Sexually transmitted infections and human immunodeficiency virus coinfection: Scenario in Western India

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Abstract

Context: Sexually transmitted infections (STIs) have a well-established synergistic relationship with human immunodeficiency virus (HIV) infection. Coinfection with HIV and STI can increase the probability of HIV transmission to an uninfected partner by increasing HIV concentrations in genital lesions, genital secretions, or both. Concurrent HIV infection alters the natural history of the classic STIs. Aims: The aim was to study the current scenario of STIs with HIV coinfection, and to recognize different manifestations of STIs than the classical presentation in people living with HIV/AIDS (PLHIV). Settings and Design: It was an open, cross-sectional, descriptive study carried out in the setting of state government hospital with attached antiretroviral therapy referral center. Subjects and Methods: The sample size of the study was duration based (30 months). Inclusion Criteria: All PLHIV presenting to the department of dermatology with STIs were included in the study. Exclusion Criteria: Non-STI causes of genital ulceration were excluded in the study. Results: The study includes total (n = 484) patients living with HIV/AIDS, prevalence of different STIs was in the following order, herpes simplex virus infections 24.17%, human papillomavirus infections 8.88%, molluscum contagiosum 7.43%, secondary syphilis 4.33%, gonorrhea 1.85%, chancreoid 1.44%, and granuloma inguinale 0.41%. Of all the patients with herpes simplex virus infections, 45.6% (n = 57) had multiple recurrences (>6/year). The incidence of mixed STI was 17.29% in the present study. Conclusions: The study represents decreasing trends in bacterial STIs and the rise of viral STIs. Atypical presentations of classic STIs were more frequent than non-HIV-infected individuals.

Key words: Mixed infection, people living with human immunodeficiency virus/AIDS, sexually transmitted infections

INTRODUCTION

The relationship between sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) infection is complex and manifold, and both are acquired through sexual transmission. The classic STIs and genital ulcer diseases (GUDs) in particular, are significant risk factors for HIV in developing countries. The natural history, manifestations, and treatment of classic STIs may be altered by concurrent HIV infection. Trends in STI incidence and prevalence can be a useful indicator of changes in sexual behavior and therefore, valuable for determining the impact of HIV/AIDS control program.

The objective of the current study was to study the current scenario of STIs in a tertiary referral center of western India. Epidemiological trends, variation in the clinical presentation, and response to the therapy were observed.

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SUBJECTS AND METHODS

It was an open, cross-sectional, descriptive study carried out in the setting of state government hospital with attached antiretroviral therapy (ART) referral center. The sample size of the study was duration based. The duration of the study was 30 months. Inclusion criteria: All people living with HIV (PLHIV) presenting to the department of dermatology with STIs. Bacterial infections such as gonorrhea, syphilis, chancroid, granuloma inguinale-producing genital ulcers, viral infections due to herpes simplex virus (HSV) of genital and nongenital type, human papillomavirus (HPV)-producing genital warts, and molluscum contagiosum virus (MCV)-causing genital molluscum contagiosum lesions were included in the study. Exclusion criteria: Patients with genital ulcers due to non-STI cause were excluded from the study. Informed consent for the use of medical records and taking photographs was obtained from every patient. A sociodemographic profile was recorded. A thorough general, systemic, and cutaneous examination was done. Based on the examination, patients were subjected to relevant investigations such as blood and serum chemistry, radiology, bedside tissue smear, and histopathological examination were carried out as required. The study was carried out as a part of thesis protocol submitted to the affiliated university.

RESULTS

Of the total 484 patients, 294 (60.74%) were male and 188 (38.84%) were female, and 2 (0.41%) were transgenders. The male-to-female ratio was 1.56:1.440 (90.90%) patients were adults (>18 years), followed by 30 (6.19%) in the pediatric age group (0–10 year) and 14 (2.84%) in adolescent age group (11–18 years). As per NACO estimates, the prevalence of HIV is highest in 15–49 years of age group (88.7%) of all HIV cases which in our study is 86.77% of the study population [Table 1].

Among the 484 patients, total mucocutaneous manifestations of HIV/AIDS were 688 out of which 34.44% (n = 237) were manifestations of STIs. Of total 237 STIs, 82.70% (n = 196) were viral, 16.45% (n = 39) were bacterial, and 0.84% (n = 2) were parasitic etiology. Thus, viral infections were the most predominant opportunistic infections in the present study.

Of all STIs in the study, genital herpes virus infections were most common 49.36% (n = 117), followed by HPV infections 18.14% (n = 43), MCV infections 15.18% (n = 36), syphilis of various stages 8.8% (n = 21), gonococcal infections 3.79% (n = 9), chancroid 2.95% (n = 7), and scabies (genital/nodular scabies presenting as STI) 0.84% (n = 2), respectively [Table 2]. Mixed venereal diseases were found in 41 patients.

Infections caused by HSV [Table 3] were most common among all STIs and it had a wide spectrum of presentation ranging from few grouped vesicular lesions to large, chronic, recurrent, vegetation, hypertrophic, and anogenital lesions [Figures 1 and 2]. The median CD4 count for perianal herpes was 161.66. The median CD4 count at primary episode was 235/µL and 348/µL for the recurrent episode, suggesting recurrences were common even with an improvement in patients’ immune status.

HPV infections were the second-most common STIs after genital herpes observed in 43 patients. All morphologies of verrucae were observed in the study. The most common were anogenital warts 68.42% (n = 39 out of 57), followed by verruca plana 10.52% (n = 6 out of

Table 1: Age and sex distribution of PLHIV attending STI clinic

| Sex       | Total | Male          | Female         | Transgender |
|-----------|-------|---------------|----------------|-------------|
| Male      | 294   | 283 (96.34%)  | 11 (3.66%)     | 2 (0.68%)   |
| Female    | 188   | 177 (94.03%)  | 11 (6.07%)     | 0 (0.00%)   |
| Transgender| 2     | 2 (100.00%)   | 0 (0.00%)      | 0 (0.00%)   |
| Total     | 484   | 294 (60.74%)  | 188 (38.84%)   | 2 (0.41%)   |

Table 2: Frequency of various sexually transmitted infections in PLHIV attending STI clinic

| Type of STI                          | n   | Percentage of total STIs | Prevalence in the present study (%) |
|--------------------------------------|-----|--------------------------|------------------------------------|
| Herpes group                         | 117 | 49.36%                   | 24.17                              |
| HPV                                  | 43  | 18.14%                   | 8.88                               |
| Molluscum contagiosum                 | 36  | 15.18%                   | 7.43                               |
| Gonorrhea                            | 9   | 3.79%                    | 0.00                               |
| Granuloma inguinale                  | 2   | 0.84%                    | 0.01                               |
| Chancroid                            | 7   | 2.95%                    | 0.16                               |
| Syphilis                             | 21  | 8.8%                     | 4.33                               |
| Scabies                              | 2   | 0.84%                    | 0.01                               |
| Total                                | 237 |                          | 100.00                             |

Table 3: Profile of herpes simplex virus infection in people living with human immunodeficiency virus

| HSV infection type | Number of patients affected | Median CD4 count | Out of total number of patients (484) |
|--------------------|-----------------------------|------------------|--------------------------------------|
| Herpes genitals    |                             |                  |                                      |
| Single episode     | 35                          | 235.37           | 117                                  |
| Recurrent episode  | 57                          | 348.70           |                                      |
| Necrotic type      | 5                           | 213.00           |                                      |
| Perianal type      | 20                          | 161.00           |                                      |

HSV=Herpes simplex virus

STI=Sexually transmitted infection; HPV=Human papillomavirus
57), epidermodysplasia verruciformis 7.01% \((n = 4 \text{ out of 57})\), Bowenoid papulosis 7.01% \((n = 4 \text{ out of 57})\), verruca vulgaris 5.26% \((n = 3 \text{ out of 57})\) [Figure 3], and one case of intraoral wart on mucosa of hard palate was observed (1.75%, \(n = 1 \text{ out of 57}\)) [Table 4]. One patient with verruca vulgaris had numerous warts distributed all over the body and size ranging from small verrucous papules to large nodular growths obstructing vision and forming hard, nodules over dorsa of both feet and hands.

MCV infections were observed in 7.43% \((n = 36)\) patients. The common clinical presentation was that of multiple lesions and giant (>2 cm in size) lesions involving extragenital sites such as face and back as well [Figure 4]. Overall, of all STIs in the current study, 82.78% were of viral origin and 16.38% were of bacterial origin.

| HPV Manifestation type                             | Number of cases | Median CD4 count |
|---------------------------------------------------|-----------------|------------------|
| Anogenital warts (including condyloma acuminate)  | 39              | 150              |
| Verruca plana                                     | 6               |                  |
| Epidermodysplasia verruciformis                   | 4               |                  |
| Bowenoid papulosis                                | 4               | 382              |
| Verruca vulgaris                                  | 3               | 221              |
| Oral wart (palatal mucosa)                        | 1               |                  |
| Total                                             | 57              |                  |

HPV=Human papillomavirus

![Figure 1: Large necrotic type of herpes genitalis: image shows well-defined, superficial erythematous erosion with slightly raised edges, the floor of the ulcer is covered with seropurulent discharge and showing areas of healing in-between lying over pubic symphysis and extending in continuity up to both labia majora and fourchette involving perineum as well](image1)

![Figure 2: Chronic, verrucous type of perianal herpes genitalis: image shows multiple, well-defined erythematous erosions in the perianal region with raised whitish, verrucous border](image2)

![Figure 3: Extensive, nodular to cauliflower such as verruca vulgaris involving the entire face of the people living with human immunodeficiency virus man. Large, filiform, and nodular warts in the periocular region are obstructing the vision in both eyes](image3)

![Figure 4: Multiple groups papulonodular lesions on the upper back of people living with human immunodeficiency virus female with some lesions showing characteristic central umbilication and few lesions of giant molluscum contagiosum](image4)
Among the classical bacterial STIs, syphilis was 8.8% ($n = 21$). Atypical presentation as compared to immunocompetent population was noted in six cases. Two cases of multiple primary chancre, two cases of rupioid syphilis, one case of psoriasiform syphilis, and one case of tertiary syphilis were noted which presented as palatal perforation secondary to syphilitic gumma. No resistance to benzathine penicillin was found in any of our cases [Figures 5-7]. Among the other bacterial STIs, the prevalence of incidence of gonorrhea was 3.79% ($n = 9$), chancreoid was 2.95% ($n = 7$) [Figure 8], and granuloma inguinale 0.84% ($n = 2$) [Figure 9], respectively. Only one out of nine patient of gonorrhea had laboratory-proven resistance to fluoroquinolones, rest of all the cases responded to tablet azithromycin 1 g stat + tablet cefixime 400 mg stat [Table 2].

**DISCUSSION**

**Herpes simplex virus and human immunodeficiency virus infection**

HSV-2 is among the most common infection in HIV-seropositive persons, as about 70% of HIV-infected
persons in the developed world and 95% in the developing world have HSV-2 antibody.[11] A study done by Ray et al., also found that HSV-2 is the most common etiological agent of STIs in PLHIV.[12] The role of HSV-2 in HIV transmission is due to the potential of epithelial breaks to allow entry to HIV and the recruitment of CD4 + lymphocytes to HSV lesions that allow for HIV initial attachment. Several studies have shown that HIV-infected persons are at increased risk for HSV-2 acquisition. Potential reasons include increased susceptibility to infection or increased risk of contact with partners who are shedding HSV-2 in the context of HIV infection. The frequent genital HSV-2 reactivation in HIV-seropositive persons results in chronic antigenic stimulation. Schacker et al. showed that HIV strains initially in herpes ulcers subsequently appear in plasma.[13] A transient increase in plasma HIV RNA has been noted during recurrent genital herpes.[14] Laboratory studies have provided supportive evidence that HSV may be an important cofactor for HIV expression. Both replicating and heat-inactivated HSV induce tumor necrosis factor-α activity and HIV expression in macrophages.[15] Herpetic lesions are associated with an influx of activated CD4-bearing lymphocytes,[16] which may result in increased expression of HIV on mucosal surfaces. In vivo, HSV-1 and HIV co-infection of epithelial cells results in a higher copy number of HSV virions.[17] Chronic persistent genital ulcers caused by HSV are among opportunistic infections included in the definition of AIDS, and a small fraction of HIV- and HSV-infected patients present with persistent chronic mucocutaneous ulcerations often involving large areas of perianal, vulvar, or penile areas.[18] Most HSV infections in persons with HIV infection will respond to antiviral therapy, and acyclovir (ACV), valaciclovir, and famciclovir have all been shown to be useful in reducing clinical and subclinical reactivation of HSV in HIV-positive persons.[19] Suppressive therapy with ACV increases the daily pill burden, but prevents most clinical episodes, reduces the risk of HSV-2 shedding, and may have indirect effects on HIV, as noted above. Some patients who initially respond to ACV may develop thymidine kinase-deficient mutants for which standard antiviral therapy is ineffective. The median CD4 count of patients presenting with perianal HSV infections was 161.66 cells/cm² in the current study which suggests that perianal HSV could be a marker for an advanced degree of immunosuppression.

**Human papillomavirus and human immunodeficiency virus infection**

In general, an increased genital HPV prevalence has been observed among patients with immune-related disorders. Numerous studies have consistently demonstrated a high prevalence of HPV among HIV-seropositive populations of women[19] and men.[20] Studies have also shown increased HPV incidence[12,13] and increased frequencies of infections with multiple HPV types among HIV-infected individuals. One interpretation for the increased prevalence among HIV-seropositive individuals is that HIV-induced immunosuppression leads to reactivation of viruses that are otherwise undetectable. A study by Chakaravarty et al. found the prevalence of HPV 26.85% in HIV-infected women.[14] In HIV infection, lesion histology may be atypical, with hyperkeratosis and verrucous changes.[21]

**Human immunodeficiency virus and molluscum contagiosum virus infection**

The increase in rates and severity of infection in patients with AIDS indicates that intact cell-mediated immunity (CMI) is important in the control of MCV, as it is for vaccinia.[15,16] However, it is not clear whether a decrease in CD4 cells, Langerhans’ cells, or another component of CMI is responsible for greater disease severity in AIDS. The majority of lesions occur on the face and neck, especially in the beard area, where they are apparently spread by shaving; anogenital infection is relatively uncommon.[17] Outbreaks with extensive lesions are common, and giant molluscum lesions are noted in up to 10% of patients. Increased use of highly active ART would be expected to result in a reduction in molluscum contagiosum among persons with HIV infection.

**Syphilis and human immunodeficiency virus infection**

Few published data support the contention that the manifestations of primary and secondary syphilis are altered by HIV infection, and in fact, prospective studies provide results that refute this notion. In contrast, concurrent HIV infection, whether before or after a diagnosis of AIDS has been made, appears to have an impact on neurologic involvement in syphilis.[18] Cases of therapeutic failures have been described after conventional doses of penicillin for primary or secondary syphilis. Numerous individual case reports have documented the apparently rapid progression of early syphilis to neurosyphilis, manifested as meningitis or cranial nerve defects (most commonly optic neuritis or deafness).[19,20] The term “quaternary neurosyphilis” has been revived to describe necrotizing encephalitis in an HIV-Infected patient.[21] In many cases, concurrent HIV infection has been documented for the first time only when neurologic complications appeared. The risk of neurosyphilis is increased substantially “three to fivefold” in HIV-infected patients with serum rapid plasma reagin titers >1:32 or in whom CD4 counts are <350.[22]

**Chancroid and human immunodeficiency virus infection**

At the end of the 1990s, several studies suggested a trend toward lower chancroid and higher HSV prevalence in endemic areas, likely due to syndromic management for bacterial agents of GUD and reactivation HSV in
patients coinfected with HIV-1. In case–control studies in areas endemic for chancroid and HIV, the relative risk of acquiring HIV infection for patients with GUD ranged from odds ratios of 3 to 18.2. Per individual sexual act, GUD is estimated to enhance HIV acquisition by 4–23-fold; the exact magnitude of the cofactor effect is difficult to estimate due to confounding variables. Multiple case reports indicated that patients who are HIV seropositive have atypical presentations of chancroid. Interestingly, the histopathology of chancroidal ulcers in HIV seropositives and seronegatives is indistinguishable. Reports from Africa on persons coinfected with HIV and chancroid also indicated that coinfected individuals have a greater number of ulcers that persist for longer periods and do not heal as readily after antibiotic treatment as patients infected with Haemophilus ducreyi alone. Antibiotic treatment failures were reported in HIV seropositives for what were suboptimal regimens even in HIV seronegatives. Treatment failure of chancroid in HIV seropositives is likely due to coinfection with HSV and does not represent failure to eradicate H. ducreyi. Taken together, the data suggest that the effect of HIV on the histopathology, clinical course, and treatment of chancroid is minimal.

**Donovanosis and human immunodeficiency virus infection**

In Durban, in a population where HIV infection had been introduced only recently, the proportion of men with donovanosis and HIV infection increased significantly as the duration of lesions increased, thereby suggesting that HIV was acquired through sexual intercourse in the presence of ulcers. The treatment of donovanosis may need to be modified in HIV-infected patients with significant immunosuppression. In Mumbai, India, the mean healing time in HIV-positive patients with donovanosis was 25.7 days compared to 16.8 days in HIV-negative individuals. However, among HIV-positive pregnant women without significant documented immunosuppression, the clinical presentation and response to treatment in donovanosis appeared to be unaltered by HIV.

**Gonorrhea and human immunodeficiency virus infection**

Gonorrhea facilitates transmission of HIV by 3–5 times. Gonococcal cervicitis increases cervical HIV shedding. The treatment of cervicitis in HIV-infected women reduces HIV shedding from the cervix and might reduce HIV transmission.

Overall marked decline in bacterial STIs, resulting in an apparent increase of viral STIs over the past 10 years or so was reported from Kerala. In our study also, viral STIs constituted a large chunk of cases.

**CONCLUSIONS**

Viral STIs predominate as a cause of STI in PLHIV. Clinicians should be aware of varied manifestation, mixed infection, and altered course of STIs in PLHIV. This shows decreasing trends in bacterial STIs and rise of Viral STIs over the period of 20 years.

**Limitation of the study**

The institute follows a syndromic approach for diagnosis of STIs and nonulcerative STIs such as vaginal discharge, pelvic inflammatory disease were not included in the study.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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