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POST-EKSPOZICIONA I PRE-EKSPOZICIONA PROFILAKSA KAO MERE PREVENCIJE HIV INFEKCIJE

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SAŽETAK

Hemioprofilaksa u prevenciji HIV infekcije praktično počinje da se koristi od registrovanja prvog leka za lečenje AIDS-a odnosno od 1987. godine. Post-ekspoziciona profilaksa (PEP) koju koriste osobe akcidentalno eksponirane HIV infekciji uglavnom je vezana za profesionalnu akcidentalnu izloženost HIV infekciji (primarno zdravstvenih radnika). Procenjuje se da PEP smanjuje rizik za 81% od HIV infekcije. Pre-ekspoziciona profilaksa (PrEP) je počela više da se ispituje i primenjuje pre desetak godina. PrEP je namenjena osobama koje nisu inficirane HIV-om, ali su u kontinuiranom riziku od HIV-a usled svog rizičnog ponašanja. Procenjuje se da PrEP smanjuje rizik od nastanka HIV infekcije za 75% i više u zavisnosti od populacije i adherencije propisanom terapijskom režimu. U Srbiji PEP i PrEP i dalje nisu potpuno regulisane, ali je rad na tome počeo 2022. godine. U zemljama sa neregulisanom PrEP prisutan je rizik od neformalne upotrebe terapije bez medicinskog nadzora, što može da dovede do manje efikasnosti PrEP i razvoja rezistentntnih oblika HIV infekcije u slučaju prethodno nedijagnostikovane HIV infekcije. Obe intervencije pripadaju biomedicinskim intervencijama vezanim za prevenciju HIV infekcije i od značaja su za dosezanje globalnih ciljeva usmerenih na okončanje AIDS-a kao „javnozdravstvene pretnje" do 2030. godine. Međutim, da bi biomedicinske intervencije bile maksimalno efikasne, potrebno je da budu praćene adekvatnim bihejvioralnim intervencijama u cilju povećanja informisanosti, adherencije propisanom terapijskom režimu i periodične kontrole zdravstvenog stanja u skladu sa definisanim preporukama za PEP i PrEP.

Ključne reči: post-ekspoziciona profilaksa, pre-ekspoziciona profilaksa, HIV infekcija, AIDS, zdravstveni radnici, biomedicinske intervencije

Uvod

Po procenama Udruženog programa Ujedinjenih nacija za HIV/AIDS (engl. *Joint United Nations Programme on Human Immunodeficiency Virus* - HIV/ *Acquired ImmunoDeficiency Syndrome* - AIDS), u daljem tekstu: UNAIDS), od početka epidemije pa do kraja 2021. godine 84,2 miliona (64,0-113,0 miliona) ljudi je inficirano HIV-om, a 40,1 milion (33,6 - 48,6 miliona) osoba je umrlo od bolesti i stanja povezanih sa AIDS-om (1). Samo u regionu Evrope, kako je definisano od strane Svetske zdravstvene organizacije (SZO), u 2021. godini ukupno je kod 106.508 osoba novodijagnostikovana HIV infekcija. Od toga, kod 5.940 osoba je HIV novodijagnostikovan u regionu Centralne Evrope, gde pripada i Srbija (sa 172 osobe kojima je HIV novodijagnostikovan). Kumulativno, od početka registrovanja HIV slučajeva do kraja 2021. godine, HIV-om je inficirano oko 2,3 miliona osoba u regionu Evrope (od kojih 106.411 u regionu Centralne Evrope, sa 4.372 osobe u Srbiji). Na kraju 2021. godine, od bolesti i stanja povezanih sa AIDS-om u regionu Evrope je umrlo 3.354 osobe (kumulativno od početka registrovanja do kraja 2021. godine 270.374), od kojih je njih 229 umrlo u regionu Cen-

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POST-EXPOSURE AND PRE-EXPOSURE PROPHYLAXIS AS HIV PREVENTIVE MEASURES

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SUMMARY

HIV chemoprophylaxis started to be used since the first AIDS drug was registered, i.e. in 1987. Post-exposure prophylaxis (PEP), used by persons accidentally exposed to HIV, is mostly related to professional accidental exposure to HIV (mostly among healthcare workers). It is estimated that PEP decreases HIV risk by 81%. Research and implementation of pre-exposure prophylaxis (PrEP) started about 10 years ago. PrEP is intended for use among those who are HIV negative, and in the continuous HIV risk due to their behavior. It is estimated that PrEP use decreases HIV risk by 75% or more, depending on the population and adherence to treatment. In Serbia, PEP and PrEP are still not fully regulated. However, in 2022, the work on regulations has started. In countries with unregulated PrEP, there is a risk from informal therapy use without medical supervision, which can lead to the development of resistant HIV cases among those with previously undiagnosed HIV infection. Both interventions belong to the biomedical HIV preventive interventions, and both are relevant for reaching the global AIDS target – to end AIDS as a "public health threat" by 2030. Nevertheless, for biomedical interventions to be at maximum efficacy, they have to be integrated with adequate behavioral ones, aiming to increase information, adherence to the therapy, and to periodical medical supervision, in line with defined PEP and PrEP recommendations.

Keywords: post-exposure prophylaxis, pre-exposure prophylaxis, HIV infection, AIDS, healthcare workers, biomedical interventions

Introduction

According to the estimates of the Joint United Nations Program on Human Immunodeficiency Virus - HIV/ Acquired Immunodeficiency Syndrome AIDS, from the beginning of the epidemic until the end of 2021, 84.2 million (64.0-113.0 million) people were infected with HIV, and 40.1 million (33.6-48.6 million) people died from AIDS-related diseases and conditions (1). Only in the European region, as defined by the World Health Organization (WHO), in 2021, a total of 106,508 people were newly diagnosed with HIV infection. Of these, 5,940 people were newly diagnosed with HIV in the region of Central Europe, which includes Serbia as well (with 172 people newly diagnosed with HIV). Cumulatively, from the beginning of registration of HIV cases until the end of 2021, about 2.3 million people in the European region were infected with HIV (of whom 106,411 in the Central European region with 4,372 people in Serbia). At the end of 2021, 3,354 people died from AIDS-related diseases and conditions in the European region (cumulatively from the beginning of registration until the end of 2021, 270,374 people), while 229 of them died in the Central European region (cumulatively 9,936) with 14 persons from Serbia (cumulatively 1,186). In the Central European region, the dominant way of transmission of HIV infection is sexual, where the transmission of HIV infection is equally shared by unprotected sexual intercourse between women and men and between men. In Serbia, sexual transmission of HIV infection is dominant, primarily the unprotected sexual intercourse among men (2).

tralne Evrope (kumulativno 9.936), sa 14 osoba iz Srbije (kumulativno 1.186). U regionu Centralne Evrope dominantan način transmsije HIV infekcije je seksualnim putem, gde je podjednako učešće transmisije HIV infekcije nezaštićenim seksualnim odnosom između muškaraca i žena i između muškaraca. U Srbiji dominira seksualni način transmsije HIV infekcije, primarno nezaštićenim seksualnim odnosnom među muškarcima (2).

Od početaka HIV/AIDS epidemije, nacionalne politike i mere za suzbijanje i prevenciju HIV/AIDS-a su bile usmerene preporukama centralnih međunarodnih organizacija koje su bile posvećene borbi protiv HIV/AIDS-a. Uspešnost odgovora je praćena dosezanjem zacrtanih ciljeva na globalnom i na nacionalnim nivoima. Globalni ciljevi definisani za 2020. godinu, određeni strategijom UNAIDS-a za 2016–2021. godinu, nisu dosegnuti. Na kraju 2020. godine, procenjuje se da je 1,5 miliona (1,2-2,0 miliona) osoba bilo novoinficirano HIV-om, što je tri puta više od strateškog cilja od 500.000 novih infekcija globalno, kao i da je 690.000 (540.000-900.000) osoba umrlo od bolesti i stanja povezanih sa AIDS-om, što je za 140.000 više osoba od strateškog cilja da bude manje od 500.000 osoba preminulih od bolesti i stanja povezanih sa AIDS-om (3). Kada je reč o dosezanju operativnog cilja 90-90-90 (da 90% osoba koje žive sa HIV-om znaju da su inficirane HIV-om, da 90% osoba koje znaju da žive sa HIV-om bude na lečenju antiretrovirusnom (ARV) terapijom i da 90% osoba koje su na lečenju ARV terapijom ima nedetektibilnu viremiju u krvi), nije ni on u potpunosti dosegnut. Na kraju 2020. godine, na globalnom nivou 83% osoba koje žive sa HIV-om su znale da su inficirane HIV-om, 87% od onih osoba koje znaju da žive sa HIV-om se lečilo ARV terapijom, a kod 90% osoba koje se leče ARV terapijom bila je postignuta nedetektibilna viremija u krvi (3).

U regionu Centralne Evrope, po podeli SZO, kao i u Srbiji, na kraju 2020. godine cilj „90-90-90“ nije dosegnut. U regionu centralne Evrope 87% osoba koje žive sa HIV-om je dijagnostikovano, 67% osoba sa dijagnostikovanom HIV infekcijom je bilo na lečenju ARV terapijom, a kod 81% osoba koje se leče ARV terapijom postignuta je supresija virusa u krvi do nedetektabilnosti (4). Na kraju 2020. godine, prema UNAIDS procenama, u Srbiji je 85% od osoba koje žive sa HIV-om znalo da su inficirane HIV-om, a 75% onih osoba koje znaju da žive sa HIV-om bilo je na lečenju ARV terapijom (3). Na žalost, naša zemlja ne raspolaže podatkom o uspešnosti lečenja ARV terapijom, odnosno da li je dosegnuta željena supresija virusa u krvi (ispod 50 kopija/ml).

Na sastanku visokog nivoa o AIDS-u redefinisani su ciljevi i UNAIDS postavljaju nove, jednako ambiciozne, za 2025. godinu: da bude manje od 370.000 osoba novoinficiranih HIV-om, kao i manje od 250.000 onih koji su umrli od bolesti i stanja povezanih sa AIDS-om, što bi vodilo ka tome da do 2030. godine ne bude novih infekcija, kao ni smrti od bolesti i stanja povezanih sa AIDS-om (5). Nedosegnuti cilj „90-90-90“ postaje ambiciozniji i prelazi u „95-95-95“ (da 95% onih koji žive sa HIV-om zna da su inficirani HIV-om, da se 95% onih koji znaju da žive sa HIV-om leče ARV terapijom, i da se kod 95% onih koji su na lečenju ARV terapijom postigne nedetektibilna viremija u krvi) (5). Ovako ambiciozni ciljevi zahtevaju i uvođenje novih intervencija, kako bihejvioralnih, tako i biomedicinskih i strukturnih. U ovom radu detaljnije ćemo predstaviti hemioprofilaktične intervencije za prevenciju HIV infekcije, primarno post-ekspozicionu i pre-ekspozicionu hemioprofilaksu.

Biomedicinske intervencije za prevenciju HIV infekcije

U poslednjih 15-ak godina biomedicinske intervencije sve više zauzimaju primat u prevenciji HIV infekcije. Ove intervencije se odnose na primenu terapije i medicinskih tehnika u cilju sprečavanja infekcije HIV-om (6). Obuhvataju muški i ženski kondom kao fizičku barijeru za inficiranje HIV-om, zatim cirkumciziju, dijagnostikovanje i lečenje polno prenosivih infekcija, hemioprofilaksu pre ili posle ekspozicije HIV infekciji ili u okviru prevencije vertikalne transmisije, lečenje ARV terapijom kao preventivnu meru kod seksualnih partnera različitog HIV statusa, i slično.

Post-ekspoziciona profilaksa

Profilaktična upotreba ARV terapije nakon ekspozicije HIV infekciji je započela već krajem 80-tih godina 20. veka, sa registrovanjem prvog leka za terapijsko lečenje AIDS-a (zidovudine, AZT) 1987. godine od strane američke Administracije za hranu i lekove (engl. *Food and Drug Administration*) (7). AZT se za prevenciju HIV infekcije najpre počeo koristiti u slučaju profesionalne ekspozicije HIV infekciji zdravstvenih radnika. Već početkom 1990. godine Centri za suzbijanje i prevenciju bolesti

Since the beginning of HIV/AIDS epidemic, national policies and measures for the suppression and prevention of HIV/AIDS have been directed by recommendations of central international organizations dedicated to the fight against HIV/AIDS. The success of the response is monitored by reaching the set goals at the global and national level. Global goals defined for the year 2020, which were determined by the UNAIDS strategy for 2016-2021, have not been reached. At the end of 2020, it was estimated that 1.5 million people (1.2-2.0 million people) were newly infected with HIV, which is three times more compared to the strategic target of 500,000 new infections globally, as well as that 690,000 (540,000-900,000) people died from AIDS-related diseases and conditions, which is 140,000 more people than the strategic goal of less than 500,000 dying from AIDS-related diseases and conditions (3). When it comes to reaching the operational goal of 90-90-90 (that 90% of people living with HIV know that they are infected with HIV, that 90% of people who know they are living with HIV are treated with antiretroviral (ARV) therapy and that 90% of people on ARV therapy have undetectable viremia in the blood), it has not been fully reached either. At the end of 2020, globally 83% of people living with HIV knew they were infected with HIV, 87% of people who knew they were living with HIV were being treated with ARV therapy, and in 90% of people treated with ARV therapy, undetectable viremia was achieved in the blood (3).

In the Central European region, according to the division of the WHO, as well as in Serbia, at the end of 2020, the "90-90-90" goal was not achieved. In the region of Central Europe, 87% of people living with HIV were diagnosed, 67% of people with diagnosed HIV infection were treated with ARV therapy, and in 81% of people treated with ARV therapy, suppression to the undetectable virus in the blood was achieved (4). At the end of 2020, according to UNAIDS estimates, 85% of people living with HIV in Serbia knew they were infected with HIV, and 75% of those people who knew they were living with HIV were treated with ARV therapy (3). Unfortunately, our country does not have data on the success of treatment with ARV therapy, that is, whether the desired suppression of the virus in the blood (below 50 copies/ml) has been achieved.

At the high level meeting on AIDS, the goals have been redefined and UNAIDS has set the new, equally ambitious goals for 2025: fewer than 370,000 newly infected people, as well as fewer than 250,000 people who died from AIDS-related diseases and conditions, which would lead to no new infections and no deaths from AIDS-related diseases and conditions by 2030 (5). The unreached goal of "90-90-90" becomes more ambitious and turns into "95-95-95" (which means that 95% of those living with HIV know they are infected with HIV, that 95% of those who know they are living with HIV are treated with ARV therapy and that in 95% of those who are on ARV therapy, undetectable viremia in the blood is achieved) (5). Such ambitious goals require the introduction of new behavioral interventions, as well as biomedical and structural. In this paper, we will present chemoprophylactic interventions for the prevention of HIV infection in more detail, primarily post-exposure and pre-exposure chemoprophylaxis.

Biomedical interventions for the prevention of HIV infection

In the last 15 years, biomedical interventions have increasingly taken precedence in the prevention of HIV infection. These interventions refer to the application of therapy and medical techniques in order to prevent HIV infection (6). They include the male and female condom as a physical barrier to HIV infection, then circumcision, diagnosis and treatment of sexually transmitted infections, chemoprophylaxis before and after exposure to HIV infection or as part of the prevention of vertical transmission, treatment with ARV therapy as a preventive measure in partners of different HIV status, and similarly.

Post-exposure prophylaxis

The prophylactic use of ARV therapy after exposure to HIV infection started already at the end of 1980s, with the registration of the first drug for therapeutic treatment of AIDS (zidovudine, AZT) in 1987 by the US Food and Drug Administration (7). AZT was first used for the prevention of HIV infection in the case of occupational exposure to HIV infection of healthcare workers. Already at the beginning of 1990, the Centers for Disease Prevention and Control (CDC) published recommendations for the prevention of HIV infection among accidentally exposed healthcare workers using post-exposure

(engl. *Centers for Disease Prevention and Control* - CDC) objavljuju preporuke za prevenciju HIV infekcije među akcidentalno eksponiranim zdravstvenim radnicima koristeći post-ekspozicionu profilaksu (PEP) AZT-om (8). Kasnijim studijama je ustanovljeno da je rizik od inficiranja HIV-om kod zdravstvenih radnika nakon perkutane ekspozicije krvi inficiranoj HIV-om 0,3% (9,10), odnosno 0,09% nakon kontaminacje sluzokože kroz kontakt sa krvlju inficiranom HIV-om (10), kao i da post-ekspoziciona profilaksa nakon perkutanih povreda smanjuje rizik za 81% od inficiranja HIV-om (9).

Među zdravstvenim radnicima profesionalni rizik predstavljaju primarno perkutane povrede (ubod na iglu ili ubodi i posekotine oštrim instrumentima), kontaminacija sluzokoža (usta, konjunktiva) i kontaminacija ledirane kože (rane, abrazije, dermatitis) kroz kontakt sa krvlju inficiranom HIV-om u trajanju minimum 15 minuta. Izvori HIV infekcije koji mogu dovesti do njenog prenošenja su primarno krv, ali i telesne tečnosti i tkiva u kojima se može naći HIV (telesne tečnosti koje imaju vidljive tragove krvi, vaginalni sekret, semena, amnionska, pleuralna, cerebrospinalna, perikardna i peritonealna tečnost). Kada je reč o stepenu rizika koji nosi sama ekspozicija, on zavisi od vrste igle i/ili oštrog instrumenta (dimenzije) s kojim je došlo do povrede, težine ozlede (dubina), količine infektivne doze kojoj je eksponiran zdravstveni radnik i stepena viremije kod pacijenta čijom krvlju je eksponiran zdravstveni radnik (11,12).

CDC prvi put preporučuje PEP za neprofesionalnu ekspoziciju HIV infekciji 2005. godine (13). Neprofesionalna ekspozicja je podrazumevala izlaganje riziku od inficiranja HIV-om putem seksualnog odnosa (posebno adresirajući seksualne napade/silovanje), injektiranja, transfuzije krvi i perkutanih povreda (primarno ubod na iglu) kada je poznato da je izvor ekspozicije inficiran HIV-om. Takođe, preporučuje se primena PEP-a do 72 sata nakon izlaganja riziku, kao i individualna procena rizika za svaki pojedinačni slučaj ekspozicije radi donošenja odluke o primeni PEP-a (13). Dve godine kasnije SZO, zajedno sa Međunarodnom organizacijom rada, publikuje vodič za PEP koji obuhvata i profesionalnu i neprofesionalnu ekspoziciju HIV infekciji (posebno adresirajući silovanje/seksualno nasilje), sa preporukom da PEP bude deo nacionalnih politika primarno u zemljama sa viskom prevalencijom HIV infekcije (14). Treba istaći da je već krajem 90-tih godina 20. veka veliki broj zemalja Evrope imao PEP procedure za profesionalnu ekspoziciju HIV infekciji primarno kod zdravstvenih radnika (15). Generalno, razvoj vodiča i preporuka je kasnio za praksom. Tako npr. tek 2007. godine se u vodiču za lečenje HIV/AIDS-a Evropskog kliničkog društva za AIDS (engl. *European AIDS Clinical Society* - EACS) definiše i protokol za PEP (16).

Da bi imao rezultate, po najnovijim preporukama EACS-a, PEP treba započeti unutar idealno 4 sata posle ekpozicije, a najkasnije unutar 72 sata nakon ekspozicije, u trajanju od 4 nedelje (28 dana). Serološka kontrola kojom se utvrđuje prisustvo HIV infekcije se vrši unutar 72 sata po ekspoziciji, a zatim nakon završetka PEP režima i ponavlja se 6 do 8 nedelja nakon završenog režima. Pre započinjanja PEP režima, potrebno je utvrditi prisustvo HIV infekcije kod izvora potencijalne infekcije, odnosno viremiju ukoliko je izvor nosilac HIV infekcije, kao i dodatna ispitivanja izvora i izložene osobe u skladu sa individualnim slučajem (12).

I pored ranog prepoznavanja PEP-a kao efikasne mere za prevenciju HIV infekcije, PEP primarno za neprofesionalnu upotrebu nije u velikoj meri implementiran. Jedna od glavnih prepreka, pored onih vezanih za razvoj i implementaciju nacionalnih politika i protokola vezanih za PEP, je bila informisanost osoba iz ključnih populacija u riziku od HIV-a (muškaraca koji imaju seks sa muškarcima, osoba koje injektiraju droge, seks radnika/ca, transrodnih osoba, zatvorenika) o postojanju i benefitima PEP-a, pravilno i pravovremeno identifikovanje izlaganja riziku od HIV infekcije, kao i pravovremeno javljanje u zdravstvenu službu radi dobijanja terapije (unutar 72 sata) (17).

Pre-ekspoziciona profilaksa

Prva ispitivanja uspešnosti upotrebe ARV terapije u prevenicji HIV infekcije, pre same ekspozicije HIV infekciji, krenula su oko 2005. godine, sa sve intenzivnijim istraživanjima oko 2010. godine. Pre-ekspoziciona profilaksa (PrEP) podrazumeva upotrebu definisane ARV terapije od strane osobe koja nije inficirana HIV-om, a koja svesno ulazi u rizik od izlaganja HIV infekciji. Jedna od pretpostavki je bila da uspešna PrEP HIV infekcije može doprineti njenom suzbijanju u ključnim populacijama, tj. onim koje su u kontinuiranom riziku od HIV infekcije. Prve randomizirane kontrolisane studije su rađene mahom u heteroseksualnoj populaciji u Africi. Jedna od prvih studija sprovedena među ženama u Africi (Gana, Kamerun i Nigerija) zbog

prophylaxis (PEP) with AZT (8). Later studies found that the risk of HIV infection in healthcare workers after percutaneous exposure to HIV-infected blood was 0.3% (9,10), that is, 0.09% after mucosal contamination through contact with HIV-infected blood (10), as well as that post-exposure prophylaxis after percutaneous injuries reduces the risk of HIV infection by 81% (9).

Among healthcare workers, the occupational risk relates primarily to percutaneous injuries (needle sticks, or punctures and cuts with sharp instruments), contamination of mucous membranes (mouth, conjunctiva), and contamination of injured skin (wounds, abrasions, dermatitis) through contact with HIV-infected blood lasting at least 15 minutes. Sources of HIV infection that lead to its transmission are primarily blood, as well as body fluids and tissues in which HIV may be present (body fluids with visible traces of blood, vaginal secretions, semen, amniotic, pleural, cerebrospinal, pericardial and peritoneal edema). When it comes to the degree of risk of exposure itself, it depends on the type of needle and/or sharp instrument (dimension) with which the injury occurred, the severity of the injury (depth), the amount of infectious dose to which the healthcare worker was exposed and the degree of viremia in the patient whose blood the healthcare worker was exposed to (11,12).

The CDC first recommended PEP for non-occupational exposure to HIV infection in 2005 (13). Non-occupational exposure included the exposure to the risk of HIV infection through sexual intercourse (specifically addressing sexual assault/rape), injection, blood transfusion and percutaneous injuries (primarily needle stick), when the source of exposure is known to be HIV-infected. Also, the application of PEP is recommended up to 72 hours after exposure to the risk, as well as the individual risk assessment for each individual case of exposure in order to make a decision on applying PEP (13). Two years later, the WHO together with the International Labor Organization, published guidelines for PEP that includes both occupational and non-occupational exposure to HIV infection (specifically addressing rape/sexual violence), with the recommendation that PEP should be part of national policies, primarily in countries with a high prevalence of HIV infection (14). It should be emphasized that already at the end of 1990s, a large number of European countries had PEP procedures for occupational exposure to HIV infection, primarily among healthcare workers (15). Generally, the development of guidelines and recommendations has lagged behind practice. For example, it was only in 2007 that the protocol for PEP was defined within the Guidelines for the treatment of HIV/AIDS of the European AIDS Clinical Society (EACS) (16).

In order to be effective, according to the latest EACS recommendations, PEP should be started ideally within 4 hours after exposure and no later than 72 hours after exposure during 4 weeks (28 days). Serological control, which determines the presence of HIV infection, is performed within 72 hours after exposure, and then after the completion of the PEP regimen, and it is repeated 6 to 8 weeks after the completed regimen. Before starting the PEP regimen, it is necessary to determine the presence of HIV infection in the source of potential infection, that is, viremia if the source is the carrier of HIV infection, as well as additional tests of the source and exposed person in accordance with each individual case (12).

Despite the early recognition of PEP as an effective measure used for the prevention of HIV infection, PEP primarily for non-occupational use has not been widely implemented. One of the main obstacles, in addition to those related to the development and implementation of national policies and protocols that consider PEP, was informing people from key populations at risk of HIV (men who have sex with men, people who inject drugs, sex workers, transgender persons, prisoners) about the existence and benefits of PEP, correct and timely identification of exposure to the risk of HIV infection, as well as timely reporting to the healthcare service in order to receive therapy (within 72 hours) (17).

Pre-exposure prophylaxis

The first studies of the success of ARV therapy in the prevention of HIV infection, before exposure to HIV infection, began around 2005, with increasingly intensive research around 2010. Pre-exposure prophylaxis (PrEP) involves the use of defined ARV therapy by a person who is not infected with HIV, and who knowingly enters the risk of exposure to HIV infection. One of the assumptions was that successful PrEP of HIV infection can contribute to its suppression in key populations, i.e. those who are at continuous risk of HIV infection. The first

malog broja slučajeva serokonverzije u eksperimentalnoj i kontrolnoj grupi nije mogla da evaluira efektivnost PrEP-a (18). Međutim, studije koje su usledile su pokazale visoku efektivnost PrEP-a na bazi tenofivir disoproxil fumarate (TDF), kasnije tenofivir alafenamide (TAF), u prevenciji HIV infekcije, kako u heteroseksualnoj populaciji, tako i među muškarcima koji imaju seks sa muškarcima i osobama koje injektiraju drogu. Tako *Partners* PrEP studija koja je realizovana 2010. godine među heteroseksualnim partnerima različitog HIV statusa nalazi da PrEP u kombinaciji TDF i emtricitabine (FTC) prevenira HIV infekciju u 75% slučajeva, dok samo TDF prevenira 67% (19). Jedna od prvih multinacionalnih randomiziranih kontrolnih studija u populaciji muškaraca koji imaju seks sa muškarcima (*Preexposure Prophylaxis Initiative* - iPrEx) je pokazala sprečavanje HIV infekcije u 44% slučajeva kod onih koji su koristili PrEP u kombinaciji TDF i FTC, ali su ukazali i na to da je efikasnost bila veća kod onih koji su koristili redovno terapiju (17). Kasnije studije su našle da je redovno korišćenje (na dnevnoj bazi ili pre i posle sekusalnog odnosa) kombinacije TDF/FTC sprečava čak 86% slučajeva HIV infekcije među muškarcima koji imaju seks sa muškarcima (20,21). Studije među osobama koje injektiraju drogu su takođe ukazale da redovno korišćenje PrEP-a (na dnevnoj bazi) utiče na smanjenje rizika od HIV infekcije za čak 83,5% kod onih sa najvećom adherencijom (22). Studije među transrodnim ženama pokazuju ograničenja u efikasnosti PrEP-a usled verovatne inetrakcije sa hormonskom terapijom kod onih transrodnih osoba koje je koriste. Neke studije su ukazale na bolje rezultate TAF/FTC terapije kada su transrodne žene u pitanju (23). Dokazana uspešnost PrEP-a u prevenciji HIV infekcije uticala je na to da američka FDA već 2012. godine odobri upotrebu TDF/FTC za prevenciju HIV infekcije kod odraslih (24). Već 2015. godine prvo Evropski centar za prevenciju i kontrolu bolesti (engl. *European Center for Disease Prevention and Control* - ECDC), a zatim SZO daju svoje preporuke da se PrEP integriše u preventivne mere na nacionalnim nivoima za ključne populacije (25).

Prema najnovijim preporukama SZO i EACS, PrEP može da se koristi na dva načina: 1) neposredno pre i posle rizičnog seksualnog odnosa (oralna upotreba duple doze leka baziranog na TDF dva do 24 sata pre rizičnog seksualnog kontakta i po jedna doza u naredna dva dana po rizičnom događaju) ili 2) kontinuirano na dnevnom nivou. SZO navodi da je prvi način prilagođeniji muškarcima, uključujući i transrodne žene koje ne koriste hormone i druge trans osobe koje su muškog pola po rođenju, a drugi im je alternativni, dok je drugi način prilagođen ženama i transrodnim osobama koje koriste određene hormonske terapije. Pre i tokom upotrebe PrEP-a potrebno je sprovesti odgovarajuće medicinske preglede i periodični monitoring određenih zdravstvenih parametara, uključujući i HIV status (12,26). Ono što je presudno za uspešnost PrEP-a jeste adherencija propisanom režimu i periodična medicinska supervizija zdravstvenog stanja (26).

Međutim, i pored svega, implementacija PrEP-a na nacionalnim nivoima u Evropi nije na zadovoljavajućem nivou. U 2021. godini, u većini zemalja Zapadne Evrope PrEP je dostupan, a individualni troškovi vezani za nabavku terapije u potpunosti ili delimično finansirani od strane nacionalnih fondova. Istovremeno, u većini zemalja Centralne i Istočne Evrope, PrEP nije bio formalno uveden (27).

Posebni rizici vezani za korišćenje PrEP-a vezani su za uzimanje PrEP-a bez medicinske supervizije. Ovi rizici su posebno zastupljeni u zemljama gde nije regulisana upotreba PrEP-a, odnosno gde osobe koje procenjuju da su u (kontinuiranom) riziku od HIV infekcije lekove za PrEP nabavljaju na neformalne načine, često bez prethodne medicinske procene i zdravstvenih pregleda. Prema jednoj studiji sprovedenoj u Nemačkoj, neformalna upotreba PrEP-a je bila povezana sa većim šansama da se osobe koje na taj način nabavljaju i koriste PrEP nisu prethodno testirale na HIV, što dalje povećava rizik od razvoja rezistencije na TDF i FTC u slučaju postojanja nedijagnostikovane HIV infekcije (28). Ove nalaze podržavaju i druge studije, dodajući i da postoji rizik od neadekvatne upotrebe ARV lekova, što smanjuje efektivnost PrEP-a (29,30).

PEP i PrEP u Srbiji

Mada je potreba za uvođenjem PEP-a i PrEP-a prepoznata praktično od početaka primene hemioprofilakse za prevenciju HIV infekcije, do sada još uvek nije formalizovana i regulisana primena ARV terapije u preventivne svrhe u Srbiji. U „Strategiji za kontrolu i prevenciju HIV infekcije i AIDS-a Republike Srbije, 2018-2025. godine" (Strategija), prepoznaje se kao posebna mera obezbeđivanje dostupnosti PEP-a i PrEP-a svima koji su imali akcidentalnu ekspoziciju HIV infekciji ili su u kontinuiranom (seksualnom) riziku od HIV infekcije

randomized studies were conducted mainly in heterosexual populations in Africa. One of the first studies conducted among women in Africa (Ghana, Cameroon, and Nigeria) could not evaluate the effectiveness of PrEP due to the small number of seroconversion cases in the experimental and control group (18). However, subsequent studies have shown the high effectiveness of PrEP based on tenofivir disoproxil fumarate (TDF), later tenofivir alafenamide (TAF) in the prevention of HIV infection, both in the heterosexual population and among men who have sex with men, as well as among people who inject drugs. Thus, the Partners PreEP study that was realized in 2010 among heterosexual partners of different HIV status found that PrEP in combination with TDF and emtricitabine (FTC) prevents HIV infection in 75% of cases, while TDF alone prevents 67% (19). One of the first multinational randomized controlled studies in the population of men who have sex with men (Preexposure Prophylaxis Initiative – iPrEx) showed the prevention of HIV infection of 44% cases in those who used PrEP in combination with TDF and FTC, but also indicated that the effectiveness was higher in those who used regular therapy (17). Later studies found that regular use (daily or before and after sexual intercourse) of the TDF/FTC combination prevented as many as 86% of HIV infections among men who have sex with men (20,21). Studies that were conducted among people who inject drugs have also shown that regular use of PrEP (on a daily basis) reduces the risk of HIV infection by as much as 83.5% among those with the highest adherence (22). Studies that were conducted among transgender women have showed limitations in the effectiveness of PrEP due to the possible interaction with hormone therapy in those transgender people who use it. Some studies have pointed out better results of TAF/FTC therapy in transgender women (23). The proven success of PrEP in the prevention of HIV infection influenced the US FDA to approve the use of TDF/FTC for the prevention of HIV infection in adults as early as 2012 (24). Already in 2015, first the European Center for Disease Prevention and Control, and then the WHO gave their recommendations to integrate PrEP into preventive measures at the national level for key populations (25).

According to the latest recommendations of the WHO and EACS, PrEP can be used in two ways: 1) immediately before and after risky sexual intercourse (oral use of a double dose of drug based on TDF two to 24 hours before the risky sexual contact and one dose in the following two days after the risky event) or 2) continuously on a daily basis. The WHO states that the first method is more suitable for men, including transgender women who do not use hormones and other trans people who are male at birth and the second is alternative to them, while the second method is suitable for women and transgender people who use certain hormone therapies. Before and during the use of PrEP, certain medical examinations and periodical monitoring of certain health parameters, including the HIV status, should necessarily be done (12, 26). What is crucial for the success of PrEP is adherence to the prescribed regimen and periodical medical supervision of health condition (26).

However, despite everything, the implementation of PrEP at national levels in Europe is not at a satisfactory level. In 2021, PrEP was available in most Western European countries, and individual costs related to the acquisition of therapy were fully or partially financed by national funds. At the same time, PrEP was not formally introduced in most countries of Central and Eastern Europe (27).

Special risks related to the use of PrEP are associated with taking PrEP without medical supervision. These risks are especially present in countries, where the use of PrEP is not regulated, that is, where people who assess that they are at (continuous) risk of HIV infection get PrEP drugs in informal ways, often without prior medical evaluation and health examinations. According to a study that was conducted in Germany, the informal use of PrEP was associated with higher chances that individuals who obtained and used PrEP in this way had not been previously tested for HIV, which further increases the risk of developing resistance to TDF and FTC in case of the presence of undiagnosed HIV infections (28). These findings have been supported by other studies, adding that there is a risk of inadequate use of ARV drugs, which reduces the effectiveness of PrEP (29,30).

PEP and PrEP in Serbia

Although the need for the introduction of PEP and PrEP has been recognized practically since the beginning of the application of chemoprophylaxis for the prevention of HIV infection, the use of ARV therapy for preventive purposes has not been formalized and regulated in Serbia yet. In

(31). Pravilnik o imunizaciji i načinu zaštite lekovima (32) identifikuje potrebu za hemioprofilaksom (pre ili posle ekspozicije) za HIV infekciju prema epidemiološkim indikacijama. Međutim, treba istaći da je, bez obzira na nedostatak pune formalne regulacije hemioprofilakse, tj. protokola za korišćenje hemioprofilakse za HIV infekciju, u našoj zemlji moguće kupiti lekove za PrEP, registrovane od strane Agencije za lekove i medicinska sredstva Srbije za osobe u riziku od seksualne transmisije HIV infekcije. Ovo je uticalo da se u većoj meri u definisanje privremenih operativnih procedura uključe zdravstveni radnici i predstavnici nevladinih organizacija, kako bi smanjili rizik od neadekvatne primene PrEP terapije primarno u populaciji muškaraca koji imaju seks sa muškarcima. Takođe, u skladu sa strateškim merama, Ministarstvo zdravlja Republike Srbije je tokom 2022. godine formiralo Radnu grupu za izradu nacionalnog vodiča za lečenje osoba sa HIV-om i korišćenje PEP i PrEP terapije. Posledično, možemo očekivati skoru regulaciju ovih preventivnih mera i u našoj zemlji i njihovu integraciju u postojeće programe prevencije HIV infekcije u ključnim populacijama u riziku od HIV-a, odnosno među zdravstvenim radnicima i drugim osobama izloženim riziku od akcidentalnog izlaganja HIV infekciji.

Zaključak

Kako je prihvaćeno da će uvek biti osoba koje ne žele ili ne mogu da promene svoje ponašanje i smanje rizik od HIV infekcije, biomedicinske intervencije sve više dobijaju na značaju. Ovo važi i za PEP i PrEP koje pripadaju grupi biomedicinskih intervencija u prevenciji HIV infekcije. Pri tome, PEP je ostao više vezan za prevenciju HIV infekcije nakon akcidentalnog izlaganja riziku od HIV-a primarno zdravstvenih radnika, ali i drugih profesionalaca, kao i žrtava seksualnog nasilja (silovanja). PrEP je više usmeren na prevenciju neprofesionalnih ekspozicija HIV infekciji osoba koje nisu inficirane HIV-om, a u kontinuiranom su riziku od HIV infekcije. Ipak, da bi biomedicinske intervencije bile efikasne, potrebno je njihovo povezivanje sa bihejvioralnim intervencijama. Odnosno, bitno je adekvatno savetovanje vezano za adherenciju propisanoj terapiji i periodične zdravstvene preglede, kako bi PrEP i PEP mogli uspešno da preveniraju HIV infekciju.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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the "Strategy for control and prevention of HIV infection and AIDS of the Republic of Serbia, 2018-2025" (Strategy), ensuring the availability of PEP and PrEP to all those who had an accidental exposure to HIV infection or who are at continuous (sexual) risk of HIV infection is recognized as a specific measure (31). The Rulebook on Immunization and Protection with Drugs (32) identifies the need for chemoprophylaxis (before or after exposure) for HIV infection according to epidemiological indications. However, it should be noted that, regardless of the lack of full formal regulation of chemoprophylaxis, i.e. lack of protocol for chemoprophylaxis for HIV infection, in our country, it is possible to buy drugs for PrEP, which are registered by the Agency for Medicines and Medical Devices of Serbia for persons at risk of sexual transmission of HIV infection. This influenced to a great extent the involvement of healthcare workers and representatives of non-governmental organizations in defining the temporary operating procedures, in order to reduce the risk of inadequate application of PrEP therapy primarily in the population of men who have sex with men. Also, in accordance with the strategic measures, the Ministry of Health of the Republic of Serbia formed in 2022 the Working group for development of national guideline for HIV treatment and use of PEP and PrEP therapy. Consequently, we can soon expect the regulation of these preventive measures in our country and their integration into the existing prevention programs for HIV infection in key populations at risk of HIV, that is, among healthcare workers and other persons exposed to the risk of accidental exposure to HIV infection.

Conclusion

Since it is accepted that there will always be people who are unwilling or unable to change their behavior and reduce the risk of HIV infection, biomedical interventions are getting more and more importance. This also applies to PEP and PrEP, which belong to the group of biomedical interventions in the prevention of HIV infection. At the same time, PEP remained more related to the prevention of HIV infection after the accidental exposure to the risk of HIV, primarily of healthcare workers, but also of other professionals, as well as victims of sexual violence (rape). PrEP is more focused on the prevention of non-occupational exposure to HIV infection of people who are not infected with HIV and who are at a continuous risk of HIV infection. However, in order for biomedical interventions to be effective, it is necessary to combine them with behavioral interventions. That is, adequate counseling related to adherence to prescribed therapy and periodic health examinations is essential, so that PrEP and PEP could successfully prevent HIV infection.

Competing interests

Authors declare no competing interests.

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