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Review Paper

HIV-TB Co-Infection: the global challenge

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ABSTRACT:
Tuberculosis was considered to be on the brink of elimination in the developed world until the late 1980s, when new HIV related TB cases and multidrug resistant TB (MDR-TB) emerged. HIV disease is manifested by immunodeficiency causing disruption of immune surveillance mechanisms, allowing for the development of opportunistic infections among which TB is most prevalent. These two infections place immense burden on health care systems worldwide. During the last two decades, sustained research and public health initiatives on prevention and therapeutic advances have allayed morbidity and mortality due to HIV and TB to a large extent, however more needs to be done. Tuberculosis (TB) is the primary cause of morbidity among HIV-positive people and is the most prevalent opportunistic infection in reactive people. The co-infection of two is one of the major global health challenges in the present time especially for people in developing nations, particularly women and adolescents.[Dembele et al.,2008] Even with effective immune reconstitution and high CD4 cell counts with antiretroviral therapy, the risk of TB in HIV-infected patients remains high, remaining above the background risk of the general population. [Sterling TR et al., 2010]. It can happen at any stage of the disease and is usually recognised as an early symptom of an undiagnosed AIDS illness. [Corbet et al., 2003] Both the infections interact in a synergistic way, with each accelerating the progression of the other thereby, leading to increased morbidity and mortality.[Swaminathan S et al.,2010] When compared to HIV-negative patients, HIV-positive patients are twenty times more likely to get this infection. [Tesfaye B et al.,2018] Immunodeficiency in HIV is manifested by the disruption of immune surveillance mechanisms, allowing for the development of opportunistic infections with malignant potential. It also plays a role in co-infection with TB as well. HIV also promotes the advancement of latent tuberculosis infection to disease.[Ramsay A et al.,2009] Therefore, HIV is the leading cause of failure to reach Tuberculosis (TB) control targets in high-HIV settings, and TB is also a leading cause of mortality among HIV-positive people.[Ahmad S et al.,2010]

Keywords: HIV TB, Co-Infection, global challenge

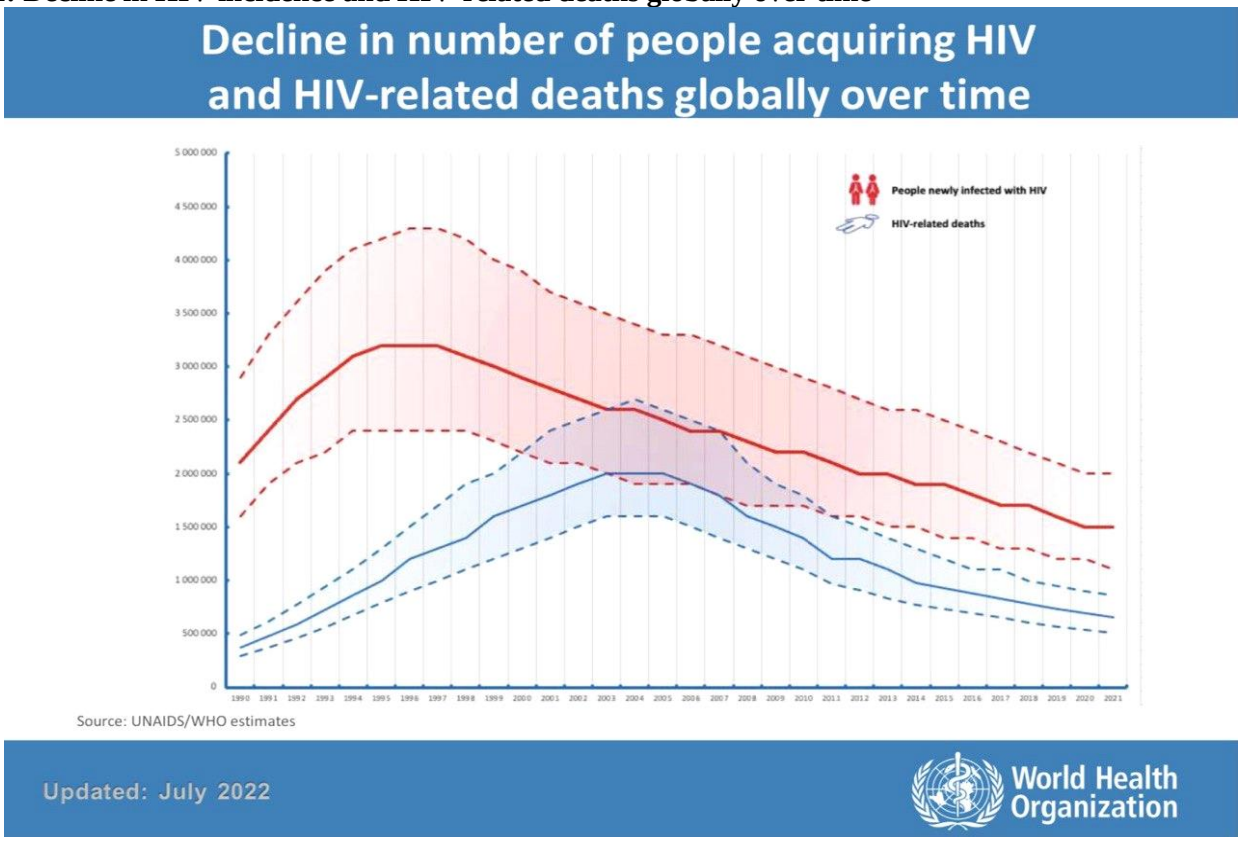
1. PROBLEM STATEMENT:

1.1 HIV INCIDENCE:

Global incidence [based on WHO Latest HIV estimates and updates on HIV policies uptake, December 2021 ;]
New HIV infections: Since the peak in 1997, new HIV infections have decreased by 52%.

- New HIV infections have decreased by 31% since 2010, falling from 2.1 million [1.5 million–2.9 million] in 2010 to 1.5 million [1.0 million–2.0 million] in 2020.
- Since 2010, the number of new HIV infections in children has dropped by 53%, from 320 000 [210 000–510 000] in 2010 to 150 000 [100 000–240 000] in 2020 [figure 1].
- 1.5 million [1.1−2.0 million] people were newly infected worldwide in 2021, down from 2.2 million [1.7−2.9 million] in 2010

Figure 1: Decline in HIV incidence and HIV-related deaths globally over time



People living with HIV (PL HIV): In 2020, there were 37.7 million [30.2 million–45.1 million] people living with HIV of which 36.0 million [28.9 million–43.2 million] were adults and 1.7 million [1.2 million–2.2 million] were children aged 0–14 years. Women and girls made for 53 percent of all HIV patients. About 6.1 million [4.9 million–7.3 million] people did not know that they were living with HIV in 2020. Approximately 38.4 million [33.9–43.8 million] people were living with HIV at the end of 2021

HIV incidence in INDIA: [based on India HIV Estimates 2020: National AIDS Control Organisation & ICMR-National Institute of Medical Statistics (2021)].

As per the recently released India HIV Estimation 2020 report, overall the estimated adult (15–49 years) HIV prevalence trend has been declining in India since the epidemic's peak in the year 2000 and has been stabilizing in recent years. The estimate for this indicator was 0.22% (0.17–0.29%) in 2020 (Table 1). In the same year, HIV prevalence among adult males (15–49 years) was estimated at 0.24% (0.18–0.32%) and among adult females at 0.20% (0.15–0.26%). The national adult prevalence continued to decline from its peak level of 0.54% in 2000-2001 through 0.33% in 2010 to 0.22% in 2020. This corresponds to a 33.3% decline in the last 10 years.

Nationally, there were an estimated 23.19 lakh (18.33 lakh – 29.78 lakh) PLHIV, with an adult (15–49 years) HIV prevalence of 0.22% (0.17%–0.29%) in 2020. This includes around 81 thousand CLHIV(Children Living with HIV) (<15YRS) accounting for 3.4% of the total PLHIV estimates and 44.3% of total infections were females.

There were 57.55 thousand (28.51 thousand –113.70 thousand) estimated new HIV infecions in 2020, which has declined by 48% since 2010 as baseline and by 89% since attaining the peak in 1997 with HIV incidence of 0.04 (0.02-0.09) per 1,000 uninfected population in 2020. It declined from 0.57 per 1,000 uninfected population in 1997 through 0.09-0.10 in 2009-10 to 0.04 per 1,000 HIV uninfected individuals in 2020.

There were approximately 31.94 thousand (20.50 thousand – 52.01 thousand) AIDS-related deaths estimated in 2020 which has declined by 82.24 % since 2010. The estimated AIDS-related mortality per 100,000 population was peaked at 24.34 per 100,000 in 2005 and declined through 15.13 in 2010 to 2.37 in 2020.

Particulars		Number/ %	Range
Adult (15–49 Years) Prevalence	**Total**	**0.22%**	**0.17–0.29**
	Male	0.23%	0.18–0.31
	Female	0.21%	0.15–0.26
Number of People Living with HIV	**Total**	**23,18,738**	**18,33,277–29,77,830**
	Adults (>15 yrs.)	22,37,308	17,73,563–28,69,016
	Women (>15 yrs.)	9,88,279	7,82,107–12,67,941
	Children (<15 yrs.)	81,430	58,650–1,09,538
PLHIV per Million Population	**Total**	**1721**	**1,361–2,210**
New HIV Infections	**Total**	**57,549**	**28.510–1,13,695**
	Adults (>15 yrs.)	51,802	25,154–1,04,339
	Women (>15 yrs.)	21,953	10,595–45,101
AIDS-related Deaths	**Total**	**31,944**	**20,467–52,007**
	Adults (>15 yrs.)	28,361	18,377–46,197
	Women (>15 yrs.)	7,201	4,046–12,837
	Children (<15 yrs.)	3,582	1,549–6,510
Pregnant women need ART for PPTCT	**Total**	**20,926**	**15,328–29,075**
Final MTCT Rate	**Total**	**27.45**	**20.30–33.52**

Table 1: National summary of the HIV/AIDS epidemic in 2020

1.2 TB INCIDENCE:

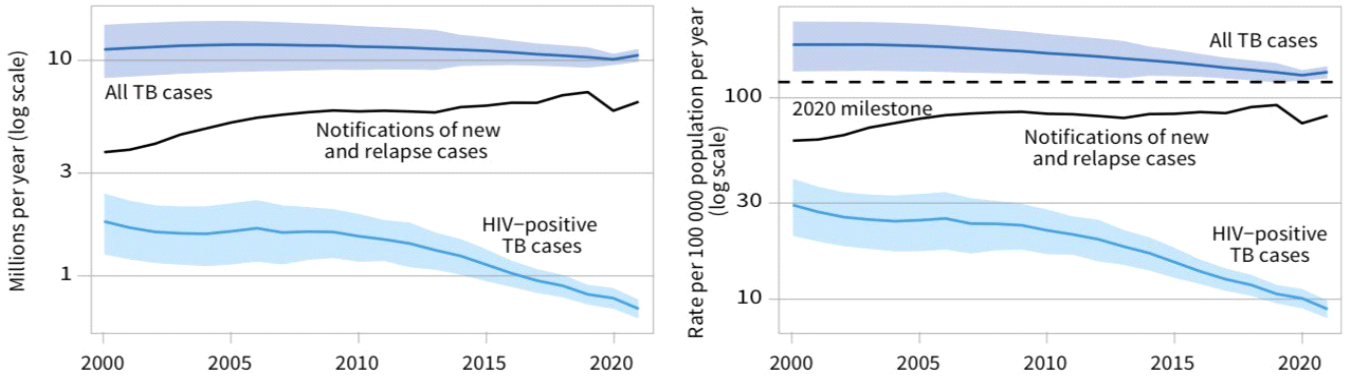
Global TB Incidence: [based on WHO global TB report 2022]

Global rise in 2021, years of decline reversed

An estimated 10.6 million people (95% UI: 9.9–11 million) fell ill with TB worldwide in 2021, an increase of 4.5% from 10.1 million (95% UI: 9.5–10.7 million) in 2020, reversing many years of slow decline (Fig. 2, left panel). Similarly, the TB incidence rate (new cases per 100 000 population per year) is estimated to have increased by 3.6% between 2020 and 2021, following declines of about 2% per year for most of the past 2 decades (Fig.2, right panel).

Figure 2. Global trends in the estimated number of incident TB cases (left) and the incidence rate (right), 2000-2020

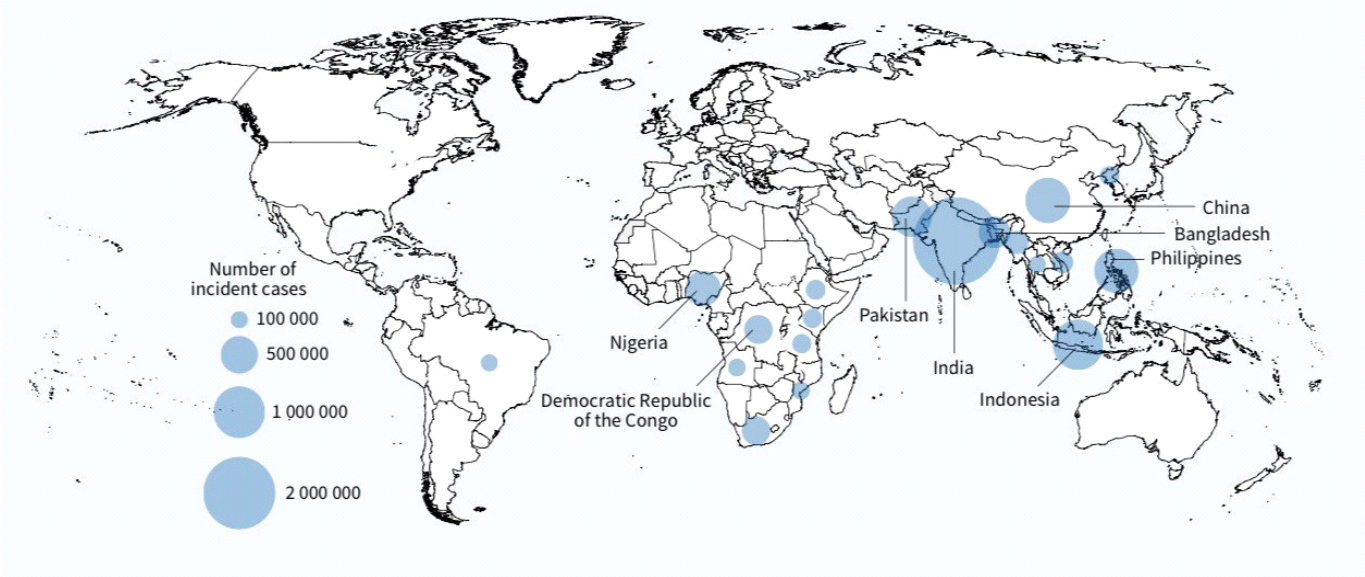
The horizontal dashed line shows the first milestone of the End TB Strategy, which was a 20% reduction in the TB incidence rate between 2015 and 2020. Shaded areas represent 95% uncertainty intervals.



Geographically, in 2021, the 30 high TB burden countries accounted for 87% of all estimated incident cases worldwide, and eight of these countries (Fig. 12) accounted for more than two thirds of the global total: India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and the Democratic Republic of the Congo (2.9%)(Figure.3)

Figure 3. Estimated TB incidence in 2021, for countries with at least 100,000 incident cases

The countries that rank first to eighth in terms of numbers of cases, and that accounted for about two thirds of global cases in 2021, are labelled.



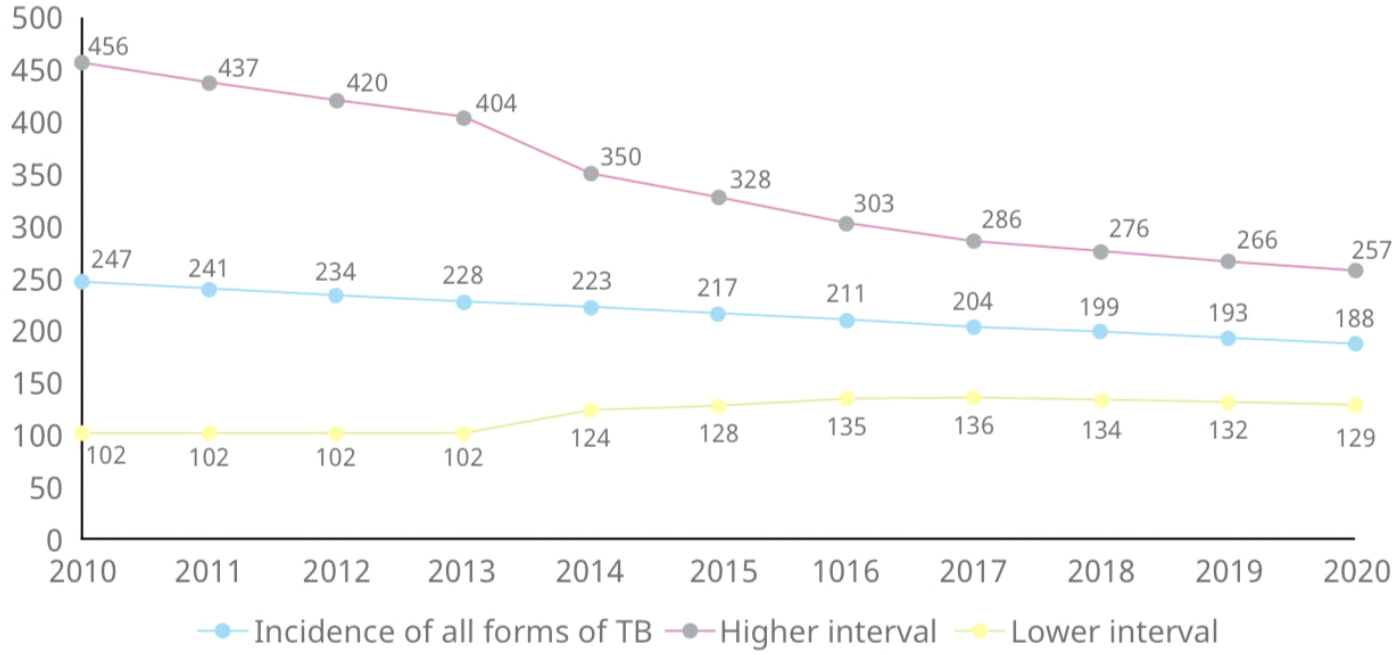
Years of progress in providing key TB services and reducing TB disease burden have been undone by the COVID-19 epidemic. Although there are occasional country and regional success stories, global TB targets are usually off track. The most visible effect is a significant reduction in the number of people newly diagnosed with TB and reported globally. This declined from 7.1 million in 2019 to 5.8 million in 2020, an 18% drop from 2012 and far short of the estimated 10 million persons who contracted tuberculosis in 2020. The reduction was accounted for by 16 countries, with India, Indonesia, and the Philippines suffering the most.

TB mortality have increased due to a lack of access to diagnosis and treatment. Best predictions for 2020 are 1.3 million HIV-negative TB fatalities (up from 1.2 million in 2019) and an additional 214 000 HIV-positive TB deaths (up from 209 000 in 2019), bringing the total back to 2017. Incidence (the number of people diagnosed with tuberculosis each year) decreases have come to a halt in recent years. In 2021 and 2022, the effects are expected to be significantly worse.

TB incidence in India: (Based on Ministry of Health and Family Welfare India TB Report 2022)

The estimated incidence of all forms of TB in India for the year 2020 was 188 per 100,000 population (129-257 per 100,000 population). The total number of incident TB patients (new & relapse) notified during 2021 was 19,33,381 which was 19% higher than that of 2020 (16,28,161) (Figure.4)

Figure 4: Estimated incidence of all forms of TB in India as per global TB report(Per lakh population)



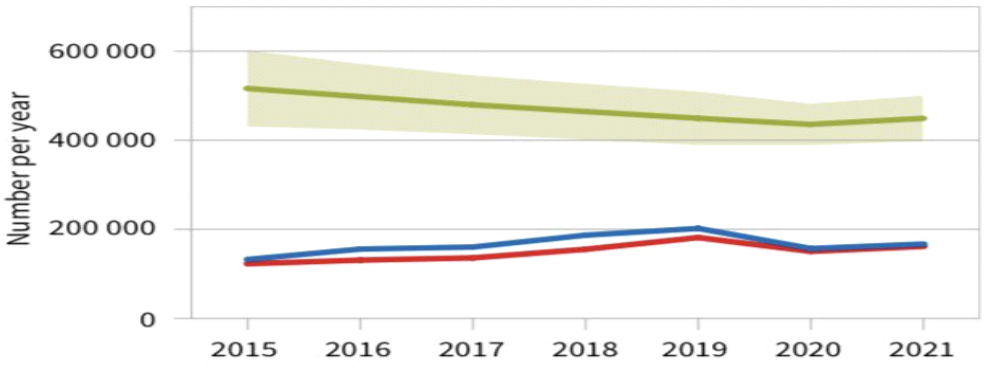
Incidence of MDR/XDR-TB: [based on WHO global TB report 2022]

Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019(Figure 5), consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020.

Figure. 5

Global number of people diagnosed with MDR/RR-TB (blue) and number enrolled on an MDR/RR-TB treatment regimen (red), compared with estimates of the global number of incident cases of MDR/RR-TB (green), 2015–2021

The shaded area represents the 95% uncertainty interval.



1.3 HIV-TB CO-INFECTION:

People living with PLHIV are 29 times (26–31) more likely to develop tuberculosis disease than people without PLHIV and living in the same country.

Table 2 : HIV-TB coinfection burden in India

Estimates of TB HIV Burden in India (Global TB Report 2021)	
HIV positive TB Incidence	53K (36K-72K) 3.8 (2.6-5.2) %
HIV positive TB mortality	11K (9.8-12K) 0.78 (0.71-0.84)/lac

2. PATHOGENESIS:

2.1 Pathogenesis of HIV*:*

HIV is known to gradually deplete native and memory CD4+ T cells and eventually lead to acquired immunodeficiency syndrome (AIDS). HIV infection has been shown to inhibit T helper 1 (Th1) cell activity and increase T helper 2 (Th2) cell activity [Becker Y et al.,2004]. This aberration is commonly referred to as Th1/Th2 cell switching [Becker Y et al.,2004], a phenomenon that Romangnani and colleagues believe is due to HIV preferential replication within Th2-like cells compared to Th1 cells which stimulate their proliferation [Romagnani S et al.,1994]. Higher CD8+ T-cell levels are thought to be a compensatory response to lower CD4+ levels [Gao L et al.,2018]. The Th1 to Th2 transition is responsible for the observed decrease in expression of IL-2 and IFN-γ and the increase in the expression of cytokines such as IL-4, IL-5 and IL-13 [Esser R et al.,1991] . The viral proteins gp120 and gp160, a subset of surface proteins on HIV, appear to be essential for this change, which also induces Th2 production of IL-4, a promoter of IgE and an inhibitor of Th1 differentiation [Secord E.A.,1996]. Depletion of CD4+ T cells severely compromises the host immune response, leaving the individual vulnerable to opportunistic infections such as tuberculosis [Granich R et al.,2010]. In acute HIV infection, type 1 interferon plays an important role in the T-cell response to HIV infection by inducing a proinflammatory state that slows viral replication [Doyle T et al.,2015]. Likewise, late-stage HIV infection involves both interferon type 1 and interferon-stimulated gene 15 protein (ISG15) as part of the antiviral response [Gao L et al.,2018]. There is evidence that the ISG15 protein, a protein released by type 1 interferons, inhibits HIV replication by disrupting Gag ubiquitination required for HIV replication [Okumura A et al.,2006].

Dendritic cells (DCs) are professional antigen presenting cells that, among other roles, are responsible for initial HIV uptake in anogenital mucosa and subsequent transport to lymph nodes and T cells [Harman A.N et al.,2006]. HIV manipulates surface receptor CCR5 for entry into DCs, a receptor that is highly expressed in CD11C+ DCs, a DC subgroup found exclusively in the human genital region [Bertram K.M et al.,2019]. HIV exploits the DCs antigen presentation abilities to present virion fractions to CD4+ T cells. To ensure access, HIV also facilitates DC maturation [Harman A.N et al.,2006].

Many viral infections result in mitochondrial dysfunction, which contributes to an accumulation of reactive oxygen species (ROS). NADPH oxidases and cytochrome P450 2E1 (CYP2E1) serve as the major sources of ROS in hepatitis C, influenza, and HIV [Gao L et al.,2018]. For HIV specifically, envelope protein Gp120 enhances the damage caused by ROS accumulation. In astrocytes, Gp120 upregulates expression of CYP2E1 and increased ROS [Shah A et al.,2013]. ROS can lead to tissue damage and chronic levels can lead to the development of spontaneous tumors [Factor V.M et al.,2000]. ROS production during HIV infections may also help initiate cell apoptosis by causing telomeric DNA damage [Zhao J et al.,2019]. HIV-induced ROS also leads to chronic inflammation that triggers the immune response and may increase the likelihood of developing other comorbidities [Van Epps P et al.,2017]

2.2 Role of HIV in exacerbation of M. tuberculosis infection:

HIV-associated local immune response dysfunction in HIV/TB coinfected patients reduce the likelihood of granuloma(one organized structure composed of epithelial macrophages surrounded by a ring of lymphocytes) to retain the tubercle bacilli, leading to their multiplication and dispersal, thereby leading to serious pathology [Lawn SD.,2002 ; Bezuidenhout J et al.,2009]. In addition, exacerbation of tuberculosis is associated with increased HIV replication in infection site of M. tuberculosis [Imperiali FG.,2001]. This is because HIV is known to replicate in activated CD4+Tcells and macrophages,known to accumulate at the site of granulomatosis [Imperiali FG.,2001]. For example, it is seen that there is an increase in the viral load in the pleural liquid more than in plasma in patients with pleural tuberculosis.

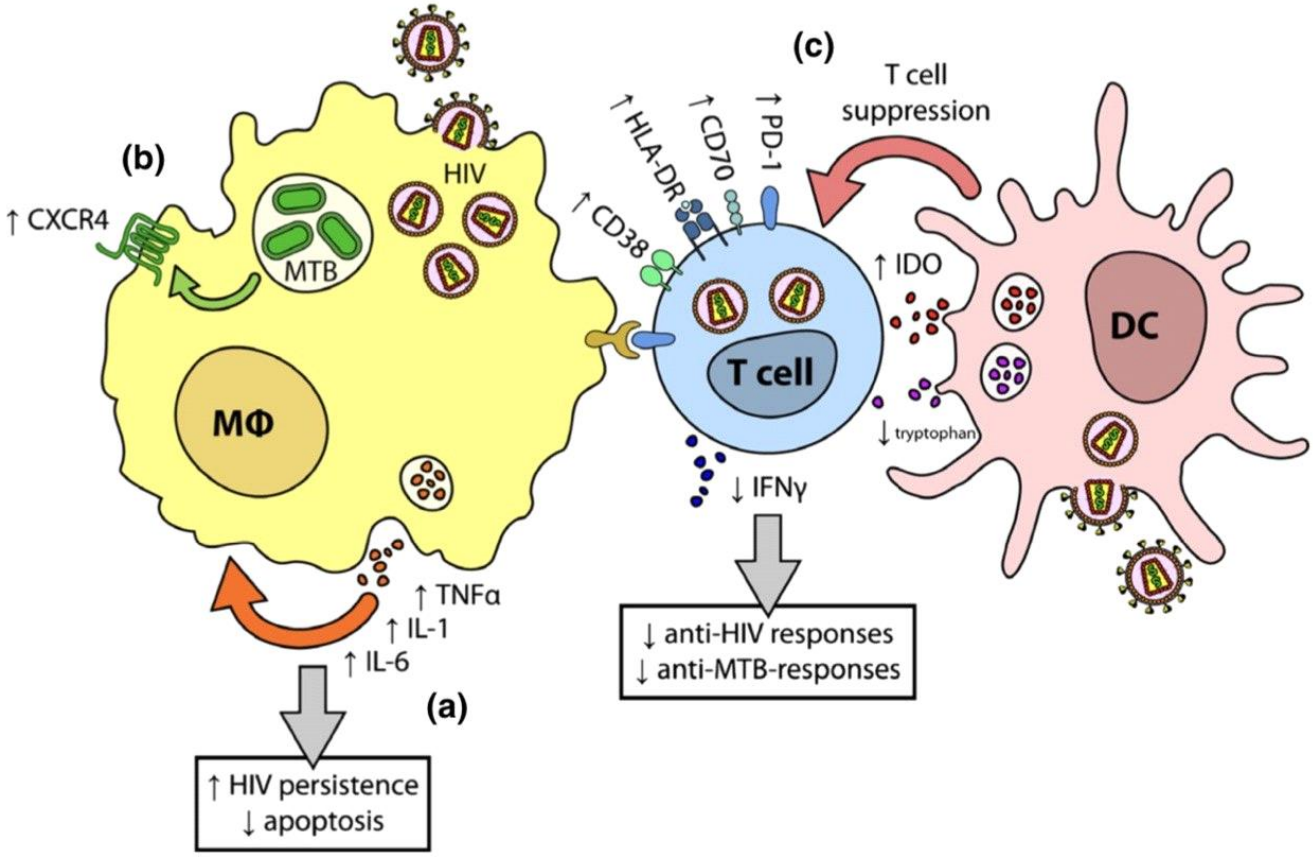
TB and HIV replication was also found to be greater in activated macrophages that are co-infected with M. tuberculosis and HIV than in only HIV-infected macrophages, emphasizing that HIV replication is increased at sites of M. tuberculosis infection [Lawn SD et al.,2002].

The killing of CD4+ T cells by HIV within granuloma is associated with primary tuberculosis or reactivation of tuberculosis [Diedrich CR et al.,2011]

The function of various immune cells such as macrophages and T cells is impaired in co-infected individuals [Patel et al.,2009 ; Geldmacher et al., 2008; Kumawat et al.,2010]. HIV/TB co-infected macrophages release tumor necrosis factor-a (TNF-α) to a lesser extent and induce lesser TNF-dependent apoptosis than those infected alone with M. tuberculosis [Patel et al.,2007 ; Kumawat et al.,2010]. In addition, there was evidence for a negative effect of HIV on the ability of TB-specific T cells to suppress bacteriogenesis. For example, after HIV infection in people with latent TB, there are fewer M. interferon-c (IFN-c)-producing M. memory T cells. In addition, studies have convincingly demonstrated that the production and proliferation of IFN-c and interleukin-2 (IL-2) by M. tuberculosis-specific T cells in HIV-infected individuals lower than in HIV-negative individuals with active TB [Hertoghe et al., 2000; Mendonca et al., 2007; Geldmacher et al., 2008].

Recent findings suggest that production of IL-10 is significantly higher in HIV and TB co-infected individuals after stimulation with M. tuberculosis, suggesting that chronic HIV infection may reduce cell mediated immunity against M. tuberculosis [Geldmacher et al.,2010]

Figure 6. Proposed model of HIV/Mycobacterium tuberculosis coinfection.



(a). Mycobacterium tuberculosis-infected resident alveolar macrophages produce increased levels of TNF-a, IL-1 and IL-6, leading to enhanced HIV replication (Briken et al., 2004) and persistence within macrophages. Furthermore, HIV/M. tuberculosis-coinfected macrophages are less prone to undergo TNF-dependent apoptosis (Kumawat et al., 2010). (b) Mycobacterium tuberculosis increases the expression of CXCR4 in alveolar macrophages, favouring entry of only X4 viruses (Wolday et al., 2005; Hoshino et al., 2004) potentially in chronic HIV infection. (c) HIV infection induces expression of immune activation markers, CD38, CD70 and HLA-DR, weakening T-cell responses against M. tuberculosis antigens (Hazenberg et al., 2003). Furthermore, high IL-10 and less IL-2 production in HIV/M. tuberculosis coinfection further explains the concept of diminished CMI responses against M. tuberculosis (Geldmacher et al., 2010)

3. STAGING OF HIV INFECTION:

In areas with adequate resources, laboratory measurements of CD4+ T cells and plasma HIV viral load are commonly used to establish a patient's degree of immunosuppression and the rate of destruction of the immune system[Simon V et al.,2006].

With insufficient resources to test CD4+ T-cell counts and plasma HIV viral load in many resource-limited settings, including many of the regions hardest hit by the HIV/AIDS epidemic, clinicians must rely on clinical parameters when assessing a patient's disease status. The WHO Clinical Staging system has been shown to be a practical and accurate way to manage HIV-infected patients, with international studies showing agreement between clinical manifestations included in the WHO staging system and laboratory markers including CD4 cell count and total lymphocyte count [Kagaayi J et al.,2007 ; Lynen L et al.,2006].

Table 3: WHO clinical staging of HIV [WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, World Health Organization, 2007]

Adults and Adolescents	**Children**
Clinical Stage 1	
• Asymptomatic • Persistent generalized lymphadenopathy (PGL)	• Asymptomatic • Persistent generalized lymphadenopathy (PGL)
Clinical Stage 2	
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (Sinusitis, Tonsillitis, Otitis Media, Pharyngitis) Herpes Zoster • Angular Cheilitis • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Seborrhoeic Dermatitis	• Unexplained persistent hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (Otitis Media, Otorrhoea, Sinusitis, Tonsillitis) • Herpes Zoster • Lineal gingival erythema • Recurrent oral ulceration • Papular Pruritic Eruption • Fungal nail infections • Extensive wart virus infection • Extensive Molluscum Contagiosum Unexplained persistent parotid enlargement
Clinical Stage 3	
• Unexplained severe weight loss (>10% of the presumed or measured body weight) Unexplained chronic diarrhoea for more than 1 month • Unexplained persistent fever (intermittent or constant for longer than 1 month)	• Unexplained moderate malnutrition not adequately responding to standard therapy Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C, intermittent or constant, for

• Persistent Oral Candidiasis • Oral Hairy Leucoplakia • Pulmonary Tuberculosis • Severe bacterial infections (such as Pneumonia, Empyema, Pyomyositis, bone or joint infection, Meningitis, bacteraemia) • Acute necrotizing ulcerative stomatitis, Gingivitis or Periodontitis • Unexplained anaemia (<8 g/dl), neutropenia(<0.5 x 109 /L) and/or chronic thrombocytopaenia (<50 x 109 /L)	longer than 1 month) • Persistent Oral Candidiasis (after the first 6 weeks of life) • Oral Hairy Leucoplakia • Lymph node Tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial Pneumonia • Acute necrotizing ulcerative gingivitis or Periodontitis • Unexplained anaemia (<**8 g/dl), neutropenia(<0.5 x 109 /L) and/or chronic thrombocytopaenia (<50 x 109 /L)** • Symptomatic Lymphoid Interstitial Pneumonitis Chronic HIV-associated lung disease, including Bronchiectasis

Clinical Stage 4	
• HIV wasting syndrome • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial Pneumonia • Chronic Herpes Simplex infection (orolabial, genital or anorectal of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi or lungs) • Extra pulmonary Tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system Toxoplasmosis HIV encephalopathy	• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis (jiroveci) Pneumonia • Recurrent severe bacterial infections (such as Empyema, Pyomyositis, bone or joint infection, Meningitis, but excluding Pneumonia) • Chronic Herpes Simplex infection (orolabial or cutaneous of more than 1 month duration or visceral at any site) • Oesophageal Candidiasis (or Candidiasis of trachea, bronchi, or lungs)

• Extra pulmonary Cryptococcosis, including Meningitis Disseminated non-tuberculous mycobacterial infection (NTM) • Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis • Chronic Isosporiasis • Disseminated mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis) Lymphoma (cerebral or B-cell non-Hodgkin's) • Symptomatic HIV-associated nephropathy or cardiomyopathy • Recurrent septicaemia (including non typhoidal Salmonella) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis	• Extra pulmonary Tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs with onset at age more than 1 month) • Central nervous system Toxoplasmosis (after the neonatal period) • HIV encephalopathy • Extra pulmonary Cryptococcosis, including Meningitis • Disseminated nontuberculous mycobacterial infection (NTM) Progressive Multifocal Leukoencephalopathy (PML) • Chronic Cryptosporidiosis (with diarrhoea) • Chronic Isosporiasis • Disseminated endemic mycosis (extra pulmonary Histoplasmosis, Coccidioidomycosis, Penicilliosis) • Cerebral or B-cell non-Hodgkin's Lymphoma • HIV-associated nephropathy or cardiomyopathy

A. In the development of this table, adolescents were defined as 15 years or older For those aged less than 15 years, the clinical staging for children should be used,
B. For children younger than 5 years, moderate malnutrition is defined as weight-for-height
C. For children younger than 5 years of age, severe wasting is defined as weight-for-height <–3 z-score; stunting is defined as length-for-age/height-for-age <–2 z-score; and severe acute malnutrition is either weight for height <–3 z-score or mid-upper-arm circumference <115 mm or the presence of oedema.

Advanced HIV Disease [National AIDS Control Organisation & ICMR-National Institute of Medical Statistics (2021). India HIV Estimates 2020: Technical Brief. New Delhi: NACO, Ministry of Health and Family Welfare, Government of India]

Definition of advanced HIV disease:

- For adults and adolescents, and children older than 5 years, advanced HIV disease is defined as CD4 cell count <200 cells/mm3 or WHO stage 3 or 4 event.
- Includes both ART-naive individuals and those who interrupt treatment and return to care.
- All children younger than 5 years of age (who are not already receiving ART and clinically stable) with HIV are considered as having advanced HIV disease.

People presenting with advanced HIV disease at the time of registration at the ART centre are at high risk of death, even after ART is started, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count < 100 cells/mm3 .

4. DIAGNOSIS:

4.1 Laboratory Diagnosis of HIV infection:

Timely HIV diagnosis in tuberculosis patients is essential to enable comprehensive management, timely initiation of antiretroviral therapy (ART), and to reduce the risk of morbidity and mortality in patients with tuberculosis/HIV coinfection. HIV infection can be determined through tests for:

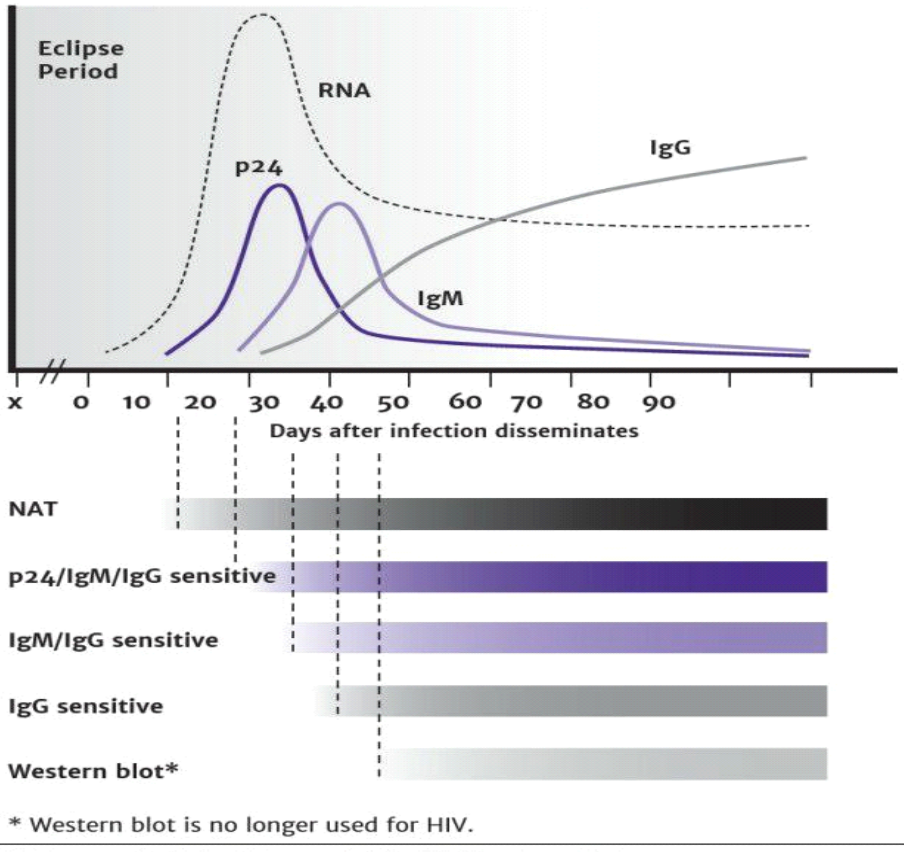
• Antibodies against the virus
• Virus antigens
• Viral RNA/DNA

In clinical practice, blood or serum tests are done (certain rapid tests may use a saliva sample) to detect antibodies or a combination of antibodies and viral antigens. The most common tests available of this type are:

- Rapid tests
- Enzyme-linked immunosorbent assay (ELISA)

These are highly reliable tests with >99% sensitivity and specificity. However, like all serological tests, they are subject to a "window period" (The time between HIV infection and the appearance of detectable antibodies or antigens which would results in a positive/reactive serological test) (fig.7). This period ranges from 2 weeks (for 4th generation tests) to 3 months from the time of infection, depending on the type of serological test and the patient's immune status.

Figure7 : HIV Test Window of Detection



Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M; NAT, nucleic acid test.

Notes:

a. Figure reproduced from CDC: HIV Diagnostic Tests.
b. Without PrEP or PEP exposure; PrEP or PEP exposure may delay seroconversion. Very early treatment of acute HIV infection may also alter the serologic response [Stekler 2022; Hare, et al. 2006; Kassutto, et al. 2005].

In view of the low prevalence of HIV in India, it is necessary to use three different principles or antigen-based rapid tests to confirm the diagnosis. Under the NACP, the most commonly used rapid tests are based on the principle of enzyme immunoassay, immuno-chromatography (lateral flow), immuno-concentration /dot-blot assays (vertical flow) and particle agglutination. All these different rapid tests should have a sensitivity of ≥ 99.5% and specificity of ≥ 98%. All samples reactive in the first test should further undergo confirmatory second/third tests based on different principles/antigens using the same serum/ plasma sample as that of the first test. The same blood sample is utilized for performing all the tests for identifying HIV antibodies. For indeterminate results, testing should be repeated on a second sample taken after 14–28 days.[National AIDS Control Organization (2021)]

In the case of sequential tests with conflicting results, the diagnosis can be confirmed using another methodology (serological or virological), always following the national algorithms.

The frequency of false positives in serological tests is very low (0.0004-0.0007%). False positives are caused by:[World Health Organization (WHO). Consolidated guidelines on HIV testing services. Geneva: WHO; 2015]

- Recent influenza vaccination
- Pregnancy (especially multiparous)
- Collagen disease (systemic lupus erythematosus)
- Chronic renal failure
- Error in sample labeling or handling

False negatives are also very rare and are almost always due to the window period mentioned above. Depending on the infection's prevalence in the population, false negatives can range from 0.03% to less than 0.001%. False negatives are caused by:

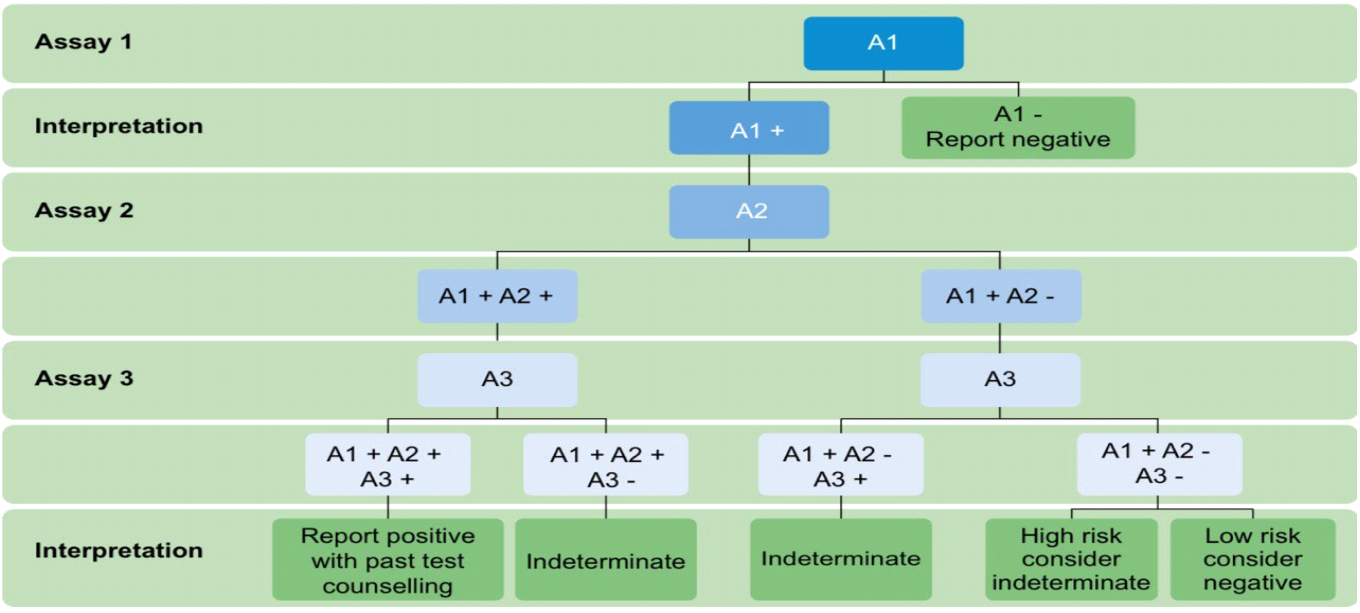
- The window period
- Advanced AIDS (very rare)
- Error in sample labeling or handling

On rare occasions, serological tests can yield indeterminate results, since they are not negative but do not meet the criteria for positivity, meaning that they could be reported as positive. Indeterminate results are caused by:

- Acute HIV infection
- Advanced AIDS
- Antibody cross-reactivity (lymphoma, multiple sclerosis, recent vaccination)
- Error in sample handling

Anyone with an indeterminate result should be assessed for risk factors for HIV infection. Presence of risk factors must prompt repeat testing for consecutive control in 14 days. If no risk factors are present, the indeterminate result should not be dismissed, and the test should be repeated while ruling out conditions other than HIV.

Fig. 8 -NACO HIV Testing Strategy



4.2 Diagnosis of TB:

4.2.1) Pulmonary TB (PTB)

Diagnosis of PTB is same in both HIV positive and HIV negative individuals and is based upon:

- Clinical manifestations
- Bacteriological tests

• Diagnostic imaging and other method

4.2.1.1 Clinical manifestations:

PTB in HIV-negative people have a wide range of clinical presentation, however, in HIV-positive people its presentation is majorly restricted to fever, weight loss, and night sweats. The clinical picture is frequently different because HIV-positive patients usually have less cavitation, inflammation, and endobronchial irritation, also chronic cough and hemoptysis are less common. If any of the four critical signs are present: fever, cough, weight loss, or night sweats, every HIV-positive individual should be tested for tuberculosis. A cough sample collected from a HIV-positive individual irrespective of its characteristics or duration should always be tested along with a sputum examination for bacteriological diagnosis of tuberculosis . Physical examination may not always help in differentiating pulmonary TB from other lung infections, moreover, auscultatory symptoms are often absent. (Farga V et al.,2011).

4.2.1.2 Bacteriological diagnosis (WHO 2015):

The bacteriological methods are:

• Smear microscopy
• Culture
• Xpert® MTB/RIF
• Immunochromatography

The isolation of M. tuberculosis in sputum or samples from bronchoalveolar lavage, preferably by molecular test, is required for a definite diagnosis of PTB. In the absence of this, smear microscopy and culture can be used. (Farga V et al.2011)

Sample Required:

According to the national norm, all HIV patients with a cough should have two to three sputum samples taken, regardless of how long they have had it. Two sputum samples are currently adequate, according to WHO standards, provided that nations have achieved optimal quality control of smear microscopy, as confirmed by an external quality assurance system.

The best sputum is the first of the morning, and a practical way of collecting two or three samples is the following :

Day 1 (sample 1): The patient offers a sputum sample on the day of his visit to the health facility after getting instructions (the sample should be collected in very-well-ventilated settings, and health workers should ideally use N-95 respirators or collect the sample outdoors). The patient will be given a receptacle to bring a second sample the following day.

Day 2 (samples 2 and 3)

• The patient collects a sample at home and brings it to the health centre early in the morning.

• When the patient brings the second sample to the health centre, he gives a third sample.

Sputum induction might be used in suspected cases of dry cough. The sputum induction technique includes collecting sputum in a safe, noninvasive manner using nebulizers to aid expectoration. To avoid contamination from nasal secretions or saliva, the treatment should be performed in the morning after cleansing the upper respiratory tract. An inhaled beta-adrenergic should be given to the patient ten minutes before starting to prevent bronchoconstriction, followed by nebulization with a 3-5 percent hypertonic solution for 10 to 15 minutes; the patient should then be encouraged to cough and spit. The sputum sample is collected in a specially designed container. If the sample is insufficient, the technique can be repeated once, half an hour later.

Processing of sputum sample for microscopy and culture: [GLI guidelines 2014]:

Purpose:

Processing sputum specimens has two objectives: decontamination of bacteria other than mycobacteria and liquefaction of mucous and organic debris in the specimen. Although there are several techniques available, none of them are ideal, meaning none of them will selectively destroy only contaminating flora and achieve complete liquefaction of the specimen. A reasonable compromise is to destroy as much of the contaminating bacteria as possible while harming as few mycobacteria as possible. All sputum specimens will be processed in this manner for preparation of AFB smears and liquid (MGIT) / solid (LJ) cultures.

Principle:

N-acetyl-L-cysteine (NALC), a mucolytic agent, is used for rapid digestion, which enables the decontaminating agent, NaOH, to be used at lower final concentration (in sputum). NALC loses activity rapidly in solution, so it is made fresh daily. Sodium citrate exerts a stabilizing effect on the NALC by chelating heavy metal ions present in the specimen. The phosphate buffer neutralizes the NaOH and dilutes the homogenate to lessen the viscosity and specific gravity prior to centrifugation. Mycobacteria have a low specific gravity and may remain buoyant during centrifugation. A relative centrifugal force of 3,000 g (not 3,000 rpm – the centrifuge must be calibrated) for 15 minutes is adequate to sediment mycobacteria. The rate at which mycobacteria sediment is critically dependent on time of centrifugation and relative centrifugal force applied to the specimen. A longer centrifugation time can offset a lower relative centrifugal force, but increased centrifugation time increases the temperature of the specimen, which leads to additional killing of

mycobacteria (hence, a refrigerated centrifuge is highly recommended).

ACID-FAST BACILLI MICROSCOPY (AFB):

Purpose:

The purpose of AFB microscopy is to detect acid-fast bacilli (AFB) by microscopic examination of clinical specimens and cultures. Both living and dead (viable and non-viable) bacilli will stain and be counted. A semi-quantitative grading system is used to report the number of AFB observed in stained smears. All sputum smears are prepared from decontaminated and concentrated specimens (Processing Sputum for Smear Microscopy and Qualitative Culture). These smears are stained with fl uorescent stains, either auramine O or auramine/rhodamine. The Ziehl-Neelsen stain can be used to confirm fluorescent smear results, but these results will not be reported. The Ziehl-Neelsen stain is used to confirm the presence of AFB in positive cultures (MGIT, LJ).

Principle:

For the fluorochrome stain, the principle of stain, decolorizer and counterstain is the same as for Ziehl-Neelsen staining. With auramine O stain, organisms fluoresce bright yellow, non-specifi c debris stains pale yellow, and the background is almost black. With auramine/ rhodamine stain, organisms fluoresce yellow-red in an almost black background. Fluorochrome stain is more sensitive than Ziehl-Neelsen because the smear can be examined under a lower power, thus more fields can be read in the same amount of time, and the bacilli stand out brightly. The Ziehl-Neelsen method uses a carbol fuchsin stain, acid alcohol decolorizer, and methylene blue counterstain. Acid-fast organisms stain red, while the background of debris stains blue. The ZN stain confirms the acid-fast property of mycobacteria.

In the lack of molecular bioassays, smear microscopy can still be used to diagnose tuberculosis in HIV positive persons. A culture should be performed for all suspected TB cases due to its low sensitivity (67 percent).

A positive sputum smear in HIV-positive persons with probable pulmonary TB confirms the diagnosis, and TB treatment should begin right once. If the sputum smear is negative, the TB investigation should proceed with a culture, DST, and a chest x-ray

LIQUID CULTURE – MYCOBACTERIA GROWTH INDICATOR TUBE (MGIT):

For the diagnosis of pulmonary tuberculosis, sputum culture is significantly more sensitive than smear microscopy and can boost diagnostic confirmation by 15- 20%. Its contribution to diagnosis is considerable, though slower, and it is more expensive and less accessible because it takes more training and technological capacity (2-8 weeks, depending on the method).

Purpose:

To amplify the number of Mycobacterium tuberculosis (MTB) organisms in a sample using a liquid culture media (MGIT) and to detect positive samples rapidly. To make a semiquantitative assessment of the bacterial load by determining the time taken for culture tubes to signal positive (time to detection, TTD) in the BACTEC MGIT 960 system. The MGIT culture result, along with confi rmatory ZN, BAP, and rapid ID tests, are the primary indicators of the presence of viable MTB in the sputum.

Principle:

Mycobacteria multiply in a nutrient-rich medium, while contaminating bacteria are inhibited by the addition of a cocktail of antibiotics. Growth of bacteria, including mycobacteria, is indicated by fluorescence, which increases proportionally as oxygen decreases in the tube. The instrument detects this fluorescence in the medium using a UV light and complex computer algorithms. Sputum specimens are processed (Processing Sputum for Smear Microscopy and Qualitative Culture), and inoculated into 7ml MGIT tubes, which are supplemented with OADC (Growth Supplement) and a cocktail of antibiotics (PANTA). The MGIT tubes contain a fluorescent compound embedded in the base of the tube, which is sensitive to the presence of oxygen dissolved in the broth. Initially, the large amount of oxygen quenches the emissions from the compound and little fluorescence is detected. Bacteria present in the concentrated sputum specimens metabolize oxygen in the culture medium, allowing the fluorescence to be detected. Blood samples are not suitable for the MGIT system.

BACTEC MGIT 960 – Instrument overview:

The BACTEC MGIT 960 instrument is capable of monitoring a total of 960, 7 ml MGIT tubes. The tubes are arranged in three continuously incubated drawers, labeled A, B, and C, each of which holds up to 320 tubes. Each drawer contains an apparatus consisting of: a.Tube rack – rack in the drawer that holds the MGIT tubes Stations – individual wells in the rack into which tubes are inserted. b.The detector assembly –sits below the rack and has 16 detectors, one for each row of stations. The assembly moves from left to right and back, taking test readings for each of the 20 station columns and the calibrator tube. c. Drawer status indicators – three lamps located on the front of each drawer; one indicates a positive (+), one indicates a negative (–), and one indicates a station error (!). d. Barcode scanner – located at the front of the instrument;

it is used to scan tube labels for specimen identification. The scanner turns on automatically. e. LCD display and keypad – presents all the information needed to monitor the instrument and station status, to enter and remove tubes, set up the instrument, print reports, and perform routine instrument maintenance.

Sputum culture should be performed routinely in HIV-positive patients because:

• It improves the detection of PTB, especially in individuals with advanced disease who are less bacilliferous.

• It is required for TB DST and typing tests (to establish whether the agent is M. tuberculosis or a non-tuberculous mycobacterium).

Xpert® MTB/RIF:

Nucleic acid amplification methods (real-time polymerase chain reaction, or PCR) such as the Xpert® MTB/RIF assay can detect and directly identify M. tuberculosis in a clinical samples. These tests have the benefit of being able to swiftly detect M. tuberculosis. For HIV-positive patients, the Xpert® MTB/RIF test is now recommended as the diagnostic method of choice. It's totally automated and enclosed, provides little biological danger, can be used at any laboratory level, and produces results in under two hours. It can identify M. tuberculosis as well as rifampicin resistance.

Its sensitivity is 40% higher than smear microscopy. In compared to culture, it has a sensitivity of 98.2 percent in patients with a positive sputum smear and 68 percent in patients with a negative sputum spear. Its specificity is greater than 95%. It may be noted that for non-respiratory specimens, sensitivity ranges from 34% to 93%. However, the specificity both in respiratory as well as non-respiratory specimens is around 99%[NACO guidelines 2021]. Its sensitivity is 79 percent in the case of TB/HIV coinfection.

In cases of suspected MDR-TB and for the diagnosis of paediatric TB in lung samples, the Xpert® MTB/RIF assay is also suggested. It is not recommended for TB treatment bacteriological surveillance.

Immunochromatography:

The LAM (lipoarabinomannan) antigen of Mycobacterium tuberculosis is detected in urine via the lateral flow urine lipoarabinomannan assay (LF-LAM). This LAM antigen is a lipopolysaccharide found in mycobacteria cell walls that is released from metabolically active or degenerating cells, and it appears to be found solely in persons with active tuberculosis. LF-LAM is a commercially available product. The test is done by manually transferring 60 litres of urine to an immunocromotographic strip and incubating it for 25 minutes at room temperature. The item is then visually examined. A reference standard is used to compare the intensity of any visible band on the strip. The advantage of this test over smear microscopy is that urine is easier to collect and preserve, and unlike sputum collection, it does not pose the danger of infecting others. Only in HIV-positive people hospitalised with signs or symptoms of TB (pulmonary and/or extrapulmonary) whose CD4 count is less than 100 cells/ or in gravely ill HIV-positive patients (with the following danger signs: respiratory rate > 30/min., temperature > 39 deg C, heart rate > 120 bpm, and unable to walk unassisted), regardless of their CD4 count or where the CD4 count is unknown, is LF-LAM recommended as support for TB diagnosis

Extra-Pulmonary TB:

Any case of bacteriologically proven or clinically diagnosed tuberculosis involving organs other than the lungs is considered an ETB case. [Farga V et al.,2011]

The following are the most prevalent HIV-related ETB types :

• Pleural
• Meningeal
• Abdominal
• Pericardial
• osteoarticular, genitourinary, cutaneous, ocular, and laryngeal and others

ETB diagnosis is not necessarily etiological and is dependent on the availability of diagnostic techniques such as x-rays, ultrasonography, biopsies, and cultures. Specimens from the suspected ETB site should be cultured (e.g., lymph nodes, blood, bone marrow, etc.). The data suggests that Xpert® MTB/RIF is beneficial for diagnosing meningeal and lymph node TB, but there isn't enough to say if it's useful for other types of ETB.

PTB should be evaluated in every patient with ETB, preferably using Xpert® MTB/RIF or other molecular tests, or smear microscopy and a chest x-ray. However, many ETB patients do not have concurrent PTB. The case is classed as PTB if both are present.

1. Lymph node tuberculosis:

In HIV-positive and HIV-negative patients, this is the most prevalent form of ETB. The cervical lymph nodes are the most usually impacted. Other lymph nodes, such as the axillary and mediastinal, can be impacted as well.

Fine-needle aspiration cytology (FNAC) and biopsy are two methods used to investigate lymphadenopathies.

Table 4. Diagnosis using FNAC

STUDY	DIAGNOSIS	RESULT
Observation of the aspirated material	Caseous material (cheese-like)	TB
Smear for AFB	AFB present	TB
Smear for cytology	Malignant cells	Malignancy

Table 5. Diagnosis with biopsy

Study	Results	Diagnosis
Observation of the sliced sample	Caseous material (Cheese-like)	TB
Fresh-slice smear for AFB	AFB present TB	TB
Freshly processed lymph node	Positive TB culture	TB
Lymph node in formalin for histology	Granuloma and AFB Malignant cells	TB Malignancy

2. Pleural tuberculosis:

Pleural tuberculosis manifests as a combination of constitutional symptoms such as fever, night sweats, and weight loss, as well as localised symptoms or observations caused by pleural effusion.

A diagnostic thoracentesis and, ideally, a pleural biopsy are always required in a person with HIV with pleural effusion . AFB is rarely detected under the microscope, and M. tuberculosis cultures take too long to guide rapid clinical therapy. Pleural tuberculosis is diagnosed with the help of a positive biochemical test called adenosine deaminase (ADA).

When a tuberculous cavity ruptures into the pleural space, a tuberculous empyema can develop. In some cases, a chest tube is required for pus drainage; the pus should be tested for AFB and non-AFB to distinguish it from a bacterial empyema.

3. Tuberculous meningitis:

Tuberculous meningitis is the most prevalent form of tuberculosis in the central nervous system. Hematogenic dissemination or rupture of a cerebral tuberculoma into the subarachnoid space allows M. tuberculosis to propagate to the meninges.

AFB is infrequently detected by microscopic investigation of the CSF. CSF culture takes time to develop and is frequently negative. The presence of increased ADA in the CSF aids in the diagnosis. The specificity of CSF PCR is high, but the sensitivity is poor, therefore a negative result does not rule out the diagnosis.

Due to the need to distinguish tuberculous meningitis from bacterial meningitis and, especially, cryptococcal meningitis, which can have very similar clinical manifestations and CSF characteristics, a Gram stain and an India ink stain of the CSF should always be ordered in HIV-positive people, in addition to the Ziehl-Neelsen stain. (Table 6).

The fungus Cryptococcus neoformans is contracted through inhalation from the environment, however it rarely causes respiratory symptoms and is never contagious. It is the most prevalent type of meningitis among HIV-positive patients, with insidious onset and a wide range of symptoms. Fever and a persistent headache are the most typical symptoms. Only around 20% of individuals exhibit a stiff neck or other specific neurological symptoms on physical examination. Given the similarity in CSF modifications between tuberculous and cryptococcal meningitis, as well as the fact that India ink staining is negative in the latter (20-40%), the only way to definitively differentiate the disorders is to identify the cryptococcal antigen or culture the cerebrospinal fluid.

Table 6. Analysis of cerebrospinal fluid to rule out diagnoses other than TB

CSF	Appearance	Leukocytes	Proteins (mg/dL)	Glucose (mg/dL)	Microscopy
Normal	Clear	< 5/mm3	20-45	50-80	Negative
Tuberculous meningitis	Clear or slightly cloudy (xanthochromic)	Elevated PMN > L (early) L > PMN	Elevated	Normal or slightly low	Positive AFB: < 20%
Cryptococcal meningitis	Clear or slightly cloudy	Elevated L > PMN	Elevated	Low	Positive India ink: 60-80%
Bacterial meningitis	Demonstrably cloudy	Elevated Presence of PMN	Elevated	Low	Gram stain: Presence of bacteria
Viral meningitis	Clear	Elevated PMN > L (early) L > PMN	Elevated	Normal	Negative
Neurosyphilis	Clear or cloudy	L > PMN	Elevated	Normal	Negative
Neoplasia	Clear or xanthochromic	> L/ normal	Elevated or normal	Low or normal	Negative
Leptospirosis	Clear	Elevated L > PMN	Elevated	Normal or low	Negative

4. Abdominal tuberculosis:

Paracentesis is used to confirm the diagnosis of peritoneal TB, which is usually presumptive. The ascitic fluid analysis reveals a yellowish fluid that is occasionally hazy or bloodstained, indicating lymphocytic exudate. AFB is rarely detected by microscopic examination or culture of ascites. A positive ADA in ascitic fluid aids in diagnosis (with a cut-off point of 39 IU/L and sensitivity and specificity values of 100% and 97%, respectively). Abdominal ultrasonography can reveal tuberculosis-related abnormalities.

5). Pericardial tuberculosis:

A pericardiocentesis, a pericardial window with biopsy, or both are used to make the conclusive diagnosis. A positive ADA in the pericardial fluid aids in the diagnosis (cut-off point: 40 IU/L, sensitivity: 88 percent, specificity: 83 percent). AFB is infrequently detected in pericardial effusions

TREATMENT:

5.1 TREATING ACTIVE TB DISEASE IN PL-HIV:

- After collecting a specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in people with HIV with clinical and radiographic presentation suggestive of HIV-related TB **(AIII).**
- DOT is recommended for all patients requiring treatment for HIV-related TB **(AII).**

For Drug-Susceptible TB
Intensive Phase (2 Months) • Isoniazid plus (rifampin or rifabutin) plus pyrazinamide plus ethambutol **(AI)** • If drug susceptibility report shows sensitivity to isoniazid and rifampin, then ethambutol may be discontinued **(AI).** **Continuation Phase (for Drug-Susceptible TB)** • Isoniazid plus (rifampin or rifabutin) daily **(AII)** **Total Duration of Therapy** • Pulmonary, drug-susceptible, uncomplicated TB: 6 months **(BII)** • Pulmonary TB and positive culture at 2 months of TB treatment, severe cavitary disease or disseminated extrapulmonary TB: 9 months **(BII)** • Extrapulmonary TB with CNS involvement: 9–12 months **(BII)** • Extrapulmonary TB in other sites: 6 months **(BII)**

For Drug-Resistant TB
Empiric Therapy for Resistance to Rifamycin Plus/Minus Resistance to Other Drugs • Isoniazid plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin) **(BII)** • Therapy should be modified once rifampin resistance is confirmed and based on drug susceptibility results to provide ≥5 active drugs **(BII).** **Resistant to Isoniazid** • (Moxifloxacin or levofloxacin) plus (rifampin or rifabutin) plus ethambutol plus pyrazinamide for 6 months **(BII)** **Resistant to Rifamycins Plus/Minus Other Antimycobacterial Agents** • Therapy should be individualized based on drug susceptibility test results and clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists **(AIII).** **Duration** • 12–24 months (see Management of Drug-Resistant TB section above for discussion of shorter-course therapy)

Rating of Recommendations: A = Strong; B = Moderate; C = Optional Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

HIV Treatment:

Recommended Choice of First-Line Regimen :[National AIDS Control Organization (2021)]

In consideration of the WHO guidelines and based on recommendations of NACO Technical Resource Group, it has been decided to include DTG-containing regimens as the preferred first line treatment for HIV-positive

adults, adolescents and children (weighing more than 20 kg/age more than 6 years) under the NACP since July 2020

The preferred first-line ART regimen for all PLHIV with age >10 years and weight >30kg is as follows:

Tenofovir (TDF 300 mg) + Lamivudine (3TC 300 mg) + DOLUTEGRAVIR (DTG 50 mg) regimen (TLD) as FDC in a single pill once a day (at a fixed time every day as per patient's convenience)

Alternate first-line ART in adults and adolescents:

Condition	Alternate First-line Regimen
PLHIV with body weight<30kgs	ABC 600 mg + Lamivudine 300mg, one tablet + DTG (50 mg) once daily in the morning or any fixed time every day as per patient's convenience
PLHIV on Rifampicin-containing ATT regimen	Tenofovir (300 mg) + Lamivudine (300 mg) + Dolutegravir (50 mg) – FDC one tablet once daily (in the morning or any fixed time every day as per patient's convenience) + Additional dose of DTG 50 mg to be provided (12 hours after taking their regular dose) until 2 weeks after completion of ATT
Women of childbearing potential who do not wish to take DTG-based ART after adequate and optimal counselling	Tenofovir (300 mg) + Lamivudine (300 mg) + Efavirenz (600mg) If Efavirenz is contraindicated (HIV-2/HIV-1&2/prior NNRTI exposure) then Tenofovir (300 mg) + Lamivudine (300 mg) + [Lopinavir (200 mg) + ritonavir (50 mg) twice daily]

Rapid ART Initiation for Newly Diagnosed PLHIV at ART Centre:

The introduction of the 'Treat All' recommendation supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication. Rapid ART initiation is defined as "ART initiation within seven days from the day of HIV diagnosis".

ART initiation in PLHIV co-infected with TB

Patient's details	Timing of ART in relation to initiation of TB treatment	ART recommendations
HIV-TB coinfected patients	• ART should be started as soon as possible within 2 weeks of initiating TB treatment, regardless of CD4 cell count, among PLHIV (except when signs and symptoms of meningitis are present). • Among PLHIV with TB meningitis, ART should be delayed at least 4 weeks (and initiated within 8	Appropriate ART regime

	weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered as adjuvant treatment for TB meningitis	

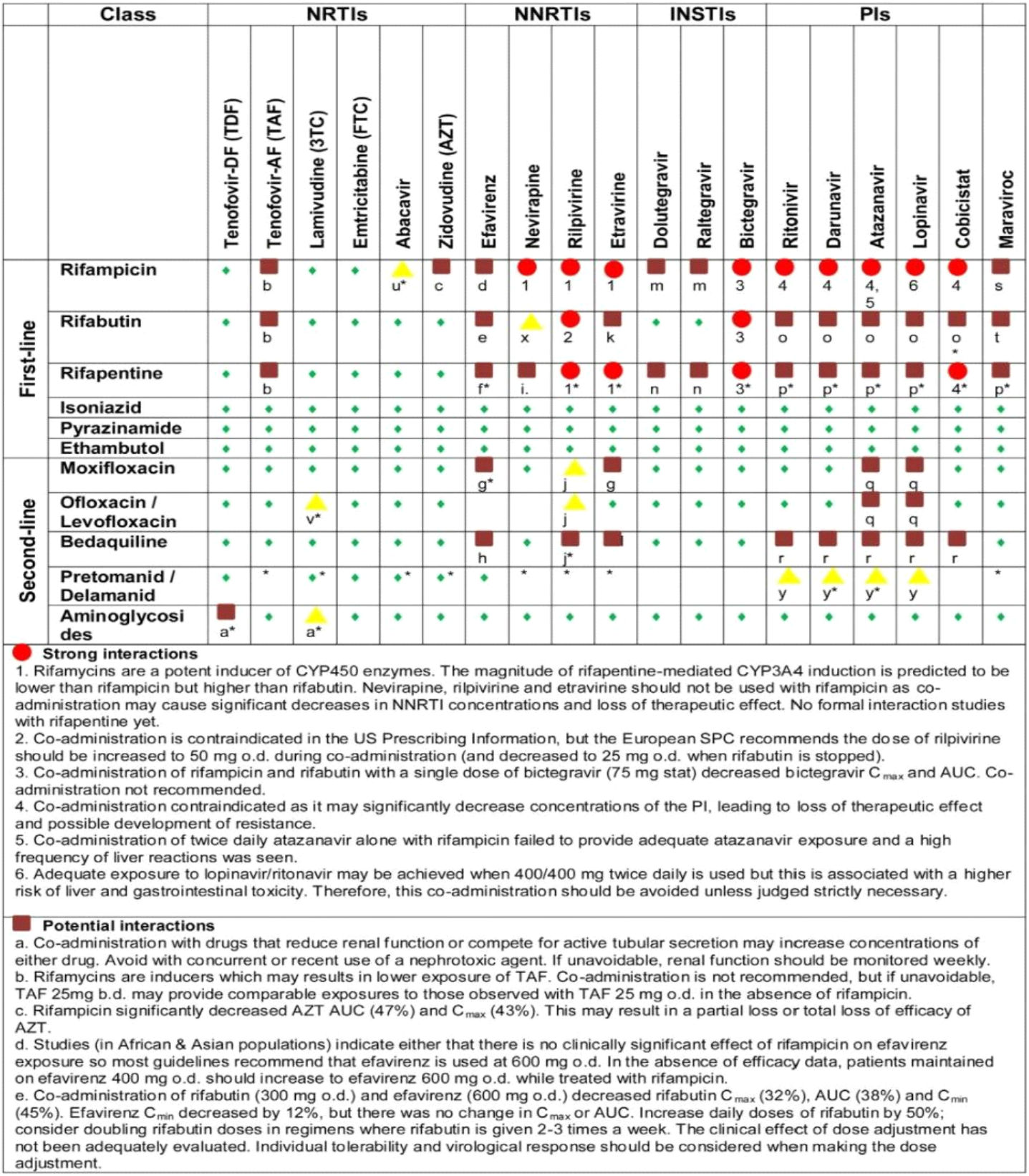
HIV-TB DRUG INTERACTION:

Rifamycins, the cornerstone of treatment for drug sensitive TB,are associated with a considerable potential for PK DDI. Rifampicin is a potent inducer of the hepatic CYP450 enzymes (including CYP2A6, CYP2B6, CYP2C, and CYP3A isoenzymes), P-glycoprotein (P-gp), and uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzymes.1 The magnitude of rifapentine-mediated CYP3A4 induction is predicted to be lower than rifampicin but higher than rifabutin. This induction alters pharmacokinetics of drugs metabolized by these pathways, reducing plasma concentrations of several antiretroviral drugs, which risks loss of efficacy and sequential development of resistance mutations. As a potent enzyme inducer, rifampicin is not recommended for use in patients receiving protease inhibitors (PI), certain non-nucleoside reverse transcriptase inhibitors (NNRTI) such as rilpivirine, nevirapine, and etravirine; some NRTI such as tenofovir-alafenamide; and some integrase strand transfer inhibitors (INSTI), such as elvitegravir and bictegravir. Rifabutin, a weaker CYP3A4 enzyme inducer is recommended as an alternative to rifampicin in patients receiving PI-based ART regimens. Because rifabutin is a substrate of the CYP450 enzyme system however, its metabolism may be affected by NNRTIs or PIs and rifabutin dosage adjustment is generally recommended. Efavirenz-based ART regimen is recommended as the preferred first-line regimen globally. Recent evidence has shown that dolutegravir, an INSTI which is currently the recommended ART regimens for initial therapy by the WHO guidelines, can be safely co-administered with rifampicin provided they are dose-adjusted to twice daily.[Dooley KE et al.,2019 , Pozniak A et al.,2018]

The recent Reflate TB2 trial, an open-label, phase 3, randomized clinical trial conducted in Brazil, Côte d'Ivoire, France, Mozambique, and Vietnam comparing another INSTI, raltegravir 400 mg BID vs. efavirenz 600 mg QD with TDF/3TC in PLHIV on standard TB treatment, failed to demonstrate non-inferiority of raltegravir at week 48.[De Castro N et al.,2019]

The variety and complexity of DDI are summarized in Fig 9. . Such challenges are particularly stark in lower income settings where the range of available ART is limited, rifabutin is frequently not available, HIV viral load monitoring is not universal, and routine genotyping for HIV resistance profiles is generally not available.

Figure 9. Table showing HIV-TB drug interactions



	Class	NRTIs						NNRTIs				INSTIs			PIs						
		Tenofovir-DF (TDF)	Tenofovir-AF (TAF)	Lamivudine (3TC)	Emtricitabine (FTC)	Abacavir	Zidovudine (AZT)	Efavirenz	Nevirapine	Rilpivirine	Etravirine	Dolutegravir	Raltegravir	Bictegravir	Ritonivir	Darunavir	Atazanavir	Lopinavir	Cobicistat	Maraviroc
First-line	Rifampicin	◆	■ b	◆	◆	▲ u*	■ c	■ d	● 1	● 1	● 1	■ m	■ m	● 3	● 4	● 4	● 4, 5	● 6	● 4	■ s
	Rifabutin	◆	■ b	◆	◆	◆	◆	■ e	▲ x	● 2	■ k	◆	◆	● 3	■ o	■ o	■ o	■ o	■ o *	■ t
	Rifapentine	◆	■ b	◆	◆	◆	◆	■ f*	■ i.	● 1*	● 1*	■ n	■ n	● 3*	■ p*	■ p*	■ p*	■ p*	● 4*	■ p*
	Isoniazid	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Pyrazinamide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
	Ethambutol	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Second-line	Moxifloxacin	◆	◆	◆	◆	◆	◆	■ g*	◆	▲ j	■ g	◆	◆	◆	◆	◆	■ q	■ q	◆	◆
	Ofloxacin / Levofloxacin	◆	◆	▲ v*	◆	◆	◆			▲ j	◆	◆	◆	◆	◆	◆	■ q	■ q	◆	◆
	Bedaquiline	◆	◆	◆	◆	◆	◆	■ h	◆	■ j*	■ i	◆	◆	◆	■ r	■ r	■ r	■ r	■ r	◆
	Pretomanid / Delamanid	◆	*	◆*	◆	◆*	◆*	◆	*	*	*				▲ y	▲ y*	▲ y*	▲ y		*
	Aminoglycosides	■ a*	◆	▲ a*	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

● Strong interactions

1. Rifamycins are a potent inducer of CYP450 enzymes. The magnitude of rifapentine-mediated CYP3A4 induction is predicted to be lower than rifampicin but higher than rifabutin. Nevirapine, rilpivirine and etravirine should not be used with rifampicin as co-administration may cause significant decreases in NNRTI concentrations and loss of therapeutic effect. No formal interaction studies with rifapentine yet.
2. Co-administration is contraindicated in the US Prescribing Information, but the European SPC recommends the dose of rilpivirine should be increased to 50 mg o.d. during co-administration (and decreased to 25 mg o.d. when rifabutin is stopped).
3. Co-administration of rifampicin and rifabutin with a single dose of bictegravir (75 mg stat) decreased bictegravir C_{max} and AUC. Co-administration not recommended.
4. Co-administration contraindicated as it may significantly decrease concentrations of the PI, leading to loss of therapeutic effect and possible development of resistance.
5. Co-administration of twice daily atazanavir alone with rifampicin failed to provide adequate atazanavir exposure and a high frequency of liver reactions was seen.
6. Adequate exposure to lopinavir/ritonavir may be achieved when 400/400 mg twice daily is used but this is associated with a higher risk of liver and gastrointestinal toxicity. Therefore, this co-administration should be avoided unless judged strictly necessary.

■ Potential interactions

a. Co-administration with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of either drug. Avoid with concurrent or recent use of a nephrotoxic agent. If unavoidable, renal function should be monitored weekly.
b. Rifamycins are inducers which may results in lower exposure of TAF. Co-administration is not recommended, but if unavoidable, TAF 25mg b.d. may provide comparable exposures to those observed with TAF 25 mg o.d. in the absence of rifampicin.
c. Rifampicin significantly decreased AZT AUC (47%) and C_{max} (43%). This may result in a partial loss or total loss of efficacy of AZT.
d. Studies (in African & Asian populations) indicate either that there is no clinically significant effect of rifampicin on efavirenz exposure so most guidelines recommend that efavirenz is used at 600 mg o.d. In the absence of efficacy data, patients maintained on efavirenz 400 mg o.d. should increase to efavirenz 600 mg o.d. while treated with rifampicin.
e. Co-administration of rifabutin (300 mg o.d.) and efavirenz (600 mg o.d.) decreased rifabutin C_{max} (32%), AUC (38%) and C_{min} (45%). Efavirenz C_{min} decreased by 12%, but there was no change in C_{max} or AUC. Increase daily doses of rifabutin by 50%; consider doubling rifabutin doses in regimens where rifabutin is given 2-3 times a week. The clinical effect of dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment.

TB- ASSOCIATED IRIS:

TB-IRIS is caused by ART-induced restoration of TB-specific immune responses, resulting in either the deterioration of a treated infection (paradoxical IRIS) or a new presentation of a previously subclinical infection (unmasking IRIS). IRIS has been reported in 8–40%

following ART initiation.[Meintjes G et al.,2010] . Predictors of IRIS include a baseline CD4 count <50 cells/L; rapid on-ART restoration of CD4 counts; high pre-ART and lower on-ART HIV viral loads; and severity of TB disease. Most TB-IRIS occurs within 3 months of the start of ART, usually within the first month. Incidence of unmasking TB-IRIS is harder to quantify but there is concern that the recent rapid upscaling of 'HIV test and start,' could result in an increased incidence of unmasking IRIS events to opportunistic infections.[Abassi M et al.,2018]

TB-IRIS ranges from mild to severe to life-threatening. Patients with mild or moderately severe IRIS can be managed symptomatically. For management of severe TB-IRIS, corticosteroids are recommended as demonstrated in a recent RCT, although data on the optimal dose, duration, and overall safety and efficacy are limited.[Meintjes G.,2010] In the presence of IRIS, ideally neither TB therapy nor ART should be stopped, as immune restoration and effective control of the bacillary burden are both essential to long term survival.

TB-IRIS prevention with prednisolone prophylaxis (40 mg/day for 2 weeks then 20 mg/day for 2 weeks started with ART) was investigated in a recent clinical trial among ART-naïve adults at high risk of TB-IRIS (within 30 days of TB treatment initiation and CD4 count ≤100 cells/L). Grade 3 adverse events occurred more frequently in the placebo arm (45.4% vs. 29.4%, p = 0.01), but grade 4 adverse events were similar by arm (8.4% vs. 7.6%, p = 0.81). The intervention reduced the risk of TB-IRIS by 30% and further reduced the requirement for corticosteroids to treat TB-IRIS by 53%.[Meintjes G et al.,2018]

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