If there are 400 copies of HIV RNA/ml in the pregnant woman's serum in the 36th week, the delivery should be performed by elective caesarean section. For women with a viral load of 50 - 399 copies of HIV RNA/ml, caesarean section should be considered while also taking into account the monitoring of the viral load throughout the pregnancy, the duration of treatment, obstetric factors, and the opinion of the pregnant woman. Also, it is important to note the conclusion drawn in previous research stating that the risk of vertical transmission of HIV is twice as high in vaginal delivery, as compared to caesarean section [31,43]. In order to reduce the probability of virus transmission during cesarean section, it is recommended to perform it between the 38th and 39th week of gestation [44].

If an HIV-infected pregnant woman gives birth vaginally, the delivery should, if possible, be carried out according to the protocol for pregnant women who are not infected with HIV. Earlier recommendations to avoid amniotomy, instrumental delivery, episiotomy and fetal blood sampling are no longer considered valid, due to the use of antiviral therapy, which

REVENCIJA NASTANKA HIV INFEKCIJE U TRUDNOĆI KOD SERODISKORDANTNIH PAROVA

Sero-diskordantnost podrazumeva da jedan partner ima HIV infekciju, a da je drugi nema. Neretko i ovakvi parovi žele začeće bezbedno po neinficiranog partnera/partnerku i potomstvo sa najmanjim rizikom za vertikalnu transmisiju virusa. Serodiskordantne parove treba lečiti pre planirane trudnoće kako bi se maksimalno smanjio rizik od prenosa infekcije kako međusobno, tako i na fetus. Ovo podrazumeva primenu antiretrovirusne terapije za partnera/partnerku inficiranog-u HIV-om i primenu svakodnevne profilakse pre izlaganja (engl. *pre-exposure prophylaxis - PrEP*) neinficiranog partnera/partnerke [49].

Kod inficiranih žena HIV-serodiskordantnih parova, intrauterina inseminacija sa ili bez stimulacije ovulacije uz pravilnu upotrebu kondoma može smanjiti rizik od prenošenja HIV-a kada je muškarac HIV neinficiran [50].

U slučaju da je muškarac inficiran, primena antivirusne terapije može dovesti do značajne promene kvaliteta sperme i posledične smanjene mogućnosti začeća [51]. Još od 1992. godine, započete su metode obrade sperme kako bi se ostvarilo začeće sa najmanjim rizikom za prenos virusa [52]. Upotreba unapređenih tehnika obrade sperme u kombinaciji sa intrauterinom inseminacijom ili *in vitro* fertilizacijom pomoću intracitoplazmatske injekcije sperme, pokazala se veoma efikasnom u sprečavanju prenosa virusa na neinficiranu partnerku i fetus [53].

PrEP podrazumeva hemoprofilaksu, odnosno, primenu specifičnih antiretrovirusnih lekova za sprečavanje zaraze HIV-om. Upotreba kombinacije tenofovirdizoproksil fumarata/emtricitabina (TDF/FTC), kao dnevnog oralnog *PrEP*-a za smanjenje zaraze HIV-om, odobrena je od strane američke Uprave za hranu i lekove (engl. *Food and Drug Administration -FDA*), 2012. godine [54]. Indikacije za *PrEP* uključuju faktore rizika za dobijanje HIV-a, kao što su seksualni odnos bez kondoma sa partnerom sa HIV-om ili intravenska upotreba droga. Kada se uzima kako je propisano, TDF/FTC obezbeđuje više od 90% zaštite od infekcije HIV-om [55].

Smatra se da žene koje su zatrudnele tokom korišćenja TDF/FTC kao *PrEP*-a mogu nastaviti sa *PrEP*-om tokom cele trudnoće. Ovo je zasnovano na studiji kojom je ispitivan *PrEP* za HIV-a u populaciji žena koje nisu imale HIV, a uzimale su placebo ili TDF/FTC. Nije primećena razlika u riziku od pojave urođenih anomalija između ovih grupa [56].

ZAKLJUČAK

HIV infekcija utiče i na trudnicu i na fetus i zato je važno pažljivo antenatalno, intrapartalno i postpartalno pra-

has greatly reduced the risk of vertical transmission of the virus [5]. The data show that the use of instruments during childbirth is not as risky for the transmission of infection as previously believed. The choice of the type of operative delivery should always ensure the least trauma to the fetus [45]. After the rupture of the fetal membranes, the delivery should be completed within 24 hours. There are data in literature indicating that during this period there is no increased risk of virus transmission [46].

In order to reduce the risk of HIV transmission from mother to the neonate during childbirth, the use of delayed umbilical cord clamping, of one to three minutes, has been investigated as a possible risk factor [47]. Delayed umbilical cord clamping is a method to reduce the risk of anemia in the newborn baby [48]. Literature data have not shown that delaying umbilical cord clamping increases the possibility of mother-to-newborn HIV transmission. Due to the proven benefits of delaying umbilical cord clamping, between one and three minutes, this is also recommended to be applied in deliveries of women living with HIV, or women with an unknown HIV status [47].

PREVENTION OF HIV INFECTION DURING PREGNANCY IN SERODISCORDANT COUPLES

Serodiscordance means that one partner has the HIV infection while the other does not. Quite often, such couples are looking for a mode of conception that would be safe for the uninfected partner and that would result in the lowest possible risk of vertical transmission of the virus to the offspring. Serodiscordant couples should be treated before the planned pregnancy, in order to minimize the risk of transmission of infection, both to each other and to the fetus. This implies the use of antiretroviral therapy for the HIV-infected partner and the use of daily pre-exposure prophylaxis (PrEP) for the non-infected partner [49].

In infected women, in HIV serodiscordant couples, intrauterine insemination, with or without ovulation stimulation, with proper condom use, can reduce the risk of HIV transmission, when the man is HIV-uninfected [50].

If the man is infected, the application of antiviral therapy can lead to a notable change in sperm quality and a consequent reduced possibility of conception [51]. Since 1992, sperm processing methods have been initiated to achieve conception with the lowest risk of viral transmission [52]. The use of advanced sperm processing techniques combined with intrauterine insemination or in vitro fertilization using intracytoplasmic sperm injection, has been shown to be highly effective in preventing virus transmission to an uninfected female partner and fetus [53].

ćenje. Osnovni ciljevi praćenja i lečenja HIV infekcije u trudnoći su prevencija prenosa virusa na fetus, očuvanje zdravlja majke i stvaranje uslova za bezbedan porođaj za majku i dete. U tom smislu je od velike važnosti postojanje nacionalnog vodiča.

Za adekvatan nadzor trudnice sa HIV infekcijom neophodan je multidisciplinarni pristup. Odluka o antiretrovirusnoj terapiji, kao i vremenu i načinu porođaja, treba da bude individualna za svaku trudnicu, a donosi se u skladu sa serumskim nivoom virusa, kliničkom slikom HIV infekcije majke i stanjem fetusa.

Sukob interesa: Nije prijavljen.

LITERATURA / *REFERENCES*

1. Castillo-Chavez C, Cooke K, Huang W, Levin SA. On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS). Part 1: Single population models. J Math Biol. 1989;27(4):373-98. doi: 10.1007/BF00290636.
2. UNAIDS. Global HIV & AIDS Statistics - fact sheet [Internet]. 2021 [pristupljeno: 2022 Jan 11]. Dostupno: https://www.unaids.org/en/resources/fact-sheet.
3. González R, Rupérez M, Sevene E, Vala A, Maculuve S, Bulo H, et al. Effects of HIV infection on maternal and neonatal health in southern Mozambique: A prospective cohort study after a decade of antiretroviral drugs roll out. PLoS One. 2017 Jun 2;12(6):e0178134. doi: 10.1371/journal.pone.0178134.
4. World Health Organization. Data on the HIV/AIDS response [Internet]. 2021 [pristupljeno: 2022 Jan 11]. Dostupno: https://www.who.int/data/gho/data/themes/hiv-aids/data-on-the-hiv-aids-response.
5. CDC. HIV and Pregnant Women, Infants, and Children [Internet]. 2021 [pristupljeno: 2022 Jan 11]. Dostupno: https://www.cdc.gov/hiv/group/gender/pregnantwomen/index.html.
6. Kwalombota M. The effect of pregnancy in HIV-infected women. AIDS Care. 2002 Jun;14(3):431-3. doi: 10.1080/09540120220123829.
7. Tjøtta E, Hungnes O, Grinde B. Survival of HIV-1 activity after disinfection, temperature and pH changes, or drying. J Med Virol. 1991 Dec;35(4):223-7. doi: 10.1002/jmv.1890350402.
8. Abdala N, Reyes R, Carney JM, Heimer R. Survival of HIV-1 in syringes: effects of temperature during storage. Subst Use Misuse. 2000 Aug;35(10):1369-83. doi: 10.3109/10826080009148220.
9. Ball J, Desselberger U, Whitwell H. Long-lasting viability of HIV after patient's death. Lancet. 1991 Jul 6;338(8758):63. doi: 10.1016/0140-6736(91)90063-u.
10. Maiques V, García-Tejedor A, Perales A, Córdoba J, Esteban RJ. HIV detection in amniotic fluid samples. Amniocentesis can be performed in HIV pregnant women? Eur J Obstet Gynecol Reprod Biol. 2003 Jun 10;108(2):137-41. doi: 10.1016/s0301-2115(02)00405-0.
11. Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. Cold Spring Harb Perspect Med. 2011 Sep;1(1):a006841. doi: 10.1101/cshperspect.a006841.
12. Magiorkinis G, Angelis K, Mamais I, Katzourakis A, Hatzakis A, Albert J, et al. The global spread of HIV-1 subtype B epidemic. Infect Genet Evol. 2016 Dec;46:169-179. doi: 10.1016/j.meegid.2016.05.041.
13. Ter Schiphorst E, Hansen KC, Holm M, Hønge BL. Mother-to-child HIV-2 transmission: comparison with HIV-1 and evaluation of factors influencing the rate of transmission. A systematic review. Trans R Soc Trop Med Hyg. 2022 May 2;116(5):399-408. doi: 10.1093/trstmh/trab165.

PrEP involves chemoprophylaxis, i.e., the use of specific antiretroviral drugs to prevent HIV infection. The use of the combination of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), as daily oral PrEP to reduce HIV infection, was approved by the United States Food and Drug Administration (FDA) in 2012 [54]. Indications for PrEP include risk factors for acquiring HIV, such as unprotected sex with an HIV-positive partner or intravenous drug use. When taken as prescribed, TDF/FTC provides protection against HIV infection of more than 90% [55].

It is considered that women who become pregnant while using TDF/FTC as PrEP may continue with PrEP throughout their pregnancy. This is based on a study that examined PrEP for HIV in a population of HIV-negative women taking placebo or TDF/FTC. There was no difference regarding the risk of congenital anomalies between these groups [56].

CONCLUSION

HIV infection affects both the pregnant woman and the fetus, therefore, careful antenatal, intrapartum, and postpartum follow-up is important. The main goals of monitoring and treating HIV infection during pregnancy are the prevention of transmission of the virus to the fetus, the preservation of the mother's health, and the provision of conditions for a safe delivery for both mother and child. In relation to this, the existence of a national guide is of foremost importance.

A multidisciplinary approach is necessary for adequate monitoring of a pregnant woman with HIV infection. The decision on antiretroviral therapy, as well as on the time and mode of delivery, should be individual for each pregnant woman, and is made based on the HIV viral load, the mother's clinical presentation of HIV infection, and the condition of the fetus.

Conflict of interest: None declared.

14. Levy JA. Pathogenesis of human immunodeficiency virus infection. Microbiol Rev. 1993 Mar;57(1):183-289. doi: 10.1128/mr.57.1.183-289.1993.
15. Turville SG, Arthos J, Donald KM, Lynch G, Naif H, Clark G, et al. HIV gp120 receptors on human dendritic cells. Blood. 2001 Oct 15;98(8):2482-8. doi: 10.1182/blood.v98.8.2482.
16. Pantaleo G, Demarest JF, Schacker T, Vaccarezza M, Cohen OJ, Daucher M, et al. The qualitative nature of the primary immune response to HIV infection is a prognosticator of disease progression independent of the initial level of plasma viremia. Proc Natl Acad Sci U S A. 1997 Jan 7;94(1):254-8. doi: 10.1073/pnas.94.1.254.
17. Appay V, Sauce D. Immune activation and inflammation in HIV-1 infection: causes and consequences. J Pathol. 2008 Jan;214(2):231-41. doi: 10.1002/path.2276.
18. Wang T, Gong N, Liu J, Kadiu I, Kraft-Terry SD, Schlautman JD, et al. HIV-1-infected astrocytes and the microglial proteome. J Neuroimmune Pharmacol. 2008 Sep;3(3):173-86. doi: 10.1007/s11481-008-9110-x.
19. Kägi D, Vignaux F, Ledermann B, Bürki K, Depraetere V, Nagata S, et al. Fas and perforin pathways as major mechanisms of T cell-mediated cytotoxicity. Science. 1994 Jul 22;265(5171):528-30. doi: 10.1126/science.7518614.
20. He J, Chen Y, Farzan M, Choe H, Ohagen A, Gartner S, et al. CCR3 and CCR5 are co-receptors for HIV-1 infection of microglia. Nature. 1997 Feb 13;385(6617):645-9. doi: 10.1038/385645a0.
21. Al-Husaini AM. Role of placenta in the vertical transmission of human immunodeficiency virus. J Perinatol. 2009 May;29(5):331-6. doi: 10.1038/jp.2008.187.
22. World Health Organization. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance: African region. Switzerland: World Health Organization; 2005. p. 11-2.
23. Gray GE, McIntyre JA. Effect of HIV on women. AIDS Read. 2006 Jul;16(7):365-8, 373-7.
24. Gray GE, McIntyre JA. HIV and pregnancy. BMJ. 2007 May 5;334(7600):950-3. doi: 10.1136/bmj.39176.674977.AD.
25. McGowan JP, Shah SS. Prevention of perinatal HIV transmission during pregnancy. J Antimicrob Chemother. 2000 Nov;46(5):657-68. doi: 10.1093/jac/46.5.657.
26. Bernstein HB, Wegman AD. HIV Infection: Antepartum Treatment and Management. Clin Obstet Gynecol. 2018 Mar;61(1):122-136. doi: 10.1097/GRF.0000000000000330.
27. Burns DN, Nourjah P, Minkoff H, Korelitz J, Biggar RJ, Landesman S, et al. Changes in CD4+ and CD8+ cell levels during pregnancy and post partum in women seropositive and seronegative for human immunodeficiency virus-1. Am J Obstet Gynecol. 1996 May;174(5):1461-8. doi: 10.1016/s0002-9378(96)70589-6.
28. Calvert C, Ronsmans C. The contribution of HIV to pregnancy-related mortality: a systematic review and meta-analysis. AIDS. 2013 Jun 19;27(10):1631-9. doi: 10.1097/QAD.0b013e32835fd940.
29. Žerjav S. Laboratorijska dijagnostika HIV infekcije. Acta Fac Med Naiss. 1999;16:75-80.
30. Chilaka VN, Konje JC. HIV in pregnancy - An update. Eur J Obstet Gynecol Reprod Biol. 2021 Jan;256:484-491. doi: 10.1016/j.ejogrb.2020.11.034.
31. Gilleece DY, Tariq DS, Bamford DA, Bhagani DS, Byrne DL, Clarke DE, et al. British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018. HIV Med. 2019 Mar;20 Suppl 3:s2-s85. doi: 10.1111/hiv.12720.
32. ACOG Committee Opinion No. 752: Prenatal and Perinatal Human Immunodeficiency Virus Testing. Obstet Gynecol. 2018 Sep;132(3):e138-e142. doi: 10.1097/AOG.0000000000002825.
33. Constantatos SN, Boutall AH, Stewart CJ. Recommendations for amniocentesis in HIV-positive women. S Afr Med J. 2014 Dec;104(12):844-5. doi: 10.7196/samj.8660.
34. Darby A, Sierra Hope J. World Health Organization Guidelines (Option A, B, and B+) for Antiretroviral Drugs to Treat Pregnant Women and Prevent HIV Infection in Infants. Embryo Project Encyclopedia [Internet]. 2021. [pristupljeno: 2022 Feb 11]. Dostupno: http://embryo.asu.edu/handle/10776/13231.
35. Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, et al.; IMPAACT 1077BF/1077FF PROMISE Study Team. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med. 2016 Nov 3;375(18):1726-1737. doi: 10.1056/NEJMoa1511691.
36. Balasundaram S, Ranganathan K, Umadevi K, Gunaseelan R, Kumaraswamy N, Solomon S, et al. Oral lesions associated with nevirapine-related Stevens Johnson syndrome: A report of four cases. J Oral Maxillofac Pathol. 2011 Jan;15(1):39-45. doi: 10.4103/0973-029X.80024.
37. Delicio AM, Lajos GJ, Amaral E, Lopes F, Cavichiolli F, Myioshi I, et al. Adverse effects of antiretroviral therapy in pregnant women infected with HIV in Brazil from 2000 to 2015: a cohort study. BMC Infect Dis. 2018 Sep 27;18(1):485. doi: 10.1186/s12879-018-3397-x.
38. Clinical info Hiv. gov. Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. What's New in the Guidelines [Internet]. [Ažurirano: 2021 December 30; pristupljeno: 2022 January 24]. Dostupno: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/teratogenicity.
39. Nielsen-Saines K, Komarow L, Cu-Uvin S, Jourdain G, Klingman KL, Shapiro DE, et al.; ACTG 5190/PACTG 1054 Study Team. Infant outcomes after maternal antiretroviral exposure in resource-limited settings. Pediatrics. 2012 Jun;129(6):e1525-32. doi: 10.1542/peds.2011-2340.
40. Watts DH, Huang S, Culnane M, Kaiser KA, Scheuerle A, Mofenson L, et al. Birth defects among a cohort of infants born to HIV-infected women on antiretroviral medication. J Perinat Med. 2011 Mar;39(2):163-70. doi: 10.1515/jpm.2010.139.
41. Knapp KM, Brogly SB, Muenz DG, Spiegel HM, Conway DH, Scott GB, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. Pediatr Infect Dis J. 2012 Feb;31(2):164-70. doi: 10.1097/INF.0b013e318235c7aa.
42. Money D, Lee T, O'Brien C, Brophy J, Bitnun A, Kakkar F, et al.; Canadian Perinatal HIV Surveillance Program. Congenital anomalies following antenatal exposure to dolutegravir: a Canadian surveillance study. BJOG. 2019 Oct;126(11):1338-1345. doi: 10.1111/1471-0528.15838.
43. International Perinatal HIV Group; Andiman W, Bryson Y, de Martino M, Fowler M, Harris D, Hutto C, et al. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1--a meta-analysis of 15 prospective cohort studies. N Engl J Med. 1999 Apr 1;340(13):977-87. doi: 10.1056/NEJM199904013401301.
44. National Institute for Health and Care Excellence. Caesarean birth [Internet]. NICE; 2021 [Ažurirano: 2021 Mar, pristupljeno: 2022 Jan 24]. Dostupno: https://www.nice.org.uk/guidance/cg132.
45. Peters H, Francis K, Harding K, Tookey PA, Thorne C. Operative vaginal delivery and invasive procedures in pregnancy among women living with HIV. Eur J Obstet Gynecol Reprod Biol. 2017 Mar;210:295-299. doi: 10.1016/j.ejogrb.2016.12.016.
46. Cotter AM, Brookfield KF, Duthely LM, Gonzalez Quintero VH, Potter JE, O'Sullivan MJ. Duration of membrane rupture and risk of perinatal transmission of HIV-1 in the era of combination antiretroviral therapy. Am J Obstet Gynecol. 2012 Dec;207(6):482.e1-5. doi: 10.1016/j.ajog.2012.10.862.

47. Pogliani L, Erba P, Nannini P, Giacomet V, Zuccotti GV. Effects and safety of delayed versus early umbilical cord clamping in newborns of HIV-infected mothers. J Matern Fetal Neonatal Med. 2019 Feb;32(4):646-649. doi: 10.1080/14767058.2017.1387896.
48. Rabe H, Gyte GM, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev. 2019 Sep 17;9(9):CD003248. doi: 10.1002/14651858.CD003248.pub4.
49. McMahon JM, Myers JE, Kurth AE, Cohen SE, Mannheimer SB, Simmons J, et al. Oral pre-exposure prophylaxis (PrEP) for prevention of HIV in serodiscordant heterosexual couples in the United States: opportunities and challenges. AIDS Patient Care STDS. 2014 Sep;28(9):462-74. doi: 10.1089/apc.2013.0302.
50. Mmeje O, van der Poel S, Workneh M, Njoroge B, Bukusi E, Cohen CR. Achieving pregnancy safely: perspectives on timed vaginal insemination among HIV-serodiscordant couples and health-care providers in Kisumu, Kenya. AIDS Care. 2015;27(1):10-6. doi: 10.1080/09540121.2014.946385.
51. Savasi V, Parisi F, Oneta M, Laoreti A, Parrilla B, Duca P, et al. Effects of highly active antiretroviral therapy on semen parameters of a cohort of 770 HIV-1 infected men. PLoS One. 2019 Feb 21;14(2):e0212194. doi: 10.1371/journal.pone.0212194.
52. Semprini AE, Levi-Setti P, Bozzo M, Ravizza M, Taglioretti A, Sulpizio P, Albani E, Oneta M, Pardi G. Insemination of HIV-negative women with processed semen of HIV-positive partners. Lancet. 1992 Nov 28;340(8831):1317-9. doi: 10.1016/0140-6736(92)92495-2.
53. Ethics Committee of American Society for Reproductive Medicine. Human immunodeficiency virus (HIV) and infertility treatment: a committee opinion. Fertil Steril. 2015 Jul;104(1):e1-8. doi: 10.1016/j.fertnstert.2015.04.004.
54. U.S. Department of Health & Human Services/U.S. Food & Drug Administration. Truvada for PrEP Fact Sheet: Ensuring Safe and Proper Use [Internet]. 2012 [pristupljeno: 2022 Feb 24]. Dostupno: https://www.fda.gov/media/83586/download.
55. Clinical info Hiv. gov. Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Pre-exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods [Internet]. 2021 [Ažurirano: 2021 Dec; pristupljeno: 2022 Jan 24]. Dostupno: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/teratogenicity.
56. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al.; Partners PrEP Study Team. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014 Jul 23-30;312(4):362-71. doi: 10.1001/jama.2014.8735.