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Associations between HIV, sexually transmitted diseases, and antimicrobial resistance in the era of combination antiretroviral therapy and antibiotics

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Abstract

The advancement of combination antiretroviral therapy (cART) has dramatically transformed the management of human immunodeficiency virus (HIV), significantly reducing morbidity and mortality rates. However, the coexistence of sexually transmitted diseases (STDs) and antimicrobial resistance (AMR) presents interconnected challenges that compromise these advances in this era. This review explores the intricate associations between HIV, STDs, and AMR in the framework of extensive cART and antibiotic usage. Published literature on epidemiological data was analyzed to identify the patterns of co-infection and resistance trends, examining how the suppression of HIV influences the prevalence and treatment outcomes of concurrent STDs. Furthermore, the impacts of antibiotic overuse or misuse on the emergence of resistant strains of common bacterial STDs were investigated, particularly focusing on pathogens such as *Neisseria gonorrhoeae* and *Mycoplasma genitalium* among HIV-infected individuals. The findings highlight the critical need for integrated surveillance, antimicrobial stewardship, expanded vaccination, and culturally sensitive public health strategies. By enhancing our understanding of these interactions, this review intends to inform alterations in the existing public health policies and to upgrade previously optimized treatment protocols in the near future to improve patient outcomes in the era of cART and antibiotics.

Keywords: HIV; Sexually transmitted disease; Antimicrobial resistance; Combination antiretroviral therapy; Antibiotic era

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1. Introduction

The global human immunodeficiency virus (HIV) epidemic remains a significant public health challenge, with millions of people affected worldwide, particularly in low- and middle-income countries. Despite the success of combination antiretroviral therapy (cART) in controlling HIV progression, the spread of sexually transmitted diseases (STDs) has surged in many regions.[1] Co-infection with STDs increases the risk of HIV transmission, leading to a vicious cycle of infection. Compounding this issue is the alarming rise of antimicrobial resistance (AMR) in common STD pathogens, such as *Neisseria gonorrhoeae*.

The emergence of AMR is undermining the effectiveness of antibiotics, making STD treatment more difficult and threatening to complicate HIV management, especially in individuals co-infected with resistant strains. Together, these trends pose a critical challenge to global public health efforts in controlling HIV and STDs, followed by the burning issue of AMR. Antibiotics play a crucial role in treating bacterial STDs, helping to prevent complications and reduce transmission. However, the overuse and misuse of antibiotics have led to the emergence of AMR, rendering standard treatments less effective and complicating STD management. Thus, several interconnecting factors need to be studied to understand the dynamics for effective management and treatment of these diseases.[2]

2. Methodology

To ensure a comprehensive review of the literature, multiple databases and sources, including PubMed, Google Scholar, ScienceDirect, and published reports, were searched. Boolean operators, such as AND, OR, and NOT, were applied to optimize search results and capture the most relevant and up-to-date information. Review articles, research papers, and reports were selected based on their relevance to HIV-STD co-infection and the emergence of AMR. The selected articles were summarized and analyzed to provide a thorough overview of the current status of HIV-STD co-infection and the role of the immune system at various stages of disease progression. The validity and reliability of the articles were assessed based on their sample sizes. In addition, factors influencing or confounding the management and severity of HIV-STD co-infection were included.

3. HIV and STDs

3.1. Development of HIV-STD co-infection

Initially, in the rise of the epidemic, Wasserheit[3] identified the link between HIV and traditional STDs that produce the irritation of the mouth or ulcers, which he coined as "epidemiologic synergy." Recent research has focused extensively on biological pathways to understand how STDs facilitate the transmission of HIV by disrupting natural defenses and amplifying viral replication. STDs, particularly those causing genital ulcers or inflammation, such as syphilis and herpes, damage mucosal barriers, making it easier for HIV to enter the body during sexual contact. Inflammation during STDs triggers immune activation, attracting immune cells, such as cluster of differentiation 4-positive ($CD4^+$) T cells, to the infection site. This increases the number of susceptible cells in the genital tract, facilitating HIV acquisition. These investigations indicate that STDs increase the contagiousness of HIV-positive individuals and the susceptibility of HIV-negative individuals. Furthermore, recent studies have highlighted that the alterations in the viral phenotype of HIV variants, particularly those enhancing viral fitness and transmissibility, play a critical role in the increasing spread of the virus. These phenotypic changes can lead to higher viral replication rates and elevated viral loads in genital secretions, especially vaginal fluid, thereby significantly increasing the risk of sexual transmission. Such adaptations not only facilitate more efficient person-to-person transmission but may also contribute to the persistence and resurgence of the epidemic in certain populations.[4]

In general, HIV R5-tropic (C-C chemokine receptor type 5-using) viruses are more commonly transmitted than X4-tropic (C-X-C chemokine receptor type 4-using) viruses. Transmitted/founder viruses often display higher replicative fitness and resistance to host restriction factors. Moreover, viruses with low glycosylation and neutralizing antibody sensitivity are more likely to establish infection during transmission.[5,6] Epidemiological studies and meta-analyses have quantified the increased risk of HIV acquisition in the presence of STDs. For example, genital ulcer diseases (e.g., syphilis and herpes) increase the risk of HIV acquisition by 2–5 times, primarily by disrupting mucosal barriers. Non-ulcerative STDs (e.g., gonorrhea and chlamydia) can increase HIV transmission risk by 1.5–3 times, mainly through inflammation and immune cell recruitment.[7]

Sexual transmission is one of the primary routes of HIV spread, with infection resulting from exposure to blood, pre-ejaculate semen, and vaginal fluids.[8] STDs, such as gonorrhea, syphilis, and herpes, can accelerate HIV progression by causing chronic inflammation and immune system activation. This immune activation increases the number of HIV target cells, facilitating viral replication and increasing viral loads, thereby leading to faster disease progression. In addition, HIV can be transmitted from an infected mother to her infant during pregnancy, at childbirth through contact with maternal blood or vaginal fluids, or during breastfeeding.[9] HIV is present in body fluids as free virus particles and as cell-associated virus within infected immune cells.[10] Maternal antiretroviral therapy (ART) reduces the risk of vertical HIV transmission to <1% when started early and maintained throughout pregnancy and breastfeeding, while pre-exposure prophylaxis (PrEP) is safe and effective for HIV-negative pregnant women with high-risk partners.[11,12] Furthermore, early ART initiation helps reduce the size and diversity of the latent HIV reservoir, according to multiple clinical studies at various places.[13-15]

As HIV weakens the immune system, the body becomes more vulnerable to infections, making STDs more persistent, severe, and difficult to treat. This interplay between HIV and STDs creates a vicious cycle that not only worsens individual health outcomes but also increases the likelihood of transmission. HIV-STD co-infection can increase HIV viral load in genital secretions, further raising the risk of transmission to sexual partners. Conversely, when the viral load of a person is undetectable, sexual transmission of HIV through condomless intercourse is exceedingly rare.[16]

Epidemiological data demonstrated that regions with high HIV prevalence, such as sub-Saharan Africa and Southeast Asia, also reported high STD burden, with co-infections particularly common among key populations such as men who have sex with men (MSM), sex workers, and adolescents.[17,18] These synergistic epidemics not only amplify disease transmission but also complicate diagnosis and treatment, underscoring the need for integrated surveillance and prevention strategies.[19,20]

The widespread use of cART has led to effective suppression of HIV viral load, substantially reducing the risk of HIV transmission. However, this success has had mixed effects on the dynamics of STD transmission. Individuals with undetectable viral loads may engage in riskier sexual behaviors due to a perceived reduction in HIV transmission risk, potentially leading to increased incidence of other STDs, such as syphilis, gonorrhea, and chlamydia. Moreover, while HIV suppression reduces systemic immune activation, it does not prevent the acquisition or transmission of bacterial or viral STDs. This interplay of behavioral, virological, and immunological factors in the era of HIV suppression necessitates the continued emphasis on regular STD screening, safer sex practices, and integrated sexual health services to control STD transmission in populations living with HIV.[21]

3.2. Insights into HIV transmission and prevention

The introduction of cART has significantly improved the life expectancy and quality of life for people living with HIV. It has also influenced the prevalence and treatment of co-infections, underscoring the importance of understanding how cART interacts with treatments for other STDs. Primary HIV infection refers to the early stage following the acquisition of HIV and represents a critical opportunity for expedited diagnosis and rapid initiation of ART. Early treatment can improve immune functions, reduce the size of the viral reservoir, and limit onward transmission. Primary HIV infection may sometimes last for 2–3 weeks, during which the virus infects susceptible $CD4^+$ T cells.[22] Rapid viral replication produces a burst of viremia, enabling widespread dissemination to lymphoid organs, the brain, and other tissues.[23]

Acute retroviral syndrome, which typically lasts for 2–3 weeks, marks the onset of HIV-specific immune responses. It often presents with infectious mononucleosis-like symptoms and usually resolves spontaneously.[24] During this phase, a transient decline in $CD4^+$ T cell counts may occur, which then stabilizes for a period before beginning a gradual decline.[25] Acute HIV infection is mostly unrecognizable in primary care settings because the non-specific symptoms of acute retroviral syndrome frequently resemble common viral illnesses such as influenza.[26]

During the asymptomatic phase of HIV infection, the body mounts a robust cellular and humoral immune response. However, the virus escapes immune-mediated clearance, developing chronic infection as the virus is never fully eliminated. This asymptomatic stage may last for 8–10 years. With therapy, cell-mediated immunity gradually recovers, and the $CD4^+$ cell count increases.[27]

Progression to the symptomatic phase of HIV infection is marked by opportunistic infections and non-infectious complications, such as early immunodepletion, persistent generalized lymphadenopathy, intermediate and severe immunodeficiency, tuberculosis, and ultimately acquired immunodeficiency syndrome.[28] HIV exists as two major types: HIV-1 and HIV-2.[29] A key accessory protein of HIV-1, viral protein R (Vpr), is a 14-kDa, 96-amino acid virion-associated protein highly conserved among primate lentiviruses, including HIV-1 and HIV-2.[30] Vpr is incorporated into virions through the p6 region of Gag, and its abundance is closely linked to Gag expression.[31] Vpr displays karyophilic properties, localizing to the nucleus despite lacking a canonical nuclear localization signal. It is required for the nuclear import of the HIV-1 genome and plays a critical role in pre-integration complex formation, enabling efficient replication in macrophages.[32] Beyond replication, Vpr arrests host cells at the G2/M phase of the cell cycle and contributes to apoptosis and HIV-associated neurotoxicity. Recent studies have explored Vpr as a therapeutic target, including inhibitors and gene-editing strategies (e.g., clustered regularly interspaced short palindromic repeats/Cas9) designed to disrupt its expression.[33(p1)-35]

As HIV infection continues to rise, prevention remains paramount, since no permanent cure, universally effective drug, or widely accessible preventive vaccine is yet available—particularly in developing countries. Information, education, and communication programs targeting men, women, and adolescents, with special emphasis on high-risk groups, are essential. These efforts should be complemented by accessible facilities for the

detection and treatment of other STDs, promotion of condom use, and dissemination of accurate information free from stigma and discrimination. HIV-infected persons usually experience recurrent illnesses and complications that require medical and nursing care, including periodic hospitalization. Even during periods of minimal infection, clinical care should include pain relief and treatment for common opportunistic infections. Effective care also requires trained healthcare providers and a reliable supply of essential medicines. With comprehensive clinical care, the lives of HIV-infected persons can be substantially prolonged and their quality of life greatly improved.

Healthcare workers, such as doctors, nurses, and paramedical staff, face a heightened risk of accidental HIV infection if safety measures are not strictly followed. Infected healthcare personnel may, in turn, pose a transmission risk to uninfected patients if appropriate precautions are neglected. Such risks can be avoided through adherence to universal precautions, such as safe handling and disposal of sharps, proper decontamination of instruments and equipment, frequent hand hygiene, and the use of protective barriers to prevent direct contact with body fluids. Implementation of universal personal protective equipment protocols is essential to reduce occupational exposure, particularly in healthcare settings managing HIV, STDs, and other infectious diseases. Routine surveillance for needlestick injuries and timely access to post-exposure prophylaxis are both critical for protecting healthcare workers. Furthermore, vaccination coverage, particularly against the hepatitis B virus (HBV) and seasonal influenza, further enhances biosafety measures. In addition, expanding the use of point-of-care diagnostic technologies minimizes unnecessary handling of infectious specimens, thereby reducing exposure risks. Vaccination against human papillomavirus (HPV) and HBV remains a cornerstone of STD prevention. In low-resource settings, various programs led by the World Health Organization (WHO) have improved HPV vaccine access, especially for girls aged 9–14.[36]

3.3. Insights into STD transmission and prevention

STDs are diseases transmitted primarily through sexual intercourse. Their transmission requires a causative agent that spreads from one person to another. STDs can affect the genital tract and other parts of the body participating in sexual interaction, including infections such as syphilis, gonorrhea, chancroid, donovanosis, non-gonococcal urethritis, genital warts, and genital herpes. STDs have a tremendous impact on public health, contributing to maternal morbidity, ectopic pregnancies, infant illness and mortality, malignancies, infertility, and increased susceptibility to HIV infection. They are a major cause of infertility in both men and women and play a significant role in adverse pregnancy outcomes, including fetal death, abortions, and low birth rates. The risk of acquiring STDs and subsequent development of cervical and other genital cancers is directly associated with the number of lifetime sexual partners, partner turnover, and sexual network dynamics.

Among viral STDs, HBV and HPV are particularly important due to their oncogenic potential. While the incidence of bacterial STDs has declined in many developed countries, the global HIV pandemic continues to spread relentlessly, exacerbating the overall burden of STDs. This problem is further compounded by the emergence of AMR in pathogens such as *N. gonorrhoeae*, herpes simplex virus (HSV), and HIV. Rising drug resistance highlights the need for continuous monitoring, novel therapeutic strategies, and adaptive clinical guidelines. In addition, early pathogen detection with advanced diagnostic technology is essential for the timely initiation of treatment.[37]

The transmission of STDs is strongly influenced by sexual behaviors and sociocultural factors. Early marriage, multiple sexual partners, rapid partner change, and high-risk sexual practices are key determinants of STD risk, while education, religion, and cultural practices further shape sexual behaviors. Pathogens such as HIV, HBV, *N. gonorrhoeae*, and *Chlamydia trachomatis* have a more efficient male-to-female than female-to-male transmission, largely due to extended mucosal exposure following sexual contact.

Viruses such as HPV are transmitted through direct sexual contact, regardless of visible wart presentation. The incubation period typically ranges from 2 to 3 months, though longer durations may occur. HPV thrives in warm, moist environments but does not survive well outside the human body, which explains its lack of transmission through inanimate objects. Genital warts may also occur in the mouth following oral sex, and vertical transmission from mother to infant can occur during delivery. In such cases, caesarean section is often recommended.[38]

Emerging challenges in STD control include the rise of AMR gonorrhea, HPV-related cancers, evaluation of HPV vaccine impact, increasing syphilis incidence among MSM, and the use of nucleic acid amplification tests for earlier and more accurate diagnosis. Newly recognized sexually transmitted pathogens, such as the hepatitis C virus and *Mycoplasma genitalium*, have also expanded the scope of concern.

The prevention of STDs aims to reduce both behavioral and biological risks. The primary steps include comprehensive risk assessments through sexual histories,

behavioral screening, and testing for biological markers associated with HIV acquisition and transmission.[39] Routine STD screening is an essential component of risk assessment: women under 25 years, older women with risk factors, and sexually active bisexual and MSM should undergo regular testing for infections such as chlamydia and gonorrhea.[40]

Preventive risk-reduction strategies include not engaging in sexual activity, reducing the number of sexual partners,[41] and promoting consistent condom use. However, sociocultural barriers significantly influence prevention. In some settings, religious conservatism may discourage condom use and hinder comprehensive sex education, while low literacy levels limit understanding of disease transmission and protective measures. In addition, gender norms and stigma surrounding STDs further deter individuals from seeking testing or disclosing infection status, thereby delaying both diagnosis and treatment and increasing transmission risks.[42,43] To overcome these barriers, intervention should include school-based and community-based education programs to raise awareness, conditional cash transfers to discourage early marriage, and youth-friendly STD clinics to provide accessible and confidential care for adolescents.[44,45]

4. Management strategies of the most common bacterial and viral STDs

4.1. Management of chlamydia

Chlamydia is caused by *C. trachomatis*, which is a gram-negative intracellular bacterium belonging to the family Chlamydiaceae, and is the most commonly reported STD in the United States (US),[46] with the highest burden among adolescents and young adults. Studies have reported that untreated *C. trachomatis* infection in women can develop into pelvic inflammatory disease (PID),[47] which is associated with serious reproductive health consequences. Approximately 20% of women with PID develop infertility, 18% experience chronic pelvic pain, and 9% have life-threatening tubal pregnancies. Symptoms of chlamydial infection are often mild or absent, contributing to underdiagnosis and delayed treatment.

In neonates, chlamydia arises primarily from perinatal exposure to an infected maternal cervix. Diagnosis in women is typically made using urine specimens or swabs from the endocervix or vagina, while in men, it is confirmed through urethral swabs or urine specimens. Rectal infections can be diagnosed using rectal swabs. The preferred diagnostic methods include nucleic acid amplification tests, cell culture, direct immunofluorescence, and nucleic acid hybridization.[48] Chlamydia treatment involves antibiotics such as azithromycin, doxycycline, erythromycin, and levofloxacin. Timely therapy not only cures the infection but also prevents progressive tissue damage and long-term complications.[39]

4.2. Management of gonorrhea

Gonorrhea is caused by *N. gonorrhoeae*, a gram-negative diplococcus with an incubation period of 3–14 days. The highest prevalence is observed among females aged 15–19 years and males aged 20–24 years. Gonorrhea cases in the US have been increasing in all races and ethnic groups.[49] Transmission occurs primarily through unprotected sexual contact with an infected partner. Common sites of infection include the urethra, vagina, cervix, rectum, pharynx, and conjunctiva. Because *N. gonorrhoeae* does not survive well outside the human host, transmission through inanimate objects such as toilet seats is highly unlikely. Vertical transmission during childbirth can result in severe conjunctivitis.[50]

Symptoms of gonorrhea vary from symptomatic urethritis, epididymitis, vaginal and pelvic discomfort, and abnormal vaginal discharge to asymptomatic infections. Both symptomatic and asymptomatic infections can progress to PIDs, leading to complications such as tubal infertility, ectopic pregnancy, and chronic pelvic pain. In rare cases, disseminated gonococcal infection can occur, resulting in arthritis, meningitis, or endocarditis.

Diagnosis of gonorrhea infection in symptomatic men can be achieved by Gram staining of urethral specimens, which typically reveal polymorphonuclear leukocytes with intracellular Gram-negative diplococci. However, in asymptomatic men, a negative Gram stain result does not exclude infection. Other diagnostic methods include culture, nucleic acid hybridization tests, and nucleic acid amplification tests.

Treatment of gonorrhea includes the use of antibiotics such as ceftriaxone, often combined with azithromycin as dual therapy. However, the emergence of AMR in *N. gonorrhoeae* poses a growing threat. Patients treated for gonorrhea should undergo follow-up testing to ensure microbiological cure and prevent further transmission.[50] Currently, increasing resistance to ceftriaxone and azithromycin has been reported. While high-level azithromycin resistance (minimum inhibitory concentration ≥256 mg/L) remains rare, its emergence threatens the long-term efficacy of empirical treatment strategies.[51,52]

4.3. Management of HPV infections

HPV is one of the most common STDs, transmitted through sexual contact and nonsexual skin-to-skin contact. HPV comprises a large family of small, double-

stranded DNA viruses that cause warts in different body parts depending on the strain. The types of warts include genital warts, common warts, plantar warts, and flat warts. Moreover, some types of HPV are implicated in cervical cancer and oral cancer.[53]

Most HPV infections are asymptomatic and transient. According to the Centers for Disease Control (CDC), 90% of infections resolve spontaneously within 2 years. However, persistent infections may lead to the development of precancerous lesions and malignancies. Importantly, HPV-related cancers are often asymptomatic until late stages, underscoring the importance of regular screening. The HPV types that cause warts are different from those that cause cancer; thus, the presence of warts does not necessarily indicate increased cancer risk.

Diagnosis of HPV infection varies by sex. In women, regular pap tests help to identify abnormal cervical cells and assess cancer risk. Colposcopy may be used for further evaluation. In men, there are currently no Food and Drug Administration-approved HPV tests; however, anal pap tests are sometimes used to screen for anal cancer.[53]

There is no permanent treatment for HPV infection, as most cases resolve spontaneously. Some warts, such as genital warts, can be treated with medications, electrocautery, or cryotherapy with liquid nitrogen. Nevertheless, wart removal does not eradicate the underlying virus, and recurrence is common. For precancerous lesions, treatment may involve chemotherapy, radiation therapy, or surgical excision.

4.4. Management of HSV infections

HSV is one of the most prevalent STDs.[54] Two major types exist: HSV-1, which is commonly acquired during childhood and primarily causes orolabial lesions, and HSV-2, which is more frequently associated with genital infections.[55(p2)] Notably, HSV-1 can be transmitted through oral secretions during oral-genital contact. Asymptomatic HSV infection is common and is known to account for over 75% of viral transmission.[56] The incubation period of HSV usually ranges from 1 to 26 days.

Primary HSV infection often presents with painful genital or anal ulcers and bilateral tender inguinal lymphadenopathy. The initial stages of HSV-1 and HSV-2 infections are usually the same.[57] Systemic flu-like symptoms may occur, and in rare cases, sacral radiculomyelopathy can develop. In women, genital and urethral lesions may cause transient urinary retention. Severe complications of HSV infection include pneumonitis, disseminated infection, hepatitis, meningitis, and encephalitis.[58]

Diagnosis of HSV infection is achieved using viral culture, cell culture, and polymerase chain reaction (PCR). Among these methods, cell culture and PCR are the most widely preferred in patients presenting with genital ulcers or mucocutaneous lesions,[59] with PCR commonly used for the detection of HSV DNA in cerebrospinal fluid during suspected central nervous system infection. Meanwhile, viral culture and serology assays based on glycoprotein G1 (HSV-1) and glycoprotein G2 (HSV-2) help to detect specific HSV types.[60] For the treatment of HSV infections, the recommended regimens include acyclovir 400 mg taken orally three times daily for 7–10 days, famciclovir 250 mg taken orally three times daily for 7–10 days, or valacyclovir 1 g taken orally twice daily for 7–10 days.[61]

4.5. AMR

Antimicrobial drugs have revolutionized modern healthcare, providing effective treatment for life-threatening bacterial, viral, fungal, and parasitic infections. However, increasing levels of AMR have threatened the health benefits achieved with antibiotics, emerging as a global crisis.[62,63] Although often described as a new phenomenon, AMR has existed long before the clinical use of antimicrobials. Ancient bacterial samples, estimated to be 2000 years and even 30,000 years old, have shown resistance to ampicillin and vancomycin, respectively.[64,65] In addition, *Staphylococcus aureus* has been known to have resistance to penicillin since the introduction of the antibiotic into clinical use.[66]

Today, AMR to traditional treatments, such as azithromycin and doxycycline, is being actively monitored through global surveillance programs, including the WHO's Gonococcal Antimicrobial Surveillance Program and the CDC's Gonococcal Isolate Surveillance Project. These initiatives track resistance trends in pathogens such as *N. gonorrhoeae* and *M. genitalium*. In response to rising resistance, treatment guidelines are shifting toward resistance-guided therapy, incorporating molecular diagnostics to tailor antibiotic selection and reduce empirical treatment failures.[52]

The misuse and overuse of antimicrobials in both human medicine and agriculture have further accelerated the spread of resistance.[67] The National Institute of Animal Health has reported that 7.5–8.6 billion chickens, 60–92 million pigs, and 275–292 million turkeys are fed with various types of antibiotics, underscoring the global scale of antimicrobial pollution. In European countries, antibiotic-resistant bacteria are responsible for an estimated 30,000 deaths annually, with Italy and Greece having the highest number of cases.[68] In low- and middle-income countries across Asia, Africa, and South America, multidrug-resistant infections have higher mortality and morbidity rates.[69,70] Projections suggest that annual global deaths

attributable to antibiotic-resistant infections may rise from 700,000 in 2014 to 10 million by 2050.[71]

4.6. Roles of antibiotics in HIV and STD management and their contribution to AMR

Antibiotics play a crucial role in managing opportunistic infections in people living with HIV and in treating bacterial STDs, such as gonorrhea, syphilis, and chlamydia. However, their frequent and often empirical use in these settings contributes significantly to the development of AMR. In HIV-positive individuals, recurrent infections and prophylactic antibiotic use can exert selective pressure, leading to the emergence of resistant strains. Similarly, the widespread and sometimes inappropriate use of antibiotics for STDs, particularly in the absence of antimicrobial susceptibility testing, has accelerated resistance in pathogens such as *N. gonorrhoeae* and *M. genitalium*. This growing AMR burden threatens the effectiveness of standard treatments, complicating care for co-infected patients and highlighting the urgent need for antibiotic stewardship programs.[72]

4.7. Mechanisms of drug resistance

AMR is the ability of microorganisms to survive in the presence of antimicrobial agents. The mechanisms of AMR are conserved across prokaryotes and eukaryotes and usually act by limiting the uptake of antimicrobial drugs, inactivating them, modifying their targets, or actively pumping them out of the cell.[73] For example, bacterial cells can resist antibiotic action by reducing the permeability of outer membranes, altering porin activity, or increasing multidrug efflux pumps.[74] Pathogens such as *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and fungal species such as *Candida lusitaniae* exemplify organisms that deploy such mechanisms.[75] Among them, the so-called ESKAPE pathogens (*Enterococcus faecium, S. aureus*, *Klebsiella pneumoniae*, *A. baumannii, P. aeruginosa*, and *Enterobacter* spp.) are responsible for the majority of hospital-acquired infections and exhibit high levels of AMR.[76]

In both prokaryotes and eukaryotes, the presence of antibiotic resistance genes (ARGs) is the main cause of bacterial resistance. These genes are often carried on plasmids, integrons, and transposons, which spread through horizontal gene transfer among strains of the same species and across different species. Even after resistant bacteria die, extracellular DNA containing ARGs stays active in the environment for a long duration, contributing to the environmental pool of resistance determinants.[77,78] In some cases, multiple resistance mechanisms coexist within a single bacterial cell, conferring high-level resistance to diverse classes of antibiotic compounds.[79] Moreover, some bacteria possess intrinsic resistance due to the lack of specific metabolic pathways, the lack of an antibiotic target, or the absence of enzymes needed for the activation of drugs.[80] For example, genes coding for a novel tripartite resistance-nodulation-cell division pump were found to be carried on a plasmid together with genes encoding for an antibiotic-targeting enzyme.[81] Furthermore, overexpression of efflux pumps is frequently observed in clinical isolates of *P. aeruginosa* and *S. aureus* from systemic infections, highlighting the importance of multidrug-resistance efflux pumps as the major resistance mechanism of AMR.[82] All such mechanistic approaches can now be identified using recently developed diagnostic technologies, which enable earlier detection of AMR.[48]

Beyond intrinsic resistance, microorganisms can also exhibit adaptive resistance, a transient, reversible phenotype triggered by environmental cues such as stress, pH changes, nutrient limitation, or exposure to subinhibitory levels of antibiotics. Adaptive resistance is often mediated through epigenetic regulation, including DNA methylation by DNA adenine methyltransferase, which drives heterogeneity in gene expression within bacterial populations. This allows subpopulations to survive antibiotic exposure and revert once the stressor is removed.[83] Mutations in drug targets also play a critical role—for example, mutations in DNA gyrase (*gyrA*), topoisomerase (*parC*) result in resistance to fluoroquinolones, the beta subunit of RNA polymerase (*rpoB*) mutations for rifampin resistance, 16s ribosomal RNA (rRNA) mutations for tetracycline and aminoglycosides resistance, and 23s rRNA mutations for linezolid resistance. Other antibiotic resistance mechanisms include the modification of target molecules. For example, in Gram-negative bacteria such as *A. baumannii*, resistance to polymyxins—cyclic antimicrobial peptides with long, hydrophobic tails that bind to bacterial lipopolysaccharides (LPSs) to disrupt cell membranes—is linked to modifications of LPS, where the addition of phosphoethanolamine to lipid A reduces colistin binding by decreasing net negative charge.

Bacteria such as *N. gonorrhoeae*, *C. trachomatis*, and *Treponema pallidum* have shown increasing resistance to first-line antibiotics, posing significant challenges to treatment protocols. *N. gonorrhoeae*, in particular, has developed resistance to multiple drug classes, including penicillins, tetracyclines, fluoroquinolones, and even extended-spectrum cephalosporins. The underlying mechanisms include mutations in penicillin-binding proteins, ribosomal targets, horizontal gene transfer, action of efflux pumps, and reduced permeability to antibiotics. The growing prevalence of multidrug-resistant strains underscores the importance of surveillance and timely

diagnostics to monitor and control the spread of AMR in STD pathogens. Without sustained monitoring and stewardship, AMR not only threatens individual health but also amplifies the transmission risks, including the spread of HIV through co-infection.

5. Behavioral and biological pathways linking STDs and increased HIV transmissibility

STDs significantly amplify the risk of HIV transmission through both behavioral and biological mechanisms**.** Behaviorally, individuals with STDs often engage in high-risk sexual practices, such as inconsistent condom use, multiple sexual partners, or transactional sex, all of which increase exposure opportunities to HIV. Biologically, STDs like gonorrhea, chlamydia, syphilis, and HSV-2 cause mucosal inflammation, ulceration, and disruption of epithelial barriers, facilitating HIV entry. In addition, these infections recruit activated $CD4^+$ T cells and dendritic cells—primary targets for HIV—to the genital mucosa, further enhancing susceptibility. In HIV-positive individuals, concurrent STDs can increase genital HIV shedding, raising the risk of transmission. Together, these interlinked pathways act synergistically, fueling the dual epidemics of HIV and STDs and underscoring the need for integrated prevention strategies.[84]

6. Novel ways to tackle AMR

AMR is one of the most pressing global health threats, and no permanent solution has yet been achieved. Despite intensive scientific efforts, progress has been slow, with current strategies focusing primarily on improving diagnostic tools, optimizing antibiotic-prescribing practices, and strengthening infection-prevention strategies. Although several new antimicrobial agents are in clinical development, most of them belong to already existing antibiotic classes and do not represent true novel drug classes. Moreover, even newly developed compounds face the risk of rapid obsolescence due to microorganisms' remarkable capacity for adaptation. Therefore, novel treatment strategies are urgently needed to address established and emerging forms of AMR.

The development pipeline for new antimicrobial compounds continues to decline for complex reasons, despite increasing AMR rates and growing awareness of antibiotic persistence. A major factor is the pharmaceutical industry's focus on more profitable treatments for non-infectious chronic diseases, such as cancers, metabolic disorders, and cardiovascular conditions. Nevertheless, novel strategies and substances are being planned and discovered in basic research and preclinical studies, offering potential treatment options for AMR in the near future.

One promising example is the discovery of chimera peptidomimetic antibiotics, which have shown broad-spectrum antibacterial properties against Gram-negative ESKAPE pathogens and other Gram-negative bacteria.[85] Luther *et al*.[85] showed that the bactericidal activity of these chimeric antibiotics involves binding to both LPSs and BamA, the primary component of the β-barrel folding complex required for folding and inserting β-barrel proteins into the outer membrane. This unique targeting strategy allows activity against Gram-negative bacteria while sparing eukaryotic cell membranes. However, the exact mechanism remains an open question. Among these antibacterial candidates, POL7306 has advanced to preclinical trials, with current research focusing on optimizing peptide designs and broadening therapeutic margins before clinical testing.[86]

In addition, the widespread and often unregulated use of antimicrobials in agriculture has emerged as a major driver of AMR. In poultry, swine, and other livestock production, antibiotics such as tetracyclines, macrolides, and fluoroquinolones are commonly administered not only for therapeutic purposes but also for disease prevention and growth promotion. This prolonged and sub-therapeutic exposure creates selective pressure, fostering the emergence and proliferation of resistant bacterial strains, including *Escherichia coli*, *Salmonella* spp., and *Campylobacter* spp. These pathogens can be transmitted to humans through multiple routes, including the consumption of contaminated food, direct contact with animals, and environmental dissemination through soil, water, and air contaminated with animal waste. Importantly, resistance genes harbored by these bacteria can also be transferred horizontally to human-associated pathogens, amplifying the risk of difficult-to-treat infections. Thus, the agricultural use of antimicrobials serves as a critical link in the broader ecology of resistance, necessitating urgent implementation of stewardship programs, regulatory oversight, and global One Health approaches to mitigate AMR at the human-animal-environment interface.[87,88]

A drug-drug interaction occurs when one drug affects the activity of another drug when administered together. Such interactions can either enhance or reduce the effectiveness or toxicity of one or both drugs. Drug-drug interactions occur through several mechanisms, including pharmacokinetic interactions, pharmacodynamic interactions, combined toxicity, and additive or synergistic effects. In pharmacokinetic interactions, the absorption, distribution, metabolism, or excretion of one or both drugs is involved. In pharmacodynamic interactions, two

drugs with similar or opposing effects interact at the same receptor site or related physiological pathways. Combined toxicity arises when co-administered drugs produce similar toxic effects, thereby increasing the risk of adverse reactions. Additive or synergistic effects occur when two drugs with similar pharmacological actions produce a combined effect greater than the sum of their individual effects.

Drug-drug interactions are a major concern in pharmacotherapy, where the pharmacological effect of a victim drug is either exaggerated or suppressed by the perpetrator drug. Combinations of drugs are clinically used to treat or cure diseases. It has been proven that, in some cases, the combination of two drugs provides superior outcomes compared to monotherapy.[89] For example, anti-tuberculosis drug combinations enhance treatment efficacy and reduce the risk of resistance in *Mycobacterium tuberculosis* infections.[90] Beyond drug-drug interactions, interactions can also occur between drugs and metabolites, endogenous substances, food, or diagnostic agents.[91]

Although drug-drug interactions can sometimes enhance drug efficacy, they may also reduce therapeutic efficacy by altering the nature, intensity, duration, side effects, or toxicity of the drugs involved.[92] In some cases, such interactions lead to unexpected adverse effects, which are considered harmful events.[93] Adverse drug reactions may result from a single drug or a combination therapy, but the risk is particularly elevated when multiple drugs are administered simultaneously.[94] This complexity increases the likelihood of clinically relevant drug–drug interactions, contributing to higher healthcare costs, increased hospitalization rates, and longer hospitalization duration.[95]

7. Urgent public health strategies to break the cycle of co-infection and AMR

Various strategies can be considered from a public health point of view to implement integrated STD and HIV service delivery, particularly in high-risk populations. Delivering integrated screening, treatment, and prevention services—including PrEP and ART—through a single platform enhances outcomes while reducing redundancy in services.[96] The following strategies need to be considered:

- Integrated STI/HIV services to ensure routine testing, treatment, and follow-up
- Antimicrobial stewardship programs in HIV clinics and STD services to curb empirical and syndromic overuse of antibiotics
- Expanded PrEP coverage, especially among high-risk groups with recurrent STDs
- Use of point-of-care molecular diagnostics to reduce inappropriate antibiotic use
- Behavioral interventions, including condom promotion and chemsex harm reduction
- Real-time genomic surveillance to detect resistant STD strains and guide treatment policies

However, several barriers hinder the effective implementation of these strategies, particularly in resource-limited settings:[97]

- Vertical programming and separate funding streams
- Shortages in trained personnel
- Stigma and discrimination in care settings
- Fragmented surveillance systems.

8. Research gaps and future directions

HIV, STDs, and AMR are interconnected through biological, clinical, and public health mechanisms. STDs increase the risk of HIV acquisition and transmission by causing mucosal disruption, local inflammation, and immune activation that enhances the availability of HIV target cells. In turn, HIV-induced immunosuppression complicates the management of STDs, often leading to persistent or recurrent infections. The frequent and often syndromic use of antibiotics for bacterial STDs—particularly among people living with HIV—contributes to the emergence and spread of resistant strains, such as *N. gonorrhoeae*, *M. genitalium*, and *T. pallidum*. This exacerbates treatment challenges and limits therapeutic options.

Moving forward, the development of combination treatment strategies that address both HIV and co-occurring STDs while minimizing AMR risk is essential. Integrated care models, antimicrobial stewardship, and the development of prophylactic vaccines against STDs, such as gonorrhea, chlamydia, and syphilis, could reduce HIV transmission by addressing key cofactors. Strengthening global surveillance systems, expanding access to healthcare for vulnerable populations, and implementing targeted public health interventions—including condom promotion, regular screening, PrEP, and comprehensive sexual health education—are critical to disrupting the cycle of HIV, STDs, and AMR.

9. Conclusion

The interplay between HIV, STDs, and AMR in the cART and antibiotic era presents complex challenges that require comprehensive, multifaceted interventions. Effective management involves the integration of HIV and STD programs to ensure coordinated screening, treatment, and prevention efforts, particularly among high-risk populations. Prioritizing epidemiological surveillance for both established and emerging pathogens, such as *M. genitalium* and drug-resistant *N. gonorrhoeae*, is essential

to inform evidence-based responses. Concurrently, the rational use of antimicrobials both in clinical and agricultural settings must be enforced through both stewardship programs and regulatory oversight to mitigate resistance development. Expanding access to preventive tools, such as PrEP, maternal ART, and vaccination (HPV, HBV), remains central to reducing transmission, especially in low-income and vulnerable communities. Furthermore, culturally sensitive health education, youth engagement, and social determinants such as early marriage, stigma, and inadequate sex education are vital for long-term behavioral change. To ensure sustained progress, investments in research and development are urgently needed to deliver novel therapeutics, vaccines, point-of-care diagnostics, and resistance-guided therapies. Ultimately, tackling these interlinked threats requires a unified strategy involving public health authorities, clinicians, researchers, policymakers, and communities working collaboratively to reduce the global burden of co-infections and drug resistance.

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