TB-HIV co-infection: epidemiology, diagnosis, and management

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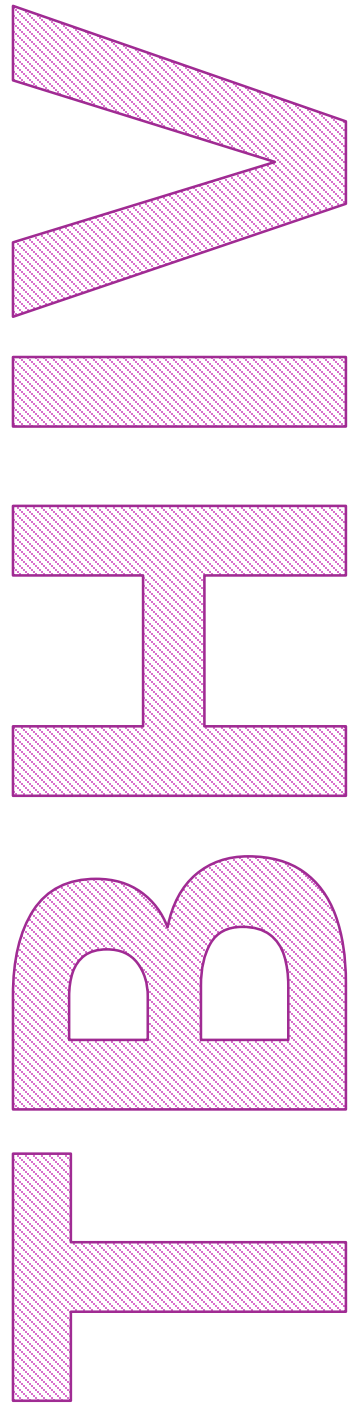


Epidemiology

- People with HIV are about 14 times more likely to develop TB disease, have poorer TB treatment outcomes and more than two-fold higher mortality during TB treatment compared to people without HIV.
- Globally, Among all incident TB cases in 2024, 5.8% were among people living with HIV.
- Despite advances in the screening, diagnosis, treatment and prevention of TB disease, TB remains the leading cause of death among people with HIV worldwide.
- TB accounted for 167 000 (27%) of global AIDS-related deaths in 2022
- Tuberculosis-related mortality is higher among people with HIV infection than among those without HIV infection
  - Tuberculosis progresses more rapidly as immunosuppression worsens.
  - It is more difficult to diagnose tuberculosis in people with HIV infection, which can result in a delayed or missed diagnosis.

Global tuberculosis report. Geneva: World Health Organization

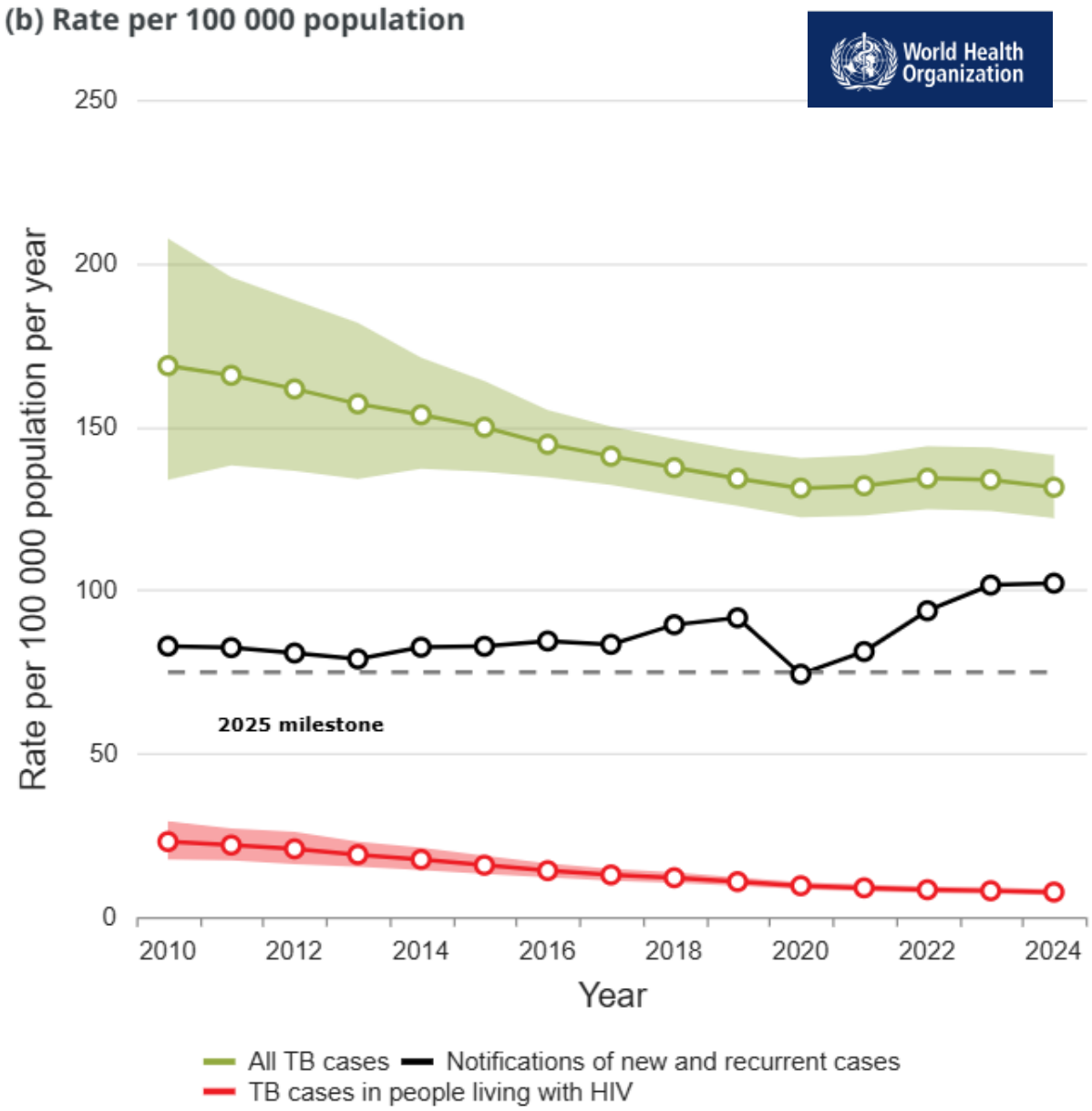
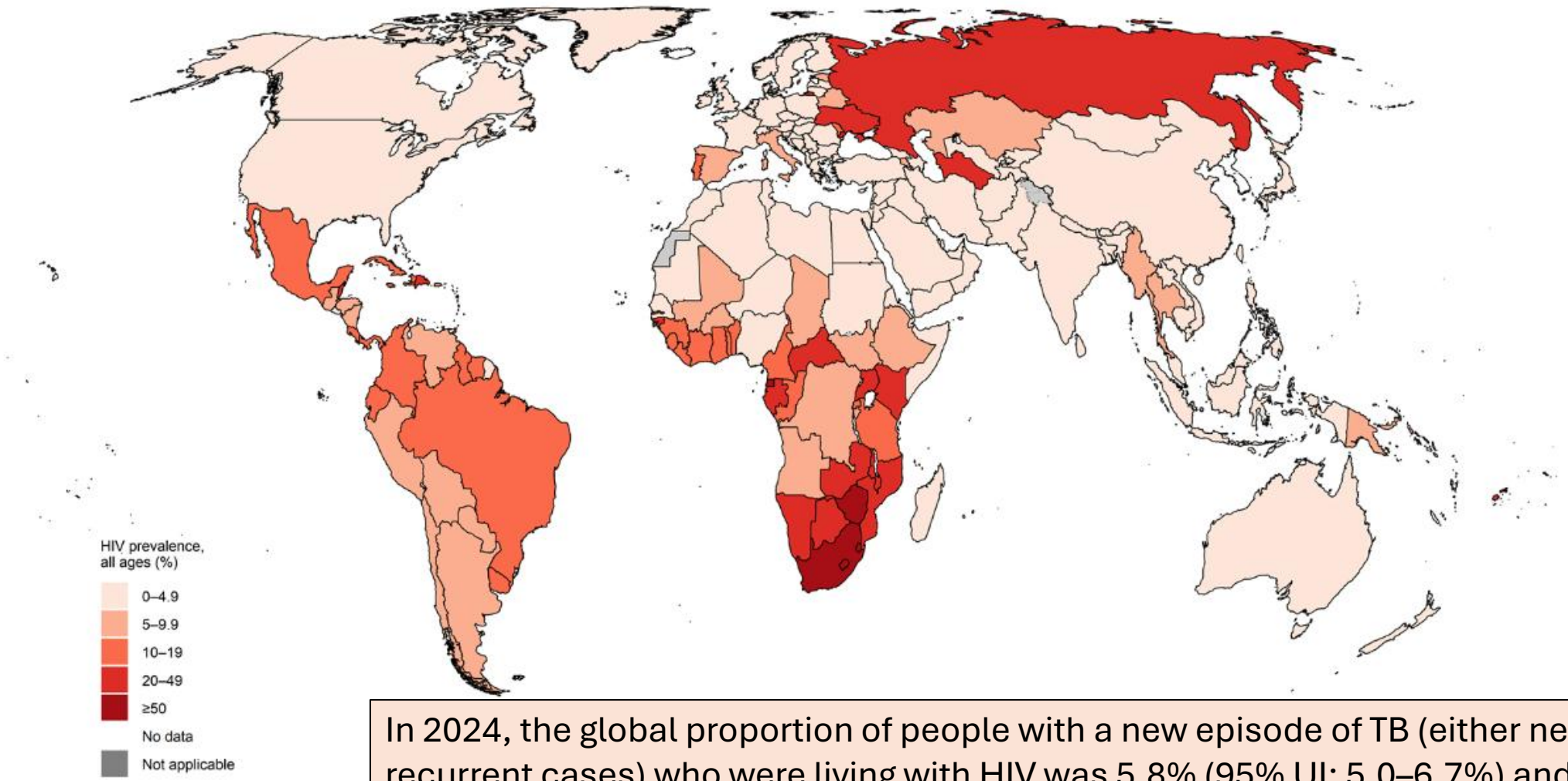


Fig. 1.1.1 Global trends in the estimated incidence rate of TB, 2010–2024

- The use of ART has been associated with a reduction in the incidence of tuberculosis among people with HIV infection
- Globally, there was a 60% reduction in the incidence of tuberculosis and a 72% reduction in deaths due to tuberculosis from 2000 through 2021 among people with HIV infection.

N Engl J Med 2024;391:343-355

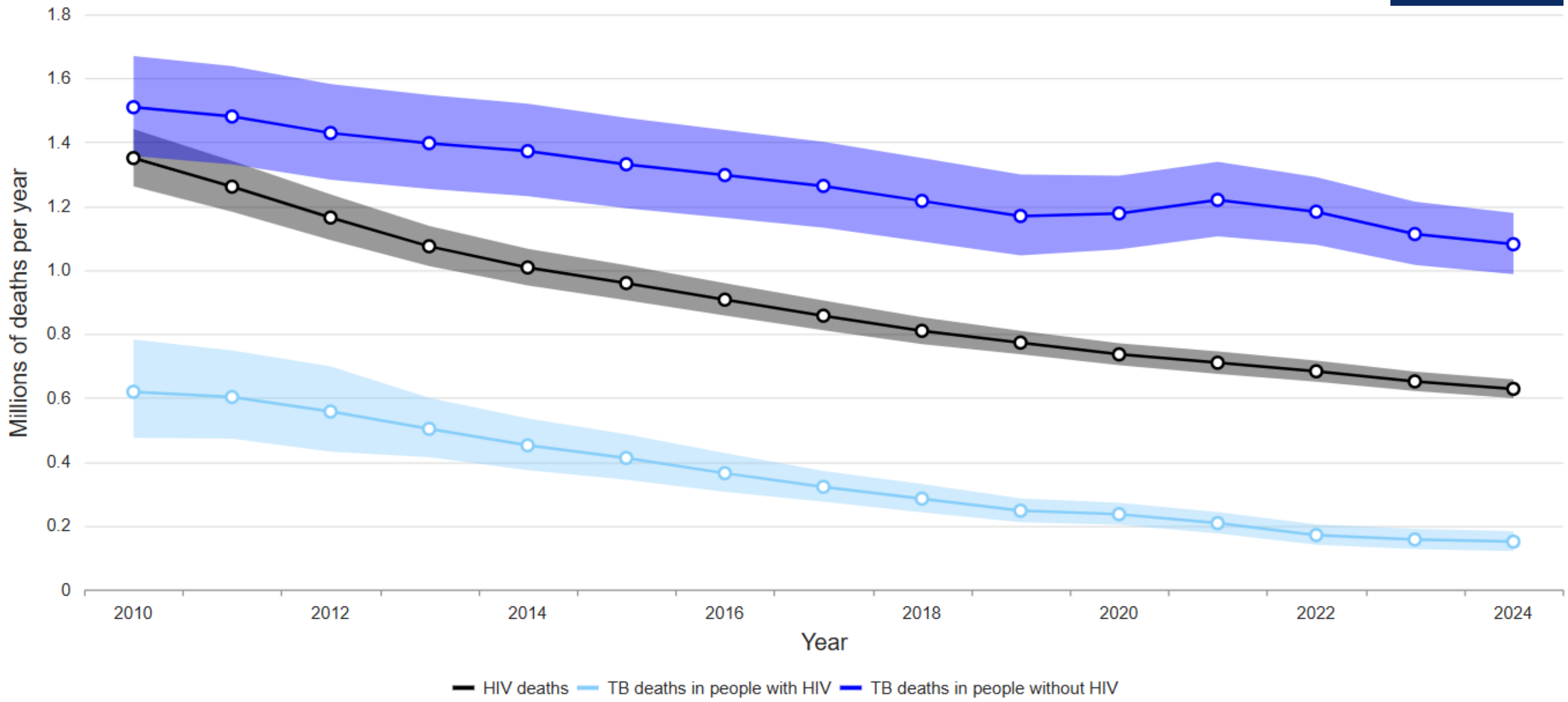
Fig. 1.1.5 Estimated HIV prevalence in people with a new episode of TB (new or recurrent cases), 2024



In 2024, the global proportion of people with a new episode of TB (either new or recurrent cases) who were living with HIV was 5.8% (95% UI: 5.0–6.7%) and was highest in countries in the WHO African Region, exceeding 50% in parts of southern Africa. The proportion has been falling for many years, following a peak at 17% in 2000.

Fig. 1.2.5 Global trends in the estimated number of deaths caused by TB and HIV (in millions), 2010–2024 [a,b]

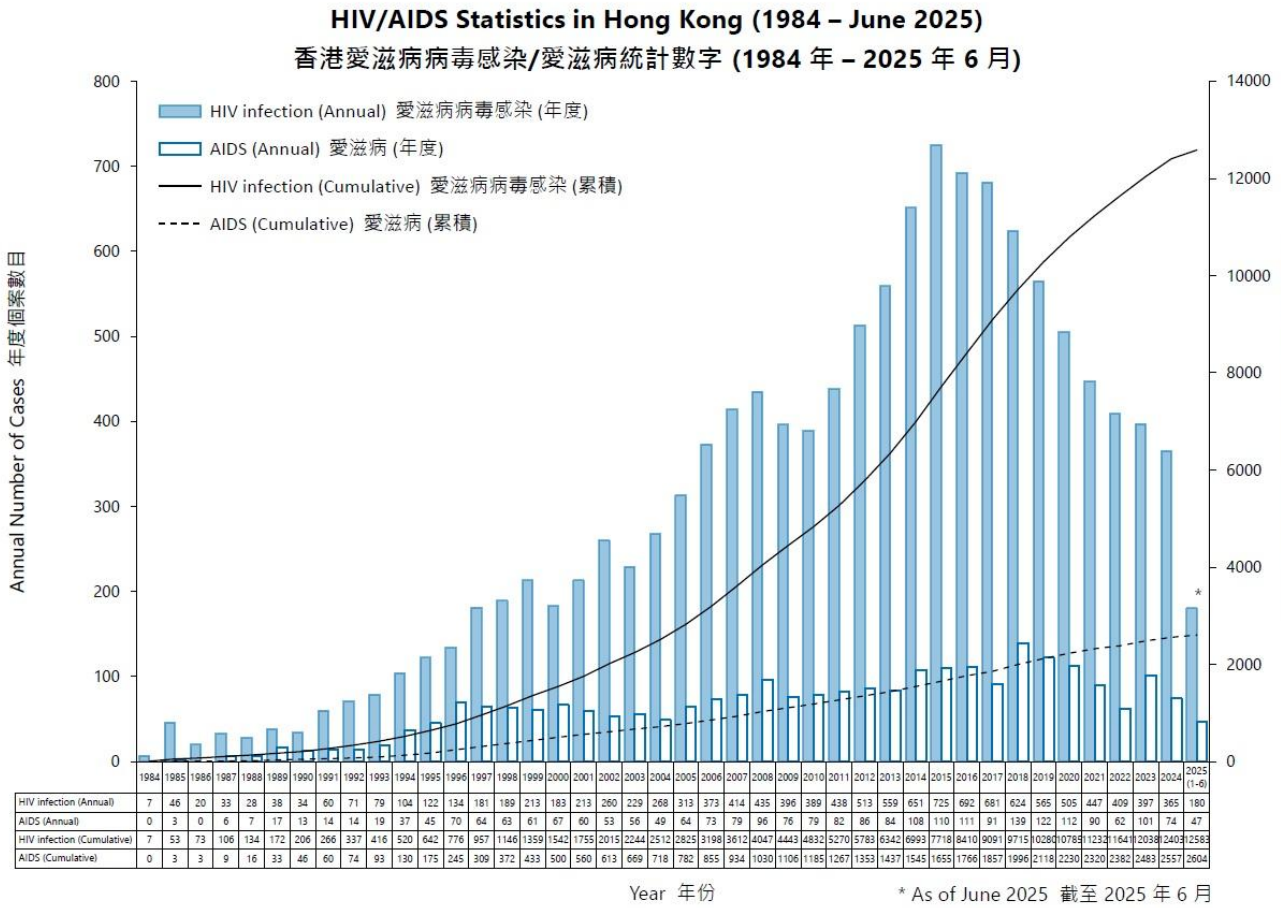
Shaded areas represent 95% uncertainty intervals.



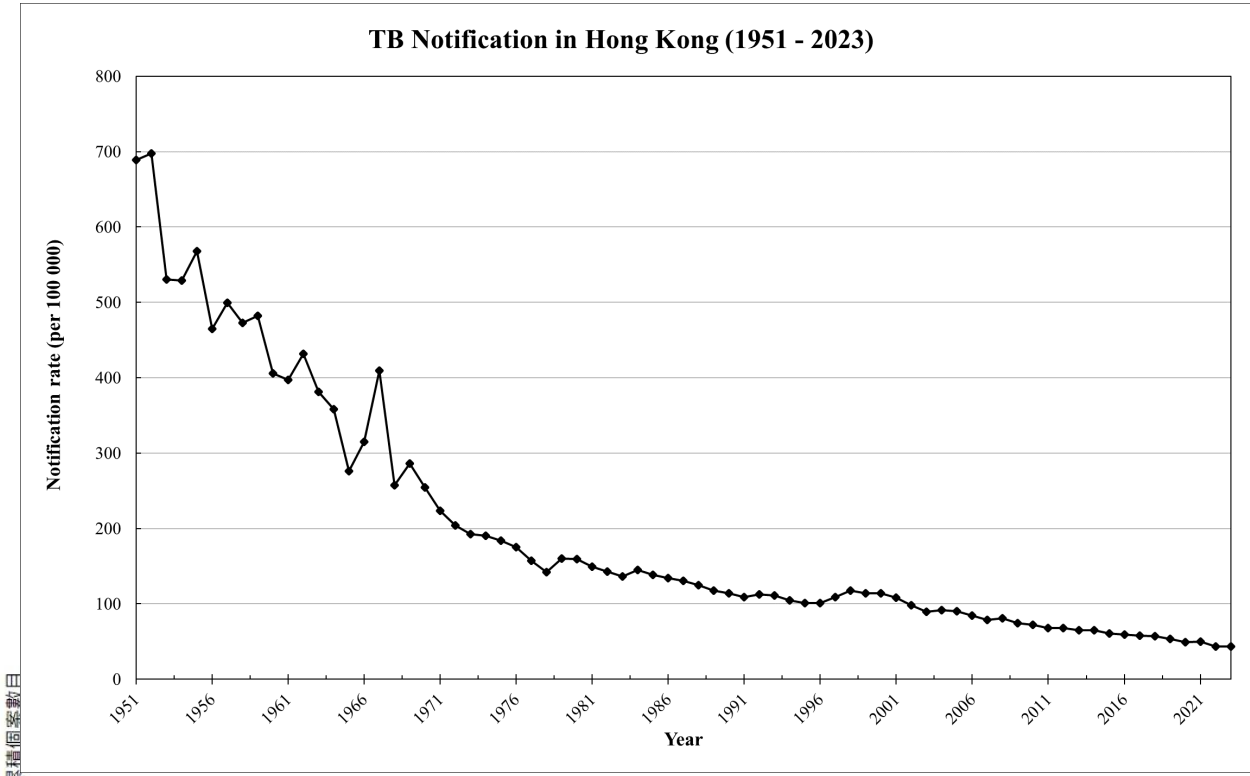
[a] For HIV/AIDS, the latest estimates of the number of deaths in 2024 are those published by UNAIDS (*3*). For TB, the estimates for 2024 are those published in this report.

[b] Deaths from TB among people with HIV are officially classified as deaths caused by HIV/AIDS in the International Classification of Diseases.

Local Epidemiology



	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025 (1-6)
HIV infection (Annual)	7	46	20	33	28	38	34	60	71	79	104	122	134	181	189	213	183	213	260	229	268	313	373	414	435	396	389	438	513	559	651	725	692	681	624	565	505	447	409	397	365	180
AIDS (Annual)	0	3	0	6	7	17	13	14	14	19	37	45	70	64	63	61	67	60	53	56	49	64	73	79	96	76	79	82	86	84	108	110	111	91	139	122	112	90	62	101	74	47
HIV infection (Cumulative)	7	53	73	106	134	172	206	266	337	416	520	642	776	957	1146	1359	1542	1755	2015	2244	2512	2825	3198	3612	4047	4443	4832	5270	5783	6342	6993	7718	8410	9091	9715	10280	10785	11232	11641	12038	12403	12583
AIDS (Cumulative)	0	3	3	9	16	33	46	60	74	93	130	175	245	309	372	433	500	560	613	669	718	782	855	934	1030	1106	1185	1267	1353	1437	1545	1655	1766	1857	1996	2118	2230	2320	2382	2483	2557	2604



Total number of TB notifications in 2025: 2936

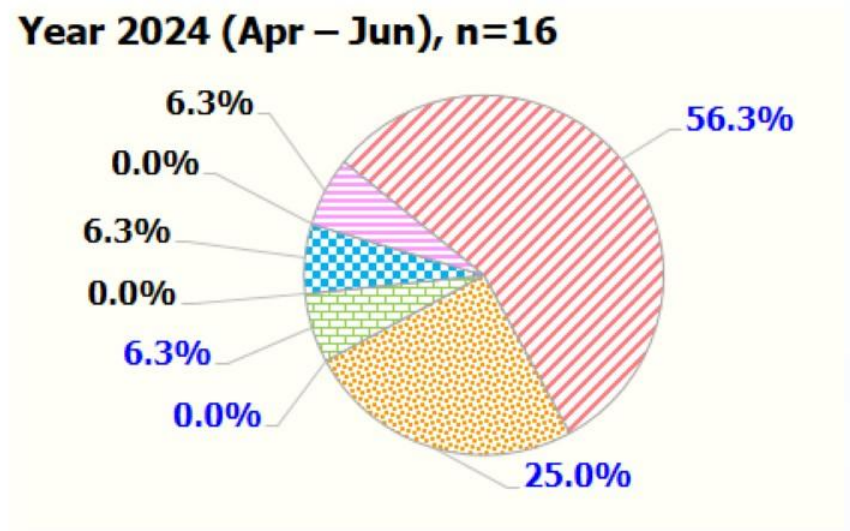
Tuberculosis & Chest Service, Centre for Health Protection, Department of Health Hong Kong: Notification rate of tuberculosis (all forms)

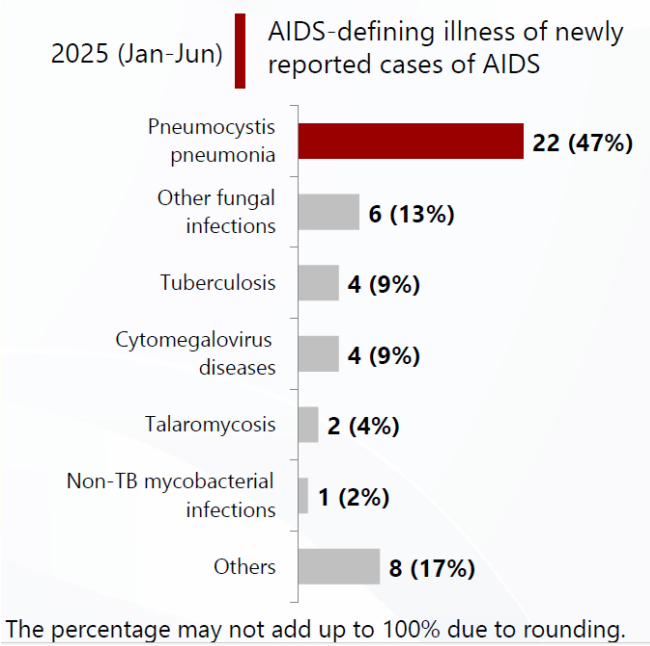
TB and HIV in Hong Kong

- From 1985 to 2019, 504 (23.8%) of reported AIDS were defined primarily by TB.
- The incidence of TB has remained <100 per 100 000 populations since 2002 and Hong Kong is regarded to have an intermediate TB disease incidence according to the World Health Organization (WHO) definition.
- It is estimated that 1% of all TB disease in Hong Kong is associated with HIV, representing a relatively low incidence of HIV-TB coinfection.
- From 1996 to 2017, 9 (1.9%) cases with positive culture result had MDR-TB, a figure that is slightly higher than the MDR-TB rate of around 1% in general population.
- Bidirectional screening

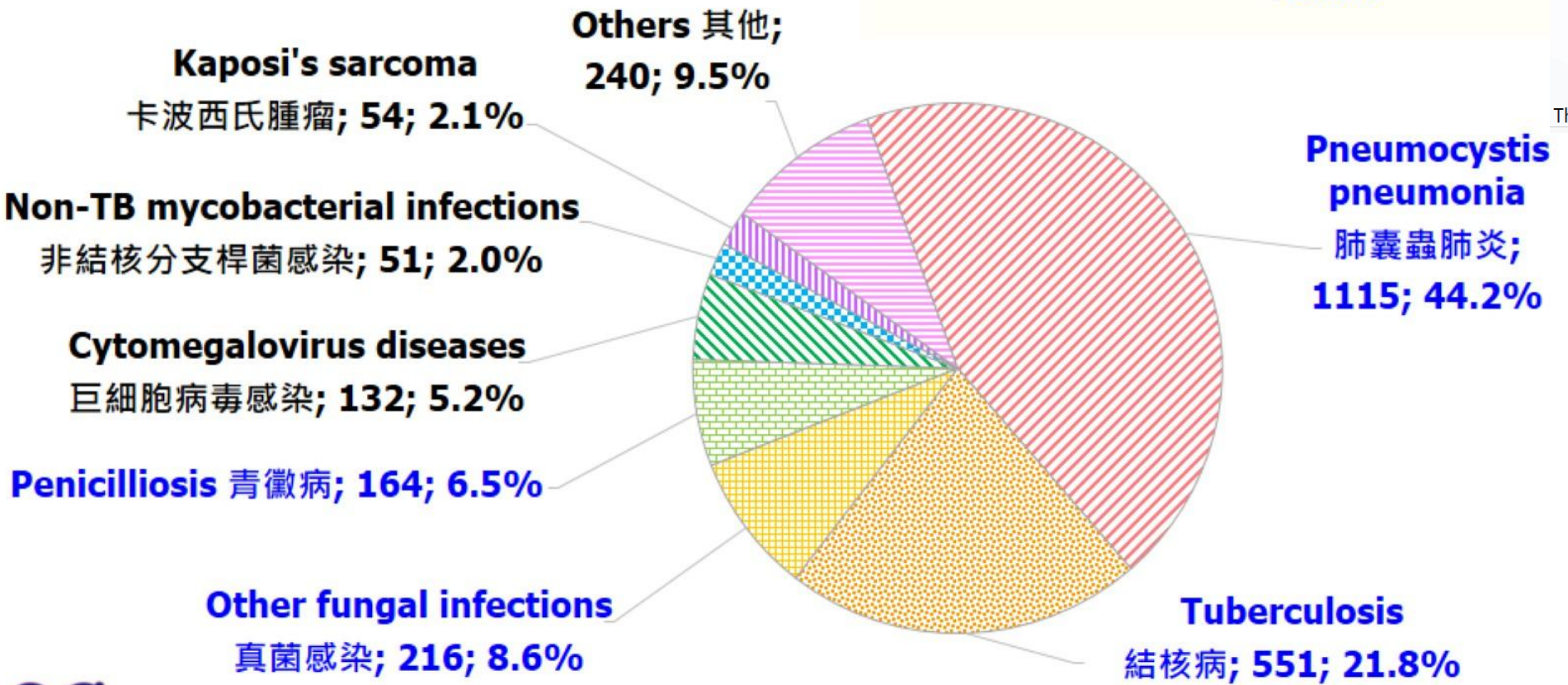
Scientific Committee on AIDS and STI Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection, CHP

AIDS – defining illnesses
愛滋病界定疾病
1985 – June 2024 (N=2523)





The percentage may not add up to 100% due to rounding.



備註：由於四捨五入關係，百分比相加可能不等於 100。

Virtual AIDS Office of Hong Kong
Department of Health
The Government of the Hong Kong Special Administrative Region

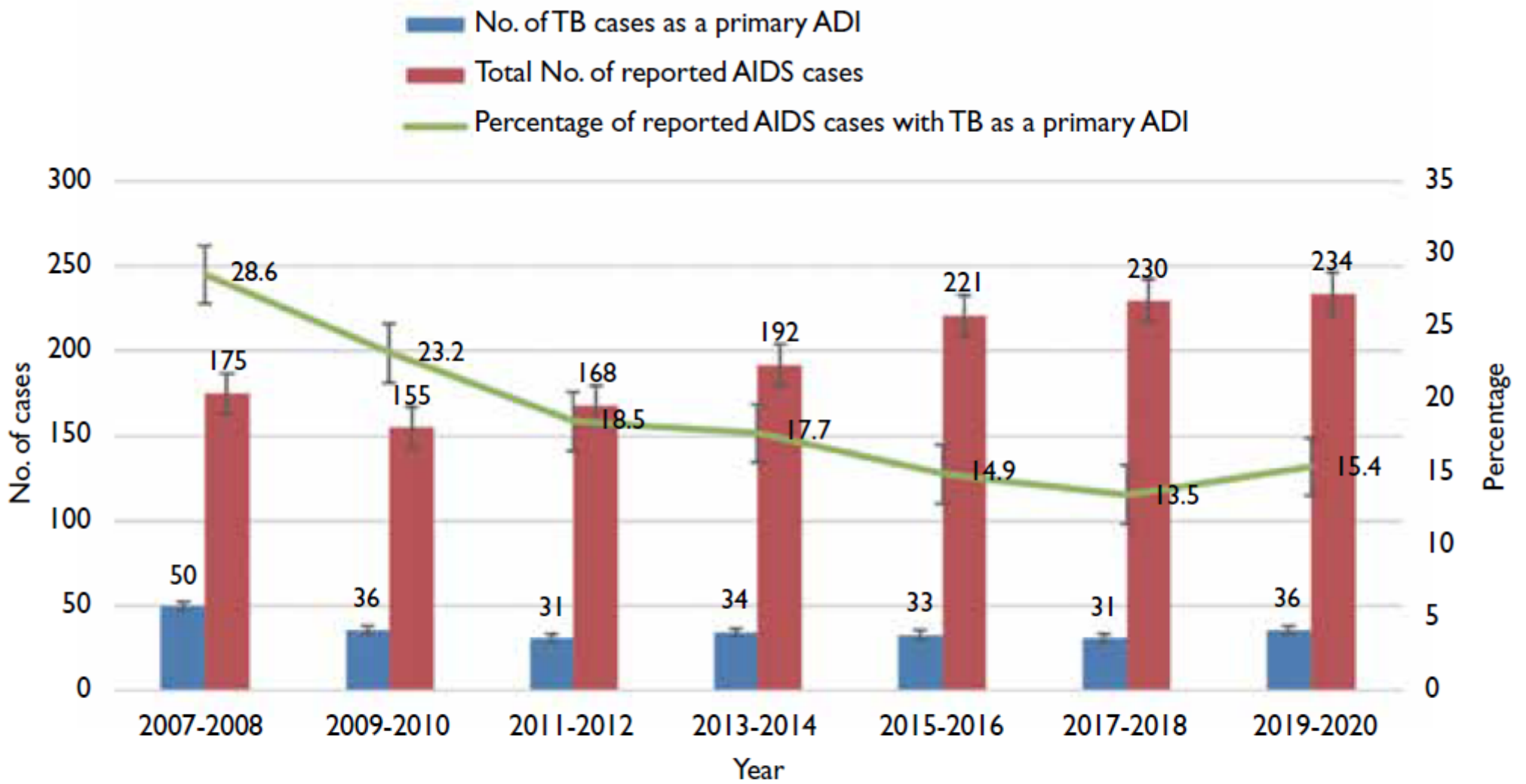
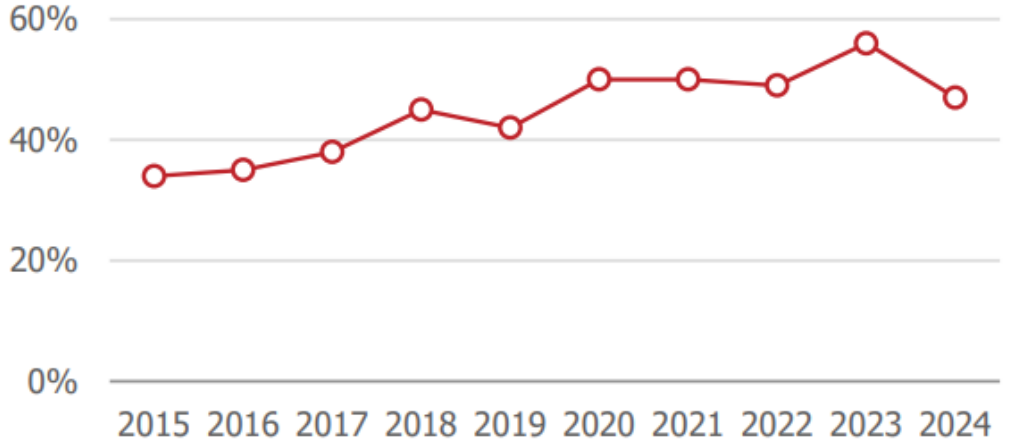


FIG. Tuberculosis as a primary acquired immunodeficiency syndrome–defining illness in Hong Kong among 390 cases reported to the Tuberculosis–Human Immunodeficiency Virus Registry from 2007 to 2020

Abbreviations: ADI = acquired immunodeficiency syndrome–defining illness; AIDS = acquired immunodeficiency syndrome; TB = tuberculosis

- Although the numbers of HIV and TB cases overall are reducing
- About half of new HIV diagnoses are late presenters
- TB in advanced HIV remains a significant burden

Figure 8. Proportion of late presenters (2015–2024)

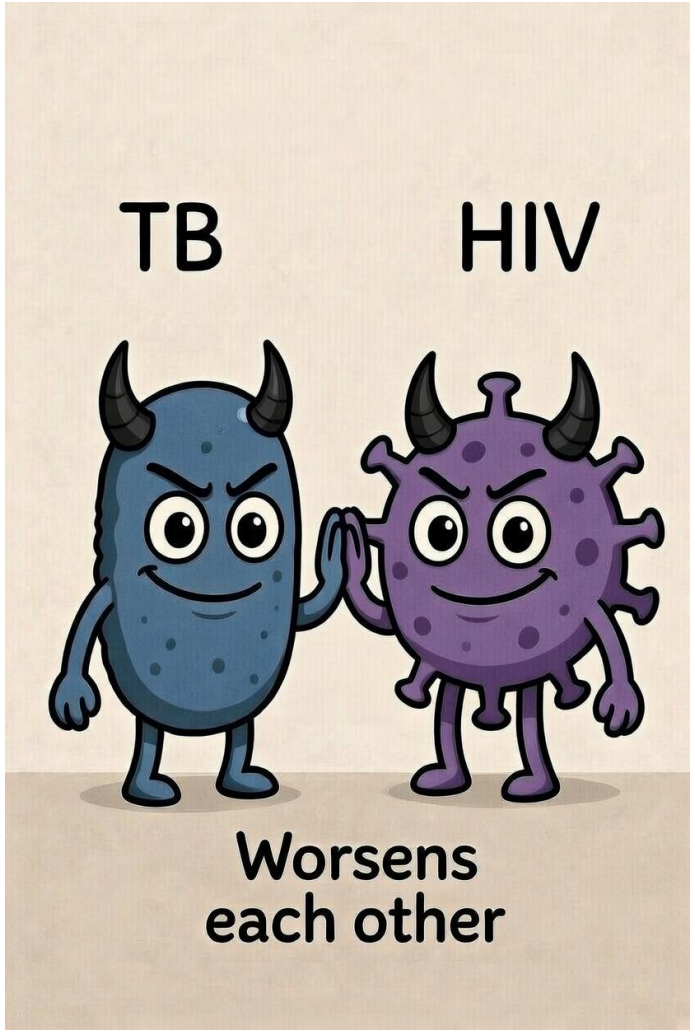


FACTSHEET on HIV/AIDS Situation in Hong Kong [2024]
Authored by Special Preventive Programme
Centre for Health Protection, Department of Health

The Double Threat

- **HIV infection increases the susceptibility to primary TB or reinfection and the risk of TB reactivation for latent TB**
  - CD4+ T cells (helper T cells) are crucial for controlling TB. They produce cytokines (e.g., IFN-γ) that activate macrophages to enhance their bactericidal activity.
  - Altered macrophage activity and reduced TNF alpha → reduced apoptosis of tuberculous bacilli
  - In normal host response, activation of T cells and induction of production of interferon gamma would contribute to granuloma formation, this is impaired in HIV infected individuals, hence the host control of the mycobacterium is compromised

- **TB also adversely impacts HIV outcomes**
  - Immune response against TB increases replication of HIV
  - active TB is associated with more rapid progression to AIDS and higher mortality
  - CD4 recovery is poorer in those with HIV-TB coinfection



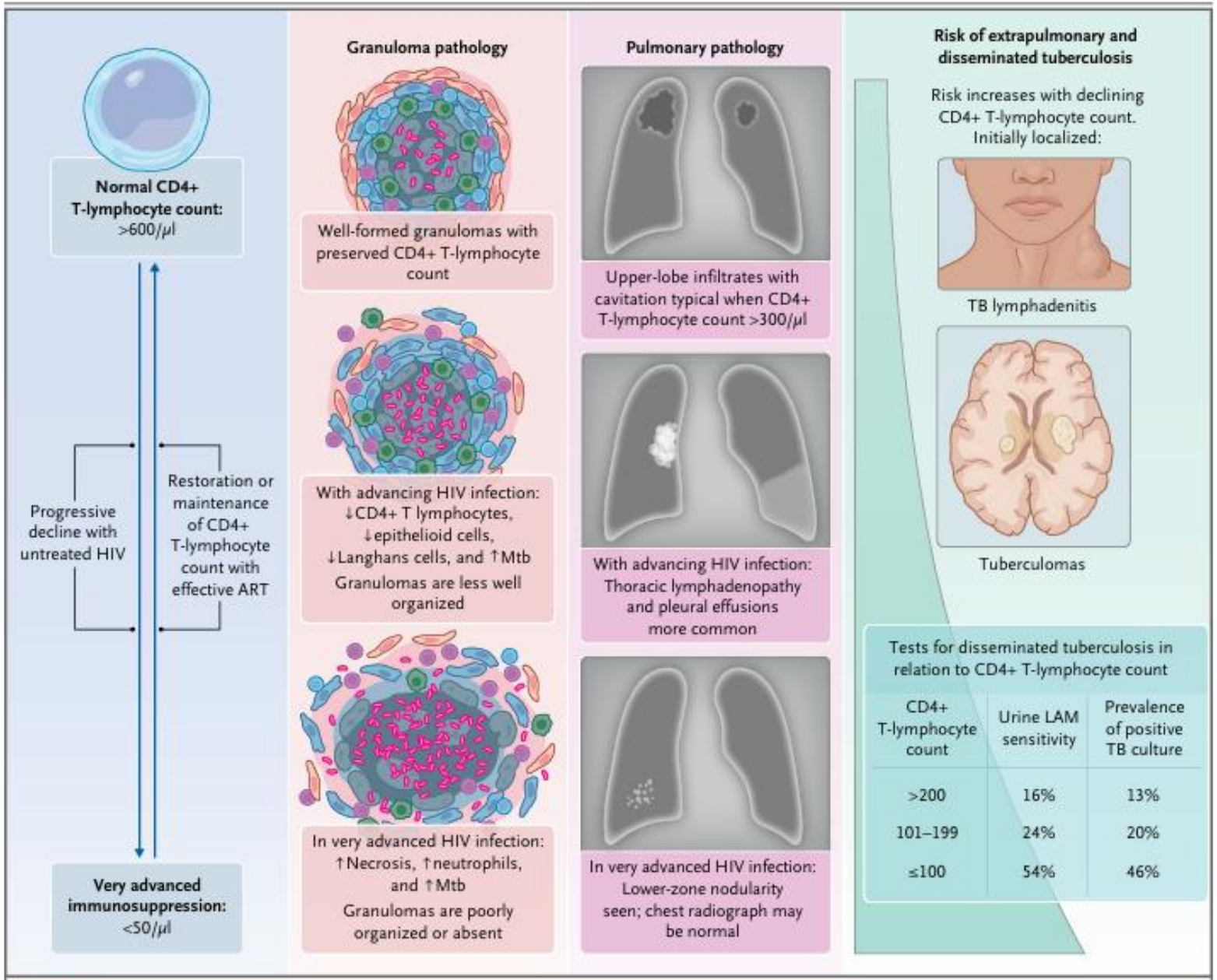


Figure 2. Relationship among the CD4+ T-Lymphocyte Count, the Pathological Features of Tuberculosis, Chest Radiology Features, and the Risks of Extrapulmonary and Disseminated Tuberculosis among People with HIV Infection.

In the table, data are shown for the sensitivity of the LAM assay (Alere)[13] and the prevalence of a positive tuberculosis (TB) blood culture[14] among patients with HIV-associated tuberculosis, stratified according to CD4+ T-lymphocyte count. LAM denotes lipoarabinomannan, and Mtb *Mycobacterium tuberculosis*.

- Immunologic control of TB is complex and involves multiple pathways and immune cells, including T cells and macrophages.

N Engl J Med 2024;391:343-355

Clinical features

	Non-HIV / Immunocompetent	PLHIV
Site	Predominantly pulmonary	Extra-pulmonary disease common (meninges, lymph nodes); often disseminated
Presentation	More classic (chronic cough, hemoptysis, prominent respiratory symptoms)	Often atypical, nonspecific (fever, weight loss, fatigue, night sweats, diarrhea more prominent); fewer "classic" respiratory symptoms
CXR	Classic: upper lobe cavitary lesions, fibrocavitary disease	Often atypical: lower/middle lobe involvement, non-cavitary infiltrates, hilar/mediastinal lymphadenopathy, interstitial patterns; may be normal in advanced HIV
Sputum AFB smear positivity	Higher yield	Often lower (paucibacillary; fewer organisms)
Granuloma	Well-formed granulomas	Poorly formed, disorganized, or absent granulomas; more necrosis

TABLE 2. Clinical manifestations of patients reported to the Tuberculosis–Human Immunodeficiency Virus Registry from 2007 to 2020 (n=390)

	2007-2008	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	2019-2020	Total	All years P value for trend in proportion of patients with reference characteristic*
Presence of symptoms									
Yes (reference)	72 (92.3%)	52 (86.7%)	43 (93.5%)	42 (91.3%)	53 (91.4%)	50 (98.0%)	50 (98.0%)	362 (92.8%)	0.050
No	6 (7.7%)	8 (13.3%)	3 (6.5%)	4 (8.7%)	5 (8.6%)	1 (2.0%)	1 (2.0%)	28 (7.2%)	
Chest symptoms									
Yes (reference)	38 (48.7%)	28 (46.7%)	26 (56.5%)	30 (65.2%)	33 (56.9%)	30 (58.8%)	25 (49.0%)	210 (53.8%)	0.358
No	40 (51.3%)	32 (53.3%)	20 (43.5%)	16 (34.8%)	25 (43.1%)	21 (41.2%)	26 (51.0%)	180 (46.2%)	
Systemic symptoms									
Yes (reference)	60 (76.9%)	40 (66.7%)	34 (73.9%)	33 (71.7%)	34 (58.6%)	37 (72.5%)	33 (64.7%)	271 (69.5%)	0.161
No	18 (23.1%)	20 (33.3%)	12 (26.1%)	13 (28.3%)	24 (41.4%)	14 (27.5%)	18 (35.3%)	119 (30.5%)	
Site-specific symptoms									
Yes (reference)	21 (26.9%)	25 (41.7%)	14 (30.4%)	20 (43.5%)	26 (44.8%)	24 (47.1%)	21 (41.2%)	151 (38.7%)	0.029
No	57 (73.1%)	35 (58.3%)	32 (69.6%)	26 (56.5%)	32 (55.2%)	27 (52.9%)	30 (58.8%)	239 (61.3%)	
Pulmonary involvement									
Yes (reference)	62 (79.5%)	46 (76.7%)	35 (76.1%)	34 (73.9%)	43 (74.1%)	35 (68.6%)	36 (70.6%)	291 (74.6%)	0.130
No	16 (20.5%)	14 (23.3%)	11 (23.9%)	12 (26.1%)	15 (25.9%)	16 (31.4%)	15 (29.4%)	99 (25.4%)	
Extrapulmonary TB involvement									
Yes (reference)	53 (67.9%)	35 (58.3%)	30 (65.2%)	35 (76.1%)	43 (74.1%)	39 (76.5%)	42 (82.4%)	277 (71.0%)	0.008
No	25 (32.1%)	25 (41.7%)	16 (34.8%)	11 (23.9%)	15 (25.9%)	12 (23.5%)	9 (17.6%)	113 (29.0%)	

Hong Kong Med J 2024 Aug;30(4):281–90 | Epub 16 Jul 2024

Diagnosis and Screening

- Initial evaluation: Symptom screen (**cough, fever, weight loss or night sweats**), Chest Radiograph
- Further work up - directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid)

Table 1. Diagnostic Performance of Tests for HIV-Associated Tuberculosis.*

Test and Sample†	Sensitivity	Specificity	Comments
	percent		
Tests for pulmonary tuberculosis			
Sputum culture	Reference standard	Reference standard	Regarded as the reference standard; a single sputum culture may fail to reveal pulmonary tuberculosis because of the sample and other technical factors, and culture will be negative in patients with isolated extrapulmonary disease
Microscopy for acid-fast bacilli, sputum	22.0–43.0 for single smear[43]; 61.8 for multiple smears[44]	99.7[44]	False positive result may occur with nontuberculous mycobacterial infection or colonization[43,44]
MTB/RIF Xpert, sputum	74.9	99.7	Meta-analysis of 3 studies involving people with HIV infection[45]
MTB/RIF Xpert Ultra, sputum	87.6	92.8	Meta-analysis of 3 studies involving people with HIV infection[45]; sputum MTB/RIF Xpert Ultra results in more false positive results than does sputum MTB/RIF Xpert, particularly in patients treated previously for tuberculosis[46]

N Engl J Med 2024;391:343-355

Diagnosis of TB in people living with HIV

Use of molecular WHO-approved rapid diagnostic tests in blood in the diagnosis of disseminated TB

8. In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB *(conditional recommendation, very low certainty of evidence) (14).*

Use of lateral flow lipoarabinomannan (LF-LAM) in the diagnosis of TB in people living with HIV

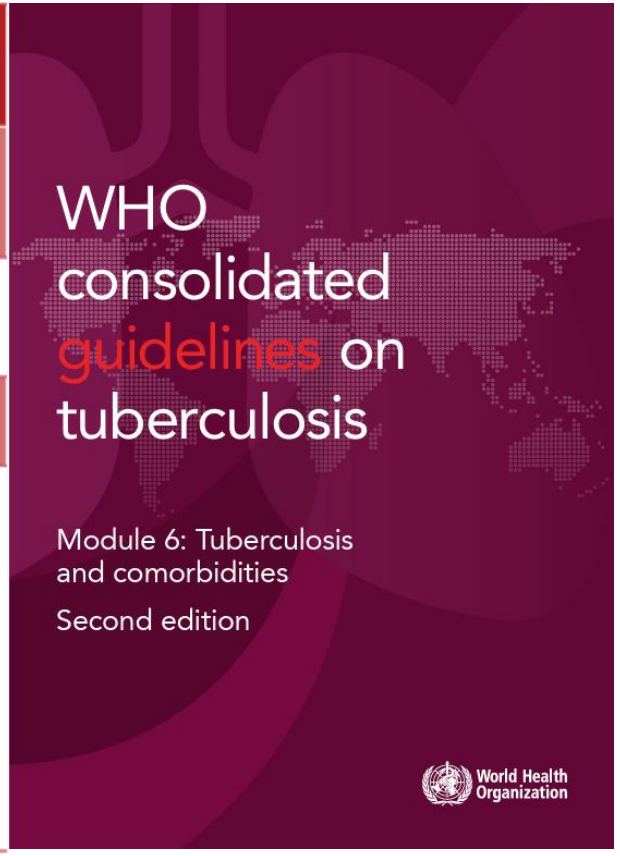
In inpatient settings

9. WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
   - with signs and symptoms of TB (pulmonary and/or extrapulmonary) *(strong recommendation, moderate certainty in the evidence about the intervention effects);* or
   - with advanced HIV disease or who are seriously ill *(strong recommendation, moderate certainty in the evidence about the intervention effects);* or
   - irrespective of signs and symptoms of TB and with a CD4 cell count of less than 200 cells/mm^3 *(strong recommendation, moderate certainty in the evidence about the intervention effects) (14).*

In outpatient settings

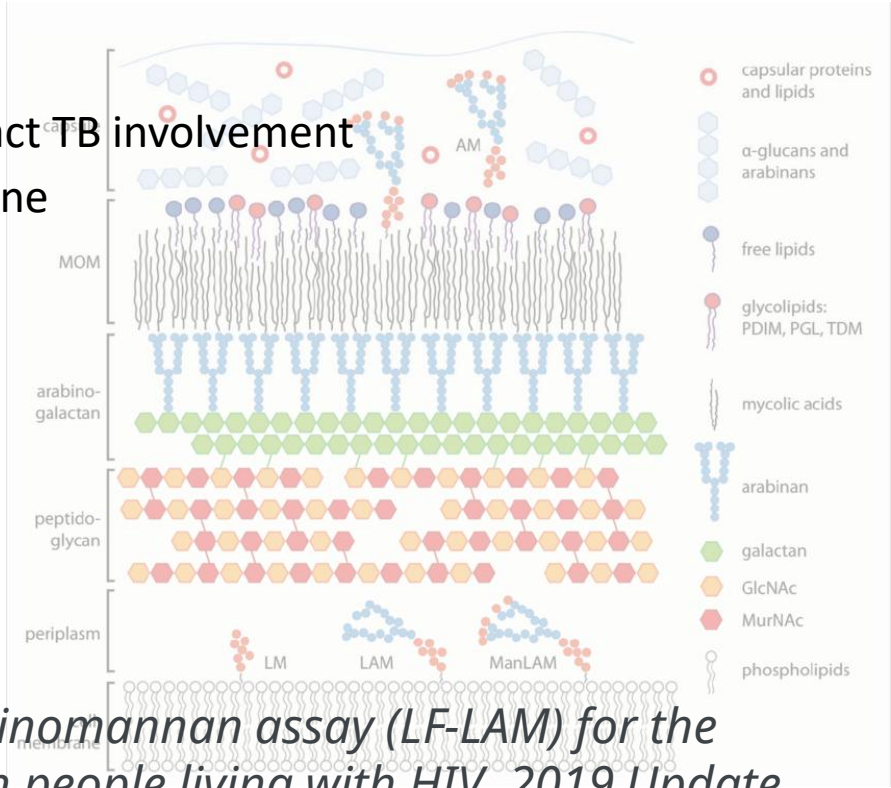
10. WHO suggests using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children:
    - with signs and symptoms of TB (pulmonary and/or extrapulmonary) or seriously ill *(conditional recommendation, low certainty in the evidence about test accuracy);* and
    - irrespective of signs and symptoms of TB and with a CD4 cell count of less than 100 cells/mm^3 *(conditional recommendation, very low certainty in the evidence about test accuracy) (14).*

WHO consolidated guidelines on tuberculosis. Module 6: tuberculosis and comorbidities, second edition. (2025)



- **Negative tests do NOT rule out TB** → pursue culture / repeat if high suspicion
- Consider empiric TB treatment if high clinical suspicion despite negative tests

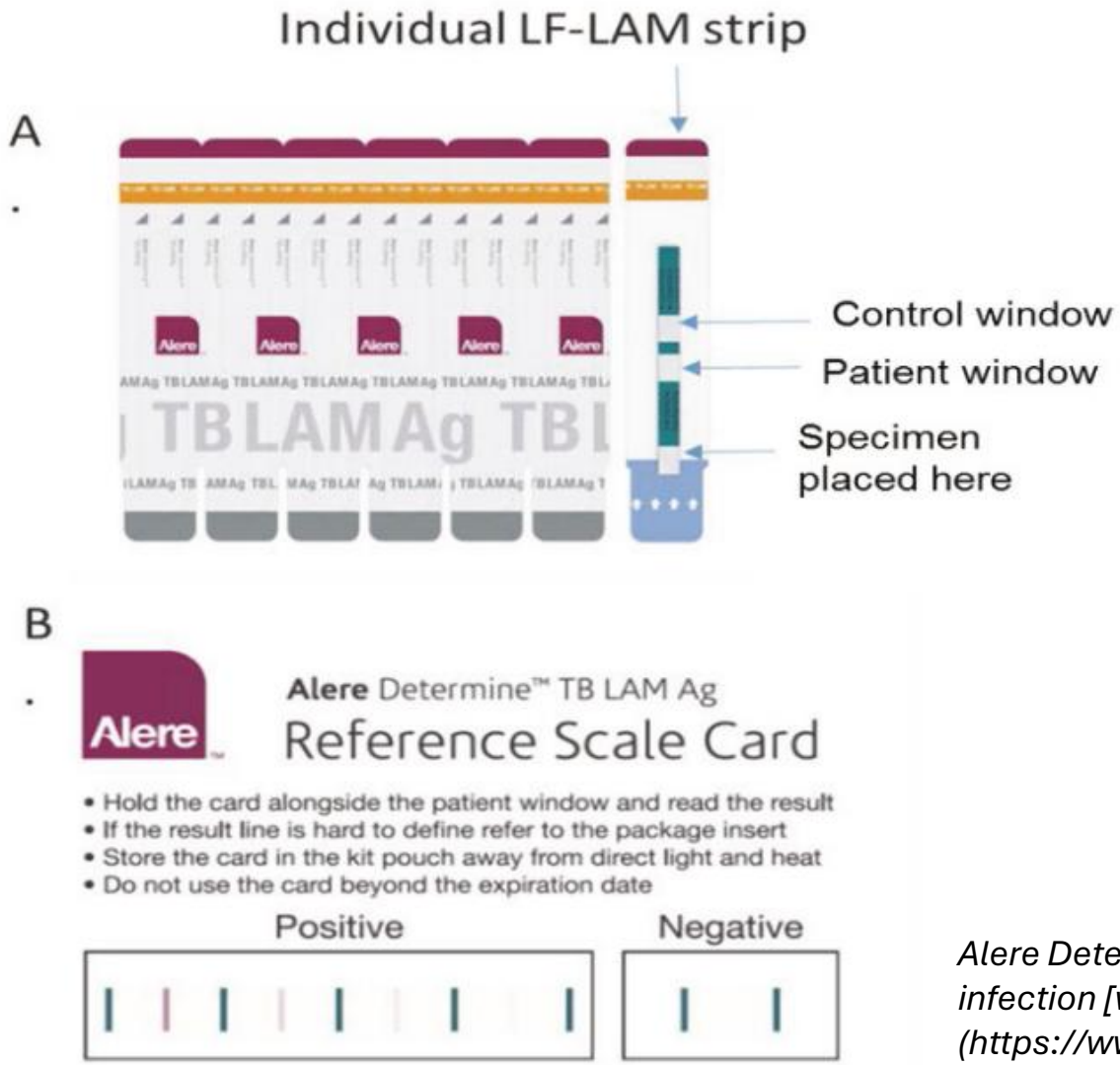
- In settings with high incidence of HIV and TB, the urine lipoarabinomannan (LAM) assay is a useful diagnostic tool, in combination with other tests, including nucleic acid testing and culture
- Urine LAM test detects lipoarabinomannan, a glycolipid component of the mycobacterial cell wall that is released from metabolically active or degenerating bacterial cells during TB disease
- The urine LAM assay is most sensitive in patients with HIV infection who are ill and those with CD4 cell counts <100 cells/µL; the sensitivity decreases as CD4 count increases, and is low in patients without HIV infection. In the populations tested, the LAM assay has moderate to high specificity (88 - 99 %)
- Hypotheses of the higher sensitivity of urine LAM detection in PLHIV:
  - higher bacillary burden and antigen load
  - increased likelihood of haematogenous dissemination and genitourinary tract TB involvement
  - greater glomerular permeability that leads to increased antigen levels in urine



WHO: Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV, 2019 Update

Fig. 1. Alere Determine ™ TB LAM Ag tests (AlereLAM)

(A) Individual test strip; (B) Reference card accompanying test strips to "grade" the test result and determine positivity.



Alere Determine™ TB LAM Ag: Rapid rule-in TB-HIV co-infection [website]. Abbott; 2019 (https://www.alere.com/en/home/product-details/determine-tb-lam.html).

Treatment

WHO recommendations

TB treatment for people living with HIV

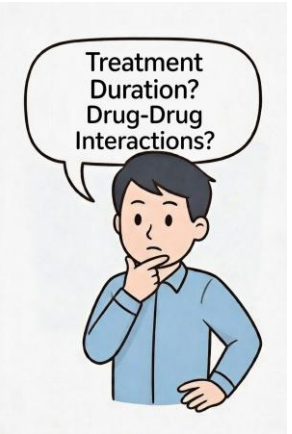
12. It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients *(strong recommendation, high certainty of evidence). (17)*

Total duration of therapy:
1. Pulmonary, drug susceptible TB: 6 months
2. Pulmonary TB & positive culture at 8 weeks of TB treatment: 9 months
3. Extrapulmonary TB with CNS involvement or disseminated TB: 9-12 months
4. Extrapulmonary TB with bone/joint involvement and in other sites: 6-9 months

EACS guidelines 2025

<u>Drug-susceptible pulmonary TB:</u>

- 6-month treatment: 2HRZE/4HR
- 4-month regime: 8 weeks of daily **isoniazid** (H), **rifapentine** (P), **moxifloxacin** (M) and **pyrazinamide** (Z) , followed by 9 weeks of daily isoniazid, rifapentine, and moxifloxacin (2HPMZ/2HPM)
  - An alternative for PLHIV with CD4 >100ells/µL
  - Evidence on efficacy of this regimen in extrapulmonary TB is <u>limited</u>.



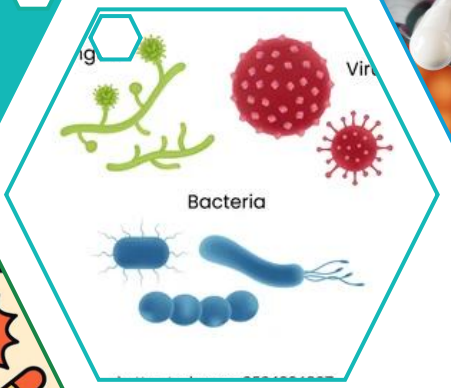
HIV-TB coinfection: the use of intermittent therapy is **<u>not</u>** recommended, especially during the intensive phase

Challenges of treatment of TB-HIV

Hepatotoxicity / other overlapping toxicities of TB drugs and ART

Drug-Drug Interactions

Concurrent infections / Ois



Polypharmacy and drug adherence

TB-IRIS

Timing of ART

Importance of ART: reduces mortality and the risk of relapse

Concerns: high pill burden, drug toxicities, drug–drug interactions, tuberculosis-associated IRIS.

WHO Recommendations

- 2010: ART to be started within 8 weeks of initiating TB treatment
- 2012: initiate ART within 2 weeks among those with CD4 count ≤ 50 cells/mm^3.
- 2021: ART should be started as soon as possible within 2 weeks of initiating TB treatment, **regardless of CD4 cell count** for people with drug-susceptible TB and in whom TB meningitis is excluded

Timing of ART initiation for TB Meningitis

❗ Risks of IRIS, Mortality from IRIS from TBM is much higher than that for non-CNS IRIS - CNS inflammation in a non-expandable space leads to life-threatening deterioration.

❗ no definite survival benefit demonstrated for **early** ART

- **WHO**: ART should be delayed by at least four weeks (and initiated within eight weeks) after TB treatment is initiated for TB meningitis, due to safety concerns.
- **DHHS**: ART should be started once the TB meningitis is under control—with either clinical improvement or improvement in CSF parameters—after at least 2 weeks of anti-TB treatment, to reduce the risk of immune reconstitution causing life-threatening inflammation in a closed space
- **EACS**: In persons with CD4 < 50 cells/µL, ART should be initiated within the first 2 weeks after initiation of TB treatment, if close monitoring and optimal TB treatment can be ensured; ART should be initiated up to 4 weeks after initiation of TB treatment in all other cases

Immune Reconstitution Inflammatory Syndrome (IRIS)

- TB-IRIS results from a disproportionate and dysregulated inflammatory response to TB produced as a consequence of rapid recovery of the immune system.
- TB-associated IRIS has been reported in 8% to 40% of patients starting ART after TB is diagnosed

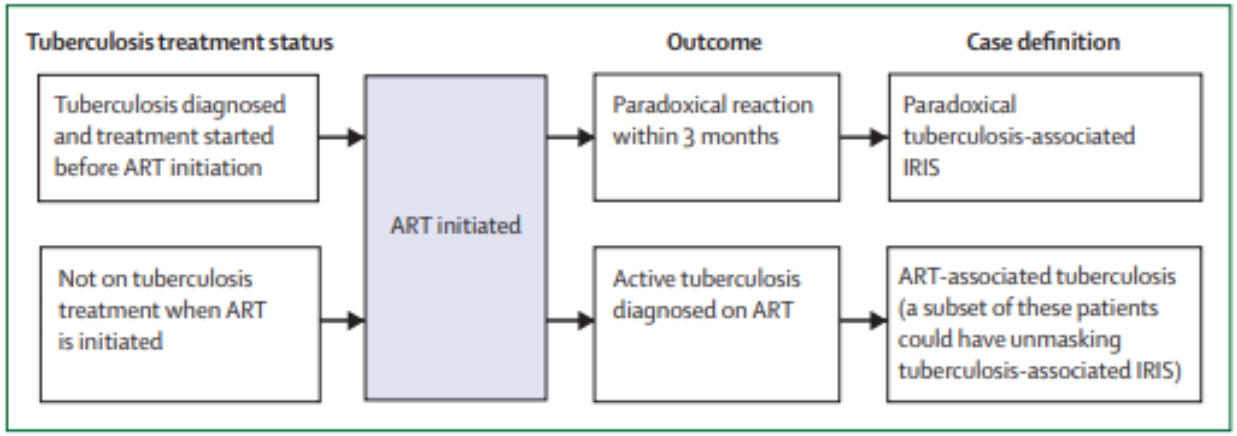


***Figure 3*: Schematic representation showing the different forms of tuberculosis-associated IRIS and ART-associated tuberculosis**
ART=antiretroviral therapy.

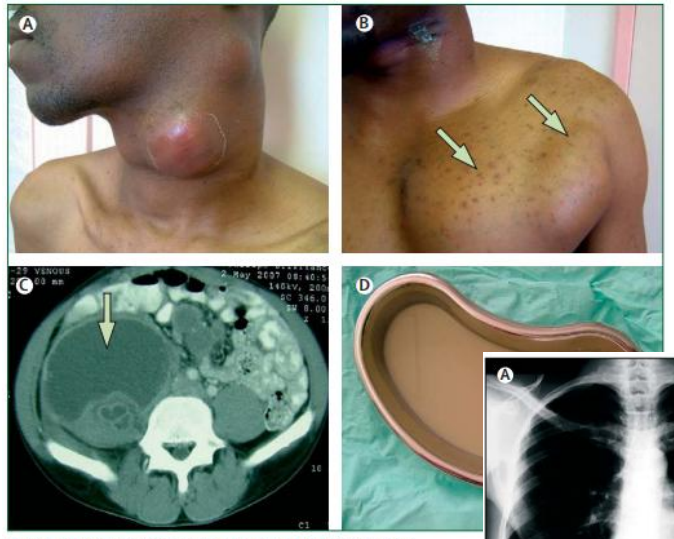


Figure 1: Illustrative case of paradoxical tuberculosis-associated IRIS

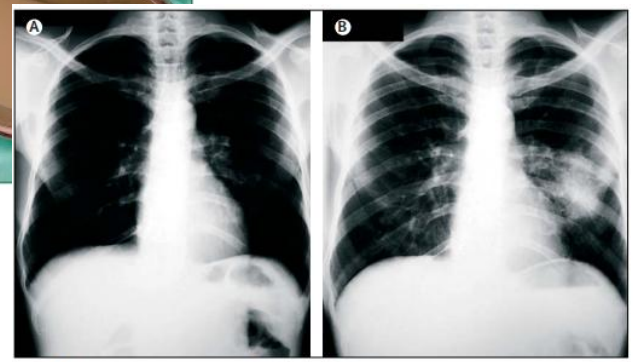


Figure 2: Illustrative case of unmasking tuberculosis-associated IRIS

Graeme Meintjes, et al. The Lancet Infectious Diseases, Volume 8, Issue 8, 2008

General IRIS case definition 2 (Shelburne et al, 2006)[13]

Criteria for IRIS diagnosis include:

- HIV-infected patient
- Receiving effective ART as evidenced by a decrease in HIV-1 RNA concentration from baseline or an increase in CD4+ T cells from baseline (may lag behind HIV-1 RNA decrease)
- Clinical symptoms consistent with inflammatory process
- Clinical course not consistent with expected course of previously diagnosed opportunistic infection, expected course of newly diagnosed opportunistic infection, or drug toxicity

Case definition specific for tuberculosis-associated IRIS (Colebunders et al, 2006)[7]

For patients receiving treatment for tuberculosis and starting ART:

Suspected tuberculosis-associated IRIS case

Cases must meet the following three criteria:

- An initial clinical response to tuberculosis treatment, based on a combination of some of the following factors: cessation of fever, relief of pulmonary symptoms, decrease in lymph node size, termination of signs of meningeal irritation (depending on presenting symptoms)
- New persistent fevers without another identifiable cause and/or one or more of the following: worsening or emergence of dyspnoea, stridor, an increase in lymph node size, development of abscesses, development of abdominal pain with ultrasound evidence of abdominal adenopathies, unexplained CNS symptoms
- Adequate adherence to ART and tuberculosis treatment

Confirmed tuberculosis-associated IRIS case

Cases must meet the following three criteria:

- Radiological examinations showing worsening or emergence of intrathoracic lymphadenopathy, pulmonary infiltrates, pleural effusions, abdominal lymph nodes, hepatosplenomegaly
- A good virological response and/or increase in CD4+ lymphocyte count, and/or conversion of tuberculin skin test from negative to positive, and/or adequate adherence to ART and tuberculosis treatment
- A clear exclusion of other conditions that could explain the clinical manifestations of the patient, such as tuberculosis treatment failure or other concomitant infections, tumours, or allergic reactions

ART=antiretroviral therapy. IRIS=immune reconstitution inflammatory syndrome.

Graeme Meintjes, et al. The Lancet Infectious Diseases, Volume 8, Issue 8, 2008

Risk factors for TB IRIS

- a low CD4+ T-lymphocyte count
- a high baseline HIV viral load
- extrapulmonary tuberculosis
- a short interval between the start of tuberculosis treatment and the initiation of ART
  - A meta-analysis of clinical trials that compared ART initiation at approximately 2 weeks after the start of tuberculosis treatment with ART initiation after 8 weeks showed that the risk of tuberculosis-associated IRIS was doubled among patients who started receiving ART earlier

TB-IRIS - management

- ART should be continued without interruption during IRIS unless life-threatening.
- Systemic steroid has been shown to confer clinical benefit when used to treat and alleviate symptoms associated with IRIS and can be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response.
- Prophylactic use of systemic steroid has also been shown in a placebo-controlled randomised trial to lower the incidence of tuberculosis-associated IRIS
- **Meintjes et al. RCT (NEJM 2018;)**:
  - **n=240 high-risk PLHIV** who started tuberculosis treatment within 30 days before initiating ART, and had a CD4 count of ≤100 cells/µL.
  - Patients received either prednisone (at a dose of 40 mg per day for 14 days, then 20 mg per day for 14 days) or placebo
  - Prednisone reduced TB-IRIS incidence (33% vs. 47%; RR 0.70, 95% CI 0.51–0.96), no significant difference in mortality or excess infections/malignancy.

- Corticosteroids are key for prevention in high-risk cases and treatment of moderate-severe paradoxical IRIS

TB-Associated IRIS

Preventing Paradoxical TB-IRIS

- In high-risk patients (i.e., starting ART within 30 days after TB treatment initiation and a CD4 count $\leq 100/mm^3$) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B **(BI):** prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks

Managing Paradoxical TB-IRIS

- Paradoxical reaction/IRIS that is not severe may be treated symptomatically **(CIII).**
- For moderately severe paradoxical TB-IRIS, use of prednisone is recommended **(AI).**
- In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks
- In patients on a rifabutin plus boosted PI-based regimen: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks
- Taper over 4 weeks (or longer) based on clinical symptoms; a more gradual tapering schedule over 2 to 3 months is recommended for patients whose signs and symptoms have not improved or have worsened due to tapering **(BIII).**

DHHS Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV

Summary of evidence for TB-IRIS treatment regimens.

Treatment	Evidence
NSAIDs	• No formal trials, based on symptomatic improvement in mild cases
Corticosteroids	• Randomized placebo-controlled trial that found more rapid improvement in symptoms, radiography, inflammatory markers, performance and quality of life with four week course of prednisone
TNF-α Inhibitors	• Two case reports found clinical improvement with infliximab in patients with TB-IRIS refractory to corticosteroids • Two case reports of adalimumab for refractory CNS TB-IRIS
Thalidomide	• Case report with three cases of steroid dependent IRIS (2 cryptococcal meningitis and one disseminated TB) that had clinical improvement and allowed steroid tapering • Case reports showing clinical and radiographic improvement of intracranial tuberculomas
Montelukast	• Case report of three cases of severe IRIS (one due to secondary syphilis and two related to tuberculosis) that saw clinical improvement with montelukast
Pentoxifylline	• Case report of one case of TB-IRIS that found clinical improvement
VEGF Inhibitors	• Case report of Bevacizumab used for CNS-TB-IRIS (retinal)

Quinn CM, et al. Tuberculosis IRIS: Pathogenesis, Presentation, and Management across the Spectrum of Disease. Life (Basel). 2020 Oct 29;10(11):262

Adjunctive steroids in TBM

- TBM in PLHIV can cause mortality up to 50%
- Death and neurologic sequelae from tuberculous meningitis are associated with intracerebral inflammation → Adjunctive corticosteroids have been used to treat TBM to control inflammation and to improve outcome, but the evidence is mixed:
- **Studies on Steroid use in TB Meningitis**:
  - **Thwaites et al. RCT (2004)**: Dexamethasone improved survival in HIV-negative TBM; underpowered for HIV.
  - **Prasad et al. Meta-Analysis (2016/updated)**: Reduced mortality/morbidity in general TBM (not HIV-specific).
  - **ACT HIV Trial (NEJM 2023; n=520 HIV+ adults)**: Dexamethasone vs. placebo showed no survival benefit (44.1% vs. 49.0% mortality; HR 0.85, 95% CI 0.66–1.10; P=0.22). No differences in neurological disability, IRIS, or adverse events; no subgroup benefits (e.g., by CD4 or severity). Concludes no role, but guidelines retain due to no harm and historical data.
  - **Recent Meta-Analyses (2025)**: One (BMJ Glob Health: 4 RCTs) showed reduced mortality in PLHIV (needs confirmation); another (CID 2025: 7 RCTs, n=1410) showed no mortality reduction (RR 0.91, 95% CI 0.79–1.04) or serious events increase.

BMJ Glob Health. 2025 Aug 14;10(8):e017923.
Clin Infect Dis. 2025 Jun 4;80(5):1156-1162

Prevention – treating Latent TB (LTBI)

- The risk of TB disease due to reactivation of LTBI for people with untreated HIV has been estimated as 3% to 16% per year
- The risk of progression from LTBI to TB disease in people with HIV is reduced both by ART and by the treatment of LTBI.
- All people with HIV should be evaluated for LTBI at the time of HIV diagnosis

Latest TB Diagnosis

Tuberculin Skin Test (TST)

- positive TST: ≥5 mm of induration at 48–72 hours in people with HIV with no clinical or radiographic evidence of TB disease
- requires two visits to place and read the test
- decreased specificity among people who received Bacillus Calmette-Guérin (BCG) vaccination
- decreased sensitivity among people with advanced immunodeficiency.

Interferon Gamma Release Assay (IGRA)

- higher specificity than the TST, may correlate better with exposure to M. tuberculosis
- less likely to cross-react with BCG vaccination or exposure to nontuberculous mycobacteria
- progressive immunodeficiency is associated with decreased sensitivity of IGRAs
- Cost and availability

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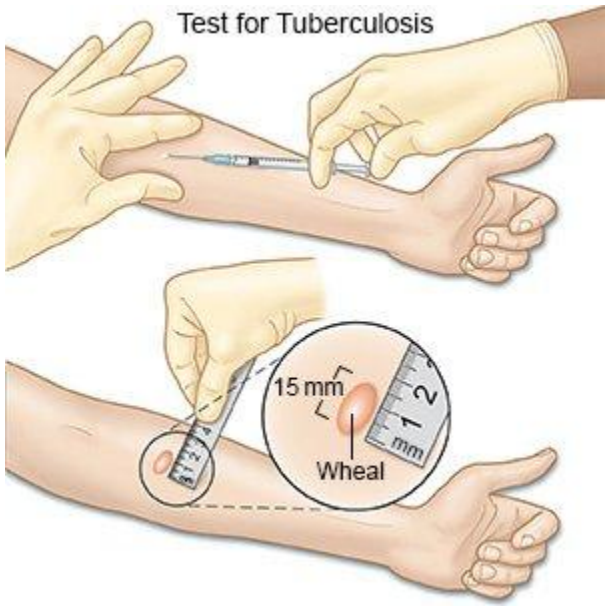
Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection

- Baseline testing of LTBI using either tuberculin skin test (TST) (with 5 mm of induration as the cutoff) or interferon-release assay (IGRA) are recommended for all PLHIV.
- Dual testing using both TST and IGRA can enhance case finding for those with CD4 count <100/μL.
- Testing should be repeated among those without additional risk factors for TB upon achieving immune reconstitution and virological suppression with antiretroviral treatment and then repeated as and when necessary, e.g. subsequent to virologic failure.
- Re-screen should be offered to those with potential exposure, while regular screening should be offered to those with potential ongoing exposure, e.g. among healthcare providers, and those whose household members have active pulmonary tuberculosis with suboptimal response to treatment.
- They should be treated for LTBI after ruling out active TB disease to achieve the best health outcomes.
- Treatment is indicated for PLHIV who have significant recent exposure to an infectious source of TB regardless of LTBI test results.



Latent TB Treatment

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Recommendations on the Management of Human Immunodeficiency Virus and Tuberculosis Coinfection

Always exclude active TB before starting preventive therapy

Isoniazid Daily for 9 months (9H)	**The standard treatment** - minimal drug-drug interactions with most of the recommended antiretroviral regimens
Isoniazid and Rifapentine Once-weekly for 3 months (3HP), taken under observation	Alternative option for those requiring shorter course - Check for potential drug-drug interactions - Lower risk of adverse events and higher completion rates
Rifampicin Daily for 4 months (4R)	Alternative option for those requiring shorter course - Check for potential drug-drug interactions - Can be considered when the source is suspected or confirmed to have isoniazid resistance

Conclusion

- HIV-associated tuberculosis remains a major global public health priority, despite notable reductions in incidence and mortality largely driven by widespread ART scale-up
- Diagnosis of TB in PLHIV is particularly challenging, while emerging tools are improving detection
- Treatment of TB in PLHIV is complex and requires careful management due to risk of TB-IRIS, drug-drug interactions, drug toxicities; consider use of steroids in prevention (for patients at high risk for TB-IRIS) and treatment of IRIS
- Prevention by screening and treating LTBI