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Review

Tuberculosis and HIV co-infection—focus on the Asia-Pacific region

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SUMMARY

Tuberculosis (TB) is the leading opportunistic disease and cause of death in patients with HIV infection. In 2013 there were 1.1 million new TB/HIV co-infected cases globally, accounting for 12% of incident TB cases and 360 000 deaths. The Asia-Pacific region, which contributes more than a half of all TB cases worldwide, traditionally reports low TB/HIV co-infection rates. However, routine testing of TB patients for HIV infection is not universally implemented and the estimated prevalence of HIV in new TB cases increased to 6.3% in 2013. Although HIV infection rates have not seen the rapid rise observed in Sub-Saharan Africa, indications are that rates are increasing among specific high-risk groups. This paper reviews the risks of TB exposure and progression to disease, including the risk of TB recurrence, in this vulnerable population. There is urgency to scale up interventions such as intensified TB case-finding, isoniazid preventive therapy, and TB infection control, as well as HIV testing and improved access to antiretroviral treatment. Increased awareness and concerted action is required to reduce TB/HIV co-infection rates in the Asia-Pacific region and to improve the outcomes of people living with HIV.

1. Introduction

In recent years, expectations of a global epidemiological transition, with a shift in emphasis from acute infections in childhood to chronic diseases in later life, has provided the central narrative of global health.[1] However, despite progress towards the World Health Organization (WHO) Millennium Development Goals (MDGs) associated with major infectious diseases, low- and middle-income countries still suffer an enormous infectious disease burden. In fact, most now face a double burden of disease with rising rates of non-communicable diseases, driven by demographic and lifestyle changes, together with an unresolved infectious diseases agenda.[2]

Among infectious diseases, both tuberculosis (TB) and HIV/AIDS represent global public health emergencies. Their mutually detrimental effect on the individual patient and at the population level is most evident in Sub-Saharan Africa.[3] The impact of TB/HIV co-infection in the Asia-Pacific region (which includes WHO-defined South East Asia and Western Pacific regions) is poorly understood; in this region, HIV infection is less common and the infrastructure to deal with co-infected patients less well developed. This review examines the disease burdens associated with TB, HIV/AIDS, and TB/HIV co-infection in the Asia-Pacific region, reflects on key management challenges, and explores the relative contribution of relapse and re-infection to TB recurrence in HIV-infected patients.

2. Tuberculosis

According to the WHO, an estimated 9.0 million people developed TB in 2013, with 1.5 million deaths attributed to TB, excluding deaths among HIV-infected patients.[3] More than 80% of cases occurred in 22 high burden countries. Nine of the 22 (41%) high burden countries are located in the Asia-Pacific region (Figure 1a).

An estimated five million new TB cases occurred in the Asia-Pacific region during 2013, representing approximately 55% of the global TB disease burden. According to the estimated number of incident cases India ranks first, China second, Indonesia fifth, Bangladesh seventh, Philippines eighth, Myanmar eleventh, Vietnam thirteenth, Thailand eighteenth, and Cambodia

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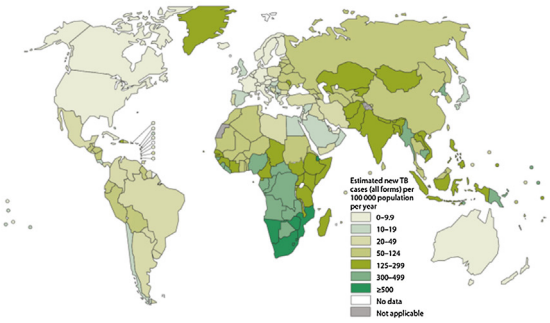
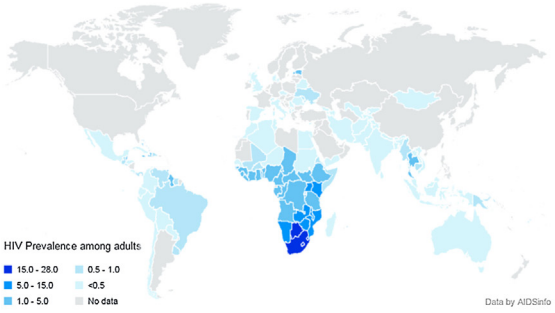
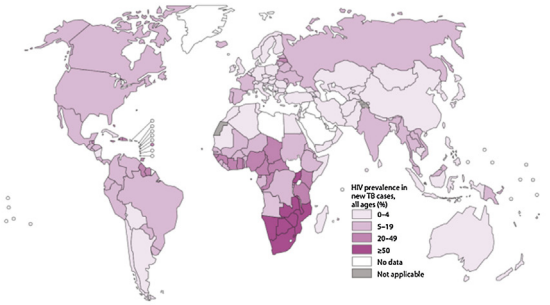
a) Global TB incidence, 2013[a]



b) Global HIV prevalence, 2013[b]



c) HIV prevalence in new TB cases, 2013[c]



TB – tuberculosis; HIV – human immunodeficiency virus infection.
[a]WHO estimated adult TB incidence rates;[3] [b]UNAIDS estimated HIV prevalence among adults (15–49 years);[91] [c]TB/HIV co-infection rates in new TB cases reported to the WHO.[3]

Figure 1. Global disease burden associated with TB and HIV.

twenty-first in the world. India accounted for 42% (2 100 000 cases) and China for 19.6% (980,000 cases) of the Asia-Pacific TB case load. Indonesia, Bangladesh, and Philippines ranked third, fourth, and fifth in the region, accounting for 9.2% (460 000 cases), 7% (350 000 cases), and 5.2% (260 000 cases) of cases, respectively.[4] Major gains in TB epidemic control reported for the Asia-Pacific region have been driven mainly by socio-economic improvements in China, and to some degree in India.[5] Countries such as Myanmar, Democratic People's Republic of Korea, East Timor, and Papua New Guinea represent TB hotspots within the Asia-Pacific region, with TB incidence rates exceeding 300/100 000 population. However, these countries have reduced visibility due to uncertain data quality and relatively small population sizes, which limit their influence on aggregated regional and global figures.

Similar to other parts of the world, TB incidence rates in the Asia-Pacific region are broadly associated with poverty and limited public health infrastructure.[6] Specific factors that contribute to TB vulnerability at the population level include rising rates of diabetes on the one hand, with persistent high rates of malnutrition on the other.[7] Diabetes is a growing concern throughout the region, but is especially prevalent in Pacific Island countries where its detrimental health impacts are most pronounced.[8] Cigarette smoking and air pollution, both indoor and outdoor, pose major threats to lung health.[9] They also increase the TB disease risk

and reduce the likelihood of a favourable treatment outcome.[6] Cigarette smoking rates are on the rise in the Asia-Pacific region, with little political will to reverse this trend.[10] Rising rates of outdoor air pollution linked to rapid economic growth and urbanization are evident throughout the region, while the use of inefficient wood- and coal-fired stoves for indoor cooking and heating remain widespread.

A particular concern for the region is its vast and mobile population, which may facilitate TB transmission, particularly in settings where vulnerable people congregate.[11] Large movements of migrant workers between different districts and countries, complicates timely TB diagnosis and treatment adherence. Prisons also act as epidemic amplifiers in some TB endemic areas and the same may apply to hospitals and clinics with poor infection control practices.[12]

3. HIV/AIDS

HIV infection is heavily concentrated in Sub-Saharan Africa (Figure 1b),[13,14] where women suffer high disease rates due to predominant heterosexual transmission. In general, HIV infection rates among antenatal attendees appear to be low in the Asia-Pacific region, but the actual HIV/AIDS burden remains poorly quantified as universal testing is rarely implemented. Emerging evidence suggests that HIV infection rates are on the rise among high-risk groups in Vietnam, including intravenous drug users, female sex workers, and men who have sex with men.[15] In addition there is potential for spread among sexually active parts of the population who may not perceive themselves to be at high risk, as illustrated by increasing rates of other sexually transmitted infections such as syphilis, chlamydia, and gonorrhea.[16,17]

4. TB/HIV co-infection

TB and HIV/AIDS display a lethal bidirectional interaction, with major epidemic overlap (Figure 1a and b). People living with HIV are almost 30 times more likely than HIV-uninfected people to develop TB, and the chronic immune stimulation resulting from active TB accelerates HIV/AIDS disease progression.[18–20] There were 360 000 TB-related deaths reported in people living with HIV during 2013.[3]

Of all TB cases identified in 2013, 1.1 million (12%) were co-infected with HIV. Sub-Saharan Africa, where the explosive spread of the HIV epidemic fuelled a nearly five-fold increase in TB notification rates between 1990 and 2005,[21,22] accounted for 75% of TB/HIV co-infected patients (Figure 1c).[3] The WHO first published policy documents on collaborative TB/HIV activities in 2004,[23] followed by updates in 2008[24] and 2012.[25] It outlined a comprehensive strategy for better integrated TB/HIV services with provider-initiated bidirectional active case finding that links TB patients who are HIV-infected to optimal HIV care, and HIV-infected patients with TB to early effective TB treatment. It emphasized the need for early initiation of antiretroviral therapy (ART), improved infection control practices, and the use of isoniazid preventive therapy (IPT).

HIV testing is recommended for all patients with TB,[23] with an aspirational target of 100% compliance by 2015.[26] Progress outside Sub-Saharan Africa has been slow,[27] particularly in the Middle-East and Asia-Pacific regions, with less than half of all TB cases tested for HIV in 2013. HIV test coverage among TB patients in Asia is less than 43%, but testing rates are highly variable, ranging from 1.1% of newly diagnosed TB patients in Bangladesh to 100% in Brunei and Bhutan.[28] Recognized barriers to HIV testing include the absence of national policy guidance, low uptake by health care workers if proposed strategies are considered unfeasible or not linked to functional HIV treatment services, a shortage of HIV testing kits, inadequate supervision by both TB and HIV programmes,[29] and concerns about stigmatization. In Africa, the perception of TB as a disease of the poor and 'dirty', low confidence in patient confidentiality, and anticipated HIV-related stigma undermines optimal care-seeking behaviour.[30] In Asia, HIV infection is intricately linked to drug abuse, previous imprisonment, and being a sex worker, which acts as a major barrier to routine testing and the provision of optimal care, due to preconceived negative perceptions by patients and health care workers.[31]

4.1. The Asia-Pacific region

TB/HIV co-infection has not been considered a major driver of the TB epidemic in the Asia-Pacific region, although HIV infection rates are high among certain groups. Up to 2011, the estimated prevalence of TB/HIV co-infection was low at 17.2% in Asian countries compared with other regions such as Africa, Europe, and Latin America.[32] Data on HIV infection rates among TB patients are unreliable since patients are infrequently tested; a minority of countries in the Asia-Pacific region tested more than two-thirds of TB patients for HIV infection in 2013.[3] The reliability of reported figures is hampered by poor monitoring systems and limited collaboration between HIV and TB control programmes.

Table 1 provides an overview of selected TB endemic countries (TB incidence rate ≥100/100 000 population) in Africa and Asia, categorized according to reported TB/HIV co-infection rates. It is notable that TB endemic countries in Asia report TB/HIV co-infection rates below 10% of notified TB cases (except Thailand and Papua New Guinea); this is in stark contrast to countries in Sub-Saharan Africa where co-infection rates generally exceed 50%, reaching up to a maximum of 74% in Swaziland.[3,28] Among other Asia-Pacific countries only Thailand

Table 1
Prevalence of HIV co-infection among incident TB cases (2013); comparing TB endemic countries in Africa and the Asia-Pacific[a]

Country	HIV prevalence (age 15–49 years)[14]	TB incidence (per 100 000 population)[3]	HIV prevalence in incident TB cases[3]
HIV prevalence ≥10%			
Swaziland	27.4%	1382	74.0%
Zimbabwe	15.0%	552	72.0%
Zambia	12.5%	410	62.0%
Botswana	21.9%	414	61.0%
South Africa	19.1%	860	61.0%
Mozambique	10.8%	552	57.0%
HIV prevalence 1–9%			
Uganda	7.4%	166	52.0%
Kenya	6.0%	268	41.0%
UR Tanzania	5.0%	164	37.0%
Nigeria	3.2%	338	25.0%
Thailand	**1.1%**	**119**	**15.0%**
Ethiopia	1.2%	224	11.0%
DR Congo	1.1%	326	7.5%
HIV prevalence <1%			
Papua New Guinea	**0.7%**	**347**	**14.0%**
Myanmar	**0.6%**	**373**	**8.8%**
Vietnam	**0.4%**	**144**	**7.2%**
India	**0.3%**	**171**	**5.7%**
Cambodia	**0.7%**	**400**	**3.9%**
Indonesia[b]	**0.5%**	**183**	**3.2%**
Bangladesh	**<0.1%**	**224**	**0.12%**
Philippines	**<0.1%**	**292**	**0.11%**

[a] Endemic countries have a TB incidence rate ≥100/100 000 population; Asia-Pacific countries are in bold type. Adapted from the World Health Organization Global Tuberculosis Report 2014.[3]

[b] Only 2.3% of TB cases were tested for HIV-infection in Indonesia.[3]

(15%), Papua New Guinea (14%), Myanmar (8.8%), Vietnam (7.2%), and India (5.7%) exceed TB/HIV co-infection rates of 5%.[3] In general, HIV infection rates have not seen the rapid rises observed in Africa and the number of incident TB/HIV co-infection cases has remained fairly constant in recent years, with an estimated 193 000 co-infected cases in 2013.[3] However, case numbers remained static despite improved control of the TB epidemic and the estimated prevalence of HIV in new TB cases in the Asia-Pacific region increased to 6.3% in 2013.[3]

On the positive side, from 2004 to 2012 the Asia-Pacific region achieved significant reductions in TB-related deaths among people living with HIV, including major reductions in Cambodia (>50%) and China (25–50%), and a moderate reduction in Vietnam (<25%).[33] However, ART coverage for people living with HIV remains inadequate; six out of seven (86%) high TB/HIV burden (>1% co-infection rate) countries reported less than 50% ART coverage among co-infected people in 2012.[34,35]

4.2. TB disease profile

Unlike other opportunistic infections, TB disproportionately affects people living with HIV even before any significant drop in CD4+ T cell counts or clinical signs suggestive of HIV/AIDS occur. Table 2 summarizes TB disease characteristics associated with different levels of HIV-induced immune compromise.[36–38] In TB endemic settings, TB is often the presenting disease in people living with HIV. An optimal screening tool requires high negative predictive value to reliably 'rule out' TB.[39] Since 24–61% of TB/HIV co-infected patients present with sputum smear-negative disease, routine sputum microscopy is not adequate to rule out active TB in people living with HIV.[40] Pragmatic active TB case finding requires regular symptomatic screening (current cough, fever/night sweats, fatigue, or weight loss),[41] with additional testing of symptomatic patients to exclude active TB.

Novel approaches such as the Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, CA, USA) have increased sensitivity compared to sputum smear microscopy. This assay is associated with a 35–45% improvement in diagnostic sensitivity for people living with HIV[42,43] and has the advantage of detecting both TB and resistance to rifampin in less than 2 h.[44] For these reasons, the WHO have endorsed Xpert MTB/RIF as a primary TB diagnostic test in symptomatic people living with HIV.[25,45] The availability of Xpert MTB/RIF has increased throughout the Asia-Pacific region, with continued expansion in Cambodia, India, Indonesia, Myanmar, the Philippines, and Vietnam as part of a UNITAID-funded project.[46] In the subgroup of severely immunocompromised patients (CD4 counts of less than 50–100 cells/ml) in whom it is most problematic to rule out active TB with confidence, use of the urine lipoarabinomannan (LAM) assay combined with sputum Xpert MTB/RIF enhances diagnostic sensitivity.[47,48] The availability of a single reliable point-of-care screening test remains a major clinical need.

The majority of TB/HIV co-infected patients develop classic pulmonary disease with fibronodular and/or cavitary lesions on chest radiograph.[26] However, clinical disease manifestations are largely dependent on the level of immunosuppression. More severely immunocompromised individuals have a greater risk of extrapulmonary and disseminated forms of TB (Table 2). Persons with CD4 cell counts of <200 cells/ml are less likely to present with cavitation and often have atypical features. Most patients with advanced immunosuppression (<100 cells/ml) have extrapulmonary and disseminated forms of TB,[49] positive mycobacterial blood cultures, and atypical chest radiography findings.[50] Common extrapulmonary sites include lymph nodes and pleura or disseminated (miliary) disease; less commonly the pericardium, meninges/brain, or abdomen is also involved.[51] Knowledge of the epidemiological context and the vulnerability profile of the patient, and assiduous efforts to obtain appropriate specimens for mycobacterial testing are essential to diagnose TB in people living with HIV.[52]

Table 2
TB risk and disease characteristics associated with different levels of HIV-induced immune compromise

CD4 count, cells/ml	TB risk and disease characteristics
≥500	Increased TB risk irrespective of CD4 count, but appreciably lower risk compared to patients with a CD4 count <500 cells/ml
<500	WHO recommendation for ART initiation[36]
350–499	Mostly still typical upper zone infiltrates with/without cavitation[36]
	Increased atypical TB features[37]
	Increased bacterial pneumonia (also super-infection with TB)[36]
	Tuberculin skin test more likely to be false-negative[37]
200–349	As above (more pronounced)
100–199	Cavitation and positive sputum smear microscopy less common
	Middle and lower lung zone infiltrates, intra-thoracic lymph node enlargement and miliary pattern more common on chest radiograph[36]
	Extra-pulmonary disease more common[37]
<100	As above (even higher rates of disseminated and/or extrapulmonary TB)[50]
	TB-IRIS (unmasking and paradoxical)[38]
	Recommendation to use combination of Xpert MTB/RIF (on sputum) and Determine TB-LAM assay (on urine) as TB screening test[47]

WHO, World Health Organization; ART, antiretroviral therapy; IRIS, immune reconstitution inflammatory syndrome.

Immune reconstitution inflammatory syndrome (IRIS) is defined as new or worsening symptoms and signs of TB within 4–8 weeks of ART initiation, despite improved virological control and immunological recovery.[39] The incidence of TB-IRIS in co-infected patients ranges from 7% to 36%.[35] In the Asia-Pacific region, the rates of TB-IRIS among co-infected patients with HIV and TB who received ART during TB treatment were 26.2% in Thailand[53] and 8% in India.[54] IRIS presentations include unmasking of previously undiagnosed TB, paradoxical deterioration of pre-existing TB lesions, or the appearance of new lesions after ART initiation. Manifestations may include high fever, lymph node enlargement, worsening respiratory symptoms and signs, cold abscess formation, or worsening of central nervous system lesions (tuberculoma and meningitis).[35,55] The key predictor of IRIS is the degree of HIV-induced immunosuppression (low CD4+ count) at ART initiation,[56] although a high viral load at the start of treatment, rapidity of viral load decline, *Mycobacterium tuberculosis* antigen load, and genetic predisposition (HLA B-44) may also influence risk.[39]

As in adults, TB is a leading cause of death in HIV-infected children.[57] Children living in HIV-affected households are at increased risk of TB exposure and infection irrespective of their own HIV status, with those who are HIV-infected being at increased risk of developing TB disease progression.[58,59] The clinical approach to TB diagnosis is similar to adults with sputum smear-negative disease, taking into account the likelihood of TB exposure, proof of *M. tuberculosis* infection (tuberculin skin test induration of ≥5 mm, or a positive *M. tuberculosis* interferon-gamma-release assay), clinical features, and chest X-ray signs suggestive of TB, as well as appropriate microbiological evaluation.[59,60]

4.3. TB infection control and prevention

The importance of infection control was put under the spotlight with the massive hospital-acquired outbreak of extensively drug-resistant tuberculosis (XDR-TB) that involved

HIV-infected patients in KwaZulu-Natal, South Africa.[60,61] Among 12 collaborative TB/HIV activities recommended by the WHO, the three 'I's (isoniazid preventive therapy, intensified case finding, and infection control) are regarded as core prevention strategies.[21,23] High infection control vigilance is required, since people living with HIV are more susceptible to progress to disease following primary or re-infection with *M. tuberculosis* than immune-competent individuals, and are more likely to be infectious themselves.

The risk of developing TB approaches 10–20% per annum among HIV-infected immunocompromised patients living in TB endemic areas.[62] Early ART initiation and universal ART access are key components in national strategies to reduce the risk of HIV-associated TB across all CD4+ T-cell strata[7]. However, ART access remains limited and highly variable across the Asia-Pacific region.[63] Only Cambodia has more than 50% of all people living with HIV currently on ART.[64] Studies in Cambodia and South Africa have indicated that early ART initiation reduces mortality in TB patients, especially among those with low CD4+ T-cell counts.[65,66] Revised WHO guidelines recommend starting ART as soon as possible and within the first 8 weeks of TB treatment initiation.[23,25]

4.4. Drug-resistant TB

The rise of drug-resistant TB threatens global TB control and is a major public health concern.[67] Outbreaks of TB and multidrug-resistant (MDR)-TB within hospital settings have been documented in diverse geographical settings.[60,68] Although MDR-TB appears not to cause infection or disease more readily than drug-susceptible TB, delayed diagnosis, inadequate initial treatment, and prolonged infectiousness contribute to increased attack rates among contacts and high case-fatality among patients.[69] In 2013, the WHO estimated that there were 480 000 new cases of MDR-TB and approximately 210 000 deaths from MDR-TB globally.[3] The Asia-Pacific region includes seven countries (India, China, Philippines, Indonesia, Myanmar, Bangladesh, and Vietnam) among the 27 high-burden MDR-TB countries that accounted for more than 50% of estimated MDR-TB cases occurring worldwide in 2013.[3,70] India and China, the two countries estimated to have the largest numbers of patients with MDR-TB, strongly influence the overall figures for the Asia-Pacific region.[3] The worldwide emergence of XDR-TB[3] and recent reports of 'totally drug-resistant TB' from Iran and India[71,72] pose a major threat to TB control and public health in general. In particular, the overlap of TB/HIV co-infection with drug-resistant TB presents a tremendous challenge and threatens recent progress in reducing the mortality associated with both diseases. Ensuring optimal treatment of all drug-susceptible TB cases, the expansion of early and rapid MDR-TB case detection, and access to adequate MDR-TB treatment must be prioritized.

4.5. TB recurrence

Besides increasing the risk of progression from latent TB infection to active disease, HIV also increases the rate of TB recurrence.[73] TB recurrence occurs when patients who were previously treated for TB develop a new disease episode, due to either relapse (recurrence of the old infection) or re-infection (infection with a new strain).[74] Relapse and re-infection cannot be differentiated by clinical features; this requires comparison of the *M. tuberculosis* strains isolated during the initial and subsequent TB episodes by molecular subtyping.[75] The prevalence of TB recurrence is greater in patients previously treated for TB than the prevalence of new TB episodes in the general population.[76] It is a particular problem in HIV-infected people living in TB endemic areas, in whom recurrence rates of up to 24.4% have been reported within 2 years of successful TB treatment completion.[13] In countries with a low TB incidence, recurrence seems to be attributable to relapse in most cases,[77] but exogenous re-infection seems to be the main driver in TB endemic areas. Molecular studies suggest that 88% of TB recurrences among people living with HIV in India are due to re-infection.[78–81]

Table 3
Advantages and disadvantages of *Mycobacterium tuberculosis* strain typing methods used to differentiate re-infection from relapse during TB recurrence

Advantages	Disadvantages
*IS*6110 *restriction fragment length polymorphism typing (RFLP)*	
• Well validated technique	• Requires a viable culture and large amount of DNA
• High discriminatory power in strains with multiple IS*6110* insertion sites	• Labour-intensive and time-consuming
• High stability (slow insertion rate)	• High level of technical expertise required
	• Reproducibility and comparability problematic
	• Supplementary methods necessary in low copy number strains, which have been prevalent in South East Asia[82]
Spoligotyping	
• Rapid, reproducible, and affordable	• Relatively poor discriminatory power
• Easy to compare results between laboratories	• Inability to differentiate some common phylogenetic lineages, Beijing in particular[88]
• Does not require a viable culture and only a small amount of DNA is needed	
• Reliable method for determining strain relationships and assigning phylogenetic lineages[87–89]	
Mycobacterial interspersed repetitive unit analysis (MIRU)	
• Rapid, reproducible, and cheaper than RFLP	• Not always able to obtain complete MIRU profile
• Easy to compare results between laboratories	• Stability/mutation rate unclear
• Does not require a viable culture and only a small amount of DNA is needed	• Limited capacity to distinguish relapse from re-infection in outbreak situations
• Higher discriminatory power than spoligotyping; MIRU-24 comparable to RFLP[90]	• Beijing lineage isolates requires additional analysis (i.e., supplementary loci) for enhanced discriminatory power[85]
Whole genome sequencing (WGS)	
• Bench-top sequencing instruments becoming more affordable	• Expensive and slow turnaround times (prices and turnaround times dropping constantly)
• Ultimate discriminatory power; complete sequencing data provide a 'future-proof' output	• High level of technical expertise
• Unprecedented levels of evolutionary insight	• Complex quality control requirements to ensure harmonization of results
• Can infer the likely direction of transmission	• Complicated bioinformatics and specialist software required[91]

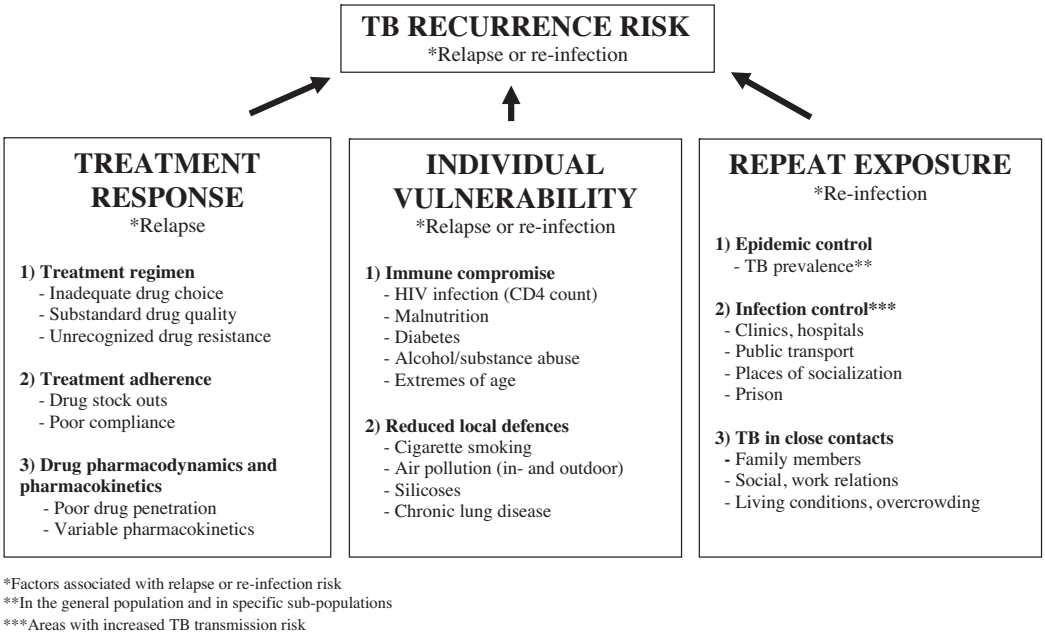


Figure 2. Determinants of TB recurrence risk due to relapse and/or re-infection.

It is unfortunate that the WHO continues to use the term 'relapse' to describe any TB recurrence during programmatic assessment. This is confusing since it fails to differentiate relapse (i.e., failure of clinical management) from re-infection (i.e., failure of public health interventions). This differentiation has important clinical and public health implications. In the case of TB relapse, reasons for treatment failure should be scrutinized carefully. If re-infection is documented, potential sources of TB exposure should be considered. In TB treatment trials, it is important to differentiate relapse from re-infection, since only the former represents treatment failure.[82]

Numerous attempts have been made to differentiate re-infection from relapse using molecular strain typing techniques. One of the earliest and most widely applied molecular typing methods is IS*6110*-based restriction fragment length polymorphism (RFLP) typing.[83] However, mycobacterial interspersed repetitive unit–variable number of tandem repeats (MIRU-VNTR) typing using 24 loci is currently the most reproducible and widely used method.[84] For rapid and reliable genotyping analysis, a combination of spoligotyping and 24-locus MIRU-VNTR is often employed. However, whole genome sequencing (WGS) offers the highest resolution possible and may soon become the new 'reference standard', given the rapid development of this technology.[85] Traditional methods are unable to distinguish relapse from re-infection within an outbreak situation, and their ability to differentiate highly monomorphic phylogenetic lineages, such as Beijing which dominates in large parts of the Asia-Pacific region, remains poor. WGS analysis has been used to differentiate relapse from re-infection in cases where the spoligotyping/MIRU-VNTR profile was not informative.[86] Table 3 summarizes the different genotyping techniques that are available, as well as the advantages and limitations associated with each method.[87–91]

Rates of TB recurrence in people living with HIV vary considerably depending on the level of care provided and the transmission/epidemic control achieved in a particular area. In South India, 88% of recurrent TB among HIV-infected patients was attributed to exogenous re-infection;[78] this percentage was reported to be 29% in Spain[92] and only 7% in North America.[77]

Figure 2 provides a comprehensive overview of factors associated with the risk of TB recurrence. Table 4 describes specific risk factors associated with relapse and re-infection.[93–97] Drug-resistant TB is an important consideration in patients who experience TB treatment failure or true disease relapse,[98] as is treatment adherence and the quality of care received.[99–101] TB recurrence due to re-infection increases with higher infection pressure and longer duration of follow-up.[76,77,102,103] A recent study from Uganda reported high TB recurrence rates both in HIV-infected and un-infected individuals.[100] The overall TB recurrence rate was 8.4/100 person-years during the 2-year study period: 9.4 and 6.7/100 person-years in HIV-infected and un-infected individuals, respectively.[100] In HIV-infected patients, the average time to TB relapse was 8.1 months and to TB re-infection 20.1 months.[104]

Table 4
Factors associated with TB recurrence in HIV-infected patients; differentiating relapse and re-infection

Type of recurrence	Risk factor
Not specified	Poor treatment adherence/drug quality[101]
	Weak treatment regimen[93]
	Age (>30 years)[94,99]
	CD4 cell count (<200/mm^3)[95,96]
	Low Hb (<12 g/dl); marker of more advanced disease[94,99]
	Poor weight gain on treatment (<3 kg after 2 months); marker of poor treatment response[94,99]
Relapse	Drug resistance[98]
	Degree of immune compromise (CD4 cell count)[97,105]
	Poor treatment adherence[83,99–101]
	Beijing genotype[106]
	Thiacetazone (T)-containing regimen[93]
Re-infection	High levels of TB exposure within the household family, community, social behaviour linked
	Poor infection control measures at health facilities[35,101,105,107]
	HIV-1 infection[79]

Hb, haemoglobin.

5. Conclusions

A slowly emerging TB/HIV co-infection epidemic in the Asia-Pacific region is suggested by increasing proportions of TB/HIV co-infected patients, despite reductions in TB case numbers. The double burden of TB and HIV, together with increasing rates of MDR-TB, complicates the management of both diseases and emphasizes the need for strong coordination between national TB and HIV/AIDS control programmes. It is important to understand the factors contributing to TB recurrence, since high rates of TB relapse demand renewed efforts to improve individual patient care, while high rates of re-infection demand improved infection and epidemic control measures. Concerted regional action is required to limit expansion of the TB/HIV co-infection epidemic and to contain the spread of drug-resistant TB in the Asia-Pacific region.[41]

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