Russian Journal of Infection and Immunity = Infektsiya i immunitet
2021, vol. 11, no. 1, pp. 79–84

Инфекция и иммунитет
2021, Т. 11, № 1, с. 79–84

TREATMENT OF HUMAN PAPILLOMAVIRUS INFECTION IN HIV-INFECTED PATIENTS

V.S. Smirnov[a,b], T.A. Kudryavtseva[b]

[a] *St. Petersburg Pasteur Institute, St. Petersburg, Russian Federation*
[b] *JSC MBSPC "Cytomed", St. Petersburg, Russian Federation*

Abstract. The first reports about HIV (human immunodeficiency virus) were appeared to the 1980s. By 2017 more than 37 million people were living with HIV. Human papilloma virus (HPV) is universally spread, with some estimates showing that about 1% of the sexually active population having genital warts. Human papilloma virus (HPV)-induced infection frequently accompanies the clinical course of HIV and can manifest itself in a full spectrum of clinical-pathologic forms ranging from common warts to malignant neoplasia. Due to the widespread use of antiretroviral therapy, the number of patients with a combined infection (HIV+HPV) is steadily increasing. Here we review current clinical treatment options for HPV manifestations. High-dose antiretroviral therapy does not impede HPV treatment, and can even improve its efficacy in some cases. The topical administration of imiquimod, an immune response modifier, is an effective conservative treatment in HIV-infected patients with HPV. The immunomodulation therapy of imiquimod can serve as an effective alternative of aggressive chemical and mechanical procedures. Maximum efficacy with the lowest replaces rates may be expected from combined use of mechanical ablation methods with a subsequent follow up treatment with imiquimod. The best therapeutic result is expected in HIV-positive patients who are received high-dose antiretroviral treatment. The advantages of Vartocid, the modified Russian equivalent of the generic imiquimod.

Key words: *HIV infection, human papillomavirus (HPV), HPV clinical manifestations, treatment methods, imiquimod, Aldara, Vartocid, immunomodulation therapy.*

ЛЕЧЕНИЕ ПАПИЛЛОМАВИРУСНОЙ ИНФЕКЦИИ ЧЕЛОВЕКА У ВИЧ-ИНФИЦИРОВАННЫХ ПАЦИЕНТОВ

Смирнов В.С.[1,2], Кудрявцева Т.А.[2]

[1] *ФБУН НИИ эпидемиологии и микробиологии им. Пастера, Санкт-Петербург, Россия*
[2] *АО МБНПК «Цитомед», Санкт-Петербург, Россия*

Резюме. Первые сообщения о ВИЧ (вирусе иммунодефицита человека) появились в 1980-х гг. К 2017 г. более 37 млн человек жили с ВИЧ. Вирус папилломы человека (ВПЧ) распространен повсеместно, и, по некоторым оценкам, около 1% сексуально активного населения имеет генитальные бородавки. Инфекция, вызванная вирусом папилломы человека, часто сопровождает клиническое течение ВИЧ и может проявляться в полном спектре клинико-патологических форм, от обычных бородавок до злокачественных неоплазий. В связи с широким применением антиретровирусной терапии число пациентов с сочетанной инфекцией (ВИЧ+ВПЧ) неуклонно растет. Здесь мы рассмотрим текущие клинические варианты лечения проявлений ВПЧ. Антиретровирусная терапия в высоких дозах не препятствует лечению ВПЧ, а в некоторых случаях даже может повысить ее эффективность. Местное введение имиквимода, модификатора иммунного ответа, является эффективным

Адрес для переписки:
Смирнов Вячеслав Сергеевич
197101, Россия, Санкт-Петербург, ул. Мира, 14,
ФБУН НИИ эпидемиологии и микробиологии имени Пастера.
Тел.: 8 911 948-59-22 (моб.).
E-mail: vssmi@mail.ru

Contacts:
Vyacheslav S. Smirnov
197101, Russian Federation, St. Petersburg, Mira str., 14,
St. Petersburg Pasteur Institute.
Phone: +7 911 948-59-22 (mobile).
E-mail: vssmi@mail.ru

Для цитирования:
Смирнов В.С., Кудрявцева Т.А. Лечение папилломавирусной инфекции человека у ВИЧ-инфицированных пациентов // Инфекция и иммунитет. 2021. Т. 11, № 1. С. 79–84. doi: 10.15789/2220-7619-TOH-1233

Citation:
Smirnov V.S., Kudryavtseva T.A. Treatment of human papillomavirus infection in HIV-infected patients // Russian Journal of Infection and Immunity = Infektsiya i immunitet, 2021, vol. 11, no. 1, pp. 79–84. doi: 10.15789/2220-7619-TOH-1233

DOI: http://dx.doi.org/10.15789/2220-7619-TOH-1233

консервативным лечением пациентов с ВИЧ, инфицированных ВПЧ. Иммуномодулирующая терапия имиквимодом может служить эффективной альтернативой агрессивным химическим и механическим терапевтическим процедурам. Максимальная эффективность с самыми низкими показателями замещения может ожидаться от комбинированного использования методов механической абляции с последующим местным применением имиквимода в виде крема на зону абляции после заживления раны. Наилучший терапевтический результат ожидается у ВИЧ-позитивных пациентов, получающих антиретровирусное лечение в высоких дозах. Обсуждаются преимущества «Вартоцида», модифицированного российского эквивалента дженерика имиквимода.

Ключевые слова: *ВИЧ-инфекция, вирус папилломы человека (ВПЧ), клинические проявления ВПЧ, методы лечения, имиквимод, «Альдара», «Вартоцид», иммуномодулирующая терапия.*

Introduction

The first registered case of secondary human immunodeficiency (HIV) induced by a retrovirus of the same name dates back to the 1980s. The disease quickly spread throughout the world, reaching pandemic proportions and posing a global problem. The current epidemic state and poor results of pandemic control are associated primarily with the tropism of the virus, which persists mainly in the $CD4^+$ cell population of the infected patient [29]. By 2012, more than 33 million people died of HIV infection, and as of 2017, more than 37 million people were living with HIV, 18 million of them contracting the disease for the first time [12, 21]. African countries in the sub-Saharan region account for more than 70% of all HIV infections. In non-African populations, the virus is most prevalent among persons who inject drugs, people undergoing medical manipulations get infected less frequently (Table).

Russia has the world's third-biggest incidence of HIV infection [1] with 1.4 million estimated as being infected at 30 September, 2020 [3]. In 2018, 86,519 new cases were reported, 941 of these being children. The following 13 regions account for more than a half (59.0%) of all reported HIV cases: Kemerovo Oblast, Novosibirsk Oblast, Perm Krai, Moscow, Irkutsk Oblast, Sverdlovsk Oblast, Samara Oblast, Krasnodar Krai, Saint Petersburg, Krasnoyarsk Krai, the Republic of Bashkortostan, Chelyabinsk Oblast, and Moscow Oblast. Despite these worrying statistics, antiretroviral therapy, which has been widely used in developed countries since the end of the 1990s, significantly influenced the survival rates among HIV-infected subjects and reduced the total number of infected cases, especially those infected by mother-to-child transmission.

Table. HIV prevalence among population groups [33]

Vulnerable group	Prevalence, %	Incidence, %	Incidence per 100,000 persons
Persons who inject drugs	45.0	23.18	12.977
Their sexual partners	8.0	5.15	3.601
Female sex workers	9.0	3.23	905
Their clients	4.0	4.07	91
Men who have sex with men	5.0	13.17	983
Their female sexual partners	2.0	2.06	308
Occasional heterosexual intercourse	2.0	3.27	146
Medical injections	1.10	0.58	1

The deterioration and functional suppression of normal innate and acquired immunity systems by HIV induces a plethora of diseases, both infectious and non-infectious in etiology. These include various types of malignant tumors and a large number of opportunistic infections induced by *Toxoplasma gondii*, *Cryptococcus neoformans*, *Pneumocystis carinii*, *Candida albicans*, *Mycobacterium tuberculosis*, hepatitis virus, and various serotypes of papillomaviruses [17, 19].

Human papillomaviruses (HPV) are universally spread, with some estimates showing that about 1% of the sexually active population having genital warts [4]. This disease is asymptomatic in 5–40% cases and can remain latent for decades.

Genital warts are always caused by human papillomaviruses, which hold a significant position among the opportunistic infections characteristic of HIV infections, where warts and papillomas occur much more frequently and tend to manifest themselves in severe and/or recurrent attacks [2]. Among the large number of diseases of papillomaviral etiology which are found in HIV-infected persons, almost all forms of pathology can be encountered: from genital warts and pointed condyloma to cervical cancer, malignant vulvovaginal neoplasia, and anal squamous intraepithelial neoplasia [15, 25]. HPV prevalence among HIV-infected persons remains high even in patients receiving active retroviral therapy [32]. Benign pointed condyloma and various malignant neoplasias, such as anal squamous intraepithelial neoplasia, vulvovaginal neoplasia, and cervical cancer, are most prevalent [9, 15, 25].

Many current treatment methods are used for these diseases, ranging from mechanical dissection and laser vaporization to removal of tumors with chemical and immunomodulating agents [25].

Anogenital warts

Anogenital warts are the most prevalent manifestation of papillomavirus infection in men who have sex with men (MSM). From the full spectrum of the virus serotypes, the persistence of serotypes 16 and 18 is the primary reason for the development of precancerous and cancerous lesions of the anogenital tract. Viruses of other serotypes, such as HIV 32, 42, 43, 44, 54, etc., promote the growth of common and anogenital warts of low malignancy [2].

Any treatment method may be applied in HIV-infected subjects with common and anogenital warts, including surgical removal, cryotherapy, electrocoagulation, or chemical removal with podophyllin and trichloracetic acid.

However, the use of aggressive chemical and mechanical procedures may be inadvisable where the patient is undergoing high-dose antiretroviral therapy or otherwise is in poor general condition [24]. In such cases, immunomodulating therapy with imiquimod can serve as an effective alternative [26, 18]. Until recently, the only existing brand of this drug was Aldara® [10]. Lately, generic equivalents have appeared on the market as well. These include the modified generic drug Vartocid produced by JSC MBSPC "Cytomed" [2].

Results reported for the original imiquimod drug (Aldara®) demonstrated complete disappearance of external genital and perianal warts in 50% following treatment of immunocompetent patients. However, this effect was significantly reduced in HIV-infected patients, although it was improved in cases of concomitant antiretroviral therapy [26, 30]. According to the authors, the rate of complete clearance of warts in HIV-infected subjects treated with the original medication 5 times per week over a 16-week course was reported as 32%. At the same time, viral DNA was detected even at the end of the treatment, involving coinfection by both benign and malignant serotypes [16]. It was possible to achieve complete viral elimination only after a refresher 16-week course of treatment.

Another study compared the efficacy of imiquimod treatment of external genital warts in HIV-positive and HIV-negative patients. Imiquimod was administered 3 times per week in a course of up to 16 weeks. Among HIV-positive subjects, complete clearance of external genital warts was observed in 31% of patients, partial clearance in 24%, and no effect was reported in 45% of patients. In the immunocompetent HIV-negative patient group, complete clearance was observed in 62% of cases, partial clearance in 24%, and no effect in 14%. Recurrence of disease was observed in 4 of 23 patients with HIV and in 2 of 31 HIV-negative subjects. The medication was well tolerated by patients, with side effects of burning sensation and hyperemia scored as minor and moderate. The authors concluded that topical 5% imiquimod cream has acceptable efficacy and safety in HIV-positive subjects [28].

Thus, the administration of 5% imiquimod cream for the treatment of external anogenital warts in HIV-infected subjects is an adequate therapy with high compliance and no significant side effects. At the same time, antiretroviral therapy not only doesn't impede the treatment of anogenital warts, and in a number of cases may also increase the elimination of HPV.

The results quoted were achieved for the original Aldara® medication. As indicated above, there are a large number of generics, one of them being a Russian drug Vartocid. In essence, it is a complete equivalent of the original Aldara® drug in terms of the active substance. However, in the process of designing the equivalent, we were challenged by the low solubility of this com-pound and the difficulty in formulating an adequate cream in the form of an oil-in-water emulsion. The solution was found by adding oleic acid and diethylene glycol monoethyl ether to the ointment base. The result was a homogenous emulsion, as confirmed by microscopic findings (see cover II).

As shown in Fig., the dispersion rate of the generic drug Vartocid equals or even slightly exceeds the original Aldara® cream. Treatment with 5% Vartocid cream by medical practitioners shows a higher efficacy of this medication in comparison to a generic equivalent Kerawort, due to possibly not only higher dispersity, but also better penetrative properties. As indicated in anecdotal reports of medical practitioners, administering Vartocid even 3 times a week results in better efficacy than the administration of Kerawort 5 times a week, and with minimal side effects or absence thereof [2].

Squamous anal intraepithelial neoplasia (AIN) and anal cancer

Papillomaviral serotypes of high malignancy are widespread among MSM and frequently cause AIN [27]. AIN is a precancerous lesion of the anal mucosa, which in turn precedes anal cancer [22]. The highest HPV-associated risk factors are HIV infection, anal sex, and sexual behavior exhibiting a frequent change of sexual partners. The development of AIN takes several years, therefor continuous clinical supervision of such patients can prevent the development of the neoplasia [25]. One study revealed 15% cases of persistant HPV of low malignancy risk and 5% HPV of high malignancy risk among 1,262 HIV-negative MSM [19]. In other words, HIV is a contributory cause to AIN development, but the virus can also persist in the absence of HIV. The treatment of AIN and anal cancer in HIV-positive subjects includes various methods for papilloma removal: surgical dissection, destructive therapy in the form of radiofrequency (RF) ablation or electrocoagulation, chemical destruction with trichloracetic acid or 5-fluorouracil, and imiquimod immunomodulating

therapy. Each of the above-mentioned methods has its advantages and disadvantages.

Surgical removal of AIN, used when the site of damage is large, often requires significant removal of normal tissue. Besides, it is associated with a high relapse incidence (9–63%) [25]. Moreover, surgical treatment is often associated with severe pain in post-surgery period. RF-therapy was followed by elimination in 64% of subjects in the course of 140 days of monitoring. However, the relapse rate in HIV-positive MSM reached 64% in the course of 14 months of monitoring and 91% in the course of 17 months [9]. Electrocoagulation demonstrated complete response in 32.5% of cases, but 33.7% failed to provide positive results. Relapse in the course of the two-year follow-up was observed in 79% of patients. Local topical treatment with trichloracetic acid (TCA) demonstrated complete elimination in 71–79% cases, and prescribing 5-fluorouracil led to complete clearance in 39%, partial clearance in 17%, and no effect in 37%. Relapse rates for both treatments reached up to 50% [5].

The alternative to TCA and 5-fluorouracil is the use of imiquimod. Fox et al. [2010] measured the efficacy of imiquimod for AIN in 53 HIV-positive MSM, 28 of whom received imiquimod, and 25 placebo. Complete or partial clearance was seen in 43% of cases among 28 subjects receiving imiquimod, and sustained response after 36 months of the medication administration in 61%. Kreuter et al. [11] conducted a concurrent study of AIN treatment efficacy in HIV-infected MSM. The overall monitoring time was 30.3 months. During this period, 17 (74%) out of 19 monitored subjects remained AIN-free. HPV relapse occurred in five subjects (26%) in the course of an average of 24.6 months. Simultaneously with papilloma clearance, a reduction in the number of HPV serotypes was noted. However, full viral clearance could not be achieved, and some patients developed AIN lesions on the untreated skin areas. This situation necessitates the monitoring of patients after AIN elimination for further efficient anti-relapse treatment.

The most probable outcome of AIN in HIV-positive MSM is its transformation to anogenital cancer [28]. It has been demonstrated that subjects who have been HIV-positive for more than 15 years get cancer 12 times more often than those infected for less than 5 years. Infrared coagulation therapy is used for treatment, with efficacy ranging from 35% to 65% in the course of 6 to 14 months of monitoring. The procedure was well tolerated, with reports of only mild to moderate anal pain, bleeding being the most prevalent side effect. TCA is used for the same purpose. The procedure was demonstrated to be safe and well tolerated. Therapeutic effect in HIV-positive subjects can reach 87%, however subsequent relapse over the following 24 months is also reported more often than for other interventions.

As of 2010, imiquimod was not approved for treating anogenital cancer in HIV-positive MSM. However, the studies have shown that it is efficient and well tolerated. In the course of 9 months monitoring, clearance was registered in the range of 46–74%. Relapse, which occurred in 29% patients, was confined to areas not treated with imiquimod.

Therefore, the methods of anal intraepithelial lesion treatment in HIV-positive MSM are, in essence, no different from those used in HIV-negative subjects. A better tolerance of imiquimod is the only thing of note in this regard. We have no conclusive data on the results of using Russian generic drug Vartocid for treating anogenital pathologies. However, it may be assumed that Vartocid, having an improved formula and better penetrative qualities, may show higher efficacy, even in smaller doses.

Imiquimod and papillomaviral pathology in HIV-positive women

HPV infection is a common genital tract pathology in HIV-infected women [24]. It is assumed that various forms of HPV occur in about 60% of HIV-positive women [23]. With genital warts being most prevalent, including vulvovaginal warts, pointed condylomas, and vulvovaginal and cervical papillomas. The latter are prone to various types of cancerization in HIV-positive women [25]. In general, HPV treatment in HIV-positive women does not differ from the treatment of any other patients with various forms of papillomatosis. The basis for therapy approach is not the elimination of the virus, but the removal of external symptoms [2]. The complete spectrum of therapeutic methods, from cryotherapy to immunomodulating therapy, is used for that purpose [11]. The overall therapy efficacy parameters and relapse rates also show no correlation with the presence or absence of HIV in a patient. In a considerable number of cases, the use of imiquimod for treating cervical papilloma, neoplasia and cancer as monotherapy or in combination with physical ablation methods permits the achievement of a steady remission with a significantly reduced relapse rate. Some increase in the therapeutic effect may be achieved by concomitant high-dose retroviral therapy.

Conclusion

In summarizing the reported data, it is worth emphasizing that HIV infection is frequently accompanied by HPV activation, promoting papillomatosis of differing localization. At the same time, a common problem is the persistence of viral serotypes with high malignancy risks, including squamous carcinoma or cervical cancer. Today there are no methods for total elimination of the virus, therefore therapy is focused on treating the morphological consequences of the infection. The full range of therapeu-

tic interventions is employed for this purpose: from surgical dissection to immunomodulating therapy with imiquimod [6, 13, 14]. In general, all these interventions achieve comparable results in the elimination of lesions in 50–90% of cases. At the same time, the relapse risk in the course of the first year of monitoring can reach 50% for mechanical, thermal and laser excision. A slightly lower relapse rate is observed for immunomodulating therapy with imiquimod. Due to deeper penetration of imiquimod the affected area, the modified composition of 5% cream Vartocid, developed in Russia, may permit higher efficacy with less frequent dosing. Maximum efficacy with the lowest relapse rates may be expected from combined use of mechanical ablation methods (cryodestruction, electrocoagulation, laser vaporization) with a subsequent follow-up treatment with imiquimod. At the same time, the best therapeutic result is expected in HIV-positive subjects who are receiving high-dose antiretroviral treatment. As for the imiquimod treatment regimen, it should be emphasized that it does not differ for HIV-negative patients. The medication is applied topically for 8 hours directly to the HPV-affected area 5 times per week. The full treatment course takes 16 weeks. In case of persistent relapses, the course may be repeated after a week-long break. In case of combined therapy, it is essential to wait until the wound heals after the physical removal of a lesion, before commencing a regular imiquimod treatment course.

Acknowledgment

The authors thank Mr. G. Redlich BA LLB DUniv for their invaluable assistance in working on the manuscript.

References

1. Покровский В.В. Синдром приобретенного иммунодефицита в России // Терапевтический архив. 2016, Т. 88, № 11. С. 4–11. [Pokrovsky V.V. Acquired immunodeficiency syndrome in Russia. *Terapevticheskii arkhiv = Therapeutic Archive, 2016, vol. 88, no. 11, pp. 4–11. (In Russ.)*] *doi: 10.17116/terarkh201688114-11*
2. Смирнов В.С., Кудрявцева Т.А. Вартоцид (Имихимод). СПб.: Гиппократ, 2017. 141 с. [Smirnov V.S., Kudryavtseva T.A. Vartocid (Imiquimod). *St. Petersburg: Hippocrates, 2017. 141 p. (In Russ.)*]
3. Федеральный научно-методический Центр по профилактике и борьбе со СПИДом. ВИЧ-инфекция в Российской Федерации на 30 сентября 2020 г. [Federal Research Center for AIDS Prevention and Control. HIV-infection in Russian Federation for 30th of September, 2020] *URL: http://www.hivrussia.info/wp-content/uploads/2020/11/Spravka-VICH-v-Rossii-9-mes-2020.pdf (27.11.2020)*
4. Cardoso J.C., Calonje E. Cutaneous manifestation of human papillomaviruses: a review. *Acta Dermatovenerol. Alp. Panonica. Adriat., 2011, vol. 20, no. 3, pp. 145–154.*
5. Fox P.A., Nathan M., Francis N., Singh N., Weir J., Dixon G., Barton S.E., Bower M.A. Double-blind, randomized controlled trial of the use of imiquimod cream for the treatment of anal canal high-grade anal intraepithelial neoplasia in HIV-positive MSM on HAART, with long-term follow-up data including the use of open-label imiquimod. *AIDS, 2010, vol. 24, no. 15, pp. 2331–2335. doi: 10.1097/QAD.0b013e32833d466c*
6. Garland S.M. Imiquimod. *Curr. Opin. Infect. Dis., 2003, vol. 16, no. 2, pp. 151–160.*
7. Godfrey J.C., Vaughan M.C., Williams J.V. Successful treatment of bowenoid papulosis in a 9-year-old girl with vertical acquired human immunodeficiency virus. *Pediatrics, 2003, vol.112, no. 1, pp. e73–e76. doi: 10.1542/peds.112.1.e73*
8. Goldstone S., Palefsky J.M., Giuliano A.R. Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men. *J. Infect. Dis., 2011, vol. 203, no. 1, pp. 66–74. doi: 10.1093/infdis/jiq016.*
9. Gormley R.H., Kovarik C.L. Dermatologic manifestations of HPV in HIV-infected individuals. *Curr. HIV/AIDS Rep., 2009, vol. 6, no. 3, pp. 130–138. doi: 10.1007/s11904-009-0018-8*
10. Gupta A.K., Browne M., Bluhm R. Imiquimod: a review. *J. Cutan. Med. Surg., 2002, vol. 6, no. 6, pp. 554–560. doi: 10.1007/s10227-001-0134-6*
11. Hampson L., Martin-Hirsch P., Hampson I.N. An overview of early investigational drugs for the treatment of human papilloma virus infection and associated dysplasia. *Expert Opin. Investig. Drugs., 2015, vol. 24, no. 12, pp. 1529–1537. doi: 10.1517/13543784.2015.1099628*
12. Hemelaar J., Elangovan R., Yun J., Dickson-Tetteh L., Fleminger I., Kirtley S., Williams B., Gouws-Williams E., Ghys P.D.; WHO-UNAIDS Network for HIV Isolation Characterisation. Global and regional molecular epidemiology of HIV-1, 1990–2015: a systematic review, global survey, and trend analysis. *Lancet Infect. Dis., 2019, vol. 19, no. 2, pp. 143–155. doi: 10.1016/S1473-3099(18)30647-9*
13. Hengge U.R., Benninghoff B., Ruzicka T., Gross M. Topical immunomodulators — progress towards treating inflammation, infection, and cancer. *Lancet Infect. Dis., 2001, vol. 1, no. 3, pp. 189–198.*
14. Hengge U.R., Ruzicka T. Topical immunomodulation on in dermatology potential of toll-like receptor agonists. *Dermatol. Surg., 2004, vol. 30, no. 8, pp. 1101–1112.*
15. Hidalgo-Tenorio C., de Jesus S.E., Esquivias J., Pasquau J. High prevalence and incidence of HPV-related anal cancer precursor lesions in HIV-positive women in the late HAART era. *Enferm. Infecc. Microbiol. Clin., 2018, vol. 36, no. 9, pp. 555–562. doi: 10.1016/j.eimc.2017.10.014*
16. Kreuter A., Potthoff A., Brockmeyer N.H., Gambichler T., Stücker M., Altmeyer P., Swoboda J., Pfister H., Wieland U.; German Competence Network HIV/AIDS. Imiquimod leads to a decrease of human papillomavirus DNA and to a sustained clearance of anal intraepithelial neoplasia in HIV-infected men. *J. Invest. Dermatol., 2008, vol. 128, no. 8, pp. 2078–2083. doi: 10.1038/jid.2008.24*

17. Krishnamurti U., Unger E.R. Pathobiology of human papillomaviruses in human immunodeficiency virus — infected persons. *Semin. Diagn. Pathol., 2017, vol. 34, no. 4, pp. 364–370. doi: 10.1053/j.semdp.2017.04.005.*
18. Lim J.H.-L., Lim K.-S., Chong W.-S. Dramatic clearance of HIV-associated bowenoid papulosis using combined oral acitretin and topical 5% Imiquimod. *J. Drugs Dermatol., 2014, vol. 13, no. 8, pp. 901–902.*
19. Lucas S., Nelson A.M. HIV and the spectrum of human disease. *J. Pathol., 2015, vol. 235, no. 2, pp. 229–241. doi: 10.1002/path.4449.*
20. Mbulawa Z.Z., Marais D.J., Johnson L.F., Boulle A., Coetzee D., Williamson A.L. Influence of human immunodeficiency virus and CD4 count on the prevalence ofhuman papillomavirus in heterosexual couples. *J. Gen. Virol., 2010, vol. 91, no. 12, pp. 3023–3031. doi: 10.1099/vir.0.020669-0.*
21. Miles to go — Global AIDS Update 2018. *Geneva: UNAIDS, 2018. 268 p. URL: https://www.unaids.org/en/20180718_GR2018 (27.11.2020)*
22. Newsom-Davis T., Bower M. HIV-associated anal cancer. *F1000 Med. Rep., 2010, vol. 2, no. 1: 85. doi: 10.3410/M2-85*
23. Obiri-Yeboah D., Akakpo P.K., Mutocheluh M., Adjei-Danso E., Allornuvor G., Amoako- Sakyi D., Adu-Sarkodie Y., Mayaud P. Epidemiology of cervical human papillomavirus (HPV) infection and squamous intraepithelial lesions (SIL) among a cohort of HIV-infected and uninfected Ghanaian women. *BMC Cancer, 2017, vol. 17, no. 1: 688. doi: 10.1186/s12885-017-3682-x*
24. Redondo P., Lloret P. Topical imiquimod for bowenoid papulosis in an HIV-positive woman. *Acta Derm. Venereol., 2002, vol. 82, no. 3, pp. 212–213. doi: 10.1080/00015550260132550*
25. Roberts J.R., Siekas L.L., Kaz A.M. Anal intraepithelial neoplasia: a review of diagnosis and management. *World J. Gastrointest. Oncol., 2017, vol. 9, no. 2, pp. 50–61. doi: 10.4251/wjgo.v9. i2.50*

Авторы:

Смирнов В.С., д.м.н., профессор, ведущий научный сотрудник лаборатории молекулярной иммунологии ФБУН НИИ эпидемиологии и микробиологии имени Пастера, Санкт-Петербург, Россия, главный научный сотрудник АО МБНПК «Цитомед», Санкт-Петербург, Россия;
Кудрявцева Т.А., к.б.н., ведущий научный сотрудник научного отдела, АО МБНПК «Цитомед», Санкт-Петербург, Россия.

Authors:

Smirnov V.S., PhD, MD (Medicine), Professor, Leading Researcher, Laboratory Molecular Immunology, St. Petersburg Pasteur Institute, St. Petersburg, Russian Federation; Head Researcher, JSC MBSPC “Cytomed”, St. Petersburg, Russian Federation;
Kudryavtseva T.A., PhD (Biology), Leading Researcher, Scientific Department, MBRD “Cytomed”, St. Petersburg, Russian Federation.

Поступила в редакцию 22.06.2019
Отправлена на доработку 23.05.2020
Принята к печати 04.07.2020

Received 22.06.2019
Revision received 23.05.2020
Accepted 04.07.2020

Иллюстрации к статье «Лечение папилломавирусной инфекции человека у ВИЧ-инфицированных пациентов» (авторы: В.С. Смирнов, Т.А. Кудрявцева) (с. 79–84)

Illustrations for the article “Treatment of human papillomavirus infection in HIV-infected patients” (authors: Smirnov V.S., Kudryavtseva T.A.) (pp. 79–84)

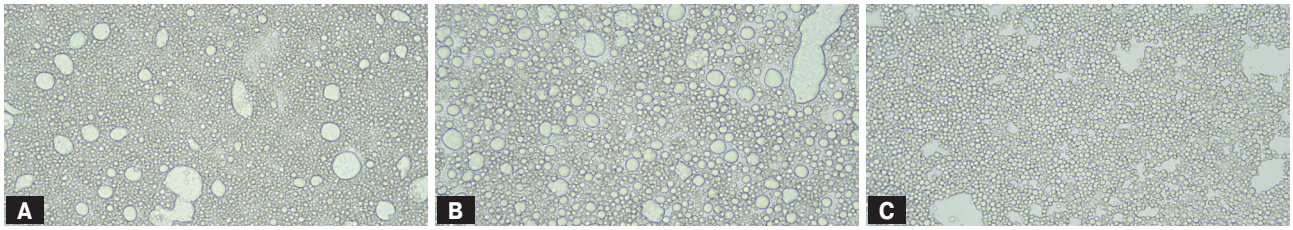

Figure. Dispersity of medication: A — Aldara (original drug), B — Kerawort (generic drug), C — Vartocid (drug created by JSC MBSPC “Cytomed”) in the form of 5% oil-in-water emulsion type cream

MIKMED microscope, ×400 magnification, regular illumination [2].