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Review Paper

Synergistic Epidemics: A Review of TB – HIV Coinfection

Aaditi Mane*, Snehalata Mali, Swati Wakchoure, Muskan Malik, Harshada Komarol

Shivajirao S. Jondhle College Of Pharmacy, Asangaon, Taluka- Shahapur, District-Thane, State-Maharashtra, Pincode-421601.

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ABSTRACT

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the world's most serious public health challenges and is the leading cause of death among people living with HIV. When someone is infected with HIV, their risk of developing TB rises significantly, even before their CD4+ T-cell counts begin to drop. The two infections feed off each other: HIV weakens the immune system, making it easier for TB to take hold, while TB further accelerates the progression of HIV For people living with both diseases, diagnosing and treating TB becomes far more difficult. However, bringing HIV and TB control program. In this review, we explore what is currently known about how HIV and TB interact, highlight promising new rapid diagnostic tests, discuss prevention strategies, and examine the development of new drugs and treatment regimens that offer hope for better management of this dangerous dual epidemic. Caring for people with HIV-associated TB is complex and requires a careful, combined approach. It includes giving effective TB treatment alongside antiretroviral therapy (ART), preventing and managing other HIV-related illnesses, watching for and controlling drug side effects, and addressing immune reconstitution inflammatory syndrome (IRIS), which can occur when the recovering immune system reacts strongly against hidden infections..

INTRODUCTION

After coronavirus disease 2019 (COVID-19), tuberculosis (TB) is the second most prevalent infectious disease-related cause of death [1]. An estimated 9.9 million new TB infections and 1.5 million TB-related deaths occurred globally in 2020 [1]. Unusual symptoms of active TB (tuberculosis) may result from HIV's 26-fold increase in risk, which also renders diagnosis and

***Corresponding Author:** Aaditi Mane
Address: *Shivajirao S. Jondhle College Of Pharmacy, Asangaon, Taluka- Shahapur, District-Thane, State-Maharashtra, Pincode-421601*
Email ✉: maneaditi996@gmail.com

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therapy more challenging and ultimately affects the prognosis of the disease [1]. The pathophysiology, diagnosis, treatment, and prevention of HIV-TB co-infection are the fundamental topics of this article [1].The two different infectious diseases which lead the biggest burden of disease in countries that have inadequate assets are tuberculosis (TB) and HIV/AIDS [2]. Mycobacterium tuberculosis and HIV constitute two diseases that reinforce one another in the individual host, leading to a breakdown of immunity [2]. Among people living with HIV in high TB-burden settings, the virus poses a dual threat — it leaves individuals more susceptible to acquiring TB for the first time or becoming reinfected, while also raising the likelihood that a dormant TB infection will progress to active disease, making HIV the foremost driver of TB disease in these populations [2]. Infection with M. tuberculosis also compromises the immune system's response to HIV, resulting in the development of AIDS [2]. Treatment of TB in patients who also have HIV is not just about giving one type of medicine. Both anti-TB drugs and ART need to be used together, while keeping an eye on possible side effects. As the immune system starts improving, problems like IRIS can occur and may need to be managed. At the same time, other HIV-related conditions should also be taken care of during treatment [2].Overview Since HIV is known to stimulate latent TB, all patients with latent or active TB should get an HIV screening. Latent Mycobacterium tuberculosis infection (LTBI) affects about 25% of the world's population [3]. Antiretroviral therapy (ART) and anti-TB medications can treat HIV and TB, however only a small percentage of patients worldwide actually obtain these therapies [3].

Epidemiology of TB-HIV Coinfection:- As reported in the WHO Global Tuberculosis Report (2022), around 7.5 million new TB cases were identified, and nearly 1.3 million people died due to the disease [4]. The spread of TB is influenced by several factors that can be controlled to some extent [4]. These include poor nutrition, HIV infection, alcohol use, smoking, and diabetes, all of which increase a person's chances of developing TB [4]. Even with widespread access to ART and TB preventive treatment, TB remains the major cause of death for people living with HIV (PLWH), despite the fact that the incidence of new TB diagnoses among this population has been declining for a number of years [4].About 1.25 million people died from tuberculosis (TB) in 2023, and 10.8 million people acquired the disease [5]. Not everyone is influenced by tuberculosis (TB); rates differ based on a person's age, sex, and place of residence, and are affected by a number of significant risk factors [5]. Around 70 percent of all HIV-related TB cases worldwide occur in the African continent, which continues to bear the largest burden [5] .More than half of these were in Southern and Eastern Africa alone [5]. One of the main causes of a decline in TB incidence and deaths among HIV-positive individuals has been the spread of antiretroviral therapy (ART) [5]. Because of its rapid spread, tuberculosis became a global public health emergency in 1993[5].In order to eliminate the HIV epidemic by 2030, the UNAIDS program has set high targets. According to their 95-95-95 goals, 95% of all HIV-positive individuals should be aware of their status [5]. Antiretroviral therapy (ART) should be administered continuously to 95% of individuals diagnosed, and 95% of ART patients should have viral suppression, or control over their virus [5]. Achieving these objectives would not only help in the prevention of HIV, but also in the prevention of tuberculosis (TB) and the Improvement of outcomes for individuals with both HIV and TB [5]. About 86% of individuals living with HIV aware of their status, 77% were taking ART, and 72% had achieved viral suppression in 2023,

indicating considerable but still insufficient progress toward these goals [5].However, many HIV-positive individuals still present to medical facilities with advanced stages of the disease, an issue that hasn't altered significantly in recent years despite the global growth of ART. This population continues to be the main target for focused interventions [5]. Another issue is drug resistance. Rifampicin, one of the main TB medications, was resistant to TB in about 3.2% of all TB cases in 2023 [5]. Among those who was treated with TB treatment, the issue was far more severe sixteen percent of them developed rifampicin-resistant TB [5].Worldwide, men exhibit about double the incidence of tuberculosis compared to women across all age demographics [5]. On the other hand, the pattern is reversed for PWH, with younger women being more affected by HIV-related TB than males [5]. In actuality, women account for a higher proportion of TB cases associated with HIV [5]. The burden of HIV-related TB is still higher for women than for males, despite the fact that the widespread use of antiretroviral therapy (ART) has significantly decreased the overall risk of TB among individuals with HIV. This is due to the higher rate of HIV infection in women [5].Although the fact that tuberculosis is treatable, there is mounting evidence that many TB survivors nevertheless have health issues and disabilities after getting treatment. About 122 million disability-adjusted life years (DALYs) were anticipated to have been caused by tuberculosis (TB) in 2019, including both the active disease and its aftereffects (the post-TB period) [5]. Surprisingly, long-term problems that arise following TB recovery identified nearly half of this burden (47%) [5]. Individuals who have both HIV and TB are considerably more disabled than those who are HIV-negative, especially when HIV is left untreated [5]. TB meningitis, which is more common in HIV-positive individuals, is one of the most severe and lethal types of TB [5].In certain places, asymptomatic individuals who have TB that has been bacteriologically confirmed that is, who carry the bacterium but possess no symptoms may also be involved in the continuous spread of the disease within populations [5]. Despite developments in TB management, serious HIV-related TB, such as disseminated TB and TB meningitis, continue to be major causes of premature death, highlighting the urgent need for more focused research and better treatment strategies [5].

Prevalence:-

The Global Tuberculosis Report 2024 states that in 2023, about 1.3 million children and adolescents were affected by TB [6]. This number makes up nearly 12% of the total new TB cases reported worldwide [6]. According to UNAIDS, 1.4 million children between the ages of 0 and 14 had HIV by 2024 [6]. A meta-analysis of 29 studies in China showed an average TB/HIV co-infection rate of 0.9% among individuals with TB, with an even lower prevalence of 0.22% recorded in Fujian Province [6]. To further understand this issue, we carried out a study in Chengdu, a large city in southwest China with a population of 21.4 million in 2023, including 13.28% youngsters aged 14 or younger [6].The rate of TB–HIV co-infection differs between countries. It was 16% in Benin in 2019 and 19.8% in Ethiopia in 2023 [7]. In Burkina Faso, the 2021 WHO report stated that there were 3.6 TB cases per 100,000 persons among individuals living with HIV [7]. The Public Health Clinical Center of Chengdu admitted 37,587 TB patients during 2018 and 2022 [7]. Out of all the patients studied, a small proportion, about 6.1% (2,301), were HIV-positive, while most of them, 93.9% (35,286), were HIV-negative [7].

When looking at the type of tuberculosis, it was observed that the majority of patients had pulmonary TB (PTB), accounting for 88.1% (33,119 cases) [7]. In comparison, fewer patients, around 11.9% (4,468), were diagnosed with extrapulmonary TB (EPTB) Focusing only on the EPTB group, most patients were HIV-negative (93.8%, 4,190), and a smaller number, 6.2% (278), were HIV-positive [7].From 2018 to 2022, a total of 37,587 patients with tuberculosis (TB) were admitted to the Public Health Clinical Center in Chengdu [8]. Out of these, most patients did not have HIV infection (93.9%, 35,286 cases), while a much smaller number were HIV-positive (6.1%, 2,301 cases) [8].When the type of TB was considered, pulmonary tuberculosis (PTB) was seen in the majority of patients, making up 88.1% (33,119 cases) [8]. On the other hand, extrapulmonary tuberculosis (EPTB) was less common, accounting for 11.9% (4,468 cases) [8]. Among the EPTB patients, most were HIV-negative (93.8%, 4,190 cases), and only a small proportion were HIV-positive (6.2%, 278 cases) [8].The proportion of tuberculosis (TB) patients who are also infected with HIV varies greatly, ranging from 0.34% to 32.8% [9]. In many countries, TB cases are continuing to rise, making it the leading infectious cause of death worldwide [9]. The number of individuals infected with Mycobacterium tuberculosis is also increasing, with HIV recognized as a major contributing factor [9].Although manystudies have examined TB and HIV separately, there is still limited and sometimes inconsistent information available on TB–HIV coinfection [9].

Methods:-

Reporting: -

In 2024, Alanazi and Hanif studied how often HIV and TB are found together by reviewing different research papers available online [9]. They followed PRISMA guidelines while arranging their work so that the process stayed clear and easy to understand. To collect the studies, they checked sources like PubMed and Google Scholar and selected papers written in English. During the search, they used terms such as HIV, AIDS, TB, and co-infection to find the needed information [9].

Criteria for Inclusion and Exclusion: -

In this analysis, studies were included if they provided information about how common HIV infection is among patients with tuberculosis (TB). The method used to diagnose the diseases was not strictly restricted, but most studies used blood tests for HIV and chest X-rays for TB [9].Some studies were not considered in this analysis. These included studies that only focused on patients who were already known to have both HIV and TB, as well as review papers. Articles with incomplete or unclear data were also left out. In addition, studies that were not freely available or were written in languages other than English were excluded [9].

Method of Data Extraction: -

A data extraction form was developed to obtain crucial information from the selected research. This form comprised details such as the first author, publication year, study design, sample size, prevalence, and risk variables. Each paper's data was separately extracted by two authors. After comparing their results, they talked about any discrepancies or ambiguous data until they came to a conclusion [9].HIV and tuberculosis together create a serious health problem because HIV gradually weakens the immune system. Due to this, the body is not able to control infections as effectively as it normally would. In many people, TB bacteria can stay in an inactive form for a long time without causing illness. But when a person is infected with HIV, this control is lost, and the

infection can easily become active [10].Because of this increased vulnerability, TB is one of the main causes of death among people living with HIV [10]. In individuals with normal immunity, the risk of latent TB becoming active is very low, around 0.1% per year [10]. However, in HIV-positive individuals, this risk increases a lot, reaching nearly 3–15% annually [10]. This difference clearly shows how much HIV affects the body's defense system [10].Looking at global figures gives a better idea of the scale of the problem. In 2020, about 37.7 million people were living with HIV, and around 1.5 million new infections were reported that year [10]. During the same period, nearly 9.9 million people developed TB, and a significant portion of these cases (about 13%) were also HIV-positive [10]. The combined effect of both diseases is quite severe, with HIV-TB coinfection contributing to approximately 215,000 deaths out of the total 1.5 million TB-related deaths [10].All of this highlights that HIV and TB are closely linked, and dealing with them separately is not enough. Effective control requires a combined approach, focusing on early diagnosis, proper treatment, and prevention strategies for both conditions [10].

Pathogenesis:-

HIV-TB co-infection has a complicated etiology. Early on, there are more circulating immune complexes, which might harm local tissue and increase the number of TB bacteria. In macrophages infected with both HIV and TB, excessive type I interferon (IFN) activity inhibits the protective effects of type II IFN, leading to poor management of TB infection and potential reactivation of the disease. Widespread immunological activation brought on by HIV-TB co-infection also takes place prior to CD4 T-cell destruction [11]. People who have diabetes mellitus (DM) are seen to get tuberculosis more easily. This mainly happens because long-term high blood sugar affects normal body functions. It can lead to problems like oxidative stress and formation of advanced glycation end products (AGEs), which slowly damage body cells [11].Due to these changes, the body is not able to fight infections properly. The response to TB bacteria becomes weaker, so the infection can develop more easily. Because of this, people with diabetes have a greater chance of getting active TB [11].HIV–TB coinfection makes it difficult for the body to properly control the TB bacteria, which is why the disease tends to progress faster in these patients. One important reason is that HIV weakens the immune cells that normally help in containing the infection. Because of this, the bacteria are not effectively trapped and can spread more easily [12].Another factor is the disturbance in immune signaling. The body is not able to produce a strong and coordinated response, so even if some defense is present, it is not enough to stop the infection. As a result, TB becomes more severe and harder to manage in people with HIV [12].In general, this type of immune dysfunction is more difficult to reverse compared to people without HIV, since the underlying immune damage continues over time [12].

Interaction between TB and HIV: -

In people with HIV, tuberculosis usually develops faster and becomes more serious. This is mainly because HIV weakens the immune system, so the body cannot control the TB infection properly. Normally, when Mycobacterium tuberculosis enters the lungs through air droplets, it is taken up by macrophages [1]. These cells start the body's defense, and other immune cells gather at the site to form granulomas, which help in containing the bacteria [1]. Inside these structures, the bacteria can remain inactive for a long time without causing major symptoms [1].

But in HIV-positive individuals, this control is not maintained well. As the immune system becomes weaker, the granulomas start breaking down. When infected cells die in an uncontrolled way, the bacteria are released and begin to multiply again [1].As the infection continues, it damages the lung tissue and can lead to cavity formation. These cavities make it easier for the bacteria to spread through the airways. Because this process happens more quickly in people with HIV, TB becomes more severe and harder to manage in them [1].Crucially, macrophage phagocytosis of MTB is crucial to regulating bacterial growth. HIV infection, however, impairs these defenses in several significant ways: limiting the efficient removal of the germs by inhibiting macrophage apoptosis. Depleting CD4+ T cells, which are crucial in immune response control [1]. Decreasing the capacity of the body to contain MTB by affecting with the structure and function of granulomas. The chances of extra pulmonary spread and active pulmonary tuberculosis is substantially raised by these effects. However, there is still discussion and research regarding the specific function that HIV infection serves in the dissemination of TB [1].

Altered Response of CD4+ T Cells in HIV-TB Coinfection: -

HIV-infected individuals are much more prone to acquiring Mycobacterium TB (Mtb) due to immune system modifications [13]. Different immune cells coordinate to recognize and counter infections like Mtb in a healthy immune system [13]. Among these, CD4+ T lymphocytes are crucial because they transport other immune cells to the infection site and coordinate their immune response [13]. But in HIV-positive individuals, the virus gradually eliminates CD4+ T cells, leading in a significant decrease in their population [13]. HIV-positive individuals are much prone to get active TB in addition to their HIV infection because this loss significantly impairs the ability of the immune system to respond to Mtb infection [13].The body's first line of defense against a disease is to identify the invasive pathogen. Important participants in this process include CD4+ T cells [13]. They identify specific fragments of the Mycobacterium tuberculosis (Mtb) bacteria that are displayed by antigen-presenting cells (APCs), which are other immune cells [13]. When CD4+ T cells are recognized, they help in the stimulation of other immune cells, particularly macrophages, which engulf and eradicate dangerous bacteria like Mtb [13]. There are fewer functional CD4+ T cells in HIV-positive individuals [13]. As a result, Mtb is able to grow and multiply since the immune system is less able to recognize and combat TB. The capacity of the body to eliminate the infection further declines when there are fewer CD4+ T cells since they lead to less activated macrophages [13].Granulomas, that are structures where macrophages surround the bacteria to contain them, are another essential defense mechanism. Granulomas in tuberculosis often have a granuloma, or central zone of cell death, around by immune cells such as B and T lymphocytes [13]. Granulomas have the ability to maintain tuberculosis in a latent condition, in which the germs are hidden but do not cause disease within the body. HIV infection, on the other hand, may enter these granulomas and destroy CD4+ T cells [13]. The granuloma structure is damaged, becoming unstable and making it easier for the TB germs to spread. Thus, HIV interferes with the body's ability to control latent tuberculosis, which often leads to its reactivation and development into an infectious, active disease [13].HIV attacks the immune system and makes the body weak, so it cannot fight infections properly [13]. Because of this, a person becomes more likely to get diseases like tuberculosis (TB) [13]. In a normal person, CD4+

T cells help in recognizing the TB bacteria (Mycobacterium tuberculosis) and controlling it [13]. They also help other cells to destroy the bacteria and form granulomas, which keep the infection limited [13].But in people who have HIV, these CD4+ T cells decrease gradually So the body is not able to respond properly to TB infection [13]. HIV also affects the cells present in granulomas, so they do not remain strong [13]. When these structures break, the bacteria can spread and grow more, which can finally cause active TB disease [13].

HIV-1 tuberculosis associated Immune Reconstitution Inflammatory Syndrome:-

Immune reconstitution inflammatory syndrome (IRIS) develops when the immune system suddenly becomes stronger and reacts too forcefully to infections [14]. TB-IRIS is well known in persons with HIV [14]. In these patients, TB symptoms can worsen after commencing antiretroviral medication because the healing immune system causes an overactive inflammatory response [14]. In HIV-negative people, TB-IRIS can also develop, although there is no standard or commonly accepted criterion for diagnosing it [14].Tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) is a disorder that occurs when the body's immune system overreacts to tuberculosis (TB) bacteria, whether they are living or dead [15]. Persons with HIV are more likely to experience an excessive inflammatory response, however persons without HIV can still experience it on occasion [15].TB-IRIS usually appears shortly after starting antiretroviral medication (ART) in people with HIV [15]. It is interesting to note that it might happen even when the medication is successfully lowering blood HIV levels [15]. Interestingly, reports of similar cases of increasing TB symptoms in HIV-negative patients date back to 1954, when TB medication was first being used [15].

Clinical Definition: -

Tuberculosis–immune reconstitution inflammatory syndrome (TB-IRIS) is a condition in which a patient, despite being on appropriate anti-tuberculosis treatment, begins to feel worse again or develops new symptoms related to TB [15]. This unexpected change can happen at any stage during treatment and, in some cases, even after completing the full course of therapy [15].

One of the main challenges with TB-IRIS is that it can look very similar to other conditions [15]. For example, the symptoms may resemble those seen in drug-resistant TB, poor adherence to treatment, relapse of the disease, or even a completely different infection [15]. Because of this, doctors need to carefully evaluate the patient and rule out these possibilities before confirming TB-IRIS [15].Typically, TB-IRIS follows a recognizable pattern [15]. In the beginning, the patient shows clear improvement with treatment, both in symptoms and sometimes on imaging tests. However, after this initial recovery, there is a sudden worsening of the condition [15]. This deterioration may occur at the original site of infection or in new parts of the body. This kind of paradoxical decline, despite ongoing and effective treatment, is a hallmark feature that helps clinicians identify TB-IRIS [15].

TB-IRIS types: -

TB-IRIS exists in two varieties: paradoxical and unmasking. Both show similarly, however they appear at different times in relation to the beginning of HIV therapy (ART) and TB treatment [16]. When a person is diagnosed with tuberculosis shortly before starting antiretroviral therapy (ART), they may develop what is known

as paradoxical TB-IRIS. Following the initiation of antituberculosis therapy, patients frequently exhibit a positive response, demonstrating significant clinical improvement [16]. Nevertheless, the subsequent introduction of antiretroviral therapy (ART) can precipitate a paradoxical worsening of symptoms, the emergence of new TB-related complications, or a resurgence of previously controlled manifestations [16]. These adverse events often manifest as lymphadenopathy, the development of abscesses, the accumulation of fluid in body cavities (serositis), and the exacerbation of radiographic abnormalities observed on chest X-rays [16]. Conversely, TB-IRIS manifests in individuals whose tuberculosis infection was undiagnosed prior to the initiation of antiretroviral therapy [16]. Following the commencement of treatment, the immune system's restoration triggers a heightened immune response, thereby unmasking a previously latent TB infection [16]. This phenomenon frequently presents acutely, potentially accompanied by significant inflammation and exacerbated clinical manifestations [16].

Incidence and risk factors: -

Clinical studies and trials suggest that several factors increase the likelihood of developing paradoxical TB-IRIS [17]. Individuals with a high burden of tuberculosis bacteria are at greater risk, particularly when antiretroviral therapy (ART) is initiated soon after starting TB treatment [17]. This risk is further amplified in patients with weakened immunity, as indicated by low CD4+ T-cell counts, along with a high HIV viral load at the time ART begins [17].Unmasking TB-IRIS, on the other hand, is more frequently observed in patients who also have high viral loads and low CD4+ counts [17]. Identifying this condition can be difficult, since diagnosing tuberculosis in people living with HIV is already challenging. Those suspected of having TB but not yet on treatment are especially vulnerable. Additional associated factors include anemia, elevated C-reactive protein (CRP) levels, weight loss, and enlarged lymph nodes visible on chest imaging [17].

Diagnostic challenge: -

Diagnosing TB-IRIS in resource-limited areas of North India can be quite confusing in real clinical practice [18]. Doctors usually have to look at the overall situation—especially whether the patient has recently started HIV treatment—and then carefully rule out other possible causes before considering TB-IRIS [18]. The condition does not present in a very distinct way, so it often blends with other TB-related problems, making diagnosis less straightforward [18].Another difficulty is the lack of advanced diagnostic facilities in many hospitals [18]. In such settings, doctors cannot always rely on sophisticated tests or imaging, so they depend mainly on clinical signs, patient history, and treatment response [18]. This makes the process more judgment-based and sometimes uncertain [18]. In addition, common issues like malnutrition and other infections further complicate the picture, as they can change how symptoms appear [18]. Because of this, identifying TB-IRIS correctly may take more time and can sometimes be mistaken for other conditions [18].

Management challenges: -

Managing TB-IRIS is rarely straightforward, especially in settings where providers have not had much exposure to the condition. Without that familiarity, it is easy to miss or misread what is happening, and the patient ends up waiting longer for the right care [18]. Making things harder is the fact that most facilities simply do not have the tools needed to confirm a diagnosis. There are no reliable blood tests or imaging findings specific to TB-IRIS, so clinicians piece things together from

what they observe—how the patient looks, how they have responded to treatment so far, and whether the timeline fits. When TB-IRIS does seem likely, the usual approach is to keep the patient on ART and bring in corticosteroids to calm the inflammation, though this is not without its own complications [18].Improving how this condition is managed at the ground level will take more than just awareness campaigns. Practical steps—like short training sessions for frontline workers, or simple scoring tools that can be used without a laboratory—could make a real difference in how quickly and accurately TB-IRIS gets picked up [18]. Managing TB-IRIS is rarely straightforward, especially in settings where providers have not had much exposure to the condition. Without that familiarity, it is easy to miss or misread what is happening, and the patient ends up waiting longer for the right care [18].Making things harder is the fact that most facilities simply do not have the tools needed to confirm a diagnosis. There are no reliable blood tests or imaging findings specific to TB-IRIS, so clinicians piece things together from what they observe—how the patient looks, how they have responded to treatment so far, and whether the timeline fits [18]. When TB-IRIS does seem likely, the usual approach is to keep the patient on ART and bring in corticosteroids to calm the inflammation, though this is not without its own complications [18]. Improving how this condition is managed at the ground level will take more than just awareness campaigns. Practical steps—like short training sessions for frontline workers, or simple scoring tools that can be used without a laboratory—could make a real difference in how quickly and accurately TB-IRIS gets picked up [18].

Management of TB-IRIS: -

In many patients, TB-IRIS causes only mild inflammation that settles on its own without requiring additional treatment [16]. However, some individuals develop more intense inflammatory reactions that can become serious or even life-threatening, making timely medical care essential [16].Corticosteroids such as prednisone have been shown to play an important role in managing more severe cases [16]. Early clinical observations, later supported by controlled studies, demonstrated that steroids can effectively reduce inflammation [16]. A typical regimen involves a 4-week course of prednisone—starting with a higher dose during the first two weeks, followed by a reduced dose for the remaining two weeks [16]. This approach has been found to improve patients' quality of life, speed up recovery, and reduce the need for hospitalization, without a significant increase in serious side effects [16].Steroids must be taken with caution, however, especially in patients with advanced HIV [16]. Some studies have suggested that their use may be associated with a higher likelihood of developing certain HIV-related conditions. These include infections like shingles, as well as cancers such as Kaposi's sarcoma [16]. Non-steroidal anti-inflammatory medications, or NSAIDs: In less severe cases, medications such as ibuprofen have been effective in controlling symptoms of TB-IRIS and other forms of IRIS (including those brought on by MAC or Cryptococcus) [16]. Thalidomide: This medication, which modifies the immune system, was first created to treat various diseases. It has been used with some success, even in children, in tough-to-treat cases of TB-IRIS (such as severe brain lesions or when steroids don't work) [16]. Leukotriene antagonists, including zileuton and montelukast, are commonly used in the management of asthma. Recently, however, they have attracted interest as possible add-on therapies in the treatment of tuberculosis [16].

In some reported cases where IRIS did not respond to steroid treatment—such as those linked to tuberculosis, syphilis, or vasculitis—montelukast has shown promising results, with patients experiencing a relatively quick improvement [16]. With time or basic anti-inflammatory medications, most of them of minor cases improve. Steroids may be required in severe situations, but they must be administered with caution. Other medications, such as Montelukast or thalidomide, may be considered for people who do not react [16].

Diagnosis:-

Identifying TB in people living with HIV can be difficult. They often have fewer bacteria in their sputum, and their weakened immunity can cause symptoms and chest findings that do not follow the usual pattern. Because of this, routine tests like sputum smear, culture, tuberculin skin test, and interferon-gamma release assays may not always detect the infection. As a result, many cases may go unnoticed [1].o overcome these challenges, newer and quicker diagnostic methods are being explored, including tests that use samples other than sputum to improve detection [1].The Centers for Disease Control and Prevention recommends routine HIV screening for individuals aged 13 to 64 as part of efforts to promote early detection and reduce transmission [19]. People who are at higher risk are advised to undergo testing more frequently—typically once a year or every 3 to 6 months [19]. For diagnosing tuberculosis in individuals living with HIV, doctors rely on a combination of tests, including sputum smear microscopy, mycobacterial culture, chest X-rays, and nucleic acid amplification tests (NAATs) [19].

Smear microscopy:-

This test uses sputum samples to view acid-fast bacteria, such as Mycobacterium tuberculosis, under a microscope. Ziehl–Neelsen staining is a commonly used method for TB detection using a light microscope [20]. It is widely used in many settings because it is simple to perform, quick, and does not require expensive equipment [20].One limitation is that it may not pick up all cases, as its sensitivity ranges from about 20–60% [20]. Fluorescent microscopy can detect more cases and allows faster screening of multiple samples, but it is more costly. The use of LED-based fluorescent microscopes has helped reduce costs while still providing reliable results [20].Microscopy has several limitations when it comes to diagnosing tuberculosis. It often fails to detect smear-negative TB, a form that is more commonly seen in people living with HIV compared to those without the infection [21]. This makes diagnosis particularly challenging in high HIV-burden settings. In addition, microscopy is not very reliable for identifying TB in children, further reducing its usefulness in certain patient groups [21].Smear-negative TB is linked to poorer treatment outcomes and higher mortality, especially in regions with a high prevalence of HIV. Because of this, there is a strong need to improve the sensitivity of diagnostic methods [21]. One approach is the use of fluorescence microscopy, which offers better detection rates and is more widely used in well-resourced healthcare settings [21].Fluorescence microscopy started being used for TB detection around the 1930s [21]. Unlike routine microscopy, it does not depend on normal light alone. Instead, it uses a stronger light source and fluorescent stains such as auramine O or auramine–rhodamine [21]. These stains make the bacteria stand out by appearing bright against a dark field, which helps the examiner pick them up more easily. In contrast, conventional methods use ordinary light and stains like Ziehl–Neelsen or Kinyoun [21]. Another difference is in how the slides are examined. With fluorescence microscopy, a lower magnification (about 25×) is usually enough, while conventional microscopy

often requires higher magnification, around 100× [21]. Because of this, slides can be checked more quickly, reducing the time and effort needed. The availability of LED-based fluorescence microscopes has further improved its practicality, as they are more durable and consume less power, making their use possible even in resource-limited settings [21].Fluorescence microscopy is commonly recommended in settings with a high burden of HIV because it is generally more sensitive than conventional light microscopy for detecting tuberculosis [21]. In addition, the staining process is simpler and faster than the Ziehl–Neelsen method, which makes it practical for routine use in laboratories with heavy workloads [21].That said, its specificity can be limited. Fluorescent dyes may bind to non-living debris or other particles in the sample, which can be mistaken for acid-fast bacilli [21]. More importantly, this technique cannot reliably distinguish Mycobacterium tuberculosis from non-tuberculous mycobacteria (NTM) on smear examination alone, meaning that organisms detected under fluorescence may not always represent true TB infection [21].

NAATs:-

The usual way to diagnose tuberculosis is by looking for acid-fast bacilli using smear microscopy or by growing the organism in culture. Smear microscopy is commonly used because it is simple, quick, and not expensive, but it does not detect all cases, so some patients may be missed [22]. Culture testing is more reliable, but it takes a long time to get results, often several weeks, and even then it does not always give a positive result.Because of these drawbacks, newer methods have been developed to improve diagnosis [22]. One of these is the nucleic acid amplification test (NAAT), which detects the genetic material of the bacteria. Unlike traditional methods, it can give results within a few hours, usually around three to six hours [22].Tests such as Xpert MTB/RIF and LAMP are now commonly used in tuberculosis diagnosis because they can detect Mycobacterium tuberculosis much faster than older methods [20]. Instead of relying on visible growth, these tests work by amplifying and detecting the bacterial DNA, which makes early identification possible [20]. An added advantage is that rifampicin resistance can also be identified during the same test, which is important for guiding treatment [20]. Techniques like real-time PCR and isothermal amplification are used for this purpose, helping to produce results in a relatively short time [20].

Loop mediated amplification test:-

The TB loop-mediated isothermal amplification (LAMP) test was introduced by Eiken Chemical Co. in Japan as a simpler way to detect tuberculosis at the molecular level [20]. It amplifies TB DNA at a single, steady temperature, so it avoids the repeated heating and cooling steps used in many other techniques. Another practical advantage is that the outcome can often be seen directly, which makes the method easier to use and relatively low in cost [20].That said, it isn't completely free of technical requirements, since some basic laboratory setup is still needed. Findings from a meta-analysis by Yuan et al. indicate that LAMP shows high specificity, around 96%, but a lower sensitivity of roughly 80% for pulmonary TB, meaning it is quite good at confirming disease but may not detect every case [20].

Xpert MTB/RIF test:-

In many clinics, the Xpert MTB/RIF test is used when a rapid answer for tuberculosis is needed [20]. WHO began recommending it in 2013 as an initial investigation, particularly in patients where drug resistance or HIV infection is a concern [20].

The test can identify Mycobacterium tuberculosis and indicate rifampicin resistance in a single step, which helps guide treatment decisions early. It is also fairly easy to carry out and does not require highly specialized laboratory skills. Results are usually more reliable in smear-positive samples, where the bacterial load is higher [20].There are a few drawbacks to keep in mind. Because the test looks for DNA, it cannot show whether the bacteria are still alive [20]. The outcome can also vary depending on how well the sample has been collected, and the cost can be a limitation in some settings [20]. In smear-negative cases, the sensitivity drops to about 67%, so some infections may go undetected—this may be due to substances in sputum that interfere with the process [20]. Researchers are trying to improve the test by refining how DNA is targeted and processed. It generally performs better with lymph node samples in extrapulmonary TB, while pleural fluid samples tend to give less consistent results [20].

Urine lipoarabinomannan lateral flow assay:-

The urine LAM lateral flow assay looks for lipoarabinomannan (LAM), a molecule that comes from the cell wall of Mycobacterium tuberculosis [21]. It is one of the factors that helps the bacteria stay alive inside the body. LAM can interfere with the normal function of macrophages, so the immune system is not able to clear the infection effectively [21].This molecule is released into the body during infection, from both living and dead bacteria. Because of that, it can be detected in different fluids such as urine, blood, cerebrospinal fluid, and sputum [23]. Its presence in urine is especially useful, since urine samples are easy to collect and can be used for simple diagnostic testing [23].

Diagnostic issues in TB-HIV Coinfection: -

Diagnosing TB in HIV patients can be tricky in real situations. Even when the infection is in the lungs, sputum smear tests often come out negative. HIV changes how TB behaves, so the usual signs doctors expect on chest X-rays or CT scans are not always there [24]. For example, lung cavities or blood in cough may not be seen, which can make the disease harder to notice early, and many patients are diagnosed later than they should be [24].Another problem is the sputum sample itself. It should be thick and enough in quantity (around 2–3 mL), but in practice, samples are sometimes mixed with saliva, which affects the result [24]. Taking more than one sample can help improve detection, but the increase is not very big each time [24]. Tests like Xpert MTB/RIF are useful, especially for checking rifampicin resistance, but diagnosing TB outside the lungs is still difficult. Better methods are still being studied for this (Lawn et al., 2011; Scott et al., 2014) [24].

Treatment:-

Treatment in HIV–TB co-infection depends on whether the person has latent TB or active disease. The approach is not always simple, because medicines used for TB and HIV can interact with each other, which can affect how well they work or cause side effects [25].People living with HIV are usually checked regularly for both latent and active TB since their risk is higher. When both infections are present, treatment has to be planned carefully [25]. Anti-TB drugs are given along with antiretroviral therapy (ART), and other health problems are also managed at the same time [25]. Doctors also need to watch for complications like immune reconstitution inflammatory syndrome (IRIS), which can occur after starting treatment [25].

Guidelines for HIV Treatment:-

Once a person is diagnosed with HIV, treatment is usually started without delay. The standard approach is to use three drugs together, most commonly two NRTIs combined with another drug from a different group like an NNRTI, INSTI, or PI [26]. Nowadays, regimens that include INSTIs are used more often, especially those with dolutegravir or bictegravir, because they tend to work faster and are easier for patients to tolerate [26].The dose of these medicines is not the same for everyone. In children, it is adjusted according to their age and weight. Doctors usually try to choose drugs that are effective but also safe and simple to take [26]. In older patients, treatment may need to be adjusted depending on other illnesses they might have, so their overall health is taken into account while deciding the dosage and drugs [26].

Treatment for Latent TB Infection in HIV Patients:

In patients with HIV, treating latent TB is important, but the choice of drugs depends on possible interactions with ART, especially in those already taking multiple medicines. The commonly used options are [26]:

1. **Isoniazid + Rifapentine (once weekly for 12 weeks): -** This is a shorter regimen, so it is easier to complete. It is usually given when there is less chance of interaction with ART. Some patients may take it under observation, while others take it at home [26].

2. **Rifampicin daily for 4 months: -** This regimen is effective but not suitable with protease inhibitors. Rifampicin can change how other drugs are metabolized in the body, which may reduce the effect of some HIV medicines, so dose changes may be needed [26].

3. **Isoniazid daily for 9 months: -** This is a longer course, but it is often preferred when other regimens may cause interactions. It is generally considered safer in such cases [26].Different organizations recommend slightly different treatments for latent TB in people with HIV. The BHIVA guidelines suggest using isoniazid with pyridoxine daily for six months as a common option [27]. They also mention a shorter three-month course using isoniazid along with rifampicin. NICE gives similar choices, either three months of rifampicin plus isoniazid or six months of isoniazid with pyridoxine [27].The CDC takes a slightly different approach and prefers a longer course of isoniazid for nine months, which can be given daily or twice a week [27]. The combination of isoniazid with rifapentine is generally not advised in patients on ART because of drug interaction issues. ART itself is important because it helps strengthen the immune system and lowers the risk of active TB. This benefit is more noticeable when CD4+ counts improve [27]. Even then, people with HIV still have a higher chance of developing TB compared to those without HIV. For this reason, treatment should be planned in a way that suits the patient, so they can complete the full course properly [27].

Treatment for Active TB Disease in HIV Patients:

In HIV patients with active TB, treatment is usually given using standard anti-TB drugs, but the choice can depend on the type of ART the patient is taking. The CDC mentions two main treatment options [26]:

1. Rifapentine-based regimen: -

In this regimen, four drugs—isoniazid, pyrazinamide, moxifloxacin, and rifapentine—are given for the first 8 weeks. After that, treatment is continued with isoniazid, moxifloxacin, and

rifapentine for about 9 more weeks. It is mainly used in patients who are on or starting efavirenz-based ART and have CD4 counts above 100 cells/µL. Weekly use of isoniazid with rifapentine is not recommended in these patients [26].

2. Rifampicin-based regimen: -This is a commonly used option. It includes isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months. Then, only isoniazid and rifampicin are continued for another 4 to 7 months. Overall, treatment usually lasts between 6 and 9 months, depending on the case [26].

Treatment of drug susceptible tuberculosis in HIV patients: -

In HIV-positive patients, drug-susceptible pulmonary TB is usually treated in two phases using standard anti-TB drugs, often given as fixed-dose combinations under directly observed therapy (DOT) [27]. However, there are a few differences compared to patients without HIV [27]. Daily dosing is preferred during both the intensive and continuation phases, and doctors need to be careful about interactions between anti-TB drugs and antiretroviral therapy (ART) [27].In more serious cases, such as severe or extra-pulmonary TB, treatment may need to be continued for longer than six months. Close monitoring is important because these patients are more likely to have other infections or liver and kidney problems [27]. Starting TB treatment early helps reduce both death and spread of the disease. In some situations, treatment may even begin before lab confirmation if TB is strongly suspected, but efforts should still be made to check for drug resistance using molecular or culture tests whenever possible [27].

Antiretroviral Therapy: -

In HIV patients who have active TB, ART should be started soon after beginning TB treatment. If the CD4+ count is below 50 cells/µL, ART is usually started within about two weeks, as early treatment helps improve outcomes [27]. This applies to both drug-sensitive and drug-resistant TB cases [27].However, in patients with TB meningitis, ART is not started immediately. It is usually delayed for around two months after starting TB treatment, as early initiation can increase the risk of serious complications [27].

When to start antiretroviral therapy (ART) in TB-HIV co-infection?

In patients who have both TB and HIV, starting ART at the right time is very important. Those who are at higher risk, especially with CD4+ counts below 200 cells/mm³ or in advanced stages of HIV (WHO stage 4), should begin ART early to reduce the risk of severe illness or death [28]. At the same time, TB treatment should be continued for an adequate duration. Studies have shown that shorter TB treatment can increase the chances of relapse, so a rifampicin-based regimen for at least six months is usually recommended, particularly in areas where HIV is common [28].Some studies have looked at how timing of ART affects outcomes [28]. In one study from Thailand, HIV patients who had not started ART before and had active TB were included, most of them with CD4 counts below 200 cells/mm³ [28]. ART was started during TB treatment. Out of 29 patients, most completed treatment successfully, although a few had complications or stopped early [28]. Another study from South Africa found that delaying ART (especially in patients with low CD4 counts or advanced disease) was linked to a higher risk of developing TB [28]. Even though ART helps reduce TB by improving immunity, people with HIV still have a much higher risk of TB compared

to those without HIV, even after a few years of treatment [28].

HIV-Associated TB Treatment :-

Short-course chemotherapy (SCC) is the main approach used to treat tuberculosis in patients who are also living with HIV. When it is given properly, it helps achieve several important outcomes at once [28]. These include lowering the risk of death, reducing the chances of the disease coming back, limiting its spread to others, and preventing the development of drug-resistant TB [28].The choice of drugs in SCC is based on how Mycobacterium tuberculosis behaves inside the body, since the bacteria exist in different states [28]. During the early stage of treatment, the focus is on rapidly multiplying bacteria, especially those found in lung cavities. Strong bactericidal drugs are used at this stage to quickly bring down the number of organisms [28].However, not all bacteria are easy to eliminate. Some are located in closed lesions where oxygen levels are low and the environment is more acidic [28]. These conditions make it harder for drugs to reach them, so medications with sterilizing properties are needed to clear these persistent organisms and reduce the risk of treatment failure [28].In addition, a small number of bacteria may remain in a near-dormant state even after the patient starts to improve [28]. These surviving bacilli can later cause the disease to relapse if they are not completely eliminated, which is why continued treatment is necessary even after symptoms begin to resolve [28].

Rifampin Based Treatment Regimens: -

Studies show that using rifampin throughout the entire TB treatment gives better results than using it only during the first 2 months. In HIV patients with low immunity, there is more risk that the bacteria can become resistant to rifampin [28]. This is seen more when rifampin or rifabutin is given only twice weekly, because the drug exposure may not be enough to kill all the bacteria [28].So, in these patients, treatment should be given more frequently [28]. If the CD4 count is less than 100 cells/mm³, they are usually treated with daily drugs or at least three times a week, especially in the first 2 months of the intensive phase [28]. This helps to reduce the chances of resistance and improves treatment outcome [28].

Role of Rifabutin: -

Rifabutin is a bactericidal antibiotic that belongs to the rifamycin class. Like rifampin, it works by targeting bacterial RNA polymerase, the enzyme responsible for initiating RNA synthesis — thereby halting bacterial replication and eventually causing cell death [28]. Despite sharing this mechanism, rifabutin has a distinct pharmacokinetic profile that makes it particularly valuable in HIV-TB co-infection management [28].After oral administration, rifabutin is reliably absorbed and spreads extensively into body tissues and fluids, achieving meaningful concentrations even in the central nervous system, including the cerebrospinal fluid [28]. The drug undergoes hepatic metabolism and is cleared primarily through biliary excretion into the feces, with only a minor fraction exiting via the kidneys. As a result, patients with renal impairment do not require dose modification [28].What sets rifabutin apart from rifampin is its greater lipid solubility. This property drives several pharmacokinetic differences: rifabutin penetrates tissues more deeply and achieves a much larger volume of distribution than rifampin [28]. At the same time, its peak concentrations in the bloodstream are lower, while it persists in the body considerably longer, resulting in an extended half-life and higher drug levels in tissues relative to plasma [28]. Additionally, rifabutin binds less avidly to plasma proteins and is a weaker inducer of

cytochrome P-450 3A (CYP3A4) enzymes in the liver compared to rifampin [28].This weaker enzyme induction is clinically significant for HIV-positive patients. Because rifampin is a potent CYP3A4 inducer, it dramatically lowers the blood levels of most protease inhibitors (PIs) and many nonnucleoside reverse transcriptase inhibitors (NNRTIs), making co-administration problematic [28]. Rifabutin, by contrast, causes a much smaller reduction in ART drug levels and can be used alongside most PIs and NNRTIs — with the notable exception of delavirdine, which raises rifabutin concentrations to potentially toxic levels [28]. Even so, when rifabutin is combined with certain antiretroviral agents, dose adjustments for one or both drugs may be necessary to maintain therapeutic efficacy and minimize adverse effects [28].

Potential challenge in treatment of HIV associated TB :-

Treating HIV together with tuberculosis can be quite difficult because both conditions need long-term treatment and involve taking many drugs at the same time [29]. One important issue is deciding when to start antiretroviral therapy (HAART) in a patient who is already receiving TB treatment [29]. Starting it too early or delaying it too much can both lead to problems, so the timing has to be chosen carefully [29]. Along with this, drug interactions are a major concern, as some TB medicines can reduce the effectiveness of HIV drugs or increase their side effects [29].Another problem is that the side effects of TB and HIV medications can overlap [29]. For instance, drugs like isoniazid, rifampin, and pyrazinamide are known to affect the liver, and this risk becomes higher when they are used along with certain HIV drugs such as protease inhibitors or non-nucleoside reverse transcriptase inhibitors [29]. Some patients may also develop immune reconstitution inflammatory syndrome (IRIS) after starting HIV treatment, where their symptoms seem to get worse for a short time as the immune system begins to recover [29].There are a few precautions that also need attention during treatment [29]. Isoniazid can lead to nerve-related side effects, so vitamin B6 (pyridoxine) is usually given to help prevent this [29]. In addition, HIV drugs like stavudine and didanosine, which can also cause nerve damage, are generally avoided [29]. Because of all these challenges, managing HIV and TB together requires careful monitoring and proper adjustment of treatment when needed [29].

Clinical relevance of Drug- Drug Interaction between Rifamycin and Antiretroviral agents:-

Drug interactions between Rifamycin and antiretroviral drugs are important because they can affect how well HIV treatment works. Rifampin, for example, can lower the levels of most protease inhibitors quite a lot, with reductions of around 75–95% [30]. When this happens, the treatment may not be as effective, and there is also a risk that the virus can become resistant. Delavirdine is affected even more strongly. If it is taken together with rifampin or rifabutin, its levels can drop by more than 90% [30]. Because of such a big decrease, this combination is usually avoided in treatment [30].However, not all interactions cause serious problems. Drug levels can naturally vary from one patient to another. So, if the change is smaller, like in the range of 10–40% [30], it may not make a big difference in most cases. These kinds of changes are often similar to normal variations seen in patients. In practical terms, this means doctors focus more on major interactions, while smaller ones are usually just monitored instead of changing the treatment completely [30].

Current recommendation for managing drug-drug Interactions involving Rifamycin and Antiretroviral drugs:-

To ensure treatment adherence and therapeutic success in patients with HIV-associated tuberculosis, directly observed therapy (DOT) is strongly recommended, and the use of intermittent dosing schedules can help facilitate its implementation [30].

According to current guidelines, the following dosing adjustments are advised:

- When rifabutin is used alongside efavirenz, the daily dose of rifabutin should be increased to between 450 and 600 mg to compensate for the reduction in drug levels [30].

- When rifabutin is administered two to three times per week in combination with protease inhibitors other than ritonavir, the standard dose of 300 mg should be maintained [30].

Regarding the use of rifampin with protease inhibitors, the situation is more complex. High-dose ritonavir monotherapy (600 mg twice daily) can theoretically be co-administered with rifampin; however, this regimen is often poorly tolerated by patients [30]. An alternative approach, combining rifampin with ritonavir at 400 mg twice daily alongside a second protease inhibitor has also been proposed, though clinical experience with this combination remains limited to a small number of cases [30].In many treatment regimens, low-dose ritonavir (100 mg twice daily) is used as a pharmacokinetic booster to enhance the plasma concentrations of other protease inhibitors, as seen in the lopinavir/ritonavir (Kaletra) combination [30]. However, even at this low boosting dose, rifampin continues to reduce lopinavir concentrations by approximately 75%, and a similar effect is expected with other protease inhibitors used in the same manner [30].

CONCLUSION

Coinfection between TB and HIV is a major risk to the general public, particularly in environments with limited resources. Together, HIV and TB increase sickness, mortality, and strain on healthcare systems. Isoniazid preventive therapy, early initiation of antiretroviral therapy (ART), along with screening all contribute to a decrease in new TB infections and an increase in survival. Drug interactions, delayed diagnosis, and the spread of multidrug-resistant tuberculosis are still issues. Better access to current HIV and TB medications, higher utilization of quick molecular diagnostic testing, and better integration of health systems are all necessary to address these challenges. Future studies should concentrate on limiting drug interactions, designing straightforward point-of-care diagnostics to differentiate between latent and active tuberculosis, and assessing community-based initiatives that facilitate long-term treatment compliance.

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