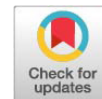


Review Article



Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) Infection: Challenges and Global Health Strategies

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Abstract | Co-infection with Hepatitis B virus (HBV), Human Immunodeficiency Virus (HIV), and Tuberculosis (TB) represents a significant intersection of three global epidemics, disproportionately affecting populations in low- and middle-income nations. These infections interact synergistically, accelerating disease progression, complicating clinical management, and increasing mortality rates. This review examines the global epidemiology, pathogenesis, and clinical ramifications of co-infections involving HBV, HIV, and TB, highlighting the distinct challenges presented by these overlapping epidemics. The World Health Organization (WHO) identifies tuberculosis (TB) as a primary cause of mortality among individuals with HIV and estimates a hepatitis B virus (HBV) prevalence of up to 7.8% among TB patients in high-burden areas. Pathogen-specific mechanisms, such as immune system interactions, drug-drug interactions, and immune reconstitution inflammatory syndrome (IRIS), complicate treatment further. Contemporary strategies to tackle these challenges encompass integrated screening, customized treatment protocols, and public health initiatives such as vaccination and enhanced healthcare systems. This review also emphasizes the necessity of multidisciplinary strategies and region-specific interventions to alleviate the effects of these co-infections, enhance patient outcomes, and attain global health objectives.

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Introduction

Co-infection, involving the concurrent presence of multiple pathogens such as bacteria and viruses in a single host, is a significant public health issue. This concern stems from the fact that most treatments are

designed to target a single infectious agent. As a result, the coexistence of multiple pathogens complicates treatment strategies and may lead to more severe health outcomes, particularly among individuals with weakened immune systems (Kasavandi *et al.*, 2024). Human Immunodeficiency Virus (HIV), tuberculosis

(TB) and chronic viral hepatitis (hepatitis B and C) rank among the world's most widespread infectious diseases, with particularly high prevalence in low- and middle-income countries (Mo et al., 2014). In sub-Saharan Africa, HIV, HBV, and tuberculosis (TB) overlap as a combined epidemic (Msomi et al., 2020).

A meta-analysis published in 2023 reported a global prevalence of Hepatitis B infection of 5.8% among patients with tuberculosis and 3.8% among TB patients living with HIV. The pooled prevalence of HBsAg positivity by WHO region was highest in the African region at 7.8%, followed by the Western Pacific at 7.5%, Europe at 6.4%, South-East Asia at 4.6%, and the Eastern Mediterranean at 4.6%, with the lowest prevalence in the Americas at 4.2% (Olaru et al., 2023).

Studies indicate that chronic liver disease heightens the risk of hepatotoxicity during anti-TB treatment. Patients co-infected with HIV and viral hepatitis face an even greater risk, with evidence showing a fourteen-fold increase in the likelihood of developing anti-TB hepatotoxicity. The hepatic toxicity of anti-TB and anti-HIV drugs can significantly increase the risk of liver failure in patients with pre-existing liver damage due to hepatitis B infection (Gebrehiwet et al., 2023).

Contemporary standalone healthcare approaches frequently neglect the intricacies of co-infections, underscoring the necessity for integrated strategies. This review seeks to synthesize evidence regarding the epidemiology, pathogenesis, and clinical challenges of these co-infections, while promoting multidisciplinary and region-specific interventions. Tackling these issues is essential for attaining global health objectives and enhancing patient outcomes.

Epidemiology of co-infections

According to the World Health Organization (WHO), tuberculosis (TB) has likely regained its position as the world's leading cause of death from a single infectious agent, following three years during which it was overtaken by coronavirus disease (COVID-19). TB remains the leading killer of people with HIV and a significant contributor to deaths associated with antimicrobial resistance. In 2023, an estimated 10.8 million people fell ill with TB worldwide, resulting in approximately 1.25 million deaths, including 161,000 among people living with HIV. HIV and TB form a

lethal combination, each accelerating the progression of the other. The WHO African Region bears the highest burden of HIV-associated TB, and in 2023, only 56% of TB patients living with HIV were on antiretroviral therapy (ART).

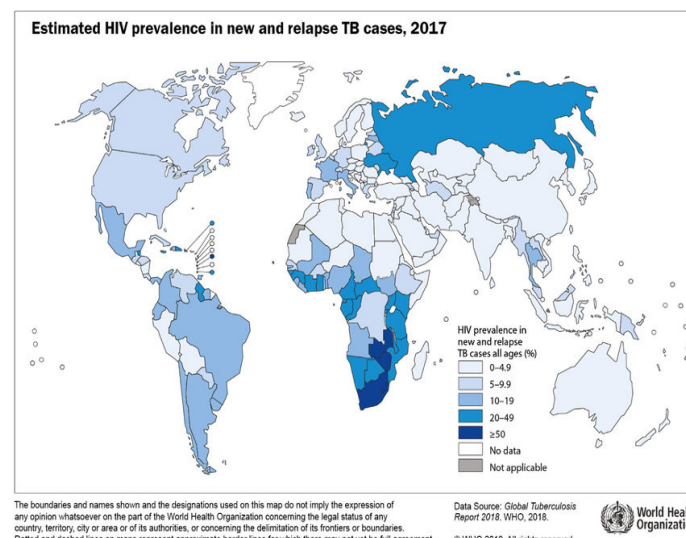


Figure 1: Prevalence of HIV in New and Relapse TB Cases in 2018 (WHO, 2018).

Over 80% of TB cases and deaths occur in low- and middle-income countries, but the disease is present in every part of the world. In 2023, the WHO South-East Asia Region accounted for the highest proportion of new TB cases (45%), followed by the African Region (24%) and the Western Pacific Region (17%). Around 87% of new TB cases occurred in the 30 high TB burden countries, with more than two-thirds of the global total found in Bangladesh, China, the Democratic Republic of the Congo, India, Indonesia, Nigeria, Pakistan, and the Philippines (WHO, 2024). As shown in Figure 1.

The Hepatitis B virus (HBV) infection constitutes a significant public health issue and a leading cause of chronic liver disease, resulting in approximately 820,000 fatalities in 2019, primarily attributable to cirrhosis and liver cancer. In 2019, the WHO estimated that 296 million individuals were chronically infected with hepatitis B, with a significantly elevated burden in low- and middle-income nations. The WHO African Region, along with the South-East Asia Region and the Western Pacific Region, constitutes 88% of the global burden (WHO, 2024). Co-infection with tuberculosis (TB) and hepatitis B virus (HBV) is relatively common, with prevalence rates ranging from 0.5% to 44%. This co-occurrence is associated with poorer treatment responses and worse patient

outcomes (Khan *et al.*, 2021).

In 2021, approximately 38 million individuals globally were living with human immunodeficiency virus (HIV), with two-thirds of these cases concentrated in sub-Saharan Africa (SSA). The region contributes substantially to the global burden, representing 18% of hepatitis B virus (HBV) cases and 29% of tuberculosis (TB) cases. These infections often overlap due to common transmission pathways, including unprotected sexual intercourse, needle sharing, and perinatal transmission. The concurrent epidemics of HIV, HBV, and TB in Sub-Saharan Africa lead to prevalent co-infections, significantly contributing to morbidity and mortality in the area (Yendewa *et al.*, 2022).

Global HBV and HIV prevalence

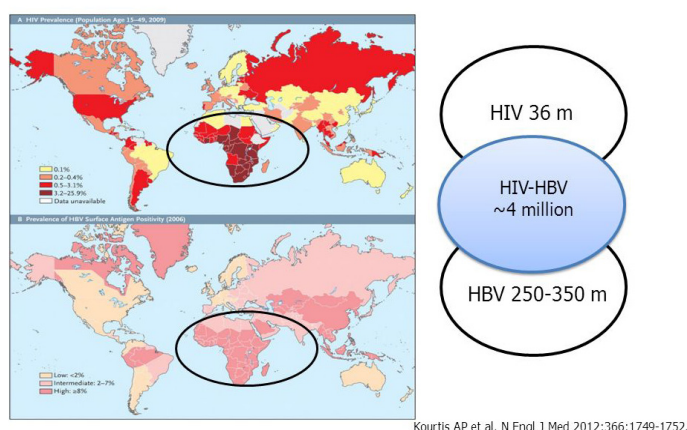


Figure 2: Global Prevalence of HBV and HIV Co-infection (Kourtis *et al.*, 2012)

Young adults, especially males, are at a higher risk of contracting infections like Hepatitis B Virus (HBV) due to being exposed to high-risk behaviors, including unprotected sexual intercourse, substance abuse (injection drug use), and other activities that promote the transmission of blood-borne pathogens. In neonates, perinatal transmission is a prominent method of HBV acquisition, especially in areas with elevated maternal infection rates and limited access to preventive measures like birth vaccination (Connors, 2023).

Unprotected sexual practices significantly increase the risk of co-infection with HIV and HBV, as both viruses utilize analogous transmission pathways, including sexual contact, blood exposure, and other bodily fluids. This highlights the significance of focused health education and behavioral interventions to mitigate these risks (NIH, 2021). In addition, socio-economic

factors including poverty, overcrowded living conditions, and restricted access to healthcare services substantially enhance susceptibility to infectious diseases. These conditions frequently restrict access to preventive healthcare, prompt diagnoses, and treatment, thereby intensifying the burden of diseases such as HBV and HIV in impacted populations (Wu *et al.*, 2023).

A comprehensive meta-analysis conducted by Olaru *et al.* (2023) provided valuable insights into the global burden of Hepatitis B infection among tuberculosis (TB) patients, including those co-infected with HIV. The study reported an overall global prevalence of Hepatitis B infection at 5.8% among TB patients and 3.8% among TB patients living with HIV, underscoring the significant overlap between these infections and their public health implications. As shown in Figure 2.

When the prevalence of HBsAg positivity, a key marker of active Hepatitis B infection was analyzed by World Health Organization (WHO) regions, the African region had the highest pooled prevalence at 7.8%. This was closely followed by the Western Pacific region at 7.5%, highlighting the substantial burden of co-infection in these high-endemic areas. The European region also recorded a notable prevalence of 6.4%, reflecting ongoing challenges in controlling Hepatitis B in this population. Meanwhile, the South-East Asia and Eastern Mediterranean regions both exhibited a pooled prevalence of 4.6%, emphasizing the need for targeted interventions in these regions where TB is already highly endemic. The lowest prevalence of HBsAg positivity was observed in the Americas, at 4.2%, suggesting relatively lower co-infection rates but still significant enough to warrant public health attention.

This regional variation in HBsAg prevalence reflects differences in epidemiological patterns, healthcare access, and public health initiatives, pointing to the necessity for region-specific strategies in managing Hepatitis B and TB co-infection, especially among populations already vulnerable to HIV.

Pathophysiology of HBV, HIV, TB co-infection

Virology of hepatitis B virus: The Hepatitis B virus (HBV) is a hepatotropic virus capable of inducing severe hepatic conditions, including acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma

(HCC). The virus is classified within the hepadnaviridae family, exhibiting a limited host range by infecting solely humans and select primate species (Chuang *et al.*, 2022). The infectious HBV virion, known as the Dane particle, possesses a spherical, double-layered structure measuring 42 nm in diameter. It comprises a lipid envelope containing HBsAg that encases an inner nucleocapsid formed by hepatitis B core antigen (HBcAg) associated with virally encoded polymerase and the viral DNA genome. The HBV genome is a partially double-stranded circular DNA comprising approximately 3.2 kilobase (kb) pairs. The infectious HBV virion, known as the Dane particle, possesses a spherical, double-layered structure measuring 42 nm in diameter. It comprises a lipid envelope containing hepatitis B surface antigen (HBsAg) that encases an inner nucleocapsid formed by hepatitis B core antigen (HBcAg) associated with virally encoded polymerase and the viral DNA genome. The HBV genome is a partially double-stranded circular DNA comprising approximately 3.2 kilobase (kb) pairs. The viral polymerase is covalently linked to the 5' terminus of the minus strand (Liang, 2009).

The viral genome has four overlapping ORFs: S, C, P, and X. The S ORF encodes the viral surface envelope proteins HBsAg and is structurally and functionally divided into pre-S1, pre-S2, and S regions. Core or C gene has precore and core regions. Depending on whether translation begins from the core or precore regions, the C ORF encodes HBcAg or HBeAg. A signal peptide from the precore ORF directs the translation product to the endoplasmic reticulum, where it is processed into HBeAg (Milich and Jake, 2003). The P ORF encodes a large protein (about 800 amino acids) called polymerase (pol), which has three functional domains: The terminal protein domain, which encapsidates and starts minus-strand synthesis; the reverse transcriptase (RT) domain, which synthesizes the genome; and the ribonuclease H domain, which degrades pregenomic RNA and aids replication. A 16.5-kd protein (HBxAg) from the HBV X ORF performs signal transduction, transcriptional activation, DNA repair, and protein degradation inhibition (Bouchard and Schneider, 2004).

Pathogenesis of HBV

HBV enters hepatocytes via its surface proteins, the filamentous HBsAg subviral protein binding specifically to hepatocellular membranes and the

spherical particles binding at a smaller extent (Gripon *et al.*, 2005). Heparan sulphate proteoglycans on the cell surface cause the virus to attach to hepatocytes by binding to the S protein's antigenic loop with low affinity, facilitating entry (Schulze *et al.*, 2007). The sodium taurocholate cotransporting polypeptide (NTCP) functions as the receptor for HBV, being exclusively expressed on hepatocytes and essential for the absorption of bile salts into these cells (Stieger, 2011). Its silencing inhibits HBV infection, whereas its expression in HepG2 cells facilitates HBV infection (Iwamoto *et al.*, 2014).

Upon entry into hepatocytes through NTCP, the virus undergoes uncoating, and its relaxed circular DNA (rcDNA) is translocated to the nucleus. In that context, rcDNA is transformed into covalently closed circular DNA (cccDNA), which functions as a transcriptional template for viral replication (Revill *et al.*, 2019). The cccDNA remains a stable episome, presenting a significant barrier to total viral eradication. The transcription of cccDNA produces pregenomic RNA (pgRNA) and subgenomic RNAs, which are subsequently translated into viral proteins. The pgRNA is reverse-transcribed by the viral polymerase into rcDNA within the nucleocapsid, which can either be recycled to the nucleus or secreted as mature virions (Seeger and Mason, 2015).

The majority of liver damage that occurs as a result of HBV infection is immune-mediated rather than coming about as a direct cytopathic effect of the virus. Apoptosis, necrosis, and subsequent regeneration of hepatocytes are the outcomes of the inflammatory response that occurs in response to infected hepatocytes. Fibrosis, which is characterized by an excessive accumulation of extracellular matrix proteins, is induced by chronic HBV infection, which leads to persistent inflammation throughout the treatment process. Hepatocellular carcinoma (HCC) and cirrhosis are two potential outcomes that can develop from fibrosis over time (Ringehan *et al.*, 2017).

HBV is also involved in the process of oncogenesis. When HBV DNA is incorporated into the genome of the host, it has the potential to prevent oncogene or tumor suppressor pathways from functioning properly. Furthermore, the viral regulatory protein known as HBx has the ability to influence cellular signaling pathways, which in turn increases cell

survival and proliferation, which in turn facilitates the development of tumors (Block *et al.*, 2007).

Pathogenesis of human immunodeficiency virus 1

The human immunodeficiency virus (HIV) is an enveloped virus characterized by a single-stranded RNA genome. The viral envelope comprises glycoproteins gp120 and gp41, which enable host cell attachment and entry. The viral core comprises two RNA molecules and three enzymes essential for viral replication: Reverse transcriptase, integrase, and protease (Piai *et al.*, 2020). The infection starts when the trimeric viral envelope glycoprotein (Env) gp120 attaches to the CD4 receptor on target cells, subsequently interacting with co-receptors CCR5 or CXCR4. These interactions enable gp41-mediated fusion of the viral envelope with the host cell membrane (Blumenthal *et al.*, 2012). Other cells expressing CD4 and chemokine receptors are also infected, including inactive CD4 T cells, monocytes, macrophages, and dendritic cells.

The glycans on the surface of HIV Env have recently been identified to be forming a 'glycan shield' that conceals conserved protein regions of HIV Env from the adaptive immune system, thereby evading neutralizing antibodies and complicating vaccine development (Doores, 2015).

Following viral binding and entry, viral RNA undergoes retro-transcription, and the provirus integrates into the cellular genome; subsequently, viral proteins are synthesized, the virus is assembled, and budding takes place (Février *et al.*, 2011).

The transmission of HIV through mucosal membranes is typically initiated by a single founder virus (Keele *et al.*, 2008). Following transmission, HIV replication quickly increases, followed by a notable activation of inflammatory cytokines and chemokines (Stacey *et al.*, 2009).

Following HIV infection, the viral load initially rises sharply before stabilizing at a level referred to as the viral setpoint. This setpoint is primarily regulated by the host's innate and adaptive immune responses. CD8⁺ cytotoxic T lymphocytes are essential in regulating viral replication by identifying and destroying productively infected cells. However, the robust adaptive immune response exerts selective pressure on the virus, leading to the emergence of mutations within key epitopes. These mutations

facilitate immune escape, enabling the virus to evade detection and continue replicating despite immune-mediated control (Goonetilleke *et al.*, 2009).

Pathogenesis of tuberculosis

Identified by Robert Koch, *Mycobacterium tuberculosis* (MTB) is the causative agent of tuberculosis (Kaufmann and Schaible, 2005). Tuberculosis is a highly contagious airborne illness and a leading cause of mortality globally. The disease primarily impacts the lungs, termed pulmonary TB, but it can also disseminate to other regions of the body, referred to as extrapulmonary TB (WHO, 2022).

Tuberculosis is transmitted through aerosol droplets containing *Mycobacterium tuberculosis*, expelled by individuals with active TB when they cough, sneeze, or speak. It begins infection by penetrating both alveolar macrophages and epithelial cells, but it predominantly multiplies within alveolar macrophages (Cohen *et al.*, 2018). Once inside the macrophages, MTB-containing phagosomes coat themselves with large amounts of the antacid 1-TbAd and avoid fusing with proton-ATPase-containing lysosomes. This effectively avoids the phagosome becoming too acidic and shields MTB from being broken down by the macrophages (Buter *et al.*, 2019).

Shortly after initial infection, MTB utilizes the ESAT-6 secretion system 1 (ESX-1) to release virulence factors ESAT-6 and CFP-10, facilitating its escape from the phagosome into the macrophage cytosol, where it can replicate more rapidly (Wel *et al.*, 2007). When macrophages are unable to inhibit or eliminate the bacilli and bacterial replication persists, lymphocytes are subsequently recruited to the site of infection, initiating a cell-mediated immune response, wherein an accumulation of immune cells arrives to neutralize the bacteria and restrict further replication (Luies and du Preez, 2020). The host remains asymptomatic, and the bacteria may be entirely eradicated or enter a latent state within the granuloma. In the context of compromised immunity, the disease rapidly advances to active tuberculosis with clinical manifestations (Schluger, 2005).

Immune system interactions during co-infection

HIV significantly increases the likelihood of contracting tuberculosis as it weakens the immune system that is mediated by cells. A large amount of CD4⁺ T cells becomes infected by the virus, and an even larger proportion of these cells experiences

rapid apoptosis, leading to immune dysregulation and immunodeficiency (Gasper-Smith *et al.*, 2008). CD4⁺ T cells in the lymphoid tissues and peripheral blood, which are essential for the maintenance of granulomas, are depleted on account of HIV, which also leads to the disintegration of granulomas and the spread of *M. tuberculosis* (Kaushal *et al.*, 2023). HIV-induced immune activation also results in the production of a microenvironment that is conducive to the reactivation of *M. tuberculosis*. The HIV infection induces the death of macrophages, which in turn leads to the destruction of granulomas, resulting to a breach in the containment of *Mtb* and its subsequent reactivation (Sharan *et al.*, 2020).

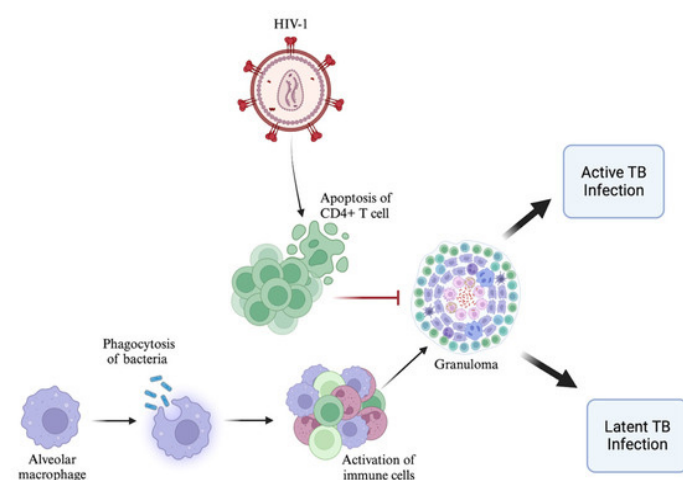


Figure 3: Impact of HIV-induced immunosuppression on host CD4⁺ T cell response to TB infection (Navasardyan *et al.*, 2024).

The mechanism by which HIV infection hastens the advancement of HBV-related liver disease encompasses the direct interaction between HIV and HBV in target cells, such as hepatocytes, the direct infection of various liver cells by HIV, increased microbial translocation, and increased levels of lipopolysaccharide (LPS) in both portal and systemic circulations, which activate Kupfer cells and hepatic stellate cells (HSC), as well as the depletion of HBV-specific T-cells (Singh *et al.*, 2017a). In the absence of viral replication during Antiretroviral therapy (ART), HIV may also induce liver inflammation and fibrosis through the binding of gp120 to CXCR4, which is expressed on hepatocytes and HSC (Hong *et al.*, 2012). In untreated HIV infection, the depletion of CD4⁺ T-cells in the gastrointestinal tract results in heightened microbial translocation and this leads to increased levels of circulating LPS (Brenchley *et al.*, 2006). Studies have shown consistently increased levels of circulating LPS in individuals co-infected with HIV and HBV compared to uninfected controls

and those solely infected with HBV (Crane *et al.*, 2014). Figure 3 in illustration.

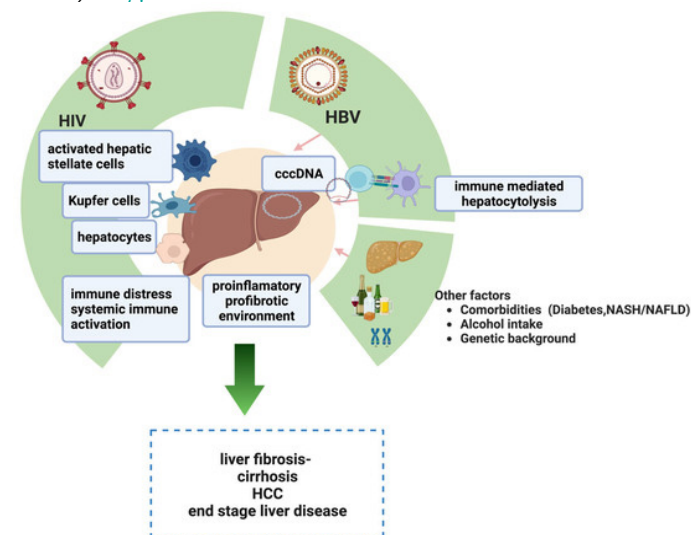


Figure 4: Mechanisms of liver injuries in HIV-HBV coinfected patients (Ruta *et al.*, 2023).

Subsequent to HBV infection, cells of the innate and adaptive immune response secrete inflammatory cytokines, including interleukin-10 (IL-10), which activate multiple pathways that inhibit viral replication (Chang and Lewin, 2007). In contrast, some of these cytokines with anti-inflammatory profile, such as IL-4, IL-13, and IL-10, inhibit T-cell-mediated immunity, which is essential for tackling *M. tuberculosis*. Consequently, individuals infected with HBV may face an elevated risk of tuberculosis reactivation or progression from latent tuberculosis infection (LTBI) to active disease (Harris *et al.*, 2007).

TB infection elicits a vigorous inflammatory response, marked by increased concentrations of pro-inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-12 (IL-12), and interleukin-23 (IL-23) (Sasindran and Torrelles, 2011). Concurrently, excessive production of TNF- α increasing the risk of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) (Jang *et al.*, 2021). Part as Figure 4 as illustrated.

Chronic HBV and TB infections induce persistent inflammatory responses, resulting in cytokine storms (Tisoncik *et al.*, 2012) that harm host tissues. This systemic inflammation diminishes host defenses, heightening vulnerability to co-infection and complicating disease management.

Clinical implications of co-infection

Accelerated disease progression: HIV aggravates

the progression of both HBV and TB infections. HIV-positive individuals co-infected with HBV face a greater threat of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) in comparison to those with HBV mono-infection. Despite effective suppression of both HIV and HBV replication, morbidity and mortality rates are considerably greater in individuals with HIV-HBV co-infection compared to those with HIV alone (Singh *et al.*, 2017). Similarly, HIV-induced progressive CD4 depletion contributes to a greater risk of TB, disseminated TB, and mortality. There is also a higher risk of additional opportunistic infections and mortality in HIV-TB co-infected patients than patients with mono-infection with the same CD4 count (Walker *et al.*, 2013).

Diagnostic challenges: Co-infection could complicate the diagnosis of each disease. For instance, patients with TB-HIV co-infection who possess a relatively intact immune system are more prone to exhibit typical pulmonary manifestations of tuberculosis, whereas those with severe immunosuppression are more likely to present with atypical and disseminated extrapulmonary forms, complicating the diagnostic process for tuberculosis. Sputum smear are more likely to test negative (Takhar *et al.*, 2018).

Treatment complexity: Drug-drug interactions are common and can lead to increased toxicity (Benesic *et al.*, 2019). Coinfections with HIV and/or HBV elevate the risk of hepatotoxicity induced by anti-TB medications, potentially requiring a withdrawal of treatment (Aires *et al.*, 2012). Hepatotoxicity is the main adverse effect associated with three first-line anti-tuberculosis agents: Isoniazid, rifampin, and pyrazinamide (Richards *et al.*, 2006). The risk of hepatotoxicity from anti-TB treatment has been reported to be 3–5 times greater in TB patients with a viral infection compared to those without (Sama *et al.*, 2017). Additionally, ART regimens incorporating tenofovir are effective against both HIV and HBV, yet necessitate careful monitoring for renal toxicity (Singh *et al.*, 2017).

Immune reconstitution disease (IRD) or immune reconstitution inflammatory syndrome (IRIS): Is described as the exacerbation of symptoms associated with an opportunistic infection or malignancy in individuals infected with HIV subsequent to the initiation of antiretroviral therapy (ART) (Shahani and Hamill, 2016). Initiation of ART in co-infected

patients can lead to IRIS, characterized by an exaggerated inflammatory response to TB or HBV antigens. This condition can lead to severe clinical manifestations, including hepatic decompensation in HBV patients and worsening of TB symptoms (Crane *et al.*, 2009; Lawn *et al.*, 2005).

Global health and management strategies

Integrated screening and diagnosis: Routine screening for HBV and TB in HIV-infected individuals is crucial. Similarly, HIV testing should be offered to all TB and HBV patients to identify co-infection early (Stabinski *et al.*, 2015; Mukhatayeva *et al.*, 2021). Integrating these screening and testing protocols into routine healthcare services promotes a holistic approach to managing these interlinked infections and aligns with global health goals to reduce the burden of HIV, HBV, and TB.

Tailored treatment protocols: Establishing standardized protocols for managing co-infected patients is crucial for optimizing treatment outcomes and improving care quality. Co-infections like HIV and TB, or HIV and HBV, pose distinct clinical challenges due to overlapping treatment regimens, potential drug-drug interactions, and exacerbated immunosuppression (Schutz *et al.*, 2010). Standardized protocols facilitate a coordinated treatment approach, reduce errors, and enhance the overall efficacy of care delivery.

For instance, the world health organization (WHO) guidelines underscore the essential necessity of commencing antiretroviral therapy (ART) for all HIV-positive tuberculosis patients, irrespective of their CD4 cell count. This recommendation is founded on substantial evidence indicating that the prompt commencement of ART markedly decreases mortality in co-infected individuals (WHO, 2016). Antiretroviral therapy (ART) not only facilitates immune recovery but also mitigates the progression of tuberculosis (TB), highlighting its life-saving efficacy.

Similarly, the WHO recommends the incorporation of HBV treatment into HIV care for patients co-infected with HBV, especially those exhibiting active HBV replication. In these instances, antiretroviral therapy (ART) regimens incorporating tenofovir disoproxil fumarate (TDF) alongside lamivudine (3TC) or emtricitabine (FTC) are preferred for their dual efficacy against both HIV and HBV (Boettiger

et al., 2016).

The world health organization recommends directly observed therapy (DOT) for the treatment of HIV-1/Tuberculosis, particularly in cases of intermittent dosing (Farmer *et al.*, 2001). Isoniazid preventive therapy (IPT) has been recommended for HIV-positive individuals and children under five years of age who have close contact with bacteriologically confirmed tuberculosis patients (Torpey *et al.*, 2020).

By aligning clinical practices with evidence-based guidelines, healthcare providers can guarantee that co-infected patients receive swift, efficient, and comprehensive care. This strategy not only diminishes morbidity and mortality but also aids in attaining global health objectives for the control of HIV, TB, and HBV.

Hepatitis B vaccination: HBV vaccination is crucial for HIV-positive individuals and those at elevated risk of TB to minimize the prevalence and consequences of HBV co-infection. Due to the heightened vulnerability to HBV in immunocompromised groups, such as those with HIV, vaccination serves as an effective preventive measure against chronic HBV infection and its related complications, including liver cirrhosis and hepatocellular carcinoma (Mohareb and Kim, 2021). Furthermore, individuals with TB, particularly those co-infected with HIV, face an increased risk of contracting hepatitis B virus due to overlapping transmission pathways (Zaongo *et al.*, 2022). Consequently, integrating HBV vaccination into standard HIV and TB care protocols can safeguard these at-risk populations. Timely vaccination not only averts HBV infection but also enhances overall immunity, facilitating improved management of both TB and HIV. In addition to vaccination, serological monitoring for HBV markers is crucial to evaluate vaccine efficacy and guarantee long-term protection, especially in immunocompromised individuals (European Association for the Study of the Liver, 2012).

Enhancing healthcare systems: Investing in healthcare infrastructure and professional training is critical for improving co-infection diagnosis and management in resource-constrained environments. This involves improving diagnostic capabilities by utilizing contemporary tools such as HIV viral load testing, CD4 count, and HIV DNA PCR, facilitating

early detection and effective treatment. Enhancing the availability of ART, anti-TB pharmaceuticals, and HBV treatments facilitates prompt interventions, while educating healthcare professionals provides them with the expertise to handle intricate co-infections and drug interactions. These investments facilitate the implementation of international health protocols for the management of HIV/TB and HIV/HBV co-infections. Enhancing the knowledge and capabilities of healthcare providers can decrease mortality and improve outcomes in co-infected patients. An enhanced healthcare system guarantees more equitable access to care, especially for at-risk populations. Ultimately, these investments advance global health objectives aimed at mitigating the prevalence of HIV, TB, and HBV globally.

Conclusions and Recommendations

Co-infection with hepatitis B virus (HBV), human immunodeficiency virus (HIV), and tuberculosis (TB) presents significant clinical and public health challenges due to their intricate synergistic interactions. These interactions not only expedite disease progression but also complicate diagnosis, treatment, and overall management. Co-infection is associated with heightened morbidity and mortality, as each pathogen influences the host's immune response and alters the progression of the other infections. Addressing these challenges necessitates prompt and precise diagnosis, cohesive and coordinated treatment approaches, and effective public health measures to avert transmission. Multidisciplinary strategies, encompassing the simultaneous administration of antiretroviral therapy, tuberculosis treatment, and antiviral therapy for hepatitis B virus, are crucial for effective management. Moreover, continuous investigation into the pathogenesis, epidemiology, and optimal treatment approaches for co-infection is vital. These efforts are essential to create targeted interventions, enhance clinical outcomes, and alleviate the impact of these concurrent epidemics on affected populations.

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Novelty Statement

This review article explores the challenges of co-infections between Hepatitis B Virus (HBV), Human Immunodeficiency Virus (HIV), and Tuberculosis (TB) and their impact on global health. It presents novel strategies for integrated management and innovative approaches to improve prevention and treatment efforts worldwide.

Author's Contribution

ADA and AO collected and analyzed the data. ASO and OO collected the data online and did further comparative analysis. OO designed the review and wrote the manuscript. OAO edited the manuscript and supervised activities. All authors read and approved the final version of the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

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