venereology

MDPI

Review

The Crosstalk Between HIV-TB Co-Infection and Associated Resistance in the Indian Population

Sushama Jadhav, Aishwarya Nair, Pratik Mahajan and Vijay Nema *

ICMR-National Institute of Translational Research and AIDS Research, Pune 411026, India; sjadhav.nari@gov.in (S.J.); aishwaryanairsp@gmail.com (A.N.); pratik.mahajan532@gmail.com (P.M.)
* Correspondence: vnema@nariindia.org or dr.vijaynema@gmail.com; Tel.: +91-020-9763675539

Abstract: Extensive research on tuberculosis (TB) and HIV co-infection reveals the diverse prevalence and co-epidemic patterns across populations, necessitating tailored public health strategies. Co-infection is bidirectional; individuals with HIV are more susceptible to TB, and vice versa. Antiretroviral therapy (ART) and antituberculosis treatment (ATT) are critical for managing these conditions, but pose risks due to drug–pathogen and drug–drug interactions, potentially leading to immune reconstitution inflammatory syndrome (IRIS) in patients with HIV/AIDS. IRIS, often triggered by highly active antiretroviral therapy (HAART), can exacerbate HIV progression, increase drug resistance, and deteriorate patients' quality of life. Approximately one-third of the global population with HIV is also infected with TB, with extensive drug-resistant (XDR) and multidrug-resistant (MDR) strains posing significant challenges. Latent TB infection (LTBI) further complicates the scenario, as it can progress to active TB, particularly in individuals with both conditions. The global and Indian mortality rates for TB-HIV co-infection remain high, emphasizing the need for new strategies. Additionally, unreported cases and inadequate post-treatment monitoring contribute to the high mortality rate, particularly among patients with LTBI. The complexity of managing HIV-TB co-infection, especially with LTBI, underscores the urgency of addressing these challenges to improve the outcomes for the affected populations.

Keywords: HIV; tuberculosis; drug resistance; interactions; challenges

Citation: Jadhav, S.; Nair, A.; Mahajan, P.; Nema, V. The Crosstalk Between HIV-TB Co-Infection and Associated Resistance in the Indian Population. *Venereology* **2024**, *3*, 183–198. https://doi.org/10.3390/venereology3040015

Academic Editors: Weiming Tang, Michael Ross and Karan Varshney

Received: 10 July 2024
Revised: 26 September 2024
Accepted: 30 October 2024
Published: 6 November 2024

1. Introduction

HIV and tuberculosis (TB) represent two significant public health challenges globally, and their coexistence, particularly in regions like India, poses unique clinical and epidemiological complexities. The existence of both these organisms is known to exacerbate disease progression and the treatment outcomes, further complicated by the emergence of drug resistance in both the pathogens. Over the years, the prevalence of HIV infection has surpassed that of tuberculosis (TB), which is an infectious illness with a significant global death rate. As a multisystemic illness, tuberculosis (TB) primarily affects the respiratory, gastrointestinal (GI), lymphoreticular, skin, central nervous, musculoskeletal, reproductive, and hepatic systems [1]. Human remains from thousands of years ago have been found to contain evidence of tuberculosis, indicating that *Mycobacterium tuberculosis* has mastered the art of survival and has endured in human cultures from antiquity to the present day, despite being a human disease with no known environmental reservoir. HIV infection accelerates the normal progression of TB, with the faster distribution of all the different types of existing tuberculosis strains among the public. Additionally, it increases the chance of the recurrence of dormant tuberculosis (TB) and progresses to a novel strain or reinfection. Human immunodeficiency virus (HIV) usually infects the CD4-positive cells of the immune system of human beings and weakens the person, leading to additional infections and the development of various diseases. HIV can be transmitted through sexual intercourse with a person who is HIV positive, sharing injecting equipment, or unprotected sex, leading to the

development of acquired immunodeficiency syndrome (AIDS) without any treatment [2]. To date, there are no curative treatments available, and the drugs used alleviate the viral load or reduce the other complications linked with HIV infection. The co-infection of HIV and TB has become a foremost community fear due to the weakening of the immune system due to HIV infection. Around 2 million individuals pass away after acquiring tuberculosis infection each year, and a projected 2 billion individuals are suspected to be infected with tuberculosis [3]. The risk factors associated with TB infection include age, gender, geographical location, the use of alcohol, smoking habits, and underlying diseases like diabetes or pulmonary diseases, as well as body mass index. A gender bias has been reported in multiple studies conducted globally, as men are more likely to be infected by TB [4]. The higher rate of infection in rural areas due to slums, overcrowding, migration, and a lack of awareness stands out as a major concern affecting the large population in India; hence, advocating for communication and public awareness is the need of the hour to control and strengthen TB eradication programs. One area of attention as we work toward the elimination of tuberculosis is preventive therapy for tuberculosis, which treats latent tuberculosis infection, the reservoir from which future tuberculosis cases are derived. Children are especially susceptible to two catastrophic illnesses, TB meningitis and widespread TB, which emphasizes the need for treating latent TB infection in the 0–18 age range [5].

In 2001, the World Health Organization (WHO) launched an initiative in Geneva aimed at combating tuberculosis (TB) through the introduction of a Global TB Drug Facility (GDF) to improve access to high-quality TB medications. Despite these efforts, the current estimate that one-third of the world's population is affected by latent TB infection (LTBI) is over two decades old. To achieve the goal of eradicating tuberculosis by 2050, there is an urgent need to invest in new tools for enhancing the detection and treatment of individuals with LTBI who are at risk of developing HIV. Improved diagnostic procedures, shorter preventive therapies, and more effective treatments are essential for managing this syndemic, particularly in the context of drug-resistant tuberculosis. Due to the rising mortality rate, all healthcare institutions must implement rapid point-of-care testing for TB diagnosis and the early detection of both HIV infection and tuberculosis. For patients who have both HIV and TB, post-treatment monitoring and follow-ups are critical, with post-treatment mortality serving as the key marker of effective TB control initiatives. Each year, over a million people die from tuberculosis, and approximately ten million individuals worldwide contract the disease [6]. In 2022, an estimated 2.77 million people were infected, with India bearing nearly 25% of the global TB burden [7].

Regardless of whether the survey participants with TB had subclinical or symptomatic TB, 27% of their home contacts were infected with TB [8]. Living and working conditions that are crowded, inadequately ventilated, and frequently linked to poverty are the primary risk factors for the spread of TB. One significant risk factor for the onset of active illness is undernutrition. Additionally, the dearth of empowerment to act on health information and inadequate general health awareness are linked to poverty. This puts people at risk of being exposed to several TB risk factors, including alcohol misuse, smoking, and HIV. Hence, these social determinants must be tackled to curb the infection rate globally.

2. Methodology

To ensure an encompassing review of the literature for our research, we systematically searched multiple comprehensive academic databases and websites, including PubMed (U.S. National Library of Medicine and the National Institutes of Health), Google Scholar, ScienceDirect, and the World Health Organization (WHO) websites and literary reports. The major key words used for the searching strategy were HIV-TB co-infection, diagnosis, point-of-care tests, and biomarkers. Several descriptive methods and Boolean logic (AND, NOT) customized for each database were used in this investigation. The following are the search terms that were used to obtain the available literature, PubMed: ("HIV-TB coinfection") AND ("diagnosis") OR ("point-of-care tests") OR ("biomarkers"); Web of Science: (((ALL = **resistance**) OR ALL = **point-of-care tests**) OR ALL = **rapid diagnosis**)

AND ALL = **HIV-TB resistance profile**; and Scopus: (**Pathways in coinfection**). We found many published records in each search. We selected review articles, research papers, and reports based on their relevance to HIV-TB co-infection. The articles were summarized and analyzed to provide a thorough overview of the current status of TB-HIV co-infection and the role of immune reconstitution inflammatory syndrome (IRIS) in this context. We assessed the validity and reliability of the articles based on their sample sizes. Additionally, we aimed to include influencing and confounding factors and their roles in the management and severity of HIV-TB co-infection. Only published research papers that were available in English language, provided the details on the diagnosis of HIV-TB co-infection and associated resistance, and research aspects covering the identification of biomarkers, as well as therapeutic strategies useful in the treatment of co-infection, were considered for exploring the crosstalk between HIV and TB co-infection.

Clinically, TB can be broadly classified as latent TB or active TB, depending on the symptoms and their transmissibility. Measures must be taken to prevent the latency of TB infection, including monitoring the molecular bacterial load, ensuring early diagnosis, promoting adherence to prescribed drugs, and encouraging lifestyle changes. Various diagnostics tests have been developed to detect *Mycobacterium tuberculosis* infection and are widely used in various regions of India. These tests are illustrated in Figure 1. The most common types of drugs prescribed during the early stages are isoniazid, rifampin, pyrazinamide, and streptomycin, which show bacteriostatic activity [9]. In order for these drugs to be effective, the individuals with this illness must adhere to them for 6–8 months, failing which the bacteria may develop resistance, making them unresponsive to these standard drugs. People with HIV are prescribed updated therapy immediately after the diagnosis of HIV. Highly active antiretroviral therapies (HAARTs) are a combination of different classes of antiretroviral medicines that help in decreasing the viral load, preventing mutations, maintaining the CD4 cell count, and improving people's the quality of life. Another complication associated with this therapy is immune reconstitution inflammatory syndrome (IRIS), which is a hyper-inflammatory response state that often develops in the early 6 months of adhering to HAART [10]. Severe IRIS can be fatal, or result in lifelong incapacity, endangering the patient's capacity to function. However, stopping combination antiretroviral medication (cART) in a patient with recurrent infections increases the risk of contracting new opportunistic infections, IRIS recurrence upon restarting therapy, and potential HIV drug resistance. Hence, in this review, we will try to comprehend this drug resistance associated with individuals with HIV-TB among the Indian population.

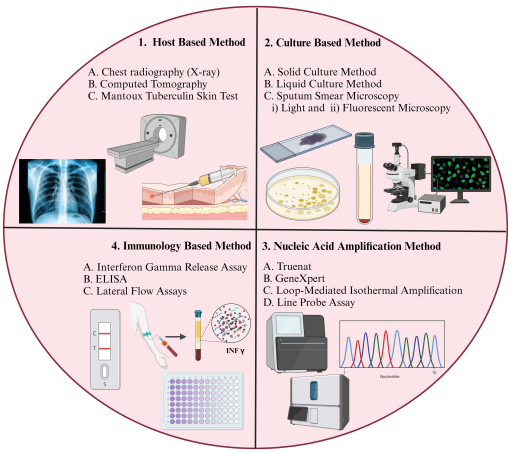

Figure 1. The techniques used for the detection of tuberculosis infection.

3. Epidemiological Landscape in India

India bears the substantial burden of both HIV and TB. According to the World Health Organization (WHO), India is home to the world's third-largest population living with HIV/AIDS. Concurrently, India also has one of the maximum loads of patients with TB glob-

ally, and the overlap of these two epidemics presents a formidable challenge to healthcare systems, particularly concerning diagnosis, treatment, and management strategies.

TB is an opportunistic infection that compromises immune systems, leading to more severe complications in people with infections compared to those who are not immunocompromised. HIV attacks and weakens the protective system of the body, rendering it very difficult to fight against the virus and opening doors for other infections, such as pneumonia, TB, Salmonella, candidiasis, and toxoplasmosis. Among these infections, the prevalence of HIV-associated tuberculosis is on the rise globally, as the prevalence of TB-HIV co-infection varies from 3.8 to 72.3%, while the prevalence of HIV-associated TB ranges from 2.9% to 64.5% [11]. Other studies suggest that HIV-associated TB impacts African nations more excessively as compared to other countries [12]. The WHO also suggested that individuals with HIV are 15–20 times more likely to be infected by TB than are those without HIV, while Africa, in 2018, faced the brunt of HIV-TB co-infection, which accounted for 84% of deaths and was the major cause of death among patients with HIV. These data suggest that infection with this virus additionally raises the risk of the development of dormant TB infection to an active form of TB, which can be seen as a four-fold increase. Hence, managing LTBI and TB infections is more essential among individuals with HIV than for those without HIV. The WHO report published under the Global HIV programme in 2020 stated that people living with HIV and receiving ART regimens are still three times more likely to die during TB treatment, which needs to be addressed in the future. The overall prevalence of HIV-TB co-infection in the adult population of Southeast Asia is 0.3%, which is lower than that in Sub-Saharan Africa (4.1%). Among the Southeast Asian countries, the major contributing nations are India, Indonesia, Thailand, and Myanmar, which have contributed approximately 160,000 new HIV infections and 110,000 deaths among individuals with HIV and HIV-TB co-infection. Approximately 25% of all HIV/AIDS fatalities worldwide occur each year as a result of the mortality risk associated with HIV-TB co-infection [13]. According to a report from the WHO published in 2021, India accounts for approximately 20% of the total TB infections, which epidemiologically looks small, but contributes to approximately 5 million people living with TB and has severe consequences for gaining momentum in curbing TB among the Indian population. The HIV status varies among the Indian subcontinent, but according to a published study, there is an increased number of HIV-positive cases in five states, namely, Manipur, Maharashtra, Karnataka, Karnataka, and Tamil Nadu [14]. According to the NACO, India ranks third globally, with a high prevalence of HIV. However, the frequency amongst adults with ages ranging from 15 to 49 years declined from 0.38 to 0.22 in 2019 [15]. The pathogenesis of HIV starts with the virus attacking CD4 cells, and thereby affecting both innate and adaptive immunity, whereas TB affects cell-mediated immunity driven by helper T cells (Th1), which produce interferon-γ (IFN-γ) and interleukin-2 (IL-2), both of which provide immunity against TB. Hence, in the case of co-infection when CD4 cells become infected, Th1 cells are depleted, alleviating cell-mediated immunity. This reduced immune response increases the susceptibility of individuals to other infections and paves the way for the increased reactivation of LTBI [16]. In addition, a decrease in the CD4-Th1 population also leads to the activation of TNF-α, which increases HIV replication in the presence of TB infection. Hence, under such co-infection conditions, individuals must be monitored for CD4+ T cells, and they should adhere to the ART and ATT prescribed to the patients based on their stage and type of TB (Figure 2). The prolonged use of these treatments will lead to multi- and extended drug-resistant TB, which should be treated at DR-TB centers across India, with approximately 553 ART centers and 1261 linked ART centers and complimentary ART program in India. ART centers were established in 2004 in India, and have expanded significantly over the years. Currently, 1.38 million patients are receiving ART, with 2800 receiving third-line ART and 60,000 receiving second-line ART. Substantial improvements have been made in the last 20 years by India's National AIDS Control Programme (NACP). Based on the available data on HIV trends and estimations, India has experienced general declines in HIV incidence, new infections, and fatalities due to AIDS. While there has been

a 30% decrease in AIDS-related mortality and a 33% decrease in new infections worldwide, India has demonstrated more than 50% of these reductions and more than 35% of these declines, making it one of the world's most effective models [17]. Research on the crosstalk between HIV-TB co-infection and the associated resistance in these pathogens in the Indian context is a critical area due to the high burden of both the diseases in the region. This co-infection complicates the treatment and management of both the diseases, leading to higher mortality rates. The Indian government and international health organizations have prioritized the diagnosis and treatment of HIV-TB co-infection, making it a key focus of public health interventions [18]. Considering the research aspect, various studies are exploring the molecular pathways involved in the crosstalk between HIV and TB, including the role of cytokines, immune activation, and chronic inflammation. The emergence of MDR-TB is a significant challenge, especially among individuals with HIV. Research is ongoing to understand the mechanisms driving drug resistance and to develop new treatment strategies.

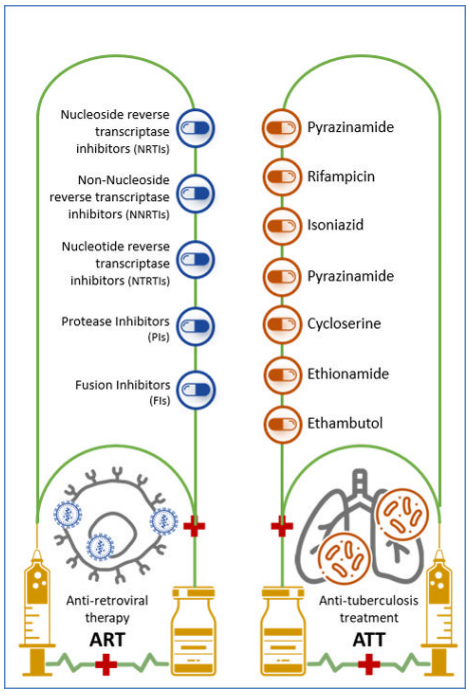

Figure 2. Drugs prescribed in ART and ATT.

Furthermore, there is an ongoing investigation into how ART interacts with TB drugs, particularly in the context of drug resistance, toxicity, and treatment efficacy. Recent studies have aimed to identify the biomarkers that could predict susceptibility to TB in patients with HIV, or indicate the development of drug resistance. Novel research focuses on how HIV and TB bacteria interact within host cells, which could reveal new targets for therapeutic intervention [19]. Recently, investigations into the genetic factors that may contribute to susceptibility to co-infection and resistance, particularly within the Indian population, are emerging as a significant research frontier. One novel area to study the crosstalk between co-infecting pathogens is the development of personalized treatment strategies based on individual patients' genetics and specific pathogen characteristics [20]. Some of the critical actions to lower morbidity and mortality among individuals with both infections include early ART and ATT initiation; the timely detection of TB among PLHIV and HIV screening among patients with TB; the provision of cotrimoxazole (trimethoprim-sulphamethoxazole) preventive therapy (CPT) and TB preventive therapy; and the management of airborne infection, as reported in an Indian context [21].

4. Impact of Co-Infection on Disease Progression

When HIV and TB coexist, each disease influences the natural history and progression of the other. HIV weakens the immune system, making individuals more susceptible to TB infection and increasing the likelihood of TB reactivation among those with latent TB infection. Conversely, TB accelerates HIV progression by causing immune activation and increasing viral replication. The synergistic effect of these infections often leads to more severe clinical presentations, higher mortality rates, and poorer treatment outcomes compared to those of individuals infected with either pathogen alone [22].

During dual interaction, the presence of M. tuberculosis negatively impacts the immunological response to HIV, hastening the transition from contracting HIV to AIDS, in addition to HIV's effect on the course of TB. Considering biological repositories like the lungs are shared by M. tuberculosis and HIV, patients with TB may have an environmental condition that promotes HIV infection. A higher risk of opportunistic infections and the expedited depletion of CD4+ T cells have been linked to active tuberculosis. It has been demonstrated that the ongoing immunological response against infection with tubercular bacilli increases the spread of HIV-1 in the bloodstream, at the pulmonary infection sites, and in some activated cells like lymphoid cells and CD14+ macrophages in the pleural space during tuberculous pericarditis. Long terminal repeats (LTRs) of HIV are transcriptionally activated when M. tuberculosis stimulates the production of proinflammatory cytokines and chemokines, such as TNF, which, in turn, activates the pathways for signaling in CD4+ T cells and monocytic cells [23].

5. Challenges in Diagnosis and Treatment of Co-Infection

The diagnosis of HIV-TB co-infection in India is hindered by several factors, including the reliance on symptom-based screening, limited access to diagnostic tools (such as GeneXpert for TB and viral load testing for HIV), and the stigma associated with both the diseases. Delayed diagnosis contributes to higher rates of advanced disease presentation and increased transmission within communities. The treatment of HIV-TB co-infection is complicated by drug interactions, overlapping toxicities, and the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of TB. India faces challenges in the management of drug-resistant TB due to inadequate infrastructure for drug susceptibility testing, the limited availability of second-line TB drugs, and difficulties in ensuring treatment adherence among patients with complex medical needs [24]. Managing the interactions between anti-TB and anti-HIV drugs is complex, but essential for the effective treatment of patients with both infections. The vigilant selection of drug regimens, dose adjustments, and close monitoring can help mitigate risks. Ongoing research and integrated healthcare strategies have been shown to improve the outcomes for individuals with HIV-TB co-infection [25].

ART does not completely eliminate the infection because the virus hides in a reservoir of cells, remaining dormant inside them. This makes the disease much harder to eradicate compared to other common infections. Even after prolonged ART treatments given to individuals with HIV for 15–25 years, they will show some pools of infected cells, tissues, or organs, which may reactivate the viral particles and worsen the condition. Hence, the role of antiretroviral therapy (ART) is to suppress the viral load, improve the health condition by reducing severe complications, and prevent the transmission of the disease. The different classes of ARV drugs are classified according to the stage of replication where they interfere, and to date there are seven classes [26]. In 1985, the first drug used for treating individuals with HIV was Zidovudine, which proved to be effective against HIV, but soon became ineffective due to the resistance developed. Later, decade-long research revealed that a combination of ARV drugs (ddC and AZT) could prevent transmission and reduce the viral load [27]. In 1996, a group of researchers found that the combination of three antiretroviral medicines called "triple-drug therapy" can help reduce transmission, but is also durable in developing resistance against ART. Triple-drug therapy is possible due to the discovery of the protease inhibitor Saquinavir, and this drug, along with ddC and AZT, was approved

by the NIAID. This therapy was then later on replaced by NRTIs and NNRTIs, and current therapy uses a combination of these drugs as the most effective ART. The main reasons are not only that HIV is developing resistance, but also there are side effects associated with protease inhibitors when used in high concentrations. Presently, the use of protease inhibitors is pertinent in some ART regimens. But still, drug discovery is evolving in the search for more effective, but less toxic ARV drugs. Drug interaction, along with adverse drug reactions among individuals with HIV, still poses a challenge in managing the disease and infection [28].

The emergence of drug resistance in both HIV and TB further complicates the management of co-infection in India. Drug-resistant TB strains, including MDR-TB and XDR-TB, have been increasingly reported, posing significant challenges to achieving successful treatment outcomes. Similarly, HIV drug resistance mutations reduce the efficacy of antiretroviral therapy (ART), necessitating regimen modifications, and potentially limiting the treatment options [29]. Molecular epidemiology studies have provided insights into India's genetic diversity and the transmission dynamics of drug-resistant strains. Genomic surveillance has become crucial for tracking transmission networks, identifying resistance mutations, and guiding public health interventions aimed at controlling the spread of resistant strains [30].

Recently, apart from drug combinations, protein-9 nuclease (Cas9) associated with clustered regularly interspaced short palindromic repeats (CRISPRs), or CRISPR/Cas9, has emerged as a potent tool for modifying the genome in the last ten years due to its high precision and efficient suppression. Cas9 endonuclease mediated by guide RNAs (gRNAs) functions as genetic scissors that may alter specific target locations. With this idea, the integrated pro-viral HIV-1 genome has been targeted by CRISPR/Cas9 in both in vitro and in vivo investigations including non-human primates [31].

6. Impact of TB Supplements on Disease Improvement

Tuberculosis is still a worldwide problem even after concentrated efforts over the last 20 years have been made to create novel diagnostic tools, medications, and vaccines with growing pipelines. Several cutting-edge diagnostic methods, including imaging, the breath analysis of volatile organic chemicals, and nucleic acid-based amplification assays, hold promise for improving point-of-care fast diagnostics for TB. Urgent HIV testing for patients newly diagnosed with tuberculosis (TB) is a proactive step that healthcare providers can take to address the increased risk of co-infection and improve health outcomes. Following TB diagnosis, immediate HIV testing is crucial, as TB and HIV often coexist, exacerbating the severity of each condition. The effective prevention strategies include initiating antiretroviral therapy (ART) for those who test positive for HIV, which not only reduces the viral load, but also lowers the risk of TB progression.

Healthcare providers play a crucial role in ensuring adherence to both TB treatment and HIV prevention protocols. This empowerment can significantly enhance patients' outcomes and reduce the burden of co-infection. Additionally, preventive measures, such as providing HIV pre-exposure prophylaxis (PrEP) to individuals at high risk, along with integrating TB and HIV care for a comprehensive approach, are essential. The creation of many novel treatment regimens and their assessment in clinical trials have been the main focus of developments in newly developed and adapted medications for the treatment of highly drug-resistant (XDR) or multidrug-resistant (MDR) TB [32]. These developments are now influencing the World Health Organization guidelines. The disease progresses in two forms like latent TB and active TB. Those who develop symptoms are recommended to obtain a molecular diagnostic test, which will help in detecting TB and identifying any associated drug resistance. After a diagnostic test, for better accuracy, assays for measuring interferon release (IGRA) and tuberculin skin testing (TST) are recommended [33]. The most commonly prescribed drugs are antibiotics like isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin, which are prescribed daily for about four to six months. Adherence to this medication is a must as stopping them abruptly can lead to multifactorial

manifestations, along with MDR, which need to be addressed further. TB resistance to these standard drugs is characterized as drug-resistant TB, starting with the patients not responding to first-line-of-defense antibiotics like isoniazid and rifampin. These drugs help in a bacteriostatic mode of action, which help in reducing viral transmission by acting on DNA-dependent RNA polymerase, and further inhibiting transcription and translational activities. When the patients stop responding to these standard drugs, then the patients are recommended second-line-of-defense drugs. However, if resistance develops to these as well, it can result in a crisis. The sign that the medications are working is the alleviation of symptoms. For drug-sensitive (DS) *Mycobacterium tuberculosis* (M. tb) strains, the front-line treatment plan currently in use is a 6-month program consisting of four different medications to which strict adherence is necessary to prevent resistance and recurrence [34].

7. Drug Resistance and Clinical Practices

The key to TB control is the early detection and prompt treatment of newly diagnosed cases, most of whom respond well to first-line anti-TB medications, and they also alleviate the infection in helping to reduce the risk of transmissibility across the community [35]. Hence, an adequate response to therapy, the prevention of drug resistance, and a reduction in drug toxicity all depend on the optimal medication dose. Non-adherence to tuberculosis therapy may adversely affect the clinical and public health outcomes. There are three major types of drug resistance: multidrug resistance TB (MDR TB), extensively drug-resistant TB and pre-extensively drug-resistant tuberculosis (pre-XDR TB). Multidrug-resistant TB is caused by TB bacteria, which are resistant to the most common drugs used to treat patients with TB, such as isoniazid and rifampin. Pre-XDR TB, also known as extensively drug-resistant tuberculosis, is a subtype of multidrug-resistant tuberculosis (MDR) generated by tuberculosis bacteria resistant to amikacin, capreomycin, and kanamycin, or to isoniazid, rifampin, and fluoroquinolone. A rare form of multidrug-resistant tuberculosis (MDR) known as extensively drug-resistant tuberculosis (XDR TB) is brought on by either TB bacteria resistant to Bedaquiline, linezolid, rifampin, fluoroquinolone, and second-line injectables (amikacin, capreomycin, and kanamycin), or TB bacteria resistant to all of the above [36]. Patients are left with far fewer effective treatment choices since XDR TB is resistant to the strongest TB medications. Individuals with HIV, as well as those with other illnesses that compromise immune function, should be especially concerned about XDR TB. These individuals have a higher chance of contracting TB after becoming infected, as well as a higher chance of succumbing to TB. Although the number of cases of XDR-TB is substantially low, the cost of treatment is extremely high. This interrupts lives, is exceedingly costly, takes a long time to finish, and may have possibly fatal adverse effects. Serious adverse effects, including depression or psychosis, hearing loss, hepatitis, and renal damage, are experienced by a significant percentage of patients receiving treatment for these drug-resistant types of tuberculosis [37]. Universal drug-susceptibility testing is essential for identifying and treating MDR- and XDR-TB (DST) [38]. Rapid molecular methods based on sequencing and nucleic amplification tests (NAATs) have emerged in recent years, marking a significant advancement in the diagnosis of tuberculosis.

Chest radiography is still the gold standard for diagnosing parenchymal illness in primary pulmonary tuberculosis (TB), while computed tomography (CT) is more accurate in identifying lymphadenopathy. CT is the preferred technique for detecting early bronchogenic spread in post-primary pulmonary tuberculosis. CT is more sensitive than radiography when it comes to characterizing the infection as active or not, and F-fluorodeoxyglucose positron emission tomography/CT, or F-FDG PET/CT, has produced encouraging results that require more validation. Even now, extrapulmonary tuberculosis diagnosis might be challenging. The diagnostic accuracy, specificity, and agreement among observers regarding the radiological diagnosis of tuberculosis using chest X-rays remains unclear. The effectiveness of each method depends on various factors, including the stages of the disease, exposure, and severity. The WHO has approved four high-throughput techniques aiding in the diagnosis of MDR-TB: the BD Max MDR-TB assay (Becton Dickinson,

Franklin Lakes, NJ 07417-1815, USA); the real-time MTB (Abbott, Chicago, IL, USA); the Roche Cobas MTB assay (Roche, Basel, Switzerland); and the Fluoro-Type MTBDR assay (Hain Life Science, Nehren, Germany) [39,40]. There are three types of HIV test available: antibody tests, antigen/antibody tests, and nucleic acid tests (NATs). When you are exposed to viruses such as HIV, your immune system generates antibodies. Antigens, which are foreign molecules, stimulate your immune system's activation even before the antibodies are produced. If you have HIV, the p24 antigen is generated. Usually, oral fluids like saliva and blood can be used for diagnosing HIV infection using a rapid oral HIV test and a rapid antigen/antibody test, respectively. Urine can also be used for these procedures. HIV drug resistance has emerged along with the growing usage of HIV medications; in recent years, the prevalence of this resistance has been rising. HIV treatment resistance results from modifications to the virus's genetic makeup that impair the medications' capacity to stop the virus from replicating. Because drug-resistant virus strains are emerging, all the antiretroviral medications now on the market, even the most recent classes, include the risk of being partially or completely inactive. HIV medication resistance poses a threat to antiretroviral medication effectiveness if left unchecked, which would raise the incidence of HIV infections, as well as morbidity and death associated with HIV.

8. Behavioral and Adherence Issues

Despite medical advancements, control over several chronic diseases has not improved, mostly due to non-adherence to treatment. Adherence to medical treatments is vital for improving the general health of the community. Many developing and developed nations are implementing policies that will help in patient management and will help in curbing behavioral science by using digital solutions. The nexus of behavioral science and technology is driving improved adherence, which opens up new avenues for patient empowerment and healthcare professional education. The degree to which a person follows health or medical advice is known as adherence (or compliance). Recent research shows that patients who follow their treatment regimens regularly achieve better health results than those who do not. Thus, adherence to the treatment regimens is one of the most important, but uncommonly researched factors influencing how well tuberculosis (TB) treatment works. Since the early Tuberculosis Research Centre and British Medical Research Council (MRC) study in South India comparing in-patient and domiciliary therapies, its significance has been recognized [40,41]. It is known that one of the most important ways to contain the TB pandemic is to provide conventional anti-TB medication for a minimum of six months. The lengthy course of TB therapy brought up the problem of non-adherence nevertheless. The clinical and public health outcomes may be adversely affected by non-adherence to tuberculosis therapy. As a result, the usual approach of directly observed treatment (DOT) has been implemented to enhance anti-TB drug adherence [42]. Rethinking TB care delivery includes considering digital technologies to improve the adherence to TB medication. From the standpoint of public health, enhancing compliance with anti-TB therapy can aid in preventing drug resistance, relapse, and community-transmitted tuberculosis [43]. A recent systematic evaluation revealed that the efficacy of DOT varies when compared to that of self-administered treatment. For instance, self-administered therapy and family-administered DOT do not significantly increase treatment adherence. However, institutional DOT for latent tuberculosis infection significantly increased the rate of treatment completion [44]. Individuals living with HIV/AIDS who do not adhere to antiretroviral medication (ART) are more likely to have drug resistance and poor virologic control. The cost, ignorance, stigma, or unhappiness with medical care are a few obstacles to ART adherence. A study conducted among Mumbai's key population showed a substantial correlation between poor pill-taking behavior and worsened virus suppression. Having "missed ART in the past three months" was also a major mediator influencing these practices and behavior. Those who remained alone had a far lower percentage of those with viral suppression than those who did not [45].

9. IRIS-Immune Responses in Recovery from Immunosuppression

Immune-mediated inflammation against a variety of antigens, such as medications, unknown autoantigens, and pathogenic microbes, during the recovery process from immunosuppressive circumstances is referred to as immune reconstitution inflammatory syndrome (IRIS). ART initiation can also cause a pathological hyper-inflammatory response to live or dead *Mycobacterium tuberculosis* (Mtb), a condition known as TB immune reconstitution inflammatory syndrome (TB-IRIS). This is true even though ART and subsequent immune reconstitution in PLHIV reduce the incidence of opportunistic infections like TB, as illustrated in Figure 3.

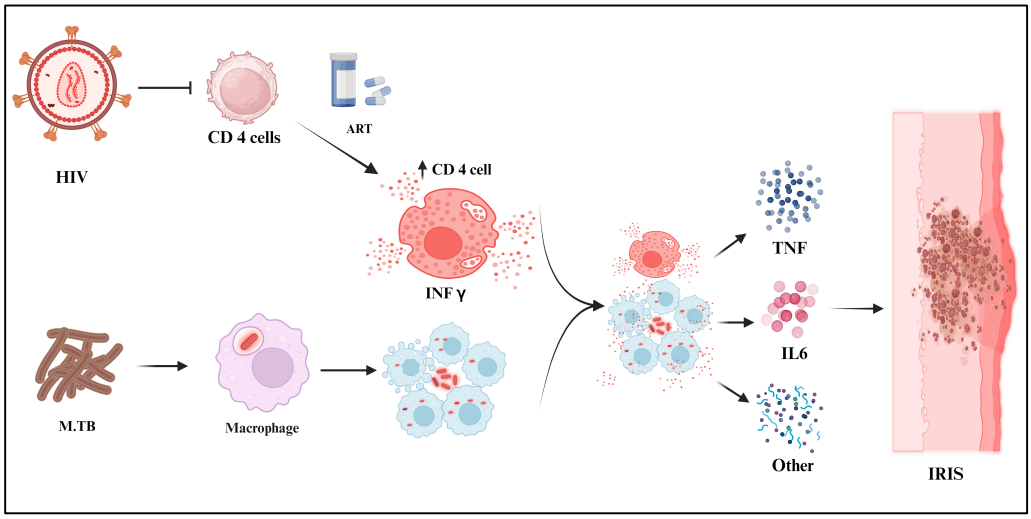

Figure 3. The pathways involved in the development of IRIS in individuals with HIV-TB.

In populations affected by HIV, IRIS is now widely known. The risk factors that play a crucial role in the development of TB-IRIS are a high bacterial load, delayed ATT or ART post-infection, a low CD4 count, etc. [46]. IRIS is characterized by both innate and adaptive immune responses, which vary based on different antigens and immune factors. In the context of Mycobacterium tuberculosis-associated IRIS, key immune factors include interferon (IFN), interleukin (IL)-2, IL-6, TNF-α, and IFN-γ-inducible protein (IP)-10. These elements play crucial roles in the immune activation and inflammation observed in this condition [47,48]. Another group demonstrated significantly elevated concentrations of IL-10 and IL-22 in patients with tuberculosis-associated IRIS compared with those in patients with tuberculosis without IRIS [49]. Additionally, there was an improvement in the effector function of T cells; a delay in decreasing the CD4 T cell levels; improvements in phagocytic function, leukocyte chemotaxis, and NK cell function; and a decrease in the TNF-α as well as interleukin-8 levels. Nonetheless, IRIS has rarely been identified in people who are immunocompromised, but do not have HIV [50]. Over the last ten years, the findings from randomized control trials have been published [34]. They have demonstrated a similar pattern of concurrent ART with TB treatment, providing a survival benefit. Furthermore, in patients with advanced HIV disease, that is, a CD4 cell count <50 cells/mm^3, starting ART within the first two weeks of TB treatment is advantageous, although it is linked to a two-fold increased occurrence of TB IRIS [51]. Paradoxical TB IRIS and unmasking TB IRIS are two forms of TB IRIS that have been documented in the literature. If TB lesions worsen following recent initiation, re-initiation, or switching to more effective ART, this condition is known as paradoxical TB-IRIS. When ATT is given for a brief period prior to starting antiretroviral therapy (ART), patients with paradoxical TB IRIS usually have positive or stable clinical outcomes. Between 8 and 42% of the epidemiologic data for paradoxical TB-IRIS is not fully understood [52]. For individuals with HIV with undetected active tuberculosis, the second pattern of unmasking TB IRIS occurs after starting antiretroviral therapy. The ensuing immunological recovery triggers

more severe tuberculosis symptoms [53]. Because of this, the likelihood of uncovering TB IRIS is dependent on how well TB is screened and whether subclinical TB is diagnosed before starting ART [54]. Pneumonitis, lymphadenitis, and a high fever are some of the clinical manifestations of tuberculosis that typically occur quickly after infection [55]. The symptoms can mimic sepsis caused by germs. Since there is no definitive consensus on diagnosis, the consensus case definitions of both these TB IRIS patterns are still up for debate.

10. Therapeutic Vaccines with ART and ATT

Doctors and pharmacists must take great care to prevent drug interactions (DIs) in modern medication therapy, where two or more prescriptions are regularly prescribed. DIs can result in adverse events and insufficient pharmacological effects, leading to the withdrawal of drugs from the market. Pharmacokinetic research elucidates the role of drug interactions in developing new drugs, thereby conveying information about potential drug targets. In 1980, increasing HIV/AIDS cases caused an epidemic that was reported by the Center for Disease control and prevention, USA, under the title CDC HIV/AIDS Timeline [56,57]. They focused on targeting the reverse transcriptase, which would help curb the viral load among individuals who have HIV/AIDS, and they used azidothymidine (AZT) as the therapeutic drug, which improved the immune status. Later, in 1987, it became the first drug approved by the FDA to reduce the transmission of HIV. Later on, they went on to discover the transcriptase inhibitor didanosine (NRTI) and zalcitabine (RTI), which proved to help reduce the AIDS incidence. These drugs were combined with AZT for better effectiveness, but soon the patients developed drug resistance [58]. Founded in the early stages of the HIV/AIDS pandemic, the National Cooperative Drug Discovery Group Program for the Treatment of AIDS (NCDDG-AIDS), funded by the NIAID, offered a framework for scientists to work on the discovery and development of new regimens to improve the symptoms induced among individuals with HIV/AIDS. Scientists funded by the NIAID created biochemical and cell culture test techniques that made it easier to screen potential drugs, and the agency was also instrumental in creating animal models for preclinical research. The FDA approved other NRTI medications in the early 1990s. The development of AZT and other NRTIs demonstrated that HIV could be treated, paving the way for the discovery and creation of additional antiretroviral medications [59].

In 1995, the ACTG 175 experiment trial demonstrated that two-drug combinations were more effective than AZT alone in halting the loss of CD4+ cells and preventing mortality. ART was also found to lower the death risk in patients with asymptomatic, intermediate-stage illness, according to the trial. Simultaneously, CPCRA 007 and the NIAID-sponsored trial evaluated combination therapy for individuals with more advanced HIV, most of whom had received AZT as their prior treatment. Antiretroviral medicine use requires careful planning, as demonstrated by the results of ACTG 175 and CPCRA 007, among other trials, which suggest that prior antiretroviral experiences can significantly impact treatment success. A significant breakthrough was made in 1996 when researchers discovered that triple-drug therapy could effectively reduce HIV replication to negligible levels over time, while erecting a strong genetic barrier to prevent the emergence of drug resistance. The emergence of a new class of antiretroviral drugs called protease inhibitors contributed to the feasibility and efficacy of triple-drug therapy, often known as highly active antiretroviral therapy or HAART. Several patients had a decline in HIV blood levels to undetectable levels using HAART, which combines medications from at least two distinct classes. Nevertheless, the early HAART regimens were far from ideal, even though they may have saved lives. Both the daily dose and the side effects were difficult to deal with. Some medications required combination doses to be taken with or without food at different times during the day. Due to their complexity, long-term adherence to the regimens took a lot of work.

Like HIV, the aim of tuberculosis (TB) drug development and discovery is to provide TB medications and regimens that are well understood and better than those on the market

today in terms of their accessibility, the ease of use for all patient populations, efficacy, the speed of action, safety, and tolerability. According to history, the first clinical antibiotics to be produced were streptomycin and para-aminosalicylic acid (PAS). Both showed efficacy against *Mycobacterium tuberculosis* (Mtb) and were swiftly succeeded by rifampicin, isoniazid, pyrazinamide, cycloserine, ethionamide, and ethambutol, among other drugs [60]. Isoniazid (INH), a thiosemicarbazone based on pyridine, was first synthesized in 1912. However, its antitubercular properties were not found until much later during the process of synthesizing thioacetazone. One of the most well-researched and clinically successful tuberculosis medications ever created is isoniazid (INH) (isonicotinic acid hydrazide) [61]. Ironically, though, INH, once associated with TB prevention and chemotherapy, has come to characterize the contemporary multidrug-resistant (MDR) and extensively drug-resistant (XDR) epidemic. The catalase-peroxidase KatG-activated prodrug INH, according to the current working model of the INH mechanism, produces a wide range of INH-derived radicals and adducts, some of which have the potency to kill Mtb by preventing it from synthesizing mycolic acids. It is unclear, therefore, what kind, how many, and how much of the other INH-derived species that KatG produces might interact with INH to enhance its exceptional whole-cell potency [62]. The development of pyrazinamide (PZA) resulted from research undertaken by Vital Chorine, who found that subcutaneous nicotinamide might prolong the survival of guinea pigs infected with MTB [63]. The drug's active form, pyrazinoic acid, is produced when the parent molecule enters the bacteria passively and is broken down by the cytoplasmic enzyme pyrazinamidase (PZase) [64,65]. The M. tuberculosis fatty acid synthetase I enzyme may be inhibited by PZA and its analogue, 5-chloro-PZA, making it a potential bacteriostatic drug. An acidic pH increases the PZA's activity against slowly growing Mtb and replicating ones [66]. Similar to PZA, ethambutol (2,2′ ethylenediimino-di-1-butanol) was initially identified at American Cynamid's Lederle Laboratories and tested on animals right away after its unique stereospecific activity was revealed. However, early biochemical research revealed that both replicating and nonreplicating mycobacteria quickly absorbed ethambutol (EMB), and that it was only effective against replicating bacilli. In these cases, it was discovered to hinder RNA production and glycerol metabolism [67,68]. Research on EMB resistance has also been shown to be challenging to interpret because high-level resistance, previously thought to be a sign of the possible main targets, was only seen when several mutations were present. Therefore, more research is necessary to gain a more accurate understanding of its primary and secondary impacts.

Initially identified as having antibiotic activity in conditioned media of the soil bacterium *Nocardia mediterranei*, rifampicin is a semisynthetic derivative of the natural substance ansamycin (named after a famous French movie about jewel heists). Surprisingly, the single constituent of this extract, known as rifamycin, that can be separated into a pure crystalline form is a small species (5–10%) with a relatively low activity level. However, it was coincidentally shown to become active during incubation in an oxygenated aqueous solution. When >96% of all the resistance mutations were found to be mapped to an 81-nucleotide region in the coding sequence of the RNA polymerase β subunit responsible for rifampicin binding, a study of rifampicin-resistant mutants subsequently confirmed that this inhibition accounted for its antitubercular activity [68,69]. Bedaquiline (BDQ; formerly TMC207 and R207910) is not only the first FDA-approved medicine produced in the current era of molecular science, but it is also the only clinical therapy approved for the treatment of TB in patients older than 40 years [70]. BDQ was found via high-throughput phenotypic screening for active compounds against *M. smegmatis*, a saprophytic mycobacterium. It was then demonstrated to exhibit activity against *M. bovis* BCG and Mtb [71]. The development of resistant mutants and subsequent whole-genome resequencing provided the first clues for the functional target of BDQ. Nevertheless, a recent investigation of resistant mutants derived from clinical isolates revealed that approximately 38% of mutations have no connection to the ATP synthase operon [72]. Thus, it is feasible that more targets have yet to be found even if the now-available data indicate that BDQ targets ATP synthase.

11. Public Health Strategies and Future Directions

Addressing the complex interplay between HIV-TB co-infection and resistance in India requires a multifaceted approach. Strengthening healthcare infrastructure, improving diagnostic capacities, expanding access to integrated HIV and TB services, and enhancing surveillance systems are paramount. Innovative strategies, such as introducing new diagnostic tools (e.g., point-of-care testing), optimizing treatment regimens, and implementing infection control measures, are critical for improving the clinical outcomes and reducing the transmission rates.

Furthermore, addressing the social determinants of health, such as poverty, malnutrition, and access to healthcare, is essential for mitigating the impact of HIV-TB co-infection in vulnerable populations. Collaborative efforts between healthcare providers, researchers, policymakers, and community stakeholders are indispensable for developing evidence-based interventions and achieving sustainable improvements in public health outcomes.

12. Conclusions

The intersection of HIV-TB co-infection and resistance presents a formidable challenge to healthcare systems in India. This review highlights the epidemiological complexities, diagnostic challenges, treatment obstacles, and public health strategies necessary to address to mitigate the impact of co-infection and resistance. Continued research, innovation, and collaborative efforts are essential to improving clinical outcomes, reducing the transmission rates, and ultimately achieving the control of both the HIV and TB epidemics in India and beyond.

Funding: This research received no external funding.

Acknowledgments: None to be acknowledged as this work did not involve funding, administrative support or technical inputs from anyone other than the enlisted authors.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Goldfeld, A.; Ellner, J.J. Pathogenesis and Management of HIV/TB Co-Infection in Asia. *Tuberculosis* **2007**, *87* (Suppl. S1), S26–S30. [CrossRef] [PubMed]
2. Bagcchi, S. WHO's Global Tuberculosis Report 2022. *Lancet Microbe* **2023**, *4*, E20. [CrossRef] [PubMed]
3. Jilani, T.N.; Avula, A.; Zafar Gondal, A.; Siddiqui, A.H. *Active Tuberculosis*; StatPearls Publising: Treasure Island, FL, USA, 2023.
4. Rao, S. Tuberculosis and Patient Gender: An Analysis and Its Implications in Tuberculosis Control. *Lung India* **2009**, *26*, 46–47. [CrossRef] [PubMed]
5. Viswanathan, V.K. Latent TB Infection in Children and Adolescents: Scientific Rationale and Programmatic Management. *Indian J. Tuberc.* **2023**, *70* (Suppl. S1), S35–S38. [CrossRef] [PubMed]
6. Spooner, E.; Reddy, S.; Ntoyanto, S.; Sakadavan, Y.; Reddy, T.; Mahomed, S.; Mlisana, K.; Dlamini, M.; Daniels, B.; Luthuli, N.; et al. TB Testing in HIV-Positive Patients Prior to Antiretroviral Treatment. *Int. J. Tuberc. Lung Dis.* **2022**, *26*, 224–231. [CrossRef] [PubMed]
7. Mandal, S.; Rao, R.; Joshi, R. Estimating the Burden of Tuberculosis in India: A Modelling Study. *Indian J. Community Med.* **2023**, *48*, 436–442. [CrossRef] [PubMed]
8. Selvaraju, S.; Velayutham, B.; Rao, R.; Rade, K.; Thiruvengadam, K.; Asthana, S.; Balachandar, R.; Bangar, S.D.; Bansal, A.K.; Bhat, J.; et al. Prevalence and Factors Associated with Tuberculosis Infection in India. *J. Infect. Public Health* **2023**, *16*, 2058–2065. [CrossRef]
9. Peloquin, C.A.; Davies, G.R. The Treatment of Tuberculosis. *Clin. Pharmacol. Ther.* **2021**, *110*, 1455–1466. [CrossRef] [PubMed]
10. Lai, R.P.J.; Meintjes, G.; Wilkinson, R.J. HIV-1 Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. *Semin. Immunopathol.* **2016**, *38*, 185–198. [CrossRef]
11. Gao, J.; Zheng, P.; Fu, H. Prevalence of TB/HIV Co-Infection in Countries except China: A Systematic Review and Meta-Analysis. *PLoS ONE* **2013**, *8*, E64915. [CrossRef] [PubMed]
12. Hamada, Y.; Getahun, H.; Tadesse, B.T.; Ford, N. HIV-Associated Tuberculosis. *Int. J. STD AIDS* **2021**, *32*, 780–790. [CrossRef] [PubMed]
13. Liu, E.; Makubi, A.; Drain, P.; Spiegelman, D.; Sando, D.; Li, N.; Chalamilla, G.; Sudfeld, C.R.; Hertzmark, E.; Fawzi, W.W. Tuberculosis Incidence Rate and Risk Factors among HIV-Infected Adults with Access to Antiretroviral Therapy. *AIDS* **2015**, *29*, 1391–1399. [CrossRef] [PubMed]

14. Williams, B.G.; Granich, R.; Chauhan, L.S.; Dharmshaktu, N.S.; Dye, C. The Impact of HIV/AIDS on the Control of Tuberculosis in India. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 9619–9624. [CrossRef] [PubMed]
15. National AIDS Control Organization. *India HIV Estimation 2017-Technical Report*; NACO, Ministry of Health and Family Welfare, Government of India: New Delhi, India, 2017. Available online: https://naco.gov.in/sites/default/files/HIV%20Estimations%202017%20Report_1.pdf (accessed on 25 September 2024).
16. Geldmacher, C.; Koup, R.A. Pathogen-Specific T Cell Depletion and Reactivation of Opportunistic Pathogens in HIV Infection. *Trends Immunol.* **2012**, *33*, 207–214. [CrossRef] [PubMed]
17. Deshmukh, R.; Shah, A.; Sachdeva, K.S.; Sreenivas, A.N.; Gupta, R.S.; Khaparde, S.D. Scaling up of HIV-TB Collaborative Activities: Achievements and Challenges in India. *Indian J. Tuberc.* **2016**, *63*, 4–7. [CrossRef] [PubMed]
18. Torpey, K.; Agyei-Nkansah, A.; Ogyiri, L.; Forson, A.; Lartey, M.; Ampofo, W.; Akamah, J.; Puplampu, P. Management of TB/HIV Co-Infection: The State of the Evidence. *Ghana Med. J.* **2020**, *54*, 186–196. [CrossRef] [PubMed]
19. Shaik, J.; Pillay, M.; Jeena, P. A Review of Host-Specific Diagnostic and Surrogate Biomarkers in Children with Pulmonary Tuberculosis. *Paediatr. Respir. Rev.* **2024**, *epub ahead of print*. [CrossRef] [PubMed]
20. Kwok, A.J.; Mentzer, A.; Knight, J.C. Host Genetics and Infectious Disease: New Tools, Insights and Translational Opportunities. *Nat. Rev. Genet.* **2021**, *22*, 137–153. [CrossRef]
21. Rewari, B.B.; Kumar, A.; Mandal, P.P.; Puri, A.K. HIV TB Coinfection—Perspectives from India. *Expert Rev. Respir. Med.* **2021**, *15*, 911–930. [CrossRef]
22. Bruchfeld, J.; Correia-Neves, M.; Källenius, G. Tuberculosis and HIV Coinfection: Table 1. *Cold Spring Harb. Perspect. Med.* **2015**, *5*, a017871. [CrossRef] [PubMed]
23. Hoshino, Y.; Hoshino, S.; Gold, J.A.; Raju, B.; Prabhakar, S.; Pine, R.; Rom, W.N.; Nakata, K.; Weiden, M. Mechanisms of Polymorphonuclear Neutrophil–Mediated Induction of HIV-1 Replication in Macrophages during Pulmonary Tuberculosis. *J. Infect. Dis.* **2007**, *195*, 1303–1310. [CrossRef] [PubMed]
24. Husain, A.A.; Kupz, A.; Kashyap, R.S. Controlling the Drug-Resistant Tuberculosis Epidemic in India: Challenges and Implications. *Epidemiol. Health* **2021**, *43*, e2021022. [CrossRef] [PubMed]
25. Aliyu, A.Y.; Adeleke, O.A. Latest Progress on Tuberculosis and HIV Co-Infection: A Closer Look at People of Different Ages. *Adv. Ther.* **2024**, 2400033. [CrossRef]
26. Updated List of HIV Medicines; 2024. Available online: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/fda-approved-hiv-medicines (accessed on 25 September 2024).
27. Tseng, A.; Seet, J.; Phillips, E.J. The Evolution of Three Decades of Antiretroviral Therapy: Challenges, Triumphs and the Promise of the Future. *Br. J. Clin. Pharmacol.* **2015**, *79*, 182–194. [CrossRef]
28. Moreno, S.; Perno, C.; Mallon, P.; Behrens, G.; Corbeau, P.; Routy, J.; Darcis, G. Two-drug *vs.* Three-drug Combinations for HIV-1: Do We Have Enough Data to Make the Switch? *HIV Med.* **2019**, *20*, 2–12. [CrossRef] [PubMed]
29. Singh, A.; Prasad, R.; Balasubramanian, V.; Gupta, N. Drug-Resistant Tuberculosis and HIV Infection: Current Perspectives. *HIVAIDS Res. Palliat. Care* **2020**, *12*, 9–31. [CrossRef]
30. Ling-Hu, T.; Rios-Guzman, E.; Lorenzo-Redondo, R.; Ozer, E.A.; Hultquist, J.F. Challenges and Opportunities for Global Genomic Surveillance Strategies in the COVID-19 Era. *Viruses* **2022**, *14*, 2532. [CrossRef]
31. Li, T.; Yang, Y.; Qi, H.; Cui, W.; Zhang, L.; Fu, X.; He, X.; Liu, M.; Li, P.; Yu, T. CRISPR/Cas9 Therapeutics: Progress and Prospects. *Signal Transduct. Target. Ther.* **2023**, *8*, 36. [CrossRef] [PubMed]
32. Farhat, M.; Cox, H.; Ghanem, M.; Denkinger, C.M.; Rodrigues, C.; Abd El Aziz, M.S.; Enkh-Amgalan, H.; Vambe, D.; Ugarte-Gil, C.; Furin, J.; et al. Drug-Resistant Tuberculosis: A Persistent Global Health Concern. *Nat. Rev. Microbiol.* **2024**. [CrossRef]
33. Islam, M.S.; Chughtai, A.A.; Seale, H. Reflecting on the Updates to the World Health Organisation 2019 Tuberculosis Infection Control Guidelines through the Lens of a Low-Income/High TB Burden Country. *J. Infect. Public Health* **2020**, *13*, 1057–1060. [CrossRef]
34. Sterling, T.R.; Njie, G.; Zenner, D.; Cohn, D.L.; Reves, R.; Ahmed, A.; Menzies, D.; Horsburgh, C.R.; Crane, C.M.; Burgos, M.; et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm. Rep.* **2020**, *69*, 1–11. [CrossRef]
35. Uplekar, M.; Weil, D.; Lonnroth, K.; Jaramillo, E.; Lienhardt, C.; Dias, H.M.; Falzon, D.; Floyd, K.; Gargioni, G.; Getahun, H.; et al. WHO's Global TB Programme. WHO's New End TB Strategy. *Lancet* **2015**, *385*, 1799–1801. [CrossRef] [PubMed]
36. Solanki, S.; Kumar Das, H. Antimicrobial Resistance: Molecular Drivers and Underlying Mechanisms. *J. Med. Surg. Public Health* **2024**, *3*, 100122. [CrossRef]
37. Lan, Z.; Ahmad, N.; Baghaei, P.; Barkane, L.; Benedetti, A.; Brode, S.K.; Brust, J.C.M.; Campbell, J.R.; Chang, V.W.L.; Falzon, D.; et al. Drug-Associated Adverse Events in the Treatment of Multidrug-Resistant Tuberculosis: An Individual Patient Data Meta-Analysis. *Lancet Respir. Med.* **2020**, *8*, 383–394. [CrossRef] [PubMed]
38. *Global Tuberculosis Report 2019*; World Health Organization: Geneva, Switzerland, 2019.
39. Migliori, G.B.; Tiberi, S.; Zumla, A.; Petersen, E.; Chakaya, J.M.; Wejse, C.; Muñoz Torrico, M.; Duarte, R.; Alffenaar, J.W.; Schaaf, H.S.; et al. MDR/XDR-TB Management of Patients and Contacts: Challenges Facing the New Decade. The 2020 Clinical Update by the Global Tuberculosis Network. *Int. J. Infect. Dis.* **2020**, *92*, S15–S25. [CrossRef] [PubMed]
40. Nema, V.; Jadhav, S. Significance of Upcoming Technologies and Their Potential Applications in Understanding Microbial Diversity. In *Microbial Diversity in the Genomic Era*; Elsevier: Amsterdam, The Netherlands, 2024; pp. 697–712, ISBN 978-0-443-13320-6.

41. Tuberculosis Chemotherapy Centre. A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India. *Bull World Health Organ.* **1959**, *21*, 51–144.
42. Sazali, M.F.; Rahim, S.S.S.A.; Mohammad, A.H.; Kadir, F.; Payus, A.O.; Avoi, R.; Jeffree, M.S.; Omar, A.; Ibrahim, M.Y.; Atil, A.; et al. Improving Tuberculosis Medication Adherence: The Potential of Integrating Digital Technology and Health Belief Model. *Tuberc. Respir. Dis.* **2023**, *86*, 82–93. [CrossRef] [PubMed]
43. Subbaraman, R.; Nathavitharana, R.R.; Mayer, K.H.; Satyanarayana, S.; Chadha, V.K.; Arinaminpathy, N.; Pai, M. Constructing Care Cascades for Active Tuberculosis: A Strategy for Program Monitoring and Identifying Gaps in Quality of Care. *PLoS Med.* **2019**, *16*, E1002754. [CrossRef] [PubMed]
44. Pradipta, I.S.; Houtsma, D.; van Boven, J.F.; Alffenaar, J.C.; Hak, E. Interventions to Improve Medication Adherence in Tuberculosis Patients: A Systematic Review of Randomized Controlled Studies. *NPJ Prim. Care Respir. Med.* **2020**, *30*, 21. [CrossRef] [PubMed]
45. Acharya, S.; Parthasarathy, M.; Palkar, A.; Keskar, P.; Setia, M.S. Barriers for Antiretroviral Therapy Adherence and Viral Suppression in Members of the Key Population in Mumbai, India: Implications for Interventions. *Indian J. Dermatol.* **2021**, *66*, 378–385. [CrossRef]
46. Manosuthi, W.; Wiboonchutikul, S.; Sungkanuparph, S. Integrated Therapy for HIV and Tuberculosis. *AIDS Res. Ther.* **2016**, *13*, 22. [CrossRef] [PubMed]
47. Sun, J.; Schiffman, J.; Raghunath, A.; Ng Tang, D.; Chen, H.; Sharma, P. Concurrent Decrease in IL-10 with Development of Immune-Related Adverse Events in a Patient Treated with Anti-CTLA-4 Therapy. *Cancer Immun.* **2008**, *8*, 9. [PubMed]
48. Sereti, I.; Rodger, A.J.; French, M.A. Biomarkers in Immune Reconstitution Inflammatory Syndrome: Signals from Pathogenesis. *Curr. Opin. HIV AIDS* **2010**, *5*, 504–510. [CrossRef] [PubMed]
49. Tadokera, R.; Wilkinson, K.A.; Meintjes, G.A. Role of the Interleukin 10 Family of Cytokines in Patients with Immune Reconstitution Inflammatory Syndrome Associated with HIV Infection and Tuberculosis. *J. Infect. Dis.* **2013**, *207*, 1148–1156. [CrossRef]
50. Cevaal, P.M.; Bekker, L.G.; Hermans, S. TB-IRIS Pathogenesis and New Strategies for Intervention: Insights from Related Inflammatory Disorders. *Tuberculosis* **2019**, *18*, 101863. [CrossRef]
51. World Health Organisation. WHO Global Tuberculosis Report 2022. Available online: https://www.iom.int/sites/g/files/tmzbdl486/files/documents/2023-03/Global-TB-Report-2022.pdf (accessed on 25 September 2024).
52. Breen, R.A.; Smith, C.J.; Bettinson, H.; Dart, S.; Bannister, B.; Johnson, M.A.; Lipman, M.C. Paradoxical Reactions during Tuberculosis Treatment in Patients with and without HIV Co-Infection. *Thorax* **2004**, *59*, 704–707. [CrossRef] [PubMed]
53. Lawn, S.D.; Wilkinson, R.J.; Lipman, M.C.; Wood, R. Immune Reconstitution and "Unmasking" of Tuberculosis during Antiretroviral Therapy. *Am. J. Respir. Crit. Care Med.* **2008**, *177*, 680–685. [CrossRef] [PubMed]
54. Breen, R.A.; Smith, C.J.; Cropley, I.; Johnson, M.A.; Lipman, M.C. Does immune reconstitution syndrome promote active tuberculosis in patients receiving highly active antiretroviral therapy? *AIDS* **2005**, *19*, 1201–1206. [CrossRef]
55. Meintjes, G.; Lawn, S.D.; Scano, F.; Maartens, G.; French, M.A.; Worodria, W.; Elliott, J.H.; Murdoch, D.; Wilkinson, R.J.; Seyler, C.; et al. Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome: Case Definitions for Use in Resource-Limited Settings. *Lancet Infect. Dis.* **2008**, *8*, 516–523. [CrossRef]
56. A Report from NIH-National Cancer Institute "The First AIDS Drug". Available online: https://Ccr.Cancer.Gov/News/Landmarks/Article/First-Aids-Drugs#:~:text=Azidothymidine%20(AZT),%20a%20compound,immune%20function%20of%20AIDS%20patients (accessed on 25 September 2024).
57. *CDC's HIV/AIDs Timeline*; CDC: Atlanta, GA, USA, 2020. Available online: https://npin.cdc.gov/pages/cdcs-hivaids-timeline#:~:text=September%2024:%20CDC%20uses%20the,first%20case%20definition%20for%20AIDS.&text=December%2010:%20Report%20of%20AIDS%20likely%20from%20blood%20transfusion.&text=December%2017:%20Reports%20of%20AIDS%20hinting%20of%20perinatal%20transmission (accessed on 25 September 2024).
58. Yarchoan, R.; Mitsuya, H.; Pluda, J.M.; Marczyk, K.S.; Thomas, R.V.; Hartman, N.R.; Brouwers, P.; Perno, C.F.; Allain, J.P.; Johns, D.G.; et al. The National Cancer Institute Phase I Study of 2′,3′-Dideoxyinosine Administration in Adults with AIDS or AIDS-Related Complex: Analysis of Activity and Toxicity Profiles. *Rev. Infect. Dis.* **1990**, *12* (Suppl. S5), S522–S533. [CrossRef]
59. Antiretroviral Drug Discovery and Development. Available online: https://www.Niaid.Nih.Gov/Diseases-Conditions/Antiretroviral-Drug-Development (accessed on 25 September 2024).
60. Zumla, A.; Nahid, P.; Cole, S.T. Advances in the Development of New Tuberculosis Drugs and Treatment Regimens. *Nat. Rev. Drug Discov.* **2013**, *12*, 388–404. [CrossRef] [PubMed]
61. Vilchèze, C.; Jacobs, W.R., Jr. The Mechanism of Isoniazid Killing: Clarity through the Scope of Genetics. *Annu. Rev. Microbiol.* **2007**, *61*, 35–50. [CrossRef] [PubMed]
62. Chakraborty, S.; Rhee, K.Y. Tuberculosis Drug Development: History and Evolution of the Mechanism-Based Paradigm. *Cold Spring Harb Perspect Med.* **2015**, *5*, A021147. [CrossRef] [PubMed]
63. Chorine, V. Action de l'amide Nicotinique Sur Les Bacilles Du Genre Mycobcaterium. *C R Hebd Seances Acad. Sci.* **1945**, *220*, 150–151.
64. Anthony, R.M.; Den Hertog, A.L.; van Soolingen, D. "Happy the Man, Who, Studying Nature's Laws, Thro" Known Effects Can Trace the Secret Cause.' Do We Have Enough Pieces to Solve the Pyrazinamide Puzzle? *J. Antimicrob. Chemother.* **2018**, *73*, 1750–1754. [CrossRef] [PubMed]

65. Lamont, E.A.; Dillon, N.A.; Baughn, A.D. The Bewildering Antitubercular Action of Pyrazinamide. *Microbiol. Mol. Biol. Rev.* **2020**, *84*, E00070-19. [CrossRef] [PubMed]
66. Vilchèze, C. Mycobacterial Cell Wall: A Source of Successful Targets for Old and New Drugs. *Appl. Sci.* **2020**, *10*, 2278. [CrossRef]
67. Thomas, J.P.; Baughn, C.O.; Wilkinson, R.G.; Shepherd, R.G. A New Synthetic Compound with Antituberculous Activity in Mice: Ethambutol (Dextro-2,2′-(Ethylenediimino)-Di-l-Butanol). *Am. Rev. Respir. Dis.* **1961**, *83*, 891–893. [PubMed]
68. Telenti, A.; Imboden, P.; Marchesi, F.; Lowrie, D.; Cole, S.; Colston, M.J.; Matter, L.; Schopfer, K.; Bodmer, T. Detection of Rifampicin-Resistance Mutations in *Mycobacterium tuberculosis*. *Lancet* **1993**, *341*, 647–650. [CrossRef]
69. Levin, M.E.; Hatfull, G.F. *Mycobacterium Smegmatis* RNA Polymerase: DNA Supercoiling, Action of Rifampicin and Mechanism of Rifampicin Resistance. *Mol. Microbiol.* **1993**, *8*, 277–285. [CrossRef]
70. Cohen, J. Infectious Disease. Approval of Novel TB Drug Celebrated—With Restraint. *Science* **2013**, *339*, 130. [CrossRef] [PubMed]
71. Andries, K.; Verhasselt, P.; Guillemont, J.; Göhlmann, H.W.; Neefs, J.M.; Winkler, H.; Van Gestel, J.; Timmerman, P.; Zhu, M.; Lee, E.; et al. A Diarylquinoline DrugZActive on the ATP Synthase of *Mycobacterium tuberculosis*. *Science* **2005**, *307*, 223–227. [CrossRef] [PubMed]
72. Huitric, E.; Verhasselt, P.; Koul, A.; Andries, K.; Hoffner, S.; Andersson, D.I. Rates and Mechanisms of Resistance Development in *Mycobacterium tuberculosis* to a Novel Diarylquinoline ATP Synthase Inhibitor. *Antimicrob. Agents Chemother.* **2010**, *54*, 1022–1028. [CrossRef] [PubMed]