

# Human Papillomavirus Infection: The Efficacy of Treatment with Inosine Pranobex

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The high frequency of the spread of human papillomavirus and a high risk of recurrence associated diseases require the search for effective therapies. The analysis of quality clinical trials showed data on the efficacy, tolerability of treatment. Our study demonstrates higher efficiency destructive methods in conjunction with the system using Isoprinosine. Even Isoprinosine mono therapy's efficiency reaches 68%.

**Key words:** human papillomavirus, therapy, immunomodulators, Isoprinosine. pbumer@mail.ru

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Human papillomavirus infection (HPV) is one of the most common sexually transmitted infections today. The rate of HPV diagnosis among the sexually active population in metropolitan areas reaches 72%. The diagnosis and treatment of diseases associated with papillomavirus infection attracted several scholars. Such concern not only arises due to the high infectivity but also its ability to create cancerous pathologies in affected organs. In gynecology, HPV is the leading exogen cause of cervical intraepithelial neoplasia (CIN I, CIN II, CIN III) and later cancer.

It has been defined several times in the literature that HPV infection in women occurs especially at young ages where the cervical epithelium is especially responsive to infection. As a result of this, cervical cancer is the number one cancer of the reproductive system in women under 30.

Constant improvement in the diagnosis and treatment of the diseases associated with HPV infection is becoming a significant struggle (figure 1)

## Diagnosis Methods of HPV infection

(Figure 1: the Diagnosis of HPV Infection)

The diagnosis of HPV infection		
Clinical methods: -examination -extended coloscopy -vulvoscopy	Laboratory methods: -PCR -real-time quantitative PCR -cytology -liquid cytology	Pathomorphological observation: biopsy + morphologic observation

There is no specific virucide developed against HPV, therefore the methods of treatment are generally uncertain and aggressive in some observations. A combination of destructive methods with adjuvant antiviral and immunomodulator treatment is commonly used in the treatment of cervical pathology associated with HPV.

Using antiviral immunity activators increases the efficiency of the treatment by reducing the recurrence rates and directly affecting the reproduction of the virus.

Today, various approaches regarding the treatment of condyloma in different locations are known. (Figure 1.)

(Figure 2. Treatment Methods for HPV Infection.)

Condyloma treatment (HPV infection)



Physical destruction: - surgical excision; -electrosurgery methods; - cryotherapy; - laser therapy (photovaporization); - radiosurgery; - plasma surgery.	Chemical destruction: - nitric acid; -trichloroacetic acid; - phenol; -organic and inorganic acid mix (Solcovagin, Solcoderm)	Cytotoxic methods: - podophyllin; - podophyllotoxin; - 5-fluorourasil.	Interferons/interferonogenez inducers: - interferon-α2b (Viferon); - interferon γ (Ingaron); - imiquimod; - Isoprinosine .	Immunomodulators: - Isoprinosine .
+	+	+		
Nonspecific antiviral agents, immunocorrector: - Lycopid; - Ferrovir; - Galavit; - Panavir; - Immunomax; - Allokin-alfa; - Indol-3-carbinol; - Glycyrrhizic acid, etc.		Combined methods: destructive + immunotherapy/ antiviral treatment	Antiviral medications: Cidofovir?	

**Efficiency and Safety of Different Treatment Methods of Localized Acute Condyloma in External Genital Area Skin**

Treatment option	Efficiency, %	Recurrence rate (3 months after the treatment), %	Side effects, %
Trichloroacetic acid	70	No data	33-50
Podophyllotoxin	40-75	10-60	50-75
Fluorouracil	60	No data	<50
Interferon-a2b	20-74	12-16	<10
Imiquimod (external)	76	9-14	1,1-70%
Isoprinosine (systemic treatment)	68 (monotherapy – our data)	10-40	1-7,1 (our data)
<b>Physical destruction</b>			
Radio wave destruction	65-100	18-25	<10
Photovapirazon (CO2 laser)	40-100	20-60	<20
cryotherapy	50-80	21-38	<20
surgical excision;	36-100	No data	<30

The efficiency of different treatments for papillomavirus infection varies considerably (see the table).

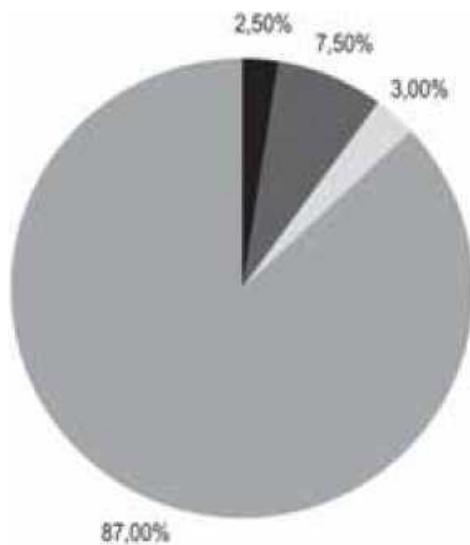
One of the immunotropic medicines is inosine pranobex (Isoprinosine). Isoprinosine is a derivate of synthetic complex purine having immunostimulator activity and non-specific antiviral activity. The antiviral activity results from its ability to inhibit the viral DNA and RNA replication through binding to cell ribosome and thus changing the stereochemical structure. Isoprinosine, when applied in combination, increases the efficiency of interferon- $\alpha$  and antiviral agents.

Besides the antiviral effect, it has immunomodulator features due to inosine complexity increasing its usability for inosine pranobex lymphocytes. Isoprinosine causes lymphocytes to regain their functions under the immunosuppressant conditions, increases the blastogenesis in monocytic cell population, stimulates the expression of membrane receptors on the surface of T-helper cells and prevents the reduction in the activity of lymphocyte cells. It stimulates the isoprinosine cytotoxic T- lymphocytes and the activity of natural killer cells, T-suppressor, and T-helper functions, increases the production of immunoglobulin G, interferon- $\gamma$ , interleukin (IL)-1 and IL-2, reduces the proinflammatory cytokines - IL-4 and IL-10, strengthens the chemotaxis of neutrophiles, monocytes and macrophages.

This feature of the medicine affects the virus transferring from a temporary form to a permanent form and the clinical presentation of the infection by enabling the change of the interaction mechanism between HPV and microorganism.

The purpose of our study is to evaluate comparatively the efficiency of Inosin pranobex (Isoprinosine) as monotherapy in HPV infection in younger women and in the complex treatment of cervical diseases.

(Figure 3. The Structure of Adverse Events During the Isoprinosine Application.)



2,50%-headache  
7,50%-nausea  
3,00%-vertigo  
87,00%-no reaction

### Materials and Methods

100 women whose ages ranged from 19 to 35 (average age  $25.4 \pm 0.2$  years) were selected for Cohort research. The reason for visiting a gynecologist was for prophylactic examination. A bacteriological observation of vaginal smear, the diagnosis of polymerase chain reaction (PCR) of sexually transmitted infections, cytologic observation of cervical scrapings and basic colposcopy were applied to all patients as part of a preventive examination. It should be considered that basic colposcopy reveals the cervical ectopia in the 100% of the cases and it is resulted from the extended colposcopy. PCR diagnosis tests detected HPV (HPV total) in all women; a combination of Papillomavirus and Chlamydia trachomatis in %15 (n=15); cytomegalovirus infection in 20% (n=20) and herpes viral infection in 9% (HSV1/2).

Therefore, an extended colposcopy was performed in 56 patients and the table was diverse: a transformation area with atypical epithelium such as ectopia, leukoplakia, iodine-negative areas having a transformation area in combination with multiple open and closed channels of the glands.

In 18% (n=10) of observations, in addition to changes in cervix, vestibular papillomatosis was diagnosed. Condyloma were observed in external genital area, especially labia minora area, the external opening of urethra and clitoris. A combination of type 16, 18 and type 6, 11 and 13 were formed in the HPV typing performed in these women. A mild dysplasia (CIN I) was detected in cervical cytology. HPV was diagnosed in 27% (n=15) of the cases. Microscopic examination of the vaginal discharge in all women showed moderate leukocytosis in the contents of the cervical canal.

After the pre-test, all participants were divided into two random groups. The main group were consisting of 25 patients with mild dysplasia (CIN I) and women having the combination of vestibular papillomatosis. Such patients only received inosine pranobex and systemic treatment. The existence of micropapiloms was especially stressed as their clinical importance is uncertain and it creates difficulties in differential diagnosis. Although there is no clear evidence as to its relation with HPV infection so far, the visual similarity of condyles and micropapiloms in vulvoscopy which are related to HPV requires a HPV scanning.

In this group, Isoprinosine was applied for 10 days, three times a day, in 1000 mg (2 tablets) tablets. The efficiency of the treatment was evaluated through the PCR diagnosis of HPV infection performed 1.5 months after the completion of the treatment. There were 31 patients in comparison group.

CIN I, which received a combined treatment: according to the described scheme; destruction of cervical condyloma with radio waves techniques as well as the systemic usage of the Isoprinosine. The efficiency of treatment was evaluated 2 and 6 months later.

When the efficiency of treatment was evaluated in the main group 2 months later, the only thing no longer existed in all the patients was the vestibular papillomatosis. The existence of mild dysplasia (CIN I) which was verified by cytological examination in 68% of the observations (n=17) was not diagnosed in extended colposcopy and cytologic examination.

PCR test performed for HPV showed that the virus had not been isolated. In 32% of the cases (n=8), Isoprinosine monotherapy was ineffective and an additional Isoprinosine treatment cure was applied. When these patients were examined 6 months after the repeated Isoprinosine cure, it was seen that CIN I had been continuing in 3 (12%) women. In other words, when the treatment duration was increased, the cumulative efficiency of Isoprinosine monotherapy became 88%.

The analysis of the adverse events showed that there was intolerance against the medicine arising with dyspeptic complaints in 7.1% of the cases and this is why it discontinued the treatment process of the patients independently.

Therefore, we found that Isoprinosine was very effective as monotherapy for the HPV infection with low monogenic and the early stages of the disease. The application of the medicine may be accompanied by adverse events in different organs and systems, however their symptoms are insignificant and easily improved after the treatment is discontinued (figure 3).

Among the patients who received combination therapy, after 2 months in 27 (87.1%), the colposcopic picture and the results of the cytological examination normalized, and no HPV was detected during PCR. After 6 months of follow-up after combined treatment, which included Isoprinosine, none of the 27 women had a relapse of the disease. Active HPV replication persisted in 2 (6.5%) of 4 examined patients with a normal colposcopic picture.

Same as the main group, 2 (6%) women showed an adverse reaction against medicine accompanied by weakness and headache. As the occurrence of such reactions stopped within four days after starting the Isoprinosine, the discontinuing of medicine was not required.

Recurrence of condyloma localized over the cervix was not observed in any of the patients. After using Isoprinosine as monotherapy, only condyloma recurring on the external genital area skin were diagnosed in 9 parties (36%) between 2 and 6 months during the

prospective study duration. In addition to this, adding Isoprinosine to the treatment in combined treatment group reduced this recurrence rate 3,7 times ((9,7%; n=3)

Combining Isoprinosine with radio wave treatment methods of cervical diseases associated with HPV increases the efficiency of the treatment by up to 93,5%.

The results of the study showed that the use of the drug Isoprinosine helps to stop the release of HPV from the lesion and normalization of the morphological picture of exo- and endocervix, increases the effectiveness of destructive methods of treatment, and also reduces the frequency of relapses.

Such characteristics make it possible to conclude that Isoprinosine (inosine pranobex) is highly effective in the treatment of HPV infection in young women of reproductive age.

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