A STUDY ON THE PREVALENCE OF HPV INFECTION IN HIV INFECTED AND HIV NON INFECTED INDIVIDUALS AND TO ANALYSE THE DIFFERENT TREATMENT MODALITIES ON ANOGENITAL WART

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CERTIFICATION

Certified that this dissertation entitled "**A STUDY ON THE PREVALENCE OF HPV INFECTION IN HIV INFECTED AND HIV NON INFECTED INDIVIDUALS AND TO ANALYSE THE DIFFERENT TREATMENT MODALITIES ON ANOGENITAL WART"** Is a Bonafide work done by **Dr.K.K.KAMALAKANNAN M.D, DVL.,** Post graduate student of the Department of Dermatology, Venereoloigy and Leprosy, Madras Medical College, Chennai during the academic year 2007 – 2010 . This work has not previously formed the basis for the award of any degree.

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CONTENTS

INTRODUCTION

Anogenital warts have been recognized as a disease entity for many centuries. They were recognized by early Greek and Roman physicians such as Hippocrates and Galen. The term Condyloma was derived from ancient Greek word meaning **"a round swelling adjacent to the anus".** The addition of the suffix acuminate is a relatively new feature, appearing towards the end of the 19th century. The viral etiology for development of human skin warts were proposed in the early 20th century[1] and viral particles were seen on electron microscopy of wart samples in the late 1960s[2]. Gissman and Zur Hausen[3], isolated HPV 6 from genital wart in 1980. Cautery was used as a treatment from 6th century onwards. Genital wart as a manifestation of HPV infection represents the tip of the iceberg when considering the total spectrum of infection. Within the spectrum of sub clinical infection there are several distinct entities. True prevalence of HPV anogenital infection in the community is not known. Current evidence suggests that over 50% of sexually active adults have been infected with one or more HPV types. Progress in HPV research was hampered by the inability to culture the virus in vitro and absence of satisfactory animal models. Major advances in molecular, biological techniques such as DNA amplification

and splicing, have in part overcome the problem in detection of Human Papilloma Virus infection. Many patients do not seek medical help.Although most anogenital wart in immunocompetent patient eventually undergoes spontaneous regression, treatment is offered to the majority of affected individuals to reduce the risk of secondary infection and to alleviate anxiety . Immunocompromised state alters the natural course of HPV infection. And increased incidence of genital wart and persistence of HPV infection is seen. Certain HPV types have been implicated in the causation of benign and malignant cancerous anogenital disease as well as benign and malignant head and neck lesions. Bearing in mind that carcinomas are considered and recorded as a sexually transmitted disease, according to the World Health Organization, its determination and the application of the respective therapeutic concepts according to the location and dimensions of the lesions is of paramount importance for the patient's prognosis. Papilloma viruses are difficult to reproduce under in vitro conditions, so generation of a "normal" vaccine is impossible. Hence virus-like particles (VLP), which are recombinant versions, are used as vaccine presently.

REVIEW OF LITERATURE

DEFINITION

Anogenital wart is a benign proliferation of skin and mucosa of anus, genitalia and its adjoining area by Human Papilloma Virus, subtypes 6 and 11 in >90% of the cases. These viruses infect differentiating epithelial cells of skin and mucosa. Patients with visible warts may be infected simultaneously with oncogenic “high risk” HPVs such as types 16 and 18, which mostly give rise to subclinical lesions associated with intraepithelial neoplasia (IN) and anogenital cancer.

EPIDEMIOLOGY

Genital warts as a manifestation of HPV infection represent the tip of the iceberg when considering the total spectrum of infection. Within the spectrum of sub clinical infection there were several distinct entities namely, acetowhite epithelium, macroscopically normal epithelium but with cytological or histological evidence of HPV infection such as koilocytes and finally macroscopically and microscopically normal epithelium in which HPV had been detected by Hybridization technique or by DNA amplification by PCR.

True prevalence of HPV anogenital infection in the community is unknown because

- Many patients do not seek medical help.
- Symptomless and subclinical infections are common.
- Most cases are diagnosed after the appearance of condylomata.
- Many individuals with genital wart consult general practitioners, who fail to notify these cases to public health authorities.

Current evidence suggests that over 50% of sexually active adults have been infected with one or more HPV types. Infection rates vary and depend on the quantity of virus particles, types,intensity,length of contact and also on the patient's immunity status. In United States, estimated prevalence of genital warts among men and women between 15 -49 years of age is 1.4 million and 19 million respectively. In Britain and Ireland 80000 new cases of anogenital warts are reported annually. HPV prevalence estimates for women in countries around the world range from 2% to 44% whereas among males it ranges from 2.3% to 34.8%. Prevalence of genital warts in India has been reported to be 5.1%

to 25.2% of STD patients[57-59]. Incidence of anogenital warts has increased from 7.2% to 8.8% among the HIV infected patients over a period of 5 years[60].

HPV after entry may remain dormant without producing any lesion or may produce symptomatic or asymptomatic lesions. Symptomatic lesions appear after an incubation period of 1 to 8 months with an average of 3 months. Rarely do they resolve spontaneously without any treatment.

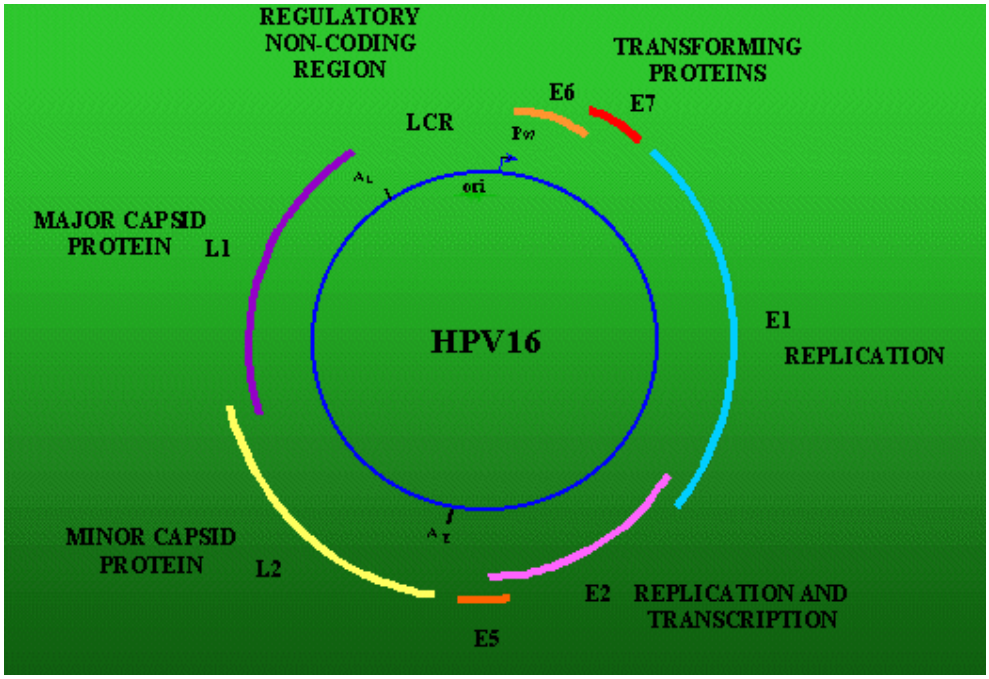
MORPHOLOGY OF HPV

HPV belongs to the Family of Papillomaviridae, formerly members of the Papovaviridae family. The following five genera contain members that infect humans who are highly host specific Alpha, Beta, Gamma, Mupa and Nupapapillomavirus.

HPV Virion is non enveloped and are composed of 72 pentameric capsomeres forming outer coat. This coat consists of major and minor capsid proteins. These are arranged on a skewed icosahedral lattice. The capsids are approximately 60 nm in diameter.

The genome is double stranded, super coiled, circular DNA of 7.2 Kilo bases, composed of approximately 8000 nucleotide base pairs. It

Fig:Genetic map of HPV 16 [13]



Consist of 3 regions, namely Early region (E1-E7), Late region (L1 & L2), Upstream Regulatory region (URR) or Long Control Region(LCR).

The early regions encode for proteins that are involved with the regulation of viral DNA replication and transcription, where as late region encodes as L1 and L2 for major and minor and capsid proteins respectively.

Early genes (E6, E7) are involved in oncogenic transformation in high risk HPV types[4, 5].

The HPV are epithileotropic and their replication depends on the presence of differentiating squamous epithelium. The capsule proteins and infectious viruses are found in the superficial differentiated cell layers.

The use of Raft culture system which forms the stratified squamous epithelium has now produced limited amount of infectious HPV. Of more than 200 types, 45 types can infect genital epithelium.

TABLE 1: FUNCTIONS OF EARLY AND LATE GENES

GENE	FUNCTION
E1	Initiation of DNA replication
E2	Transcriptional regulation/DNA replication
E3	
E4	Disrupts cytoskeleton
E5	Transforming protein, interacts with growth factor receptors
E6	Transforming protein, binds to p53, leading to degradation
E7	Transforming protein, binds to pRB
LCR	Early promoter, transcriptional regulatory motifs.
L1	Major capsid protein
L2	Minor capsid protein

TYPES OF HPV

Cutaneous (nongenital) types : HPV 1, 2, 3 and 4

Genital-mucosal types : HPV 6 (a-f), 11 (a & b), 16, and 18

Those isolated from EV : HPV 5 and 8 (>20 types)

TABLE 2: HPV TYPES AND CLINICAL DISEASE[6]

CLINICAL DISEASE	HPV TYPES (FREQUENT)
Condylomata acuminata	6, 11
Cervical intraepithelial neoplasia	
Low grade	6, 11
High grade	16, 18
Bowenoid papillosis	16
Cervical cancer	16, 18
Giant condyloma of bushke and Lowenstein	6, 11
Other verrucous carcinomas	
Oral and laryngeal papilloma	6, 11
In HIV patients	7,72,73

TRANSMISSION OF HPV VIRUS:

- Genital HPV infection is transmitted primarily through sexual contact. The infectivity of HPV infection between sexual partners is estimated to be about 60%. During the sexual act, micro abrasions occur in male and female genitalia and anus in

homosexuals; through this micro abrasion transfer of HPV virions from the epithelial cells of infected partner to the basal layer of recipient occurs.

- Auto-inoculation by Digital transmission and adjacent contiguous epithelium[8].

- Vertical (Perinatal) transmission has been observed in infants born to women with genital wart during pregnancy. These infants develop laryngeal papilloma and congenital condylomas[9].

- HPV virus is neither blood-borne nor is transmitted by fomites.

- Smoking tobacco may also be a risk factor for the development of genital wart. But this association is uncertain[7].

PATHOGENESIS[10, 11]

Inoculation of virus into the epithelium occurs through abrasions after sexual contact with HPV infected individuals. Inoculated virus infects basal cells through binding with α6 integrin and laminin receptors .Cell surface heparan sulfate binds HPV particles with high affinity followed by Clathrin/caveolin mediated endocytosis. HPV genome gets incorporated into differentiating cells of the epidermis. The

integration of viral proteins in human cells disturbs cellular homeostasis. The expression of E6 and E7 genes leads to immortalization of keratinocytes and stimulates cellular proliferation. HPV DNA replicates as cell differentiation occurs. Capsid proteins are synthesized in the upper layer of the epidermis and assembled into virion. Viral particles are then shed from the lesions.

IMMUNOLOGY

Both cell mediated immunity (CMI) and humoral immunity develop against human papilloma viral infection.

HUMORAL IMMUNITY

"One way cross reactivity" [12]: The cutaneous warts are auto inoculable on to genital mucosa, but genital warts are not able to produce infection on to glabrous skin. These differences are seen not only to their infectivity but also serologically. Antibodies against cutaneous warts reacts not only to antigen of cutaneous wart, also reacts to antigen of genital warts. But antibodies against genital warts react only to antigen of genital wart. Almedia analyzed that only 50% of patients had demonstrable antibody. No particular correlation between presence of antibody, types and duration of lesions were seen, but

recurrences occur due to absence of antibodies. Antibodies produced against L1 protein i.e capsid antigen, are type specific and act as neutralizing antibody which prevents recurrences. The median time to seroconversion is approximately one year and antibodies persist for decades. In regressing warts, IgM (100%), IgG (97%) and IgA (80%) classes of antibody to HPV were detected. The cure rate was high when complement fixing antibodies (CF) IgG antibodies were seen in the serum. In the absence of CF antibodies, healing process occur slowly. Increasing titre of circulating antibodies has been demonstrated in regressing warts.

CELL MEDIATED IMMUNITY

CMI plays a major role in both elimination and prevention of recurrence of infection. Histopathology of Spontaneous regression of wart shows stromal edema and a dense sub epithelial and epithelial infiltrate of T lymphocytes in which CD4+ cells out number CD8+ cells[15,16]. Prominent infiltration of macrophages in the stroma are seen[16]. These infiltrating cells have increased expression of CD25 (α chain of interleukin 2 receptor) and HLA DR. The majority of T cells express CD45RO isoform but 10-15% CD 45RA isoform are also expressed. Keratinocytes in regressing warts shows expression of HLA DR and

ICAM-1 result of production of cytokines such as IFN ע and TNFα by infiltrating and activated CD4+ cells and macrophages . The endothelial cells in the blood vessels of the stroma show up regulation of ICAM-1, E-SELECTIN and VCAM-1 which are important in lymphocyte homing to site of inflammation. Spontaneous regression of condyloma acuminata results from a TH1 type response.

EVIDENCE FOR ROLE OF CMI

The role of CMI in genital wart protection is evidenced by the increased incidence of genital warts in immunodeficiency patients and in Children who showed reduced tuberculin reactivity[14]. Marked mononuclear cell dermal infiltrate in spontaneously resolving lesions is a further proof to the role of CMI.

Certain patients shows spontaneous regression of warts but others show persistent of warts which is due to reduced local immune responses. Reduced local responses may be due to presence of Virus producing cells which are away from basement membrane (BM), inadequate production of viral antigens, Insufficient HLA expression and Local inhibitory effect of the primary infected cells to the immune system.

HPV AND ONCOGENESIS

Certain HPV types have been implicated in the causation of benign and malignant cancerous anogenital diseases as well as benign and malignant head and neck lesions.

High cancer risk	**:**	HPV types 16, 18, 45, 31 and 33
Intermediate cancer risk	**:**	HPV types 30,31,33,35,39,51–53,56,58,59,66,68,73 and 82
Low cancer risk	**:**	HPV types 6, 11, 40, 42–44, 54, 61, 70, 72 and 81

The Human Papilloma Viral DNA integrates with Human DNA followed by disruption of the E1/E2 open reading frames and Up regulation of E6 and E7 proteins. This E6 and E7 proteins binds with p^{53} p^{RB} and tumor suppressor protein respectively. A key carcinogenic process is production of E7 protein by the virus which interferes with the host p^{RB} (retinoblastoma protein) tumor suppressor protein. The E6 protein of the virus is capable of destroying the p^{53} protein of the host cell, which inhibits accumulation of genetic mutation during replication usually through apoptosis, resulting in proliferation occurs in viral infected cells.

The development of genital and anal carcinomas from the persisting anogenital warts are considered to be rare. More often, these cases involve verrucous carcinomas, which are HPV 6 and 11 positive. Cervical carcinoma, as well as penile and vulvar carcinomas are considered to have originated on the basis of premalignant neoplastic lesions, known as CIN (cervical intraepithelial neoplasia), AIN (anal intraepithelial neoplasia), VIN (vulvar intraepithelial neoplasia), and PIN (penile intraepithelial neoplasia). By definition, bowenoid papulosis represents a severe form of penile, perianal and vulvar neoplasia.

About one-fourth of women with anogenital warts present with similar vaginal and/or cervical alterations, and this makes colposcopy inevitable. Bearing in mind that cervical carcinoma is considered and recorded as a sexually transmitted disease, according to the World Health Organization, the determination of cervical or vaginal intra-epithelial neoplasia and the application of the respective therapeutic concepts according to the location and dimensions of the lesions is of paramount importance for the patient's prognosis.

HPV IN IMMUNOCOMPROMISED

Immunocompromised state alters the natural course of HPV infection. Increased incidence of genital wart and persistence of HPV infection is seen in immune compromised individuals with decreased cell mediated immunity such as leukemia, lymphoma and AIDS. Prevalence of HPV infection and Ano genital wart is higher in Organ transplanted individuals[24]. The prevalence of cervical and anal Squamous intra epithelial lesion(SIL) is higher in women with renal transplantation[17]. HPV16 and HPV 18 DNA were found more often in immunosuppressed individuals [17, 18]. The prevalence of HPV infection was higher in HIV infected women whose CD4+ count was less than 500 cells/mm^3 [(20)]. The prevalence of high risk HPV's like HPV 16, 18 is high among HIV seropositive individuals. Multiple HPV types are also common in HIV infected individuals[19]. The persistence of the infection with high risk HPV types is found in persons with CD4 count <200cells/mm3[20]. Most important factors for high grade SIL s have shown to be low CD4 count, persistent HPV infection, infection with multiple types of HPV and infection with oncogenic type of HPV[21]. The increased risk of malignant transformation is due to the **TAT** protein of HIV virus which potentiates the expression of E6 and E7 region of HPV

16[22]. Patients with HIV infection commonly develop Papilliferous lesions of oral cavity with predominant association of HPV type 7 and 32[23].

CLINICAL FEATURES

HPV after entry may remain dormant without producing any lesion[25] or may produce symptomatic or asymptomatic lesions. The lesions can occur after the incubation period of 1 -8 months with an average of 3months. In uncircumcised men, the preputial cavity, glans penis, coronal sulcus, frenulum, inner aspect of the foreskin are most commonly affected, while in circumcised men the shaft of the penis is often involved. Warts may also occur on the scrotum, groin, perineum, and anal area. Wart in urethral meatus is common in men (25%) but in women its incidence is only 4 to 8 %. In women common sites are posterior part of introitus, labia, perineum and perianal region. The lesions can also be seen intra vaginally or in the cervix. But these are affected more in sub clinical infections.

Depending upon the clinical appearance, warts can be classified as

Condylomata Acuminate

Acuminate warts are found in mucosal surfaces and are characterized by pedunculated mass red to pink or white in colour with warty digitations, irregular surface and fissures and are seen mostly in partly keratinized epithelium[26].

Papular wart

Non pedunculated hemispherical masses or dome shaped masses 1 to 4mm in diameter located on fully keratinized epithelium[26] and lack the finger-like surface irregularities of acuminate warts.

Keratotic wart

These are firm papular lesions of varying sizes with slightly rough horny surface with no pedicle, ranging from a few mm to a few cms seen on the dry areas like shaft of penis, outer aspect of prepuce, labia majora and perineum[26]. Sessile warts are tiny lesions with no horny surface seen on fully keratinized epithelium.

Flat topped papular wart

These appear macular to slightly raised lesion seen on the partially or fully keratinized epithelium[26].

Bowenoid papulosis

Variant of papular wart characterized by hyper pigmented dome shaped, smooth, velvety, flat topped papules of size 7 to 10 mm in diameter. The colour of the lesion on mucous membrane sites is brownish or salmon red or greyish white and on cutaneous sites ash grey to brownish black. Bowenoid Papulosis appears at 25–35 years. Histologically high grade squamous intra epithelial neoplasia and is positive for HPV 16 DNA. Recurrence rate is 20%.

"GIANT CONDYLOMA" or Buschke Lowenstein tumour

This is a very rare variant of HPV 6 and 11 associated disease. In HIV infected patients Anogenital warts tend to be multiple and even diffuse. Usually asymptomatic sometimes they develop very large lesions and become locally invasive and destructive but non metastasizing tumors seen in shaft of penis, vulva and perianal areas[26]. In soft areas lesions have papillomatous surface whereas in hard areas the surface is smooth. There is a significant risk of transformation of this giant wart into squamous cell carcinoma.A complex histological pattern may exist with areas of benign condyloma intermixed with foci of atypical epithelial cells or well differentiated sqamous cell carcinoma.

Diagnosis of Buschke-Loewenstein tumour often requires multiple surgical biopsies, computed tomography or magnetic resonance imaging.

Anal Warts

Occurs commonly in homosexuals. It is also seen in children subjected to sexual abuse, immunocompromised persons and along with genital wart.

Oral Warts

As a result of oral sex are commonly seen over the lips, tongue and palate.

HPV IN SPECIAL SITUATIONS

PREGNANCY

Anogenital warts increase in number and size due to increased vascularity, hormonal influence and decreased cell mediated immunity is seen. It usually resolves after delivery but sometimes excessive bleeding may occur or it may remain as such[52]. Complications like dystocia, fetal laryngeal papilloma, bleeding and ulceration are not uncommon.

WARTS IN CHILDREN

Mode of infection is uncertain. If acquired during delivery results in genital and laryngeal disease. It can also occur as a result of sexual abuse or rarely through non sexual contact within the family.

DIFFRENTIAL DIAGNOSIS

ANATOMICAL

Skin tag, Pearly Penile Papule, Ectopic sebaceous glands, Dry smegma, Anal tag and Mucosal tag.

PATHOLOGICAL

Condyloma lata, tuberculosis verrucosa cutis, Venereal granuloma, Lympho granuloma venereum, Squamous cell carcinoma, Seborrhoeic keratosis, Molluscum contagiosum, Lichen planus, Hirsutoid papillosis, Lipoma, Herpes, Urethral caruncle, Schwannoma[27], Granuloma, Sentinel piles and Focal dermal hypoplasia[28](Goltz syndrome).

VERRUCOUS LESION

Tuberculosis verrucosa cutis, Verrucous type of granuloma inguinale, Malignancy, Condyloma lata of syphilis, Non- venereal treponematoses, Skin tag.

PAPULAR WARTS

Pearly penile papules, Herpes progenitalis, Molluscum contagiosum, Fordyce's spots, Urethral caruncle and Foreign body granuloma.

DIAGNOSIS

Most of the cases are diagnosed clinically. Rarely it requires biopsy and histopathological examination to make the diagnosis. The acetic acid test may be valuable for delineation of disease before biopsy and surgical treatment.

HISTOPATHOLOGICAL EXAMINATION[31]

The histological characteristics of the classical protuberant type of condyloma acuminatum in the anogenital region are mainly varying degrees of parakeratotic hyperkeratosis, moderate granulomatosis, pronounced acanthosis, marked papillomatosis and thickening and

elongation of rete ridges. A branching fibro vascular core is seen in the dermis. Other clinical variants have similar features but less pronounced fibro vascular branching. The most characteristic feature for the diagnosis is the presence of epithelial cells with distinct perinuclear vacuolization, such cells are known as koilocytes(Greek ward koilos means empty).The vacuoles in koilocytes are sharply demarcated from the peripheral rim of cytoplasm. The nucleus is large hyper chromatic and pushed to periphery of the cells. Intra nuclear basophilic inclusions are also seen. It is important to remember that vacuolization is normal feature in the upper portion of mucosa, therefore, it is considered pathognomonic only if it extends to the deeper layers of stratum malpighii. Hyperkeratosis is not a feature of condyloma acuminatum of the genital area where the stratum corneum consists of one or two layer of parakeratosis. In genital wart virus particles are scanty

ACETIC ACID TEST[30]

Following application of 5% acetic acid, HPV lesions may turn greyish white within few minutes. As the test has poor specificity it is only recommended for use in specialist settings where colposcopy is available and is not recommended for screening purposes. However, it may be valuable in identifying lesions for targeted biopsy and for

demarcating lesions during surgical therapy. False positive results are commonly due to inflammatory conditions (For example, lichen sclerosus et atrophicus, lichen planus, psoriasis, balanoposthitis and Vulvovaginitis, eczema, genital herpes, and traumatic micro abrasions) and give rise to ragged, irregular acetowhite borders. There may be varying degrees of underlying hyperaemia and capillaries lack the vascular punctuation suggestive of HPV.

IN CASE OF CERVICAL AND VAGINAL WART

Speculum examination, Colposcopic examination and Pap smear fixed in ethanol and stained with papanicolou stains are useful to diagnose squamous intraepithelial neoplasia. In doubtful cases, acetowhite staining to be done with 3 to 5 % acetic acid.

Cytological diagnosis of SIL

Cytological diagnosis is based on Bethesda system. Terms used in this systems are Low grade squamous intra epithelial lesion (L-SIL) and high grade squamous intra epithelial lesion(H-SIL).

L-SILs previously classified as mild dysplasia(CIN 1) denotes protective HPV infection with variety of HPV types. The cell nuclei are enlarged often angulated, hyper chromatic and multinucleated cells may

be seen. Cells with vacuolated cytoplasm (koilocytes) are found in the superficial layer of cervical epithelium. The cells contain diploid or polypoid DNA pattern.

H-SILs, previously classified as moderate - severe dysplasia, composts of proliferating basal type cells that have a high nuclear to cytoplasm ratio. The lesions are usually aneuploid.

Ultra structural studies show virus in some of the cell nuclei as particles. These particles are crystalloid aggregates and can be diffusely located in chains and/or groups. Routine application of electron microscopy in the initial diagnosis is not considered as a standard method now. Viral antigen can be demonstrated in the nuclei of cells in the stratum granulosum by peroxidase- anti peroxidase test, indirect immunoflourescence and indirect immune alkaline phosphatase reaction.

The most sensitive method of detection of HPV infection is HPV DNA PCR which is primarily used for research purposes only. PCR performed with the help of specific PCR group-specific probes is a highly sensitive and promising method finding wider application in

modern dermatology clinics. This method helps to prove the presence of even the smallest quantities of papilloma viruses in the cells.

DNA hybridization of histological tissues by means of both radioactive and non-radioactive techniques can be performed on HPV-infected cells. Due to the fact that this technique is not suitable for the detection of high-risk malignant HPV strains and is also time and labor intensive; with sensitivity which is similar to PCR methods, its application is limited.

Gel electrophoresis and restriction endonuclease cleavage[32], Southern blot hybridization, Filter in situ hybridization, Dot blot hybridization are other methods employed in detection of viral warts.

Anal warts may require proctoscopy for diagnosis and Urethroscopy or meatoscopy for diagnosis of urethral warts. As a rule, posterior urethra is not involved without previous or simultaneous growth of meatal warts.

MANAGEMENT OF ANO-GENITAL WARTS

Although most Anogenital warts in immunocompetent patients eventually undergoes spontaneous regression, treatment is offered to the majority of affected individuals with moist hyperplastic condylomata

acuminata to reduce the risk of secondary infection and to alleviate anxiety. Soon after the diagnosis of the Anogenital wart all patient should be counseled carefully about the infection. Before initiation of wart therapy it is important to attend local infection whether it is sexually transmitted or not. All treatments of HPV infections have significant failure and relapse rate. A number of treatment modalities is available for Anogenital wart and are listed below, broadly divided into medical and surgical modalities as follows. The efficacy of the various treatments available for use in treatment of external anogenital warts has recently been reviewed by Beutner and Wiley[33].

Patient counselling—key points [29]

- Patients should receive clear information, preferably written, as to the cause, treatment, outcomes, and possible complications of anogenital warts

- Reassure patients that although wart clearance may take 1–6 months and recurrences may occur, complete clearance will occur sooner or later

- Smokers with recalcitrant lesions should stop smoking as a correlation exists with wart development.

- Advise female patients about regular participation in cervical cytology screening programmes. Reassure that risk of cervical cancer is low and ample time exists for detection and removal of any CIN.

Treatment—key points[29]

- First line treatment will achieve clearance in most patients within 1–6 months, although disease persists in up to one third of patients

- Home therapy can be proposed in most cases as first line therapy for first attack of acuminate warts. Acuminate warts respond in up to 90% but papular and macular lesions in only 50% of cases.

- Few, small lesions can be easily treated under local anaesthesia by scissors excision, diathermy, cryotherapy or TCA.

- TCA should not be used on large lesions and multiple sessions are not well tolerated by patients.

- Lesions occurring at new sites during treatment or after clearance do not necessitate a change of the treatment modality.

- Persistence or reappearance of the treated lesion is usually an indication to switch to another treatment modality.
- Patients should be evaluated regularly until the warts are cleared.
- Patients should be informed that periods of coital rest throughout the course of the therapy might reduce therapy related symptoms such as pain or discomfort.

MEDICAL THERAPY

20%Podophyllin, 0.5%Podophyllo toxin (0.5%),5% w/v 5 flurouracil,80-90%Trichloroaceticacid,Bicloro ethanoic acid, Interferon, 5%Imiquimod, Inosine pranobex, Cidofovir.

Immunotherapy – Intralesional mycobacterium w vaccine

SURGICAL THERAPY

Scissor excision,Electro surgical methods like Electro cautery,Electro fulguration, Electro desiccation, Cutting

CRYOTHERAPY

LASER THERAPY

PHOTODYNAMIC THERAMEDICAL THERAPY

PODOPHYLLIN

Kaplan first described the use of podophyllotoxin in 1942. It is ethanol extract prepared from the dried rhizome and roots of plant podophyllum species (podo – foot, phyllum-leaf) American species podopyllum peltatum grows in moist shady places from New England to Caroline. A second species of therapeutic interest is podophyllum emodi. It is seen in Himalayan mountains and Kashmir.

Preparation of podophyllin

Syrupy ethanal extract is poured into cold water and then acidified with hydrochloric acid to form a precipitate which is dried and powdered, Light brown to greenish yellow in colour, it darkens on exposure to light and heat. In podophyllum peltatum the lignan content was found to consists of podophyllotoxin 10% and alpha and beta peltatin 13%. In extracts from P.emodi , Podophyllotoxin was 40 % and 4 – d methyl podophyllotoxin 2%. Unfortunately the amount of active material in any extract varies considerably from batch to batch[34], as does the amount of lignans such as quercetin which are responsible for most of the side effect of the drug. The suspension has a relatively short half

life, although probably stable up to 3 months without undue loss of potency.

Mode of action

Podophyllotoxin has been shown to be the most active lignan contained in podophyllin resin[35, 36] and produces destructive effect on keratinocytes and dermal cells, at low concentration (1 mmol). Podophyllotoxin acts in a similar manner to colchicines and binds to site of tubulin, a component of microtubules. Microtubules form the principle fibrous protein of the mitotic spindle and are an essential component of the biological machinery that moves chromosome and other cytoplasmic components. It arrests cell division in metaphase stage. At higher concentration (10 to 100 mmol) podophyllotoxin inhibits nucleoside transport and leads to cell destruction[37].

Recommendation for podophyllin use

25% Podophyllin in tincture benzoin once or twice a week, the suspension being washed off after 4 to 6 hours. Available as various formulations[38], the drug can be given about 0.5 ml once only as application by trained personnel with adjacent skin being protected by yellow or white soft paraffin. The use of single container for repeated

applications in clinics is condemned as it may bring risk of cross infection. It is good practice to treat with small amounts of 25% podophyllin in liquid paraffin or methylated spirit of not more than 0.3ml at a time at frequent interval of every 3 to 7 days. Patient should be advised to wash off podophyllin after an interval of 4 to 6 hours. The application of podophyllin to large condylomata (more than or equal to 10 cm square area) often results in extensive tissue necrosis with pain and swelling and caution should be taken in using podophyllin in treatment of such lesions.

Clinical effect

About 4 to 6 hours following application of podophyllin the treated condylomata show blanching and later a drying effect is seen when the pink or red moist wart appear white or grey and dry, sometimes there is dark brown discoloration. In 4 to 24 hours the condylomata decrease in size and in 48 hours there is complete involution[39]. The penetration of podophyllin was prevented by the dry keratinized surface which caused treatment failure in some cases.

Unwanted effects

Varies from local itching, burning, tenderness , erythema , pain, swelling and ulceration. Balanoposthitis may be severe with or without phimosis, if neglected lead to a necrotizing balanitis. When podophyllin has been used aggressively and in quantities beyond that is recommended, systemic ill effects have been recorded including dizziness, lethargy, pre coma, nausea, vomiting, abdominal pain, respiratory distress and cold clammy skin. Reversible bone marrow suppression with thrombocytopenia and leucopenia has been recognized[40] and irreversible peripheral neuropathy may occur followed by systemic toxicity[41]. In pregnancy, the drug is potentially mutogenic and it causes teratogenecity theoretically[41].

Efficacy

At least 3 months after the cessation of the therapy, the reported clearance rate of anogenital warts was between 22% to 73%. The recurrence rate was between 23% to 55%[33].

PODOPHYLLOTOXIN

Active agent of podophyllin has been purified and available as liquid and cream. It is considerably more expensive than podophyllin but is suitable for home treatment.

Preparation

Available as acidic solution in ethanol 0.5%w/v and as a cream or gel 0.15%w/v

Recommendation for podophyllotoxin use

Podophyllotoxin (0.5% w/v) is applied twice daily for 3 days of each week for a maximum of 4 weeks.volume of the solution should not exceed 0.5 ml or 50 single application per session and the area treated per session with solution, cream or gel should not exceed 10 cm square.it is recommended that physician or nurse should apply the first treatment to demonstrate the proper application[43] .

Unwanted side effects

Mild tenderness, burning and pain are common; erythema , edema and minor erosions are also frequently seen[33]. The highest incidence of these effects is seen during the first week of treatment[42].

The safety of podophyllotoxin in pregnancy remains to be established and is probably best avoided as of now.

Mode of action and clinical effects are similar to podophyllin.

Efficacy

Compared with podophyllin, podophyllotoxin is more effective in producing complete clearance of warts after 6 weeks of treatment. Complete clearance after 6 weeks of therapy podophyllotoxin was 88% whereas with podophyllin clearance rate was 63%.[61]

MONOCHLOROACETIC ACID & TRICHLOROACETIC ACID

The use of caustic agents such as mono or trichloroacetic acid is of value especially in the treatment of keratinized wart. The acid acts by coagulating tissue protein with resultant necrosis. The acid in an 80% to 90% w/v solution in water is applied once weekly to the wart. The agent is best applied by touching the wart with an orange stick that has been dipped in the acid. It should not be applied with a swab as the amount of acid may be excessive and may damage adjacent normal skin. Care should be taken to avoid contact with adjacent normal skin. Patient often experience a warm sensation on application of the acid and the solution should be allowed to dry before the patients sit or stand[43]. The

treated area rapidly goes white. The use of such agents at the meatus is best avoided as scarring leads to meatal stenosis. Local ulceration and pain may occur[44]. If the pain is intense it can be neutralized by dusting with sodium bicarbonate. There is no systemic toxicity and thus is safe to use in pregnancy.

Efficacy

In patients with Anogenital wart, treated with 95% TCA solution and cryotherapy for the period of 6 weeks.70% of TCA patients and 86% of cryotherapy patients shows complete clearance of the wart 3month after completion of treatment. But local ulceration was noted in patients treated with TCA[44].

CRYOTHERAPY

Liquid nitrogen, carbon di oxide or nitrous oxide can be used as cryogens. It can be used on keratinized and unkeratinized warts; it is not restricted to use at specific anatomical sites and is safe in pregnancy. The perianal wart does not respond as well as genital warts to freezing.

MODE OF ACTION[45]

Cryotherapy destroys warts by cytolysis directly as a result of formation of intracellular ice crystals and later thawing; and from a injury to microcirculation as a result of vasoconstriction and damage to endothelium which causes thrombosis in arterioles and venules of the tissues. The optimum temperature required to induce cell death is around -50 degree Celsius or lower. The effectiveness of cryotherapy can be assessed by its formation of an iceball of 1 to 2 mm beyond the periphery of the lesion[45]. Within 30 seconds of freezing, cells begin to show pyknotic nuclei edema and other cytoplasmic changes. At the edge of the frozen area, cells have eosinophilic cytoplasm and basophilic nuclei. Cellular infiltrate is mainly polymorphonuclear cells with some lymphocytes and plasma cells most obvious at the edge of the frozen area. Destruction of epidermal cell is associated with vesiculation followed by sloughing. Resolution begins within 3 days and healing usually occurs without scarring [46].

Cryotherapy methods

The application of liquid nitrogen of boiling point of -195.8 degree Celsius to discreet warts is often used. The aim should be to

freeze the wart until a halo of frozen skin is just visible at the base. A cotton wool dipped applicator can be immersed in a vacuum flask of liquid nitrogen and then applied to the wart exposed and immobilized by stretching the skin between the fingers.

A hand held insulated and pressurized flask filled with liquid nitrogen and with a control valve to which a range of sprays of different diameter may be fitted is satisfactory for the treatment of most external genital warts. The risk of cross infection is minimal by using this method.

Closed cryotherapy system operate by providing a continuous supply of liquid nitrous oxide or carbon dioxide from a cylinder to a gun that controls the flow of liquid gas to a removable probe. To prevent cross infection, probes must be autoclaved before use on to different patients.

Efficacy

3 months after the clearance of external genital wart with cryotherapy is 63% to 93%[33] .Perianal wart do not respond to cryotherapy as good as genital wart[62].

Side effects

About 20% of the patients have mild pain during and for a few hours after the treatment. More severe pain and ulceration with secondary infection has been reported in the treatment of perianal wart with liquid nitrogen compared to genital wart[47].

IMIQUIMOD

It is an immune response modifier that has a potent anti tumor and antiviral activity. As it modulates innate immunity by activating macrophages thereby inducing type 1 response considered responsible for wart regression. More expensive compared to other forms of treatment. Not suitable for the treatment of long standing and fibrotic wart.

Mode of action[48]

Local application of IMIQUIMOD releases cytokines including interferon gamma, tumor necrosis factor alpha, IL-1 alpha, IL-1 beta, IL-6, IL-8 , IL-10, IL-12, GM-CSF, G-CSF, MIP-1 alpha, IL-1 receptor antagonist by peripheral mononuclear blood cells and lymphocytes. IMIQUIMOD induces cytokine expression in keratinocytes resulting in TH-1 response. There is no direct anti viral activity.

Recommendations of IMIQUIMOD use

5% cream is applied to wart with finger, 3 times per week every other night up to 16 weeks. The area is washed with mild soap and water 6 to 10 hours after application. The most commonly reported side effect is local irritation. As the cream may weaken condom and diaphragm alternative means of contraception should be considered until treatment has been completed.

Efficacy

No significant difference between vehicle and imiquimod with respect of complete clearance of the wart in immune compromised patients. But with imiquimod, reduction in wart area of >50% is reported.[63] but in immune competent patients,37% of 51 showed complete resolution of wart with in 8 weeks of treatment period[65].

Side effects

Erythema and local irritation develops in majority of individuals treated with IMIQUIMOD but excoriation and erosions are found in less than 50% of the patients. Indurations, vesiculation, scabbing, ulceration occur less commonly. The safety of IMIQUIMOD in the treatment of genital wart in pregnancy has not yet been established.

Other Immunomodulatory agent is inosine pranobex whose efficacy has not yet been proved[49].

5 FLOUROURACIL

This antimetabolite has in the past been used topically for the treatment of wart. It is a pyramidine analogue that is incorporated into RNA in preference to natural substrate of uracil. It inhibits thymidalate synthetase thereby impairing RNA and DNA synthesis. It becomes effective in S phase of cell cycle and causes disturbance of cell growth and division. Available as 5% cream, the cream is applied once or twice per day to the wart until they regress or until pain or ulceration necessitates cessation of treatment. It can also be used for 2 consecutive nights per week for 10 weeks. Condylomata at the urethral meatus responds well to 5FU cream applied daily for 3 weeks

Side effects - irritation and ulceration limits its use.

INTERFERONS

Interferons are endogenous intracellular proteins possessing not only antitumor but also antiviral and immunomodulating effect. The application of interferon α is already a standard therapy in a number of countries in Europe and the USA. Several studies have shown good

results of systematic therapy with interferon in combination with a CO2 laser, surgical methods and electrodessication. The subcutaneous application of interferon α2a and interferon α2b within three cycles of one week each, at doses of 1-3 MIO I.U. is recommended as a good preoperative option. The intermission between each cycle lasts approximately 4 weeks. Its advantage compared to an intralesional application is the absence of pain and frequent visits to physicians. It is very interesting that Interferon does not always have a synergistic effect with other treatment modalities in the treatment of condyloma. Subcutaneous IFN α2a combined with cryotherapy was no more effective than cryotherapy alone in the treatment of primary anogential warts. Similarly, IFNα2a in combination with podophyllin was no more effective in the treatment of primary anogenital warts than podophyllin alone and is associated with more adverse events.

However combining Interferon with other treatments increases the likelihood of effective treatment. The additional application of subcutaneously administered interferon α2b to laser treated patients with resistant genital lesions significantly enhanced the chance of eliminating these warts. There are also data that suggest a gel containing interferon helps to treat vaginal warts.

There are drawbacks due to the side effects of interferons, which are most frequently in form of sub-febrile temperatures, headache and faintness. Interferon α in the form of a gel shows good compatibility.The application of this gel containing 0.15 Mio I.U/g interferon-α, to patients whose warts have been surgically removed was compared to the application of a placebo gel after one-month of use. The subsequent 24-month observation showed that 75% of the patients treated by the placebo gel had recurrences. Fifty-four percent of the patients treated by interferon gel also showed recurrences. The high percentage of the patients who have profited from the local application during the postoperative period is the basis for the more and more frequent application of this preparation. It is suggested that interferon is able to protect the basal keratinocytes from HPV infection by the activation of Th-1 cells and their cytotoxic effect is probably the basis of the effect.

The combined systemic therapy of anogenital warts by interferon α2a and isotretinoin (0.5-1 mg/kg/d) has promising effects. Promising also are current results of single use PEG-IFN (pegylated interferon- α) 80 microgram per week for 24 weeks, which led to full remission in HIV-positive patients at the stage of viraemia. Interferon α has probably an additional suppressive impact on viral replication with a synergetic

effect added to the effect mediated by T Lymphocytes. They are expensive and side effects like flu like symptoms are common.

CIDOFOVIR

Cidofovir is an acyclic nucleoside phosphonate with a wide-range antiviral effect with respect to some HPV-induced tumors. This substance can be locally applied in the form of 1% or 3.5% gel or ointment, as well as administered intravenously. The substance can provoke programmed cell death among the cells of the tumor population. This preparation also gave good results when applied to the inguinal area of a 3-year old patient. The topical single perianal use of 1% cidofovir in the form of an ointment in HIV-positive patients led to full remission within 14 days and absence of any recurrences of warts during the next 14 months. Cidofovir provides good results as adjuvant therapy after electrodessication and operative removal of CIN, PIN and VIN.

ELECTROCAUTERY

The thermal damage to wart tissue results from the application of a resistant wire heated with an electric current. It is an effective treatment in case of genital warts that are discreet and pedunculated. The

aim should be to coagulate the wart down to the basement membrane and cause minimal damage to surrounding skin. Before the procedure topical 1% solution of lidocaine is used as a local anaesthetic. The ulceration during the electrocautery is inevitable but usually heals within 7 to 10 days with little scarring.

ELECTROSURGICAL METHODS

In this method heat is produced in the tissue at the point of entry of high frequency current[50]. Several methods which may be useful in the treatment of genital warts are

Electro fulguration

High voltage low amperage current sparks across an air gap between the electrode and the wart without touching it. There is little thermal damage so healing is rapid.

Electrodessication

Similar to electrofulguration except that the electrode is in direct contact with the tissues.

Electrocutting

Electrocutting Occurs under the conditions of very high current density when temperature rises rapidly and sufficiently to damage the tissues[51]. Cutting diathermy is generally used in the treatment of large condylomata and its use may require general anesthesia. Large loop excision of T zone of the uterine cervix is used in suspected SIL and cervical condylomata. Local anesthesia for this procedure is necessary (Prilocaine hydrochloride 30 mg/ml into the cervix with a dental syringe).

Efficacy

10 of 11 patients treated with ECT shows complete clearance of the wart 3 months after treatment by Simmons et al[64].

Unwanted effects

Intens**iv**e coagulation can result in slow wound healing, secondary hemorrhage, infection and scarring [50].It can also lead to complications like burns, electrocution, fire and interference with cardiac pace maker.

SCISSOR EXCISION

Scissor excision of perianal and intra anal wart can be done under general anaesthesia with wart bearing area being infiltrated with saline adrenaline solution. The wart that has separated and become discrete are then removed with fine pointed curved scissor by cutting at the base of the wart from back to front. Cell mediated responses were measured and this appears to be enhanced by this technique. The recurrence rate following scissor excision is low when compared to patient treated with podophyllin.

IMMUNE THERAPY

Intralesional mycobacterium w vaccine: Patients with anogenital warts to be injected with mycobacterium w vaccine 0.1ml initially in the deltoid region on both sides. Two weeks later, mycobacterium w vaccine to be injected Intralesionally into few lesions of genital warts. Then Intralesional injections to be repeated every week till the complete clearance of the lesion occurs or for a maximum of 10 weeks.

LASER THERAPY

CO2 laser is most widely used in the treatment of anogenital wart. Infrared radiation produced by the laser is focused by series of mirrors

and lenses. All types of tissues absorb this energy; different power densities produce different biological effects. A beam of 0.1 mm diameter is suitable for incising tissues whereas a defocused beam of about 2mm spot size can be used to vaporize the tissue. Around the zone of vaporization there is a margin of coagulation[51]. As thermal necrosis of healthy tissue is limited to about 50 micrometer beneath the zone of vaporization. Smoke evacuator is necessary for vaporization.

Laser therapy is seldom used as a first line treatment for Anogenital wart. As there is a perfect control of tissue destruction and a reduced risk of hemorrhage this form of treatment may be preferable to electrocautery, diathermy or scissor excision in the management of extensive lesions. Flash lamp pulsed dye laser can also be used without much side effect. Good results in removing HPV-associated lesions are achieved by ERB YAG laser.

Disadvantage

However, laser treatment is more complex and costly than electrosurgery or cryotherapy. It needs additional training to operate the laser equipments. Larger lesions and some patients (especially children) may require general anesthesia.As HPV DNA may be released during

laser vaporization of genital HPV infected lesions; there is more chance to infect the operator. Risk factors for transmission of genital warts by vaporization are the HPV type, thickness of the skin and viral burden. The risk of scarring is greater than in cryotherapy.

Clinical efficacy

The efficacy of laser treatment ranged from 23% to 52% with 3-18 months follow up. Recurrence rates ranged from 60% to 77%. On comparing extensive genital warts in HIV-positive and HIV-negative patients, the clearance and recurrence rates were similar for both groups. In some rare cases of inter-anal warts located closely to the linea dentata, some invasive methods have been described such as loop colostomy. The purpose of these techniques is to minimize the contamination over the linea dentate.

VACCINATION

Papilloma viruses are difficult to reproduce under in vitro conditions, so generation of a "normal" vaccine is impossible. Vaccine can be prophylactic or therapeutic. Vaccine preparation based on generation of virus-like particles (VLP), which are recombinant version of major capsid protein of relevant HPV types. Antibodies formed

against VLP are neutralizing antibodies which are seen in sufficient titre in genital secretion which can protect from HPV infection[53]. The VLP lack nucleic acid and are thus incapable of replication and are non infectious.

Bivalent vaccines contain, virus like particles of HPV 16 and 18 types. Bivalent vaccine offer protection against cervical intraepithelial neoplasia. The tetravalent vaccine contains virus like particles of 16,18,6 and 11 types and therefore, it additionally protects against condylomata accuminata.

The bivalent vaccine contains, in the form of adjuvant not only aluminium salts but also ASO4 (monophosphoryl lipid A). This ingredient is purposed to intensify the immune response. ASO4 is able to induce higher antibody titer levels on one side and on the other side have longer persistence in patient's serum in contrast to a similar vaccine containing aluminum salts only.

The recommendations concerning vaccination of bi and tetravalent vaccines are approximately similar. Regarding the bivalent vaccine, triple intramuscular application of 0 and 1 and 2 months is recommended, and regarding the tetravalent vaccine 0, 2 and 6th month application is recommended. The single vaccination dose contains 0.5 ml or 20-40 μg of antigen of the respective virus-like particles.

The tetravalent vaccination against HPV 6, 11, 16 and 18 (Gardasil™) is the most popular one.

Therapeutic vaccine

Although neutralizing antibodies produced against VLP can prevent the disease but cannot alter the course of the disease, for which it needs cell mediated immune response.

Other therapeutic vaccines for the treatment of genital warts are fusion protein vaccines[54], but its clinical efficacy is less. The concept of so called chimeric vaccines, that is VLP with addition of an early protein[55] theoretically has both therapeutic and prophylactic function.

PARTNER MANAGEMENT

Current partners and if advisable, other partners within the past 6 months should be assessed for the presence of lesions and for education and counselling about STDs and their prevention.

PREVENTION

Regular use of condom can reduce the risk of acquiring genital warts[56].The use of condom not only during treatment, but three months after post treatment can prevent transmission as well as recurrence. However there is no scientific justification regarding this statement.

PROBLEMATIC GROUPS OF PATIENTS AND SUPPLEMENTARY THERAPEUTIC ALTERNATIVES

The fact that podophyllotoxin, interferon α, and imiquimod are contraindicated during pregnancy must be considered. Their side effects such as intrauterine death and the appearance of different malformations (podophyllotoxin) are the basis of this contraindication. The application of highly concentrated (85%) trichloracetic acid is a good therapeutic alternative during pregnancy. In case of strong pains and concerns of overdosing, rapid neutralization is possible with sodium bicarbonate.

The second problematic groups are children infected during birth by HPV 6, 11 and in rare occasions by HPV 16, 18, 31 and 35 viral strains. Cryosurgery, electrodessication and laser ablation under a short incubation narcosis are suitable options for this group of patients.

Therapy of patients suffering from AIDS and transplant recipients is frequently difficult but rarely ineffective. The reason is in the multifocal invasion of the lesions due to the weakened T-cell immunity. Because of this weakness, recurrences frequently arise. Surgical removal followed by prophylaxis with cidofovir/interferon gel provides promising results.

AIM OF STUDY

To study the prevalence of HPV infection in HIV infected and NON HIV infected individuals and to analyse the different treatment modalities.

OBJECTIVES

- To study the prevalence of HIV infection among STD male OPD attendees
- To study the prevalence of genital wart among STD male OPD attendees
- To study the prevalence of genital wart among HIV Non infected individuals attending STD male OPD.
- To study the prevalence of genital wart among HIV infected individuals attending STD male OPD.
- To analyse the different treatment modalities and responses on exophytic anogenital wart those attending STD male OPD.
- To compare the different treatment modalities and responses on exophytic anogenital wart among HIV Non infected individuals and HIV infected individuals those attending STD male OPD
- To find out the difficulties in managing the patients with genital wart.

MATERIALS AND METHODS

A screening of HPV infection among male patients who attended Institute of Venerology, Government General Hospital, Chennai, during the period between June 2007 - May 2009, was conducted by means of history taking and clinical examination to find out Anogenital wart and HIV screening by ELISA method was done in this study after giving the pretest counselling. CD 4+ count was done in the patients with HIV and genital wart. Blood VDRL and routine laboratory investigations were also done.

Among the screened population a total of 98 male Anogenital wart patients were enrolled in randomized open clinical trial to analyse the different modalities of treatment response on exophytic Anogenital wart. Random selection was based on the day treatment was started, i.e on Mondays 20% podophyllin with tincture benzoin solution, on Tuesdays 80% w/v trichloroacetic acid, on Wednesdays 5% imiquimod cream, on Thursdays liquid nitrogen and on Saturdays electrocautery therapy.

Patients treated on Mondays were taken as study group I, similarly on Tuesdays, Wednesdays, Thursdays and Saturdays were taken as study group III, IV, II and V respectively.

After getting informed consent, pre treatment counselling regarding the nature of the disease, its transmission, spontaneous regression and recurrence was given to those patients included in the study. Examination and treatment was given in examination couch in lying position.

MATERIALS

THE FOLLOWING TREATMENT MODALITIES WERE APPLIED FOR ANALYTICAL STUDY ON EXOPHYTIC ANOGENITAL WART

Five types of treatment modalities were taken for this study. They were 20% podophyllin in 10% tincture benzoin solution, liquid nitrogen, 80% w/v trichloroacetic acid solution, 5%imiquimod cream and electrocautery. Each therapy was given a maximum of 6 sittings except 5% imiquimod cream which was given a maximum of 10 sittings. Interval between each sitting was 1 week except liquid nitrogen which was given at an interval of 2 weeks.

Patients were instructed to attend the STD OPD whenever he developed local or systemic discomfort. Here the common local side effects like itching, burning, erythema, pain, tenderness and erosion was considered as local acceptable (LA) side effects. Those who developed side effects like swelling, ulcer, necrotising balanoposthitis and phimosis were considered as local but not acceptable (LNA) side effects.

Patient's clinical responses were calculated as follows

GRADE A - Lesions completely resolved.

GRADE B - Lesions reduced in size but not completely resolved.

GRADE C - Lesions not responding to treatment even after completion of treatment.

DCT - Treatment discontinued.

Patients with GRADE A responses were considered as treatment success .If lesions did not respond to treatment or partially resolve even after 6 sittings (except 5% imiquimod) or patients who developed any local but not acceptable side effects or systemic side effects, their therapeutic modality was changed (TC). Patients who had partially resolved or not responding to treatment even after the completion of

their treatment after maximum period was considered as treatment failed. Patients whose treatment were changed during the course of treatment period for any reason (for example patient those who developed local but not acceptable level of side effects) are also considered as treatment failed. Patients who developed local but not acceptable side effects, their treatment were changed after curing their ill effects. Patients who were not coming for treatment during the course was considered as treatment discontinued (DCT). Anytime after the clearance of wart, Patients those who developed the lesion over the already resolved site were taken as recurrences. Treatment was changed for recurrent lesions. Patient was instructed to come to STD OPD whenever he developed new or recurrent lesions, others were instructed to attend STD OPD for follow up for after 3 months. Those who were not coming for follow up were considered as follow up failed.

1. 20% podophyllin in 10% tincture benzoin solution: After obtaining investigation reports, on every Monday, 0.3 ml of 20% podophyllin in 10% tincture benzoin was applied with cotton tipped swab once a week for a maximum of 6 weeks and the surrounding skin was covered with zinc oxide cream. Patients were instructed to wash the genitalia after 4 hrs. If there was no problem, the patients were

instructed to be reviewed on every Mondays for 7 weeks from the starting date of treatment and patients were instructed to attend the STD OPD whenever he developed local or systemic discomfort. For every patient separate podophyllin containers was used.

2. LIQUID NITROGEN: Liquid nitrogen applied by cotton wool swab on orange sticks dipped in liquid nitrogen on the warts once in alternative Thursdays, by double freeze – thaw cycles technique which consisted of one sitting. Like this, a maximum of 6 sittings were applied. Tissues were held frozen for 15 and 30 seconds. Adequacy of freezing was assessed by formation of ice ball 1-2 mm beyond the periphery of the lesion. If there was no problem, patients were instructed to review on the alternative Thursdays for 7 sittings from the starting date of the treatment and patients were instructed to attend the STD OPD whenever he developed local or systemic discomfort. For every patient and for every cycle, separate sticks were used.

3. 80% W/V TRICHLOROACETIC ACID SOLUTION: 80% w/v trichloroacetic acid in water was applied once on every Tuesdays for a maximum of 6 weeks, by using wooden applicator stick with the surrounding skin protected with zinc oxide cream. Patients were reviewed on every Tuesdays if there was no problem. Patients

were instructed to attend the STD OPD whenever he developed local or systemic discomfort. For every patient, separate sticks was used.

4. 5 % IMIQUIMOD: 5% imiquimod cream was applied by the patient himself as a thin layer of cream (by using digits) and three times in a week (Wednesday/Friday/Sunday) preferably at night times for a maximum of 10 weeks. The first application was done in the OPD itself. On Wednesdays 3 sachets (5%imiquimod cream) was given. Each sachet for every other day. Patients were instructed to wash imiquimod applied area with soap and water after 10 hours and patients were reviewed once every Wednesday if there was no problem. Patients were instructed to attend the STD OPD whenever he developed local or systemic discomfort.

5. ELECTROCAUTERY: 1 hr after the application of topical EMLA, electro cautery was done. Patients with GRADE A response to treatment were considered as treatment success. A patient whose responses to treatment were GRADE B, GRADE C or development of any local but not acceptable side effects or systemic side effects; for those patients therapeutic modality was changed. Patients, whose treatment was changed during the course of treatment, were considered as treatment failed.

RESULTS

TABLE 1

TOTAL PREVALENCE OF ANOGENITAL WART AND HIV INFECTION AMONG STD MALE OPD ATTENDEES FOR THE PERIOD OF JUNE 2007 – MAY 2009

- The Prevalence of Anogenital wart among STD male OPD attendees– 1.91%
- The Prevalence of HIV infection among STD male OPD attendees of– 2.69%

TABLE 2

PREVALENCE OF WART IN HIV INFECTED AND HIV NON INFECTED

- The Prevalence of HIV infected with Anogenital warts among STD male OPD attendees - 13.14%
- The Prevalence of HIV Non infected with Anogenital warts among STD male OPD attendees -1.60**%**
- Prevalence of genital wart is 8.2 times higher among HIV infected patients when compared to HIV Non infected patients.

TABLE 3

COMPARISON OF PROPORTION OF TREATMENT RESPONSE AT THE END OF THE TREATMENT AMONG DIFFERENT STUDY

- Complete clearance of warts (GRADE A response) is highest among study Group V (ELETROCAUTERY) followed by study group II, I, III and IV.

TABLE 4

COMPARISON OF PROPORTION OF TREATMENT RESPONSE AFTER 3 MONTHS AMONG DIFFERENT STUDY GROUPS

- Recurrence rate after 3 month of treatment is lowest among Group V followed by Group II, IV, I and III.
- Complete clearance after 3 month of treatment is highest among Group V followed by Group II, III, I and IV

TABLE 5

COMPARISON OF PROPORTION OF SIDE EFFECTS AMONG DIFFERENT STUDY GROUPS

- Patients complete their treatment without side effects seen highest among study group IV followed by group II, III, V and I.
- Patients complete their treatment with local acceptable side effects seen highest among study group I followed by group III, V, II and IV.
- Patients complete their treatment with local but not acceptable side effects seen only with group II.

TABLE 6

COMPARISON OF PROPORTION OF HIV STATUS AMONG DIFFERENT STUDY GROUPS

- Almost all study group had equal number of HIV infected cases.

TABLE 7

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP I

- Complete clearance of the warts (Grade A response) with podophyllin (Group I) among HIV infected and HIV Non infected cases were 80% and 77.8% respectively. i.e almost equal.

TABLE 8

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP II

- Complete clearance of the warts (Grade A response) with liquid nitrogen (Group II) among HIV infected and HIV Non infected were 75% and 81.3% respectively. i.e almost equal.

TABLE 9

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP III

- Complete clearance of warts (Grade A response) with 80%TCA (Group III) among HIV infected and HIV Non infected cases were 100% and 68.8% respectively.

TABLE 10

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP IV

- Complete clearance of the warts (Grade A response) with 5%imiquimod (Group IV)among HIV infected and HIV Non infected cases were 50% and 45.5% respectively**.** i.e,almost equal.

TABLE 11

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP V

- Complete clearance of the warts (Grade A response) with ECT (Group V) among HIV infected and HIV Non infected cases were 75% and 100% respectively.

TABLE 12

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP I

- Clearance rate after 3 month of treatment with podophyllin (Group I) among HIV infected and HIV Non infected cases were 40% and 44.4% respectively. i.e, almost equal.

TABLE 13

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP II

- Clearance rate after 3 month of treatment with liquid nitrogen(Group II) among HIV infected and HIV Non infected cases were 25% and 56.3% respectively.

TABLE 14

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP III

- Clearance rate after 3 month of treatment with 80%TCA(Group III) among HIV infected and HIV Non infected cases were 50% and 46.7%respectively.i.e, almost equal.

TABLE 15

COMPARISON OF PROPOFORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP IV

- Clearance rate after 3 month of treatment with5%imiquimod (Group IV) among HIV infected and HIV Non infected cases were 50% and 10% respectively.

TABLE 16

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP V

- Clearance rate after 3 month of treatment with ECT(Group V) among HIV infected and HIV Non infected cases were 50% and 93.8% respectively.

TABLE 17

COMPARISON OF MEAN RESPONSE DURATION AMONG DIFFERENT STUDY GROUPS

- Among all study groups, ECT (Group V) takes minimal duration(**1.8 ± 0.8)** of time for the complete clearance of the warts.

RESULTS

TABLE 1

TOTAL PREVALENCE OF ANOGENITAL WART AND HIV INFECTION

Condition	Total Number	Number Positive	Prevalence (%)
Wart	6504	124	1.91
HIV	6504	175	2.69

TABLE 2

PREVALENCE OF WART IN HIV INFECTED AND NON HIV INFECTED CASES

	Total Number	Number Positive	Prevalence (%)	P-Value*
HIV +ve	175	23	13.14	<0.0001 (Sig.)
HIV -ve	6329	101	1.60	

*Fisher's Exact Test (2-tailed) was used to calculate the P-value

INFERENCE

The prevalence of wart in HIV infected cases (13.14%) is significantly higher than in Non HIV infected cases (1.60%) ($P<0.0001$).

TABLE 3

COMPARISON OF PROPORTION OF TREATMENT RESPONSE AT THE END OF THE TREATMENT AMONG DIFFERENT STUDY GROUPS

Rx Response	Group I		Group II		Group III		Group IV		Group V		P-value*
	No	%	No	%	No	%	No	%	No	%	
Grade - A	18	78.3	16	80.0	15	75.0	7	46.7	19	95.0	0.03 (Sig.)
Grade - B	1	4.3	3	15.0	4	20.0	6	40.0	1	5.0	
Grade - C	4	17.4	1	5.0	0	0.0	1	6.7	0	0.0	
DCT	0	0.0	0	0.0	1	5.0	1	6.7	0	0.0	

***Chi-square test was used to calculate the P-Value**

INFERENCE

There is significant association between response to treatment and different study groups (P=0.03). That is, the distribution of response to treatment is not similar in all study groups.

TABLE 4

COMPARISON OF PROPORTION OF TREATMENT RESPONSE AFTER 3 MONTHS AMONG DIFFERENT STUDY GROUPS

Rx Response	Group I		Group II		Group III		Group IV		Group V		P-value*
	No	%	No	%	No	%	No	%	No	%	
FF	1	4.3	1	5.0	0	0.0	0	0.0	1	5.0	0.09 (N.S.)
NOR	10	43.5	10	50.0	9	47.4	3	21.4	17	85.0	
RO	7	30.4	5	25.0	6	31.6	4	28.6	1	5.0	
TC	5	21.7	4	20.0	4	20.0	7	50.0	1	5.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment at the end of 3 months and different study groups (P=0.09). That is, the distribution of response to treatment at the end of 3 months is almost similar in all study groups.

TABLE 5

COMPARISON OF PROPORTION OF SIDE EFFECTS AMONG DIFFERENT STUDY GROUPS

Side effect	Group I		Group II		Group III		Group IV		Group V		P-value*
	No	%	No	%	No	%	No	%	No	%	
LA+	20	87.0	11	55.0	16	80.0	7	50.0	16	80.0	0.01 (Sig.)
LNA+	0	0.0	3	15.0	0	0.0	0	0.0	0	0.0	
NIL	3	13.0	6	30.0	4	20.0	7	50.0	4	20.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is significant association between side effect and different study groups (P=0.01). That is, the distribution of side effect is not similar in all five study groups.

TABLE 6

COMPARISON OF PROPORTION OF HIV STATUS AMONG DIFFERENT STUDY GROUPS

HIV status	Group I		Group II		Group III		Group IV		Group V		P-value*
	No	%	No	%	No	%	No	%	No	%	
NR	18	78.3	16	80.0	16	80.0	11	73.3	16	80.0	0.99 (N.S.)
R	5	21.7	4	20.0	4	20.0	4	26.7	4	20.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between HIV status and different study groups (P=0.99). That is, the distribution of HIV status is almost similar in all five study groups.

TABLE 7

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP I

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
Grade - A	14	77.8	4	80.0	0.86 (N.S.)
Grade - B	1	5.6	0	0.0	
Grade - C	3	16.7	1	20.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment and HIV status in Group I (P=0.86). That is, the distribution of response to treatment in both HIV status is almost similar in Group I.

TABLE 8

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP II

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
Grade - A	13	81.3	3	75.0	0.74 (N.S.)
Grade - B	2	12.5	1	25.0	
Grade - C	1	6.3	0	0.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment and HIV status in Group II (P=0.74). That is, the distribution of response to treatment in both HIV status is almost similar in Group II.

TABLE 9

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP III

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
Grade - A	11	68.8	4	100.0	0.44 (N.S.)
Grade - B	4	25.0	0	0.0	
Grade - C	0	0.0	0	0.0	
DCT	1	6.3	0	0.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment and HIV status in Group III (P=0.44). That is, the distribution of response to treatment in both HIV status is almost similar in Group III.

TABLE 10

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP IV

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
Grade - A	5	45.5	2	50.0	0.83 (N.S.)
Grade - B	4	36.4	2	50.0	
Grade - C	1	9.1	0	0.0	
DCT	1	9.1	0	0.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment and HIV status in Group IV (P=0.83). That is, the distribution of response to treatment in both HIV status is almost similar in Group IV.

TABLE 11

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AND HIV STATUS IN GROUP V

Rx Response	HIV - NR		HIV – R		P-value#
	No	%	No	%	
Grade - A	16	100.0	3	75.0	0.20 (N.S.)
Grade - B	0	0.0	1	25.0	
Grade - C	0	0.0	0	0.0	

#Fisher's Exact test (2-tailed) was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment and HIV status in Group V (P=0.20). That is, the distribution of response to treatment in both HIV status is almost similar in Group V.

TABLE 12

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP I

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
FF	1	5.6	0	0.0	0.92 (N.S.)
NOR	8	44.4	2	40.0	
RO	5	27.8	2	40.0	
TC	4	22.2	1	20.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment at 3 months and HIV status in Group I (P=0.92). That is, the distribution of response to treatment in both HIV status is almost similar in Group I.

TABLE 13

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP II

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
FF	1	6.3	0	0.0	0.53 (N.S.)
NOR	9	56.3	1	25.0	
RO	3	18.8	2	50.0	
TC	3	18.8	1	25.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment at 3 months and HIV status in Group II (P=0.53). That is, the distribution of response to treatment in both HIV status is almost similar in Group II.

TABLE 14

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP III

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
FF	0	0.0	0	0.0	0.58 (N.S.)
NOR	7	46.7	2	50.0	
RO	4	26.7	2	50.0	
TC	4	26.7	0	0.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment at 3 months and HIV status in Group III (P=0.58). That is, the distribution of response to treatment in both HIV status is almost similar in Group III.

TABLE 15

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP IV

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
FF	**0**	**0.0**	**0**	**0.0**	**0.23 (N.S.)**
NOR	**1**	**10.0**	**2**	**50.0**	
RO	**4**	**40.0**	**0**	**0.0**	
TC	**5**	**50.0**	**2**	**50.0**	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is no significant association between response to treatment at 3 months and HIV status in Group IV (P=0.23). That is, the distribution of response to treatment in both HIV status is almost similar in Group IV.

TABLE 16

COMPARISON OF PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS AND HIV STATUS IN GROUP V

Rx Response	HIV - NR		HIV – R		P-value*
	No	%	No	%	
FF	0	0.0	1	25.0	0.03 (Sig.)
NOR	15	93.8	2	50.0	
RO	1	6.3	0	0.0	
TC	0	0.0	1	25.0	

*Chi-square test was used to calculate the P-Value

INFERENCE

There is significant association between response to treatment at 3 months and HIV status in Group V (P=0.03). That is, the distribution of response to treatment in both HIV status is not similar in Group V.

TABLE 17

COMPARISON OF MEAN RESPONSE DURATION AMONG DIFFERENT STUDY GROUPS

Group	Mean ± S.D.	Overall P-value*	Significant groups at 5% level#
I	4.0 ± 1.6	<0.0001 (Sig.)	I vs. II, IV, V. II vs. III, V. III vs. IV, V. IV vs. V.
II	8.4 ± 1.9		
III	5.0 ± 0.9		
IV	9.1 ± 1.6		
V	1.8 ± 0.8		

*Kruskal-Wallis One Way ANOVA was used to calculate the P-value
#Mann-Whitney U test followed by Bonferroni correction procedure was employed to identify the significant groups at 5% level

INFERENCE

- The mean duration for treatment response is highest in Group IV (**9.1 ± 1.6**) followed by Group II (**8.4 ± 1.9**), Group III (**5.0 ± 0.9**), Group I (**4.0 ± 1.6**) and the lowest in Group V (**1.8 ± 0.8**).
- The mean duration for treatment response in Group IV (**9.1 ± 1.6**) is significantly higher than Group I (**1.8 ± 0.8**), Group III (**5.0 ± 0.9**) and Group V (**1.8 ± 0.8**) ($P<0.05$).
- Also The mean duration for treatment response in Group II (**8.4 ± 1.9**) is significantly higher than Group III (**5.0 ± 0.9**) and Group V (**1.8 ± 0.8**) ($P<0.05$).
- Further, The mean duration for treatment response in Group I (**1.8 ± 0.8**) and Group III (**5.0 ± 0.9**) are significantly higher than Group V (**1.8 ± 0.8**) ($P<0.05$).
- However, no other contrasts are statistically significant ($P>0.05$).

Figure No. 1

PREVALENCE OF WART AND HIV

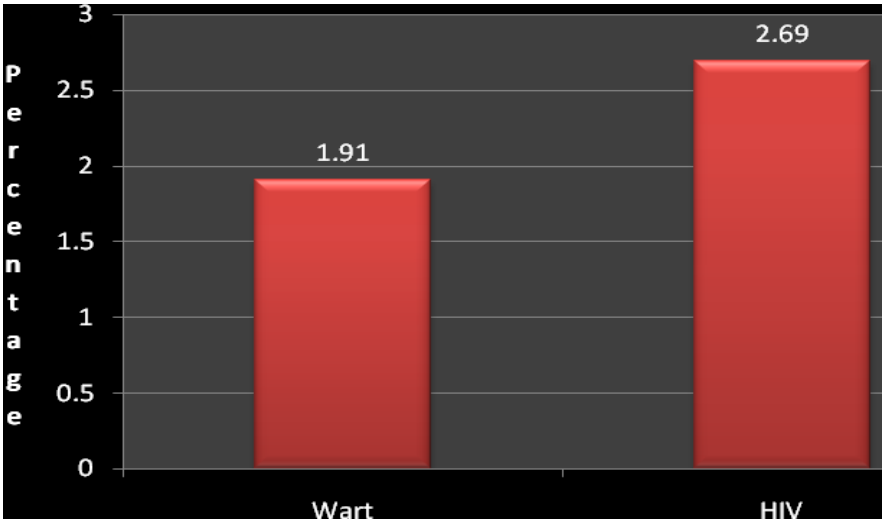


Figure No. 2

PREVALENCE OF WART IN HIV+VE AND HIV-VE CASES

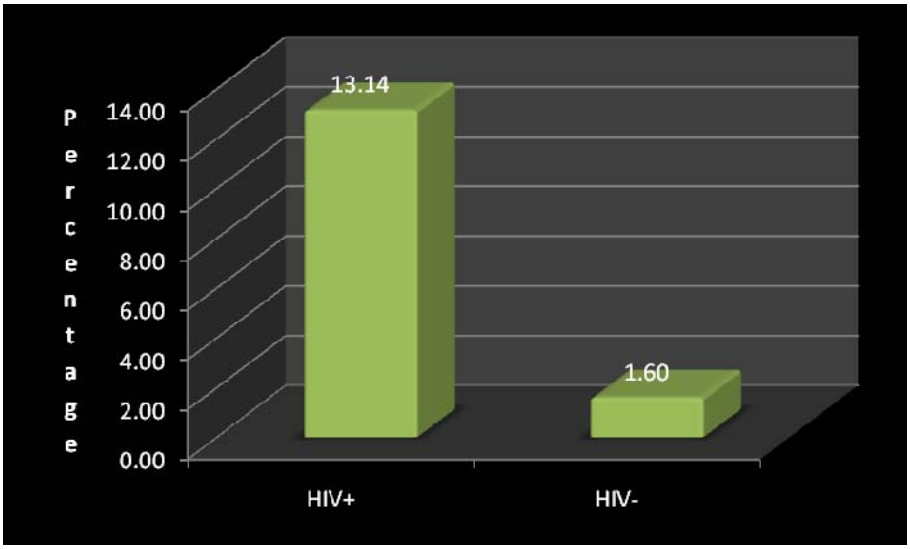


Figure No. 3

PROPORTION OF TREATMENT RESPONSE AT THE END OF THE TREATMENT IN DIFFERENT STUDY GROUPS

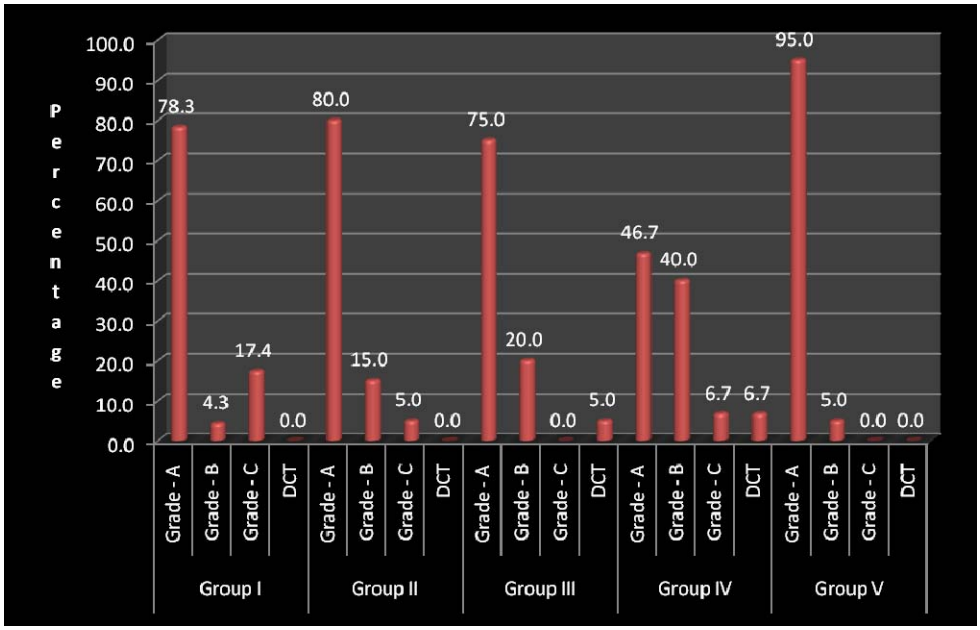


Figure No. 4

PROPORTION OF TREATMENT RESPONSE AFTER 3 MONTHS IN DIFFERENT STUDY GROUPS

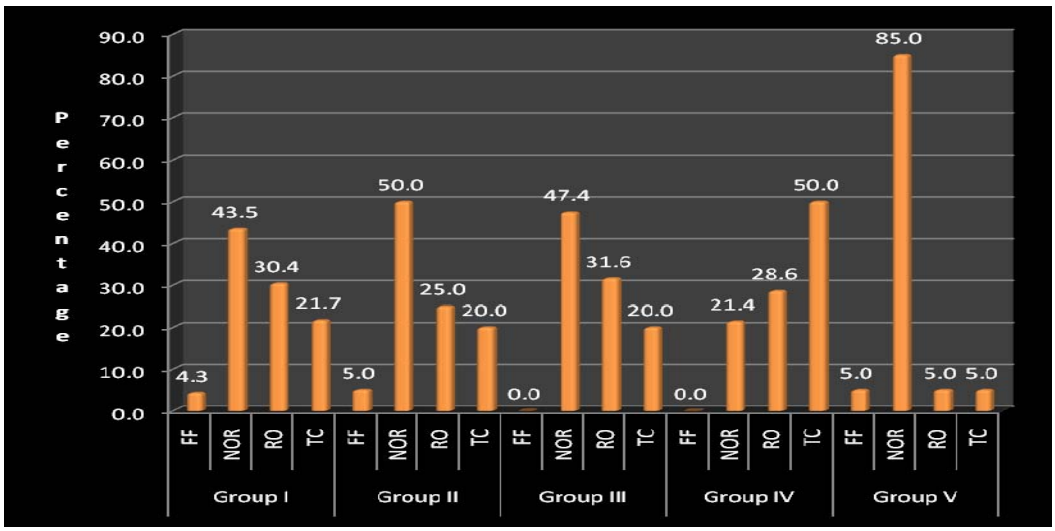


Figure No. 5

PROPORTION OF SIDE EFFECTS IN DIFFERENT STUDY GROUPS

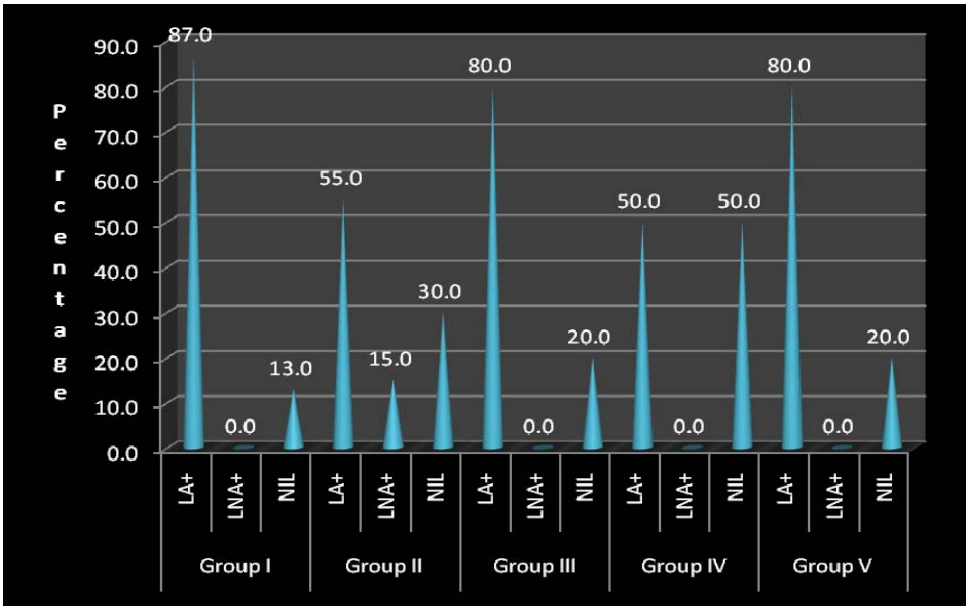


Figure No. 6

PROPORTION OF HIV STATUS IN DIFFERENT STUDY GROUPS

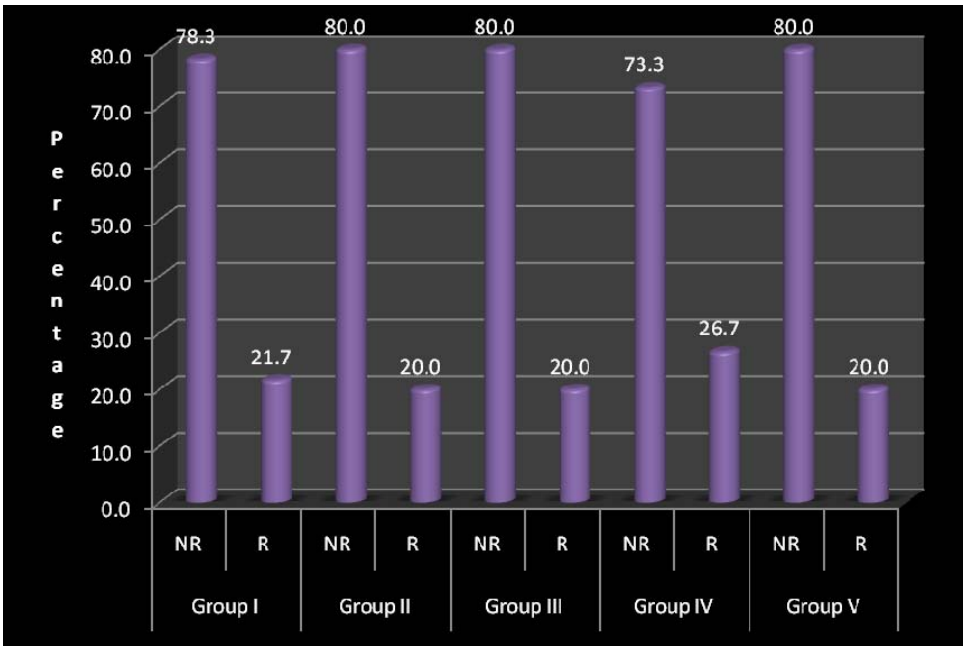


Figure No. 7

PROPORTION OF RESPONSE TO TREATMENT IN HIV-NR AND HIV-R CASES IN GROUP I

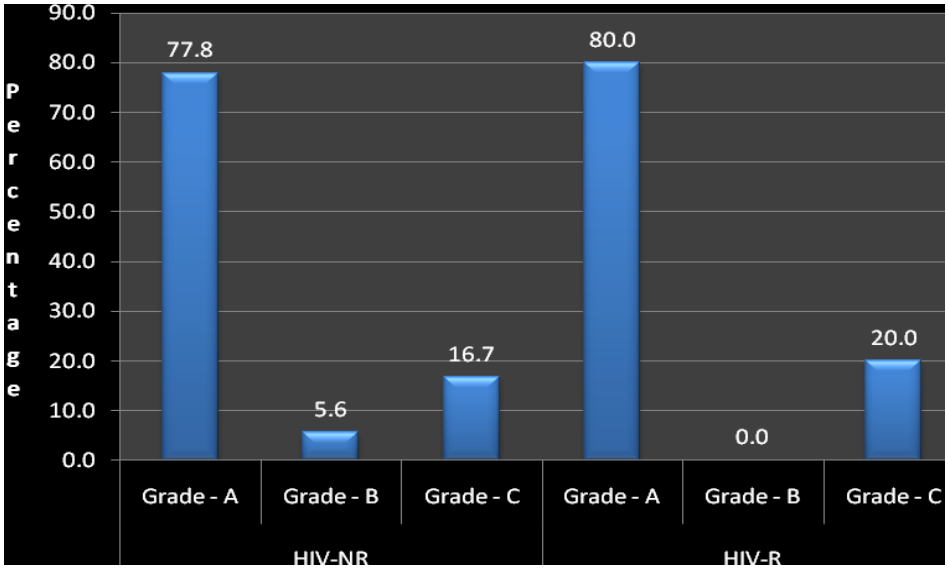


Figure No. 8

PROPORTION OF RESPONSE TO TREATMENT IN HIV-NR AND HIV-R CASES IN GROUP II

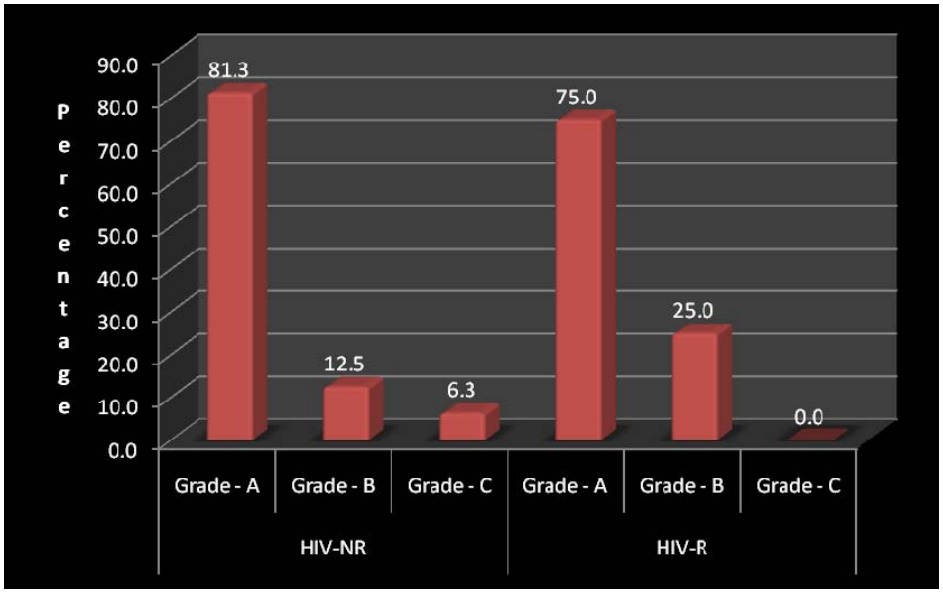


Figure No. 9

PROPORTION OF RESPONSE TO TREATMENT IN HIV-NR AND HIV-R CASES IN GROUP III

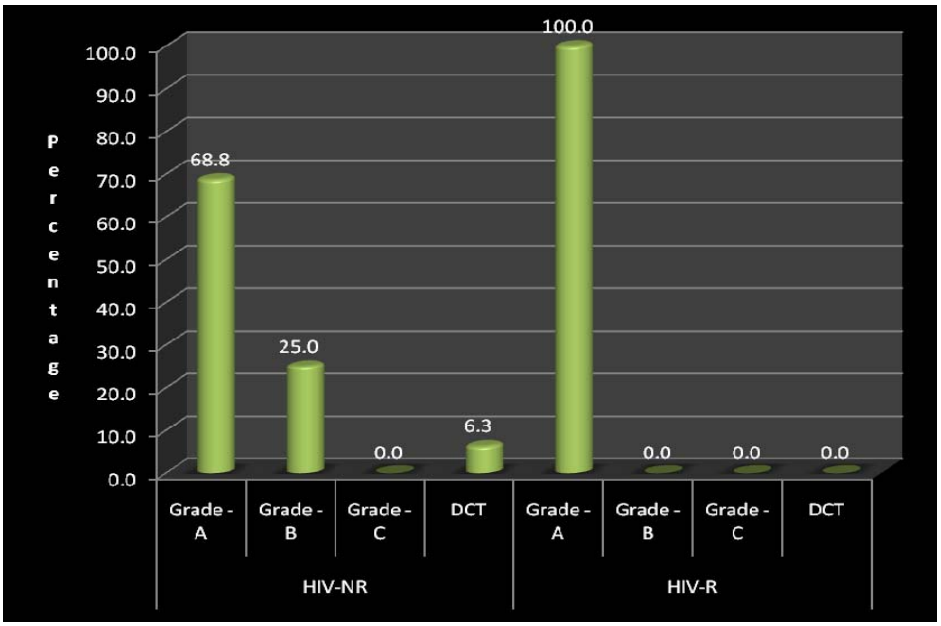


Figure No. 10

PROPORTION OF RESPONSE TO TREATMENT IN HIV-NR AND HIV-R CASES IN GROUP IV

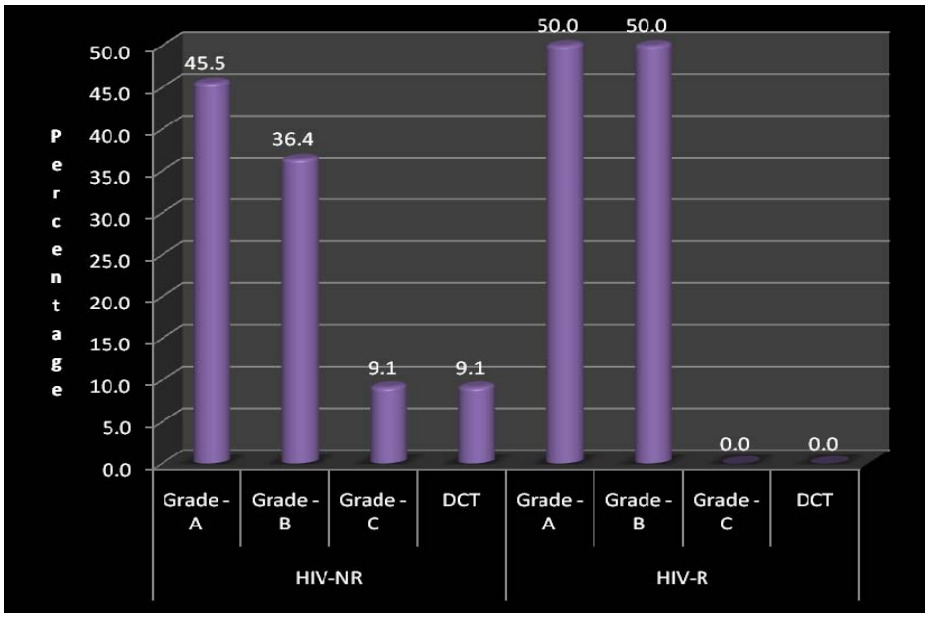


Figure No. 11

PROPORTION OF RESPONSE TO TREATMENT IN HIV-NR AND HIV-R CASES IN GROUP V

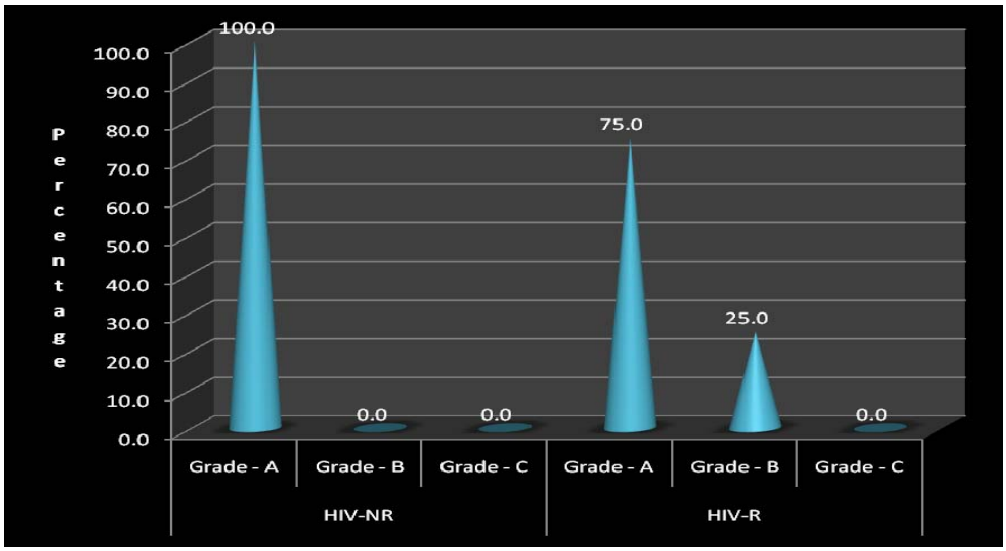


Figure No. 12

PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS IN HIV-NR AND HIV-R CASES IN GROUP I

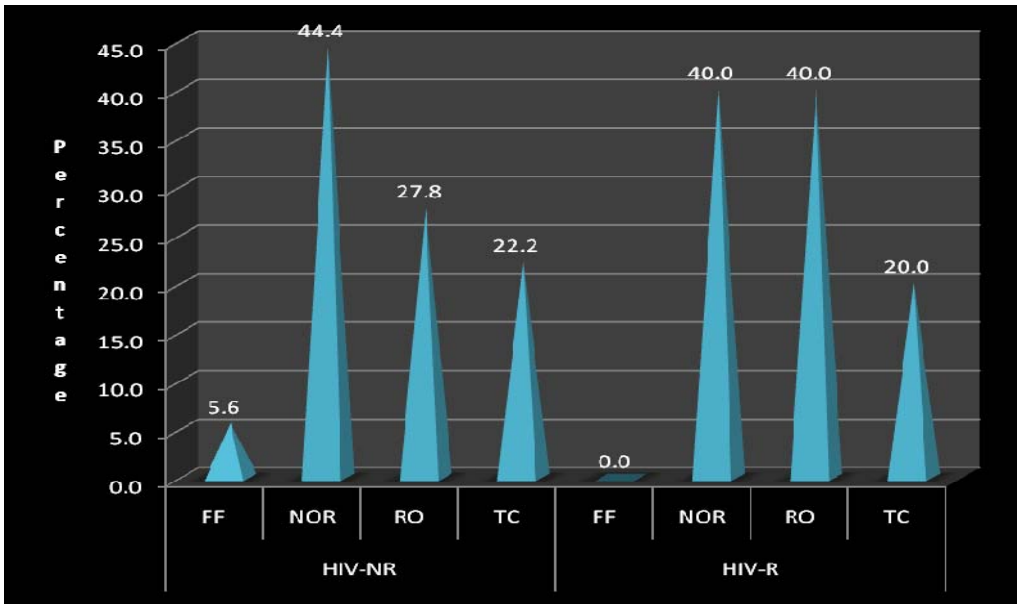


Figure No. 13

PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS IN HIV-NR AND HIV-R CASES IN GROUP II

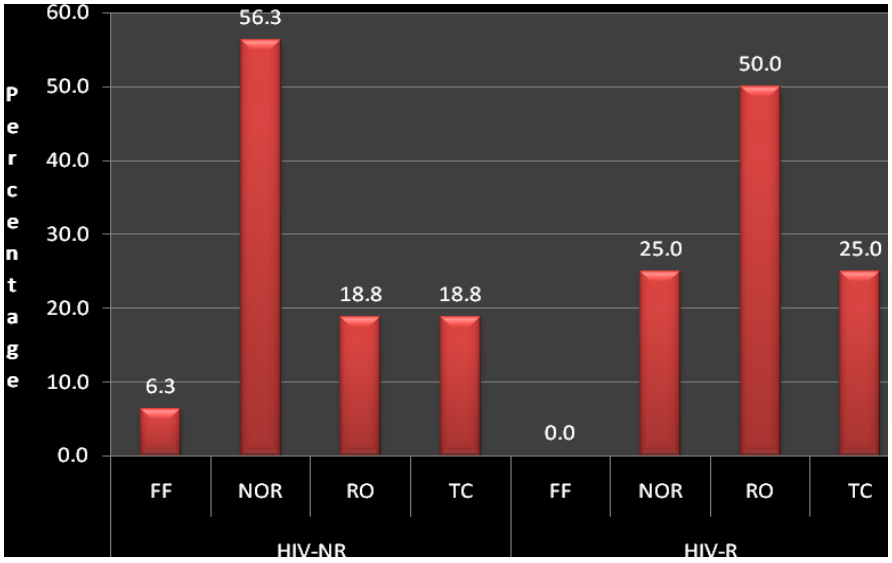


Figure No. 14

PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS IN HIV-NR AND HIV-R CASES IN GROUP III

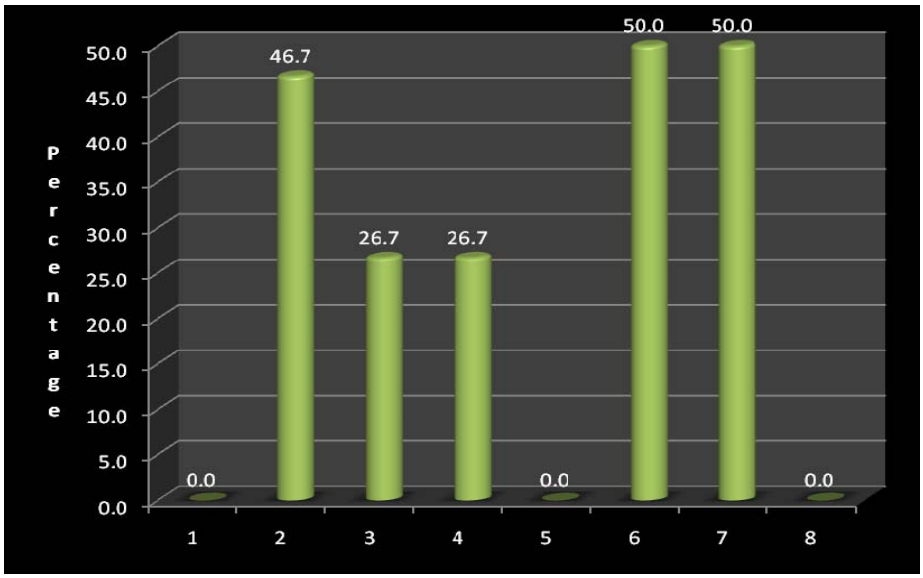


Figure No. 15

PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS IN HIV-NR AND HIV-R CASES IN GROUP IV

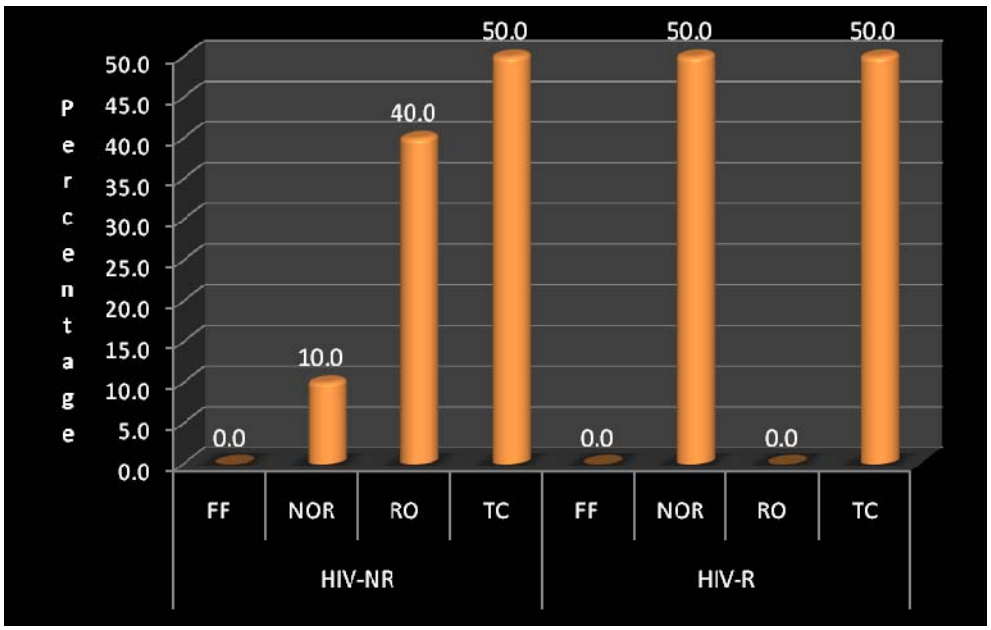


Figure No. 16

PROPORTION OF RESPONSE TO TREATMENT AT THE END OF 3 MONTHS IN HIV-NR AND HIV-R CASES IN GROUP V

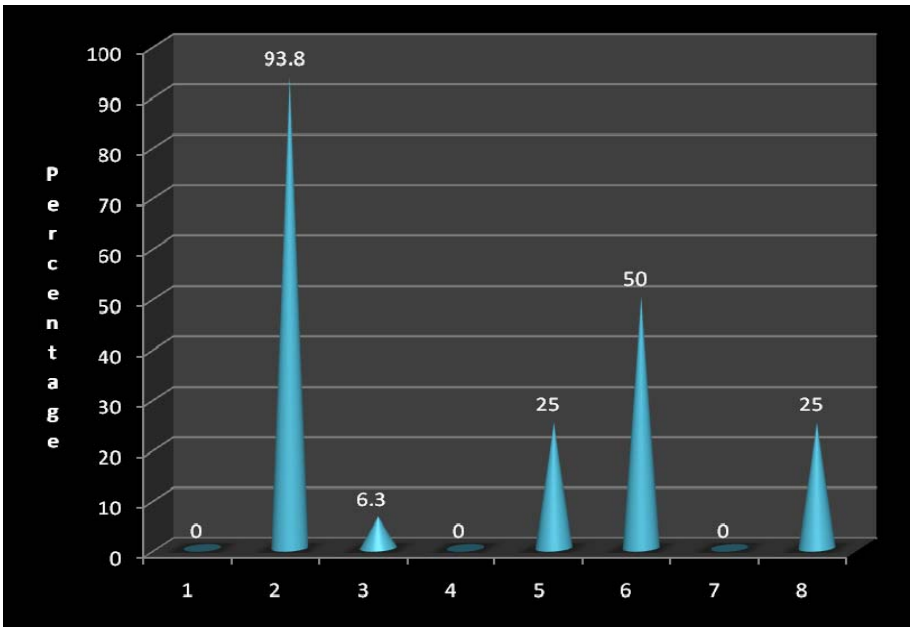
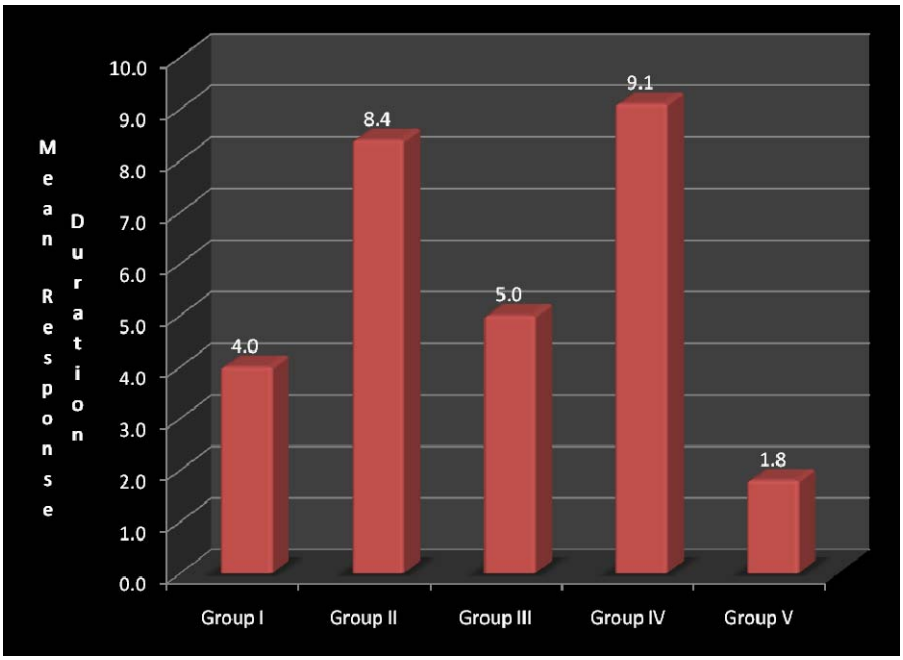
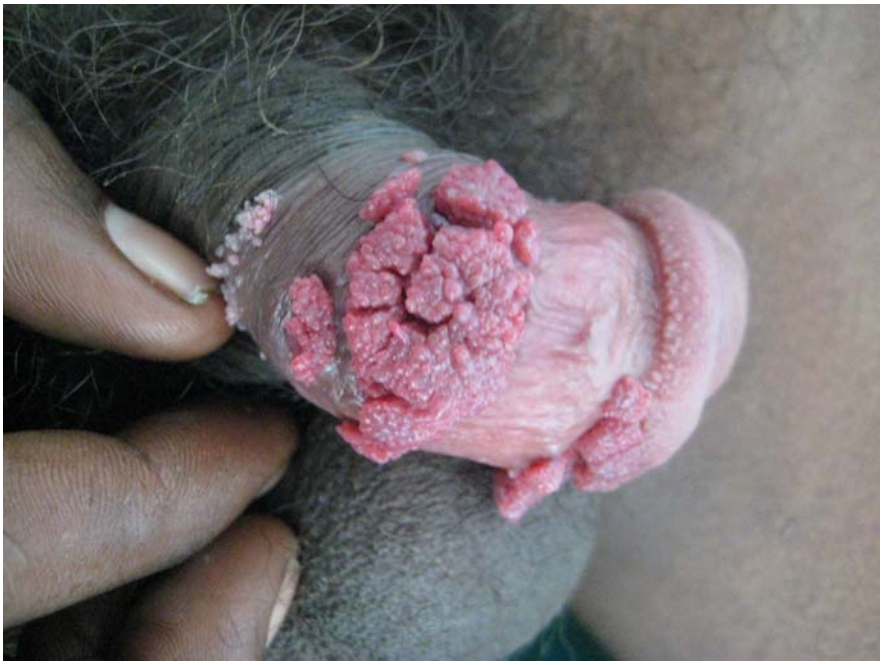


Figure No. 17

MEAN RESPONSE DURATION IN DIFFERENT STUDY GROUPS



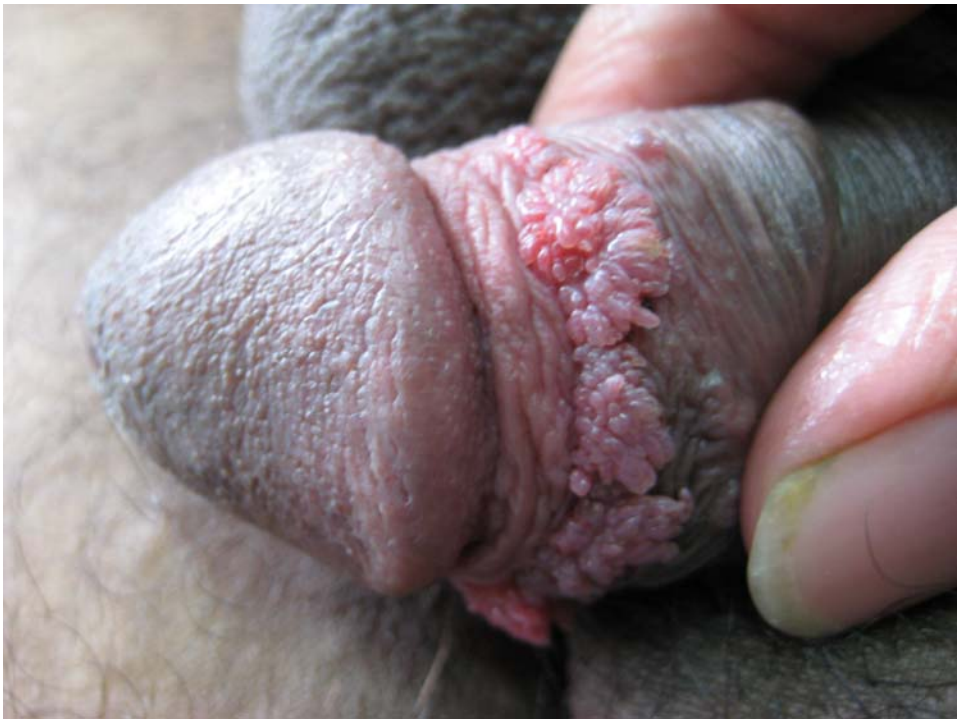


CONDYLOMATA ACUMINATA

RESOLVING GENITAL WARTS (TREATED WITH PODOPHYLLIN)

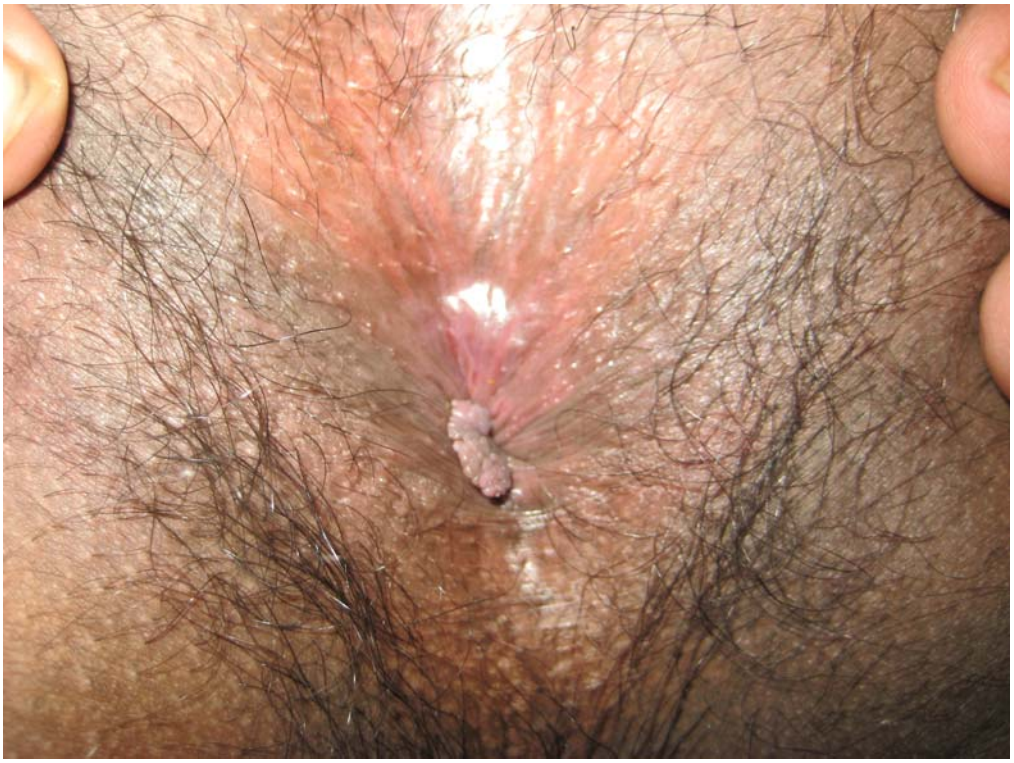
GENITAL WARTS (Inner lining of prepuce)

GENITAL WARTS IN PREPUTIAL CAVITY



GENITAL WARTS IN INNER LINING OF PREPUCE

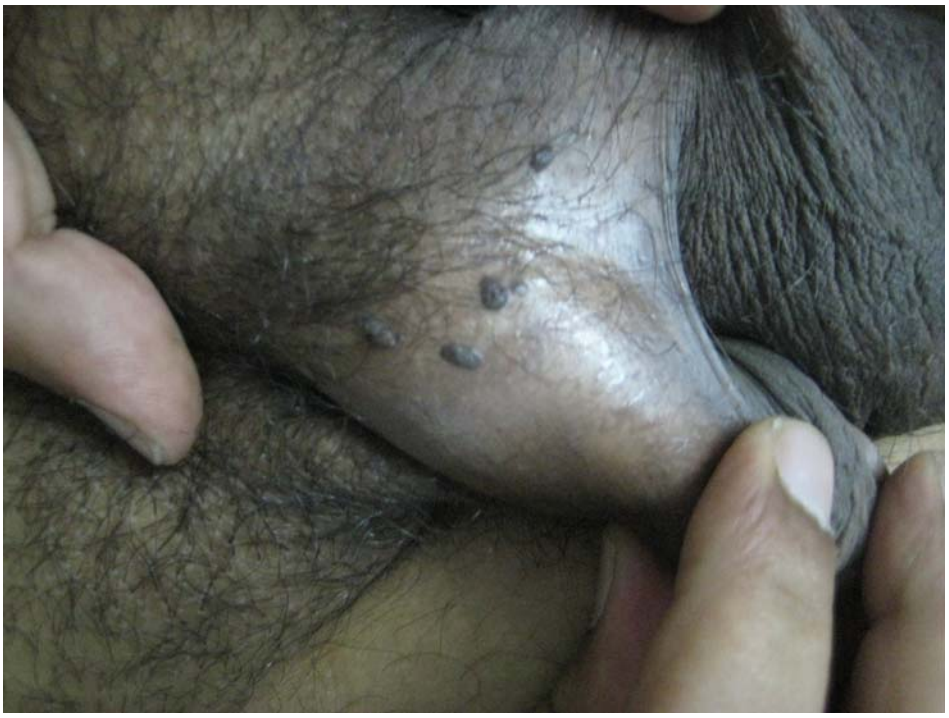
GENITAL WARTS IN THE GROIN REGION



PERIANAL WARTS

CONDYLOMATA ACUMINATA

GENITAL WARTS (PAPULAR TYPE)



GENITAL WARTS (ROOT OF THE PENIS)

DISCUSSION

This study highlights the prevalence of Anogenital wart, prevalence of HIV infection and different treatment modalities and treatment responses on exophytic anogenital wart among the patients who attended STD male OPD.

During the period of 2 yrs from June 2007 – May 2009, total number of patients who attended STD male OPD were 6504 which included both NON HIV and HIV infected individuals. Out of 6504 patients 1.91% and 2.69% were infected with genital wart and HIV respectively. A recent study shows the prevalence of genital warts in India to be between 5.1% to 25.2% of STD patients.

Among the male NON HIV infected individuals 1.60% of 6329 patients had genital wart and among the male HIV infected individuals 13.14% of 175 patients had genital wart. Prevalence of genital wart was 8.2 times higher among HIV infected patients when compared to HIV Non infected patients. This was comparable with a report by Arora et al incidence of Anogenital warts have increased from 7.2% to 8.8% among the HIV infected patients over a period of 5 years.

98 (79%) of 124 genital wart patients were enrolled in the randomised open clinical trial on different treatment modalities and treatment response on exophytic genital wart. Among the 98 patients with genital wart 23, 20, 20, 15 and 20 patients were treated with podophyllin(groupI),liquidnitrogen(groupII) trichloroaceticacid (groupIII),imiquimod(groupIV) and electrocautery (groupV) respectively and their grade A response(complete clearance of wart) at the end of the treatment were78.3%, 80%, 75%, 46.7% and 95% respectively. Study GroupV shows good response followed by groupII, groupI, groupIII, groupIV in descending order. Their recurrence rate after 3 months of treatment were 30.4%,25%,31.6%,28.6% and 5% respectively. Once again it shows study groupV have good response followed by groupII, groupIII, groupI and groupIV in descending order. This study shows electrocautery therapy and cryotherapy are more efficacious than other modalities.

On comparing the side effects, irrespective of their clearance rate in all study group most of them developed local acceptable side effects (70%). Few patients complete their treatment without any side effects. But 15% of patients in study group II show local but not acceptable side effects whereas other study group did not develop local but not

acceptable side effects. None of the study group developed systemic side effects.

This study was comparable with the study done by Beutner KR, Wiley D J et at. In their study, they compared the efficacy of podophyllin, liquid nitrogen, trichloroacetic acid and electrocautery. As per their study, efficacy of therapy at the end of the treatment and recurrence rate were 32-79%, 63-88%, 50-81%, 93-94% and 11-65%, 0-39%, 36%,24% respectively. According to their study electrocautery and cryotherapy were more efficacious than other modalities.

When compared with a randomised clinical trial by K M Stone, T M Becker, A Hadgu, S J Kraus on Treatment of external genital warts using podophyllin, cryotherapy, and electro desiccation the following were noted**.** In their study, four hundred and fifty patients were enrolled into a randomised clinical trial in a public sexually transmitted diseases clinic to evaluate the efficacy of podophyllin, cryotherapy, and electro desiccation for treatment of external genital warts. Complete clearance of warts was observed in 41%, 79% and 94% of patients who received up to six weekly treatments of podophyllin, cryotherapy and electro desiccation respectively. Relapses occurred in 25% of all patients, yielding 3 month clearance rates of 17%, 55% and 71% for podophyllin, cryotherapy and electro desiccation respectively. Wart volume and

duration did not influence treatment outcome. Electro desiccation and cryotherapy were more effective than podophyllin for the treatment of external genital warts.

Statistically, there is a significant association between response to treatment and different study groups (P=0.03). That is, the distribution of response to treatment is not similar in all study groups but there is no significant association between response to treatment at the end of 3 months and different study groups (P=0.09). That is, the distribution of response to treatment at the end of 3 months is almost similar in all study groups. There is significant association between side effect and different study groups (P=0.01). That is, the distribution of side effect is not similar in all five study groups.

In this study, all study groups had HIV patients almost equally. When compared to the treatment response at the end of the treatment among HIV Non infected and HIV infected patients in study group I shows response to treatment in was almost similar that is complete clearance of wart HIV Non infected and HIV infected were 77.8% and 80% respectively. In the study, group II showed almost similar response to treatment that is complete clearance of wart in both HIV Non infected and HIV infected were 81.3% and 75% respectively. Similarly study groupIII, IV, V showed almost similar response to treatment at the end

of treatment for both HIV Non infected and HIV infected patients. But treatment response after 3 month in both HIV Non infected and HIV infected patients were almost similar in all study group except study group V (ECT) where the complete clearance of the wart at end of 3 month were 93.8% among HIV non reactive and 50% among HIV infected patient which is statistically significant.($p = 0.03$)

The mean duration for treatment response is highest in Group IV (9.1 ± 1.6) followed by Group II (8.4 ± 1.9), Group III (5.0 ± 0.9), Group I (4.0 ± 1.6) and the lowest in Group V (1.8 ± 0.8).

The mean duration for treatment response in Group IV (9.1 ± 1.6) is significantly higher than Group I (1.8 ± 0.8), Group III (5.0 ± 0.9) and Group V (1.8 ± 0.8) ($P<0.05$).

Also the mean duration for treatment response in Group II (8.4 ± 1.9) is significantly higher than Group III (5.0 ± 0.9) and Group V (1.8 ± 0.8) ($P<0.05$).

Further, The mean duration for treatment response in Group I (1.8 ± 0.8) and Group III (5.0 ± 0.9) are significantly higher than Group V (1.8 ± 0.8) ($P<0.05$).

It shows that study group V had favorable outcome with in short period followed by group I and III.

CONCLUSION

This study was conducted for a period of 2 years from June 2007 to May 2009 in those patients who attended STD male OPD in Institute of Venereology, Madras Medical College, Chennai. This study showed the prevalence of genital warts among the STD male OPD attendees to be 1.91%. The prevalence of HIV infection among STD male OPD attendees was 2.69%. The prevalence of genital warts was 8.2 times higher among HIV infected patients than HIV non infected patients. Among all study groups, study group V and study group II shows more efficacy than other treatment modalities i.e electrocautery therapy and liquid nitrogen therapy respectively. But while compared to liquid nitrogen, electrocautery showed low recurrence rate with minimum number of applications to obtain maximum response with acceptable level of side effects. When compared to treatment response at the end of treatment among HIV Non infected and HIV infected individuals shows there is no statistical significance between these two for all study groups. Similarly treatment response after 3 months showed statistically insignificant difference except for study group V(electrocautery). Most

of the patients developed local acceptable side effect during the course of treatment but it resolved on its own.

Note :

I would like to mention that due to the constraints in total no of cases attended and selected for the study, the result may not be fully conclusive, therefore further detailed evaluation and research may be necessary to documented conclusion.

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MC-PREVALENCE OF HPV INFECTION AND HIV INFECTION

MONTH	NON HIV CASES	TOTAL NO. OF WART IN HIV-VE CASES	TOTAL NO. OF HIV CASES	TOTAL NO. OF WART IN HIV +VE CASES	TOTAL NO.OF CASES IN STD OPD	TOTAL NO. OF WART CASES
Jun-07	257	2	4	1	261	3
Jul-07	244	2	4	1	248	3
Aug-07	277	4	12	3	289	7
Sep-07	256	1	0	nil	256	1
Oct-07	288	2	15	4	303	6
Nov-07	258	3	7	2	265	5
Dec-07	223	5	3	1	226	6
Jan-08	274	5	9	1	283	6
Feb-08	296	4	5	nil	301	4
Mar-08	248	4	7	nil	255	4
Apr-08	276	7	8	nil	284	7
May-08	261	5	11	1	272	6
Jun-08	262	10	8	nil	270	10
Jul-08	262	10	8	4	270	14
Aug-08	359	5	4	nil	363	05
Sep-08	280	6	14	nil	294	06
Oct-08	225	1	4	nil	229	01
Nov-08	242	5	15	1	257	06
Dec-08	285	5	3	nil	288	05
Jan-09	270	7	11	nil	281	07
Feb-09	258	2	4	nil	262	02
Mar-09	276	3	2	nil	278	03
Apr-09	255	3	7	1	262	04
May-09	197	nil	10	3	207	03
TOTAL	**6329**	**101**	**175**	**23**	**6504**	**124**

PROFORMA

CASE NO :

NAME OF THE PATIENT :

AGE/SEX :

MALE STD OP NO :

OCCUPATION & INCOME:

STD CLINIC NO :

ADDRESS :

MARITAL STATUS : MARRIED (MD) /UNMARRIED (UM)/ WIDOWER (W)

PRESENTING COMPLAINTS:

TREATMENT TAKEN FOR PRESENTING ILLNESS:

PAST HISTORY: Previous STDs and Treatment taken/Similar illness & Details/Diabetes/Hypertension/Surgeries/Blood Transfusion/TB/ Asthma

CONTACT HISTORY:
Partner Name/ Occupation/History and Investigation

SEXUAL HISTORY:

SEXUAL ORIENTATION: HeteroSexuals(HT)/Homosexuals(H)/Bisexual(BI)

SEXUAL CONTACT: Premarital Contact(PMC)/Marital Contact(MC)/Extramarital Contact(EMC)/Last Contact(LC)

RECENT EXPOSURE: With Known Person(K)Or Unknown Person(UK)/Protected (P)/UnProtected (UP) Sex/Paid (PD) /Not Paid (NPD)

PERSONAL HISTORY: Alcohol / Smoking/ Betelnut Chewing/ Drug Abuse/ Blood Transfusion

GENERAL EXAMINATION (NAD –NO ABNORMALITY DETECTED):

PR/BP/Anemia/Jaundice/Clubbing/Lymphadenopathy/Cyanosis/CVS/

RS/Abdomen/CNS

GENITAL EXAMINATION:

Uncircumcised/Circumcised

Penile ulcer /penile scar/urethral discharge /sub preputial discharge/urethral meatus Inguinal lymph nodes/skin and mucous membrane/ bone & joints

SITE OF WART - Inner Lining Of Prepuce/Glans Penis/Corona Glandis/Shaft Of The Penis/Pubis/Perineum/Perianal Region/Frenelum

TYPE OF WART:
Condylomata Acuminata(A)/ Papular Wart(PW)/ Keratotic Wart(KW)/ Flat Topped Papule(FP)Per Rectal Examination

INVESTIGATION :

URINE: Albumin/Sugar/Deposits

BLOOD: Complete Blood Count -Normal Value (NV) /Abnormal Value (AB)
Liver Function Test -Normal Value (NV)/Abnormal Value (AB)
Renal Function Test -Normal Value (NV)/Abnormal Value (AB)
SEROLOGICAL: VDRL – Reactive(R)/Nonreactive (NR)
ELISA FOR HIV-Reactive(R)/Nonreactive (NR)
CD 4+ COUNT

PROCTOSCOPY/MEATOSCOPY:

BIOPSY:
TREATMENT GIVEN :

GROUP I - Patients treated with 20% podophyllin

GROUP II - Patients treated with liquid nitrogen

GROUP III - Patients treated with trichloroacetic acid

GROUP IV - Patients treated with imiquimod

GROUP V - Patients treated with electro cautery

TREATMENT RESPONSE :

GRADE A - Lesions Completely Resolved

GRADE B - Lesions reduced in size

GRADE C - Lesions not responding to treatment even after completion of treatment.

DCT - Treatment Discontinued

SIDE EFFECTS :

LA+	-	Local acceptable side effect(itching, burning, erythema, pain, tenderness and erosion)
LNA+	-	Local but not acceptable side effects (swelling, ulcer, necrotising balanoposthitis and phimosis)
NIL	-	No side effect
S +	-	Systemic side effects: dizziness, lethargy, precoma, nausea, vomiting, abdominal pain, respiratory distress and cold clammy skin. Reversible bone marrow suppression with thrombocytopenia and leucopenia

RECURRENCE & FOLLOW UP: (EVERY 3 MONTH)

FF	-	Follow up failed
RO	-	Recurrence
NOR	-	No recurrence
TC	-	Treatment changed

CLINICAL PHOTOS:

ABBREVIATION IN TABLES AND MASTER CHART

A	-	CONDYLOMA ACUMINATE
KW	-	KERATOTIC WART
PW	-	PAPULAR WART
FP	-	FLAT TOPPED PAPULAR WART
NR	-	NON REACTIVE
R	-	REACTIVE
GROUP I	-	PATIENTS TREATED WITH 20% PODOPHYLLIN
GROUP II	-	PATIENTS TREATED WITH LIQUID NITROGEN
GROUP III	-	PATIENTS TREATED WITH TRICHLOROACETIC ACID
GROUP IV	-	PATIENTS TREATED WITH IMIQUIMOD
GROUP V	-	PATIENTS TREATED WITH ELECTRO CAUTERY
GRADE A	-	LESIONS COMPLETELY RESOLVED.
GRADE B	-	LESIONS REDUCED IN SIZE BUT NOT COMPLETELY RESOLVED.
GRADE C	-	LESIONS NOT RESPONDING TO TREATMENT EVEN AFTER COMPLETION OF TREATMENT.
DCT	-	TREATMENT DISCONTINUED.
RO	-	RECURRENCE
NOR	-	NO RECURRENCE
TC	-	TREATMENT CHANGED
FF	-	FOLLOW UP FAILED
LA+	-	LOCAL ACCEPTABLE SIDE EFFECT(ITCHING , BURNING, ERYTHEMA, PAIN, TENDERNESS AND EROSION)
LNA+	-	LOCAL BUT NOT ACCEPTABLE SIDE EFFECTs (SWELLING, ULCER, NECROTISING BALANOPOSTHITIS AND PHIMOSIS)

NIL	-	NO SIDE EFFECT
Md	-	MARRIED
UM	-	UNMARRIED
W	-	WIDOW
HT	-	HETEROSEXUAL
H	-	HOMOSEXUAL
Bi	-	BISEXUAL
UK	-	UNKNOWN
K	-	KNOWN
UP	-	UNPROTECTED
P	-	PROTECTED
NPD	-	NOT PAID
PD	-	PAID
MC	-	MARITAL CONTACT
NAD	-	NO ABNORMALITY DETECTED
NV	-	NORMAL VALUES
AB	-	ABNORMAL VALUES
VDRL	-	VENERAL DISEASE RESEARCH LABORATORY
LFT	-	LIVER FUNCTION TEST
RFT	-	RENAL FUNCTION TEST
CBC	-	COMPLETE BLOOD COUNT

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TOTAL	**6329**	**101**	**175**	**23**	**6504**	**124**

case	age/	STUDY	MARITAL	SEXUAL	PMC	EMC	SIMILAR	OTHER	SMOK	GEN	CIRCUMCISION	SITE		INVESTGATION			WART	DURA	HIV	CD4+	NO OF TIME	RESULT	RESPONSE	RESULT	RECURR	SIDE
no	SEX	GROUP	STATUS	ORIENT			ILLNESS	STI	ING	EXAM	STATUS		VDRL	LFT	RFT	CBC	TYPE	TION	STATUS	COUNT	APPLIED	AT END	AT(WKS)	AT 3 MON	ENCE	EFFECT
79	34/M	Group 5	Md	HT	+	+	NO	NO	6 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	2 MON	NR	--	1	GRADE-A	1	NOR	NIL	LA+
80	46/M	Group 5	Md	HT	+	+	NO	NO	10 YRS	NAD	UNCIRCUMCISED	GLANS/	NR	NV	NV	NV	A	6WKS	R	450	3	GRADE-B	3	TC	----	LA+
81	22/M	Group 5	UM	HT	-	-	NO	NO	--	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	3 MON	NR	--	2	GRADE-A	2	NOR	NIL	LA+
82	39/M	Group 5	Md	HT	+	DENIES	NO	NO	16 YRS	NAD	UNCIRCUMCISED	GLANS/FRENULUM	NR	NV	NV	NV	A	3WKS	NR	--	1	GRADE-A	1	NOR	NIL	LA+
83	29/M	Group 5	UM	HT	-	-	NO	NO	5 YRS	NAD	CIRCUMCISED	PERINEUM/ SHAFT	NR	NV	NV	NV	KW	1YR	NR	--	2	GRADE-A	2	NOR	NIL	LA+
84	32/M	Group 5	Md	HT	DENIES	+	NO	NO	8YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	6WKS	NR	--	2	GRADE-A	2	NOR	NIL	LA+
85	43/M	Group 5	Md	HT	+	DENIES	NO	NO	15 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	2MON	R	300	1	GRADE-A	1	FF	----	LA+
86	49/M	Group 5	Md	HT	+	+	NO	NO	20 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	PW	4WKS	NR	--	2	GRADE-A	2	NOR	NIL	LA+
87	47/M	Group 5	Md	HT	DENIES	+	NO	NO	9YRS	NAD	UNCIRCUMCISED	GLANS/FRENULUM	NR	NV	NV	NV	FP	5WKS	NR	--	2	GRADE-A	2	NOR	NIL	LA+
88	35/M	Group 5	Md	HT	+	DENIES	NO	NO	---	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	6 WKS	NR	--	3	GRADE-A	3	RO	+	LA+
89	27/M	Group 5	UM	HT	-	-	NO	NO	6 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	4MON	NR	--	2	GRADE-A	2	NOR	NIL	NIL
90	33/M	Group 5	UM	HT	-	-	NO	NO	10 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	12WKS	NR	--	1	GRADE-A	1	NOR	NIL	NIL
91	45/M	Group 5	Md	HT	DENIES	+	NO	NO	--	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	3 MON	NR	--	2	GRADE-A	3	NOR	NIL	LA+
92	29/M	Group 5	UM	HT	--	-	NO	NO	5 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	6WKS	NR	--	1	GRADE-A	1	NOR	NIL	LA+
93	35/M	Group 5	Md	HT	DENIES	DENIES	NO	NO	15 YRS	NAD	CIRCUMCISED	PERINEUM/ SHAFT	NR	NV	NV	NV	A	1YR	NR	--	1	GRADE-A	1	NOR	NIL	LA+
94	46/M	Group 5	Md	HT	DENIES	+	NO	NO	8YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	6WKS	R	200	2	GRADE-A	2	NOR	NIL	LA+
95	41/M	Group 5	Md	HT	+	DENIES	NO	NO	15 YRS	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	A	2MON	NR	--	3	GRADE-A	3	NOR	NIL	NIL
96	35/M	Group 5	Md	HT	DENIES	+	NO	NO	10 YRS	NAD	CIRCUMCISED	GLANS/FRENULUM	NR	NV	NV	NV	A	4WKS	R	300	2	GRADE-A	2	NOR	NIL	NIL
97	25/M	Group 5	UM	HT	DENIES	+	NO	NO	--	NAD	UNCIRCUMCISED	GROIN/PERINEUM/ SHAFT	NR	NV	NV	NV	KW	8WKS	NR	--	1	GRADE-A	1	NOR	NIL	LA+
98	39/M	Group 5	Md	HT	+	DENIES	NO	NO	---	NAD	UNCIRCUMCISED	INNER LINING PREPUCE	NR	NV	NV	NV	PW	6 WKS	NR	--	1	GRADE-A	1	NOR	NIL	LA+