Sexually Transmitted Viral Infections

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LEARNING OBJECTIVES:

1. Explain the different disease signs and symptoms of viral sexually transmitted diseases.
2. Illustrate the connection between advances in diagnostics and better treatment outcomes.
3. Describe the link between appropriate HIV treatment and HIV viral mutations.

ABSTRACT

Sexually transmitted diseases (STD) of viral origin comprise the most prevalent STDs on earth. The impact of viral STDs is compounded because, while they are treatable, they are not curable. Symptoms of infection are dependent on the type of infecting virus and can range from immune deficiency to skin lesions, warts, and cancer. Because of advances in antiviral therapies and rapid molecular diagnostics, patients harbor long-term, yet manageable conditions with this group of STDs.

ABBREVIATIONS: STD - Sexually Transmitted Disease, HIV - Human Immunodeficiency Virus, HSV - Herpes simplex virus , HPV - Human Papillomavirus, ssRNA - single stranded RNA, CDC - Center for Disease Control, NAT - Nucleic Acid Test, ART - Antiretroviral Therapy, NIH - National Institutes of Health, AIDS - Acquired Immunodeficiency Syndrome, CCR5 - C-C chemokine receptor, CSF - cerebral spinal fluid

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INTRODUCTION

Sexually transmitted viral infections are widespread, diverse, and generally incurable. The variance in viral types that cause sexually transmitted viral infections show an equal diversity in transmission mechanisms, symptoms, and treatment options. Hepatitis B, which causes liver damage, and Zika virus, which causes mild flu-like symptoms and congenital birth defects, are members of the *Flaviviridae* family. Herpes simplex virus (HSV), a nerve-cell infecting virus that causes skin lesions, and Cytomegalovirus, which is typically symptomless in healthy adults, but can cause congenital birth defects, are members of the *Herpesviridae* family. Human Papillomavirus, or HPV, is the cause of genital warts and some types of cancer; it is a member of the dsDNA *Papillomaviridae* family. Human Immunodeficiency Virus (HIV), which infects white blood cells and suppresses the immune system, is a single-stranded RNA (ssRNA) virus of the family *Retroviridae*.

HPV

Human papillomavirus, or HPV, is a large and diverse group of viruses with over 150 different types. HPV is a ubiquitous infection that transmits to approximately 14 million people per year.[1] Benign types of HPV infect the skin and cause harmless genital warts called condylomata acuminate,[2] while approximately 40 types infect the mucosal layer and can cause cancer.[3] The majority (91%) of HPV infections are cleared by the immune system within two years of infection. However, there are 18 high-risk HPV types that have been linked as the cause of 30,700 cervical, penile, anorectal, and oropharyngeal cancers in the U.S. per year.[4,5] HPV, specifically types 16 and 18, is almost the sole cause of cervical cancer and causes 95% of anal cancer, 70% of oropharyngeal cancers, and 35% of penile cancers.[2]

Diagnostics

Screenings for cervical cancer occur during a yearly female health exam. Abnormal results on a Pap smear, such as cell dysplasias that may signal pre-cancer or cancerous conditions, will reflex follow-up testing.[2] If

atypical cells are found that indicate the possibility of cancer, it is recommended to perform a nucleic acid test (NAT) for HPV.[3,6] Many women's health exams have begun co-testing for cervical cancer by performing the Pap test and the HPV NAT concurrently as it increases the chance of early detection.[7]

Treatment

Treatment for non-cancerous HPV involves removal of the infected tissue. Since FDA approval of HPV vaccines, the focus has shifted to prevention. Current Center for Disease Control (CDC) recommendations are for children to receive two doses of vaccine prior to their 15th birthday. The vaccine is recommended to begin at age 11-12, to ensure immunity before sexual maturity and exposure to the virus can take place.[1]

HIV

Current CDC estimates state that 1.2 million people in the US are infected with HIV. Of those, the estimated 156,300 people (16%) who do not know that they are infected are responsible for transmitting 30% of new infections.[8] HIV testing is recommended for low-risk individuals at least once during a routine physical; high-risk individuals are recommended to get tested annually.

Study of HIV transmission in Ugandan monogamous heterosexual couples where the infected partner was not undergoing antiretroviral therapy estimates that the probability of infection per coital act is 0.0001 if viral load is low and 0.0023 when viral load was high.[9] Analysis of multiple studies looking in terms of rate of infection per 100 person years showed that the HIV transmission rate was 5.64 without taking viral load into consideration and up to 9.03 if the infected partner had a high viral load of 50,000 copies per milliliter.[10]

Testing

Testing for HIV comes in two major forms: screening and confirmation. Traditional screening tests involved a Western blot or an ELISA to detect circulating anti-HIV antibodies. Acute infection is not detected in early generation HIV tests because antibodies can take up to six weeks to appear in sufficient quantity to be detected.[11] This delay in detection compounds the problem of HIV transmission as viral load is higher, and thus the risk of transmission is greater, during the acute phase of the disease. The clearance of fourth generation antigen/antibody testing for HIV has increased the accuracy and efficiency with which detection can occur.[12,13] The CDC recommends an algorithm that includes an initial screen with the fourth generation test followed by antibody differentiation immunoassay or NAT as a confirmation.[11] A NAT detects the viral load within 7-28 days post-exposure. It is used for confirmation testing and acute phase testing in patients with a known exposure.[8]

Treatment

HIV is a retrovirus that can evolve rapidly, with an estimated 10 mutations per viral genome per replication cycle,[14] once infection takes hold. HIV sequenced from a single individual can have viral sequences that differ by more than 10%,[15] which demonstrates the potential for mutations leading to antiretroviral therapy (ART) failures. Beginning treatment with ART in the early stages of infection limits the number of HIV mutant types present in an infected individual on a long-term treatment regimen[16,17] because, with HIV replication halted, the proliferation of the virus is due to the proliferation of the original immune cells that it invaded.[17] Due to the high mutation rate, the National Institutes of Health (NIH) recommends that each patient undergo HIV drug-resistance testing prior to beginning ART or when changing ART regimens.[18]

The use of ART and recommendations for when to begin therapy have evolved as new sets of drugs have been developed that target different methods of HIV functionality. Early treatment of Acquired Immunodeficiency Syndrome (AIDS) in the 1980s consisted of treating the illnesses that developed due to immune system suppression instead of treating the underlying viral cause itself.[14] By the mid-1990s, monotherapy of antiretroviral agents was replaced with the now-standard cocktail of antiretroviral drugs that have the ability to suppress viral load to undetectable ranges[19,20] but initiation of treatment was based on low CD4 T cell counts.[18] Currently, multiple different types of drugs can be combined in ART, including nucleoside/nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, entry inhibitors, and small-molecule C-C chemokine receptor (CCR5) antagonists.[14] The NIH now recommends that ART begin as soon as a positive test is reported, regardless of the patient's CD4 counts, to minimize morbidity, mortality, and the risk of transmission.[18]

HERPES VIRUS

While infection with HSV is not a CDC reportable disease, data collected for physicians' offices indicate that 299,000 initial visits for genital herpes occurred in 2014.[21] HSV infects neuronal cells where it can lie dormant for years until activated by a suppression in the immune system.[22] Two types of Herpes Simplex Virus are the primary causes of sexually transmitted genital herpes. HSV-2 has traditionally been linked to genital infection while HSV-1 was linked to oral/facial infection. Interestingly, while there is a decrease of primary HSV-1 infection in children (by approximately 23%) there is an increase in HSV-1 genital infection upon initiation of sexual activity.[23,24]

Patients may present with a variety of manifestations of genital herpes that vary according to the signs and symptoms and their severity. The majority of infected individuals are asymptomatic. Typical symptoms include small blisters, itching, burning, or soreness in in the area of sexual contact. In the classic form of infection, symptoms include clusters of small painful blisters that ulcerate, crust, and heal when found in nonmucosal areas, and/or ulcers with no blisters or crusting when found in mucosal areas.[25]

The primary symptomatic episode is the most severe outbreak in terms of ulceration and pain. Symptoms include fever, headache, myalgias, and sometimes aseptic meningitis; inguinal lymphadenopathy; dysuria; vaginal or urethral discharge; itching; associated cervicitis (in about 80% of women); and new lesion formation for approximately 10 days. The time from the onset of symptoms to healing is usually 3 weeks. The nonprimary first episode is not as severe as a primary first episode. Symptoms include fever, headache, myalgia, and sometimes aseptic meningitis. The time from the onset of symptoms to healing is usually 3 weeks.[25]

Subsequent reactivation episodes are less severe than the primary episodes. Half of the patients will have a prodrome of burning, tingling, or pain in the genital or sacral area up to 2 days before lesions appear. Lesions will not develop in 20% to 40% of recurrences, despite prodromal symptoms. The time from the onset of symptoms to healing is usually 5 days.[25]

Primary infection through physical contact is not the only major concern in transmission of HSV. Congenital infection of neonates can lead to severe encephalitis and meningitis, which then causes neurological impairment.[26] Seventy percent of infected neonates are born to asymptomatic mothers. The initial sign of cerebral spinal fluid (CSF) infection is typically a seizure and skin lesions.[26]

Diagnostic Methods

Although HSV-1 and HSV-2 have identical symptoms in genital infections, HSV-1 reoccurs with lower frequency and exhibits a lessor amount of viral shedding.[24] Therefore, typing of the infection is beneficial for the patient. The original method for typing was by viral culture but low sensitivity makes it no longer the gold standard.[27] Direct immunofluorescence techniques have also been utilized. The current recommended method is by nucleic acid testing, which can not only provide the type identification but also determine if the patient is actively shedding virus.[24] Serologic tests that identify the presence of antibodies against HSV-1 and/or HSV-2 can be used in the absence of lesions.[21,24]

Treatment

The stage of herpes infection is a determinant for what treatment is prescribed. Initial infections are treated with larger doses of the antivirals acyclovir, valacyclovir, or famiclovir.[5] After initial treatment, suppressive therapy can be prescribed to prevent a future outbreak.[21,28] Suppressive therapy consists of lower doses of the same antiviral medications used for initial treatment. Long-term treatment, evident by the persistence of lesions after 1 week of treatment, can lead to resistance to the antiviral medication. For acyclovir, the resistance rate is 1% of immunocompetent patients, 5% in HIV-infected patients, and 30% in those that have received a hematopoietic stem cell transplant.[24,29,30] Neonatal encephalitis is treated with intravenous acyclovir or cidofovir.[26]

CONCLUSION

The viral sexually transmitted diseases caused by HPV, HIV, and HSV are responsible for over 15 million new infections per year. While HSV infection leads to skin lesions that are life-altering but not fatal, infection with HIV (through immune suppression) and HPV (through high-risk strains that are cancer-linked) can lead to death if undiagnosed and untreated. The standard for diagnosis is molecular testing, which has simplified identifying

specific strain information for HSV and HPV and can assist in determining the aggressiveness of treatment. For HIV, a combination of rapid serology tests and molecular testing can lead to diagnosis weeks to months earlier than what could be expected a decade ago.

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