**Should we consider a “fourth 90” for Tuberculosis?**

**Perspective for IJTLD**

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**ABSTRACT**

The international community has committed to end the tuberculosis (TB) epidemic by 2030. To facilitate the meeting of the global incidence and mortality indicators set by the World Health Organization’s End TB Strategy, the Stop TB Partnership launched the three 90-(90)-90 diagnostic and treatment targets in 2014. In this paper we argue that a “fourth 90” be considered: “*To ensure that 90% of all people successfully completing treatment for TB can have a good health-related quality of life*”. Many individuals who successfully complete anti-TB treatment are burdened with life-long co-morbidities such as HIV and diabetes mellitus, obstructive and restrictive lung disease including lung destruction, cavitation, fibrosis and bronchiectasis that either pre-existed or developed as a result of TB, chronic pulmonary aspergillosis, permanent disability such as hearing loss resulting from second-line anti-tuberculosis drugs and mental health disorders. These need to be identified during TB treatment and appropriate care and support provided after anti-TB treatment is successfully completed. A “fourth 90” has also been proposed for the UNAIDS 90-90-90 targets similar in scope to what is being suggested here for TB. Adoption by both HIV and TB control programmes would honour the current focus on integrated person- and family-centred services.

**KEY WORDS:**

“fourth 90”; tuberculosis 90-90-90 targets; AIDS 90-90-90 targets; people- and family-centred care

**SHORT RUNNING TITLE:**

Considering a “fourth 90” for TB

*“What gets measured gets done”*

**The Three 90’s for TB and HIV/AIDS**

The international community, through the WHO End TB Strategy,1 the United Nations Sustainable Development Goals,2 and the United Nations High-Level Meeting on the fight against tuberculosis (TB),3 has committed to end the Global TB Epidemic. Targets for meeting this goal include a 90% reduction in TB deaths and an 80% reduction in TB incidence by 2030 compared with 2015.1 A multi-sectoral approach will be needed to achieve this goal and these targets. Within this broad framework, National TB Programmes play a vital role with responsibility for delivering high quality and effective preventive, diagnostic and treatment services, which can interrupt the transmission of *Mycobacterium tuberculosis* in the community. To facilitate the meeting of these global incidence and mortality indicators, the Stop TB Partnership in 2015 launched the 90-(90)-90 TB diagnostic and treatment targets (**Table 1**).4

These TB diagnostic and treatment targets were inspired by and are similar in scope to those developed and launched by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2014.5 The HIV/AIDS targets specify that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people diagnosed with HIV will receive sustained antiretroviral therapy and 90% of all people receiving antiretroviral therapy will have viral suppression. Modelling suggests that achievement of these targets by 2020 will enable the world to end the AIDS epidemic by 2030.5

**The “fourth 90” for HIV/AIDS**

In 2016, Lazarus and his colleagues proposed adding a “fourth 90” to the UNAIDS testing and treatment targets.6 The “fourth 90” would ensure that 90% of people with viral load suppression have a good health-related quality of life and this entails attention to two key domains – co-morbidities and self-perceived quality of life. This “fourth 90” target takes into account the needs of people living with HIV who have achieved viral suppression but still have to contend with a multitude of other challenges such as non-communicable diseases, mental health disorders, pain management, stigma and discrimination. To meet these needs, health services and health systems must become more integrated and people-centred. This is fully in line with the WHO’s Global Health Sector Strategy on HIV 7 and with current concepts of universal health coverage, the public health approach and the continuum of services. While UNAIDS has yet to formally endorse the “fourth 90”, its recent surveys that take into account mental wellness are believed to be a step in the right direction.8

**Is there a need for a “fourth 90” for TB?**

If successfully completing treatment for TB was always a satisfactory result for the person with TB, the door could be closed on an illness that has occupied that individual’s life for the past one to two years. Unfortunately, for many individuals, the successful completion of anti-TB treatment or even being cured of TB does not mean a good healthy quality of life away from the attentions of the health care system.

First, TB is associated with a number of co-morbidities that require regular life-long access to health care facilities, indefinite medication and/or long-term laboratory follow-up. In 2017, there were nearly 465,000 HIV-positive individuals notified with TB. With an expected treatment success rate of about 75% or more, this means nearly 350,000 patients who need long-term antiretroviral therapy (ART) and follow-up, many of them from low- and middle-income countries in sub-Saharan Africa.9 Long-term follow-up is required to ensure retention on ART and to monitor for adverse drug events and the ever present risk of HIV drug resistance and subsequent treatment failure.10 A “fourth 90” for TB would reinforce the “fourth 90” for HIV by encouraging the screening for non-communicable diseases, such as atherosclerotic cardiovascular disease which people living with HIV are more at risk of and for which they need prevention, care and treatment in their own right.11

A recent systematic review of almost 2.3 million persons with active TB found a pooled prevalence of diabetes mellitus of 15.3%, with high rates found particularly in the Western Pacific and Southeast Asia.12 If these data are extrapolated to the 4.8 million persons with new and relapse TB who successfully completed anti-TB treatment in 2017,9 this means about 725,000 persons with diabetes who need long-term follow-up with life-style behavioural change, oral hypoglycaemic drugs and/or insulin in order to prevent or reduce the macrovascular and/or microvascular complications of the disease.

A large international population-based study found that both obstructive and restrictive airways disease was twice as common in people who had recovered from TB compared with those who had never had TB, with these differences especially apparent in people from low- and middle-income countries.13 Two recently published studies from sub-Saharan Africa have emphasised these issues. In Benin, 45% of persons declared cured after anti-TB treatment had impaired lung function as measured by spirometry and a six-minute walk test,14 while in Zimbabwe, 33% had persistent respiratory symptoms, 26% had poor walk-tests and 12% had moderate to severe airways obstruction on spirometry.15 Chronic pulmonary aspergillosis has recently been recognised as an important complication of pulmonary TB, often mistaken for smear-negative tuberculosis and/or treatment failure.16 In Uganda, chronic pulmonary aspergillosis complicated 5% of patients with treated pulmonary TB with the prevalence rising to 26% in those with residual cavitation.17 The disease can be diagnosed with Aspergillus-specific IgG tests and treated with antifungal drugs.

There are other co-morbidities, conditions and determinants that increase the risk of TB and which often persist after successful completion of anti-TB treatment. These include exposure to silica dust and silicosis in miners,18 and people who have non HIV-related suppression of cellular immunity such as those on dialysis for end-stage renal disease,19 those who have received hematologic or organ transplantations,20, 21 and those on treatment with tumour necrosis factor α (TNF- α) for Crohn’s disease or rheumatoid arthritis.22 Malnutrition is a risk for TB with a dose-response relationship observed between decreasing body mass index and increasing risk of TB,23 and this brings into play multi-sectoral issues that can continue long after anti-TB treatment is completed such as poverty reduction and food security. Important determinants such as cigarette smoking and excess alcohol consumption are both associated with an increased risk of TB,24, 25 In the 22 highest burden TB countries, smoking and alcohol use accounted for 26.5% and 9.8% of the population attributable fraction of TB,26 and while attempts should have been made to help people quit both of these harmful substances there is a risk that a person can restart after anti-TB treatment is completed.

Second, anti-TB treatment is effective but not benign and each medication has a number of well recognised adverse events. Most of these resolve after treatment is completed. However, there is one notable exception and that involves second-line injectable agents for treating multidrug-resistant TB (MDR-TB). The most dreaded adverse event of these drugs is ototoxicity where hearing loss can be progressive, even after treatment is discontinued, and permanent, and this can occur in up to 60% of persons treated for MDR-TB. 27 Hearing loss can have a huge negative impact on quality of life and is said to be the third most common cause of years lost to disability globally.28 While injectable second line agents are no longer recommended in MDR-TB treatment regimens,29 this will not help the thousands of patients who have already completed treatment with permanent hearing loss.

Third, the prevalence of mental illness amongst people with TB may reach 70%,30 with a systematic review in people with MDR-TB finding a pooled prevalence of 25% for depression, 24% for anxiety and 10% for psychosis.31 Causes are many and include stigma, discrimination, isolation, inadequate social support, adverse events of medications such as cycloserine, and common risk factors shared with TB such as poverty, homelessness and substance abuse. How much mental illness remains after successful completion of TB treatment is poorly documented and this should be formally assessed through qualitative research.

The co-morbidities, the long-lasting side effects of anti-TB treatment and the mental health disorders that are associated with TB all suggest that a considerable proportion of people affected by TB need help and support after treatment is completed.

**How should the “fourth 90” be formulated?**

We suggest that the “fourth 90” should state” *To ensure that 90% of all people successfully completing treatment for TB can have a good health-related quality of life*”. This means that important co-morbidities such as HIV and diabetes are identified before or during anti-TB treatment and that the persons are formally referred back to HIV care and treatment clinics or diabetic clinics for quality assured care. Cessation support should be maintained for modifiable risk factors such as smoking and alcohol / substance use. Simple assessments that could be carried out at peripheral health facilities, such as the six-minute walk test,32 could be used to assess respiratory function at the end of anti-TB treatment and those with pulmonary impairment could be offered further investigations and a package of care and support. On-going respiratory symptoms from bronchiectasis, for example, can mimic TB and needless repeat courses of anti-TB treatment could be avoided by making a definitive diagnosis. A pulmonary rehabilitation package, supervised by physiotherapists and essentially offering aerobic and resistance exercises that can be learnt and then undertaken at home improved quality of life and respiratory outcomes in adults with post-TB lung disease in Uganda.33 While this package is a potentially simple and useful intervention, there is limited evidence about its cost-effectiveness and which components can make a difference: there is an urgent need to address this knowledge gap. Finally, those rendered deaf through second-line injectable agents and those identified with mental health disorders can receive on-going support and care.

The Lancet Commission on building a TB-free world focused on the need for person-centred and family-centred services to improve the quality and delivery of care.34 These services need to become fully integrated so that the multiple co-morbidities that either pre-exist or arise during TB treatment are not ignored when patients are discharged from TB programme care. Countries need to focus on Universal Health Coverage and ensure that their health systems address the interconnected health issues that affect people and communities touched by TB. The “fourth 90” for TB provides that specific indicator that assesses how well integration has occurred and is perfectly aligned with the “fourth 90” proposed for HIV/AIDS.5 It reminds the health care workforce that the ticked outcome “successfully treated” means that their job is not yet done and an extra effort is required to help the people in their care acquire and maintain a good health-related quality of life.

**Conflicts of Interest**

None declared.

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**Table 1: 90-(90)-90 Stop TB partnership Global Targets for Tuberculosis**

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| * Reach and treat at least 90% of all people with TB a * As a part of this approach reach and treat at least (90%) of the key populations b * Achieve at least 90% treatment success for all people diagnosed with TB c |

TB = tuberculosis

a - includes people with drug-susceptible and drug-resistant TB and people who require preventive therapy (for example, people living with HIV and those in contact with TB patients)

b  includes at-risk populations which can vary depending on country context

c - includes achieving 90% treatment success among people diagnosed with drug-susceptible and drug-resistant TB and people who require TB preventive therapy

*Adapted from reference 4*