Chapter 1

INTRODUCTION AND

REVIEW OF LITERATURE
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Sexually transmitted diseases (STDs) include diseases that are transmitted by sexual intercourse. Sexual transmission requires an agent to be present in one partner and other partner to be susceptible to infection with that agent and that sex partner engages in sexual practices that can transmit the pathogen (Sharma and Khandpur, 2003). They are actually a group of diseases whose reservoirs are human, transmitters are humans and sufferers are human. The causative agent adapts itself to changing ecology and continues its existence with adjustable biomechanisms (Thappa, 2002).

Sexually transmitted diseases were previously known as venereal diseases. The term venereal being derived from Greek word “Venus” the goddess of love. The great Sir William Osler called - “Venereal disease the most formidable enemy of the human race an enemy entrenched behind strongest human passions and deepest social prejudice”. The term venereal was quite misleading as people read exclusion of conjugal sexual relations from within its preview hence the present concept of sexually transmitted diseases was born (Arnold, 1993).

Sexually transmitted diseases are not just biological and medical problems, but also behavioural, social, political and economic problems (Mayaud and McCormick 2001). STDs are closely related to social circumstances and human behaviour. People consider these diseases as something unmentionable and consequently try to hide them.

STDs have been known to mankind since time immemorial with written references in Biblical, Chinese, Hindu and Greek records. Towards the end of 15th century a devastating epidemic of infectious syphilis swept Western Europe. Observers
quickly perceived the disease to be transmitted sexually, but this group of venereal disease was subsequently regarded as unproblematic until it was noted to be severe problem among military personnel in the 19th and the 20th century.

Until 1917, knowledge of subject of STDs was rudimentary and only three venereal diseases - syphilis, gonorrhoea and chancroid were legally defined as venereal diseases in United Kingdom (Thappa, 2002). The golden era of microbiology in the late 19th and early 20th centuries identified the microbes responsible for the five traditional venereal diseases—gonorrhoea, syphilis, chancroid, lymphogranuloma venereum (LGV) and donovanosis. After the world war II, new diagnostic techniques and defined clinical and epidemiological studies in North America and Europe established that many ‘non traditional’ microbes could produce infection when transmitted sexually. Interest in STDs was further fuelled in early 1980s by the advent of HIV/AIDS epidemic and recognition of their role in facilitating the sexual transmission of HIV.

Traditionally sexual problems in India are known as gupt rog (secretive ailments) which refer to culturally defined illness of secret parts of the body and are therefore problems that are shameful and need to be kept a secret (Sharma and Khandpur, 2003). STDs are also attributed to “body heat” (‘garmi’) a concept perpetuated by the Indian Ayurvedic Medicine and many do not seek treatment for them. As these STDs are not completely treated, they enhance biological vulnerability to HIV infection.

STDs are the epidemics of tremendous health and economic consequences spread all over the world. STDs constitute an important public health problem for following reasons.
• They are frequent with high prevalence and incidence;
• They can result in serious complications and sequelae;
• They have serious social and economic consequences and
• They have been identified as facilitating the spread of HIV.

The epidemiological profile of STDs is more dynamic than most other infectious
diseases and varies not only from country to country but also from place to place within
the same country depending on prevailing socio-economic status, moral outlook of the
population, available health care system and treatment facilities and information
regarding the awareness of preventive measures.

STDs infect the reproductive tract as the primary site, with transmission occurring
during sexual intercourse or from mother to child during pregnancy and child birth. As a
result the greatest risk of infection is found among sexually active individuals and infants
born to infected mothers. Multiple infections within the same individual are also frequent,
as is reinfection if the partner has not been adequately treated.

STDs impose an enormous burden on morbidity and mortality, both directly
through their impact on reproductive and child health and indirectly through their role in
facilitating the sexual transmission of HIV infection (Mayaud and Mc Cormick 2001).
STDs lead to severe medical and psychological consequences for millions of people
(WHO, 1999).

STDs have a tremendous impact on the national health. They are responsible for
significant proportion of maternal morbidity, ectopic pregnancy, infant illness and death,
malignancies, infertility and increased susceptibility to HIV infection. STDs are also one
of the significant contributors of foetal death, abortions and low birth weight (Sharma and Khandpur, 2003).

**Epidemiology of STDs**

The incidence of STDs continues to escalate worldwide inspite of available effective treatment for bacterial STDs. Worldwide more than 330 million new cases of curable STDs occur each year of these more than 80 percent are believed to occur in the developing countries (Lamptey, 2002; Khanna, 2002).

In the industrialized world the United States has the highest rates of STDs with an estimated 15.3 million new cases of STDs being reported each year (American Social Health Association, 1998). In the United States, of the top 11 reportable diseases in 1996, five were transmitted sexually (gonorrhoea, chlamydia infection, syphilis, hepatitis B and AIDS) (CDC, 1997).

WHO estimated that during 1999, 340 million new cases of selected but curable STDs (STIs) occurred worldwide (WHO, 2001). The largest number of new infections occurred in the region of South and South-East Asia, followed by Sub-Saharan Africa, Latin America and the Caribbean. However the highest rate of new cases per 1000 population has occurred in Sub-Saharan Africa.

Several studies have reported an alarming increase in the incidence of STD in developing countries including India. Annual sexually transmitted diseases (STDs) incidence in India is estimated at 5 percent with over 40 million new infections per year (NACO, 2002). In India the highest incidence of STDs is in Maharashtra followed by Tamilnadu, Gujarat, Orissa, Madhya Pradesh and Karnataka. These states account for
nearly 80 percent of cases, while West Bengal and Delhi accounts for a quarter of remaining 20 percent.

STDs most commonly affect people in the age group of 15 to 44 years usually the most economically productive group causing loss of productive life, measured as disability adjusted life years (DALYs) lost (Gerbase et al., 1998). The world bank estimates that STDs, excluding HIV are the second commonest cause of healthy life years lost in women in 15-44 years age group, responsible for some 17% of the total burden of disease in women of reproductive ages, outranked only by causes of maternal morbidity (Mayaud and mc Cormick, 2001).

The presence of an untreated STD can also increase the risk of both acquisition and transmission of HIV by a factor of up to 10 (WHO, 1999).

**Relationship between STDs and HIV infection**

There is a complex relationship between STDs and HIV infection (Kar, 2003).

- The predominant mode of transmission of both HIV infection and other STD is through sexual route.
- STDs are biological cofactors for acquisition, transmission of HIV infection.
- Concurrent HIV infection alters the natural history of classic STD.
- STDs are markers for high risk behaviour for HIV infection.
- Many of the measures for prevention of sexually transmission of HIV and STD are the same as are the target audiences for these interventions.
• STD clinical services are important access point for persons at high risk not only for diagnosis and treatment but also for education on prevention and treatment and counseling for HIV infection.

• Management of STD may reduce HIV transmission, particularly in developing countries.

• Trend in STD incidence and prevalence can be useful indicators of changes in sexual behaviour and are easier to monitor than trends in HIV seroprevalence and therefore valuable in determining the impact of HIV/AIDS control programme.

STDs act as an important cofactor in HIV transmission by increasing susceptibility to HIV (Jha et al., 2001). Individuals who are infected with STDs are at least two to five times more likely than uninfected individuals to acquire HIV if they are exposed to the virus through sexual contact. Moreover if an HIV infected individual is also infected with another STD, that person is more likely to transmit HIV through sexual contact than other HIV-infected person (Wasserheit, 1992).

HIV by causing immunosuppression, can modify the natural history (duration), clinical presentation (severity), and response to treatment of certain STDs (Mayaud and Mc Cormick, 2001).

Biological evidences demonstrate that the presence of other STDs increases the likelihood of both transmitting and acquiring HIV (Fleming and Wasserheit, 1999).
STDs and HIV interaction

STDs can both increase susceptibility as well as increase infectiousness. STDs probably increase susceptibility to HIV infection by two mechanisms: Genital ulcers (e.g., syphilis, herpes, chancroid) results in breaks in the genital tract lining or skin thereby creating a portal of entry for HIV. Non ulcerative STDs (gonorrhoea, chlamydia and trichomoniasis) increase concentration of cells (CD4+ cells) in genital secretions that can serve as a targets for HIV.

Studies have also shown that when an HIV infected individual is also infected with other STDs, they are more likely to have HIV in their genital secretions. HIV is more readily detected in semen of men with urethritis or gonorrhoea infection (Barry, 2000).

In India few studies have shown increasing prevalence of HIV infection among STD clinic attendees. Prevalence was found higher among GUD patients than for non-ulcerative STD patients.

Treating STDs in HIV infected individuals decrease both the amount of HIV they shed and how often they shed the virus (Fleming and Wasserheit, 1999).

The determinants and various risk factors responsible for STDs including HIV

The individuals sexual behaviour is a key determinant of STD transmission risk (Fentor et al., 2005). The behavioural risk factors are related to greater probability of exposure to STDs, acquiring the disease and higher risk of developing complications.
The various risk factors and determinants for STDs and HIV include:

- Age at first intercourse (or) “coitarche”
- Gender
- Education status and socioeconomic status
- Marital status of the individual
- Frequency of sexual intercourse
- Number of life time partners
- Rate and type of sexual partner recruited
- Rate of partner change
- Number of current relationships
- Age difference between the partners
- Sexual mixing with high risk groups such as commercial sex workers (CSW), truck drivers, mine workers etc.
- Addictions such as drug abuse, alcoholism, and smoking
- Type of sexual practices (vaginal, anal, oral intercourse).

Age at first intercourse

There is a direct relationship between the acquisition of STD and young age at first intercourse. Early sexual debut leads to higher rates of partner exchange and greater chances of STD transmission. Several studies in India have shown the average age of sexual debut in STD clinic attendees is between 15-20 yrs. (Subramanian et al., 2003).

In the United States an estimated 15.3 million new cases of STDs occur each year, one quarter of them among teenagers (American Social Health Association, 1998).
Though data from the developing world is limited it is estimated that one in twenty adolescents acquire STD each year (Dallabetta et al., 2005).

The higher incidence has been related to greater number of sexual partners, inconsistent and incorrect use of condoms, poor knowledge of the diseases along with other high risk homosexual / bisexual behaviour. Biologically young women appears to have increased susceptibility due to hormonal changes and lack of immunity to STD pathogen (Brookman, 1990).

**Gender**

STDs are more frequently common in males as compared to females. In females the infection is often asymptomatic in majority of cases. Less degree of freedom in the society, lower awareness among women for availing medical facilities, and frequent consultation in gynecology clinic instead of STD clinic.

**Education status and socioeconomic status**

In India illiterates and individuals with primary level of education and low income groups are particularly more vulnerable to STDs including HIV (Khandpur et al., 2001).

**Marital Status**

Various studies from India and abroad have shown that married individuals especially women are at a higher risk of acquiring STD including HIV. A higher frequency of unprotected sex within a marriage results in higher probability of disease transmission compared with casual partnerships where sexual intercourse is less frequent.
Number of Life time sexual partners

Risk of exposure to STD and the development of cervical and other genital cancers is directly associated with number of life time sexual partners, rate of partner recruitment and partner change. However this correlation is complicated by differences in patterns with respect to choice of partner, partners own sexual behaviour and degree of his infectiousness.

Age difference between sexual partners

Few studies have shown that greater age difference (>11 years) between sexual partners was found to increase the risk of STD and HIV, especially in women.

High-Risk groups

Commercial sex worker (CSW)

CSW or prostitute is defined as a person who provides sexual service for money or other material gains. They include those who work in brothels, night clubs, hotels, massage parlours or bars or are casual freelance sex workers. Contact with CSW has been implicated as an important risk factor for STD transmission, because they experience higher rate of partner change, longer period of exposure to infection, poorer access to health care facilities and efficient transmission from sexual exposure.

The role of prostitutes has been assessed by monitoring the incidence of STD in this group and the proportion of male STD patients who acknowledge recent sex with a prostitute. The incidence of STDs is directly related to early age of commencement of
sexual work, longer duration of prostitution and current age of CSW. Many epidemiological studies have shown that in developing countries, Genital ulcerative diseases (GUDs) are most common among commercial sex workers.

In Mumbai the HIV seroprevalence in commercial sex workers increased from 20% (1990), 35% (1991), 40% (1992) and 45% (1993) (Khanna, 1997); 42.9% from Pune (Mehendale et al., 1994), 13.3% from Allahabad (Pande, 1997) and 25% among CSWs in Tirupati (Lakshmi and Kumar, 1994). In Vellore South India, the HIV seroprevalence rose from 0.26% in 1986 to 3.94% in 1992 and 2.64% in 1993 (Jacob et al., 1995).

Transport Workers (Drivers)

India has one of the largest road networks in the world and an estimated 2 to 5 million long distance truck drivers and helpers. They have been identified as male occupational group at high risk of STDs and AIDS acquisition. This group is particularly vulnerable to HIV because long distances from home particularly results in increased number of sexual contacts. During the rest stops frequented by drivers they often come in contact with various types of sex workers such as homosexuals and prostitutes who are also critical vectors of spreading the virus. Poverty, illiteracy and low level of awareness about STD and HIV along with low condom usage are other contributing factors. Due to their geographical mobility they may play an important role in dissemination of these infections.
In studies conducted in Pondicherry between 1997 and 1999, truck drivers were found to have the highest rates of HbsAg (23.8%) and HIV (47.6%) and second highest rate of hepatitis C positivity (42.8%) (Singh et al. 2001).

Migrant workers

They are the population who migrate for economic reason. In 1993, almost 25% of population migrated for economic reason. The conditions that put migrant workers at risk include: Urban, unhygienic slum settings, isolation from family and cultural/language barriers, long working hours along with lack of healthy recreation facilities.

Restaurant workers

They are another high risk population group in the transmission of STD. In a survey conducted among restaurant workers along a highway in Assam, over one third had sexual contact with multiple partners or CSW and 2% were engaged in homosexual activity. Majority of them were illiterate, 30% were alcoholic and smokers and 3% were addicted to cannabis (Biswas, 1999). GUD was present in 25.7% of workers, 11.8% had gonorrhoea.

Transsexuals

In the Indian subcontinent, male sex workers are predominantly transvestites and transsexuals known as ‘Hijras’. Their origin dates back many centuries to India where Hijras believed themselves to be incarnation of Lord Krishna. This community now
engages in commercial sex and is at a high risk for STD and HIV. It indulges mainly in insertive ano-genital intercourse with men.

**Prison inmates**

STD tends to cluster in socially excluded populations such as those like prisoners. Numerous studies have found high rates of STDs among prison inmates. Moreover increasing rate of imprisonment rate of drug users is linked to the spread of HIV and hepatitis B and C.

An epidemiological study conducted among prison inmates in district jail around Delhi showed that 4.6% of the inmates had primary syphilis, 33.33% were positive for HbsAg, 5% were reactive for HCV infection and 1.3% were Western blot confirmed HIV-1 positive cases. (Singh et al., 1999). 28.8% of inmates were homo/bisexuals, 54.2% had multiple sex partners, 83% had contact with CSW and 80.6% indulged in unprotected sex. 68% of the inmates were alcoholics, 24% consumed smack while 4.8% were IV drug abusers.

**Addictions**

Population of drug abusers have been associated with the epidemics of STDs especially HIV infection.

**Crack Cocaine Users**

The drug most often associated with STD is smokable freebase (crack) cocaine. Research suggests that crack addiction forces young women to sell sex directly for
money to buy crack. Also sex workers under the influence of drug may be less careful when choosing sexual practices or partners. Epidemiological data indicate that ‘crack for sex’ exchange differs from other prostitution because a high proportion of adolescent population involved with drug abuse. Oral sex is the predominant type of sexual activity and crack user often indulge in unprotected sex.

Intravenous drug abuse

Epidemiological studies in intravenous drug abusers have shown a high frequency of blood borne STDs including HIV, HBV, HCV infections and syphilis. In a study in Bangladesh, syphilis, HBV and HCV rates were found to be 23%, 66.5% and 1.4% respectively among IV drug abusers (Azim et al., 2002). In Manipur the prevalence of HIV among IV drug abusers was 80% and vaginal discharge was strongly associated with HIV Positivity (Sharma and Khandpur, 2003).

A study of sexual behaviour among IV drug abusers in Delhi showed greater number of sex partners, high rates of anal intercourse (25.7%), greater frequency of visit to CSW and hence significantly higher prevalence of STD in this age group. (Sharma et al., 2002).

Alcoholism and Smoking

Smoking have been shown to be strongly associated with persistence of oncogenic HPV cervical infection. Moreover adolescent women with alcohol use disorder in the US appeared to be at substantially high risk of HSV-2 infection, with a
seroprevalence of 19% as compared to 10% in those without this disorder. (Cook et al., 2002).

**High risk sexual practices**

Certain sexual practices are associated with higher risk of acquiring STD. The high risk sexual practice includes receptive ano-genital intercourse which increases the risk of STDs such as ano-rectal gonorrhoea, condyloma acuminata at anus and ano-rectal LGV.

Insertive ano-genital intercourse which may cause gonococcal or non-gonococcal urethritis, herpes genitalis, condyloma acuminata, LGV or donovanosis.

A study from USA in 1987 showed the incidence of anal carcinoma among homosexual men estimated to be 35/100,000. In HIV seropositive men especially those with CD4 counts<500/ml, there is an increased risk of high grade anal squamous intraepithelial lesions (Darling et al., 1987).

In India, the prevalence of STD among the homosexuals have been shown to vary from 2.2% to 6.16% confirming that frequent mucosal damage caused by intercourse through the unnatural route in this group poses a high risk for STD transmission (Khandpur et al., 2001; Singh et al., 2001).

**Other sexual practices**

These are well characterized health behaviour and the sexual practices that may influence the risk of acquiring or transmitting STDs. These include dry sex, sex during menses, and vaginal douching practices. Sex during the menstruation has been associated
with the increased risk of acquiring gonorrhoea, trichomoniasis and HIV (Tanfer and Aral, 1996).

Condoms

Barrier methods like condoms offer significant protection against organisms like chlamydia trachomatis and Neisseria gonorrhoeae and only partial protection against those which commonly infect the stratified squamous epithelium such as herpes simplex and human papilloma viruses. In developing countries the rate of condom use varies from 3% to 50%.

In a study undertaken in Ghana, Africa, showed a significant decline in the prevalence of gonorrhoea (from 33% to 11%), genital ulcers (from 21% to 4%), syphilis (from 21% to 2%), trichomoniasis (from 26% to 11%) and HIV infection (from 89% to 32%) between 1992-1998, owing mainly to increase in condom use. (Ghys et al., 2002).

A recent review from the National Institute of Health says that condoms are protective against HIV infection, reducing the probability of HIV transmission per sex act by as much as 95% and reducing the annual HIV incidence in serodiscordant couples by 90-95% when used consistently (Pinkerton and Abramson, 1997).

Oral contraceptives

Oral contraceptives have been associated with lower risk of PID and higher risk of cervical infections with chlamydia trachomatis, HPV and Neisseria gonorrhoea and candidial vulvovaginitis. High estrogen containing oral contraceptives has shown a strong correlation with risk of hepatitis B and HPV induced cervical cancers.
Intrauterine Devices

There is a strong correlation between the use of intrauterine devices (IUD) and PID. In a study from Mumbai, India, prevalence of genital chlamydial infection among Cu-T users (14%) was found to be significantly lower than among the non-users (20%).

Circumcision

It is strongly related to specific religions, ethnicity or culture and socio-economic status. Lack of circumcision has been implicated as a major risk factor for STD including syphilis, chancroid, genital herpes, gonorrhoea, genital warts, candidial and non specific balanitis and HIV infection.

Biological evidences suggests that inner mucosal surface of the foreskin contains less protective keratin than the outer surface of the foreskin, and is also rich in Langerhan’s cells with HIV receptors. These cells are likely to be primary point of viral entry into penis (Szabo et al., 2000).

Studies have shown that male circumcision is associated with a reduced risk of ulcerative STDs especially syphilis and chancroid (Moses et al., 1998).

Gonorrhoea

It is a ubiquitous bacterial infection, characterised by purulent urethral discharge caused by Neisseria gonorrhoeae, almost exclusively acquired through sexual intercourse with an infected partner.
History

Gonorrhoea was the first specifically documented bacterial disease amongst the sexually transmitted diseases. Gonorrhoeal symptomatology has also been mentioned in ancient literature from Greece, China, Egypt, Rome and also in the old testament. Hippocrates (400 BC) referred to 'strangury' which appears to be gonorrhoea and resulting from "Pleasures of Venus" (Reddy and Khandpur, 2005). The word 'gonorrhoea' is derived from Greek, Gonos, "seed" and rhoea "flow" meaning 'flow of seed' and was so named by Galen in the second century (130-200 AD). Since 1536 BC, gonorrhoea and syphilis were presumed to be related and caused by same agent (Tiwari et al., 2001).

John Hunter's experiment on himself in 1767 with gonorrhoeal pus and his death later due to syphilis, supported the contemperory hypothesis of a single agent causing gonorrhoea and syphilis. In 1838, Philippe Ricord finally established the separate identities of syphilis and gonorrhoea (Tiwari et al. 2001). Albert Ludwig Neisser identified the gonococcus as the causative organism of gonorrhoea in 1879. Demonstration of the organism was possible with Gram staining introduced by Hans gram in 1884.

Epidemiology

It is among the most common and widely recognised sexually transmitted disease throughout the world with an estimated annual incidence of 62 million cases (WHO, 2001). The incidence of gonorrhoea in developed countries has decreased during the last
decade. Part of this decrease has been attributed to the impact of behavioral changes made to reduce the risk of HIV infection and use of antibiotics for other illness.

The incidence of gonorrhea varies with the age. Seventy-seven percent of reported cases in the United States occurred in persons aged 15-29 years with highest rates occurring in the 15-19 years old age group. Race was reported to be a risk factor in USA. In 1995 when rates of gonorrhea occurring in blacks were 37-fold higher than in whites (CDC, 1996).

Other demographic risk factors included low socioeconomic status, early onset of sexual activity, unmarried marital status and past history of gonorrhea. Among the causes of increase in new cases of gonorrhea are the population explosion, industrialization, urbanization, promiscuity, large scale migration, rejection of traditional moral principles, microbial resistance of antibiotics, and asymptomatic female carriers of the infection (Tiwari et al., 2001).

Bacteriology

Neisseria gonorrhoeae is the causative organism of gonorrhea in humans, who are the only host for this pathogen. Neisseria gonorrhoea is a gram negative, nonmotile, non spore forming diplococci, which characteristically grows in pair. The organism is present either intracellularly in the polymorphonuclear leucocytes (PMN) or extracellularly. The average size of gonococci is 0.8 x 0.6 μm. They stain readily with aniline dyes and are decolorised by Gram's method. Drying, heat and disinfectant can destroy the organism outside the body. It ferments dextrose but not maltose, lactose,
succrose or mannitol. Gonococci can synthesize their own lipids about 8 to 10% of the dry weight of the organism is made up of lipids and phospholipids (Tiwari et al., 2001).

The gonococcus was cultivated for the first time by Leistikow in 1882 (Judson, 1990). Gonococci need enriched media for their growth. The various media employed contain heated blood (chocolate agar), glucose, glutamine, thiamine, pyrophosphate, ferric ions and cystine. Carbon dioxide supplementation is necessary for initiating growth. The optimal CO$_2$ need is 5 to 10% and the optimum temperature 34°C to 38°C. Refrigerated storage (near 4°C) kills the organism. The pH of the medium should be between 7.2 and 7.6. Stuart’s solid medium has been used as a satisfactory transport medium.

Identification of gonococci is based on its colony characteristics, oxidase reaction, sugar fermentation, gram’s staining and fluorescent antibody staining. Penicillinase producing N. gonorrhoea were isolated in 1976. They are penicillin resistant.

Ultrastructure of N. gonorrhoea

Cell wall

Ultra structure examination of gonococci by transmission electron microscopy reveals a gram negative outer cell wall overlying a relatively thin layer composed of mucopolysaccharides or peptidoglycan containing N- acetyl glucosamine, N-acetyl muramic acid, glutamic acid, diaminopimelic acid and alanine (Hook and Holmes, 1985).

The organism lacks a true polysaccharide capsule. Instead it produces a “pseudocapsule,” which is responsible for the hydrophilic negatively charged cell surface of the organism. Several blebs (sausage shape pouchings) project out from the cell wall.
Lipo oligosaccharides

Inner to the cell wall is the outer cell membrane made up of lipo-oligosaccharide (LOS). This layer consists of a lipid -A moiety and core polysaccharide made up of keto-deoxyoctanoic acid (KDO), glucose, galactose, glucosamine and haptose. Six distinct entities of LOS varying in size from 3 to 7 kDa are recognised. LOS act as endotoxins. Exotoxins are not elaborated by gonococci. LOS is a target for bactericidal antibodies.

Pili

By X-ray crystallographic techniques numerous hair-like structures called pili can be demonstrated on the surface of gonococci. Pili are known to increase adhesion to host cells. They promote virulence by preventing neutrophilic phagocytosis of the organism and are also involved in exchange of genetic material. Pili are expressed by pilin genes present on the gonococcal chromosome.

Porin Protein

The cell membrane contains 34-36 kDa protein called porin protein. It serves the function of forming anion rich channels through cell membrane. It is a target for bactericidal opsonic antibodies (Sparling, 1999).
Opacity Proteins

It helps in adhesion of gonococci within colonies and also attachment to the host cells. Other antigenic proteins are Reduction modifiable protein (Rmp) and Iron or oxygen repressible proteins.

Auxotypes

Strains of gonococci that need specific requirements for certain nutritional growth factors are known as auxotypes. Almost 15 different growth factors including amino acids (like valine, leucine, lysine, arginine and proline), purines and pyrimidines and other specific nutrients are essential for organism.

Transmission

The infection is commonly transmitted by sexual intercourse. The efficiency of gonorrhoea transmission depends on the anatomic sites infected and exposed as well as number of exposures. The risk of acquiring infection from male to female is 50 to 90 percent as against 20 percent risk from female to male because of the retention of infected ejaculate within the vagina (Hook and Handsfield, 1999).

The disease is asymptomatic in approximately 75-80% of women which makes them efficient reservoir for disease perpetuation among the male contacts (Reddy et al., 2005). In women use of hormonal contraception may increase the risk of acquiring gonorrhoea, and use of spermicides and/or diaphragm clearly have a protective influence. Transmission by fomites or through non sexual contact is extremely rare (Hook and Handsfield, 1999).
It is transmitted perinatally to the neonate. The eyes of the neonate may also be infected during parturition (Tiwari et al., 2001).

**Pathogenesis**

*N. gonorrhoea* has a predilection for columnar and cuboidal epithelium. Cornified or stratified squamous and transitional epithelia are resistant to the organism.

*N. gonorrhoea* after entering the genital tract, adheres to the mucosal cells (non-ciliated) by means of pili and surface protein especially Opa (Hook and Handsfield, 1999). Following adherence the organism is enfolded by pseudopods and pinocytosed by epithelial cells where it divides and multiplies. Intracellularly the organisms are resistant to immune attack. Gonococcal invasion is mediated by Por proteins. After adherence of the organism to the epithelial cell membrane, the Por is translocated from bacterial cell membrane to epithelial cell membrane. Gonococci containing Por A transfers Por into the epithelial cell membrane more readily than those containing Por B. Epithelial cell damage is mediated by release of certain enzymes like phospholipase and peptidase or due to LOS and peptidoglycan. The organisms are exocytosed into submucosal region where they elicit a severe neutrophilic response and form microabscesses followed by exudation of purulent material into the lumen of infected organ.

Primary infection commonly occurs in the columnar epithelium of the urethra, paraurethral ducts and glands, cervix, conjunctiva, Bartholin's ducts, and rectum. Primary infection may also occur in the stratified squamous epithelium of the vagina in prepubertal girls (gonococcal vulvovaginitis). The female urethra often escapes infection, owing to its lining with stratified squamous epithelium, while in males urethra is lined by
stratified or pseudo stratified columnar epithelium which favours the penetration of gonococcus (Venkateshwaran and Mohan, 2003).

In the females the cervix, urethra and Bartholin’s gland are the usual sites of primary infection and one or more of these structures may be involved at the same time. The rectum is frequently the site of secondary infection in female and is rarely the primary focus (Venkateshwaran and Mohan, 2003).

**Clinical manifestations**

The incubation period ranges from 1 to 14 days but majority of men develop symptoms within 2 to 5 days (Hook and Handsfield, 1999). Anterior urethritis is the most common manifestation of gonococcal infection in men. It starts with mild irritation, scanty mucopurulent or mucoid discharge per urethra in men. As it progresses within 24 hours the discharge becomes thick, purulent and profuse with intense burning and pain during micturation. It is associated with increased frequency and urgency.

In females the primary site of infection is the endocervical canal and only about 50% of the infected females are symptomatic. The commonest symptoms in females are moderate burning micturation, frequency and urgency. The discharge may be scant because of the short urethra in female. There may be perimeatal erythema and oedema.

**Anorectal gonorrhoea**

Anorectal gonorrhoea may be primary or secondary. Secondary infection occurs chiefly in women and prepubertal girls with primary genitourinary infection and occasionally due to bursting of gonorrheal abscesses into the rectum. Primary infection
usually occurs from anal intercourse but may be accidental and in many cases it has followed the insertion of contaminated thermometers or enema nozzles. In the MSM, it occurs due to direct inoculation through receptive anal intercourse.

**Pharyngeal gonorrhoea**

Oropharyngeal infection has been reported in about 3-7% of heterosexual men with gonorrhoea, 10-20% of infected women and 10-25% of homosexual men (Sherrard, 1996). It is the sole site of infection in approximately 5% of cases. The infection is transmitted by oro-genital contact and is more efficiently acquired by fellatio than by cunnilingus. It manifests as pharyngitis or tonsillitis associated with fever and cervical lymphadenopathy. It is also a risk factor for developing disseminated gonococcal infection.

**Gonococcal conjunctivitis**

It is a rare entity in adults and often seen in patients with concomitant anogenital gonorrhoea as a consequence of direct contamination by fingers or towels. The condition may vary from asymptomatic or mild infection to severe forms resulting in corneal ulcerations and panophthalmitis.

**Complications of gonococcal urethritis**

**Complications in Males**

The complications in males include posterior urethritis, infection of Cowpers and Tyson’s gland, epididymitis, acute and chronic prostatitis, seminal vesiculitis and periurethral abscess.
Complications in Females

Complications in females are classified as local, metastatic and complications during pregnancy. Local complications include bartholinitis, skinitis, salpingitis, vulvitis, chronic cervicitis, proctitis and Pelvic inflammatory disease (PID).

Complications in infants

Ophthalmia Neonatorum

Primary gonococcal infection of the conjunctiva occurs rarely in adults but it is common in babies infected during birth, starting within 21 days of birth. It accounts for 5-15% of conjunctivitis in the new born. It is characterized by intense redness and swelling of the conjunctiva, associated with profuse purulent and often blood stained discharge.

Metastatic complications

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI) is the most common systemic complication of acute gonorrhoea. It manifests as acute arthritis-dermatitis syndrome. The syndrome has been estimated to occur in 0.5 to 3 percent of patients with untreated gonorrhoea. DGI results from gonococcal bacteremia and is most often manifested by acute arthritis, tenosynovitis, dermatitis or combination of these findings (Venkateshwaran and Mohan, 2003).
The diagnostic tests for Gonorrhoea

Microscopy

The specimen is collected with the help of sterile cotton wool swabs. If no discharge is present, urethral or prostatic massage is performed and specimen is collected from the distal urethral meatus. In females specimen is collected from the endocervix, urethra, rectum or oropharynx. The urethral discharge is homogenously spread over the slide by rolling the swab onto a clean slide. Allow the smear to dry before it is stained. Fix the dried smear by passing the slide rapidly three to four times over the flame. The slide is stained with gram stain and examined under the oil immersion 100x objective. The gonococci are seen as gram-negative diplococci within the polymorphonuclear leucocytes (PMN) cells.

The specificity of the gram stain is 95-97% from culture positive male urethral discharge, 40-60% from endocervical secretion and in asymptomatic patients, the smear is mostly negative.

Culture

The culture is the most specific investigation and the commonly used selective media for N. gonorrhoeae are Modified Thayer Martin (MTM), Chacko Nair Medium (Trypsin digested beef extract), Martin Lewis (ML) media, and New York City (NYC) medium. The direct plating of the organism has a better success in growing the organism. If direct plating is not available the swabs are transported to the laboratory in Stuart’s medium or Amie’s medium. The inoculated plates are placed in an atmosphere
containing 5% CO₂ at 37°C and examined every 18-24 hours until 48-72 hours. Small pinpoint colonies of 0.5 to 1 mm diameter of N. gonorrhoeae can be seen.

Gonococci are fastidious organisms, it requires an enriched culture media for its growth, which also selectively suppresses the normal flora. Vancomycin, colistin, trimethoprim and nyastatin are added to inhibit the growth of bacterial and fungal organisms.

**Oxidase test**

Strips of filter paper soaked in 10% solution of tetramethyl paraphenylene diamine hydrochloride are placed over the growing colonies of N. gonorrhoeae which turn blue. This helps in the specification of gonococci in mixed cultures.

**Sugar fermentation test**

It is possible to differentiate various species of Neisseria by observing their sugar utilization patterns. Subcultures of Neisseria colonies were formerly used, but the more recent rapid sugar utilization tests permit quick diagnosis. N. gonorrhoeae ferments only glucose.

**Fluorescent antibody test**

Gonococcal smears as well as cultures can be identified by a fluorescent antibody test. A direct smear from the culture/exudate is exposed to gonococcal antibody conjugated with a fluorescein isothiocyanate and examined under a fluorescent microscope. Green fluorescence is suggestive of gonococci.
Newer tests

Non-amplified DNA probe tests are most widely used non culture tests for gonorrhoea diagnosis in USA. Such tests have a sensitivity of 89-97% and specificity of 99%.

Another test is an amplified nucleic acid detection test, a ligase chain reaction assay, that is as sensitive as culture for detecting N. gonorrhoeae, and has an added advantage of being equally sensitive when first-void urine specimens are used. Both the tests have an advantage that a single specimen collected can be tested for both N.gonorrhoeae and C. trachomatis.

Detection of N. gonorrhoea antigen

Gonococcal antigen is detected by an enzyme immunoassay. It is similar to Gram stain in sensitivity and specificity for presumptive diagnosis in men; but it is less sensitive in respect to endocervical swabs.

Detection of N.gonorrhoeae RNA

A two-hour RNA probe hybridization assay is a rapid, sensitive and specific assay. Specimen collection kits contain swabs and transport media that lyses the organisms and releases the RNA. Similar kit can be used to detect C.trachomatis RNA in same sample.
Amplification and detection of *N.* gonorrhoeae DNA

Polymerase Chain reaction (PCR)

It can be used for *N.* gonorrhoea and *C.* trachomatis DNA from the same sample. The kit includes an internal standard that is amplified also to prevent false negative results.

Ligase Chain Reaction (LCR)

This is another DNA amplification technique where amplicons are detected in an automated instrument designed to minimize false positive samples. The enzymes used are less sensitive than the enzymes used in PCR.

PCR and LCR are extremely sensitive to detect *N.* gonorrhoea from endocervical, urethral and urine samples.

Treatment (CDC 2002)

According to the Centre for disease control the following treatment is prescribed for patients with gonorrhoea.

Cefixime 400mg orally in a single dose

or

Ceftriaxone 125 mg IM in a single dose

or

Ciprofloxacin 500mg orally in a single dose

or
Ofloxacin 400mg orally in a single dose

or

Levofloxacin 250 mg orally in a single dose

Management of sex partner (Partner notification)

All sex partners who have N. gonorrhoeae infection should be evaluated and treated for N. gonorrhoea and C. trachomatis infection if their last sexual contact with the patient was within 60 days before the onset of symptoms or diagnosis of infection in patient. Patients should be instructed to avoid sexual intercourse until therapy is completed and until their sex partners no longer have symptoms.

Follow Up

Treated patients with CDC regimen need not follow up to confirm their cure but the patient with persistent symptoms may be tested for antibiotic susceptibility and other cause and treated accordingly.

Gonorrhoea and HIV

Studies have shown that man who are infected with both gonorrhoea and HIV are more than twice likely to shed HIV in their genital secretions than those who are infected only with HIV. Moreover the median concentration of HIV in semen is as much as 10 times higher in men, who are infected with both gonorrhoea and HIV than in men only infected with HIV (Moss et al., 1995).
Treatment of Gonorrhoea in patients co-infected with HIV

Patients who have gonococcal infection and also are infected with HIV should receive the same treatment regimen as those who are not infected with HIV.

SYPHILIS

Syphilis, the “great imitator”, has been defined by Stokes as a chronic systemic infectious disease caused by the organism Treponema pallidum. It may affect any organ of the body during its course and it may result in life threatening consequences that occur in the cardiovascular and the nervous systems. It is distinguished by florid manifestations on one hand and years of asymptomatic latency on the other. In a minority of cases it may succeed to late symptomatic disease. It is transmissible to offspring in man, certain laboratory animals and is treatable to the point of presumptive care. The sexually transmitted form is acquired syphilis, while infection in utero produces prenatal syphilis.

Origins of Syphilis

The disease acquired its name from a poem “Syphilis sive morbus gallicus” written in 1530 by an Italian pathologist Girolamo Fracastoro about an infected mythical shepherd named Syphilis (Sanchez and Luger, 1993). There are three theories regarding the origin of syphilis, one is the Columbian theory, according to which syphilis was brought to Europe with the return of Columbus in 1493 after his discovery of America where the disease was existing in American Indians. From Europe the disease came to India and Far East through Portuguese sailors. Other is the Unitarian theory, according to which the disease originated in the tropics as a primitive treponemal disease (such as
yaws) and later spread to more temperate climates affecting more advanced communities where transmission by sexual contact became the usual mode of spread of disease (Thin, 1990). The third possibility is that syphilis developed in both hemispheres from related diseases bejel and yaws (Gupta and Kumar, 2005).

Origins of syphilis in India

Evidences suggest that syphilis was unknown in India before the early sixteenth century (Arnold, 1993). Careful examination of available records suggests that Charaka and Sushruta did not know anything about syphilis. Some of the first references to the disease and its treatment are to be found in Bhavaprakasa, a mid-sixteenth century text, of an Ayurvedic physician Bhavamisra of Benaras (now Varanasi). During that period and subsequently for a long time, syphilis was known in India as Portuguese disease or Firanga or Firangi roga. The disease was first recognised in India in 1498 after arrival of Vasco de Gama from Portugal (Thappa, 2002).

The experiment by John Hunter (1728-1793) gave rise to a misconception of common etiology of syphilis and gonorrhoea. He had inoculated himself with the patient’s urethral discharge. The development of chancre as well as gonorrhoea made him propagate this concept. Later Philip Ricord in 1838 proved the concept to be erroneous and established syphilis and gonorrhoea as two distinct disease entities. Fritz Schaudinn and Eric Hofmann of Hamburg in 1905 discovered the organism T. pallidum (Thin, 1990; Bingham, 2005).
Epidemiology of syphilis

Syphilis occurs all over the world without any restriction to any social class (Siddappa and Ravindra, 2001). The prevalence of syphilis has declined worldwide with the introduction of penicillin in 1950s. In many western countries this trend was followed by an increase in 1960s and 1970s, probably due to sexual liberation taking place during that period. During the last decade the prevalence of syphilis has decreased in many countries. However syphilis still remains to be a major public health problem in many developing countries and a cause of increase concern in countries of Eastern Europe and Asia (Borisenko et al., 1999). WHO estimates that 12 million new cases of syphilis occurred worldwide in 1999 (WHO, 2001).

Syphilis in India

A country's socioeconomic structure and its functioning determine the prevalence of syphilis in a community (Siddappa and Ravindra, 2001). In India prostitution is still an important cause for spread of STDs. In prostitutes a significant association with syphilis has been observed for periods of exposure (i.e., age and years of working as a prostitute). Economic factors play a considerable role in prostitution particularly among the underprivileged.

In India syphilis has been reported to be the commonest STD accounting for 10.4% to 36.1% of STDs cases (Siddappa and Ravindra, 2001). A study from Ahmedabad by Parmar et al. (2001) reported syphilis in 28.90% of STD cases. In a study conducted from Rohtak by Aggarwal et al. (2002) found syphilis to be a major STD accounting for 24% of STD cases. While studies from Delhi by Khandpur et al. (2001)
and Davangere by Murugesh et al. (2004) reported syphilis in 15.56% of STD cases. A study conducted from (serving soldiers) all male patients from Jabalpur reported syphilis in 20.8% of the cases (Chatterjee and Ramadasan, 2004).

Classification of Treponemes:

Treponema pallidum ssp pallidum is the causative agent of syphilis. It belongs to the family Spirochaetaceae which also includes the genera Leptospira and Borrelia (Sanchez and Luger, 1993; Stamm, 1999).

Morphology of Treponema pallidum

T. pallidum is a fine motile microscopic organism measuring 6 to 20 μm in length and 0.10 to 0.18 μm in thickness. It has 6-20 regular tight spirals with a coil wavelength of 1.1μm and amplitude 0.2 to 0.3 μm but it lacks the capsule. It has an outer membrane, an inner (cytoplasmic) membrane and a thin cell wall composed of peptidoglycan (Stamm, 1999).

Ultra microscopic studies reveals 3 main elements of the organism viz the protoplasmic cylinder (protoplast), 6 periplasmic flagellar axial filaments that are twisted around the periplast in one or two bundles and the cell wall. Six axial filaments three attach at either ends are responsible for the motility and participate in cell attachment which are essential early steps in the pathogenesis (Sanchez and Luger, 1993): The periplasmic flagella are composed of a hook basal body complex and a flagellar filament made up of multiple proteins that are arranged into an outer sheath and central core. T. pallidum also contains cytoplasmic filaments that are ribbon like structures (7 to 7.5 nm.
wide) that run along the length of the organism. An array of four to six cytoplasmic filaments lie beneath the inner membrane and parallel to the periplasmic flagella (Stamm, 1999).

Movement of the organism

The organism has a characteristic purposeful movements, namely rotation around its long axis like a corkscrew, a slow backward and forward movement, bending, compression and expansion and looping with the shape of rigid coils being maintained. These characteristic movements are observed under the dark – field microscope. It is because of the spiral shape of the organism and the unique location of the flagella that the organism is able to retain its motility in viscous fluids like those found in the eyes, joints, and extracellular matrix of the skin.

Characteristics of T. pallidum

T. pallidum is unusual in a number of aspects, including

- The small genome size
- Inability to grow under in-vitro conditions.
- Microaerophilism
- Apparent paucity of outer membrane proteins
- Structurally complex periplasmic flagella
- Ability to evade the host immune responses and cause disease over a period of years to decades.
T. pallidum is difficult to stain with usual dyes and special staining methods like the silver impregnation method and immunofluorescent staining are required to demonstrate it.

The outer membrane spanning proteins, referred to as treponemal rare outer membrane proteins (TROMP), represents potential surface-exposed virulence determinants and targets of host immunity (Blanco et al., 1997).

The organism divides by transverse fission every 30-33 hrs in early syphilis and presumably at a much slower rate in late syphilis. The organism requires moisture for its survival (Sanchez and Luger, 1993).

The organism has so far not been cultured in any artificial media but it can be propagated and kept viable in tissues like the testis and eyes of rabbits. The rabbit inoculation test (RIT) is considered to be very sensitive and specific method to detect T. pallidum in clinical specimens in research settings. It is susceptible to heat, drying, freezing, antiseptics and antibiotics (Siddappa and Ravindra, 2001). Twenty different strains of T. pallidum has been isolated from cerebrospinal fluid, aqueous humor, blood and chancre.

Classification of Syphilis

Syphilis is classified into the acquired type and the prenatal type based on the mode of transmission (Musher, 1990).
Acquired syphilis

**Early infectious phase** (Diagnosed in first two years of infection):

Primary stage
Secondary stage
Recurrent stage
Early latent stage

**Late, non-infectious phase:** (Diagnosed after the second year of infection):

Late latent stage
Late benign stage (gumma)
Cardiovascular syphilis
Central nervous system syphilis

**Prenatal syphilis**

(Since T. pallidum is introduced directly into the fetal circulation, there is no primary stage as seen in acquired syphilis)

**Early phase** (within the first two years of life):

Analogous to secondary stage of acquired syphilis

**Late phase** (After two years of age):

Analogous to the tertiary stage of acquired syphilis
Stigmata
Scars and deformities resulting from early or late lesions which have healed.

Transmission
Syphilis spreads through contact with infectious lesions or body fluids. It is acquired through direct sexual contact with an infected person in the early stages of the disease or via transplacental route from an infected mother to foetus in prenatal syphilis. Late stage of syphilis is non-infectious. The variable factors that influence the transmission of infection include the number of exposures, the type of sexual activity and morphology and distribution of lesions in infected partners (Brown et al., 1999).

The term ‘syphilis brephotropica’ was coined by Jadassohn referring to syphilis transmitted while performing baby care or handling children. Breast feeding does not result in transmission of syphilis unless an infectious lesion is present on the breast. In patients with syphilitic lesions on the lips (or) oral cavity, moist kisses are another mode of transmission (Brown et al., 1999).

Syphilis can also be transmitted by transfusion of infected blood. Routinely the blood is screened for syphilis by serological tests but in up to 75% of patients with early primary syphilis the test may be negative. Treponemes remain alive in the blood stored at 4°C only for 2 to 3 days minimizing the risk of transmission. Patients receiving fresh blood are at a higher risk of transmission if the donor is in the window period. Transfusion transmitted syphilis presents directly as secondary syphilis (bypasses primary stage) and is known as ‘syphilis d’emblee.'
Pathogenesis and Course of the disease

To enter the body T.pallidum probably needs a macroscopic or microscopic trauma in the squamous or columnar epithelium which occurs during sexual intercourse. Following inoculation, T.pallidum attaches to the host cells and starts multiplication. Within a few hours some organisms stay at the site of entry but significant members reach the regional lymphnodes via the lymphatic system and disseminate throughout the body via the circulation.

A chancre develops at the site of inoculation after an incubation period ranging from 9-90 days (average 21 days) depending upon the inoculum the average incubation period (21 days) suggests the introduction of an average inoculum of 500-1000 organisms. The primary lesion slowly heals by scar formation.

A similar tissue reaction in the regional lymph nodes results in a characteristic enlargement of lymph nodes. Dark field examination is positive during the early stage. On the other hand, nontreponemal serological tests are usually negative until one week after the appearance of the chancre (seronegative primary syphilis); they are usually positive by 4 weeks after the appearance of lesion (seropositive primary syphilis).

The lesions of secondary syphilis results from a generalized tissue reaction to the presence of T.pallidum that have been disseminated through the circulation. Their appearance is subject to variation. They usually appear 6 to 8 weeks after the appearance of chancre. Secondary lesions recede in 4-12 weeks but relapses occur in about 25% of untreated patients within the first year. In some cases the tissue reaction in the primary and secondary stages are so slight that they go unnoticed.
After the resolution of the secondary stage, the disease enters into the stage of latency with no signs and symptoms, yet the infection is still present (particularly in the spleen and lymphnodes) and active. Sometimes the immunity fails to control the infection and the treponemes again multiply, producing either a recurrence of primary lesions or lesions of secondary type.

The latent stage which follows the secondary stage may persist for life in asymptomatic form in 60-70% of patients, or progress to neurosyphilis (6.5%), cardiovascular syphilis (9.6%) or late benign gummatous syphilis (16%) (Sanchez and Luger, 1993).

**Primary syphilis**

(Primary sore or chancre, Hard sore or chancre, Hunterian chancre)

After an incubation period of 3 to 90 days primary chancre develops at the site of inoculation. Initially it develops as a small red macule which soon becomes a papule and subsequently ulcerates to form a chancre, which is a classical lesion of primary syphilis. The classic hunterian chancre is a single, painless, indurated (cartiligenous) ulcer, round to oval in shape, clearly defined, with rolled borders and 'ham colour smooth base but sometimes may be covered with grayish slough or slightly haemorrhagic crust. The size of the chancre varies from 0.3cm to 3cm.

Most chancre are genital (90-95%). The usual sites in males are coronal sulcus (35%), glans (29%), shaft (22%), prepuce (19%), frenulum (10%) and in urinary meatus (1%) (Sanchez, 2003). In homosexual and bisexual males who practice receptive anorectal intercourse chancre are seen to occur on anus or in anal canal or rectum.
In females lesions occur on the cervix in almost half of the cases and hence may be hidden. The other sites include the outer and inner aspect of labia, vulva, and around clitoris, urethral orifice, fourchette or vagina.

**Extragenital lesions**

They occur in 5-10% of patients with primary syphilis. They usually occur from contact with genital or extragenital lesions in partner during sexual foreplay or due to anal or oral sex. The most common site involved are the lips, tongue, tonsils, fingers, and breast.

**Lymph nodes**

In majority of cases the regional lymphnodes becomes enlarged within a week of appearance of primary lesion. They are often bilateral in case of genital or anal ulcers, and unilateral in case of extragenital ulcers. The lymph nodes are discrete, painless, small to moderate in size, of a firm rubbery consistency and nonsuppurative.

**Chancre redux (‘Monorecidive’)**

It is the recurrence of a primary sore at the site of the original lesion. It is considered as a form of relapse. The lesion is infectious as the treponemes can be obtained.
Pseudochancre redux

It also occurs at the site of the original chancre, however unlike true chancre redux, it is non-infectious granulomatous lesion of late syphilis from which treponemes cannot be recovered.

Syphilis balanitis of Follman

It is a noninflammatory reaction of glans penis in primary syphilis to T.pallidum, which may develop instead of, before, after or simultaneously with primary chancre. The treponemes are present which can be demonstrated by DGI or in histologic sections. The balanitis is superficial as the organism is seen only in epidermal cell layers.

Syphilis d' emblee

It is defined as syphilis without chancre. It is a consequence of direct inoculation into the blood as a result of transfusion of infected blood or blood component or puncture with an infected needle. As the inoculation is directly into the blood generalized syphilis develops without a local reaction.

Condom Chancre

It occurs when the proximal portion of the shaft of penis, the pubis or the groin are involved when the penis is protected by a condom (“condom chancre”). Kissing chancre on coronal sulcus in males and on labia minora in females are not uncommon.

An untreated primary chancre resolves on its own after a period of 3 to 6 weeks living behind thin atrophic scar which can be an important diagnostic clue in patients
presenting with rash of secondary syphilis. With adequate treatment the ulcer heals in one to two weeks time (Musher, 1999).

Complications

Includes oedema, phimosis, erosive balanitis, lymphangitis, and thrombophlebitis of the dorsal vein. Phagedenic chancre is due to coinfection with fusospirochaetes characterized by necrotizing perforation of prepuce, or in some patients gangrene.

Secondary syphilis (S2)

The secondary stage begins two to eight weeks after the appearance of primary chancre. One fourth of the patients are probably still recovering from primary chancre when secondary stage becomes manifested.

The clinical manifestations of secondary stage are protean and can involve any organ. (Kumar et al., 2001). Signs and symptoms may be transient or obvious, indolent and occasionally destructive (Sanchez and Luger, 1993). Some patients may develop a flu-like prodrome manifestating as fever, malaise, headache, stiff neck, myalgia, arthralgia and rhinorrhoea. However skin rash and lymphadenopathy are common manifestations of secondary syphilis and are seen in 67% to 92% and 63% to 100% patients, respectively (Kumar et al., 2001).

The skin rash is the most common presenting feature of secondary syphilis, as many as 60% of patients with serological evidence of syphilis do not recall any type of lesions. The rash is often subtle and sometimes consisting of one or two lesions that may pass unnoticed. The rash can be of various types such as maculopapular,
papulosquamous, psoriasiform, annular, pustular or follicular. Macular or maculopapular rash is the commonest and is seen in about 50% of the patients. Classically the lesions are described as “raw ham” or copper coloured, however in patients with pigmented skin this characteristic color is absent.

The rash is usually distributed bilaterally and symmetrically. Macular eruptions also known as roseola syphilidica, consist of 0.5 cm to 2 cm pink, discrete, round to oval, macules distributed over the trunk, flexor aspect of upper extremities and palms and soles. Face is usually spared.

Papular or papulosquamous lesions evolve from macular lesions. Papules along the hairline on forehead are sometimes arranged in a crown like pattern that is known as “corona veneris.”

There is a deep dermal tenderness that is elicited by applying pressure with a blunt side of pin over the papule. The sign is pathognomonic for syphilis and is known as Buschke Ollendorf sign. The other variants of skin lesions are nodular, lichenoid, annular and corymbose.

**Condyloma lata**

They are usually seen in warm moist areas of the body, such as genitals, perineum, perianal region, under pendulous breast, axilla and groin, the skin and mucosal lesions of secondary syphilis may proliferate into pale, elevated, moist sharply demarcated papules with flat surfaces. These lesions are highly infectious and are seen in some 25% to 60% of patients with secondary syphilis. At the labial commissures and nasolabial folds these lesions become elevated and fissured and are called “split papules.”
Mucous membrane

Its involvement is common in secondary syphilis. Mucosal lesions on genitalia are more common in women because moisture, friction and some irritation favour their development. They can also occur on the external genitalia as well as on cervix. All these moist lesions on the skin or mucosa are teeming with treponemes and are highly infectious.

Follicular rash on scalp may give rise to two pattern of hair loss one is "moth eaten" alopecia that occurs on the margin of scalp or rarely in other hairy areas including the beard, eyebrows and legs. Telogen effluvium has also been noted in patients with secondary syphilis.

Rarely involvement of nail fold or nail matrix by rash of secondary syphilis results in nail changes, which include pitting, onycholysis, onychodystrophy and Beau’s lines.

Systemic manifestations of syphilis

Systemic manifestations of syphilis include malaise, fever, mild hepatitis with elevated liver enzymes, iritis, uveitis, arthritis, parotitis, pulmonary changes and glomerulo nephritis. Neurological involvement is common but is often asymptomatic. A study by Rolfs et al. (1997) demonstrated that T. pallidum invades the central nervous system in at least one fourth of the patients with early syphilis irrespective of HIV status. Accelerated course of syphilis has been observed in association with immunosuppression caused by concurrent HIV infection.
Headache is present in up to one-thirds of patients and fever is usually low grade seldom exceeding 100°F.

Gastrointestinal symptoms include anorexia, nausea, and occasionally vomiting.

Hepatosplenomegaly is reported to occur in 4% to 23% of patients and Jaundice in up to 12% of patients with early syphilis.

Kidney involvement is extremely rare, but asymptomatic proteinuria is well documented other renal manifestations include nephritic syndrome, rapidly progressive glomerulonephritis and renal failure.

Cardiovascular complications in secondary syphilis is rare. Myocarditis and ventricular arrhythmia are well documented.

Lymphadenopathy involving two or more groups is seen in 60% to 100% of patients. Enlarged lymphnodes are rubbery, painless, discrete, and non-tender. The occipital, axillary, inguinal, epitrochlear groups of lymph nodes are most commonly involved.

Lues maligna or malignant secondary syphilis is an explosive, wide spread form of secondary syphilis that is characterized by prodrome of fever, headache, and myalgia followed by papulo-pustular eruption that rapidly transforms into necrotic, sharply margined ulcers with haemorrhagic brown crusts that are organized in rupoid layers (Kumar et al., 1998). The term lues maligna was coined by Bazin and Dubue in the mid 1800s to describe mutilating noduloulcerative variants of secondary syphilis. With the onset of HIV epidemic several cases of lues maligna in association with HIV infection induced suppression have been reported (Kumar B et al., 2001).
Latent syphilis

Early latent Syphilis

After healing of the secondary syphilitic lesions and occasionally directly after primary stage the patient enters into a long phase of latency. The dividing line of two years between early and late latent syphilis is rather an arbitrary one and Centre for Disease Control (CDC) puts the limit at one year. There are no clinical symptoms and signs and diagnosis is based on finding positive reaginic and specific test of syphilis.

Early Relapsing Syphilis

Relapse occurs in about 25% of the patients during latent phase among untreated syphilitics. About 75% relapses are observed during the first six months, 90% within the first year and none after five years. Occasional occurrence of a relapsing lesion resembling a primary chancre has been referred as ‘monorecidive’ or ‘chancre redux’. It is the result of the proliferation of residual treponemes at the initial site.

Late syphilis

After 2 years the disease enters the non-infective stage. For the majority of untreated patients it remains latent without any clinical manifestations and can be suspected only during blood testing for blood donation, antenatal check ups for immigration purposes. VDRL serology is positive in low dilutions it needs to be confirmed by specific tests for syphilis and in all such cases more serious asymptomatic
neurosyphilis needs to be excluded by CSF examination. The tell-tale signs of early syphilis like the penile scar of healed primary sore may be evident.

Tertiary Syphilis

The lesions of tertiary syphilis usually manifests at about 3 to 10 years after the primary infection. The tissues most commonly involved are skin, mucous membranes, subcutaneous tissue, bones, joints, muscles, ligaments. The characteristic lesion in late syphilis is gumma, which may occur singly, or in isolated groups. Gumma can be in nodular, nodulo-ulcerative, or subcutaneous form. Gumma can involve mucous membrane of throat, palate, pharynx, larynx and nasal septum.

Cardiovascular syphilis

Cardiovascular syphilis becomes clinically manifest only in tertiary stage of the disease after about 15-40 years of primary syphilis. It is more common in men. It may lead to aortic aneurysm, coronary stenosis, aortic valve insufficiency (commonly regurgitation) and rarely myocarditis. In the post-antibiotic era, cardiovascular syphilis has become rare even in patients with AIDS. (Swartz et al., 1999).

Neurosyphilis

In the penicillin era and before and during the early years of HIV epidemic, there were few recognised cases of neurosyphilis. However following HIV epidemic, there has been an increase in the incidence of early (acute syphilitic meningitis) and later forms of neurosyphilis like Tabes dorsalis, meningo-vascular syphilis and generalised paresis.
Classification of neurosyphilis

Classification is difficult because its different clinical syndromes may overlap amongst different patients and even within the same patient. However the classification given by H.H. Meritt is commonly used (Swartz et al., 1999).

Classification of Neurosyphilis

<table>
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<th>Meningeal</th>
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<td>Spinal</td>
<td>Optic atrophy</td>
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Neurosyphilis and HIV

In HIV infected persons, rapid progression of syphilis to neurosyphilis and treatment failure are common. HIV infected persons may be more likely to develop secondary syphilis, atypical neurosyphilis and atypical serological tests for syphilis. As both the diseases affect the neurological symptoms, the clinical picture may sometimes be confusing.

Syphilis in pregnancy

Syphilis can seriously complicate pregnancy resulting in spontaneous abortion, stillbirth, intrauterine growth restriction, and perinatal death as well as serious sequelae in liveborn infected children, such as hepato-splenomegaly, cardiac manifestations etc. The
prevalence of syphilis seroreactivity among pregnant women varies from as low as 0.02% to as high as 12.1% in different parts of the world (Lumbiganon et al., 2002).

The rate of transmission to foetus in untreated women is approximately 70% to 100% in primary and secondary syphilis, 40% in early latent syphilis and 10% in late latent syphilis (Sanchez and Luger, 1993). A high rate of foetal morbidity and mortality occurs in untreated first and second trimester infection in comparison to third trimester infection which is often asymptomatic (Wicher and Witcher, 2001).

**Congenital syphilis**

Transmission of a syphilitic infection from the mother to the foetus via the placenta is congenital syphilis. It may occur when the infected women becomes pregnant or when a pregnant women becomes infected.

**Outcome of Pregnancy**

The following may happen to untreated syphilitic pregnant women:

1. Miscarriage may ensue at some period later than 12-16 weeks, following the formation of placenta.

2. In about 30% of the cases, the foetus may die in utero late in pregnancy resulting in still birth/macerated foetus.

3. In a few cases the foetus may be born apparently normal, but develops signs of early congenital syphilis during the first few weeks or months (Profeta's law).
4. In a few cases the foetus may be born showing the signs of congenital syphilis.

5. The infant with early congenital syphilis subsequently may or may not show signs of late congenital syphilis.

6. The child may not show early congenital syphilis but may develop late congenital syphilis in later years.

7. The foetus may escape the infection. This may occur with increasing probability with longer duration of the disease in expectant mother.

The observations that the untreated syphilitic mother tends to improve on the past performances; that is to have later and later miscarriages, then syphilitic and finally non-syphilitic children. (Diday’s or Kassowitz’s law).

Colles (1837) had made an observation that the syphilitic infant did not infect its own mother but is capable of infecting others (Colles’ law). It is now clear that it is because the mother is probably having latent form of syphilis and has a degree of immunity to super infection from her own child.

The incidence of congenital syphilis is quite low though the reported incidence in India varies from 0.5% to 5% (Singh, 2003).

The prevention of congenital syphilis depends on adequate follow-up during pregnancy. An ideal routine for antenatal clinic would be to examine the pregnant woman and take blood for VDRL checkup as early and as late in pregnancy as possible. The control of congenital syphilis depends on adequate treatment being given to the infected pregnant women at the earliest. Congenital syphilis is a preventable disease. Adequate
therapy before the fourth month of pregnancy almost always prevents the infection in the newborn.

**Early Congenital Syphilis**

There is no primary stage and signs are similar to those of secondary stage of acquired syphilis. If a lesion resembling primary chancre is seen in an infant, it may be due to acquired syphilis from genital lesion of very recent infection in the mother. Condylomata lata lesions at mucocutaneous and intertriginous areas of perianal skin are markers of untreated congenital syphilis, which shows recurrences.

**Signs of early congenital syphilis**

1. Vesiculobullous lesions on palms and soles
2. Condyloma lata at anus
3. Snuffles—serosanguinous nasal discharge
4. Pseudoparalysis of extremities due to epiphysitis of long bones.
5. Hepatosplenomegaly
6. Pleural effusion and pneumonia Alba
7. Ascites
8. Hydrocephalus, meningitis and encephalitis.

**Late congenital syphilis**

The late stage of congenital syphilis is beyond second year of life. The early stage may go unnoticed in approximately 80% of cases of late congenital syphilis. The classical
syndrome of late congenital syphilis is now rare because of concomitant antibiotic treatment of other intercurrent infections.

The clinical manifestations may be due to hypersensitivity or inflammatory reaction to T. pallidum and some are mentioned below.

1. **Interstitial keratitis**

   It is the most common late manifestation, particularly in female child. It appears at any time between the age of 5 and 16 years. The symptoms are photophobia, pain, excessive watering of the eyes and blurred vision.

**Teeth**

I. **Hutchinson's teeth**

   The permanent upper central incisors are barrel or peg shaped with a notch in the biting edge.

II. **Mulberry or Moon’s molar**

   It affects the first lower molars. The cusps of the affected teeth are underdeveloped and poorly enamelled. Due to poor development of enamel, the teeth are predisposed to cavity formation.

2. **Neural deafness**

   It occurs due to osteochondritis of the otic capsule leading to cochlear degeneration. It may be preceded by tinnitus, vertigo and loss of hearing.
3. Cluttons joints:

Some children with congenital syphilis may develop symmetrical painless swelling of knees (occasionally elbows) often following trauma.

4. Gummas

Gummata of the palate, throat and nasal septum may occur in late childhood or even adulthood, and lead to painless perforation of soft palate and septum usually in the midline. Similarly deep ulcers may occur in throat and on tongue.

5. Bones

Tibia is commonly involved and the thickening of the middle third of the bone may give appearance called ‘sabre tibia’. The vault of the skull shows formation of rounded bony swellings called ‘Parrot’s nodes’ and the frontal and the parietal bones show permanent thickening called ‘craniotabes’.

Congenital neurosyphilis

It is often asymptomatic. Symptomatic neurosyphilis is usually delayed until adolescence and manifests similar to adult pattern.
Laboratory test for syphilis

Serological tests for Syphilis and their application

Serological testing is the most common method of demonstrating infection with T. pallidum (Larsen et al., 1995). Cultivation in artificial culture media, chick embryo or tissue culture is not possible, and microscopy can be misleading if results are negative. Serological test for syphilis can be classified into two groups:

I. Non treponemal test - detects non specific treponemal antibody, eg. The Venereal Disease Research Laboratory (VDRL) or Rapid Plasma Reagin (RPR).

II. Treponemal test - detects specific treponemal antibody, eg. Treponema pallidum haemagglutination assay (TPHA), fluorescent treponemal antibody-absorbtion (FTA-Abs) and enzyme immunoassay (EIA) tests.

Non treponemal test

In 1906, Wassermann et al adapted the complement fixation test, for serological testing of syphilis. The antigen used in the Wassermann test for syphilis was an extract of liver from newborns, who have died of congenital syphilis and latter beef heart extracted in alcohol, served equally well as an antigen. The main disadvantage of this test were the test being too complicated to perform, requiring many reagents and requiring as long as 24 hours to complete.
Kahn in 1922 introduced a flocculation test without complement that could be read microscopically in a few hours but the antigen, a crude extract of the tissue, varied in quality.

Pangborn in 1941 successfully isolated from beef heart the active antigenic component, a phospholipid cardiolipin. Cardiolipin when combined with lecithin and cholesterol, forms a serologically active antigen for the detection of syphilitic antibody. This cardiolipin-cholesterol-lecithin antigens could be standardised chemically as well as serologically, thus ensuring greater reproducibility of test results both within and between laboratories.

Non-treponemal tests can be used as qualitative tests for initial screening or quantitative tests to follow treatment. The nontreponemal (reagin) tests measures IgM and IgG antibodies to lipoidal material released from damaged host cell as well as to lipoprotein like material and possibly to cardiolipin released from treponeme.

Disadvantages

Antibodies against cardiolipin may also occur in absence of treponemal infection and give what has been referred as biological false positive (BFP) reactions.

BFP reactions are defined as those present in patients whose serum gives positive cardiolipin antigen test but negative specific treponemal antigen test in presence of past or present treponemal infection.

False positive reactions can be divided into two groups: those that are acute false positive reactions of less than 6 month in duration and those that are chronic false positive reactions that persist for more than 6 month. Acute false positive reactions have
been associated with hepatitis, infectious mononucleosis, viral pneumonia, chicken pox, measles, other viral infections, malaria, pregnancy and laboratory and technical error.

Chronic false positive reactions have been associated with connective tissue diseases such as SLE or disease associated with immunoglobulin abnormalities which are more common in women and in conditions like narcotic addiction, aging, leprosy and malignancy.

**Basis of Non treponemal tests**

<table>
<thead>
<tr>
<th>Capture system</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomes in suspension producing visible flocculation with lipoidal antibodies</td>
<td>VDRL</td>
</tr>
<tr>
<td>Liposomes in suspension + unattached charcoal particles producing dark coloured flocculation due to trapping of charcoal particles in lattice formed by antigen-antibody complex</td>
<td>RPR</td>
</tr>
<tr>
<td>VDRL antigen coated onto wells of microtitre plates and attached antibody detected by enzyme immunoassay</td>
<td>EIA (Reagin)</td>
</tr>
</tbody>
</table>

Two commonly available non treponemal test are Venereal Disease Research Laboratory (VDRL) test and Rapid Plasma Reagin (RPR) card test. Both test have the same standardised antigen comprising of lecithin, cholesterol, and purified cardiolipin (a component of mammalian cell membranes) to detect antibody against cardiolipin. Both test have same sensitivity and specificity.
**Venereal Disease Research Laboratory (VDRL test) (Harris test)**

In 1946 Harris et al., described the Harris or Venereal disease research Laboratory (VDRL) slide test, a flocculation reaction (Thin, 1990).

VDRL slide test has to be read using a microscope. The test is performed on serum heated at 56°C for 30 minutes. Serum and antigen are mixed within the ring on a glass slide by rotating it mechanically and results are read in a microscope at 100X magnification. If anticardiolipin antibodies are present, the antigen rods aggregate to form clumps. A quantitative test can be performed using serial dilutions of serum.

**Rapid plasma Reagin test (RPR test)**

RPR test can be read visually (macroscopically) because of presence of coloured substance in the antigen preparation. It is performed on plastic coated cards onto which circles have been imprinted. Standardised amounts of undiluted serum and stabilised antigen suspension containing charcoal particles are mixed within the circles and spread over it. To perform quantitatively, serially diluted serum is mixed with antigen. The card is rotated at 100 rpm for 8 minutes. Presence of anticardiolipin antibodies produces flocculation of charcoal particles, which is considered as a positive test.

The RPR test has several advantages over VDRL test. It can be read macroscopically because of addition of charcoal particles, the antigen used is stabilized and cards are used instead of slides and it is performed with unheated serum.

**The variants of VDRL test**
The unheated serum reagin (USR) test

This test uses a stabilized VDRL antigen and is performed in unheated serum. The results are comparable to VDRL although the sensitivity and specificity are a little lower.

The automated reagin test (ART)

The reagents of the RPR test are used in this test but it can be performed in an autoanalyzer. The results of photometric reading are printed on record forms.

Toluidine red unheated serum test (TRUST)

This test is identical to RPR test except that the antigen remains stable over a period of six months. Toluidine blue is substituted for charcoal and provides better visualization. Sensitivity, specificity and reproducibility are 2% less compared to VDRL and RPR test.

Treponemal test

In 1949, Nelson and Mayer developed the first treponemal antibody test, the T. pallidum immobilization (TPI) test. The TPI test uses T. pallidum (Nichol’s strain) grown in rabbit testes as an antigen and is based on the ability of the patient’s antibody and complement to immobilize living treponemes as observed by dark field microscopy. The TPI test is a specific test for syphilis but as the test is complicated, technically difficult, time consuming and expensive to perform a simpler procedure was sought.

In 1957, a major breakthrough in treponemal antigen tests occurred with the development of the fluorescent treponemal antibody (FTA) test.
The role of ELISA in the serological diagnosis of syphilis is currently limited. Only a few companies are able to offer tests and detect anti-syphilis immunoglobulin G (IgG) and anti-syphilis immunoglobulin M (IgM).

**Basis of treponemal tests**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Capture system</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact Treponemes</td>
<td>Treponemes fixed onto microscope slides</td>
<td>FTA-ABS</td>
</tr>
<tr>
<td>Purified and sonicated treponemes</td>
<td>Attached to red blood cells</td>
<td>TPHA</td>
</tr>
<tr>
<td></td>
<td>Attached to gelatin particles</td>
<td>TPPA</td>
</tr>
<tr>
<td></td>
<td>Attached to microtitre plates</td>
<td>EIA</td>
</tr>
<tr>
<td></td>
<td>Proteins separated by PAGE and transferred to filter paper by Western blotting</td>
<td>Immunoblots</td>
</tr>
<tr>
<td>Recombinant antigens</td>
<td>Attached to microtitre plates</td>
<td>EIA</td>
</tr>
<tr>
<td></td>
<td>Attached to latex particles</td>
<td>Latex agglutination</td>
</tr>
</tbody>
</table>

PAGE – Polyacrylamide gel electrophoresis

**The variants of TPHA test**

- The microhemagglutination assay with T. pallidum antigen (MHA-TP)
- The automated microhemagglutination assay with T. pallidum antigen (AMHA-TP)
Syphilis and HIV

There is a strong epidemiological association between infection with Treponema pallidum and infection with HIV (Gwanzura et al., 1999). Coinfection with T. pallidum and HIV interact at several levels. Both are sexually transmitted and both facilitate transmission of each other.

The three features of syphilitic chancre, which have been considered to contribute, are:

- The breach in continuity of the epithelium creating a portal of entry,
- The influx of large number of macrophages and T cells that provide an environment enriched with receptors for HIV and
- Production of cytokines by macrophages (stimulated by treponemal lipoproteins) may enhance HIV replication.

In HIV seropositive individuals, the primary chancre presents in various morphological forms including the gangrenous, phagedenic and erosive. It may still be present even when lesions of secondary syphilis appears. This could be due to rapid progression of disease or delayed healing of primary lesion. Similarly clinical variants like corymbose, annular, nodular or pustular of secondary syphilis are seen more frequently in HIV seropositive patients.
Ulcerating secondary syphilis (malignant syphilis) with general symptoms like headache, high fever and weakness are about 60 times more frequent in HIV positive individuals than in HIV negative individuals (Schofer et al., 1996).

Syphilis occurring in advanced HIV disease may have more atypical findings, which are more common in patients with low CD4+ lymphocyte counts (Hutchinson et al., 1994). In general HIV infected patients with advanced immunosuppression tend to have larger primary chancre, multiple ulcers, more frequent systemic symptoms in secondary stage, simultaneous multiorgan involvement, accelerated course and development of neurosyphilis in early stage of infection.

Majority of HIV infected patients have a normal serological response to treponemal infection, while some demonstrate an exaggerated immune response and some a lack of immune response, resulting in diverse serological presentations. Syphilitic patients who are HIV seropositive are less likely to experience serological improvement after recommended therapy than patients who are HIV negative. Therefore considerations should be given to design alternative therapeutic regimens.

**Treatment for syphilis**

Treatment regimens for early syphilis

**Recommended Regimen:** (CDC, 2002).

- Benzathine penicillin, G 2.4 million units intramuscular (IM) half in each buttocks in a single dose (or)
- Procaine penicillin G 1.2 million units IM daily for 10 days.
Alternative drugs (in patients allergic to penicillin) (Any one)
(CDC, 2002)
Doxycycline 100 mg orally twice a day (bid) for 2 weeks
Tetracycline 500 mg orally four times a day (qds) for 2 weeks
Erythromycin 500 mg orally four times a day for x10 days
Azithromycin 500 mg orally twice daily x 10 days
Ceftriaxone 1 gm IM daily x 8-10 days.

Chancroid
(Synonyms - Soft chancre, ulcus molle, soft sore, chancre mou)

Definition
Chancroid is an acute localized, auto innoculable, sexually transmitted genital ulcerative disease caused by gram negative bacillus Haemophilus ducreyi. It is characterised by soft painful ulcerations at the site of inoculation often associated with suppurative regional lymphadenitis.

History
According to Kampmerer, chancroid was first described in France by Ricord and Bassereau in 1852 as ulcus molle, who differenciated it from the hard chancre of primary syphilis (Kampmerer, 1982).

In 1889 Augusto Ducreyi, a bacteriologist at the University of Naples first identified the bacillus Haemophilus ducreyi as the causative organism of chancroid by
serial inoculation of purulent material on the forearm of patients from their own genital ulceration (Reddy and Nanda 2005).

Unna in 1892 described the histology of chancroid and found the chains of gram negative rods in the lesions (Jaiswal et al., 2001).

The intradermal skin test with H. ducreyi was reported by Ito in 1913 and the work was confirmed by Reenstierna in 1923 (Balachandran and Pai, 2003).

Epidemiology

Chancroid has been described as the disease of the socially unenlightened, economically unfortunate and unwashed. It is a major genital ulcerative disease in Africa, South-East Asia, the Carribean, and Latin America.

According to WHO the annual estimate of the disease is around 7 million. (WHO, 1995). It is also associated with augmented transmission of Human Immunodeficiency Virus (HIV).

A gradual decrease in the prevalence of H. ducreyi was found in patients attending STD clinic in Durban, South-Africa from 35% in 1995 to 6% in 1998 (Kharsary et al., 2000). In USA the number of reported cases of chancroid has come down drastically from 4986 cases in 1987 to 243 cases in 1997 (CDC, 1997). It is a rare disease in Australia, United Kingdom and Scandinavian countries, mainly seen in travelers returning from South-East Asia or in the aborigines population (Over et al., 1996). The reported incidence of chancroid among STD patients in India varies from 8 to 35 percent (Jaiswal et al., 2001).
Age

It is primarily the disease of sexually active individuals mostly belonging to age group of 20-30 years (Jaiswal et al., 2001).

Sex

Males are far more affected than females. The ratio of males to females in various studies range from 3:1 to 53:1 (Balachandran and Pai, 2003). The exact reasons for this vast difference is unknown, but it may be due to because of following factors.

1. The environment provided by the foreskin makes males more susceptible to H. ducreyi.
2. In women ulcers are often asymptomatic and hidden.
3. Existence of asymptomatic carrier state in women.
4. Low socio-economic status: It is prevalent in individuals of lower socio-economic group, living under low hygienic conditions, who frequently visit prostitutes. The other contributing factors are
   a. Lack of circumcision.
   b. Alcohol.
   c. Drug use particularly crack cocaine.

Transmission

The disease spread from person to person only through sexual contact, and in the same person it can spread through autoinoculation. Prostitutes of lower middle social strata are main reservoir of H. ducreyi. There are no reports of chancroid occurring in infants born to women with active chancroid at delivery. Auto inoculation of fingers or
other sites is reported occasionally. Fomites have not been shown to play any role in transmission (Ronald and Albritton, 1999).

Plummer et al. (1983) has reported that the chances of acquiring infection during single act of unprotected exposure from men to women are as high as 63%. In absence of treatment, the duration of infection has been estimated to be 45 days in women, and it appears that the risk of transmitting the disease is much more with patients having visible lesions.

**Etiology**

**Taxonomy**

H. ducreyi is gram-negative, facultative anaerobic bacillus, which is small (1.2 x 0.5μm), non motile non spore forming streptobacillary rod with rounded ends. Groups of organisms are often found in short chains, giving the appearance of a “school of fish” or “rail rod tracks” which are seen in smears from cultures (Albritton, 1989).

**Biochemistry**

It has distinguishable biochemical factors. Nitrate reduction is the characteristic feature of the genus. It is oxidase positive and catalase negative and has a broad range of phosphatase activity. The alkaline phosphatase reaction is used as a differential marker for identification (Albritton, 1989).
Growth medium

*H. ducreyi* is a fastidious bacillus that require hemix (X factor) for growth. Various media are used such as heart infusion agar, with 5% defibrinated rabbit blood. All these media are enriched with 1% isovitalex, 5% fetal bovine serum and 3μg/ml vancomycin. They are incubated at 30-35°C in a humidified 6% CO₂ atmosphere. The plates are held for 7 days before being reported as negative. Small waxy yellow colonies are typical for *H. ducreyi* and can be subcultured on chocolate II agar for further identification (Albritton, 1989).

Pathogenesis

Presence of trauma or abrasion of epidermis is necessary for *H. ducreyi* to penetrate epidermis, and the inoculum size required to cause infection is greater than 10⁴. In tissue the organism is usually present within macrophages, neutrophils and also as clumps in the interstitium. Cytotoxin produced by the organism cause cell damage which may result in formation of ulcer (Balachandran and Pai, 2003).

Incubation period

The incubation period is usually short and ranges from 1 to 14 days (Felman and Nikitas, 1983), with a median of 7 days between inoculation and appearance of first skin lesion (Ronald and Plummer, 1985).
Clinical-manifestations

Type of ulcer

The ulcer begins as a soft tender papule with erythematous halo, within 24-48 hrs evolves to a pustule, erosion and ulcer. The ulcer may be single or multiple. Multiple ulcers arise by autoinnoculation. The diameter of the ulcer may vary from 1mm to 2 cm. The edges of the ulcer are sharp, ragged and undermined. The base is nonindurated and is usually covered by (slough) yellowish gray necrotic exudates covering granulation tissue that bleeds readily on manipulation. Edema of prepuce is common, and phimosis or paraphimosis can be the initial presentation. The lesions are very painful.

Site of ulcer

In males in order of frequency they are seen on prepuce, frenulum or coronal sulcus. The glans, meatus and shaft of penis are less frequently involved. Rarely the ulcer is localised in the urethra causing purulent urethritis.

In females the lesions are localised mainly on vulva especially on the fourchette, labia minora and vestibule. Vaginal, cervical and perianal ulcers have also been reported.

The extragenital sites are less commonly involved and have been described on the tongue, fingers, lips breasts, oral mucosa and perianal area.
Clinical variants of chancroid

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Types of chancroid</th>
<th>Size of ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Giant chancroid</td>
<td>Extensive ulcer more than 2cm diameter</td>
</tr>
<tr>
<td>2.</td>
<td>Phagedenic chancroid</td>
<td>Large and destructive ulcer with wide spread necrosis of tissue.</td>
</tr>
<tr>
<td></td>
<td>&quot;Ulcus molle gangrenosum&quot;</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Papular chancroid</td>
<td>Starts as an ulcer but becomes raised particularly around edges</td>
</tr>
<tr>
<td></td>
<td>&quot;Ulcus molle elevatum&quot;</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Transient chancroid</td>
<td>Small ulcer which resolves spontaneously in few days</td>
</tr>
<tr>
<td></td>
<td>&quot;chancre mou Volant&quot;</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Dwarf chancroid</td>
<td>Small and superficial ulcers which may resemble ulcers of herpes-genitalis (HP)</td>
</tr>
<tr>
<td>6.</td>
<td>Follicular chancroid</td>
<td>Originates in follicles, first stimulates pyogenic folliculitis.</td>
</tr>
<tr>
<td>7.</td>
<td>Serpiginous chancroid</td>
<td>Long and narrow ulcer that forms by confluence and auto inoculation of multiple ulcers.</td>
</tr>
<tr>
<td></td>
<td>&quot;Ulcus molle serpiginosum&quot;</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Granulomatous chancroid</td>
<td>It is another variant with hypergranulation tissue</td>
</tr>
</tbody>
</table>

Lymphadenopathy

A tender inguinal adenitis (more commonly unilateral) occurs in up to 50% of patients. It appears within a few days to 2 weeks (average 1 week) after onset of primary lesion. It may resolve or soften to form a unilocular abscess (bubo), when the overlying skin becomes typically erythematous. The bubo may rupture spontaneously. Both lymphadenitis and bubo formation is less common in females.
H. ducreyi has not been shown to cause systemic infections. No adverse effect of chancroid on pregnancy outcome or on the foetus have been reported.

Diagnosis

The laboratory confirmation of chancroid can be difficult due to the fastidious nature of H. ducreyi. Therefore the diagnosis of chancroid is essentially clinical, coupled with exclusion of other causes of genital ulcer diseases (GUDs). A combination of painful ulcer and tender suppurative inguinal adenopathy is almost pathognomonic of chancroid.

The various laboratory methods are as follows:

Microscopic examination of smears

Smears are taken with cotton swabs from beneath the undermined edges of the ulcers and stained with gram or Wright stain. The smear shows cluster of extracellular coccobacillary forms seen in groups of two or four, giving characteristic ‘school of fish’ or ‘rail road track’ appearance (Ronald and Albritton, 1999).

Culture and Identification

H. ducreyi is a fastidious microorganism and it is difficult to isolate from genital ulcer specimens. H. ducreyi survives for only 2 to 4 hours on a swab unless refrigerated. No satisfactory transport system is available. The swabs taken from the ulcer base has to be cleaned with sterile saline and immediately rolled on H. ducreyi selective culture
medium. Characteristic small, non-mucoid, yellow gray, translucent colonies appear 2 to 4 days after inoculation. The reported culture positivity rates vary from 35 to 80 percent.

**Polymerase Chain Reaction (PCR)**

A multiplex PCR (M-PCR) assay has been developed for simultaneous amplification of DNA targets from *H. ducreyi*.

**Chancroid and HIV**

Chancroidal ulcers are one of the common cause of genital ulceration and an important risk factor in heterosexual spread of HIV. Patients with chancroid are almost five times more likely to acquire HIV, than those without genital ulcer disease (Czelusta et al., 2000).

The biological bases for enhanced transmission of HIV in patients with chancroid are- Genital ulcers acts as both portal of entry and exit for HIV; and *H. ducreyi* infection recruits CD4+ T-lymphocytes and macrophages to genital surface, which are principal early targets of HIV infection.

In HIV infected patients with chancroid the ulcers are large in size and number with atypical presentations and severity. Extensive, necrotizing lesions, maggot formation and multilocular buboes may occur (Czelusta et al., 2000). The ulcers may take longer duration to heal.
Treatment

Chancroid without treatment is a protracted illness with slow and often incomplete resolution. Infection does not confer immunity and reinfection is possible. (Ronald and Albritton, 1999). Proper treatment of chancroid cures the infection, resolves the clinical symptoms, and prevents the transmission to others.

The CDC recommends the following treatment for chancroid (CDC, 2002).

Azithromycin 1gm orally in a single dose

or

Inj. Ceftriaxone 250mg intramuscularly in a single dose

or

Ciprofloxacin 500mg orally two times a day for 3 days.

or

Erythromycin base 500mg orally four times a day for 7 days.

In HIV infected patients with chancroid there appears to be reduced response to standard therapy especially single dose regimes, thus treatment for longer duration and increased dosage is required (Reddy and Nanda, 2005).

Follow up

After initiating the treatment, patients should be reviewed at day 3 and day 7. Genital ulcers are likely to improve symptomatically within 3 days and significant reepithelialization occurs within 7 days.
Herpes Progenitalis (HP) or Genital herpes

Genital herpes simplex virus infections are at present considered one of the most common sexually transmitted diseases (STDs) affecting both men and women. Its incidence has increased manifolds in the last two decades and has assumed major public health significance especially because of its association with HIV infection. The reasons for its increase are: the decrease in treatable bacterial STD, the high recurrence rates and asymptomatic recurrences with transmission in absence of symptoms.

History

Herpes (Greek herpain = to creep) was known as early as 100 AD. The French physician Jean Astruc is given the credit for the first full description of Genital herpes which appeared in his “Treaties of venereal disease” in 1754 (Thappa, 2002).

Jean Louis Alibert (1766-1837 AD) first described the condition in women, as well as men thereby suggesting the possibility of sexual transmission (Bingham, 2005).

Francis Booth Greenough (1837-1904 AD) described the natural history of herpes. He suggested that the disease was not serious, and that it had a tendency to relapse and produce mental anxiety.

Genital Herpes was rarely considered in the differential diagnosis of genital ulcer prior to 1965. It was only in 1966 that herpes genitalis was recognized as a venereal disease.
Epidemiology

The human herpes viruses consist of two closely related viruses designated herpes simplex virus type-1 (HSV-1) and herpes simplex virus type -2 (HSV-2) (Crumpacker, 1999). Both HSV-1 and HSV-2 are found worldwide and causes common infections in both male and female population of developed and underdeveloped countries (Mindel, 1998; Kumar et al., 2001).

The incidence of herpes simplex virus type-2 (HSV-2) continues to increase in the United States (Corey and Wald, 1999). In USA, about one in five persons over the age of 12 i.e. approximately 45 million people are infected with HSV-2 infection with up to one million new HSV-2 infections transmitted annually (Johnson, et al., 1989). Among STD clinic attenders in USA the seroprevalence varies from 30 percent to 70 percent (Koutsky et al., 1992).

Although majority of cases of genital herpes are caused by HSV-2, HSV-1 has also been reported with an increasing number of genital ulcer cases in UK. Among STD clinic attendees in UK from 1995-1999, 62% of males and 77% of females were found to have HSV-1 isolate in their genital lesions (Vyse et al., 2000).

In Singapore, seroprevalence of herpes infection increased from 17% in 1980 to 72% in 1993 (Chau and Cheong, 1995). In Thailand the seroprevalence of HSV-2 among STD clinic attendees with GUDs using multiplex PCR technique was found to be 82 percent (Beyrer et al., 1998).
The HSV seroprevalence in STD clinic in Italy was 24.6% (Cusini et al., 2000), Spain 25%, (Varela et al., 2001), Newzealand (25.7%) (Perkins et al., 1996) and 55.6% in STD clinic attendees in Paris (Janier et al., 1999).

Genital herpes was the most common cause of genital ulcer disease in sub-Saharan Africa. The prevalence of genital herpes in patients with genitoulcerative diseases (GUDs) were 19% in Rwanda (Bogaerts et al., 1998), 42.5% in Nigeria (Fawole et al., 2000), 49% in Uganda (Kamya et al., 1995), 35.8% in South Africa (Chen et al., 2000) and 42.9% among STD clinic attendees in Tanzania.

In India there has been a significant increase in the proportion of viral STDs especially herpes simplex virus (HSV) infection with the incidence rates varying from 4.11 percent to 27.9 percent among STD clinic attendees in different regions of the country (Jaiswal et al., 1998; Mehta et al., 1998; Aggrawal et al., 2001; Murugesh et al., 2004; Parmar et al., 2001).

Taxonomy and genomic organization

Herpes genitalis is caused by a DNA virus, herpes simplex virus (HSV)(herpes virus homonis) which belongs to the family Herpes viridae subfamily alpha herpes viruses (Corey and Wald, 1999). It was recognized in the 1960s that there are two sero types of HSV, type 1 and type 2. The predominant type isolated from genital area is type 2, although in about one-third of cases type 1 may be isolated. (Corey and Wald, 1999). Out of approximately 100 herpes viruses, only 8 are known to be pathogenic to humans. Depending on the genomic and biological behaviour they are classified into 3 categories.
Classification of Herpes virus

Alpha herpes viruses

- Herpes simplex virus type 1 (HSV-1)
- Herpes simplex virus type 2 (HSV-2)
- Varicella-zoster virus (VZV)

Beta herpes viruses

- Cytomegalovirus (CMV)
- Human herpes virus 6 (HHV-6)
- Human herpes virus 7 (HHV-7)

Gamma herpes viruses

- Epstein-Barr virus (EBV)
- Human herpes virus 8 (HHV-8) or Kaposi’s Sarcoma associated herpesvirus (KSHV).

All the herpes viruses are morphologically similar and they consist of four main elements:

- An electron opaque core which contains its DNA.
- An icosahedral capsid surrounding the core
- An amorphous tegument containing number of viral encoded proteins, surrounding the capsid and
An outer lipid envelope which contains 11 glycoproteins which are major target of humoral and cellular immune response.

The overall diameter of HSV is about 160 nm. The genome of HSV is linear, double stranded DNA molecule ($100 \times 10^6$) that encodes about 80 gene products.

**Pathogenicity**

The virus replicates in the skin or mucous membrane at the initial site of infection, then migrates up the neuron and becomes latent in the sensory ganglion cells. In general, HSV-1 becomes latent in the trigeminal ganglia, whereas HSV-2 becomes latent in the lumbar and sacral ganglia. During latency, most if not all-viral DNA is located in the cytoplasm rather than integrated into nuclear DNA. The virus can be reactivated from the latent state by a variety of inducers, e.g. sunlight, hormonal changes, trauma, stress, and fever at which times it migrates down the neuron and replicates in the skin, causing lesions.

The typical skin lesion is a vesicle that contains serous fluid filled with virus particles and cell debris. When the vesicle ruptures, virus is liberated and can be transmitted to other individuals. Multinucleated giant cells are typically found at the base of herpes virus lesions.

Immunity is type-specific, but some cross-protection exists. However, immunity is incomplete, and both re infection and reactivation occur in presence of circulating IgG. Cell mediated immunity is important in limiting herpes viruses, because its suppression often results in reactivation, spread and severe disease (Levinson and Ernest, 2002).
TRANSMISSION OF HSV

Infections result from inoculation of virus into mucous membranes or adjacent skin by breaks in the surface epithelium during sexual intercourse. Certain factors like gender, previous infection with HSV, frequency of recurrence, presence of active lesions at intercourse, use of barrier contraceptives, use of HSV suppressive therapy in partners with herpes are also largely responsible for HSV transmission (Wald, 1998).

In couples where one partner has a history of herpes, serological tests shows that in 25% of these couples, both the partners are seropositive, suggesting that infection has already been transmitted. Where as in couples who are serologically discordant for HSV antibodies, the mean rate of transmission was 12 percent per year (Mertz et al., 1988).

The risk of transmission is greater with HSV-2 than HSV-1 and from males to females especially when barrier methods like condoms are not used (Mertz et al., 1992).

The virus is inactivated at room temperature and by drying, and therefore is usually not transmitted by aerosol and fomites. All patients with HSV infection may be potentially contagious, whether they have visible lesions or not. Viral shedding continues to occur from the mucosal surfaces even if the host is asymptomatic.

After the initial infection, which may be symptomatic or asymptomatic, HSV ascends peripheral sensory nerves and enters the sensory or autonomic nerve root ganglia where it remains latent. During this latent stage the virus cannot be detected by the host defences. The virus reactivates and replicates under the influence of various host and viral factors. When reactivated, it travels peripherally to the skin and mucous membranes and replicates to cause recurrent disease.
Clinical manifestations of genital herpes

The severity and frequency of clinical manifestations are influenced by a number of viral and host factors. Viral factors include viral type (type 1 or type 2) and host factors include the immune status of the host and prior exposure to the virus. The clinical manifestations of genital herpes can be divided into -

First clinical episode

It is subdivided into

Primary infection or (true primary) - occurring in a person without prior HSV-1 or HSV-2 antibody.

Non primary infection- occurring in a person with prior HSV-1 or HSV-2 antibody.

Primary genital herpes

If a nonimmune person develops herpes genitalis after exposure to an infected person, it is called primary genital herpes. The incubation period varies from 2 to 12 days (commonly 3-5 days). The first episode is usually more severe and frequently associated with systemic symptoms. However in some individuals the infection may remain unnoticed without any signs and symptoms.
Clinical manifestations

The lesions start as grouped vesicles which become pustular and ulcerate. The new lesions continue to form for 8 to 10 days and complete reepithelization takes as long as three weeks or more. Scarring is uncommon.

The systemic symptoms like fever, headache, myalgias are also associated. The systemic symptoms are more severe in females than in males. Inguinal lymphadenopathy is also associated.

Sites of lesions in males are glans, prepuce, penile shaft, urethra and perianal region. Less frequent sites are scrotum, thighs and buttocks.

In females the sites involved are introitus, urethral meatus and labia minora and labia majora. Less frequently perineum, perianal or buttocks may be involved.

Complications

Cervicitis is commonly found in (up to 90%) in women with HSV-2 infection. Cervix shows ulcerative and necrotic lesions. Proctitis is seen in homosexual males. Pharyngeal involvement may be found with orogenital exposure.

Aseptic meningitis, transverse myelitis and sacral radiculitis are rare serious complications.

Non-primary-first episode:

This is found in an immune person already infected with by HSV virus. They are seropositive. The episode is milder and shorter in duration than primary herpes but more
severe than recurrent attacks. The pre-existing antibodies are thought to reduce the severity of the disease.

**Recurrent genital herpes**

Recurrences generally follow the first episode of infection. The recurrent episodes are milder and lasting for only 5 to 7 days. Over 90% of the patients with recurrent lesions have prodromal symptoms like mild burning or tingling sensation to shooting pain a few hours or a day prior to the appearance of lesions.

**Rate of recurrences**

After primary episode, patient with HSV-2 infection have more frequent recurrences than with HSV-1. The time to the first recurrence after primary infection is about 10 months for HSV-1 while only 6 weeks for HSV-2 infection (Waid et al., 2000). The patients with more severe and prolonged first episode i.e. > 5 weeks have more frequent recurrences than those with shorter episode.

Genital herpes caused by HSV-2 may recur up to 6 times more frequently than caused by HSV-1. Almost 90% have 1 or more recurrences, 38% have 6 or more and 20% have 10 or more recurrences, following HSV-2 primary infection (Benedetti et al., 1999).

Recurrences are more common in men but are more painful in females. The number of recurrences varies from 4 to 5 per year. In contrast to HSV-2, only 60% of the patients with HSV-1 shows recurrences. The rate of recurrences are low i.e. 1 to 2 per year in first year.
Asymptomatic shedding

Although HSV infections are frequent, less than 20% of them are aware of their status. The majority of HSV seropositive individuals are unaware of their infection and yet are capable of shedding the virus and hence transmitting the infection. Asymptomatic viral shedding is responsible for at least 70% of viral transmission.

Genital HSV infection in pregnancy

Genital herpes during pregnancy has been associated with an increased frequency of spontaneous abortions and premature births. The risk of transmission increases more than ten fold if a woman acquires genital HSV in the third trimester and delivers the baby before she develops antibodies.

Neonatal herpes is associated with high mortality and morbidity.

Laboratory diagnosis

1. Tzanck smear

The fresh vesicle is ruptured with a scalpel and the material is obtained by scraping the floor of the vesicle. Staining is done by Giemsa or Papanicolaou stain. The smear shows multinucleated giant cells with intranuclear inclusions.

2. Viral culture

It is done on chorioallantoic membrane of chick embryo or on ‘HeLa’ cell lines. It is time consuming, expensive and requires a special laboratory services.
3. **Serological tests for anti HSV antibodies**

They are useful in diagnosis of subclinical infection and for epidemiological studies.

1. **Polymerase chain reaction (PCR)**

They are very expensive but highly sensitive to diagnose HSV encephalitis.

2. **Detection of HSV antigen**
   - Direct immunofluorescent assay
   - Amplification and detection of DNA

**Genital Herpes and HIV**

Genital herpes is the commonest sexually transmitted disease in HIV seropositive individuals (Hook et al., 1992 and Severson et al., 1999).

In India the frequency of HIV seropositivity in patients with genital herpes varies from (0.5%) in 1995 to (20%) in 1999 in various parts of India (Thappa et al., 1999) and (Kumar et al., 2001).

Herpetic ulcers facilitate HIV transmission through the reduced epithelial barrier and infiltration of CD4+ lymphocytes in herpetic lesions that are possible targets for HIV attachment and entry (Heng et al., 1994).

Asymptomatic HSV shedding occurs four times more commonly in HIV seropositive than in HIV seronegative women (Augenbraun et al., 1995). In HSV-2 infected women even in absence of genital ulcer, HSV-2 genital shedding occurs in HIV
seropositive individuals (Mayaud and McCormick, 2001). Asymptomatic perianal HSV shedding also occurs more commonly in HIV seropositive individuals.

The HSV regulatory proteins ICP0 and ICP4 (infected cell protein no. 0 and 4) transactivate long terminal repeat (LTR) of HIV-1 and both upregulate HIV expression in CD4+ lymphoid cells. The transactivating protein of HSV i.e. Vp 16 acts synergistically with HIV-1 tat protein to increase HIV transcription from HIV-1 LTR (Schacker et al., 1997).

Treatment

Although without treatment herpes lesions may heal spontaneously within 10 days, the discomfort most patients experience usually warrants treatment. Many patients may have pain, burning and considerable anxiety which justify the use of systemic drug therapy. Education and discussion with the patient about the disease including its precipitation factors, and prevention are also essential for effective treatment.

The Centers for disease control and prevention (CDC) recommends the following treatment for genital herpes (CDC, 2002)

Treatment for first clinical episode of genital herpes

**Recommended regimens:**

- Acyclovir 200 mg orally five times a day for 7-10 days; or
- Famciclovir 250 mg orally three times a day for 7-10 days or
- Valacyclovir 1 gm orally twice a day for 7-10 days or
- Acyclovir 400 mg orally three times a day for 7-10 days.
Treatment for recurrent episodes of HSV disease (CDC, 2002).

1. Episodic therapy for recurrent genital herpes
2. Suppressive therapy for recurrent genital herpes

**Episodic therapy for recurrent genital herpes**

For effective episodic treatment of recurrent herpes, therapy should be initiated either within 24 hours of onset of lesions, or during the prodrome that precedes the onset of lesion.

**Recommended regimens**

- Acyclovir 200 mg orally five times a day for 5 days; or
- Famciclovir 125 mg orally twice a day for 5 days or
- Valacyclovir 500 mg orally twice a day for 3-5 days or

**Suppressive therapy for recurrent genital herpes**

Suppressive therapy reduces the frequency of reactivation of genital herpes among patients who have frequent recurrences (those who have more than 6 recurrences per year) and also symptomatic outbreaks. Daily therapy with acyclovir for as long as 2 years, and that with valacyclovir or famcyclovir for 1 year has been proven to be safe and effective.
With the passage of time the frequency of recurrent outbreaks reduces in many patients and periodically, discontinuation of therapy may be considered. However suppressive antiviral therapy does not eliminate sub-clinical viral shedding.

**Recommended regimens:**

- Acyclovir 400 mg orally twice a day or
- Famciclovir 250 mg orally twice a day or
- Valacyclovir 500 mg orally once a day or
- Valacyclovir 1 gm orally once a day

**Counselling**

Counselling of infected person and their sex partners, to help them cope with the infection and to prevent sexual and perinatal transmission is an integral component of management of genital herpes.

**Counselling must focus on following issues**

- Education regarding the natural history of genital herpes disease with special emphasis on the recurrent nature of infection.
- **Awareness regarding asymptomatic nature of disease**
  HSV may continue to be transmitted sexually even in absence of symptoms and that asymptomatic viral shedding is more frequent in genital HSV-2 infection than genital HSV-1 infection. It is most frequent in first 12 months of acquiring HSV-2.
Partner notification

- The patients are advised to inform their regular partner or their spouses about genital herpes infection and the risk of transmission to others.

- Information regarding abstaining from sexual activity with uninfected partners when they develop prodromal symptoms or lesions.

- Information regarding regular and correct usage of latex condoms to reduce the risk of genital herpes when infected areas are covered by condoms.

- Patients are made aware that though their sexual partners may be infected they can still be asymptomatic.

- All patients are made aware about the risk of neonatal HSV infection.

- In pregnant women not infected with HSV-2 should be advised to avoid intercourse during the third trimester with men who have genital herpes.

- All patients are to be explained about antiviral therapy, particularly episodic and suppressive regimen and their efficacy in shortening the duration of recurrent episodes.

Genital warts

(synonyms - Condyloma acuminata or Anogenital warts)

Definition

Genital warts also called condyloma acuminata are caused by infection with human papilloma virus (HPV). It can affect both the skin and the mucosa. The genital warts are soft flesh coloured, papillomatous, pedunculated or sessile growths most obvious manifestations of human papilloma virus infection.
**Historical Background**

Genital warts (condyloma acuminata) have been known since ancient times. Greek physicians first described the disorder and coined the term “Condyloma” (meaning rounded tumour) (Wikstrom, 1995).

Roman physicians discussed the etiology and called it as “Thymus” (due to resemblance to the plant Thymus capitatus) and “Ficus” (due to its similarity to the surface of the plant Ficus sycomorus). “Feigwarze” is a German word for condyloma and there it is still in use.

At the end of 15th century, after the arrival of syphilis to Europe, genital warts were also considered as a manifestation of syphilis. Hence some of the specific lesions in secondary syphilis are still referred to as “Condyloma lata” (Wikstrom, 1995).

Fallopius made distinction between condyloma acuminata and condyloma lata (a feature of secondary syphilis) in the mid-sixteen century (Sonnex, 2005). In 1901, Heidingsfeld described the transmission of the disease through sexual contact. An Italian physician Ciuffo showed the infectious nature of the warts in 1907 by demonstrating person-to-person transmission of lesions by cell free, wart filtrates (Stanley, 2005). In 1930s Richard Shope identified the first animal papilloma-virus, the cottontail rabbit virus (CRPV), which caused skin warts or papilloma-virus on rabbits. In 1949, Strauss et al, isolated the agent responsible for warts, the human papilloma virus. Since then HPV has become recognized as a significant human pathogen (Brentjens et al., 2002).
In 1980 Gissman and Zur Hausen isolated and characterised Human papilloma virus (HPV 6) from genital wart thus defining the aetiological agent for the development of ano-genital warts (Rowen, 2005).

Epidemiology

The incidence and prevalence of clinical HPV genital infection have been steadily increasing since the mid-1960s, but the true prevalence of HPV anogenital infections in the community is unknown because (Mc Millan and Ugilvie, 2002).

• The disease is symptomless and subclinical infection is common.
• Many individuals do not seek medical help.
• Most patients consult general practitioners, who won’t notify the infection to public health authorities.
• Even in many STI clinics, from which accurate data are generally available, the diagnosis is made only when condyloma are seen.

Current evidences suggests that over 50% of the sexually active adults (15-25 years of age) have been infected with one or more HPV types (Usman, 2003).

In United States, the estimate prevalence of genital warts among men and women aged between 15-49 years is 1.4 million and with sub clinical infection is 19 million (Koutsky and Kiviat, 1999). In Britain and Ireland 80,000 new cases of ano-genital warts are reported annually (Maw, 1999 and Usman, 2003).
The prevalence of anogenital warts in India has been reported to be 5.1 percent to 25.25 percent of STD patients (Usman, 2003).

Aetiology

The causative agent of anogenital warts is human papilloma virus (HPV). It belongs to the family papillomaviridae, which includes papillomavirus affecting other species (Brentjens et al., 2002).

Human papilloma virus are non-enveloped and have icosahedral symmetry with 72 pentameric capsomers forming an outer coat (Brentjens et al., 2002). This coat consists of major and minor capsid proteins. The capsids are approximately 60nm in diameter. Within this coat are circular, supercoiled, double stranded DNA molecule of approximately 8000 base pairs (8 kb) in size, which is tiny compared to pox or herpes viuses (Stanley, 2005).

The genes are distributed into early genes (E1-E7) and late genes (L1 and L2). The early genes (E1-E7) encode for proteins that are involved with the regulation of viral DNA replication and transcription, and also with oncogenic transformation (E6 and E7) while the late genes L1 and L2 encode the major and minor capsid proteins respectively (Brentjens et al., 2002).

At present more than 130 HPV types have been described but, fortunately only a small number are found commonly in clinical lesions in the genital tract (Stanley, 2005).

Papillomaviruses are classified by genotype, i.e. DNA sequence, not by serotype (Stanley, 2005). HPV are epitheliotropic, and their replication depends on the presence of differentiating squamous epithelium.
Genital warts are shown to be predominantly associated with HPV-6 and 11, viruses that are almost never detected in carcinomas (Stanley, 2005) and are responsible for more than 90 percent of anogenital wart cases (Von Krogh et al., 2000). Several types of HPV can co-exist in the same wart. These HPV types cannot be grown in-vitro (Thappa et al., 2004).

Transmission of the virus

Genital HPV are transmitted primarily through sexual contact. The infectivity of HPV between sexual partners is estimated to be 60%. During sexual act, micro-abrasions occur in male and female genitalia and anus in homosexuals. It is believed that these micro-abrasions permit the transfer of HPV virions from the epithelial cells of the infected partner to the basal layer of the recipient. Transfer by fomites is not a known factor in transmission of genital HPV.

Perianal transmission has been reported in infants born to women with genital warts during pregnancy. These infants develop laryngeal papillomas and congenital condylomas which is a very rare form of transmission (Koutsky and Kiviat, 1999).
Pathogenesis (Koutsky and Kiviat, 1999).

Trauma (e.g. abrasion during sexual contact) to the epithelial cells of penis (or) vulva

1. Virus entry
2. Infect the basal cell layer
3. Latent phase (from several months to years)
   - Production of viral DNA in basal cell nuclei (only dividing cells in epidermis)
   - Expression of viral DNA leading to proliferation of keratinocytes and blood vessels
4. Formation of warts

Clinical features

HPV after entry remains dormant without producing any lesions or may produce symptomatic or asymptomatic lesions. The incubation period of genital warts is 3 weeks to 8 months, with majority of lesions developing at 2-3 months (Sonnex, 2005). Warts may be single or multiple.

The most commonly affected sites in uncircumcised men are the glans penis, inner aspect of the foreskin, coronal sulcus and frenulum. The penile shaft is more frequently affected in circumcised men. Urethral and meatal warts have been found in 5
and 23% of men with penile warts. Meatoscopy is useful for detecting intra-meatal and distal urethral warts.

Anal warts have been reported to be several times common than penile warts in homosexual men, with lesions often extending into the anal canal. Anal warts are well recognised in heterosexual men and have been reported in 30-45% of those with penile warts (Sonnex, 2005). Colposcopic examination of anal canal via proctoscope is an excellent way of detecting both warts and anal intra-epithelial neoplasia (AIN) lesions. HIV infected homosexual men are at a particular risk of developing AIN.

Genital warts in women are most commonly found in the vestibulam, on the labia and the posterior fourchette of the vulva. The urethral meatus is affected in 4-8% of females. Cervical warts have been documented in 6-8% of women with genital warts, vaginal warts in 10-15% and anal warts in approximately 20%. Most cervical HPV infection is subclinical and may be detected by cervical cytology or colposcopic examination following application of acetic acid (Sonnex, 2005).

Clinical types of Genital warts

- Condyloma acuminata
- Papular warts
- Verruca vulgaris type or keratotic warts
- Sessile warts
- Flat warts
- Intraepithelial neoplasia- Bowenoid papulosis & Bowen's disease
- "Giant condyloma" (Buschke-Lowenstein tumor).
**Condyloma acuminata (acuminate warts)**

They have pointed, irregular, fissured appearance, and called “classical warts'. They coalesce to form large plaques or pedunculated cauliflower like lesions.

**Papular warts**

They are dome-shaped, non-pedunculated lesions and may be multiple.

**Verruca vulgaris or keratotic warts**

They are non-pedunculated, papular lesions with rough horny surface. Their size ranges from a few millimeters to few centimeters in diameter.

**Macular or flat warts**

They are found on the vulval or vaginal mucosa. They are difficult to see with the naked eyes. Aceto-whitening (on application of acetic acid they show white discoloration) is required for visualization.

**Bowenoid papulosis**

Bowenoid papulosis (BP) are dark coloured, multiple, verrucous papules caused by oncogenic HPV-16 virus.
"Giant condyloma" (Buschke – Lowenstein tumor)

This entity was first described by Buschke and Lowenstein in 1925. It is caused by HPV types 6 and 11. The lesions are very large in size and histopathology reveals atypical cells.

Complications

If untreated they enlarge in size leading to interference with normal sexual activity and in pregnant patients it causes obstruction during labour. Long standing warts can undergo squamous cell carcinoma.

Sub-clinical infections

Sub-clinical HPV infection together with latent infection are probably the most likely outcome after exposure to HPV. They are associated with symptoms such as itching, burning, fissuring and dyspareunia. In general the mucosal surface is normal looking until acetic acid is applied, after which well demarcated, roundish white lesions might appear. Treatment should be offered to only those patients who are symptomatic. But predominantly sub-clinical infections are asymptomatic.

Genital warts in pregnancy

Genital warts flourish during pregnancy in both number and in size. It may be due to the influence of increased hormone level, vascularity and immune deficiency which are seen in pregnancy. Even without treatment warts may resolve after delivery. The new
born may pick up the infection during labour. It is advisable to prefer elective caesarean section to prevent transmission of infection to the neonate.

Genital warts in children

Genital warts in children may result from several modes of transmission. Acquisition at birth by HPV transmission from maternal genital tract, autoinoculation from finger wart, and non sexual transmission from family members and caretakers (Von Krogh et al., 2000). In young children condyloma acuminata may also result from sexual abuse.

Genital warts and HIV infection:

In immunocompromised patients, the warts are larger in size, becomes multicentric and they are refractory to treatment. HIV infection influences local immunity by altering HPV transcription and by systemic immunodeficiency (Aramy et al., 1988).

Laboratory methods

Clinical diagnosis

Diagnosis of warts in the anogenital region is based on the history of exposure, clinical appearance, evidence supporting warts in the sexual contact (Usman, 2003). Biopsy confirms the diagnosis. Direct detection of HPV DNA- requires specialised technique and laboratory facilities.
**Polymerase chain reaction**

It is the most sensitive method for the detection of HPV DNA, being able to detect one viral genome in 100,000 cells (Wikstrom, 1995).

**Treatment of genital warts:**

Many different methods of treatment are available for genital warts. Unfortunately, none gives a 100% chance of clearance or 0% chance of recurrence.

- Application of podophyllin resin 20-25% or Podofilox
- Imiquimod 5% cream
- Cryotherapy with liquid nitrogen
- Electrocauterization
- Surgical removal if lesions are large in size.

**Molluscum contagiosum**

**Definition**

Molluscum contagiosum is a common, benign, viral infection of the skin and mucous membranes caused by molluscum contagiosum virus (MCV). Its spread is apparently by close contact in children while in adults the condition may be transmitted through intimate sexual contact with lesions appearing on the genital area (Thappa, 2005).

It is an infection caused by pox virus (MCV-1 to MCV-4 and their variants) (Waugh, 2005). The incubation period averages two to three months, with range of one
week to six months (Douglas, 1999). The fully developed lesion is an umbilicated papule, and most patients have multiple lesions. Molluscum contagiosum may be extensive in patients with AIDS or other disorders associated with immunological deficiency (Douglas, 1999). The asymptomatic lesions are usually 2 to 6 mm in size, skin coloured to milky white, shiny, umbilicated papules. Multiple lesions are usually present. The trunk, extremities and face are commonly involved. (Thappa, 2005).

History

The characteristic appearance of this virus was first described in 1817 by Bateman, who labeled the disorder “molluscum,” a common term then for pedunculated lesions, and described it as “contagiosum” to signify its apparent transmissibility, which was due to the “milky fluid” which could be expressed from the lesion (Waugh, 2005). In 1841 Henderson and Paterson described cellular elements with large intracytoplasmic inclusion bodies that have been named Henderson-Paterson, or molluscum bodies. In the beginning of the twentieth century, Juliusberg in 1905 and Wile and Kingery in 1919 were able to extract filterable virus from lesions and show transmissibility.

Epidemiology

The epidemiology of molluscum contagiosum has been limited by several factors. In most patients the lesions cause few problems and are self limited so infected patients do not seek medical attention. Since molluscum contagiosum is not a reportable disease few population based data are available. Further inability to cultivate MCV in cell culture has restricted studies on viral transmission (Douglas, 1999).
Aetiology

The disease is caused by molluscum contagiosum virus (MCV), a DNA virus that is a member of pox virus family which includes small pox and vaccinia virus. MCV is brick shaped, approximately 300x220x100 nm in volume. The viral genome consists of a linear double stranded DNA 180-200 kilobases long. The virus cannot be grown on cell culture, presumably because of its need for highly differenciated keratinocytes, which cannot be maintained in vitro.

Recent studies have identified four major subtypes of MCV, including three MCV-1 variants, and MCV-2, MCV-3 and MCV-4. MCV-1 subtypes dominates worldwide and in one report MCV-1 subtype occurred exclusively in children under the age of 15 (Waugh, 2005).

Pathogenesis

Within the cell the virion colony is encased and isolated in a protective sac, thus preventing the triggering of the host immune response. Because of this infection with molluscum contagiosum virus produces little cell-mediated immune response compared to other pox viruses. Mechanical trauma appears to facilitate the transmission of MCV. Small breaks in the epidermis or in the infundibular portion of the hair follicle provide a portal of entry for the virus during skin to skin contact (Gottleib and Myskowski, 1994; Waugh, 1998). In both HIV positive and HIV negative patients, the bulk of viral load has been localized to hair follicles.
Transmission

MCV appears to be transmitted by both sexual as well as non sexual routes with transmission enhanced by warmth and humidity. The non sexual form of the disease occurs primarily in children. It involves the face, trunk and upper extremities. It is apparently transmitted by direct contact with skin of the infected individuals and/or fomites. In the last 30 years molluscum contagiosum has been accepted as a common sexually transmitted infection in young adults (Waugh, 2005).

Clinical Features

The incubation period of molluscum contagiosum is 2-3 months though the range varies from 2 weeks to 6 months. The lesions are skin coloured or pearly white to flesh coloured papules, 3 to 6 mm in diameter. Papules are firm, dome shaped and umbilicated with a central pore from which cheesy material can be expressed. The onset is gradual and most patients are asymptomatic. The most common complication of molluscum contagiosum include inflammation, irritation and secondary infection. Rarely some lesions become very large reaching up to 1 to 2 cm or larger in size and are called as giant molluscum contagiosum.

In adults the lesions most often occur on the thighs, inguinal region, buttocks, lower abdominal wall, external genitalia (shaft of penis) and perianal region especially mucosal surfaces. In children the lesions are usually distributed on exposed areas of the limbs, face and neck. However 10 to 50% of children may have lesions on the genital area.
The average duration of untreated disease is reported to be approximately two years, ranging from two weeks to four years; individual lesions usually resolve within two months. Recurrences after clearance occurs in approximately 15 to 35 percent of patients whether these represent new infections or exacerbation of subclinical infection is not clear.

**MCV in HIV disease**

MCV is a common cutaneous pathogen in HIV infection. Between 10% to 30% of patients with symptomatic HIV disease or AIDS have molluscum contagiosum (MC) (Matis et al., 1987). The prevalence and the severity of the disease increase with advancing immunodeficiency and lesions occur in up to one third of patients with CD4+ T-cell counts of 100/µL or lower (Koopman et al., 1992). The distribution of lesions of molluscum contagiosum in HIV infected individuals is usually over the face, including eyelids and ears, neck and in intertriginous areas like axilla, groin or buttocks rather than the genitalia. The lesions may be in hundreds and of larger size ranging from 1 cm to 5-10 cm. These may be follicular. Mucosal lesions are seen when the CD4 cell count is less than 50/mm³.

Although typical umbilicate papules occur in HIV positive patients, verrucous, warty papules, polypoidal lesions as well as giant molluscum greater than 1 cm diameter are also seen (Vozmediano, et al., 1996). Both verrucus MC and Giant MC are seen in late stage of disease with Low CD4+ counts and high viral load (Smith, et al., 2002). In late stage HIV disease MCV infection becomes chronic (Schwartz, et al., 1992).
Diagnosis

The diagnosis of molluscum contagiosum is typically apparent and is based on characteristic morphology with umbilicated papules (Waugh, 2005).

Direct microscopic examination of unstained curetted lesion crushed on a slide establishes diagnosis. Thin smears of the expressed cheesy core material stained with Wright, Giemsa or Gram stain demonstrates the pathognomic enlarged epithelial cells with cytoplasmic molluscum bodies.

Diagnosis is confirmed by histopathological examination. Typically brightly eosinophilic cytoplasmic inclusion bodies—"molluscum bodies" also known as Henderson-Paterson bodies can be demonstrated in lower epidermis.

Antibodies were demonstrated in both HIV positive and negative persons and there was no correlation with number of lesions and duration. Other methods of detection includes electron microscopy, detection of MCV antigen by fluorescent antibody techniques or using dot blot hybridization techniques to demonstrate MCV DNA.

Treatment

The disease is self-limiting and may clear spontaneously. However to prevent auto inoculation and spread to others, therapy is needed.

Chemical cauterization by AgNO₃, Trichloro acetic acid or iodine.

Cryotherapy by liquid nitrogen (N₂)

Electrocauterization

Topical phenol (10-20%), 5% Imiquimod, 5% KOH, 0.5% Podophyllotoxin etc.
In the immunocompromised patients no therapy is effective because of increased occurrence of new lesions. However in HIV positive patients on Highly Active Antiretroviral Therapy (HAART) may lead to regression of lesions.

Donovanosis

Synonyms - Granuloma venereum, Granuloma inguinale, ulcerating granuloma of pudenda.

Definition

It is a chronic, destructive mildly contagious, slowly progressive, sexually transmitted granulomatous disease of the genito-inguinal region caused by a pleomorphic gram-negative bacillus known as Calymmatobacterium granulomatis.

Donovanosis is a sexually transmitted infection that usually manifests itself as chronic genital ulceration (O'Farrel, 2002). The causative organism is Calymmatobacterium granulomatis otherwise known as Klebsiella granulomatis. The condition tends to be found in populations that are marginalized, impoverished and with limited power of advocacy (O'Farrel, 2002).

History

Donovanosis, formerly called as Granuloma Inguinale was first recognized and described in India. It was first described in 1881 in Madras, (now Chennai), India under the name of 'serpinginous ulcer' by Kenneth MacLeod, a scot, who joined the Indian Medical Service and became professor of surgery in Calcutta (now Kolkata) (Gupta et al., 2005).
In 1905, Colonel Charles Donovan, described intracellular bodies, also called "Donovan bodies" which bear his name in specimens obtained from oral lesions in a ward boy of general hospital in Madras.

Goldzeiher and Peck gave classical description of the disease in 1926. The credit for identifying Donovan bodies (DB) in the histological sections too belongs to them (Hart et al., 1999).

In 1937, Fund and Greenblatt gave precise description of pathognomic cells of granuloma inguinale; large mononuclear cells filled with intracytoplasmic cysts containing deeply staining bodies (Hart et al., 1999).

Anderson succeeded in cultivating the organism in the yolk sac of developing chick embryo in 1943 and later proposed a new name “Donovania granulomatis” (Reddy, 2001).

Two Indian venerologists Rajam and Rangiah gave detail monograph of donovanosis (Gupta et al., 2005).

Epidemiology

It is predominantly encountered in tropical and subtropical climates. It usually affects the people of low socio economic status having a poor personal hygiene. The disease is rarely found from the developed world.

Currently reports of the disease are only sporadic and largely confined to Papua New Guinea, India, South Africa, Zambia, Zimbabwe, Brazil, Argentina, Caribbean and Australia (aborigins) (O’Farrell 1999).
In India it is fairly common in some parts especially Tamilnadu, Pondicherry, Andrapradesh, Orissa and Pahari dwellers of Himachal Pradesh, but sporadic cases have been reported from other parts of India (Reddy et al., 2001). In Pondicherry, South India, donovanosis constituted 14 percent of genital ulcer disease cases, 15 percent of whom were HIV positive between 1993-1997. In the recent years the proportionate morbidity of donovanosis is also reported to be getting lesser and lesser in India (Garg et al., 1989; Thappa et al., 2004).

**Predisposing factors**

*Sex* - Recent studies shows male preponderance (O’Farrell, 1993) which may actually reflect a cultural and behavioural pattern.

*Age* - The disease is seen in the sexually mature age group of 20-40 years (Reddy et al., 2001).

*Uncircumcised state* - Rajam and Rangiah had highlighted the preponderance of infection in uncircumcised men in 1954 (Gupta et al., 2005). In a report comprising of 130 patients with donovanosis only one was found to be circumcised (O’Farrell, 1993).

*Human leukocyte antigen (HLA)* - A possible link between donovanosis and HLA B57 has been reported in South African Zulus (Gupta et al., 2005).
Climate - The disease is more prevalent in the regions with a constantly high temperature of 75° to 90°F all throughout the year with moderate relative humidity ranging from 50 to 70 percent. High relative humidity and heavy rainfall adversely affect its prevalence.

Race - Aboriginal (Australia) and Zulus (South Africa) are the most susceptible population (O'Farrell and Hammond, 1991). In India the disease is prevalent mainly in areas inhabited mostly by people of Dravidian origin (Gupta et al., 2005). It is more common in local natives than in Europeans in New Guinea, and in Negroes than in poor whites in USA (Reddy, 2001).

Nature of transmission

It is universally believed that donovanosis is a sexually transmitted disease. This view is supported by the fact that in a majority of donovanosis patients there is a history of sexual exposure prior to the lesion, the initial lesions occurs on the genitalia, the coexistence of other STDs, the prominence of anal lesions in the homosexuals, and the presence of lesions in conjugal steady sexual partners.

Extra genital lesions of the skin can occur by continuity of genital lesions or through auto inoculation via fingers or other non sexual contact. Infants may acquire infection at birth through infected mothers and may manifest with disseminate form of donovanosis (O'Farrel, 1999).
**Aetiology**

*Calymmatobacterium granulomatis* otherwise known as *Klebsiella granulomatis* is an obligate intracellular, gram negative, pleomorphic bacterium that can be identified as Donovan bodies in the infected tissue.

The organism is ovoid/bean shaped, varying in size from 1 to 1.5 μm in length and 0.5-0.7μm in width (Richens, 1991) surrounded by cell membrane and an overlying cell wall. The mature forms are capsulated. The organism is seen in two characteristic forms, which may co-exist in the same host cell.

**Capsulated forms**

These are ovoid or bean shape body. Well defined pinkish material surrounds the blue bacillary body with dark blue or black chromatin inclusions. The inclusions may be rounded, rod shaped and may be central, peripheral or bipolar in position.

**Non-capsulated forms**

These have minute deeply staining coccoid, bacillary or diplococcoid bodies, which are often shaped as a closed safety pin or telephone handle, surrounded by a halo of unstained area.

Donovan identified the characteristic intracellular bacterial inclusions, known as ‘Donovan bodies’ in the macrophages and epithelial cells of the stratum malpighii. The organisms are usually seen within the vacuoles of large mononuclear cells (histiocytes) or occasionally inside the polymorphonuclear cells. Large mononuclear cells, 25 to 90 mm
in diameter, containing intracytoplasmic vacuoles filled with clusters of Donovan bodies are the hallmark of the disease.

Ultrastructural studies reveal trilaminar cell wall structures like that of gram negative bacteria, surrounded by an electron lucent layer of capsule. The electron dense polar material giving the bipolar staining with Giemsa is contained in the cytoplasm (Kharsany et al., 1996). The organism has ultrastructural and antigenic similarities to Klebsiella sp. It has been suggested recently that C. granulomatis should be reclassified as Klebsiella granulomatis on the basis of phylogenetic evidence (Carter et al., 1999; Kharsany et al., 1999).

Culture

It is possible to grow the organism in the yolk sac of embryonated hen egg. The optimal temperature required for its growth is 37°C. Kharsany et al. (1996) cultured the organism in human monocytes, while Carter et al. (1999) could obtain its growth in human epithelial (Hep-2) cells.

Pathogenesis

The disease has an affinity for stratified epithelium of cutaneous, mucous and mucocutaneous surfaces of the genital, anal and oral sites. The organism gains entry through a breach on the surface due to trauma or intercourse and initiate an inflammatory reaction in the cutis.
Clinical features

The initial lesion starts as a Painless papule or a nodule which later becomes boggy, swollen and gets eroded to form a sharp, circumscribed, non indurated ulcer with a beefy granulomatous base. Multiple ulcers may develop due to auto inoculation.

Pain and lymphadenopathy are absent unless there is secondary infection. In some cases a subcutaneous swelling of varying size may be the early lesion, which gradually softens and results in a small abscess. Systemic spread occurs rarely and the lesions may occur in lung, liver, intestine, bone etc.

Incubation period

The exact incubation period is not certain but it is reported to vary from 8 days to 3 months in different studies even extending up to 1 year (Reddy, 2001). Greenblat et al noted typical granulomatous lesion between 42-50 days following the subcutaneous injection of pus containing Donovanon organisms in human volunteers.

The sites of lesions

In a majority of cases the primary lesion affects the ano-genital region. In males, prepuce, coronal sulcus, shaft, glans and perineum are usually the affected sites, while in females, labia minora, fourchette and labia majora are the commonly involved sites (Reddy, 2001).

Extra genital areas are occasional sites of primary lesions. They could be due to either contagious spread from anogenital region to nearby organs like fallopian tubes, epididymis, colon and bladder or may result from dissemination through the
haematogenous route or even by autoinoculation. Exogenous inoculation following injury/trauma may also lead to development of distant extragenital lesions.

Clinical types of GI

Ulcerative/Ulcerogranulomatous form

This is the most common manifestation, characterized by fleshy, beefy red, exuberant granulation tissue that is soft, non-indurated and non tender. It bleeds readily on touch. The lesion expands slowly by direct extension or inoculation into the adjacent skin (O’Farrel; 2002).

Hypertrophic verrucous type

The ulcers are typically large and pale red in colour with firm granulation tissue at the base and thickened and raised edges. They occur in both the sexes and may remain stationary for months with slow spread. DB may be readily demonstrated from underlying deeper tissues of the ulcer (O’Farrel, 2002).

Sclerotic or Cicatricial type

It is an uncommon variant, which occurs in form of a sclerotic scar on the external genitalia. Donovan bodies are hard to detect in the tissue smear. The ulcer, if present has undermined edge, dry, non-bleeding base, with band like scarring (Hart, 1999). Lymphadema may be a prominent associate feature.
Necrotic type (Phagedena)

The lesions are uncommon (<1%) and multilating with profuse foul smelling exudates that rapidly destroy the genitalia (O’Farrell 1993). Occasionally the whole external genitalia is destroyed before the disease burns itself off.

In donovanosis, the genital region is affected in 90 percent of cases and inguinal region in 10 percent (O Farrel, 2002). Lymphatic involvement is not a common feature of the disease. However, swelling in the inguinal region, ‘pseudobuboes’ are often due to subcutaneous granulomata. At times secondary infection of the ulcers may produce true lymphadenopathy.

Natural history of the disease

Donovanosis is a chronic, slowly progressive condition with little or no tendency for spontaneous healing. Recurrences of ulcerations in apparently healed lesions are common. Extensive mutilation of the affected sites may occur. Scarring and fibrosis may cause mechanical problems such as stenosis of the urethral, vaginal anal and oral orifices. In long standing cases, malignant transformation may occur occasionally. Carcinoma is the most serious complications of donovanosis but is relatively rare - 0.25 percent in Rajam and Rangiah’s series (O’Farrel, 2002).

Complications and sequelae

With the wide spread use of antibiotics as an effective treatment the complications are uncommon in the recent years. Pseudoelephantiasis (esthiomene) secondary to
obstruction of lymphatics may occur in 15 to 20% of the patients more commonly in the females.

Stenosis of the urethral, vaginal, anal and oral orifices in the cicatricial form of donovanosis may result in serious mechanical difficulties during micturition, defecation, sexual intercourse and parturition.

Extensive scar formation may lead to progressive mutilation and deformities of the affected sites in long standing cases.

Carcinoma is the most serious complications of donovanosis but is relatively rare - 0.25 percent in Rajam and Rangiah’s series (O’Farrel, 2002).

Pregnancy and Donovanosis

Lesions of donovanosis tend to proliferate or recur during pregnancy. They may show a diminished response to standard anti-microbial therapy. Cervical lesions may rapidly enlarge during pregnancy or in the early puerperium. The lesions may also extend to pelvic structures and disseminate resulting in foetal haemorrhage at the time of delivery. These events are due to increased vascularity of the tissue and the immunosuppressive effects of pregnancy.

I. Laboratory diagnosis

The clinical diagnosis of donovanosis comprises of a characteristic indolent, painless, granulomatous ulcer with a velvety, bright pink base and wavy edges, occurring in the genito-inguinal region, with a preceding history of sexual exposure. The diagnosis can be confirmed with the demonstration of Donovan bodies (DB) in tissue smears.
II. Detection by Microscopy

III. Tissue smears

The demonstration of donovan body (DB) in tissue smear is the most reliable and useful diagnostic measure in donovanosis. The ulcer is cleaned with a gauze soaked in saline, and a small piece of tissue is obtained from the active edge of the lesion with the help of a forcep, scalpel blade or punch. Uniform smear can be obtained by keeping the tissue between two glass slides and gently pressing them with a circular movement.

Alternatively the impression smears are made on glass slide by holding the tissue with a forceps. The smears are stained with Giemsa or Leishman stains and examined microscopically under oil immersion lens for donovan bodies which appear as bright pink ovoid bodies, 2 μm x 1.6 μm in size, containing dark blue nuclei with typical bipolar condensation of the chromatin particles.

The tissue smear may be negative for DB in early and late lesions, besides sclerotic and necrotic types. However the smear should be repeated on at least three consecutive days before being considered negative.

IV. Biopsy

In suspected cases of donovanosis where DB cannot be demonstrated in tissue smears, a biopsy can be obtained from the active edge of the ulcer for the confirmation of the diagnosis. Special stains such as Giemsa and Delafield’s hematoxyline stains can be used to identify donovan bodies in histological sections.
V. Serological tests

Serological tests are not available for routine use. An indirect immunofluorescence technique has been developed.

VI. Detection of C. granulomatis DNA

DNA extracted from biopsy specimens is added to PCR mixtures. However this technique is time consuming and available only for research purpose.

Donovanosis and HIV

A break in the continuity of the skin and/or mucous membrane is the prime facilitator for transmission of HIV (Czelusta et al., 2000).

Donovanosis is one of the prime GUDs, for HIV infection amongst Zulu men in Africa (O'Farrell et al., 1990).

In South Africa, the highest risk of HIV transmission appears to be in men with donovanosis. The probability of the increase of HIV-1 seropositivity in men with STDs in a Durban clinic was directly proportionate to the duration of the disease (O'Farrell et al., 1991). Currently it is well established that in South Africa men with donovanosis should be regarded as superspreader or core group at a very high risk of acquiring and transmitting HIV (O'Farrell, 1995). In a study from South India HIV seropositivity was found in 15.1% of patients of donovanosis attending the STD clinic, which was second only to genital herpes (Thappa et al., 1999).
An Indian study has shown that the mean duration of healing of an donovanosis ulcer was 25.7 days in HIV positive patients compared to 16.8 days in HIV negative (Jamkhedkar et al., 1998).

**Treatment**

Treatment of donovanosis stops the disease from progressing further. Prolonged treatment may be required to permit granulation and re-epithelialisation of ulcers. Although the treatment may be apparently effective, the disease may relapse 6 to 18 months after therapy.

**Recommended regimen by NACO (2002)**

- Doxycycline 100mg orally bid for 14 days/ Tetracycline 500 mg orally qid for 14 days or
- Erythromycin base/stearate 500 mg orally qid for 14 days or
- Azithromycin 500 mg orally bid for 14 days.

**Partner notification**

All sex partners should be examined and treated. Epidemiological treatment is not recommended routinely. Local hygiene is generally enough. Surgical repair of the scar may not be rewarding.
Follow Up

Patients must complete the recommended course. It is advisable to review the patient for first 3 months when concomitant syphilis and HIV can be ruled out. Subsequent follow up depends on level of healing and possible relapse. Partner notification and safe sex education with condom promotion must be emphasized.

Lymphogranuloma venereum (LGV)

(synonyms- Climatic bubo, tropical bubo, lymphopathia venereum, poradenitis inguinalis, strumous bubo, Durand-Nicholas-Favre disease).

Definition

Lymphogranuloma venereum (LGV) is a sexually transmitted disease of the lymph channels caused by chlamydia trachomatis serovars L1, L2 and L3. It is characterised by small fleeting primary lesion followed by the development of suppurative regional lymphadenitis.

History

The Greek, Roman and Arabian Physicians had recognized the lymphadenitis of Lymphogranuloma venereum (LGV). They called the disease by several names, Panniculus, Inguen, Struma, and Althaum.

In the 15th and 16th centuries, the disease was noticed among Spaniards in America. It was called 'Buba' and was observed among Spaniards who co-habitated with Indian women. (Thappa, 2002).
Nelaton in 1890 and his pupil L’Hardy (1894) pointed to the venereal nature of this disease (Rangiah, 2001). Caddy (1902) was first to record cases in India under the title ‘Climatic Bubo’ (Siddappa and Rangiah, 2001). Durand Nicholas and Favre described the clinical and histological features of LGV and differentiated them from syphilis and tuberculosis. They established it as a distinct clinico-pathologic entity in 1913 under the name ‘lymphogranuloma inguinale’ (Rangiah, 2001). Frei for the first time in 1925 developed an intracutaneous test with biologic bubo material and suggested that climatic bubo and LGV had the same etiology (Siddappa and Rangiah, 2001).

Chlamydia trachomatis was first identified as the causative agent of LGV in 1927 (Bajaj and Sharma, 2003). Miyagawa succeeded in growing LGV related chlamydia in embryonated hen’s eggs in 1935 (Reddy, 2005).

Prevalence

LGV has a worldwide distribution and no predilection for any race, colour or religion. However it occurs more commonly in the tropical and subtropical regions. It is endemic in India and South-East Asia, East and West Africa, South America and the Caribbean islands (Perine and Stamm, 1999).

Data from some STD clinics in different parts of India indicates a prevalence rate of 6%, ranging from 0.27% to 11.5% (Bajaj, 2003). It is less common compared to other STDs. Recently a decreasing trend in its incidence is observed.
Aetiology

Lymphogranuloma venereum is caused by one of the three serovars of Chlamydia trachomatis types L1, L2 and L3. Chlamydia are gram negative, intracellular, obligate parasites. They measure 0.3 to 1μ. In the infective state they have cell wall, contains both DNA and RNA and divide by fission.

Chlamydia are divided into four species, Chlamydia trachomatis, chlamydia psittaci, Chlamydia pneumoniae, and C. pecorum. C trachomatis has two major biovars, ‘TRIC agent’ TRachoma Inclusion Conjunctivitis) and LGV. There are 15 serotypes and types L1, L2 and L3 cause LGV (Bauwens et al., 2002).

Infection occurs by a metabolically inactive form of chlamydia called ‘elementary bodies’. These undergo changes to form a metabolically active ‘reticular body’ in 6-8 hours of infection. The organisms lacks the ability to synthesize high energy compounds such as ATP. They multiply in the host cells by binary fission. After a few such fissions, the reticular body cells condense and forms an elementary body. The newly form elementary bodies burst out of the host cells. The complete cycle takes about 48-72 hours.

Human beings are the sole natural hosts for C. trachomatis. It can be experimentally transmitted to monkeys, mice and guinea pigs. It can be grown on the yolk sac of developing chick embryo, HeLa 229 cell line culture, and Mc Coy tissue culture. It can be inactivated by low concentrations of formalin, phenol or ether and by heat (56°C).
Transmission

LGV is primarily a sexually transmitted infection although close non sexual contact with infectious secretions can result in transmission. There is no vertical transmission of infection but infection may occur while passing through an infected birth canal (Perine and Stamm, 1999).

Clinical manifestations

LGV is a chronic disease that has a variety of acute and late manifestations. The course of the disease is characterized by primary stage, a secondary stage (inguinal syndrome) and a tertiary stage (ano-genito-rectal syndrome) (Faro, 1989).

Primary stage

The incubation period is usually of 3-12 days but longer incubation periods have been reported. The commonest form of primary lesion observed is the herpetiform, superficial, painless and evanescent lesion. If present it usually lasts for 2-3 days and heals without leaving a scar.

The common sites of occurrence of primary lesion are the coronal sulcus, frenulum, prepuce, penile shaft, urethra, glans and scrotum in males and posterior vaginal wall, fourchette, posterior lip of the cervix and vulva in females.

In homosexual men, primary rectal inoculation produces bloody anal discharge, diarrhoea and cramps.
Primary lesions of mouth, pharynx or tonsils can result from oral sexual exposure and typically heal within a period of one week without scar formation (Reddy and Khandpur, 2005).

Secondary stage or Inguinal syndrome:

Inguinal syndrome or bubo is the inflammatory swelling of the inguinal lymphnodes. It may be unilateral or bilateral. The time taken from exposure to inguinal bubo varies from 10-30 days but can be as long as 3 to 4 months (Perine and Stamm, 1999).

In 20 percent of cases femoral lymphnodes may be enlarged. The inguinal and femoral lymphnodes are seperated by Poupart's ligament causing "Groove sign" or "Greenblatt sign". Constitutional symptoms like fever, joint pain, myalgia etc develop with bubo formation (Perine and Stamm, 1999).

Bilateral inguinal syndrome can lead to elephantiasis of male genitalia (sexophone penis) and 'esthiomene' in female. Dissemination of infection causes hepatitis, pneumonitis, endocarditis and skin lesions (Perine and Stamm, 1999).

Tertiary stage or Genito ano-rectal syndrome:

Usually seen in females. Due to lymphangitis the female genitalia develops polypoid growths and disfigurement called esthiomene. There can be associated proctitis leading to rectal strictures, piles, fissures and fistulae formation. In 2 to 5 percent of cases rectal strictures develop into carcinoma of rectum.
Diagnosis

The clinical diagnosis is established by taking careful history and proper clinical examination especially for inguinal adenopathy.

Serology: Antibody detection by Microimmunofluorescence Test (MIF)

It is the most accurate serological assay. It uses formalin fixed EBs grown in yolk sac as antigen. During the active phase of LGV, patients shows high levels of IgM (titres>1:32) and IgG (titres>1:512) with the antigen type of the infecting strain and much lower cross reactivity with other C. trachomatis strains. The preparation of antigen for this test is complex and laborious and to date, the use of MIF has been limited to a few research laboratories.

Immunoperoxidase test

It a simple and a rapid test for detecting C. trachomatis specific IgG and IgA antibodies (Ray K et al., 1993). IgG titre >1:128 and IgA> 1:16 is suggestive of active infection. It has been found to be positive in 83.3% of cases of LGV (Ray et al. 1993).

Polymerase Chain Reaction (PCR)

This method provides accurate diagnosis in low prevalence areas without the need for cell culture (Kellock et al., 1997).
Antigen detection assays

It comprises of Enzyme immunoassays (EIAs) and Rapid assays

Enzyme immunoassays (EIAs)

This method is suitable for antigen detection in ulcer scrapings or bubo aspirates but not for rectal samples. It has a sensitivity of 75-80%.

Treatment for LGV

The treatment is aimed at eliminating the organism to render the patient non-infectious and prevent complications.

Centre for disease control, Atlanta, USA recommends either

- Doxycycline 100mg orally bid for 3 weeks (not for use in pregnant mother)
- Erythromycin base 500 mg orally qid for 3 weeks (specially for pregnant and nursing mothers, children under 8 years of age and patients sensitive to doxycycline).

Follow up of the patient and management of sex partner:

Patients should be followed clinically until signs and symptoms have resolved.

Treatment of sex partner must be done simultaneously if partner has complaints.

Follow up must be done at every three months for one year.
Coinfection of LGV with HIV

In a retrospective analysis of 27 cases of LGV seen in the Paris Hospital, 6 cases with concomitant HIV infection were found (Scieux et al., 1989). However HIV appeared to have no effect on clinical presentation in these cases. Few other studies have demonstrated reactivation of latent LGV with development of multiple groin abscesses in HIV Positive patients.

In both HIV-positive and negative cases, the diagnosis can be established by high chlamydial complement fixation antibody titres (>1:64) (Czelusta et al., 2000). Centre for disease control (CDC) recommends the same treatment regimen for LGV in HIV-Positive and negative patients.

In early 2005, infection with lymphogranuloma venereum was confirmed in four residents of New York City by DNA sequencing of Chlamydia trachomatis detected in anorectal swab specimens. These four patients (all men who had sex with men, including three who were HIV positive) were among the first confirmed cases of LGV in USA. All had same serovar (L2) and had clinical presentations similar to cases of LGV in men who had sex with men in western Europe: rectal pain and bloody rectal discharge. The four patients responded well to 3-week regimens of doxycycline antibiotic (Susan and Schillinger, 2005).

Nongonococcal urethritis (NGU)

Historical aspects

In 1966, Dunlop et al described the NGU and the causative organisms were called "TRIC agents (Trachoma, Inclusion conjunctivitis). Later on mycoplasma, ureaplasma
urealyticum, corynbacteria and Haemophilus were described as causative agents (Majumdar and Sara, 2003).

**Epidemiology**

NGU is prevalent all over the world. In STD clinics in USA, the incidence varies from 19 to 78% (Hook et al., 1999). The peak age group affected is 20-24 years. In USA, 4-5 million cases occur annually (CDC, 1997) and is found in white educated individuals of higher socioeconomic status.

In developing countries, owing to limited laboratory facilities, exact incidence is difficult to assess.

**Etiology**

Chlamydia trachomatis

Ureaplasma urealyticum

Mycoplasma

Trichomonas vaginalis

**Other infectious causes**

Bacteria

Staphylococci saprophyticus

Haemophilus
Yeasts

Viral

Herpes simplex

Adenovirus

Non infectious causes

Trauma

Foreign body e.g. Catheterisation

Alcohol, caffeine

Allergic

Neoplastic

Clinical features

The incubation period is highly variable i.e. 1 to 3 weeks but it may be shorten or prolonged. There is mild urethritis with scanty mucoid urethral discharge and dysuria.

Complications

In men, Littritis, epididymitis, prostatitis, proctitis etc. In females, cervicitis, urethritis, endometritis, salpingitis, Bartholinitis or perihepatitis can occur.
Infection in pregnancy

Chlamydial infection in pregnancy can cause spontaneous abortion, Low birth weight of baby, neonatal conjunctivitis, preterm delivery, pneumonia etc.

Treatment (CDC, 2002)

Azithromycin 1 gm orally single dose.
Doxycycline 100 mg twice a day for 7 days
Erythromycin 500 mg four times a day for 7 days.

Sexual partner should be treated to reduce the recurrence rate.

Balanoposthitis

Definition

Balanitis is the inflammation of the glans penis and posthitis is the inflammation of mucous surface of the prepuce. It may occur individually or in combination i.e. balanoposthitis.

Incidence

The overall incidence of balanoposthitis reported is less than 2 percent. However in the recent years, the incidence has gone up to 20 percent.
Aetiology

Balanoposthitis is the disease confined to uncircumcised males. The warm humid and relatively anaerobic environment of the prepuce sac predisposes to the growth of aerobic and anaerobic organisms. Balanitis alone is far less seen in circumcised males. Balanoposthitis occurring for the first time in elderly males is highly suggestive of diabetes mellitus whereas in younger age group it commonly results from sexually transmitted diseases. The various predisposing and etiological factors are given below.

Predisposing factors

Poor personal hygiene, long prepuce, congenital or acquired phimosis, failure to dry the glans and prepuce after a bath, hot and humid climate.

Systemic diseases like diabetes mellitus, candidiasis, Reiter’s disease, Crohn’s disease, ulcerative colitis, HIV infection and other diseases or drugs leading to immunosuppression also predispose to balanoposthitis.

Classification of Balanoposthitis (Waugh, 1998)

Infections

Fungal

Candida albicans (commonest cause of infective balanoposthitis)

Pityrosporum orbiculare

Anaerobic Organisms

Diptheria, Diptheroids, Fusospirochetes
Spirochaetal
Treponema pallidum

Viral
Herpes simplex and Human papilloma virus (HPV)

Aerobic organisms
Gardenella vaginalis, Group B streptococcus, Staphylococcus aureus, Pseudomonas, Gonococci, Haemophilus ducreyi, Chlamydia.

Protozoal
Trichomonas vaginalis and Entamoeba histolytica

Parasitic
Scabies and Pediculosis

Irritants
Smegma, Retention of soaps or detergents in prepucial sac, Persistent moisture, Contraceptives, Irritation from infected urine, faeces and vaginal secretions, Spermicidal lubricants and Condoms

Trauma
Postcoital or post masturbation trauma, Frictional trauma by zips of trousers,

Fixed Drug Eruptions
Sulfonamides, Tetracycline, Quinine, Erythromycin, Carbamazepine, Dapsone etc.

Premalignant conditions
Erythroplasia of Queyrat (Bowen’s disease of the glans penis), Leukoplakia, Extramammary Paget’s disease.
Malignant diseases
Squamous cell carcinoma, metastatic carcinoma, melanoma

Miscellaneous
Circinate balanitis, Zoon’s balanitis, Balanitis xerotica obliterans (BXO)

Clinical manifestations
The natural course of the disease depends on the etiological factors mentioned above leading to inflammation with or without ulcerations of the glans or undersurface of the prepuce. This is followed by prepucial oedema, phimosis, and copious thick, offensive subprepucial discharge accompanied with pain, pruritus, feeling of pricking or of insect crawling or sense of stretching of the affected parts, meatal inflammation and burning micturition. Occasionally painful lymphadenopathy develops if left untreated and may progress to extensive ulcerations, perforation of prepuce and even sloughing gangrenous ulceration (phagaedena) of the glans an or prepuce, particularly when infected with fusospirochetes. The progress of the disease is arrested as the symptomatic treatment is started and the underlying cause is dealt.

Manifestations of balanoposthitis irrespective of aetiology are much more severe when associated with HIV infection, particularly so in the advanced stage.

Treatment
Treatment for balanoposthitis comprises specific and general treatment. Specific treatment depends upon aetiology, where as general measures are as follows.
> Advice subpreputial washes with Condy's solution (1:10000 KMnO₄) for 15 minutes each, 3-4 times a day, for patients who cannot retract the prepuce due to balanoposthitis.

> Anti-inflammatory drugs are used to reduce pain and discomfort.

> Simultaneous evaluation and treatment of sex partner/s.

> Counsel the patient about the maintenance of good personal hygiene.

> Advice circumcision to patients who have phimosis.

> Consider surgical management of complications like adhesions, perforation, stricture, meatitis and scarring to prevent recurrences.

**History of HIV-AIDS**

It was at the Center for Disease Control and Prevention (CDC) that the first indication of the impending AIDS epidemic became evident in 1980. Between October 1980 and May 1981 Dr. Michael Gottleib and his colleagues in Los Angeles, saw five young male patients with highly unusual form of pneumonia due to a parasite ‘Pneumocystis Jiroveci’ previously known as ‘Pneumocystis carinii’. They also had cytomegalovirus infection, oral thrush, and immunosuppression. All of them were homosexuals. Out of five, two of them died and remaining three were seriously ill. The first report of these observations appeared in Morbidity and Mortality Weekly Report of CDC on 5th June 1981 (Schoub, 1999).

A month later, the third July issue carried a similar report of 26 homosexual men 20 from NewYork and six from California with a very uncommon tumor called Kaposis sarcoma (named after nineteenth-century Hungarian dermatologist, Moritz Kaposi who
first described skin tumor). As with original five PCP patients the Kaposis sarcoma (KS) patient also had evidence of infection such as CMV, thrush and PCP. Meanwhile a further 10 PCP cases in homosexual men were also reported from California. (Schoub, 1999).

By September 1983, 2259 cases had been reported in USA, resulting in 917 deaths. Approximately 70% of these were homosexuals which led to the syndrome initially called gay-related immune deficiency (GRID) (Clarke, 2004). But later on cases were also reported in intravenous drug users, female sexual partners of the index cases, children of affected women and in heterosexual men and women from Haiti resident in the US. As this disease was clearly not linked exclusively to homosexuality, the term acquired immune deficiency syndrome (AIDS) was adopted (Quinn, 1996).

In 1983 Dr. Francoise Barre Sinoussi together with Professor Luc Montagnier isolated a reverse transcriptase containing virus from the lymph node of a man with persistent lymphadenopathy, one of the disease manifestation which precedes AIDS, and called it the LAV (lymphadenopathy associated virus). The following year Dr. Robert Gallo’s laboratory at National Cancer Institute at the National Institute of health (NIH) Washington DC reported isolation of human retrovirus that was distinct from HTLV, which they named human T-cell leukaemia virus type III (HTLV-III). To compound the confusion, a virus isolated from an AIDS patient by Dr. Jay Levy of University of California, soon after Gallo’s first isolation, was given yet another name “AIDS related virus” or “AIDS associated virus” (ARV) (Schoub, 1999).

The three viruses LAV, HTLV-III, and ARV were soon recognised as being Lentiviruses, a genus within the retrovirus group and in 1986 they were collectively
recommended the name (HIV) by International Committee on Taxonomy of Viruses. HIV was the name given to the causative agent of AIDS. In 1986, a second HIV virus was isolated by Luc Montagnier's group from AIDS patient in Guinea Bissau and Cape Verde Islands and was called Lymphadenopathy associated virus-2 or (LAV-2). At about the same time an American group under Myron Essex from Senegal isolated a second virus which they called Human T- cell lymphotropic virus- IV (HTLV-IV). Subsequently it was shown to be the same virus and was called HIV-2.

The AIDS Epidemic

HIV is a formidable enemy both biologically and socio-politically. HIV is perhaps the most complex and devastating problem humanity has ever faced. HIV-AIDS is the leading cause of morbidity and mortality followed by tuberculosis and malaria (Playfair and Bancroft, 2004).

Over 65 million people have been infected with HIV, of which 25 million have died of AIDS. Worldwide some 14,000 people are infected everyday, 95% of them in developing countries (Lamptey, 2002).

Although the rates of HIV infection and AIDS death have declined in richer countries of the developed world, infection rates are souring in developing countries. AIDS is now the leading cause of death in Africa and fourth leading cause of death globally.

In seven Sub-Saharan African nations, more than 22 percent of the population aged 15-49 is infected with HIV (Singhal and Rogers, 2003). In Botswana a nation with highest HIV infection rate in the world, 38% of the adults are infected with HIV. In
Zimbabwe as many as one in four adults carries the virus; and in South Africa one in five. In six of the southern African countries- Botswana, Lesotho, Namibia, South Africa, Swaziland and Zimbabwe the prevalence in pregnant women are above 20 percent (UN AIDS and WHO, 2005).

Out of global 40.3 million people (38 million adults and 2.3 million children) living with HIV/AIDS, 25.8 million were in Sub Saharan Africa followed by 7.4 million in South and South East Asia (UN AIDS and WHO, 2005).

Globally the young sexually active adults in their reproductive years are most vulnerable group. Data from UNAIDS/WHO shows that one-third of those currently living with HIV/AIDS are in the young age group of 15-24 years (UN AIDS and WHO, 2005).

**HIV AIDS Epidemic in India**

India is experiencing a rapid and extensive spread of HIV. This is particularly worrisome in a country like India which is home to a population of 1 billion people. Recent estimates by National AIDS Control Organization (NACO) suggests that 5.21 million people are living with the virus at the end of December 2005. (NACO, 2006). Although the HIV prevalence is low (0.9%), the overall number of people living with HIV in India is extremely high.

Globally India accounts for almost 10 percent of 40 million people living with HIV AIDS and over 60 percent of the 7.4 million people living with HIV/AIDS (PLWHA) in Asia and Pacific region (UN AIDS and WHO, 2005).
In India there is no one epidemic but several localised epidemics among the vulnerable population such as sex workers and the virus has started to spread from the vulnerable population into the general population. Sexual route is the most common mode of acquiring AIDS accounting for 85.81% of cases, followed by perinatal transmission 3.57%, injectable drug use 2.53%, blood and blood products 2.03% and other non specified routes accounting 6.06% of cases.

Data on surveillance for AIDS cases in India suggests that by the end of July 2005, the total number of AIDS cases reported in India was 1,11,608 of whom 32,567 were women. The data indicates that 37% of reported AIDS cases were diagnosed among people under 30 years (NACO, 2005).

The first AIDS patient in India was diagnosed by Dr. Suniti Solomon, a microbiology professor at Madras medical College in Chennai in 1986 in a group of 102 commercial females sex workers (Simoes et al., 1987). The blood samples were tested by ELISA at the Christian medical college in Vellore, and rechecked by Western blot analysis in the United States of which ten were found to be HIV positive.

The epidemic of HIV in India has been categorised into three categories based on the results of sentinel surveillance of states and union territories.

**High prevalence**

Maharashtra, Tamilnadu, Manipur, Andhra Pradesh, Karnataka and Nagaland states which have HIV prevalence rates exceeding 5% among groups with high risk behaviour and 1% among women attending antenatal clinics.
Concentrated epidemics

Gujarat, Pondicherry and Goa where HIV prevalence among population with high risk behaviour has been found to be 5% or more, but HIV prevalence rate remain below 1% among women attending antenatal clinics.

Low prevalence

All other states and Union territories fall in this category where HIV prevalence among the vulnerable population is below 5 percent and less than 1% among women attending antenatal clinics.

Recent surveillance data indicate that in high prevalence states, the epidemic is spreading gradually from urban to rural areas and from high risk groups to general population. Young people in India are amongst the most vulnerable to HIV. Over 35% of all reported HIV/AIDS cases in India occur among young people in the age group of 15-24 years.

Several sub-epidemics are evolving with potentially explosive spread among groups of injecting drug users (IDUs) and among Men having sex with Men (MSM). Recent research shows that men who have sex with men also have sex with women.

HIV infection has now been detected in all Indian states. Some states in India, like Maharashtra and Tamilnadu have very high rates of HIV infection. In the city of Mumbai, HIV prevalence among CSWs rose from less than 10 percent in early 1990s to 50 percent in 2000 and to 70 percent in 2001 (Singhal and Rogers, 2003).

Among the newly infected HIV cases, half are women. A report estimates that in India, almost 30% HIV infection occurs in those women who have sexual intercourse
with a single male partner (ICMR Bulletin, 1999) with majority of infections occurring in
the age group of 15-44 years.

The epidemic shifts from the highest risk groups (commercial sex workers, drug
users) to bridge populations (clients of sex workers, STD patients, partners of drug users)
and then to general population.

High level of sexually transmitted diseases (STDs), the presence of sexual
networks and migration all contributes to the significant vulnerability. Moreover factors
such as unequal power in decision making between men and women and the women’s
inability to negotiate safer sex remains major obstacle.

Various modes of HIV transmission

HIV infection can be transmitted sexually, through parenteral exposure, and
perinatally during pregnancy, child birth and post partum (Barry, 2000).

Sexual transmission

Sexual transmission is by far one of the most common modes of HIV
transmission. Sexual transmission of HIV infection can occur following vaginal and anal
intercourse, and also potentially through oral sex.

Heterosexual transmission:

Worldwide, 75% to 85% of the cases are attributed to heterosexual contact
(Royce et al., 1997). Initially it was postulated that breaches in the integrity of vaginal or
penile epithelium were essential for transmission to take place, even if these were only
due to microscopic abrasions or lesions, as commonly does occur during sexual intercourse. However demonstration of Langerhans cells as receptor cell for HIV infection and their abundance in genital mucosa has now established that virus could be transmitted through intact mucous membrane (Barry, 2000).

Male to female penile-vaginal transmission appears to be 2-3 times more efficient than female to male transmission (Vincenzi, 1994). The female is theoretically, considered more vulnerable to infection because her vagina is receptacle for a relatively large volume of infected semen, which then remains in contact with substantial area of susceptible vaginal and cervical epithelium for prolonged periods of time. In contrast to this, the exposure of a susceptible male to an infected female involves only a brief contact with an infected epithelial surface and the retention of a thin film of vaginal and cervical secretion onto susceptible epithelial surface of the penis and the urethra.

**Homosexual exposure**

The AIDS epidemic in the developed countries has been dominated by homosexual men and their lifestyle practices. In the United Kingdom close to 90% of all reported AIDS cases occur in sexually active homosexual and bisexual men. Rectal intercourse probably is a high risk activity likely to promote the transmission of HIV. The receptive partner in the sexual intercourse is at a higher risk of acquiring infection because of high frequency of trauma to the mucosal lining of the rectum during rectal intercourse. Receptive anal intercourse appears to be more risky than receptive vaginal intercourse with obvious implications for spread among men who have sex with men (MSM) (Caceres and Van Griensven, 1994).
The rectal mucosa is relatively delicate and friable epithelium composed of lining of one cell thickness in contrast to multi-cell layered and relatively robust vaginal epithelium which is far better equipped to withstand the injuries which may take place during intercourse. Further the rectal wall is richly supplied with lymphoid tissue which can provide a ready access for the virus to susceptible lymphocytes. The vaginal wall on the other hand has only sparse lymphoid tissue. Also the narrowness of the rectal canal makes it more vulnerable to trauma (Schoub, 1999). The risk of HIV infection is estimated to be 3.6 times higher for man practising receptive anogenital sex compared to men practising only insertive anogenital sex.

Oral transmission of HIV may occur in homosexual men, but the risk is considered to be low. The most risky form of oral sex, from an infected person is receptive fellatio with ejaculation in the mouth. The risk is further increased if there is an ulceration (or) inflammation in mouth. Recent studies in predominantly homosexual men in London suggest that 6% to 8% of those infected with HIV have acquired it through oral sex (Khan, 2000).

It is unknown whether HIV is transmissible via kissing, including so-called ‘deep kissing’ or ‘french kissing’ which involves exchange of saliva. The risk of transmission of virus would, of course, be substantially increased if infected blood is present in the saliva and, similarly, the susceptibility to infection would increase if there were abrasions or lesions in mouth due to trauma or disease. Therefore exposure to an infected person by deep kissing with salivary exchange is strongly discouraged.

Female homosexuality or lesbianism has on the other hand no role in the epidemiology of STDs. A few freakish incidents of HIV transmission between lesbians as
a result of oro-genital contact have been reported. However infections in lesbians have been due to heterosexual contact, intravenous drug abuse and in some cases, infection has been acquired from artificial insemination with semen which was obtained from high risk homosexual male donars (Schoub, 1999).

Other factors that increase the risk of sexual transmission include advanced stage of HIV infection in the index case, sex with an HIV infected women during menstruation, the older age of the susceptible female partner (European study Group, 1992).

Sexual transmission also depends greatly on the infectiousness of the infected partner. Higher viral loads in the later stages of the disease are associated with increased probability of transmission but infectiousness has also been shown to be higher at the time of seroconversion (Vernazza et al., 2000). Data are also conflicting on whether increased risk is related to high levels of HIV in semen of men with advanced HIV disease (Barry, 2000).

Sexually transmitted diseases facilitate sexual acquisition of HIV (Wasserheit, 1992). These include ulcerative STDs (e.g. syphilis, herpes, chancroid) (Fleming and Wasserheit, 1999 and Hayes et al., 1995) and nonulcerative (e.g. chlamydia, gonorrhoea, trichomoniasis). In addition, an HIV-infected person with another STD may be more infectious and may transmit the virus to an uninfected partner more easily (Wasserheit, 1992) and (Cohen et al., 1997).

Circumcision is associate with decrease risk of HIV transmission (Barry, 2000; Kreiss et al., 1993). Condoms have been found to offer effective protection against both unintended pregnancies as well as against sexual transmitted diseases including HIV (Pinkerton and Abramson, 1997).
Parenteral transmission of HIV

Parenteral transmission includes exposure through IDU (Injecting drug users), transmission of HIV infected blood or blood products, and nosocomial exposure through non-sterile medical supplies, such as needles and syringes.

Injecting drug users

The risk factors that have been associated with acquisition among injection-drug users include the number of injections, frequency of needle sharing, number of needle sharing partners, number of injections in “shooting galleries”, average number of injections per month, prevalence of HIV infection in the geographic area (Barry, 2000; Allen et al., 1992).

HIV transmission by blood exchange

HIV transmission from transfusion of infected blood or blood products declined rapidly following the introduction of screening blood donations for HIV antibodies in 1985. Moreover exclusion of donars whose specimens are positive for other pathogens (e.g., hepatitis B, hepatitis C, or syphils), and heat treatment of clotting factors also have contributed to reduced risk. Although concerns has been expressed about HIV transmission from blood donations given during the “window period” before the development of antibodies.

Parenteral HIV transmission related to use of non-sterile medical equipment has been reported, but its relative contribution to HIV transmission overall is likely small.
Risk of transmission to health care workers from percutaneous exposure to blood is approximately 0.3%, following mucous membrane exposure, the risk is 0.09% (Bell, 1997) and (Barry, 2000). In a case control study of health workers who sustained percutaneous exposure to HIV found that risk increased with deep injury, injury with a device visibly contaminated with blood, a procedure that involved a needle placed directly in a vein or artery, or exposure to blood from a person who died of AIDS within 2 months of the incident (Cardo et al., 1997).

**Mother to child transmission (MTCT)**

**Perinatal transmission**

The Mother to child transmission (MTCT) also referred to as vertical transmission is a major route of transmission of paediatric infection. The overall risk of transmission from an infected mother to her infant is about 30 percent (Schoub, 1999).

Around two-thirds of MTCT occurs in utero and at delivery and one-third occurs during breast feeding. Infection can be transmitted while the foetus is still in the uterus or during the delivery process as the infant moves down the birth canal and through the mothers genitalia and is bathed by the mothers blood during the birth process. Infection may also be acquired after birth by the baby ingesting milk from the mother (Schoub, 1999).

Breast feeding has been associated with increased risk of HIV transmission. In developing countries, it may increase the risk of HIV transmission by 10% to 20% with rates as high as 50% among mothers who become infected during late pregnancy or after
delivery (Dunn et al., 1992). Moreover a short course of nevirapine may also be effective in preventing MTCT.

Factors that increase the risk of HIV transmission include advanced maternal viral load, the presence of genital ulcerative diseases, chorioamnionitis, and prolonged rupture of the membranes (European Collaborative study, 1992; Barry, 2000).

**Structure of HIV**

HIV is a retrovirus and belongs to the family of lentiviruses.
Retroviruses

They comprise a large family of viruses that are associated with many diseases like malignancies, wasting diseases, neurological disorders and immunodeficiencies.

Lentiviruses

Infection with lentiviruses typically shows a chronic course of the disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system.

Like the Human immunodeficiency virus (HIV) that causes AIDS in humans, the simian immunodeficiency virus (SIV) in monkeys, Bovine immunodeficiency virus (BIV) in cattle, Equine infectious anaemia virus (EIAV) in horse, Maedi-Visna virus in sheep, Caprine arthritis encephalitis virus (CAEV) in goat, and feline immunodeficiency virus in cat are typical examples of lentivirus infection (Weber, 1998).

Both HIV-1 and HIV-2 resemble each other strikingly. However they differ with regard to the molecular weight of the proteins as well as having differences in their accessory genes. Both HIV-1 and HIV-2 replicate in the CD4+ T cells and are regarded as pathogenic in infected persons although the actual immune deficiency may be less severe in HIV-2 infected individuals.

Morphological structure of HIV.

The structure of Human immunodeficiency virus (HIV) consist of two main parts.

- The Viral Envelope
- The Viral core
The Viral envelope or Lipoprotein membrane

HIV is spherical in shape and is about 100-150 nm in diameter. The outer coat of the virus is known as viral envelope. The envelope like all viral particles is derived from the cell membrane of the host cell as the virus buds through the final stages of its replication. The envelope protects the virus while it is extracellular. The envelope is important for the pathogenicity of the virus (Barre-Sinoussi, 1996) and (Schoub, 1999).

Each viral particle contains 72 glycoprotein complexes which are integrated into the lipid membrane and each composed of trimers of an external glycoprotein gp 120 and a transmembrane spanning protein gp41 (Andrea et al., 2003).

The ‘gp’ stands for glycoprotein which is a molecule composed of a carbohydrate component (‘glyco’- from ‘glukeros’ =Greek for ‘sweet’) and a protein component. The molecular weight of gp 120 and gp 41 proteins are 120000 and 41000 daltons respectively (Schoub, 1999).

The surface glycoprotein gp 120 is responsible for adhesion to target cell membrane whereas the transmembrane glyprotein gp 41 is necessary for penetration into the target cell. The glycoprotein GP 160 is the precursor necessary for the synthesis of both glycoproteins and is found within the replicating cells as well as in plasma. Several host proteins including MHC class I and class II antigens are also present within this bilayer.
The Viral core or the Central core

Within the envelope of mature HIV particle is bullet shaped core or capsid, made up of 2000 copies of another viral protein, p24. The core protein antigen p24 is detectable very early in the course of the disease even when there is no signs of the infection and it is a target for antibodies that are used for diagnosis of HIV infection by Enzyme linked Immunosorbent Assay (ELISA).

The capsid surrounds two single strands of HTV RNA, each of which has a copy of the virus’s nine genes. Three of the genes gag, pol, and env contain information needed to make structural proteins for new virus particles.

The three regulatory genes tat, rev and nef and three auxiliary genes, vif, vpr and vpu contain information necessary for the production of proteins that control the ability of HIV to infect the cell, produce new copies of virus or cause disease.

The ends of each strand of HIV RNA contains an RNA sequence called long terminal repeat (LTR). Region in LTR acts as switches to control production of new viruses and can be triggered by proteins from either HIV or host cell.

The various enzymes present within the core include reverse transcriptase, integrase, protease and ribonuclease. The core of HIV also includes a protein called p7, the nucleocapsid protein.

Another HIV protein called p17, or the Matrix protein, lies between the viral core and the viral envelope.
Genomic organization of HIV

The genome of HIV is 9.5-kb in length and encodes nine genes. They are as under:

**Structural gene**
- Gag gene (stands for group antigen)
- Pol gene (codes for polymerase gene)
- Env gene (envelope gene)

**Regulatory gene**
- Tat gene (transactivating gene)
- Rev gene (regulatory viral protein)
- Nef gene (negative factor gene)

**Accessory gene**
- Vpr gene (viral protein r)
- Vif gene (viral infectivity factor)
- Vpx gene (viral protein X) present in HIV-2
- Vpu gene (viral protein u) present in HIV-1

**Viral proteins and their functions**

**Gag (group specific antigen)**

It gives rise to a 55 kilodalton (kd) gag precursor protein also called p55. After the process of budding p55 is cleaved by virally encoded protease enzyme (a product of pol
gene) into four smaller proteins designated as MA (matrix [p17]), CA (capsid [p24]) and NC (nucleocapsid [p7] and [p6]).

**Pol gene (Pol is short for polymerase) (Schoub, 1999)**

The pol gene product results in formation of HIV virion enzyme-

- Reverse transcriptase RT- required for DNA synthesis.
- Ribonuclease- which cleaves RNA
- Integrase- which promotes integration of nucleic acid into host cells chromosome.
- Protease-which splits protease into small fragments.

**Env gene (envelope gene)**

The envelope gene is found in all retroviruses. It makes proteins for the envelope to the virus. The envelope gene is 2.5kb in size and encodes for a 160kD precursor glycoprotein composed of 850 amino acids, which is cleaved by endopeptidase into two glycoproteins gp 120 (surface envelope[SU]) and gp 41 (transmembrane [TM]). Gp120 contains binding site for CD4 receptor and gp 41 domain chemokine receptor serves as coreceptor for HIV-1.

**Regulatory genes**

**Tat:**

- It is a transcriptional transactivator, essential for HIV-1 replication. Tat promotes the elongation phase of HIV- transcription, so that full-length transcripts can be produced. In absence of Tat expression, HIV generates primarily short transcripts.
• Tat activates the expression of numerous cellular genes including tumour necrosis factor beta and transforming growth factor beta.

• Tat is an important in HIV immunoregulation and pathogenicity. Tat is expressed early in the virus life cycle and functions both as a regulatory and virulence factor during the course of HIV infection.

• It is secreted from the infected cells and exerts potent suppressive effects, which serves to counteract the host immune surveillance mechanisms and promote new rounds of viral replication.

• Tat has been demonstrated to inhibit Natural killer (NK) cell function by blocking L type calcium channels (Zoechi et al., 1998).

• Tat upregulate both CCR5 and CXCR4 coreceptor expression, enhancing cell susceptibility to new viral infections (Huang et al., 1998).

• Various observational clinical studies in HIV infected humans have provided evidence that antibody directed against Tat is associated with delayed disease progression (Cohen et al., 1999). Long term non progression (LTNP) has also been correlated with presence of Tat-specific cytotoxic T- cells.

Rev: (Regulator of expression of viral proteins)

It is essential for HIV-1 replication, but exerts its effect at post transcriptional level by regulating the transport of viral messenger m-RNAs from nucleus to cytoplasm (Cotran, 1999).
Nef: (negative factor gene) (Greenway et al., 2003)

- It is a 27 Kda protein. Nef produces a protein which acts on section of LTR (long terminal repeat) called NRE (negative regulatory element which in turn sends a message down regulating viral replication by inhibiting the production of structural proteins (gag, pol, and env). It is needed by virus for efficient replication. (Schoub, 1999; Greenway et al., 2003).

- It stimulates infectivity of HIV virion.

- Nef interferes with T cell activation by binding to various protein that are involved in intracellular signal transduction pathways.

- In HIV infected rhesus macaques an intact nef gene was essential for high rates of virus production and progression of disease.

- HIV-1 with deletion in nef results in long term non progression.

Accessory genes

These proteins are not absolutely required for viral replication in viral systems but represents critical virulence factors in vivo.

Vpr

It helps to increase virus production by several mechanisms.

- It allows non dividing cells such as macrophages to be infected with HIV.

- It causes cell cycle arrest in the G2 phase of the cell cycle, during which the viral long terminal repeat (LTR) is most active, thus maximizing virus protection (Cotran, 1999).
Vif (viral or viron infectivity factor) (Schoub, 1999)

- It is a 23-KD polypeptide that is essential for replication of HIV in peripheral blood lymphocytes, macrophages etc.
- It influences the infectivity of viral particles and also the release of infectious virus from the cells.
- In absence of vif the produced viral particles are defective, while cell to cell transmission of virus is not affected.

Vpu (Viral protein u)

- It is present only in HIV-1. It is a 16-Kd protein. It is important for the virus budding process. It is known to enhance the production of virus particles by promoting the release of infectious virus from the cells.
- Vpu is also involved when CD4-gp160 complexes are degraded within the endoplasmic reticulum and therefore allow recycling of gp160 for the formation of new virions.

Vpx (Viral protein x)

It is an accessory gene and homolog of HIV-1 Vpu. It is present only in HIV-2. Its function is yet unknown.
Subtypes of HIV

Human immunodeficiency viruses (HIV-1 and HIV-2) are the etiological agents for AIDS in humans (Gottlieb, 2001; Gallo et al., 2003; Lal et al., 2005). HIV-1 has spread in most parts of the world, while HIV-2 has remained largely restricted to West Africa. HIV-1’s great diversity is seeded by the lack of proof-reading mechanism in RNA viral polymerase reverse transcriptase, and consequential high error rate (0.2-2 mutations per genome per cycle) (Korber et al., 2001) along with rapid viral turnover ($10^{10}$ viral particles /per day in HIV infected individuals (Boswell et al., 2000).

Zoonotic transmission of lentiviruses

HIV-1 and HIV-2 and the closely related simian immunodeficiency viruses (SIV) belong to the lentivirus subfamily of retroviruses. Humans are exposed to a plethora of primate lentiviruses through hunting and handling of primate bushmeat in Central Africa (Lal et al., 2005).

Both HIV-1 and HIV-2 are the result of zoonotic transmission of SIVcpz in chimpanzees (Pan troglodytes troglodytes) from West central Africa (Gao et al., 1999) and SIVsm in sooty mangabeys (Cercocebus atys) from West Africa (Gao et al., 1992) respectively.

Genetic variants of HIV

HIV-1 variants have been divided into three groups, M (major) O (Outlier), and N. On the basis of Phylogenetic analysis of numerous isolates obtained from diverse
geographic origins, HIV is divided into types, groups, subtypes, sub-subtypes (sub-clusters), circulating recombinant forms (CRFs) and unique recombinant forms (URFs) (Lal et al., 2005).

HIV-1 group M, accounts for the majority of infections worldwide. Based on genetic variability across the whole genome, at least nine distinct subtypes of HIV-1 group M exist: A-D, F-H, J and K.

HIV-1 groups O and N, which are genetically very divergent from group M, represents less than 5 percent of infections worldwide and have almost exclusively been detected in West Central Africa (Lemey et al., 2004).

The outlier group or ‘O’ group viruses have been identified mainly from persons with epidemiological links to west central Africa, mainly Cameroon and some neighbouring countries.

The HIV-1 group N infection has only been identified in Cameroon, a country endemic of HIV-1, with all major groups in cocirculation (Lal et al., 2005).

List of circulating recombinant forms identified to date

There are at least 16 different circulating recombinant forms (CRFs) to date (Peeters, 2000).
<table>
<thead>
<tr>
<th>Various circulating recombinant forms</th>
<th>Subtypes Involved</th>
<th>Places found</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF_01 AE</td>
<td>A and E</td>
<td>Thailand, Vietnam, Cambodia, Myanmar and China, Central African republic, Cameroon, Democratic Republic of Congo</td>
</tr>
<tr>
<td>CRF_02 AG</td>
<td>A and G</td>
<td>West and west Central Africa, Europe, US and South America</td>
</tr>
<tr>
<td>CRF03_AB</td>
<td>A and B (In IDUs)</td>
<td>Kaliningrad-Russia</td>
</tr>
<tr>
<td>CRF04_cpx</td>
<td>A, G, H, K and unknown fragment with multiple break points (Complex mosaic type)</td>
<td>Cyprus</td>
</tr>
<tr>
<td>CRF05_DF</td>
<td>D and F</td>
<td>Democratic republic of Congo</td>
</tr>
<tr>
<td>CRF06_cpx</td>
<td>A, G, K and J</td>
<td>Senegal, Mali, Burkino Faso, Ivory coast, Niger and Nigeria</td>
</tr>
<tr>
<td>CRF07_BC</td>
<td>B and C (IDUs)</td>
<td>Northwestern China</td>
</tr>
<tr>
<td>CRF08_BC</td>
<td>B and C (IDUs)</td>
<td>Guangxi (Southern China), Myanmar</td>
</tr>
<tr>
<td>CRF09_cpx</td>
<td></td>
<td>Senegal</td>
</tr>
<tr>
<td>CRF10_CD</td>
<td>C and D</td>
<td>Dar-es-Salaam (Tanzania)</td>
</tr>
<tr>
<td>CRF12_BF</td>
<td>B and F</td>
<td>Argentina and Uruguay</td>
</tr>
<tr>
<td>CRF13_cpx</td>
<td>A, G, J and CRF01_AE</td>
<td>Cameroon</td>
</tr>
<tr>
<td>CRF14_BG</td>
<td>subtype B most prevalent and G</td>
<td>Spain</td>
</tr>
<tr>
<td>CRF15_01B</td>
<td></td>
<td>Thailand</td>
</tr>
<tr>
<td>CRF16_A2D</td>
<td></td>
<td>Kenya, South Korea and Argentina</td>
</tr>
</tbody>
</table>
Few HIV-2 infections have been identified, almost all of these represent infections with HIV-2 subtype A (Bhanja P et al., 2004).

The initial analysis of small fragments of V3-V5 envelope region of subtype C sequences from India along with sequences from other countries with predominance of subtype C has revealed that Indian C sequences form a phylogenetically distinct lineage within subtype C, designated as C3-Indian reference strain (IND868), almost a third of an infections shows homology to C2-Zambian strain (ZM18) and a minor percentage shows close resemblance to C1-Malawi strain (MA959) (Gadkari et al., 1998).

HIV Receptors

Till now only CCR5 and CXCR4 has been shown to function as coreceptor for HIV-1 in vivo and all HIV-1 isolates can use one or both. Both of them are members of seven G- transmembrane protein family of chemokine receptors (Clapham et al., 2001).

The CCR5 molecule, present on the surface of macrophages and CD4 cells, is the principal coreceptor used by macrophage tropic (nonsyncytium-inducing [NSI]) viral strains that predominate in the early stages of HIV infection (Wu et al., 1996; Dragic et al., 1996; Boswell and Fuller, 2000).

CXCR4 (also called fusin) is found on T lymphocytes and laboratory adapted T-cell lines and is the main coreceptor used by T-tropic (syncytium-inducing [SI]) viral strains that often predominate in the later stages of HIV disease (Feng et al., 1996).

Transmitted virus seems to have a predilection to bind to CCR5. These viruses have recently been named as R5 viruses in reference to their co receptor requirement, where as the virus which require CXCR4 are referred to as X4 viruses. Recent data
suggests that within the mucosa, HIV first targets dendritic cells (e.g., langerhan’s cells). These harbor the CD4 receptors and the coreceptor CCR5 but do not seem to express CXCR4. These observations may suggest the predominant role of R5 viruses in the acute HIV infection. (Kahn et al., 1998).

The pathogenesis of AIDS

The human immunodeficiency virus has a peculiar affinity for CD4 receptors. Hence all CD4 receptor bearing cells are selectively infected and the virus uses cellular machinery of these cells to continuously replicate within the body. Once it has completely used up the cell machinery for its own replication, the cell dies releasing hundreds of virions that are ready to infect new cells.

The rapid proliferation of the virus in T lymphocytes from blood and lymphoid tissues results in lowering of the CD4 lymphocyte count. About 1% of circulating CD4 T cells is infected during primary HIV infection which is accompanied by a moderate reduction in CD4 T cell count. However, this CD4 count reduction is reversible (almost fully) as it reverts back to nearly normal value after subsidence of primary illness.

About 1 billion new virions are produced daily in the body tissues and the immune system responds by producing 1-2 billion new CD4 positive T cells everyday. This massive killing of CD4 T lymphocytes is countered by matching production of new CD4 T lymphocytes thereby maintaining a dynamic balance. However, this tremendous turn over of T cells finally lead to immune exhaustion over a period of few years.

In the early phase of HIV disease HIV specific CD8 positive T cells (cytotoxic T cells) appear in the blood following seroconversion and their increasing number
contributes to reversal of CD4/CD8 ratio that characterizes HIV infection. These virus-specific CD8 T cells are responsible for preventing the appearance of the virus in the peripheral blood. During the asymptomatic phase that sets in after primary illness, the virus proliferates almost exclusively in lymphoid tissues of the lymph nodes, adenoids, tonsils, and the gastrointestinal tract (thymus in fetuses and in children).

As the HIV infection progresses the virus can no longer be contained by lymphoid tissues and begins to appear in increasing numbers in the peripheral blood CD4 T lymphocytes. Killing of the CD4 T lymphocytes in the peripheral blood as well as tissues compromises immunity leading to symptomatic HIV infection.

Stimulation of viral replication may occur through the release of pro-inflammatory cytokines like TNF alpha (tumor necrosis factor alpha) or interleukin 1 and interleukin 6 which stimulates viral replication, aggravates immunosuppression, and hastens progression of the disease.

Superantigens in the internal or external environment can activate CD4 T cells and thereby stimulate viral replication. Recent reports suggest that infective agents like M. tuberculosis and cytomegalovirus may act as superantigens and hastens progression of the disease.

**Life cycle of HIV or Replication cycle of HIV**

HIV interacts with CD4 and a seven transmembrane (7TM) co-receptor to trigger entry into the cells. The envelope glycoprotein spikes on the surface of virus particles comprises an outer surface gp 120 (SU) non-covalently linked to a transmembrane gp41 (TM). Each spike on the surface of virus particle comprises a trimer of three gp 120 and
three gp41 molecules. Binding of CD4 to gp120 triggers a structural change, which exposes a binding site for a co-receptor (CCR5 or CXCR4). Further structural rearrangements are initiated when coreceptor is bound. These changes occur predominantly in gp41 and are thought to be sufficient to trigger fusion of viral and cellular membranes and entry of the virion core into the cell’s cytoplasm (Paul et al., 2001).

The process of replication involves following steps:

**Reverse transcription**

In the cytoplasm of the cell, HIV reverse transcriptase converts viral RNA into DNA, the nucleic acid form in which cell carries the genes.

**Integration**

The newly made HIV DNA moves to the cell nucleus, where it is spliced into the host’s DNA with help of HIV integrase. HIV DNA that enters the DNA of the cell is called provirus.

**Transcription**

For a provirus to produce new viruses, RNA copies must be made that can be read by the host cells protein machinery. These copies are called messenger RNA (mRNA), and production of mRNA is called transcription, a process that involves the host cell’s own enzymes. Viral genes in concert with cellular machinery control this process. The tat gene, encodes a protein that accelerates transcription. Genomic RNA is also transcribed for later incorporation in the budding virion.
Cytokines, proteins involved in the normal regulation of immune response, may also regulate transcription. Molecules like tumour necrosis factor (TNF)-alpha and interleukin (IL-6) secreted by the cells of HIV infected people may help to activate HIV proviruses.

**Translation**

After HIV mRNA is processed in cell’s nucleus, it is transported to the cytoplasm. In the cytoplasm, the virus co-opts the cells protein making machinery- including structures called ribosomes- to make long chain of viral proteins and enzymes, using mRNA as a template. This process is called translation.

**Assembly and budding**

Newly made HIV core proteins, enzymes and genomic RNA gather inside the cell and an immature viral particle is formed and buds out from the cell, acquiring an envelop that includes both cellular and HIV proteins from the cell membrane. During this period of the viral life cycle the core of the virus is immature and the virus is not yet infectious. The long chain of proteins and enzymes that make up the immature viral core are now cut into small pieces by viral enzyme protease. This step results in infectious viral particles.

The newly matured HIV particles are ready to infect another cell and begin the replication process. Thus the virus quickly spreads throughout the human body and once a person is infected they can pass HIV on to others in their bodily fluids.
**Host and viral factors for HIV progression**

Several host factors have been associated with HIV infection and can influence the rate of progression to AIDS among HIV infected patients. Host responses are considered as important regulators for progression of HIV infection.

The presence of long term non progressors and exposed yet uninfected individuals indicates that natural and acquired immunity to HIV exist and are possibly major determinants of clinical outcomes.

**HIV specific Cytotoxic T-cell response**

Cytotoxic T lymphocytes recognize HIV infected cells through HIV antigens expressed at the surface of infected cells in association with HLA Class I peptides. This activity requires cell to cell contact. The cytotoxic T cells induce biochemical pathways in the target cells that ultimately leads to destruction of cells. By destroying infected cells the CTLs put halts to the multiplication of HIV (Paranjape, 2005).

In humans HIV-1 specific CD8+ T cell response is the earliest adaptive immune response generated and is temporally associated with decline in viremia during acute HIV infection (Paranjape, 2005).

Strong virus specific CTL responses have been demonstrated in HIV-1 infected individuals with long term non progressive disease (Cao et al., 1995).

In highly exposed but uninfected individuals (HEPS) the HIV specific CTL response has been detected. Studies conducted in Nairobi cohort of commercial sex workers have shown that the subjects considerably exposed to HIV infection but still not infected exhibit HIV-specific CTL response at vaginal mucosal level (Paranjape, 2005).
T-Helper cell response

T-helper cell responses have been shown to be important in maintaining CD4+ T-cell responses in other persistent viral infections. They are activated when they bind to recognizable viral epitopes present on MHC class II molecule. Once activated they secrete interleukin (IL-2) and other cytokines to enhance the CTL and humoral responses. Both quantitative and functional defects in T-helper cells contribute to immune defect depending on the stage of the disease.

Humoral immunity

Evidences suggests that the humoral arm of the immune system is not fully protective. Events during primary HIV infection shows that humoral immunity may not play a major role in preventing and controlling infection. Antibodies to HIV begin to appear within 2 to 3 weeks after infection, but viral replication persists despite this event.

Genetic factors

- Chemokines

One of the strongest association of genetic polymorphism and HIV susceptibility and disease progression has been reported in case of mutation of 32 base pair deletion in CCR5 receptor gene (CCR5Δ32). Individuals homozygous for this mutation have decreased susceptibility to HIV infection (Haung et al., 1996; Clapham et al., 2001). Individuals heterozygous for CCR5Δ32 are not less susceptible to HIV infection, but are more likely to become long term non-progressors/survivors (Haung et al., 1996).
HIV disease progression has also been reported to be influenced by mutations in coreceptor CCR2, CCR2-V64I. Persons exhibiting this mutation may progress more slowly to AIDS (Paranjape, 2005).

A mutation in stromal derived factor 1 (SDF-1), ligand for CXCR4, may delay progression of AIDS and also increase survival after diagnosis of AIDS.

These genetic factors not only influence disease progression but may also be important in developing patient specific anti-retroviral strategies and development of vaccine.

Cytokines

In vitro studies of peripheral blood mononuclear cells and lymph node mononuclear cells from HIV-infected persons indicates that cytokines control HIV replication.

Tumor necrosis factor-TNF-α, TNF-β, Interleukin IL-1 and IL6 are proinflammatory cytokines whose levels are elevated in HIV infected persons and that enhance HIV replication. Other cytokines, such as IL-2, IL-4, IL-10, Transforming growth factor (TGF-β) and Interferon γ induces or suppresses HIV expression.

HLA types

Several studies have revealed association between certain HLA alleles with rapid or slow disease progression.

The alleles B57, B14, C8 and B 27 have been shown to be associated with long term non-progressor status (Klein et al., 1998; Paranjape, 2005). Homozygosity of HLA
BW-4 was found to be associated with long term non progression to AIDS (Paranjape, 2005).

The TH₁/TH₂ Immune response

Depending upon the secretion pattern of the cytokines CD4+ T cells may be differentiated into TH₁ and TH₂ cells. TH₁ CD4+ T cells primarily produce interleukin-2 (IL-2) and IFNγ, which represents cytokines that support the effector functions of the immune system (CTLs, NK-cells, macrophages). TH₂ cells predominantly produce IL-4, IL-10, IL-5 and IL-6, which represents cytokines that favour the development of humoral immune response. Since TH₁ cytokines are critical for the generation of CTLs, an HIV-1 specific TH₁ response is regarded as being protective immune response.

Apoptosis

Apoptosis or “Programmed cell death” is a mechanism normally used by the body to eliminate redundant cell populations and defective cells, it is utilised by HIV to destroy both infected and uninfected cells. It is one of the important mechanism that contributes to T cell destruction. Elevated levels of apoptosis are found to correlate directly with disease progression and inversely with T helper cell count.

HIV proteins such as gp120, Tat, Nef and Vpu have been shown to induce cell death in uninfected cells (Paranjape, 2005).

HIV nef protein in extracellular matrix can induce cell death in uninfected T cells (Paranjape, 2005).
HIV tat protein may induce apoptosis through both Fas-mediated and Fas independent mechanisms (Paranjape, 2005).

**Neutralizing antibodies**

Studies of neutralizing antibody response in individuals with established infection shows that Long term non progressors (LTNPs) have broad and high titered neutralizing activity compared to individuals that show rapid disease progression (Cecilia et al., 1999).

**Direct or single cell killing**

Infected CD4 cells may be killed directly when large number of virus is produced and bud off from the cell membrane or when viral proteins and nucleic acids collect inside the cell interfering with cellular machinery (Garry, 1989).

**Syncytia formation**

Infected cell may fuse with the nearby uninfected cells, forming balloon-like giant cells called syncytia which are associated with rapid risk of disease progression in HIV infected individuals. Their formation may be regulated by leukocyte adhesion molecule (LFA-1) produced by CD4+ T lymphocytes inoculated with HIV (Wachu, 2005).
**Innocent bystanders**

Uninfected cells may die by an innocent bystander effect. HIV particles may bind to cell surface, making them appear as infected cells and marking them for destruction by killer T cells. Since HIV envelope proteins have some resemblance to certain molecules that might appear on CD4+T cells, the body's immune responses might mistakenly damage such cells (Wachu, 2005).

**Superantigens**

The Nef protein is a putative viral super-antigen of HIV and due to its superantigen properties, the CD4+ cells are transformed to activated state for virus replication (Wachu, 2005).

**Natural history of HIV infection**

The course of the disease from the time of initial infection to the development of full blown AIDS is divided into the following stages

1. **Primary HIV infection / Acute Retroviral syndrome**
2. **Asymptomatic stage**
3. **Symptomatic HIV infection previously known as AIDS related complex**
4. **AIDS (CD4 counts of 50-200 cells/mm³)**.
5. **Advanced HIV disease (CD4 count < 50 cells/mm³)**

1. **Primary HIV infection / Acute Retroviral syndrome**

   It is experienced in up to 80 to 90 percent of HIV infected patients. The time from infection to onset of symptoms is 2-4 weeks. The clinical symptoms include fever,
lymphadenopathy, arthralgia, myalgia, diarrhoea, vomiting, oral candidiasis, skin rashes, meningo-encephalitis, neuropathy, psychosis etc.

Laboratory findings include lymphopenia, low CD4 cell count and high CD8 cells.

2. **Asymptomatic HIV infection**

During this phase the patient is clinically asymptomatic but some cases have PGL (persistent generalized lymphadenopathy). Detailed history reveals history of STDs, herpes zoster, oral candidiasis etc.

3. **Symptomatic HIV infection**

During this stage the skin and the mucous membrane are involved. Multidermatomal herpes zoster, mollusci, orall candidiasis, oral hairy leucoplaikia, folliculitis, fungal infections, pruritic skin lesions etc are found in this stage. Kaposis sarcoma, pulmonary tuberculosis and pneumonia can occur. CD4 count is usually between 200-499 cells/mm³

4. **AIDS**

This stage is characterized by opportunistic infections and malignancies. The constitutional symptoms like fever, arthralgia, myalgia, diarrhoea, loss of weight (more than 10 percent of body weight in one month), neurological symptoms persist. The CD4 count is 50-200 cells/mm³ (Fauci et al., 2001).
5. **Advanced HIV disease (CD4 count < 50 cells/mm³)**

   In this stage some infections like M. Avium complex, cytomegalovirus, cryptococcosis, histoplasmosis can occur which are fatal. CNS involvement is very prominent. The patient develops AIDS Dementia complex, CNS lymphomas etc.

**Guidelines by The World Health Organization for resource-poor settings**

(December 1, 2003)

In resource-poor settings, facilities for viral load or CD4 count may not be available. Hence the WHO has proposed a clinical staging system for HIV infection

WHO staging system for HIV infection and disease in adults and adolescents

**Clinical stage I**

1. Asymptomatic

2. Persistent generalized lymphadenopathy (PGL)

   Performance scale 1: Asymptomatic, normal activity

**Clinical stage II:**

1. Weight loss, > 10% of body weight

2. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis)

3. Herpes Zoster, within last 5 years

4. Recurrent upper respiratory tract infections (i.e., bacterial sinusitis)

   And/or Performance scale 2: symptomatic, normal activity
Clinical Stage III:

1. Weight loss, > 10% of body weight
2. Unexplained chronic diarrhoea, > 1month
3. Unexplained prolonged fever (intermittent or constant), > 1 month
4. Oral candidiasis (thrush)
5. Oral hairy leukoplakia
6. Pulmonary tuberculosis, within the past year
7. Severe bacterial infections (i.e., pneumonia, pyomyositis)

And/or performance scale 3: bed-ridden, < 50% of the day during the last month

Clinical stage IV:

1. HIV wasting syndrome*
2. Pneumocystis carinii pneumonia
3. Toxoplasmosis of the brain
4. Cryptosporidiosis with diarrhoea, > 1 month
5. Cryptococcosis, extrapulmonary
6. Cytomeglovirus (CMV) disease of an organ other than liver, spleen or lymph node (ex: retinitis)
7. Herpes simplex virus (HSV) infection, mucocutaneous (>1 month) or visceral
8. Progressive multifocal leukoencephalopathy (PML)
9. Any disseminated endemic mycosis
10. Candidiasis of the oesophagus, trachea, bronchi
11. Atypical mycobacteriosis, disseminated or lungs
12. Non typhoid Salmonella septicaemia
13. Extrapulmonary tuberculosis
14. Lymphoma
15. Kaposis Sarcoma (KS)
16. HIV encephalopathy**

And/or performance scale 4: bed ridden, > 50% of the day during the last month.

**Mucocutaneous Manifestations of HIV Infection and AIDS**

Mucocutaneous diseases are amongst the first recognised clinical manifestations of AIDS. Over the past decade, it has become increasingly clear that cutaneous disorders are associated not only with the terminal stages of immunodeficiency but occur throughout the course of HIV infection.

**Mucocutaneous disorders as indicators for HIV serotesting (Johnson, 1999)**

<table>
<thead>
<tr>
<th>Disorders strongly associated with HIV infection</th>
</tr>
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<tbody>
<tr>
<td>Candidiasis – oropharyngeal or recurrent vulvovaginal</td>
</tr>
<tr>
<td>Herpes zoster – multidermatomal or disseminated</td>
</tr>
<tr>
<td>Chronic herpes simplex infection</td>
</tr>
<tr>
<td>Oral hairy leukoplaikia</td>
</tr>
<tr>
<td>Papular eruptions of HIV</td>
</tr>
<tr>
<td>Molluscum contagiosum – face involvement in an adult or giant molluscum contagiosum</td>
</tr>
<tr>
<td>Proximal white subungual onychomycosis</td>
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<tr>
<td>Kaposis’s sarcoma</td>
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</tbody>
</table>
### Disorders commonly associated with HIV infection

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any sexually transmitted disease – indicative of unsafe sexual behaviour</td>
</tr>
<tr>
<td>Signs of injecting drug use</td>
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### Disorders associated with HIV infection

<table>
<thead>
<tr>
<th>Disorder</th>
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<tbody>
<tr>
<td>Generalized lymphadenopathy</td>
</tr>
<tr>
<td>Psoriasis vulgaris</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis – in an adult, extensive and refractory to therapy</td>
</tr>
<tr>
<td>Aphthous ulcers – recurrent, refractory to therapy</td>
</tr>
<tr>
<td>Crusted scabies</td>
</tr>
</tbody>
</table>

### The classification of mucocutaneous lesions:

- Infections
- Fungal
- Viral
- Bacterial
- Arthropod
- Protozoal

### Non infectious

### Neoplasms

### Infections
**Fungal Infections**

They may be superficial or deep. Cutaneous or mucosal fungal infections may give a clue to the underlying HIV infection. Sometimes these infections are more extensive, often atypical, aggressive and sometimes life threatening.

**Candidiasis**

Oropharyngeal candidiasis is the most common opportunistic infection in HIV infected patients occurring up to 90% of the patients at some point of time during the course of HIV disease. Oral candidiasis is a sign of transition to AIDS.

Candidiasis is the most often caused by yeast, Candida albicans, and sometimes by other species like C. tropicalis, c. parapsilosis, C. krusei and C. glabrata.

The most common pattern of oral thrush is pseudomembranous type. It appears creamy white exudative plaques (cottage cheese like) on the tongue, palate, tonsils and buccal mucosa and can be easily removed with a tongue depressor leaving an inflammatory erythematosus surface beneath the lesion.

Candidial oesophagitis is the most common cause of dysphagia in HIV disease. It is the first opportunistic infection in 3% to 10% of HIV infected patients. It is considered the second most common AIDS defining disease after pneumocystis jiroveci pneumonia.

Vulvovaginal candidiasis is the common and early manifestation in HIV infected women. It generally presents as erythema, often with white exudative plaques involving both vagina and vulva often associated with a burning or itching sensation.

Chronic candidial paronychia and nail dystrophy are common in young children with HIV disease.
The diagnosis of candida can be done by microscopic examination from scrapings of affected mucosa. A 10% potassium hydroxide (KOH) preparation reveals spores, budding yeast forms (pseudo-mycelia) and mycelial elements.

**Superficial dermatophytosis**

Over one-third of HIV patients have dermatophytosis. The most commonly responsible fungus is Trichophyton rubrum. HIV infected individuals frequently acquire proximal white subungual onychomycosis a dermatophyte infection in nails that is rare in individuals with intact immune system.

**Pityrosporum infection**

Pityrosporum ovale causes pityriasis (tinea) versicolor and Pityrosporum folliculitis which is characterised by numerous pruritic papules or pustules occurring on upper trunk or proximal arms.

**Deep and systemic mycoses**

**Cryptococcosis**

Cryptococcosis is the second most common fungal infection in HIV infected individuals. It is an opportunistic infection caused by encapsulated yeast Cryptococcus neoformans found ubiquitously in soil, dust and pigeon excreta. It occurs in up to 10% of patients with AIDS. Patients with CNS cryptococcosis presents with fever, headache and vomiting. The skin lesions occurs as papules or pustules.
Penicillinosis

It is caused by Penicillium marneffei. It is endemic in Far East. It is a dimorphic fungus and cause systemic mycosis particularly in the immunocompromised patients. The condition is fatal.

Histoplasmosis

It is caused by Histoplasma capsulatum. Disseminated histoplasmosis can present as acute, sub acute or chronic illness often accompanied by fever, weight loss, hepatosplenomegaly and pulmonary symptoms. It may mimic pulmonary tuberculosis.

Coccidioidomycosis

It is caused by Coccidioides immitis. It is seen in late stage of HIV infection.

Sporotrichosis

It is caused by Sporothrix schenckii. In HIV disease disseminated infection involving the skin and other organs are described.

Blastomycosis

It is caused by Blastomyces dermatitidis, a dimorphic fungus. It is rarely seen in HIV infection.
Aspergillosis

It is a rare opportunistic infection in HIV disease. Risk factors include leucopenia, broad spectrum antibiotics and antineoplastic agents.

Viral infections

They are the major pathogens causing opportunistic infections in HIV infected patients with most of them manifesting at mucocutaneous sites.

Herpes simplex virus infection

In HIV infected patients HSV presents as tender, often painful, ulcerative lesions on the penis, perianal area and the lip region which is the hallmark of HIV infection. If untreated the lesions may continue to enlarge peripherally sometimes reaching over 100cm² (Thappa, 2005). According to the revised CDC diagnostic criteria for AIDS, in absence of other cause of immunodeficiency, the ulcerative HSV infection persisting for longer than one month is considered diagnostic of AIDS.

Varicella zoster virus (VZV)

Herpes zoster or reactivation of latent VZV may be the first sign of immunosuppression and its occurrence should always raise the issue of HIV sero testing. Herpes zoster occurring in HIV disease is usually multidermatomal, recurrent or disseminated with hemorrhagic ulcerative or necrotic lesions.
Cytomegalovirus infection (CMV)

It is seen in the advanced stage of HIV disease. Cutaneous manifestations include petechiae and purpura (due to CMV induced thrombocytopenia) vesicular and bullous eruptions, a generalised morbiliform eruption and persistent perianal ulcerations.

Epstein Barr Virus (EBV)

Oral hairy leukoplakia (OHL) was first described in 1984 by Greenspan et al. It is caused by Epstein Barr virus and recently renamed as EBV leukoplakia. It is thought to signal a more rapid progression to clinical AIDS. It is usually asymptomatic, vertically ribbed, keratinised plaque that is characteristically situated on the lateral aspects of tongue but extensive involvement of oral mucosa can occur.

Molluscum Contagiosum Virus (MCV)

It is a clinical sign of marked HIV progression and very low CD4+ cell counts. Lesions in healthy sexually active adults occur on lower abdomen, inner thighs and genitalia. HIV infected patients may have lesions with this distribution, but lesions on face and neck are more common. The lesions may be innumerable and of giant size.

Human Papilloma virus (HPV)

In HIV disease the prevalence of HPV infection is increased, with higher incidence of genital warts, intra epithelial neoplasia and possibly invasive squamous cell carcinoma. With moderate or advanced HIV induced immunodeficiency warts may become much more numerous and refractory to usual treatment.
Arthropod infestations

Scabies

During early HIV infection with the immune system relatively intact scabies behaves as in normal individuals. As immunodeficiency progresses, HIV patients are more liable to experience crusted (Norwegian) scabies, in which the number of infestating mites can be in millions.

Demodicidosis

It is caused by mite Demodex folliculorum. It causes pruritic papular eruption mainly limited to face and neck. Skin scrapings shows numerous Demodex mites.

Protozoal infestations

- Extrapulmonary pneumocystosis

  Widespread violaceous papules and nodules arising on the torso, arms and legs resembling Kaposi's sarcoma have been described.

- Leishmaniasis

  In immunocompromised patients leishmaniasis may present with typical lesions. The incidence of visceral leishmaniasis is high in HIV disease.

- Cutaneous toxoplasmosis

  Erythematous nontender papules on the face, neck and limbs are described.
Cutaneous amoebiasis

Skin lesions appear as either pustules, nodules, cellulitis, indurated plaques and non healing ulcers.

Bacterial infection

Staphylococcus aureus is the most common pathogen in cutaneous and systemic bacterial infections occurring in HIV infected individuals. Infections include impetigo, bullous impetigo, eczema, papular and plaque like folliculitis, furuncles and carbuncles, cellulitis, botryomycosis and pyomyositis.

Bacillary angiomatosis

It was first described in 1983 among HIV infected patients with cutaneous and subcutaneous vascular lesions mimicking Kaposis’s sarcoma.

It is caused by Bartonella henselae or occasionally by B. quintata both argyrophilic bacilli. Cutaneous lesions begins as tiny pin point papules resembling cherry angiomas, often in large numbers and very wide spread. If injured lesion bleeds promptly.

Mycobacterial infections

Mycobacterium tuberculosis is one of the most common systemic infection in HIV disease. In developing countries it is the most common opportunistic infection in HIV disease. Periorificial tuberculosis is seen in HIV infection with low CD4 count.
Role of Sexually transmitted diseases

Many patients with HIV have sexually transmitted diseases in addition to HIV infection.

Syphilis

An individual with long standing HIV infection with some degree of immunodeficiency who become infected with Treponema pallidum may experience an altered course of syphilis (Glover et al., 1992).

The following variations are noted

- Limited or absent antibody response to infection with repeatedly negative VDRL or RPR.
- Increased severity of clinical manifestations.
- Polymorphic lesions such as pustules, nodules, ulcers are seen.
- Shortened latent period before developing tertiary syphilis.
- Lack of response to penicillin therapy.

Chancroid

Complications like large ulceration (giant chancroid) has been observed in HIV patients. Patients respond well to conventional treatment but treatment has to be continued for longer period of time.
Donovanosis

Patients present with multiple large ulcers that are aggressive in nature. Malignant changes occur in some patients.

Non infectious skin lesions

Seborrheic dermatitis

Psoriasis

Reiter’s syndrome

Xerosis

Pruritic papules

Eosinophilic folliculitis

Addisonian pigmentation

Steven-Johnson’s syndrome due to sulfonamides, pyrimethamine, thiacetazone etc.

Kaposis Sarcoma

It is rare in Indian patients but commonly seen in Africa. It starts as purple or brown coloured macules involving trunk, legs, face and oral mucosa. It can involve liver and spleen. The lesions are increased with immunosuppression.

HIV associated neoplasia

Basal cell carcinoma, squamous cell carcinoma, Burkitt’s Lymphoma, Malignant melanoma can occur in late stage of AIDS.
Antiretroviral therapy

The introduction of Antiretroviral therapy (ART) has transformed HIV infection into a treatable, chronic condition. Highly active antiretroviral therapy (HAART) has had a dramatic impact on the clinical course of HIV-1 in the developed world. As chronically infected patients experience virologic control of HIV-1 after starting these medications, and increase in the total CD4+ cells count is nearly always seen.

The clinical benefits of HAART has been demonstrated by the impressive decrease in mortality and morbidity since HAART became available. The currently available antiretroviral medications do not eliminate HIV-1 from several latently-infected reservoirs which means that life long therapy may be necessary.

A very high replication rate of HIV with increased susceptibility to mutations in the process has led to emergence of strains less sensitive to antiretroviral agents (Nischal et al., 2005).

Goals of antiretroviral therapy (DHHS, 2004)

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Goals</th>
<th>Indicators of goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clinical</td>
<td>Prolongation and improved quality of life.</td>
</tr>
<tr>
<td>2</td>
<td>Virological</td>
<td>Suppress viral load to undetectable levels (&lt;50 copies/ml)</td>
</tr>
<tr>
<td>3</td>
<td>Immunological</td>
<td>Quantitative (CD4 cell count in normal range)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Qualitative (pathogen specific immune reconstitution)</td>
</tr>
<tr>
<td>4</td>
<td>Epidemiological</td>
<td>Reduce HIV transmission</td>
</tr>
<tr>
<td>5</td>
<td>Therapeutic</td>
<td>Rational sequencing of drugs which:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a. Maintains future therapeutic options</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b. Is relatively free of side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>c. Has a high probability of adherence</td>
</tr>
</tbody>
</table>
Classification of antiretroviral drugs

Nucleoside reverse transcriptase inhibitors (NsRTIs)-
Zidovudine, Lamivudine, Stavudine, Didanosine, Zalcitabine, Abacavir, Emtricitabine

Nucleotide reverse transcriptase inhibitors (NtRTIs)-
Tenofovir

Non- Nucleoside Reverse transcriptase inhibitors (NNRTI)-
Nevirapine, Delavirdine, Efavirenz

Protease inhibitors (PI)-

Fusion inhibitors
Enfuvirtide

Indications for initiating Antiretroviral therapy

The term HAART (Highly Active Antiretroviral therapy) indicates use of 2 NRTI along with one NNRTI or a PI so as to achieve the goals of maximal and durable suppression of viral load, restoration and preservation of immune function, improvement on the quality of life and reduction in HIV related morbidity and mortality.
Vaccines for HIV

An effective vaccine against HIV infection is still a distant dream since the virus changes its genomic structure with each replication, thereby preventing the emergence of protective immunity (Khopkar, 2000). So far, education programmes have only managed to slow, but not cease, the HIV spread, while powerful drug combinations are too costly and complex for the majority of HIV infected people they are unable to clear HIV from the body.

HIV evades effectively both humoral and cellular immune responses mainly due to high antigenic variability facilitated by a combination of an error-prone reverse transcriptase (10^4 per base), and a high replication rate (10^9 new virions per day in an infected individual) even during the asymptomatic phase of infection.

Types of HIV vaccine

Preventive

To protect against those people who are not infected with HIV.

Therapeutic

To stimulate the immune system in HIV positive individuals and prevent progression to AIDS. This is not a true vaccine.

Perinatal

To prevent the spread to the fetus in pregnant women.
The ideal characteristics of an AIDS vaccine include:

1. Efficacy in preventing transmission by mucosal and parenteral routes.
2. Excellent safety profile
3. Single dose administration
4. Long lived effect resulting in protection many years after vaccination
5. Low cost
6. Ability to induce protection against infection with diverse viral isolates preventing the need for many isolates specific vaccines.

Prominent current vaccine trials in progress

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA vaccines</td>
<td>Clade-B gag codon optimized</td>
</tr>
<tr>
<td>HIVA</td>
<td>gag p17 and p24 + clade-A CTL epitopes</td>
</tr>
<tr>
<td>VRC4302</td>
<td>gag/pol in frame fusion expressing Pro, RT, and IN</td>
</tr>
<tr>
<td>VRC-HIV DNA-009</td>
<td>Clade-B gag, nef; clade A, B, C env</td>
</tr>
<tr>
<td>EPHIV-1090</td>
<td>Clade-B CTL epitopes gag, pol, env, nef, rev, vpr</td>
</tr>
<tr>
<td>WLV003</td>
<td>Clade-B gag + DNA encoding IL-12 as adjuvant</td>
</tr>
<tr>
<td>WLV003</td>
<td>Clade-B gag + DNA encoding IL-15 as adjuvant</td>
</tr>
</tbody>
</table>
### Recombinant viral vector vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clade and Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALVACvCP205</td>
<td>Clade-B gp120-41, gag, pol</td>
</tr>
<tr>
<td>ALVACVcp1452</td>
<td>Clade-B env, pol, gag + CTL epitopes</td>
</tr>
<tr>
<td>MVA/HIVA</td>
<td>Clade-A CTL epitopes from nef, pol</td>
</tr>
<tr>
<td>VRC-HIVADV-010</td>
<td>Clade - B gag, pol, nef; Clade A, B, C env</td>
</tr>
<tr>
<td>AIDSVAX B/B (VaxGen (R))</td>
<td>Clade B env, CCR5 (R5), rgp120</td>
</tr>
</tbody>
</table>

### Recombinant protein subunit vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clade and Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nef tat + gp120W61D</td>
<td>Clade B nef-tat fusion + gp120 (W61D)</td>
</tr>
</tbody>
</table>

### Prime-boost vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Clade and Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA/MVA</td>
<td>Clade-B env, gag, pro, RT, tat, rev, vpu</td>
</tr>
<tr>
<td>DNA/Ad5</td>
<td>Clade-B gag, pol, nef; Clade A, B, C env</td>
</tr>
<tr>
<td>DNA/Protein subunit</td>
<td>Clade-B gag, env; PLG adjuvant clade-B env</td>
</tr>
</tbody>
</table>

### AIDS Vaccine trial in India

Recently the National AIDS Research Institute (NARI), Pune is conducting an international multicentric phase-I HIV-vaccine trial in healthy volunteers under the joint auspices of National AIDS Control Organization (NACO), the Indian Council of Medical Research (ICMR), and sponsored by International AIDS Vaccine Initiative (IAVI). The vaccine being tested is called tgAAC09. The vaccine does not contain HIV virus. Therefore the volunteers cannot get infected with HIV from this vaccine. This is a preventive vaccine intended for people who are not infected with HIV. It has been tested in animals prior to this trial. Data from animals and preclinical studies indicate that the vaccine is safe and well tolerated, allowing testing in human beings. The phase-I trial of this vaccine is also ongoing in Belgium and Germany (Nigam et al., 2006).
At present AIDS is considered as one of the most dreadful and killer disease affecting human life and sexually transmitted diseases (STDs) are one of the main routes of transmission of HIV. Moreover Gujarat state stands in moderate HIV prevalent category. It is very important to conduct the present study showing pattern of STDs and HIV prevalence in Gujarat.