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HPV and cervical lesion spread type specificity in women of reproductive age in Saint Petersburg

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HIV infection is a risk factor for cervical cancer and both diseases show steady increase in Saint Petersburg. HIV-positive women are at greater risk of cervical dysplasia than HIV-negative women which may be as a result of immunosupression, hence adding more burdens to their already worsening health condition. The impact of highly active antiretroviral therapy (HAART) on HPV infection and cervical diseases associated with HPV remains uncertain. Type-specific prevalence of HR-HPV, risk factors for cervical precancer and cancer among Russian HIV-positive women were not previously estimated. The present study objective is determined by lack of HPV infection feature data as well as that of HPV-associated cervical disease, depending on HIV infection severity and HAART employment in HIV-infected St. Petersburg female population.

Keywords: HPV infection, immunosuppression, cervical dysplasia, HIV, HAART.

Introduction

Since the beginning of HIV epidemic in Russia and St. Petersburg HIV-infected the female population with advanced HIV infection and opportunistic diseases development including cervical cancer shows definite increase. The persistence of high-risk human

papillomaviruses (HR-HPV) is the major risk factor (HIV infection is an HPV cofactor) associated with cervical dysplasia development and cancer.

Nowadays there is an increase of women number with advanced HIV infection deuteropathy stage including oncological diseases [1–3]. According to official statistics there were 968 698 registered HIV infected cases in Russia by 01.05.2018 (the general number of HIV cases may reach 1.3 million). In St. Petersburg 2892 new cases were discovered in 2018 (Saint Petersburg AIDS 2019 newsletter). 41 % of the infected are women of whom 80 % in reproductive age. The persistence of high-risk human papillomaviruses is the leading risk factor for squamous intraepithelial neoplasia [4] while HIV-infection is a HPV cofactor in case of HPV-associated uterine cervix diseases [5–7]. In the meantime there is no reliable data of HPV structure and HPV-associated cervical lesions in HIV-infected women in St. Petersburg.

According to WHO report 527,624 new cervical cancer cases were registered in 2012 and 265,672 cases were lethal [8]. The Ministry of Health of the Russian Federation has reported of 25,5 % growth of cervical cancer cases in 2006–2016. The cervical cancer rate in St. Petersburg is lower than Russian average, but stays stable (9.7 per 100,000 in 2002, 10.0 — in 2007 and 9.6 — in 2009), along with that constant case rate growth is seen in women of younger ages — 20–45 years [9].

The results of Russian investigations show different rates of high oncogenic risk HPV types depending on region and studied group features. Thus high oncogenic risk HPV types have been detected only in 13 % of 30–65 years old women in St. Petersburg [10] and 15.4 % of 16–79 years old studied women in Ulyanovsk [11]. Higher case rate of high oncogenic risk HPV types (39.1 %) has been established in 17–54 years old women, examined in RAS Scientific Center of Obstetrics, Gynecology and Pediatrics, Moscow [12], considerably larger spread of high oncogenic risk HPV was established in women with sexually-transmitted infections — 90.9 % [13]. Type 16 HPV is the most spread one in all Russian regions while other high-risk oncogenic HPV type rate structure has definite difference [10; 11; 14; 15].

The HPV high infection rate along with high probability of persistent high-risk human papillomaviruses (HR-HPV) in HIV-positive women [16–22] inevitably whip up HPV-associated disease risks including cervical cancer [23; 24]. The existing data of much higher cervical cancer case rate against women of common population allow considering this tumor to be HIV dependent. The cervical cancer invasive form is an AIDS criterion for HIV-infected patients according to US Center for Disease Control and Russian HIV clinical classification. Disputable also remains the issue of HAART effect on HPV and HPV associated cervical disease progression [25–32]. The persistent HPV and HPV-associated cervical disease dependence on immune suppression expression along with HIV activity rates allowed supposing HAART employment importance for decreasing squamous intraepithelial cervical injuries. The advantages of HAART for such HIV-associated malignant tumors as Kaposi sarcoma and non-Hodgkin lymphoma have been also evaluated [35; 36]. Yet the HAART effect on cervical cancer remains uncertain since the registry data witness stable higher cervical cancer rate in HIV-infected women than in the general population for time periods differing in the aspect of HIV treatment possibilities [37]. Also a number of clinical studies have reported of contradicting results concerning HAART effect on HPV and HPV-associated cervical disease progression [26; 29–32; 38–43].

Studying of regional HPV cervical indications dependent on HIV severity and treatment effectiveness may allow specifying different risk group peculiarities and justify cervical cancer personalized prophylaxis in HIV-infected women.

Methods

Prospective cohort study of HIV-infected women who received care in 2009–2013 at Center of Infectious Diseases and Prophylaxis, Saint-Petersburg, Russia. Women enrolled had PCR test for HPV infection (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 types) from cervical canal and cervix surface, cervical cytology, colposcopy, biopsy and histopathologic examination. HIV viral load and CD4 cell count were accessed as care standard.

Results

The study enrolled 305 HIV-infected women and 90 HIV-uninfected women with HR-HPV. High-risk oncogenic HPV types were detected in 72.5% (n = 221) of HIV-infected women. Statistically significant differences were detected with respect to 5 types HPV (31, 35, 52, 56, 59) (Table 1). The results are obtained by the authors of the article (A. M. Gzgzyan, L. Kh. Dzhemlikhanova, M. M. Martirosyan, D. A. Niauri, O. I. Sokolova, G. Kh. Safarian, E. S. Borodina).

Table 1. **The prevalence of HR-HPV among HIV/HPV co-infected women and among HIV-uninfected women with HPV**

HPV types	HIV+/HPV+ women, n = 221		HIV-/HPV+ women, n = 90	
	n	%	n	%
16	88	39.8	36	40.0
18	35	15.8	14	15.6
31	52	23.5*	10	11.1
33	53	24.0	16	17.8
35	23	10.4*	4	4.4
39	42	19.0	12	13.3
45	40	18.1	12	13.3
51	46	20.8	16	17.8
52	58	26.2*	12	13.3
56	69	31.2***	8	8.9
58	28	12.7	6	6.7
59	28	12.7**	3	3.3
2 or more types	152	68.8**	44	48.9

*** — $p < 0.001$, ** — $p < 0.01$, * — $p < 0.05$ as compared with the HIV-/HPV+ group

The HR-HPV types rate in HIV-positive women was 77.1 % (81/105) in HAART receiving group at entry stage compared to 70.0 % (140/200) without HAART ($p > 0.05$). HAART duration for 1 year or more was also not associated with the HR-HPV rate change ($p > 0.05$).

Repeated testing for HR-HPV in 12–17 (median follow-up 14.9) months after detection of an initial HPV infection performed on 81 women co-infected with HIV and HPV: in 29 cases (35.8 %) HR-HPV were not identified, in 52 cases (64.2 %) the virus was detected again and in 42 cases (51.9 %) one or more same initially identified HPV types were found again.

The same HPV type re-identification frequency differed depending on the virus type (Table 2). The results are obtained by the authors of the article (A. M. Gzgzyan, L. Kh. Dzhemlikhanova, M. M. Martirosyan, D. A. Niauri, O. I. Sokolova, G. Kh. Safarian, E. S. Borodina).

Table 2. **Results of re-identification of HR-HPV types in HIV-infected women**

Types of HPV	HIV/HPV co-infected women. tested for the HR-HPV types again after 12–17 months. n = 81			
	Women identified in the initial assessment of HPV types detected again		Women identified in the initial assessment of HPV types not detected again	
	n	%	n	%
16	19	59.4	13	40.6
18	3	30.0	7	70.0
31	10	47.6	11	52.4
33	3	16.7	15	83.3
35	7	77.8	2	22.2
39	5	33.3	10	66.7
45	8	61.5	5	38.5
51	6	33.3	12	66.7
52	7	36.8	12	63.2
56	5	20.0	20	80.0
58	3	30.0	7	70.0
59	3	33.3	6	66.7

Abnormal results of cervical cytology were observed in 21.3 % (47/221) of all HIV/HPV co-infected women enrolled. Structure of cervical diseases after cervical biopsy and histological examination (performed on HIV/HPV co-infected women with abnormal results of cervical cytology and/or colposcopy) is shown in figure (the results are obtained by the authors of the article (A. M. Gzgzyan, L. Kh. Dzhemlikhanova, M. M. Martirosyan, D. A. Niauri, O. I. Sokolova, G. Kh. Safarian, E. S. Borodina).

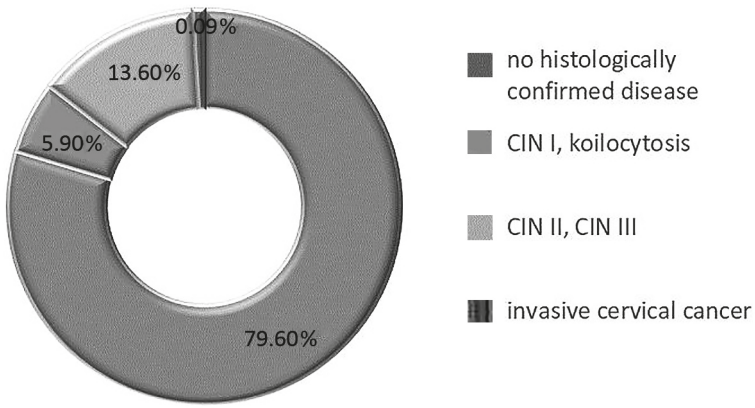

Figure. Structure of cervical diseases after cervical biopsy and histological examination

In the group of HIV/HPV co-infected women receiving HAART, the proportion of patients with HPV-associated cervical pathology was 18.5 % (15/81) while in women without HIV infection treatment it was 21.4 % (30/140) ($p > 0.05$). In women receiving treatment for less than one year, or without HAART, the HPV-associated cervical disease rate was higher than in those receiving HAART for a year or more — 23.8 % (39/164) and 10.5 % (6/57) respectively (Table 3). The results are obtained by the authors of the article (A. M. Gzgzyan, L. Kh. Dzhemlikhanova, M. M. Martirosyan, D. A. Niauri, O. I. Sokolova, G. Kh. Safarian, E. S. Borodina).

Table 3. **Structure of HPV-associated cervical diseases in HIV-infected women depending on HAART duration**

Study group / Cervical tissue characteristics	HIV-infected women with HR-HPV receiving HAART for less than 1 year or without HIV-infection treatment, n = 164		HIV-infected women with HR-HPV, receiving HAART for 1 year or more, n = 57	
	n	%	n	%
No histologically confirmed disease	125	76.2*	51	89.5
CIN I, koilocytosis	10	6.1	3	5.3
CIN II, CIN III, invasive cervical cancer	29	17.7*	3	5.3

* $p < 0.05$ as compared to the group with HAART duration for a year or more

Discussion

The results of the investigation prove that high oncogenic risk HPV infection rate in HIV infected reproductive age women of St. Petersburg was up to 72.5 %. 16 and 18 HPV type spread did not authentically differ in women with or without HIV. High oncogenic

risk HPV typospecifity show type 16 domination, which is detected in 39.8 % cases, while types 56, 52, 33 and 31 occur with 23.5 %–31.2 % frequency. In HIV-negative women the dominant high oncogenic risk HPV is also type 16. However according to our data there are certain peculiarities about HPV spread typospecifity in HIV-positive women: HPV types 31, 35, 52, 56 and 59 are veraciously more frequently detected in HIV-positive against HIV-negative women, especially in cases of simultaneous infection with two or more cancer inducing HPV types. Some foreign studies give contradictive reports of really detected peculiarities concerning HPV structure in HIV-positive cases. In several studies no significant difference in various HPV type proportions was detected for HIV-positive women against the HIV non-infected in a higher HPV spread general context as well as that of certain HPV types [16; 21]. On the other hand, some other studies definitely show HPV spread typospecifity peculiarities depending on being HIV-positive [32; 44–46].

Some foreign studies have showed more probable HPV persistence development in HIV-positive women compared to HIV non-infected with elaborated HIV isolates in female genital organ tissues [6; 17; 19; 32; 37; 47–49]. According to our data the reexamination of HIV-positive women with initially detected HPV after 14.9 month average terms did not discover any high oncogenic risk HPV type in 35.8 % patients. The virus was detected in the other 64.2 %, wherein 51.9 % cases showed persistence of one or several initially diagnosed virus types sometimes combined with new types. In 12.3 % patients the reexamination detected only new virus types different from those diagnosed at the study entry. We have managed to show the frequency of high oncogenic risk HPV types repeated diagnosis in HIV-positive women to be a little higher than in the general ST. Petersburg female population (44 %) in reexamination 6 months after the initial study [15]. Similar data of repeated HPV detection were presented in results of a USA HIV-positive women investigation: 16, 18, 31 and 45 type HPV persistence was observed in 64.6 % patients after 12 months monitoring and in 58.1 % in 18 month, while that of 33, 35, 39, 51, 52, 56, 58, 59, 68 HPV type — in 58.9 % after 12 month monitoring and 52.3 % — after 18 months [17].

Generally high oncogenic risk HPV infection frequency does not depend on HAART employment or duration. However, the dependence of papilloma associated cervical disorders on HIV immunosuppression, viremia expression and HIV-infection progressing allowed assuming HAART importance for CIN and cervical cancer frequency reduction. HIV-associated squamous intraepithelial neoplasia risk factors may be jugulated only under the condition of long term HAART employment. This dependency may explain the data showing no significant HAART effect on CIN and cervical cancer frequency in HIV-positive women with HPV co-infection obtained by several studies where HIV-infection therapy duration was not taken into account [50–52]. According to our present study data CIN and cervical cancer detection in women receiving HAART for a year or more is authentically lower than in patients without HAART or when HAART had less than 1 year duration — 15 % and 21.5 % respectively. This is the reason why no dependency of the very fact of HAART could be established. No evidence of HAART effect on CIN I was obtained, while the much more severe cervical pathology in women receiving HIV-infection therapy was veraciously less often detected comparing to the group of HAART shorter duration or completely without HAART — 7.5 % and 16 % respectively. So it could be taken as reason that HAART employment as "treat-all" principle in case of HIV diagnosis should be considered an additional variant

of HIV-associated visceropathy and carcinogenesis prophylaxis concerning squamous intraepithelial cervical diseases.

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