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Review

Bidirectional Association within HIV and Syphilis Coinfection: A Pathophysiological and Clinical Review

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Abstract: HIV and syphilis coinfection were a major public health problem worldwide due to similar modes of transmission and pathophysiological interactions. HIV facilitates syphilis transmission by suppressing immunity, while syphilis enhances HIV replication and transmission through mucosal damage and immunological changes. The clinical manifestations of coinfection may differ from the usual course of the disease, complicating diagnosis and treatment. Coinfection increases the likelihood of treatment failure, immunological suppression, and serious sequelae such as neurosyphilis. Controlling this dual epidemic requires comprehensive policies that prioritize early detection, ongoing monitoring, and targeted therapy, especially among high-risk groups such as men who have sex with men and commercial sex workers. This review examines the epidemiology, immunopathogenesis, and clinical aspects of HIV and syphilis coinfection, emphasizing the importance of integrated prevention and treatment strategies.

Keywords: Bidirectional association, coinfection, HIV, syphilis.

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Introduction

Human immunodeficiency virus (HIV) is a pathogen that attacks the human immune system, especially all cells with CD4+ markers on their surface, such as macrophages and T lymphocytes. HIV infects white blood cells, which leads to a decrease in human immunity [1]. A study of global HIV prevalence trends among adolescents and young adults showed a decrease in incidence from 34.5 per 100,000 population in 1990 to 22.7 per 100,000 population in 2019 [2]. About 49,000 new infections are registered annually [3]. Mucosal sexual transmission is the most common route of HIV transmission worldwide. In addition, there are other routes such as transmission through drug injection, contact with blood, contact with blood products through transfusion, and contact with the fetus or infant of an HIV-infected mother [4, 5].

HIV transmission is often associated with other sexually transmitted infections such as early syphilis. The incidence of HIV and syphilis coinfection increases with the incidence of high-risk sexual contact among men who have sex with men (MSM). According to the U.S. data for 2003-2004, more than 60% of syphilis cases were found in the MSM group, where the majority of this group were also infected with HIV. In this group, 94% also had sex with women, leading to an increase in the prevalence of syphilis and HIV infection among both men and women. Results from studies in Europe show that the increasing trend in HIV incidence corresponds to the increasing incidence of syphilis. Several high-risk groups for HIV and syphilis transmission include MSM, commercial sex workers (CSWs), and injection drug users [6, 7]. The study showed that out of 8,585 people infected with HIV, 19.9% (1,708) were infected with syphilis. The risk of syphilis infection was higher in older people with HIV infection (from 35-47 to 15-35 years of age): OR (95% CI) = 1.81 (1.49; 2.21) [8].

Considering that HIV and syphilis are sexually transmitted infections (STIs), coinfection with them is common. Therefore, HIV testing is recommended for patients with syphilis and vice versa. Several previous epidemiological studies showed that syphilis is one of the factors that contribute to HIV transmission. This is evidenced by the data demonstrating that HIV+ patients have an 8-fold higher risk of serological detection of syphilis [6, 7]. This literature review discusses the frequency of HIV and syphilis coinfection in more detail. We summarize the mechanistic understanding of the bidirectional association within HIV and syphilis coinfection, demonstrating how syphilis-induced mucosal damage and immunomodulation facilitate HIV transmission, while HIV influences the clinical course of syphilis and treatment outcomes. Unlike previous reviews that predominantly focused on general epidemiological trends or specific high-risk groups, our review combines detailed pathophysiological analysis with contemporary clinical challenges.

Methods

This review employed a systematic literature search specifically designed to elucidate the pathophysiological and clinical aspects of HIV-syphilis coinfection. Data sources included electronic databases such as PubMed (MEDLINE), ScienceDirect

(EMBASE), and Google Scholar, with a publication range from 2015 to 2025 to include relevant studies. The search strategy was developed using the PICOS framework and Medical Subject Headings (MeSH) terms (e.g., HIV, syphilis, coinfection, pathophysiology, clinical management, epidemiology, immunomodulation, mucosal injury, treatment outcomes). Advanced search methods, bibliographic search, and Boolean operators (AND, OR, NOT) were used to optimize results. Article selection involved a three-step process of identification, screening, and quality assessment. Inclusion criteria required full text availability of a publication in English.

HIV/AIDS

Definition

HIV is a retrovirus consisting of single-stranded viral RNA that enters the nucleus of the host cell and is transcribed into the host DNA upon infection. Over time, HIV can damage many CD4 cells, leading to a decrease in immunity and a complete inability to fight infection and disease. This infection develops into acquired immunodeficiency syndrome (AIDS). Thus, it can be stated that AIDS is the final stage in a series of immunological and clinical disorders known as the HIV spectrum [9, 10].

Etiology

HIV infection and AIDS are caused by the human immunodeficiency virus, which is classified as a retrovirus of the *Lentivirus* genus in the *Retroviridae* family. This virus has two subtypes: HIV-1 and HIV-2. The HIV-1 subtype is the most common and causes AIDS in most countries worldwide. HIV-2 is found primarily in West Africa and is much less common [11]. Despite the structural similarity of their genomes, the two viruses differ significantly at the amino acid level. HIV-1 and HIV-2 are only 60% identical at the amino acid level and have only 48% identity at the nucleotide level. HIV-1 and HIV-2 particles consist of a lipid membrane surrounded by a protein capsid. The capsid contains a nucleoprotein complex consisting of two identical copies of RNA and the nucleocapsid proteins, integrase, and reverse transcriptase. The capsid proteins are arranged in a lattice structure, which gives the capsid its characteristic shape. These two viruses originate from two different zoonotic routes of transmission of simian immunodeficiency virus and therefore differ significantly in disease severity, transmission routes and prognosis. In addition, HIV is transmitted through various body fluids, including blood, amniotic fluid, breast milk, semen, pre-ejaculate and vaginal secretions. HIV can be transmitted sexually, during pregnancy and childbirth, and through reusable medical equipment or syringes [2].

Epidemiology

HIV infection is considered a pandemic [12]. Since its first identification, approximately 40 million people have died from HIV infection, and more than 38 million people are currently living with HIV. The prevalence of HIV/AIDS has increased in recent years [11]. In 2022, there were 1.3 million new HIV infections worldwide, and 630,000 HIV-related deaths in the same year. Although some countries are reporting an increase in new infections, the overall global trend is towards a decrease in HIV incidence. A study of global trends in HIV infection among adolescents and young adults showed a decrease in incidence from 34.5 per 100,000 population in 1990 to 22.7 per 100,000 population in 2019. However, between 2010 and 2022, a quarter of new infections in the Asia-Pacific region were among people aged 15 to 24 years and their partners, with some countries reporting almost half of all new infections in this population group. Overall, new HIV infections in the region have declined by only 14%. In some regions, HIV incidence is increasing. The WHO Middle East and North Africa region saw a 61% increase in HIV incidence between 2010 and 2022, the largest increase in the world [2].

In Indonesia, there were an estimated 613,435 HIV patients in 2015. As in other countries of the Asia-Pacific region, HIV and AIDS in Indonesia remain concentrated in populations at risk of HIV transmission due to their behavior. They are commonly referred to as key populations (KPs) and include female sex workers and their clients, injecting drug users (IDUs), MSM, and transgender people. National HIV prevalence among people aged 15 years and older was estimated at 0.33% in 2015. Provincial HIV prevalence estimates range from 0.1% to over 2.0%. The highest numbers of PLWHA are found in Jakarta, the densely populated provinces of Java, and Papua and West Papua. Although needle sharing among IDUs was previously associated with HIV transmission, sexual contact is now the main mode of HIV transmission. The annual number of new infections is estimated at approximately 49,000 [3].

Pathogenesis

Mucosal sexual transmission is the most common route of HIV transmission worldwide. In addition, there are other routes of transmission such as drug injection, exposure to blood, exposure to blood products through transfusion, and exposure to the fetus or child of an HIV-infected mother [4,5]. The process of HIV replication then begins. Replication involves six steps: 1) viral binding and invasion, 2) uncoating, 3) reverse transcription, 4) provirus integration, 5) synthesis and assembly of viral proteins, and 6) budding. The entry of HIV-1 and HIV-2 can be divided into three main processes: viral binding to cells, activation, and fusion. The HIV structure, viz., gp120, binds a 58-kDa monomeric glycoprotein known as CD4, which is expressed on the surface of approximately 60% of circulating T lymphocytes, on T cell precursors in the bone marrow and thymus, and on monocytes/macrophages, eosinophils, dendritic cells, and microglial cells in the central nervous system. The CD4 molecule normally functions as a coreceptor for major histocompatibility complex class II molecules in the recognition of foreign antigens by T cells. Upon binding of gp120 to the CD4 protein, the viral envelope complex undergoes structural changes, exposing specific domains of gp120 that are capable of binding to chemokine receptors on the cell membrane. This binding allows the virus to fuse with the cell membrane, penetrating the viral capsid [4].

The period between infection and the development of detectable antibodies in the laboratory is called the window period, which lasts 2-12 weeks. During the window period, the patient is highly infectious, easily transmitting the virus to others even if laboratory tests are still negative. About 2-4 weeks after viral transmission, the individual may develop acute HIV syndrome, a flu-like illness with high plasma viremia, often accompanied by fever and lymphadenopathy. In addition, symptoms such as myalgia, headache, anorexia, and diarrhea may occur. During this early phase, HIV replicates aggressively before the immune response is established. Then it spontaneously

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declines over several months until it reaches a steady state, or viral set point. The latter condition is critical as a determinant of disease progression in patients not receiving antiretrovirals (ARVs) [4].

Clinical manifestations and disease progression

The clinical manifestations of HIV are closely related to the progression of the virus in the body, varying depending on the stage of the disease. The initial seroconversion or acute phase occurs shortly after infection, characterized by high viremia and the development of HIV-specific antibodies. About 70% of patients in this phase develop acute retroviral syndrome (ARS), a mononucleosis-like condition characterized by nonspecific symptoms such as fever, joint pain, night sweats, diarrhea, myalgia, rash, lymphadenopathy, and sore throat, along with intense viremia and decreased lymphocyte counts (Wati 2020). Symptoms typically appear 2–4 weeks after infection, last about 18 days, and resolve when the viral set point is established after about 30 days. Severe symptoms or higher viral loads during this phase predict worse outcomes without treatment. Mucocutaneous ulceration, the hallmark of acute HIV infection, presents as shallow ulcers with sharp edges, a white base, and an erythematous halo, occurring in areas such as the oral mucosa, anus, penis, or esophagus, depending on the route of transmission [2, 13].

Subsequently, within one week to three months after infection, a specific cellular immune response to HIV occurs. This response is associated with a significant decrease in plasma viremia and is also associated with the onset of symptoms of acute HIV infection. Following the acute phase of HIV infection, which includes viral dissemination and the appearance of specific immune responses, infected individuals enter the second stage of infection, the asymptomatic period, also known as the latent or chronic phase [13]. However, in some cases, this phase is not completely asymptomatic. Symptoms such as nonspecific fatigue may occur, along with persistent generalized lymphadenopathy. Generalized lymphadenopathy is defined as enlargement of lymph nodes in at least two noncontiguous sites, excluding the inguinal, for more than 3 to 6 months without an identifiable lymphoproliferative or infectious cause. Patients with chronic HIV infection without AIDS may present with conditions such as oropharyngeal candidiasis, recurrent vulvovaginal candidiasis, oral hairy leukoplakia, disseminated herpes simplex virus infections, and cervical dysplasia or cervical carcinoma in situ. Cutaneous manifestations including seborrheic dermatitis, bacillary angiomatosis, varicella zoster virus reactivation, and molluscum contagiosum infections are common and typically severe in patients with HIV [2]. AIDS-defining illnesses are most common in patients with CD4+ counts below 200 cells/mm^3, which correlates with untreated advanced HIV disease due to a progressive decline in total lymphocyte counts over time [2].

Bidirectional association within HIV and syphilis coinfection

Epidemiology and risk factors of HIV and syphilis coinfection

Some HIV-infected patients often have coinfection with syphilis. This is because one of the routes of transmission is the same: sexual intercourse. Studies confirm that syphilis can facilitate the transmission and acquisition of HIV infection, enhance the transmission of infection by affecting HIV shedding, HIV replication and increasing viral diversity, and increase susceptibility to infection through mucosal lesions, immune changes in the genital tract and effects on the genital tract microenvironment. HIV can modify the manifestations of syphilis and blur the distinction between its stages. Patients with HIV and syphilis coinfection are also at higher risk of treatment failure and the development of neurosyphilis. Due to the mutual synergistic interaction of syphilis and HIV, the growing epidemic of syphilis and HIV coinfection remains difficult to control. Currently, China is facing a dual problem of syphilis and HIV. To better control the prevalence of syphilis and HIV, it is important to make coinfection of these two diseases the starting point for prevention and treatment, and it is essential to strengthen the monitoring and treatment of syphilis in HIV infection [8].

The study [8] showed that of 8,585 people infected with HIV, 19.9% (1,708 people) tested positive for syphilis. Among people with both infections or only HIV infection, men predominated (n=6332 or 73.77%), followed by women (n=2,173 or 25.32%) and male-to-female transgender people (n=78 people or 0.91%). The mean age of people infected with HIV in combination with syphilis was 42.5±12.8 years. In the HIV-infected group, women had a lower risk of contracting syphilis than men (OR [95% CI] = 0.28 [0.18; 0.43]), whereas there was no difference between men and transgender people (OR 1.04 [0.49; 2.06]). In addition, older HIV-infected individuals (from 35 to 47 years to 15-35 years of age) had a higher risk of contracting syphilis (OR 1.81 [1.49; 2.21]). Notably, women had a lower risk of reinfection with syphilis than men (OR 0.51 [0.23; 1.02]). The risk of reinfection increased with age, as those aged 35-47 years had a higher risk than those aged 15-35 years (OR 1.31 [1.04; 1.67]). The risk of reinfection was also higher among MSM (OR 2.71 [1.89; 3.96]) [8]. A recent study in Turkey conducted from 2010 to 2018 revealed that the prevalence of syphilis and HIV coinfection was 8% [14]. Meanwhile, a similar study in Thailand recently demonstrated a higher prevalence of syphilis (14.3%) among MSM with acute HIV infection [15]. Another study reported a 9.5% prevalence of syphilis among adults with HIV infection [16]. The data presented above elucidate that patients infected with HIV have the possibility of acquiring syphilis and vice versa. It depends very much on their sexual behavior. Hence, it is quite possible that if casual sex continues to occur, the prevalence of both infections may increase simultaneously.

Immunopathogenesis of HIV and syphilis coinfection

Syphilis is common in people infected with HIV. Coinfection with HIV and syphilis has a worse prognosis because HIV increases the likelihood of syphilis treatment failure and coinfection may also cause more severe neurocognitive impairment [17–19]. Although active antiretroviral therapy (ART) can successfully control HIV infection and improve the quality of life in PLWHA, reduced innate and adaptive immune responses to syphilis may increase susceptibility to infection [20]. In contrast, syphilis increases the likelihood of HIV transmission because it can negatively affect the immune system and increase HIV viral load and reduce CD4+ T cell counts in PLWHA receiving ART [21, 22].

Fan et al. [23] found that individuals who were coinfected with HIV and syphilis before initiating ART had a higher likelihood of virologic failure, accompanied by a smaller increase in CD4+ T cell count and CD4/CD8 ratio over seven years of ART vs. individuals who were infected with HIV alone [23]. Furthermore, syphilis has a negative impact on immune reconstitution during HIV infection. In addition to changes in CD4+ T cell count, Fan et al [23] also found

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that the CD4/CD8 ratio was decreased in individuals coinfected with HIV and syphilis at baseline and after seven years of ART. The CD4/CD8 ratio is a strong marker of immune activation and immune aging. Furthermore, a lower CD4/CD8 ratio also indicates residual HIV viremia in virologically suppressed patients [24, 25]. Overall, these results imply that coinfection with syphilis contributes to poor immune reconstitution and subsequently increases the likelihood of virologic failure [23]. Furthermore, coinfection with syphilis may enhance HIV replication via increasing host immune cell activation, altering cytokine secretion including TNF-α, and increasing the content of transcription factors such as nuclear factor kappa beta [26].

Overall, the immunopathogenesis of HIV and syphilis coinfection is supported as both infections share similar characteristics that result in negative synergistic effects on the host. HIV causes a decrease in CD4+ T lymphocytes, while syphilis causes a decrease in humoral and cellular immunity early in the infection. Syphilis is associated with concanavalin A (Con A)- and phytohemagglutinin (PHA)-induced reduced proliferation of purified T lymphocytes, leading to decreased lymphocyte blastogenesis. This condition facilitates the spread of infection in the early stages [7].

Syphilis and HIV also have a negative impact on the humoral immune system. The host can produce antibodies to the cardiolipin component of *Treponema* bacteria, while HIV can trigger a polyclonal expansion of immunoglobulins (Ig). This condition causes secondary activation of B cells due to decreased CD8+ T cells. This can trigger uncontrolled Ig production, which is common in HIV coinfection cases, which then leads to uncertainty in the diagnosis of syphilis in HIV-coinfected patients [7].

In addition, there is also an ineffectiveness of macrophages as antigen presenting cells (APCs). In this context, macrophages are one of the main targets of HIV infection, so macrophages are ineffective in presenting antigens to B cells, which leads to a decrease in the humoral immune response, including against syphilis. On the other hand, this condition is also aggravated by the help function normally provided by CD4+ T cells. The latter are also reduced in numbers by HIV infection [7].

One of the cytokines that plays a role in the pathogenesis of HIV infection and syphilis is interleukin 10 (IL-10). IL-10 is an important anti-inflammatory, immunosuppressive, and immunomodulatory cytokine associated with many diseases and involved in the regulation of inflammatory responses, autoimmunity, infection progression, tumorigenesis, and transplant tolerance [27]. However, when IL-10 production is excessive, as observed in infections caused by a number of pathogens such as HIV, hepatitis C virus, and mycobacteria, it can suppress the proinflammatory response, allowing the pathogen to escape from the control of the immune system and lead to fatal or chronic infections that are refractory to treatment. A recent meta-analysis showed that IL-10 polymorphisms at positions -592 or -1082 cause increased IL-10 production and are associated with susceptibility to HIV infection. In addition, it has been reported that people infected with HIV with certain IL-10 promoter haplotypes may progress to AIDS more rapidly [28]. Similarly, in syphilis, cellular immunity plays an important role in the natural history of *Treponema pallidum* infection. Overproduction of IL-10 was observed in late syphilis. In a study by Wurong Li et al., only IL-10 was significantly elevated in the cerebrospinal fluid of patients with neurosyphilis, and IL-10 levels were positively correlated with markers of nerve damage [29].

Impact of HIV infection on syphilis

HIV and syphilis are two STIs for which coinfection frequently occurs, and the two diseases influence each other. All patients infected with syphilis should be tested for HIV, and vice versa [30]. In geographic areas with high HIV prevalence, patients with primary syphilis should be retested for HIV in three months if the initial HIV test result is negative [31].

The presence of HIV coinfection may alter the clinical presentation of syphilis and confuse the stages of syphilis, leading to impaired clinical decision making [31]. In primary syphilis with HIV coinfection, clinical presentation may include larger, deeper, and multiple chancres and may require longer healing. In people with HIV, primary lesions are more likely to have multiple chancres (70%) vs. people without HIV [32]. In secondary syphilis with HIV coinfection, although rare, clinical presentation may include malignant syphilis. In addition, spirochete replication occurs more rapidly in HIV-infected patients, accelerating dissemination of the infection in multiple organ systems. Not surprisingly, in some cases, symptoms of secondary syphilis appear before the primary lesions disappear [32].

In addition, tertiary syphilis with HIV coinfection also increases the risk of developing neurosyphilis and ocular syphilis. In patients with HIV infection, the progression of gummas and neurosyphilis is faster. Several previous studies showed that the prevalence of neurosyphilis in patients with a history of HIV infection is 23.5-40%, compared to the prevalence of neurosyphilis in patients without HIV, which is only 10% [19]. Several studies also established that in patients with HIV coinfection, it can accelerate and modify the course of neurosyphilis [32]. Interestingly, HIV-infected patients with syphilis coinfection had higher CD4 cell counts. Syphilis affected the changes in CD4 cell counts and HIV-1 RNA 6 months after HIV diagnosis, but this was not statistically significant. This finding was demonstrated in a study by Somia et al. who found that HIV-positive MSM coinfected with syphilis had a significantly higher mean baseline CD4 count than those without syphilis (P=0.017). There was no difference in the median baseline plasma HIV-1 RNA level between HIV-positive MSM with and without syphilis (P=0.885). The mean change in CD4 count from baseline to month 6 was similar in HIV-positive MSM with (n=11) and without syphilis (n=20) (P=0.860). Similarly, there was no significant difference in the median change in HIV-1 RNA between patients with (n=8) and without (n=11) syphilis (P=1.000) [33].

With regard to treatment, patients with syphilis and HIV coinfection also have an increased risk of treatment failure. That is why a longer follow-up period, both clinical and serological, is required to monitor cases of treatment failure [31].

Impact of syphilis on HIV infection

Syphilis is a global public health problem with high prevalence. In 2016, the global prevalence of syphilis was estimated to reach 6 million new cases, mostly among MSM. The high prevalence of syphilis is also accompanied by an increase in HIV coinfection. Syphilis and HIV are two types of STIs with similar risk factors. Several previous studies reported that untreated syphilis infection can lead to HIV transmission and coinfection [31].

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A meta-analysis by Wu et al. showed that of over 65,000 high-risk participants, HIV prevalence was increased two-fold in patients with a history of syphilis (OR: 2.67; $p<0.05$; 95% CI: 2.05-3.47). These data suggest that patients with syphilis in high-risk groups have an increased risk of acquiring HIV [31]. Similar results were obtained in previous epidemiological studies, which provided convincing evidence that syphilis, one of the causes of genital ulcers, can facilitate and increase HIV transmission [34, 35]. Other studies have also shown that HIV-infected patients are up to 8 times more likely to have positive serological results for syphilis, since hard ulcers in syphilis physically disrupt the integrity of the epithelium and mucosa, which can be an entry point for the HIV virus. These ulcers can also cause local penetration of CD4 + lymphocytes [7].

The increased risk of HIV infection in this group of patients with syphilis is due to several factors. The first factor is associated with the presence of genital ulcers in patients with syphilis, which cause damage to the mucosal barrier, which becomes an entry point for HIV. In the primary syphilis stage, regulatory T cells play a role in the clearance of *T. pallidum* at the site of infection by activating IFN-γ, which enhances the ability for phagocytosis and degradation by macrophages. However, it is the increase in the number of macrophages and T cells expressing CD4 at the site of infection that is actually the target of HIV infection [31].

The lipoprotein layer on the outer membrane of *T. pallidum* plays an important role in HIV coinfection due to its high immunogenicity and proinflammatory properties. This layer triggers the activation of macrophages and dendritic cells via the TLR-2 signaling pathway and induces HIV-1 gene expression in monocytes via an NF-κB-dependent mechanism, promoting latent transmission of HIV in syphilis [31]. In addition, the lipoprotein increases the expression of CCR5 on monocytes, increasing susceptibility to HIV, since CCR5 serves as a key co-receptor for M-tropic HIV strains, the most infectious type. Syphilis, especially in the secondary stage, also enhances HIV replication through cytokine secretion and increased levels of transcription factors, altering the cell cycle. Coinfection affects HIV monitoring parameters: acute syphilis results in an increase of the viral load (median increase of 0.5 log10 copies/mL) and a decrease in CD4+ T lymphocytes, returning to normal after treatment [36, 37]. This was confirmed by another study [38], where a decrease in lymphocytes (CD4+ and CD8+) was observed during episodes of syphilis in HIV patients receiving ART, followed by recovery after syphilis treatment.

Conclusion

The coinfection of HIV and syphilis is one of the health problems that causes high morbidity and mortality. The presence of syphilis in patients with HIV or vice versa leads to more severe clinical consequences that require more complicated treatment.

Conflict of interest

No potential conflicts of interest are declared.

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