Review Article

VAGINAL MICROBIOCENOSIS FEATURES IN HIV-POSITIVE WOMEN OF FERTILE AGE

Abstract:

HIV remains a major global public health problem.

The aim of our study *is to analyzethe research data that has been aimed at studying the effect of HIV infection on vaginal microbiocenosis. To determine the differences in dysbiotic disorders in seronegative and seropositive women. To establish the effect of vaginal microbiota on pre-exposure prophylaxis of HIV.*

Materials and methods: *Evaluation of the Russian and other countries results on the microbiota of HIV-positive women studies, published in international databases.*

Results:*the analysis of the research data aimed at studying the effect of HIV infection on the vaginal microbiocenosis indicates that dysbiotic disorders in HIV-infected patients are significantly more frequent. It has been revealed that the atypical clinical picture of changes in the vaginal microbiocenosis prevails. It has been noted that there is a correlation of vaginal microbiocenosis in HIV-positive women and indicators of systemic immunity, CD4 + cell levels.*

Conclusion: *Based onanalyzis of published in international databases Russian and other countries studies resultson the HIV-positive women microbiota, it was found that there is a need for additional studies of the qualitative and quantitative composition of the microbiota of HIV-positive women. It is need to assess the of the vaginal microbiota and other possible connected factors ability to change the concentration of antiretroviral drugs.*

Keywords: *vaginal microbiocenosis, HIV infection, dysbiotic disorders*

Introduction

HIV remains a major problem for public health services. According to the AIDS Center of the Irkutsk region, the number of HIV-positive women who are sexually infected increases every year. In 2018, the incidence rate was 141.7 cases per 100 thousand people in the Irkutsk region, among which 44.8 % were women, mostly of reproductive age [1, 47, 48].

The interrelation between bacterial vaginosis and the risk of HIV transmission.

The vaginal microflora includes more than 300 species of micro-organisms that are closely related to the structural components of the vagina. The vaginal epithelium is covered with a multi-layer flat non-corneal epithelium, which changes in response to the action of body hormones. Under the influence of estrogens, epithelial cells are **saturated** with glycogen, which **saturates** microorganisms [2]. *Lactobacillus* participates in maintaining the homeostasis of the microbiocenosis of the vagina, performing a barrier function, limiting the reproduction of the transitory microflora. The microflora also contains microorganisms that can produce lactic acid**;** these include opportunistic agents (*Megasphaeraspp., Prevotellabivia, Leptotrichiaspp.*) and some agents that indicate a violation of the vaginal microbiota (*Atopobiumvaginae)* [3, 4, 5, 6].

One of the main factors that increase the risk of sexual infection with HIV is a violation of the vaginal microflora and the presence of sexually transmitted diseases. When bacterial vaginosis occurs*, Gardnerella vaginalis* is present in 95% of cases. The formation of *Gardnerella vaginalis* bio-film on the vaginal epithelium is accompanied by the release of cytokines that contribute to the destruction of epithelial cells. Reduced growth of *Lactobacillus* leads to the

increase in the concentration of enzymes (mucinase, sialidase, collagenase, protease, phospholipase A2 and C), organic acids, di-and polyamines. Damage of the vaginaprotective epithelium increases the possibility of rapid attachment of bacteria to epithelial cells [7].

In bacterial vaginosis, the environment is leached and targets for HIVCD4 + lymphocytes are activated, which consequently increases the risk of infection of partners of HIV-positive women [8, 9].Long-term excessive formation of active forms of oxygen leads to oxidative stress and, as a result, to a number of pathological changes [10, 11]. Immunodeficiency is associated with the progression of HIV infection, which can lead to changes in the vaginal microbiocenosis and the addition of opportunistic infections [12]. Due to the **disturbances** in the quantitative and qualitative composition of the microbiota, and the antioxidant defense enzymes activity decreases [13]. The hyper peroxidation process with a decrease in the adaptive capabilities of the antioxidant defense system leads to the oxidative stress increasing [14, 15].

Most studies related to the black race Africa HIV-positive women vaginal microbiota investigations. To evaluate the data, microscopic methods have mainly been used, which create an incomplete picture of the micro-biota of the vagina.

C. Christelet al.(2017) published the results of the study conducted in two Chicago(USA) hospitals. Scientists evaluated the impact of HIV infection on the vaginal microbiota and its interrelation with treatment and demographic factors; compared samples of vaginal micro-biota taken from HIV-positive and HIV-negative women. The authors used 16s ribosomal RNA gene sequencing to characterize the types of bacterial communities. C. Christel et al. have found that HIV infection can contribute to the violations of the vaginal microflora, despite effective anti-retroviral therapy. The high incidence of bacterial vaginosis is a marker of socio-economic, genetic, or other factors that are also positively associated with HIV infection but are not correlated with it [16]. C. Christel et al. confirmed the link between vaginal dysbiotic disorders and an increased risk of HIV infection. Authors found that if woman has an aerobes dominating genital

bacterial communities, other than *Gardnerella,* they had a higher risk of HIV infection and an increased number of activated CD4+T-cell lysis compared to those with a predominant *lactobacilluscrispatus* community. Anaerobic taxa (*Megasphaera, Clostridium, Prevotella, Atopobiumvaginae, and Sneathia*) have been associated with increased inflammation in the cervical canal. Cervical epithelial cells produced higher concentrations of IL-6 and IL-8 when co-cultured with *Gardnerella vaginalis*, *Prevotellabivia, and Prevotellaamnii* compared to *Lactobacillus crispatus*. *Prevotellamelaninogenica, Veillonellamontpellierensis, Mycoplasma spp., prevotellabivia and Neathiasanguinegens* are associated with increased inflammation of the genitals and are also associated with the acquisition of HIV. That is, the presence of bacterial vaginosis increases the risk of HIV infection, causing favorable conditions for the creation of target cells for HIV infection [17]. Other scientists have come to the same conclusion[18, 19, 20, 21].

J. S. Coleman et al.have noted that with a reduced number of *Lactobacillus*, women have an increase in HIV-1 RNA in the cervical channel compared to women with normocenosis [22]. The study in Kenya has shown that impaired vaginal microbiocenosis contributes to HIV infection and gonorrhea [23]. Other studies have shown that HIV-positive women with bacterial vaginosis have a higher concentration of the pathogen in the vaginal contents [24]. Taking into consideration the rapid spread of HIV infection it is very important fact. The evaluation of data conducted in Zimbabwe revealed links between the prevalence of HIV and various infections of the reproductive tract in women in the absence of clinical manifestations.E.M. Mbizvoet al. have noted that there is a direct correlation between HIV infection and bacterial vaginosis [25].

In 2015, C. R. Eadeet al. published data obtained during the co-cultivation of epithelium of the cervical canal and *Atopobiumvaginae* in HIV-positive women. The authors noted that bacterial vaginosis contributes to the transmission of HIV infection by increasing the activity of secreted low molecular weight peptides [26]. In the same year426 African women were examined by V. Jespers et al.usingpolymerase chain reaction to determine the likelihood of developing

dysbacteriosis. It was noted that *Gardnerella vaginalis* (p = 0.204) and *Atopobiumvaginae* (p = 0.001) were widely represented in women with a Nugent score of 4-6 points (intermediate smear type) and a score of 7-10 points (presence of bacterial vaginosis) compared to women with a score of 0-3 points (normal flora) [27].

Features of vaginal microbiocenosis in highly active anti-retroviral therapy and the local use of drugs

Nowadays the drugs for pre-exposure prophylaxis of HIVare widely studied[28, 29]. Daily oral administration of tenofovir-based drugs is very effective for reducing the incidence of HIV; this type of prevention applies to population groups with a high risk of HIV infection [30, 31]. The drugs containing, for example, dapivirin, **tenofoviralafenamide**, maraviroc, etc., are also at various stages of research and can become promising options for HIV prevention with prolonged action [32, 33,34]. However, in 2017 N. R. Klatt et al. suggested that the effectiveness of locally applied drugs for pre-exposure prophylaxis of HIV may **decrease their activity** if the vaginal microflora is disturbed [35]. This is a serious health problem, given the wide spread of bacterial vaginosis in women in the areas most involved in the epidemic process[36].

The secondary analysis from the CAPRISA-004 cohort has shown that the effect of a 1% tenofovir-based gel in the presence of a vaginal microbiota dominated by *Gardnerella vaginalis* and other anaerobic bacteria is absent [37].In 2017, a data analysis was published comparing the effectiveness of oral and topical **tenofovir-based** drugs for pre-exposure prophylaxis of HIVfor women with and without bacterial vaginosis. It has been found that the effectiveness of oral drugs for pre-exposure prophylaxis of HIV does not change in the presence of bacterial vaginosis. *Gardnerella vaginalis* can rapidly metabolize tenofovir, especially when it is only applied locally, and prevent the medicine from entering cells. Vaginal dysbiosis associated with *Gardnerella vaginalis* disrupts metabolism and reduces the effectiveness of 1% tenofovir gel, but not of oral tenofovir-baseddrugs for pre-

exposure prophylaxis of HIV. There were no significant differences in the efficiency between oral drugs for pre-exposure prophylaxis of HIV in the period when a woman does not have a microbiota disorder (Nugent score 0-3 points), in the intermediate smear type (4-6 points) and bacterial vaginosis (score 7-10 points) [38].All this lead to suggestion, that vaginal dysbiotic disorders may not significantly reduce the effectiveness of oral drugs for pre-exposure prophylaxis of HIV. Active metabolites of tenofovir are systemically distributed and are found in higher concentrations in blood plasma when used orally than when used locally [38, 39].

Tenofovir metabolism can occur fairly quickly; studies have shown a decrease in the level of tenofovir diphosphate (the active form of tenofovir) in the cervical tissue within two hours and a decrease in its concentration in the cervicovaginal fluid and plasma after one week in the presence of an excess amount of *Gardnerella vaginalis*[40].

The use of **highly active antiretroviral therapy** (HAART) has significantly increased the life expectancy of HIV-positive patients. However, one of the important problems for such patients is the addition of opportunistic infections [41].In 2015, M. Lallaret al. published data on the prevalence of bacterial vaginosis, candidiasis, and trichomoniasis in HIV-seropositive women. The authors have evaluated the interrelation between the use of HAART and CD4 +.The study involved 200 HIV-positive women aged from 18 to 45 years. Bacterial vaginosis was detected in 47.7% of cases, candidiasis-in 43.2% and trichomoniasis-in 8.8% of cases among them. Reproductive tract infection has been found in 30% of cases in women with the number of CD4+ lymphocytes <200 cells/ml and in 17 % of cases in women with the level of CD4+ >200 cells / ml. Reproductive tract infection was detected in 23% of cases while receiving HAART, and in 18.6% of cases when there was no antiretroviral therapy.At low CD4+ levels in HIV-positive women, the detection of reproductive tract infection is higher, but the use of HAART does not reduce the prevalence of it [42].The main goal of HAART is to interrupt virus replication in the body and increase the

number of CD4 + lymphocytes to restore a normal immune response. In HIV-positive pregnant women, when taking HAART, there was an increase in cases of normocenosis, a decrease in cases of violation of vaginal microbiocenosis associated with *Mycoplasma spp*. [43, 44, 45, 46].The restoration of local immunity, namely the presence of a stable vaginal microbiocenosis, is possible due to the implementation of the clinical effect of antiretroviral therapy.

Conclusion

Most studies reflecting the high prevalence of vaginal microflora disorders in HIV-positive women, compared to seronegative women, have been conducted among the African women.

The data on the study of the microbiota of HIV-positive women of European and Asian race are not available. It is necessary to assess the qualitative and quantitative composition of HIV-positive women in our country.

The results of the research have indicated that vaginal dysbacteriosis can reduce the effectiveness of local drugs for pre-exposure prophylaxis of HIV based on tenofovir by changing the drug concentration.

When developing new and relevant HIV prevention strategies, it is necessary to clarify the factors that influence the changes in the bioavailability and effectiveness of drugs. This problem remains important to achieve the reduction of the infection rate of the population.

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