Human immunodeficiency virus (HIV) & sexually transmitted diseases (STDs)

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Among various factors associated with the sexual transmission of HIV, sexually transmitted diseases (STDs) seem to contribute significantly. Hence, the efforts for prevention and control of HIV have to rely largely on STD control measures. In the developing countries, both prevalence and incidence of STDs are very high. STDs impact women’s health adversely for a variety of reasons such as more susceptibility than men, asymptomatic nature of infection, etc. Enormous evidence is available indicating that both ulcerative and inflammatory STDs increase the risk of HIV infection. STDs promote HIV transmission by facilitating HIV shedding in the genital tract, causing disruption of normal epithelial barrier and by deploying and activating HIV susceptible cells at the site. The effect of STD treatment intervention was studied in three controlled clinical trials conducted in Africa. Though the STD treatment intervention was shown to reduce the STD incidence in all the three studies, the decline in HIV incidence was noticed in only one of them, which, might be attributed to the differences in the study designs. To obtain reliable epidemiological data on various STDs in different communities and regions, countrywide development of adequate laboratory infrastructure for accurate diagnosis of STDs, increased outreach of awareness programmes to communities in the rural areas are some of the key issues in the fight against HIV epidemic in India.

Key words Gonorrhoea - herpes simplex virus - human immunodeficiency virus - sexually transmitted diseases

Since the detection of the first case of HIV infection during 1981 in USA, this epidemic has been the most devastating. After Africa, the South East Asia region happens to be the most affected. Many developing nations, including India, have borne the brunt of HIV/AIDS pandemic. Among the various factors associated with the sexual transmission of HIV, sexually transmitted diseases (STDs) seem to contribute significantly. Though, several advances have been made in the management of HIV disease, development of safe and potent vaccine to prevent HIV infection still remains a big challenge. Thus, the efforts for prevention and control of HIV largely rely on STD control measures.

STD burden

World Health Organization (WHO) estimated that there were 333 million new cases of the four curable STDs¹, worldwide in 1995 among adults (15-49 yr age). In developing countries, both prevalence and incidence of STDs are very high. Conjecture, in the early years of HIV epidemic, of high rates of STDs
as the reason for rapid spread of HIV, has now been perceived as a reality.

As a result, newer pathogens were identified expanding the list to more than 25 members. Several research studies carried out globally have provided ample evidence that the STDs remain as the single largest factor tremendously enhancing the spread of HIV. In the developing countries, STDs have been documented to be the second leading cause of healthy life lost in women of the reproductive age group.

The AIDS Prevention and Control (APAC) Project jointly undertaken by Voluntary Health Services (VHS) and US Agency for International Development (USAID) in a community of urban, rural adult population of Tamil Nadu State revealed that the HIV prevalence in the study community was 1.8 per cent and that of any STD was 15.8 per cent with the classical STDs being 9.7 per cent. Genital discharge was the most common STD syndrome (41.5%) in women and trichomoniasis (5.1%), Chlamydia (3.9%), and gonorrhoea (3.7%) were the most common etiologies. The age group of 30-39 yr was at the highest risk for any STD.

A survey carried out in over 600 men in the three large slum communities in Mumbai, under project RISHTA of International Institute for Population Sciences (IIPS), revealed that the burden of active STI in the communities was found to be 5.53 per cent, with gonorrhoea identified in 3.58 per cent men and Chlamydia infection in only two men. Prevalence of active syphilis was found to be 1.01 per cent and the past history of syphilis was identified in 4.4 per cent. The lifetime herpes simplex virus exposure was seen in 8.96 per cent and active infection was identified in one out of every hundred men (unpublished data).

Though, not much published data are available, the general consensus is that the bacterial STDs are declining all over the world and may also be in India. A retrospective analysis of data from an STD clinic in northern India revealed that the bacterial STDs such as chancroid, donovanosis, and gonorrhoea showed a declining trend in recent years (1993-2000) compared to that in the earlier years (1970-1985) while, an approximately two-fold increase in the prevalence of genital herpes was seen in the recent years (11.4% vs 20.5%).

STDs in women

STDs impact women’s health adversely for a variety of reasons. Biologically, women are more susceptible to STDs than men. STDs are often silent in women and even when symptoms of STD occur, they may not arouse suspicion of a STD. It is also often more difficult to diagnose STDs in women. Complications of STDs are greater and more frequent among women than in men, and are a significant cause of reproductive health morbidity in women. Several studies in sub-Saharan African region have reported that HIV prevalence in young women is higher than in young men. A sentinel surveillance Kenyan study among a large number of STD patients revealed that HIV infection was associated with female gender and this association persisted after controlling for age groups, marital status, place of residence, level of education, and presence of STD syndromes. Further, this pattern had been consistent over 12 yr.

Drug resistance in Neisseria gonorrhoeae

Antibiotic resistance in etiologic pathogens could pose an important obstacle in prevention and control of STDs. For example, over the past decade, strains of N. gonorrhoea have been reported to develop high levels of resistance against several antimicrobial agents, previously used for the treatment of gonorrhoea. Indian studies have also reported increase in the spectrum and level of antibiotic resistance of N. gonorrhoea isolates in the recent year compared to that seen previously. Minimum inhibitory concentrations (MICs) of ciprofloxacin and penicillin against the isolates studied in the years 1996 to 1999 and 2000 to 2001 showed increase in resistant isolates from 21.8 to 67.3 per cent, and from 10.9 to 35.3 per cent, respectively.

Antibiotic susceptibility tests by disc diffusion on 277 N. gonorrhoea isolates obtained in Pune during 1996-2002 revealed that the per cent resistant isolates showed an increasing trend over the years, for all antibiotics. Penicillin resistant isolates increased from
11 per cent in the year 1996 to 33 per cent in 2002. Similarly, ciprofloxacin resistant isolates increased from 74 to 100 per cent and tetracycline resistant from 28 to 80 per cent during the same period. Isolates showing lower susceptibility to ceftriaxone appeared from 1999 onwards with one in 1999 and two each in the years 2000, 2001 and 2002, respectively (NARI, unpublished data).

HIV STD link/interaction

Enormous evidence indicating that both ulcerative and inflammatory STDs increase the risk of HIV infection has become available in the last two decades. Initially, in Africa9 and subsequently in other places10, it was reported that the individuals with recent genital ulcerative disease were at a significant risk of acquiring HIV infection from an infected partner. Studies on the role of STDs in HIV transmission were reviewed by Wasserheit11 and she concluded that both ulcerative and non ulcerative STDs increase the risk of HIV transmission by 3 to 5 fold and due to higher frequency of non ulcerative STDs, these infections may be responsible for more HIV transmission compared to genital ulcers. Prevalence of genital ulcer disease is reported to be associated with an increased relative risk of HIV infection, ranging from 1.5 to 7.0 and gonorrhoea, Chlamydia and Trichomonas infections are associated with a relative increase of 60 to 340 per cent in the prevalence of HIV infection in both men and women12. In 1999, Fleming and Wasserheit13, after reviewing multiple studies with different study designs, reported that both ulcerative and non ulcerative STDs promote HIV transmission via a variety of biological mechanisms. Various biological mechanisms were suggested and studied which could explain higher probability of HIV transmission in presence of other STDs. STDs facilitate HIV shedding in the genital tract. Detection of HIV-1 virus or viral DNA from genital ulcer exudates was also reported14-16. Similarly, an evidence of HIV-1 virus was also found in HIV infected individuals suffering from urethritis/cervicitis due to gonococcal/clamydial etiology. These infections were shown to increase the viral load in genital secretions and that the treatment of these infections resulted in reduction of HIV viral load in the genital secretions17,18. In a study conducted among female sex workers, Ghys et al19 concluded that the genital HIV virus shedding was associated with STDs such as gonorrhoea, Chlamydia infection and cervical or vaginal ulcer and no independent association was found between cervicovaginal HIV-1 shedding and serum viral load when data were controlled for levels of immunosuppression.

Genital ulcers facilitate acquisition of HIV infection, by causing disruption of normal epithelial barrier, which provides a portal of entry to HIV virus and also may be by recruiting and activating HIV susceptible cells at the site. Genital discharge due to non-ulcerative STDs contains cells expressing molecules to which HIV can attach, such as CD4 and chemokine receptor CCR5 making these patients more susceptible to HIV infection. The median concentration of endocervical CD4 T-lymphocytes was shown to be higher in patients with gonorrhoea, Chlamydia infection or trichomoniases compared to patients without these diseases, which indicates that the non ulcerative STDs may facilitate HIV acquisition by recruiting HIV target cells to the endocervix20. Gonococcal infection was associated with a significantly increased risk of HIV seroconversion in the cohort studies of female sex workers in Nairobi21 and in Kinshasa22. The Kinshasa study also reported significant association of Chlamydia infection and Trichomonas vaginalis with the risk of HIV seroconversion.

Herpes simplex virus type 2 (HSV-2)

HSV-2 infection deserves a special mention for being unique among the STDs and for posing a major hurdle in the prevention and control strategies worldwide. HSV-2 infection is characterized by its high prevalence worldwide, especially in the developing countries1, and its chronicity and infectiousness during both symptomatic and asymptomatic phases, and its synergistic relationship with HIV infection. It is now gaining special recognition as a very significant risk factor for acquisition of HIV and is emerging as an area of focus for HIV preventive interventions. A study in Pune, India23 revealed that HSV-2 was the most common single etiology of genital ulcer with 26 per cent ulcer swab specimen being HSV-2 positive in multiplex
PCR. A meta-analysis of studies on HSV-2 revealed that prior infection with HSV-2 doubled the risk of HIV acquisition through the sexual route. A study in Africa reported a strong association between HSV-2 status and HIV seroconversion and that the risk of HIV incidence was higher for the male subjects who seroconverted to HSV-2 during the two-year follow up period than for those who were HSV-2 seropositive at baseline. Similarly, a study in Pune, India revealed that the individuals with newly acquired HSV-2 during the study period were as much as 3.2 times likely to acquire HIV infection. Moreover, HSV-2 re-activation can also increase the risk of HIV transmission. In dually (HSV-2 and HIV) infected men, HIV-1 RNA was detected in lesions in 25 out of 26 episodes. Finally, the HSV-2 prevalence has been thought to be one of the factors that may explain different outcomes in the STD intervention community trials. Taking the lead from these observations, several intervention trials have been initiated. Results of these studies will be helpful in developing strategies to control HSV-2 infection aided HIV transmission.

**Effect of STD treatment on HIV spread**

STD treatment reduces an individual’s ability to transmit HIV by decreasing the amount and frequency of HIV shedding.

*Community studies:* Once the important role that other STDs play in the transmission of HIV was known, it was natural to expect that the provision of early diagnosis and efficient treatment of STDs could significantly impact the HIV spread. Though, this expectation could be indirectly supported from the results of some studies, effect of such an intervention could not be viewed in depth until the results from controlled clinical trials in the community became available.

Of the three such trials undertaken in Africa to date, the results of the first trial in Mwanza region of Tanzania were very encouraging. Continued access to improved treatment for symptomatic STDs was provided to intervention communities whereas, the control communities received the STD clinical services that had existed previously. HIV incidence in the intervention communities was seen to have reduced by 38 per cent compared to the control communities over a period of 24 months. Prevalence of syphilis was significantly reduced and reduction in the incidence of syphilis and symptomatic urethritis was also noted in the intervention communities.

In Rakai, Uganda the intervention community received directly observed mass treatment for curable STDs at 10-monthly intervals whereas, the control community was provided with mass treatment for helminthes infections. Though, the STD incidence declined in the intervention community, the HIV incidence was similar in the intervention and the control communities.

Among the multiple factors that might have contributed to the divergent results, Fleming and Wasserheit put forth four possible explanations for the divergent results of the two trials. (i) Continued access to improved STD treatment in Mwanza would be more effective than intermittent mass treatment provided in Rakai. (ii) Focusing on symptomatic STDs as done in Mwanza may be a very effective way to target STD treatment interventions. (iii) STDs may play a greater role in HIV transmission in the earlier phases of an HIV epidemic than in the later phase. Hence, significant reduction in HIV transmission was seen in Mwanza trial where prevalence of HIV was 4 per cent compared to 16 per cent in Rakai where the intervention did not result in the reduction of HIV incidence. (iv) The local STD incidence, prevalence and etiological spectrum are critical determinants of the impact of STD treatment intervention.

Results of a trial in Masaka, Uganda became available in 2003. Villages were randomly allocated to three arms. One group where general community development was undertaken served as a control arm. In the second group, information, education, and communication services were instituted, while in the third group; information, education and communication (IEC) activities with enhanced STD services were provided. Though the incidence of STDs declined in the intervention groups, no effect was seen on HIV incidence, which might have been due to the role played by the factors enumerated above.
Community intervention trials are extremely difficult to conduct due to their demand for enormous inputs. However, results of well designed trials could be immensely useful for developing strategies, since they present a real scenario in the community under study. Since the results of these three trials were divergent, it appears that we may have to wait further for the results of additional studies to become available based on which future STD treatment interventions in the communities could be designed and implemented.

**Effect of HIV on other STDs**

Impact of HIV infection on other STDs has not been studied extensively. Some data available on HIV-syphilis and HIV-HSV-2 co-infections indicate that concurrent HIV infection may affect the natural history and thereby the clinical presentation of these STDs. It may affect the laboratory results or may impact the response to treatment. However, contrary to this some reports state that HIV does not impact co-existing STDs. Musher *et al*\(^{31}\) found that early development of neurosyphilis, a complication, which was exceedingly rare in the first three decades of penicillin use, was commonly seen among HIV infected syphilis patients. Additionally, preliminary data suggested that skin lesions and VDRL antibody in HIV infected patients with secondary syphilis responded more slowly to conventional penicillin therapy\(^{31}\).

Similar findings were also noted by Johns *et al*\(^{32}\) that the concurrent HIV infection might alter the natural history of syphilis by increasing the propensity of the disease to progress to neurosyphilis, decreasing the latency period before the onset of neurosyphilis, increasing the severity of the manifestations, or rendering standard therapy for primary and secondary syphilis inadequate.

Contrary to this, a study during 1986-1988 and 1990-1992 on over thousand patients with genital ulcer in Kigali, Rwanda\(^{13}\) revealed that the clinical presentation of ulcers as well as laboratory diagnosis were similar in the HIV-1 seropositive and seronegative groups. The relative frequency of all laboratory diagnoses remained unchanged over time. HIV-1 seropositivity had no impact on ulcer healing.

In order to compare clinical presentations of patients with early syphilis who did or did not have HIV infection, patients attending Baltimore City Health Department’s STD clinics during 1990-1991 were studied\(^{34}\). The rate of decline in the rapid plasma reagin titres during a 12-month period after treatment did not differ between patients with and without HIV infection. The study concluded that the clinical presentation of syphilis in patients with HIV infection differs from that of patients without HIV infection in that patients with HIV infection present more often in the secondary stage and those with secondary syphilis are more likely to have Chancre\(^{34}\).

HSV-2 infection in HIV-seropositive patients can be more severe, prolonged, and sometimes less responsive to antiviral therapy when compared with HIV-seronegative patients\(^{35}\). HSV-2 ulcers in HIV infected patients often present as chronic non-healing ulcer and hence, HSV-2 lesions with duration above one month are considered an AIDS-defining illness by the CDC\(^{36}\). HSV-2 reactivation and duration of recurrences are significantly increased in HIV infected individuals. The frequency and severity of recurrences increases as CD4 T-lymphocyte counts decrease\(^{36}, 37\).

**Key issues and strategies for future**

Major Key issues in the Indian context are: (i) Accurate epidemiological data on prevalence and spectrum of various STDs in the different geographic regions in India are not available; (ii) Most of the available data are from clinic-based studies. Very limited data are available from community-based studies; (iii) Laboratory infrastructure for accurate diagnosis of STDs is limited to metropolitan cities; (iv) Efforts to reach awareness programmes to the communities in the rural areas is a challenging task and needs to be accomplished; (v) There is a need for continuous monitoring of antimicrobial resistance in STD pathogens, especially in *N. gonorrhoea*.

Some suggested steps to address these include:

(i) **Integration of STD prevention programmes with the ongoing public health services:** STD prevention and control efforts should form a part of comprehensive package for ongoing public health
services such as family planning or the National AIDS Control and Prevention Programme. The National AIDS Control Organization (NACO) perceived the need and has taken steps in that direction. Establishment of STD cells at district headquarters level is one such move. However, it is important to ensure continued strengthening, uninterrupted drug and reagent supply to all these centers.

(ii) Targeting population subgroups at risk: In India, female and male sex workers, long distance truck drivers and migrant workers have been identified as core groups. Efforts to reach prevention education with or without clinical services to these core groups were undertaken by numerous governmental and non-governmental agencies in the last decade. Now, the time has come to move in the communities and to identify the population subgroups that are at risk of HIV/STDs due to their behaviours. Targeting these subgroups for education, coupled with provision of STD diagnostic and treatment services would be an important step towards future prevention efforts. The clinical care services are important to reduce the disease burden and to decrease number of incident cases. (Targeted intervention programme implemented in Sonagachi area of Calcutta was proved successful).

(iii) Involvement of private sector: As in the case of HIV, to achieve prevention and control of STDs, it is essential to include private sector as partners. Development and manufacture of cheap, reliable and easy to perform assays for STD diagnosis can be achieved by active participation of these partners.

(iv) Training of health care workers: It is important to make provision for adequate training and refresher training for health care workers in both governmental and private sectors. It is estimated that a majority of patients seek care from the private practitioners and hence in order to ensure success in the prevention programme it is essential that private health care givers are also included.

(v) Epidemiological studies: Intervention strategies are based on the information obtained through epidemiological studies. There is an urgent need to have information on prevalence and trends of different STDs in different geographic areas of the country. Annual HIV sentinel surveillance among STD patients instituted by NACO has been useful to provide limited information. In a country like India, such data can be collected by networking of laboratories in different regions. NACO has successfully developed network of HIV laboratories for implementing external quality assessment programme for HIV diagnosis. Network of STD laboratories on the similar lines will help to obtain reliable STD data in the country. Linking of STD surveillance including surveillance for drug resistance, to existing HIV surveillance programme, expansion of this programme to rural and low prevalence areas needs to be undertaken.

(vi) Focus on young adolescents: Educating adolescents on reproductive and sexual health is of paramount importance. A large school based adolescent education programme and national campaign to raise awareness about STDs and treatments are important steps from NACO in this direction. It is essential that these efforts are expanded and continued on long-term basis.

(vii) STD services for women: Due to differential impact of STDs on women's health, a special attention is needed for the prevention and control of STDs in women. Reproductive health services should be strengthened to address STD diagnosis and treatment services. Women should be adequately educated to prevent/recognize STD infections. Importance of early diagnosis of STDs including asymptomatic infections and treatment needs to be emphasized.

To sum up, enormous data are available to indicate that STDs play a major and decisive role in the spread of HIV. It may be possible that a high prevalence of STDs, mostly unknown, has resulted in a rapid spread of HIV in India. In the absence of potent HIV vaccine, prevention and control of STDs remains the only attainable tool at hand for the HIV preventive efforts.

On a population level, prevention of STDs is a challenging task. In addition to the factors discussed above, social issues have tremendous influence on transmission of STDs. Some fundamental societal problems such as poverty, lack of education, and social inequity indirectly increase the prevalence of STDs in certain populations. To address these issues is even more challenging. While an attempt is made to address these issues, other direct STD control efforts need to be undertaken as fast as possible to achieve a significant dent in the HIV epidemic in India.
References


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