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Original Research Article

Genital herpes and HIV status: a clinical study

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ABSTRACT

Background: Genital herpes (GH) is a sexually transmitted infection (STI) increases risk of human immunodeficiency virus (HIV) infection. Some risk factors like age, sex, previous genital ulcerative disease (GUD), number of sex partners and clinical presentations like number and size of erosions, number of episodes, inter-episode duration, healing period with acyclovir & co-STDs are studied with reference to HIV status.
Methods: This is a longitudinal, observational study comparing 25 patients each in HIV positive and negative groups of GH between 15-60 years of age in both genders. Chi square test (or Fisher's exact test) for nominal data and 't' test for continuous data was used in case of association. Mann Whitney U test was used for comparison of mean ranks and median.
Results: Adolescents were 18%. HIV positivity was significantly associated with age group above 45 years, multiple sex partners, average number of episodes & the duration between them and number of erosions ($p < 0.05$). Healing period with acyclovir in HIV positive patients was significantly longer than in HIV negative patients. Secondary syphilis a co-STD had significant association with HIV positivity. Though previous GUD alone was not associated with HIV positivity significantly; however GUD in patients with multiple sexual partners showed significant association with HIV.
Conclusions: High proportion of adolescents amongst GH patients is notable. Adolescents & older patients above 45 years should not be neglected in STD & HIV awareness. Risk factors must be interviewed with patients. Clinical parameters & risk factors, differs with HIV status.

Keywords: Herpes genitalis, Adolescents, Risk, Comparison, HIV

INTRODUCTION

According to a world health organization (WHO) updated report in August 2016, worldwide more than 1 million STIs and 500 million herpes simplex infections (HSV) are acquired yearly.[1]

HSV has 2 subtypes: HIV 1 which is predominantly an oro-labial infection and HSV 2 which is acquired during sexual activities i.e. GH. HSV at the site of virus contact manifests as grouped vesicles which are flaccid, so burst open to form a shallow ulcer or erosion. Ulcers/erosions vary in numbers and are painful. HSV remains latent in dorsal nerve root ganglia of infected persons and is thought to reactivate several times yearly. Secondary infection on GH erosions can delay the healing. HSV erosions heal with nucleosides analogues like acyclovir. GH also termed herpes genitalis (HG), is a genital ulcerative disease (GUD) which increases the risk of HIV infection by 2 to 3 folds.[2]

METHODS

Objectives

The objectives of the study was to compare clinical presentation of GH in terms of number, recurrence, inter-episode duration, number and size of erosions and healing period with Acyclovir treatment with reference to

HIV status, to study the risk factors like age, number of sexual partners and previous history of GUD in HIV positive and negative patients of genital herpes and to identify the presence and significance of co-STDs if any.

Settings and design

This longitudinal comparative study was conducted over 2-year period from November 2014 to October 2016 after approval of the Institutional Ethics Committee of the Hospital. Patients, attending to the Dermatology outpatient with complaints of erosion on and near the genitalia were examined. Inclusion criteria were patients of either gender between 15-60 years, willing to undergo HIV testing and to participate in this study.

Confidential interviews were undertaken to elicit risk factors like number of sex partners and history of GUD. Suspected patients were screened for possible presence of GH and co-STDs clinically. GH was confirmed by Tzanck smear and co-STDs were confirmed by blood tests. VDRL test was done in all patients. Tests like Giemsa stain, microscopic examination of urine, Gram's stain and biopsy were done as indicated. All patients were screened for HIV by Trio-Dot testing with requisite pre and post-test counselling and taking written informed consent. HIV testing was done in the hospital laboratory though patients who wished to get their HIV test by "ELISA" method done from other standard laboratories were allowed to do so.

Simple consecutive sampling of patients with GH was done in HIV positive and negative groups to include 50 patients in the study– 25 in each group. Those patients already undergoing treatment for GH were excluded. The patients diagnosed with GH were treated with Acyclovir tablet as per Centre for disease control i.e. CDC guidelines-2015.

Calculation of erosion size

The surface area of the "largest" erosion in case of multiple erosions was used for statistical calculation. Surface area in millimetres of each erosion was calculated using the 'Wound tracing by manual method' described by Fette.[3] This two-dimensional wound measurement tool is "wound tracing," in which a pen is used to trace the outline of the wound directly onto sterile transparent film or paper.[3] This is then placed over graph paper and with a metric grid the numbers of squares of a known area are counted. This graph paper technique may be preferable in most clinical settings, because it is low in cost and easy to use.[4,5]

All the patients were examined daily until healing of erosions. Healing period was calculated as time taken in maximum days in which all the ulcers heal with epithelisation where in entire surface of it to form a continuous film of an epithelium up to the surrounding level of skin. Number of episodes and inter-episode duration were recorded till the last day of healing whilst the patients were in the study. All information was entered in the Performa. Results entered in 'observational tables.' All information was transferred to the master-chart in MS-Excel-07 and analyzed for statistical significance.

Statistical analysis

All the measurable data i.e. quantitative variables were expressed in terms of their mean, standard deviation (SD) and category variables in terms of proportion or percentages. Continuous data was analyzed using unpaired "t-test" and 'Z' test was used for comparison of columns (proportion). Nominal data was analyzed using Chi Square test for nominal data or Fisher Exact test when applicable. Mann Whitney U test was used to compare mean ranks or medians. Descriptive statistics was calculated by using SPSS-V 20.0. Test results were considered significance at $p < 0.05$.

RESULTS

Table 1 showed the comparisons GH in HIV positive and HIV negative patients. HIV positive patients showed significance in higher age, number of episodes, number of erosions, shorter inter-episode duration and longer time for healing. No significant difference was seen in erosion area based on HIV status. By z test, significantly moderate association was noted with more patients being HIV positive in the age group of 45-60 years as shown in Table 2.

Chi Square test results in Table 3 revealed that more HIV positive patients admitted to multiple sexual partners while higher number of HIV negative patients had single partners ($p < 0.05$). No significant difference was noted in gender distribution, presence of recurrences& history of GUD with respect to their HIV status ($p > 0.05$). Table 4 showed patients with multiple partners were of higher age compared to those with single partners using Student t test ($p = 0.002$). By z test it was shown that patients of 45-60 years. There were 9 subjects amongst the HSV patients who were adolescents below as per Table 5. By z test for proportion, significantly all adolescents who admitted to single sexual partner were HIV negative ($z < 0.05$). Of the 9 adolescents, 4 were males. No significant association was found between gender and HIV status of the adolescents.

Mann Whitney U test was used to compare mean ranks of number of episodes and inter-episode duration as given in Table 6. HIV positive patients showed higher number of time ($p < 0.05$). Figure 1 shows increasing HIV positivity with increased number of episodes. Chi Square test showed strong association of HIV status with number of episodes (χ^2 (3) =13.105; $p = 0.003$). Figure 2 shows the higher mean value of surface area of erosions in HIV positive patients ($p < 0.05$).

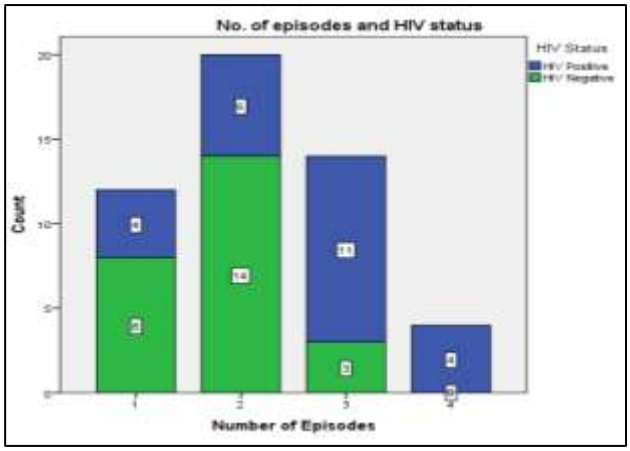

Figure 1: Number of episodes with HIV status.

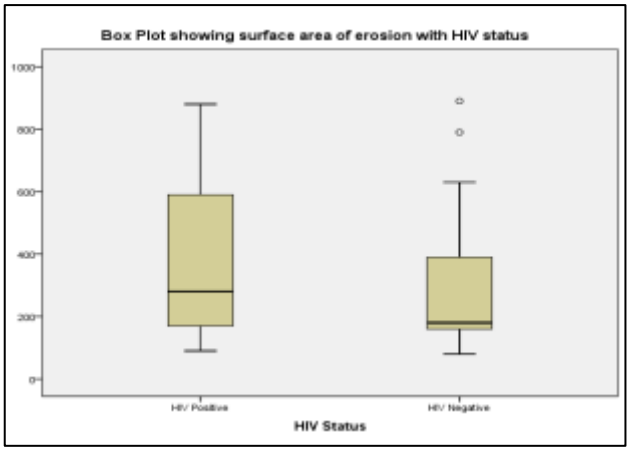

Figure 2: Surface area of erosions with HIV status.

Table 1: Comparison of GH in HIV positive and HIV negative patients.

Variables	HIV Status	N	Mean	Std. Deviation	Std. Error Mean	P value
Age	HIV Positive	25	40.44	13.556	2.711	0.000
	HIV Negative	25	27.24	9.501	1.900	
Number of episodes	HIV Positive	25	2.60	0.957	0.191	0.001
	HIV Negative	25	1.80	0.645	0.129	
Inter episode duration (weeks)	HIV Positive	24	5.38	1.583	0.323	.000
	HIV Negative	25	8.44	2.238	0.448	
Erosion numbers	HIV Positive	25	1.08	0.277	0.055	0.000
	HIV Negative	25	2.08	0.812	0.162	
Erosion Area (millimeters)	HIV Positive	25	348.80	235.855	47.171	0.314
	HIV Negative	25	282.00	228.145	45.629	
Healing (days)	HIV Positive	25	22.20	5.788	1.158	0.000
	HIV Negative	25	15.80	4.252	0.850	

Table 2: HIV status and age group cross-tabulation.

HIV Status	Age group			Total	Significance
	15-30 years	30.1 -45 years	45.1 - 60 years		
HIV Positive	10	5	10	25	0.029
HIV Negative	16	7	2	25	Cramers V = 0.376
Total	26	12	12	50	

Table 3: Nominal characteristics with HIV status.

Variables		HIV Status		Total	P value
		Positive	Negative		
Gender	Female	12	6	18	0.070
	Male	13	19	32	
Total		25	25	25	
Partners	One Partner	2	15	17	0.000 Phi = 0.549
	Multiple	23	10	33	
Total		25	25	50	
Recurrence	Primary	4	8	12	0.321
	Recurrent	21	17	38	
Total		25	25	50	
Hist. of _GUD	No	5	9	14	0.345
	Yes	20	16	36	
Total		25	25	50	

Table 4: Mean age with reference to number of sexual partners.

Sexual Partners		N	Mean age	Std. Deviation	Std. Error Mean	P value
Age	One Partner	17	25.94	9.601	2.329	0.002
	Multiple partners	33	37.91	13.314	2.318	

Table 5: Number of sexual partners of adolescents and HIV status.

Variables	Count and %		HIV status		Total	P value
			HIV positive	HIV negative		
No of Partners	One partner	Count	0_a	6_b	6	0.083
		% within partners	0.0%	100.0%	100.0%	
	Multiple partner	Count	2_a	1_b	3	
		% within partners	66.7%	33.3%	100.0%	
Total		Count	2	7	9	
		% within partners	22.2%	77.8%	100.0%	

Table 6: Comparison of mean ranks of episode number and duration with reference to HIV status.

Variables	HIV status	N	Mean rank	Sum of ranks	Test statistic
Int. Episd. Duration	HIV Positive	24	16.08	386.00	0.000
	HIV Negative	25	33.56	839.00	Mann Whitney U 86.000
	Total	49			
Number of Episodes	HIV Positive	25	31.58	789.50	0.002
	HIV Negative	25	19.42	485.50	Mann Whitney U 160.000
	Total	50			

Table 7: Median number and area of erosions.

Variables	HIV Status	Median	P value
Erosion No.	HIV Positive	2	0.000
	HIV Negative	1	
Erosion Area	HIV Positive	280	0.202
	HIV Negative	180	

Table 8: Partners, erosion numbers and HIV status cross-tabulation.

Erosion No.	Number of Sexual Partners		HIV Status		Total	P value
			HIV Positive	HIV Negative		
1	Partners	One partner	0_a	13_b	13	
		Multiple partners	7_a	10_b	17	0.008
	Total		7	23	30	
2	Partners	One partner	1_a	2_b	3	
		Multiple partners	8_a	0_b	8	0.001
	Total		9	2	11	
3	Partners	One partner	1		1	
		Multiple partners	8		8	-
	Total		9		9	
Total	Partners	One partner	2_a	15_b	17	
		Multiple partners	23_a	10_b	33	0.000
	Total		25	25	50	

Each subscript letter denotes a subset whose column proportions do not differ significantly from each other at the 0.05 level.

Mann Whitney U Test showed significantly higher number of erosions in HIV positive patients ($p < 0.05$). Median area of erosion was higher in HIV positive patients though not statistically significantly ($p > 0.05$) as shown in Table 7. In Table 8, layering with sexual partner numbers, revealed that patients with single lesions and single partner were all HIV negative while those with multiple erosions and multiple partners were all HIV

positive (z <0.05 for both). Table 9 shows that patients with history of GUD had significantly were more likely to have multiple partners, recurrence and more episodes of HSV infections compared to those without history of GUD (all p <0.05).

Table 10 shows the strong association of HIV status with presence of co-STDs in the patients using Chi Square test (p <0.05). Table 11 reveals that patient with secondary syphilis were significantly HIV positive.

Table 9: History of GUD and number of sex partners cross-tabulation.

Variables		History of GUD		Total	P value
		No	Yes		
Partners	One Partner	5	12	17	0.032
	Multiple partners	9	24	33	
Total		14	36	50	
Recurrence	Primary	12	0	12	0.000
	Recurrent	2	36	38	
Total		14	36	50	
Episode numbers	1	12	0	12	0.000
	2	1	19	20	
	3	1	13	14	
	4	0	4	4	
Total		14	36	50	

Table 10: Co-STD present and HIV status, cross-tabulation.

Variables			HIV Status		Total	Stats
			HIV Positive	HIV Negative		
Co-STD present	Yes	Count	12_a	3_b	15	
		% within HIV Status	48.0%	12.0%	30.0%	P =0.005
	No	Count	13_a	22_b	35	
		% within HIV Status	52.0%	88.0%	70.0%	Phi =0.393
Total		Count	25	25	50	
		% within HIV Status	100.0%	100.0%	100.0%	

Table 11: Different Co-STDs and HIV positivity.

Co-STD	HIV positive	HIV negative	p value
Secondary syphilis	7 (28%)	1(4%)	0.002**
Ano-genital warts	3(12%)	1(4%)	0.29 (NS)
Genital Molluscum	2(8%)	1(4%)	0.55(NS)

DISCUSSION

This study was undertaken at a teaching hospital where majority patients come from a low socio-economic background and semi-urban or rural areas. These settings have been discussed in the studies of Amudha et al and Balaeva Tatiana et al both of which found significant correlation of HSV infection with low socioeconomic status.[6,7]

Age

In an Indian study by Banerjee et al in 2011 found a mean age of HIV positivity in STIs of 30.6 years.[8] In another Indian study by Amudha et al in 2014, most of them belonged to 35-39 age group.[6] HIV positivity in GH in our study had mean age of 40.44±13.556 as shown in Table 1. This is higher than above study, may be due to unnoticed infections in women, low education and lower health awareness so as to get diagnosed at earlier. In this study adolescents i.e. up to 19 years of age were18%.[9] e Silva et al in Netherland, in 2016 in a mass survey found that adolescents were capable of sexual activity and they were engaged in intercourse by various ways of social mixings with opposite gender, for which this population must be counseled for risk of sexual behavior in adolescence.[10] Newbern et al stated that adolescents are in the developmental phase in terms of sexual behavior and susceptible to peer pressure in their schools and risky sexual behaviors like sex with multiple partners& inadequate protection during sex.[11,12] This imposes a substantial responsibility on the emphasis given to sex education and counseling of the youth. Out of the 9 adolescents 5 are female showing they too are equally victimized to GH and should not be underestimated.[13]

The majority patients were in age group below 30 years when factors such as un-married state or cohabitating could contribute to various high risk sexual behaviors such as poly-partners in the subjects themselves (or their contacts) or experimentation in sexual experiences and early age of sexual experience.[14]

Significantly this study found a statistically higher reporting of multiple partners amongst those with HIV positivity with the mean age of those reporting multiple partners being statistically higher as given in Table 3 and 4. This is in variance with studies that ascribe unsafe sex more to adolescents.[10, 11]

The significant positive association of HIV with older age groups as provided in Table-2, has been explained by various factors such as loss of sexual spouse lack of stable partner, alcoholism and better economic situation to afford commercial sex workers (CSWs). Increased economic capability of higher ages could translate into higher use of CSW. These risk factors with potentially longer duration of sexual activity with more than one partner could contribute to high HIV positivity.[15] Other probable cause is lack of STD/AIDS awareness and safe sex practices. In an Indian study Narasimhalu and Muhilan noted that those in age group 18-30 had the highest awareness (73.9%) while age group >40 years had the lowest awareness (46.7%).[16] A review of sexual health and activity in later life by paul et al in the UK also observed that older adults are sexually active in later life despite the commonly held assumption of lower or absent sexual drive.[17] The review points, that this age population lacks awareness and safe sex practices including barrier contraception i.e. condom use.

Sex

CDC fact sheet (2011) states that the diminished symptoms of STIs in females may lead to failure to notice the disease and hence to report it.[18] This explains the lower proportion of females in this study. In men, attitude of sex with poly-partners & unwanted sex makes them outnumber than female.[19]

Though not statistically significant, 66.7% of females were HIV positive against 40.6% of males as given in Table 3. A report by Reniers et al agreed that women may be more susceptible to infection due to forced sex, women's susceptibility or acquisition probability per coital act with an HIV-infected partner is higher than that of men & longer survival of HIV-positive women than HIV-positive men.[20]

Number of sexual partners

Significant association of HIV status with number of sexual partners as given in Table 3 is consistent with Swartzendruber who in 2013 noted that the "risk in HSV sero-positivity increases with the number of sex partners.[12] O'Sullivan et al in a study in US in 2006 of 104 men and 103 female, stated that both are engaged with multiple partners which increases risk of HIV.[19] Titania et al conducted a study which included 1243 adults and found significant association with up to five sex partners.[7]

2 out of 3 Adolescents reporting multiple partners in this study were HIV positive as in Table 5. These numbers may be small but indicate the need to address vulnerable populations through education, monitoring and counseling.

History of previous GUD

A higher proportion of HIV positivity in patients with previous history of GUD though not significant was noted in this study and by other researchers too as given in Table 3. Syphilis and GH, both these GUDs are associated with multiple sex partners resulted in HIV positivity.[21] Patients with positive history of GUD had significantly higher number of partners, all had recurrent episodes and revealed higher number of episodes compared to those without history of GUD as in Table 9. This corroborates with both increased exposure to new infections and/or re-infection from infected non-treated partners as in Table 9.

Jeanne et al in 2007 proved that GUD is a potent facilitator of HIV-1 transmission is well established, immune cells recruited to genital ulcer sites express not only CD4, the major receptor for HIV, but also CCR5, a key co-receptor important for efficient viral entry into cells.[22] Co-infection with HIV facilitates the acquisition and transmission of HSV due to the fact that the frequency, severity, duration and more frequent episodes of clinical reactivation of HSV-2 is increased by HIV infection. [23]

Recurrence, episodes number and frequency

Table 1 reveals the statistically significant higher number of episodes and shorter inter-episode duration in HIV positive patients. HIV negative patients too reported recurrent episodes but only HIV positive patients reported more than 3 episodes in the first year.

In the US, rate of symptomatic recurrence in has been stated to be 75-90% in the first year.[24] John Beauman in 2005, in his review of genital herpes noted that immunosuppression is a triggering factor for frequent recurrences and reported more recurrences per year with shorter span.[25] Median of 4 recurrences per year with about 40% of patients having at least six recurrences and 20% having more than ten recurrences in the first year was also reported by Benedetti et al.[26]

This study demonstrates median recurrences in both HIV positive and negative patients of lower than four. This could be due to the fact that reactivated erosions of GH are often asymptomatic, many patients are unaware of

their infection, the full range of lesions are often not appreciated even by clinicians and antibodies are not commonly used for testing for HSV infections.[27] The low recurrence noted even in HIV positive patients could also be due to greater treatment coverage of HIV positive patients in the last decade.

HIV positive patients showed higher incidence of recurrence (84% vs. 68%) compared to HIV negative patients though it was surprisingly not statistically significant. This is due to a relatively high proportion of HIV negative patients reporting recurrence. However, it was seen that no HIV positive patient had more than 3 episodes and HIV positivity was significantly related to increasing number of episodes as exhibited in Table 6 and Figure 1.

Bush Larry et al, noted that in the presence of HIV infection, individuals co-infected with HSV-2 experience more frequent episodes of mucosal shedding. [23]

Erosions–number and surface area

A clinically simple and cheap method was used to calculate the wound surface area (in millimeters), as described in the methodology.[3-5] This does not require any digital image or computers as in "visitreck" method of measuring the surface area.[28]

The median number and rank of area of the erosions was compared as were the mean surface areas in HIV positive and HIV negative patients as in Table 7 and Figure 2. HIV positive patients significantly showed greater mean and median number of erosions. They also showed higher mean and median surface area of erosions though not statistically significant. Patients with single lesions and single partner were all HIV negative which could reflect a lesser sexual experience or duration of sexual activity. Those with multiple erosions and multiple partners were all HIV positive in this study which bears out our previous discussions as in Table 8. Previous researchers have found that the size/surface area of an erosion can be extensive with increased severity and duration of HSV infections on a background of low CD4 T- lymphocyte counts and has more frequent episodes of mucosal shedding, when co-infected with HIV.[23,29] This study did not find statistically significant increased surface area of erosions in patients co-infected with HIV though mean area was higher as given in Table 1 and 7.

Healing with Acyclovir

As per CDC guidelines 2015, "primary" episodes in the GH were treated with acyclovir 400 mg. three times a day for 10 days & re-activated or recurrent episodes for 5 days.[30] Celum et al in 2010 noted that acyclovir has a protective roll by inhibiting HSV replication and it prevents viral copies in herpetic ulcers.[31] Agarwal et al in India in 2007 noticed herpetic lesions in HIV positive too respond well to heal with acyclovir.[32]

Researchers have reported acyclovir resistance in 4%–7%, in HIV positive, patients.[33]However, all our patients showed complete healing with acyclovir irrespective of HIV status**.** HIV co-infected patients took significantly longer to heal as given in Table 1.

Co- STDs along with present GH

Tobian et al in 2009 proved that relationship between GHSV, syphilis and HIV, establishing that both syphilitic and GH infected tissue have increased numbers of chemokine receptor 5-expressing T cells reflecting the viral synergy between HSV-2 and HIV.[34] The commonest co-STD as given in Table-10 and Table-11 noted was secondary syphilis which was significantly more in HIV positive patients than other STDs (P=0.02**). Enhanced Syndromic approach to GUDs has been studied by many researchers. These cases would have been left untreated for syphilis in syndromic approach (management), which do not, includes the use of laboratory tests like VDRL.

Limitations of study

The limited sample size is a reflection of the reduced prevalence of STIs in the general population. Exclusion criteria of ongoing treatment, non-consent for HIV testing and non-consent for other STIs also contributed to the limited sample size. Socioeconomic factors have not been studied in this study. This was due to predominantly single strata of patients attending our hospital. Apart from Herpes and secondary syphilis, other STIs were clinically diagnosed. Diagnosis of other STDs was done only clinically except T-zanck smear in herpes & blood VDRL lab test in secondary syphilis.

CONCLUSION

A remarkable incidence i.e.18%, of adolescents in this study is notable. Majority patients of GH were in younger age group. Patients in older age group showed significant association with HIV positivity. This underlines the need to include both ends of the age group spectra in all efforts to reduce the prevalence of STIs. HIV status was significantly associated with number of sexual partners admitted by the patients. HIV positive patients had significantly higher number of episodes, reduced inter-episode duration and more number of erosions, longer healing period and greater association of co-STIs. Amongst patients with multiple sexual partners, significantly those with increased number of erosions and history of genital ulcerative disease showed higher prevalence of HIV positive state. These findings reflect the impact of high risk behavior on all STIs and lowered immune status of HIV patients.

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