

## Response to Acyclovir in Immunocompetent and Immunocompromised herpes genitalis patients

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### Abstract

**Introduction:** Sexually Transmitted Infections (STIs) act as cofactor for Human Immunodeficiency Virus (HIV) infection. Herpes genitalis is the leading cause of genital ulcers in the present scenario replacing the classical genital ulcer diseases.

**Objectives:** A prospective study was undertaken in the department to study if there is any drug resistance to oral acyclovir in herpes genitalis patients and to compare the response of immunocompetent and immunocompromised patients with herpes genitalis to oral acyclovir given in a fixed dose for a fixed duration.

**Methodology:** Patients diagnosed with herpes genitalis were screened for HIV and were put on oral acyclovir in a fixed dose for a fixed duration irrespective of their serological status. On follow up, they were assessed clinically for the resolution of ulcers. The results were tabulated and analysed.

**Results:** Of the total 246 patients, none of the patients, either with immunocompetent or immunocompromised status showed any resistance to acyclovir in the form of non healing of the ulcers. At the same time 5 and 2 patients with first and recurrent episodes respectively with immunocompromised status required prolonged duration of treatment.

**Conclusion:** This study has shown that there is no resistance to acyclovir in patients with herpes genitalis, be it be immunocompetent or immunocompromised patients. But at the same time statistically significant number of immunocompromised patients required prolonged duration of the same treatment.

**Keywords:** Acyclovir, First episode of herpes genitalis, immunocompetent patients, immunocompromised patients, recurrent episode of herpes genitalis

### Introduction

The Acquired Immuno Deficiency Syndrome (AIDS) was first recognized in 1981 and is caused by Human Immunodeficiency Virus (HIV). The major modes of spread are sexual, parenteral and vertical; the major route of transmission

worldwide is heterosexual. Since 1981 AIDS has grown to be the second leading cause of disease burden worldwide and the leading cause of death in Africa<sup>(1)</sup>. In a number of sites in South East Asia, HIV infection rates among STI patients range from 4 to 10%. One out of every five STI

patients was tested positive for HIV in samples in Hubli and Pune<sup>(2)</sup>. In Tanzania, a program of aggressive treatment of STIs resulted in a reduction of 42% in the incidence of new HIV infection compared with communities without such a program<sup>(2)</sup>. Genital ulcers may facilitate HIV transmission through the reduced epithelial barrier and infiltration of CD<sub>4</sub> lymphocytes into the lesions that are the possible targets for HIV attachment and entry<sup>(3)</sup>. Herpes simplex virus (HSV) is the most common cause of infection related genital ulceration worldwide<sup>(4)</sup>. The reasons for increased incidence of Herpes genitalis are the decrease in the treatable bacterial STDs, the high recurrence rate and the asymptomatic recurrences with transmission in the absence of symptoms<sup>(5)</sup>.

Herpes genitalis caused by Herpes simplex 1&2 virus is characterized by (a) the appearance of vesicular lesions in the genital region which later rupture to form superficial ulcers and (b) the occurrence of recurrent episodes. It is recurrent in at least 90% of infected persons and 88% have at least one occurrence within 12 months of the initial episode<sup>(6)</sup>.

When the first episode is seen in a HSV seronegative individual it is called True Primary Episode and if it is seen in a previously infected individual as observed by the presence of antibodies, it is called Non Primary First Episode. First episodes of genital herpes are often associated with severe symptoms and prolonged duration of lesions with viral shedding and involve multiple lesions<sup>(6,7)</sup>. However the acquisition in many individuals may go unnoticed and without any associated signs and symptoms and in one study about half of the seroconversion of HSV-2 infection were asymptomatic<sup>(8)</sup>. Recurrent episodes can be triggered by stress and intercurrent illness. In contrast to first episode of genital infection, the symptoms, signs and anatomic sites of infection of recurrent genital herpes are localized to the genital region<sup>(9)</sup>. All the

manifestations of HSV infections seen in the immunocompetent host can also be seen in immunocompromised (by HIV) patients but they are more severe, extensive, difficult to treat and more frequent. Despite the frequent occurrence of atypical disease, genital herpes is often diagnosed on clinical grounds alone<sup>(10)</sup>. Laboratory tests that are used for diagnosis are Tzanck smear test, Histopathology (ART)<sup>(12,13)</sup>. Suppressive herpes therapy in HIV infected people with detectable viral loads has, Serology and very rarely viral culture. The 3 commonly used drugs for herpes genitalis are acyclovir, famcyclovir and valacyclovir. Acute episodes of HSV infection can simulate HIV replication with increased HIV Viral RNA levels detectable in the plasma in individuals not on Anti Retro Viral therapy been shown to decrease the levels of HIV viraemia between 1/4 and 1/2 log<sup>(14)</sup>. In this context, renewed interest in the hope that HSV control may help in controlling the HIV epidemic has been noted.

### **Objectives**

In this context, a prospective study was undertaken in the department of DVL, Guntur, India. The objectives of the study are (1) To administer oral acyclovir to both immunocompetent and immunocompromised patients presenting with herpes genitalis and to observe if there is any drug resistance in the form of non healing of the genital ulcers and (2) To administer oral acyclovir in a fixed dose for a fixed duration for patients presenting with first episode and recurrent episode irrespective of their immunostatus and to observe if the same duration of same dose of oral acyclovir is sufficient for both immunocompetent and immunocompromised patients for the resolution of the ulcers.

### **Materials and methods**

Patients presenting to the department of DVL between 01-01-2014 and 31-12-2014

with genital ulcers were investigated using Venereal Disease Research laboratory (VDRL) testing, Tzanck smear test, Gram stain. After taking their consent HIV status was assessed using National AIDS Control Organisation (NACO) guidelines. Patients who were diagnosed to be suffering with herpes genitalis were included in the study after taking their consent. Those patients who refused to know or reveal their HIV status and those patients on suppressive therapy for recurrent herpes genitalis were excluded from the study.

According to the NACO guidelines, the treatment for the first episode of herpes genitalis is acyclovir orally 400mg thrice daily for 7 days and for the recurrent episodes it is orally 400 mg thrice daily for 5 days.<sup>(15)</sup> This management protocol was adopted in our study. All the patients were asked to come for follow up. The response to acyclovir was assessed clinically in the form of resolution of the ulcers. The results were compared by calculating the percentage and the statistical significance was measured using chi-square test with Yate's correction. The results were analysed.

### **Results**

A total of 246 patients were diagnosed to be suffering with herpes genitalis and were included in the study (table no.1). Among them 94 patients presented with the first episode of herpes genitalis and 19 among them are reactive for HIV antibodies and the rest 75 are non reactive (table no.2). On follow up after treatment, all the 75 immunocompetent patients responded to the treatment protocol (100%) while among the 19 HIV seropositive patients, 14 patients responded totally (73.69%) and 5 patients responded only partially to the standard 7day treatment and needed the same dose for a further period of 7days (table no.2).

Among the total 246 patients, 152 patients presented with a recurrent episode (table

no.1). Among them 109 patients were immunocompetent and all of them responded to the standard treatment protocol given for 5 days (100%) (table no.3). 43 among the 152 patients with recurrent episode are immunocompromised. Of the 43 immunocompromised patients, 41 patients responded to the protocol treatment totally (95.35%) (table no.3). The rest 2 patients responded only partially (4.65%) and needed a further course of same dose of treatment for a further period of 10 days.

### **Analysis**

In HIV patients acyclovir resistance has been noted according to two studies<sup>(16)(17)</sup>. But according to another study by Crumacker, drug resistance has not been a major problem in genital herpes<sup>(18)</sup>. Similar to Crumacker's study, in our study also none of the patients, either immunocompetent or immunocompromised, either presenting with the first episode or with the recurrent episode did not manifest any drug resistance to acyclovir.

In the patients presenting with the first episode, there is 100% clinical response in immunocompetent patients whereas 5 of the 19 immunocompromised patients required prolonged duration of treatment for total clinical response (26.31%). Using Chi square test with Yate's correction, chi square equals 5.960 with 1<sup>0</sup> of freedom and the two tailed p value equals 0.416 which is statistically significant.

In the patients presenting with recurrent episode, there is 100% clinical response in the immunocompetent patients. Out of the 43 immunocompromised patients, only 2 patients required prolonged course of treatment for total clinical response (4.65%). Though this appears to be insignificant, chi square equals to 29.895 with 1<sup>0</sup> freedom and the 2 tailed p value is less than 0.001 which is extremely statistically significant.

According to Drew, et al, higher dose of acyclovir has been recommended for HIV patients with severe genital infection for

prolonged duration<sup>(19)</sup>. But in our study, it has been shown that same dose of acyclovir but for prolonged duration of time is needed in some HIV patients whose number is statistically significant.

**Table 1: Patients with herpes genitalis.**

Total patients with herpes genitalis	Patients with first episode	Patients with recurrent episode
246	94	152

**Table 2: First episode of herpes genitalis.**

With first episode	94 patients
Immunocompetent	75 patients
Response to treatment	75 patients (100%)
Immunocompromised	14 patients
Need for prolonged treatment	5 patients (26.32%)

**Table 3: Recurrent episode of herpes genitalis.**

With recurrent episode	152 patients
Immunocompetent	109 patients
Response to treatment	109 patients (100%)
Immunocompromised	43 patients
Need for prolonged treatment	2 patients (4.65%)

### Conclusion

The morbidity in herpes genitalis is due it's recurrences, chronicity and psychological stress to the patient. Among all the drugs used for herpes genitalis, acyclovir is cost effective with minimal side effects. There were reports of resistance to acyclovir in some students. But in our study, not a single case of resistance to acyclovir has been noted. At the same time, some immunocompromised patients required prolonged duration of treatment as seen in some other studies. In contrast to the other studies, in our study increased dose of treatment is not needed either in the first or

recurrent episodes in the immunocompromised patients. So it is apt to conclude from our study that oral acyclovir is the best drug for herpes genitalis in both immunocompetent and immunocompromised patients either in the first episode or recurrent episode necessitating prolonged duration of treatment in some (statistically significant) immunocompromised patients.

**Conflicts of interest:** None

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