Target regimen profiles for long-acting injectables for tuberculosis prevention and treatment



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Abbreviations and acronyms

ADR	adverse drug reaction
AE	adverse effect
BPaL	bedaquiline, pretomanid and linezolid
BPaLM	bedaquiline, pretomanid, linezolid and moxifloxacin
DOT	directly observed therapy
DR-TB	drug-resistant tuberculosis
GEG	guidance on evidence generation
HIV	human immunodeficiency virus
HRZE	isoniazid, rifampicin, pyrazinamide and ethambutol
IM	intramuscular
LAI	long-acting injectable
LAT	long-acting technology
LMIC	low- and middle-income countries
MDR-TB	multidrug-resistant tuberculosis
NGO	nongovernmental organization
NTP	national tuberculosis programme
PD	pharmacodynamic
PK	pharmacokinetic
pre-XDR-TB	pre-extensively drug-resistant tuberculosis[1]
R&D	research and development
RR-TB	rifampicin-resistant tuberculosis
RS-TB	rifampicin-susceptible tuberculosis
SC	subcutaneous
SoC	standard of care
TAG	Treatment Action Group
TB	tuberculosis
TDG	Scientific TRP Development Group
TPP	target product profile

[1] Pre-XDR-TB is TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

TPT	tuberculosis preventive treatment
TRP	target regimen profile
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis[2]

[2] XDR-TB is TB caused by a strain of *M. tuberculosis* that is resistant to rifampicin (and which may also be resistant to isoniazid), as well as resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and at least one other "Group A" drug (bedaquiline or linezolid).



Executive summary

TB prevention and treatment still depend on daily oral regimens taken over months. Sustaining adherence over such periods is difficult for many people, and interrupted treatment contributes to poor outcomes and to the acquisition of drug resistance. Long-acting injectables (LAIs) shift the burden of adherence from the person taking the medicine to the delivery system itself. They have already changed the management of other conditions, most visibly HIV, and several LAI candidates for TB are now entering or approaching clinical development.

A target regimen profile (TRP) states, early in development, what a new regimen would have to achieve to be useful in practice. Each characteristic is set at two levels: a **minimal requirement**, which a product must meet to be worth pursuing, and an **optimal requirement**, representing the most desirable yet realistically achievable target. Making these expectations explicit before candidates are far advanced aligns developers, regulatory and procurement agencies and funders around a common target.

This document sets out WHO TRPs for LAIs, both for TB preventive treatment (TPT) and for the treatment of TB disease. Its scope is deliberately confined to LAIs. Other long-acting technologies are under investigation, but LAIs are the furthest along in clinical development for TB and are considered the most feasible to implement in the near term, particularly in low- and middle-income countries. The intended audience is the pharmaceutical industry, academia, research institutions, product development partners, TB-affected communities, nongovernmental and civil society organizations, and donors.

How the profiles were developed. In May 2025 WHO constituted a Scientific TRP Development Group, bringing together trialists, scientists, pharmacologists, regulators, national TB programme officers, public health officials, people with lived experience of TB and civil society representatives. The group reviewed a landscape of LAI development and successive drafts of the document. The draft was opened to public comment for one month in April and May 2026, and the comments received were incorporated into a revised version that was reviewed by the group and by external reviewers. Evidence on the values and preferences of end users was gathered through community and provider surveys, focus group discussions and a multicountry discrete choice experiment. Outstanding issues were settled at a four-day virtual consensus meeting of the Scientific TRP Development Group held from 29 June to 2 July 2026, the agenda of which is reproduced in Annex 3.

Requirements for TB preventive treatment (Table 4.1). The profile for TPT is built around radical simplification. Optimally, a full course would be delivered at a single encounter, as one injection of a single drug; minimally, two encounters, up to two injections and no more than two component drugs, with a treatment duration of up to 1 month. At both levels there should be no oral lead-in and no combination with oral medicines. Efficacy should be at least

as good as that of current oral TPT regimens, and optimally effectiveness should be better. This direction is supported by the end-user research: 79% of survey respondents preferred a single-injection TPT given at one encounter to a 1-month oral regimen, 6% were neutral and 15% preferred the oral option.

Requirements for the treatment of TB disease (Table 5.1). Treating TB disease is more complex, and the profile is correspondingly more permissive while keeping the same direction. The minimal requirement is three dosing encounters, with one or two as the optimum; duration of coverage for a single drug of at least 2 months, optimally at least 4 months; and a total treatment duration of no more than 4 months, optimally no more than 2 months. Three or four component drugs are expected throughout the regimen. Minimally these would be given as three or four separate injections at each encounter, one per drug; the optimal requirement of one or two injections presupposes co-formulation of several drugs in a single vial or prefilled syringe, and is intended to press development in that direction. An oral lead-in of no longer than 1 month is acceptable at the minimal level; optimally there is none. Efficacy should match that of the standard of care, and optimally effectiveness should exceed it.

Requirements common to both. For both indications, injections should be administered by a trained health worker at the lowest feasible level of the health system, preferably in community or primary care settings. A dosing interval flexibility of ±2 days is required as a minimum and ±4 days optimally, so that programmatic delays do not compromise the regimen. Injection volumes should not exceed 2 mL subcutaneously in adults, and optimally 1 mL. No cold chain should be required. Non-injection-related adverse events should be no more frequent or severe than with current oral regimens, and optimally less so; injections themselves should cause only mild or moderate reactions, and optimally only mild ones. The potential to select for resistance to TB medicines should be no greater than with current regimens.

Trade-offs and cross-cutting considerations. Optimizing one characteristic is often at odds with optimizing another, and the trade-offs are not symmetrical. Efficacy, safety and the preservation of existing TB medicines against resistance should not be traded away for convenience, whereas dosing frequency, dosing interval flexibility, route of administration and the number of dosing encounters allow more latitude. A candidate regimen should meet most of the minimal requirements and as many of the optimal requirements as possible. The document also addresses matters that bear on whether these products reach the people who need them: trial design and the distinction between efficacy and effectiveness, overall treatment burden, scalability, equitable access and transparent pricing, and cost. Work on better oral regimens should continue in parallel, for people who need them or who would prefer not to receive injections, and implementation should preserve patient choice, including the option to return to an oral regimen where clinically appropriate.



1. Introduction

This document provides target product profiles (TPPs) and target regimen profiles (TRPs) for long-acting injectables (LAIs) for tuberculosis (TB) prevention and treatment.

1.1 Background

1.1.1 Scope

A TPP outlines the desired product characteristics to be considered and prioritized early on during the product development process. It describes, for a given disease or use, the intended purpose of a product, the populations it is meant to serve and the attributes it should achieve (e.g. efficacy, safety, formulation and conditions of use). The attributes are set at two levels: a minimally acceptable profile that a product must meet to be worth pursuing; and a preferred, optimal profile that represents the most desirable yet realistically achievable target. By making such expectations explicit early in development, a TPP sets research and development (R&D) targets that align developers, regulatory and procurement agencies, and funders around shared public health priorities; also, it treats access, equity and affordability as integral to the innovation process rather than concerns deferred until a product reaches the market *(1)*. A TRP extends this same approach from a single medicine to a treatment regimen; that is, a combination of medicines that are used together. By specifying the characteristics a new regimen should achieve, the TRP helps to steer development towards regimens that are effective, usable and suited to programmatic delivery across diverse settings. The TRPs are intended to guide R&D; they are not regulatory criteria and do not replace the quality, safety, efficacy, pharmacovigilance and risk-management requirements of national regulatory authorities.

To inform the R&D targets for funders and developers, the World Health Organization (WHO) Global Programme on Tuberculosis and Lung Health has developed updated TRPs for TB preventive treatment (TPT); the treatment of rifampicin-susceptible TB (RS-TB) and rifampicin-resistant TB (RR-TB); and a pan-TB treatment regimen *(2, 3)*. TRPs are developed through a series of interactive document reviews and consensus seeking, keeping in mind the objectives of the product to be developed, and its usability and utility for the end user. The current document considers drug regimens for either TPT or the treatment of all forms of TB using LAIs, and aligns with the TRPs for TPT and TB treatment.

The scope of this document is intentionally limited to LAIs. Although there are other long-acting technologies (LATs) – for example, implants, microarray patches and long-acting oral technologies – LAIs are the furthest along in clinical development for TB; also, they are considered to be a potentially accessible and cost-effective technology to develop and implement in the near term for TB prevention and treatment programmes, particularly

in low- and middle-income countries (LMIC). This focused approach ensures that the TRPs address the most immediately feasible and impactful product characteristics, to accelerate the availability of simplified, adherence-improving TB regimens.

1.1.2 Features of LAI

LAIs are a form of sustained-release medication, given by injection via the intramuscular (IM) or subcutaneous (SC) route. They are groundbreaking technologies that have already demonstrated their potential in managing various diseases, including HIV *(4)*. In the case of HIV, the recent introduction of lenacapavir (a twice-yearly SC capsid inhibitor) has built on the success of 2-monthly cabotegravir to further shift the prevention paradigm; lenacapavir has shown high efficacy in clinical trials and received a WHO recommendation in 2025 *(5)*. LAIs for TB treatment and TPT are currently entering clinical development, creating a pressing need for well-defined TRPs. LAI formulations have shown better adherence and health outcomes in high-income countries for conditions such as schizophrenia *(6)* and opioid substitution therapy *(7)*. Long-acting technologies for hormonal contraception, which has high efficacy, has become the preferred method for many women in LMIC *(8)*. Potential benefits to people affected by TB include greater ease of adherence; lower risk of generating resistance owing to improved adherence; reduction in time spent interacting with the health system and time away from work, with associated economic impacts (e.g. time saved, more home time and lower transit costs); reduced pill burden; reduced overall dosage of medication received; and reduced stigma.

LAIs primarily address the burden and reliability of medication-taking; that is, dosing frequency, the number of health system encounters and the adherence required. The programme would need to invest in complementary efforts to resolve the other determinants of effective prevention and treatment, such as case detection; testing for infection; exclusion of active TB disease; managing comorbidity and severe disease; management of drug–drug interactions; contact investigation; and the supply, financing and health system capacity needed to deliver care. Hence, LAIs should be regarded as one component of a broader package of tools, whose value will vary with the epidemiological and health system context. Although LAIs could improve efficiencies, reduce long-term health system costs and offer other benefits, it is expected – based on anticipated production and development costs – that the LAIs for TPT and TB treatment will enter the market with a higher price than existing oral formulations. International collaboration and support may be required to ensure affordability, especially during initial roll-out.

1.1.3 LAIs and current challenges in TPT and TB treatment

Poor adherence to TB medication reduces regimen effectiveness and increases the risk of prolonged infectiousness, drug resistance, relapse and death *(9)*. Factors contributing to erratic TB treatment adherence include access to health facilities, health service issues, social context (e.g. poverty and lack of support), treatment-related adverse events, tolerability and acceptability of the treatment, treatment-associated stigma and patient health literacy. WHO recommends several evidence-based actions to support medication adherence, such as patient education and use of digital technologies *(10)*; however, these actions require programmatic effort to implement. LAIs hold the promise of revolutionizing the prevention and treatment of TB, reducing the frequency of drug administration, facilitating medication adherence and potentially improving the care experience for people affected by TB. However, LAIs may also present concerns for safety and tolerability, which are discussed later in this section.

TPT is one of the WHO-recommended strategies that can benefit both individual and public health, with an efficacy of about 60–90%, which can last several years *(11)*. It fits within a larger range of actions that programmes can adopt to prevent TB, ranging from infection prevention and control, early detection and screening, and management of health risks that predispose people to TB (e.g. diabetes, smoking and undernutrition). The array of tools to prevent TB is expected to soon be supplemented with effective TB vaccines. The successful expansion of LAIs for TPT in the near future is anticipated to complement novel TB vaccines, and maximization of population coverage with a comprehensive, multilayered approach to prevention. An efficacious TPT, if coupled with novel tests to identify those at highest risk of disease progression, is an important step towards accelerating global progress to end TB. However, there are several challenges to implementing TPT at scale, primarily owing to the hesitancy of people offered TPT – who are usually asymptomatic – to start and continue medication, and the implications for programmatic logistics. First, current TPT guidelines recommend testing for TB infection to identify those who are more likely to benefit from medication (except for people living with HIV and children aged under 5 years in contact with TB patients). In many settings, these tests are unavailable owing to logistical constraints or costs, creating a barrier to implementing TPT. Second, in every situation in which TPT is considered, TB disease needs to be ruled out, because current TPT regimens cannot be relied upon to resolve early forms of TB disease. Reliably ruling out TB disease can be challenging; however, in the future, the development of affordable, portable and accurate screening tools would make it easier to rule out TB disease before the start of TPT, and thus make TPT more feasible to deploy. Third, although current TPT regimens are effective, they are relatively long and prone to generate adverse drug reactions (ADRs). Although most of the ADRs associated with TPT are low grade, they still affect tolerability in people offered TPT, who are usually healthy and symptom-free. TPT is thus often interrupted and not completed as prescribed *(12, 13)*. Finally, if the infecting strain is resistant to one or more TPT drugs, then TPT may be less effective.

At the time of writing, there is no TPT regimen that is reliably effective, short and convenient as a "pan-TPT" regimen. The prospect of having TPT administered as an LAI, employing compounds that are safer than today's medication but equally or even more effective, is of interest given that such an LAI could overcome several of the challenges to TPT expansion. A TPT regimen of 1 month of daily rifapentine and isoniazid has been proven to be effective *(14)*, making it conceivable that LAI regimens acting over a similarly short period could also prevent TB; this would minimize the number of encounters needed to administer medication, compared with daily oral medication, dramatically simplifying the programmatic management of TPT. A single injection, without any associated oral treatment, may be more acceptable than a full pill-based therapy, provided the injection is safe and any toxicity is reversible. The efficacy of large-scale TPT interventions depends on their feasibility in primary care and community-based settings; in a similar fashion, it would be important that LAIs could also be administered in a decentralized setting.

In conclusion, the effective implementation of LAI TPT will depend heavily on operational factors such as access to diagnostics; capacity to rule out TB disease; procurement and supply; and education of health workers, patients and contacts. If LAIs are to contribute to preventive efforts, some of the challenges facing the implementation of TPT – including detecting TB infection, ruling out TB disease and creating demand – would still need to be strengthened.

LAIs also have the potential to address several barriers to the successful treatment of TB disease. They can reduce the risk of acquired drug resistance by reducing treatment interruption, missed doses or ineffective monotherapy. Also, by ensuring the

desired concentration of TB medicines in serum and tissues for prolonged periods, they could overcome the pharmacokinetic (PK) variability associated with oral dosing, such as food effects and malabsorption. Nonetheless, developers will need to have strategies to reverse or manage LAI-related ADRs. LAIs could simplify treatment delivery by removing the need for daily pill intake and frequent clinic visits, which are often required for TB therapy. By reducing the number of health facility contacts, they can ease the burden on both patients and health systems, minimizing the risk of TB transmission, lowering service-delivery costs and freeing resources for other aspects of care. Simplified, less frequent dosing may also improve adherence and treatment completion rates, particularly among patients who face structural or social barriers to consistent treatment. For TB disease, LAIs could facilitate treatment by requiring only a few administrations spaced several months apart, and thus offering a more manageable alternative to prolonged multidrug regimens. This approach could effectively shorten the duration of TB treatment to a few months, advancing a long-standing programmatic goal that has been difficult to achieve with conventional oral therapies.

Beyond individual adherence and system efficiency, LAIs could help to reduce the stigma associated with TPT and TB treatment by minimizing the visible daily pill taking and reducing the frequency of clinic visits. Their use may also complement future TB vaccines and community-based interventions, supporting a more integrated approach to TB prevention and control. It is envisaged that LAIs may be given once or more times to the same individual, either as an exclusively injectable regimen or with a brief initial phase of oral medication ("oral lead-in") before the injectable regimen. TB treatment regimens are composed of more drugs than TPT regimens and it may be possible that oral drugs will have to be administered concurrently with LAIs to maintain efficacy and forestall resistance, particularly when drugs with a long half-life are used in LAIs.

1.1.4 Potential downsides of LAI

Despite the revolutionary promise of LAIs, their development and implementation face several significant limitations and operational challenges that must be addressed in the TRPs. The first key safety challenge is the difficulty of reversing administration. With the current technologies being developed, once an LAI has been injected, removal will not be possible; hence, the medicine may remain in the patient's system for the whole coverage period and may continue causing adverse effects (AEs), making management of intolerance, drug–drug interactions or toxicity particularly challenging. The sustained-release properties of LAIs could prolong any ADRs that emerge. This has negative implications in situations where newly identified contraindications, including pregnancy, may be recognized after administration of a drug. Moreover, new TB drugs that may be used in LAI formulations may present unfamiliar reactions.

Another issue is that the physical experience of administration may be a barrier, with some individuals being less tolerant of injections than oral treatment. Some people, especially children, may have needle phobia, and the pain at the site of administration of an LAI is expected to be more uncomfortable than taking an oral medication. Depending on the design of LAIs, trained staff may be needed to administer them. Another issue stems from the complexity of treating TB disease, which typically requires a multidrug regimen. Currently, there are not enough LAI medicines available to form a complete all-LAI multidrug regimen; thus, a combination of LAIs and oral medicines will be needed. This requirement for a combined approach risks diminishing some of the core LAI benefits, such as simplified adherence, and significantly reduced or eliminated pill burden.

A significant concern with LAIs is the PK tail; that is, the period of prolonged, subtherapeutic drug decline after treatment is stopped or a dose is missed, particularly for drugs like bedaquiline that have a long half-life. If different drugs in a regimen have mismatched tails, a patient may be exposed to functional monotherapy, where only one drug remains at an active level, potentially creating a "selective window" for drug resistance, with implications for both individual patient care and transmission. However, the clinical risk of amplifying resistance is highly dependent on the timing of this exposure. During the early "intensive phase", when the bacterial load is high, functional monotherapy presents a higher risk. Conversely, if the tail occurs towards the end of a successful treatment course, when the bacterial burden has been significantly reduced and the regimen is close to eliminating the final persistent bacilli, the risk of selecting for resistance is substantially lower, because there is a smaller population of bacteria available to mutate.

Finally, the co-administration of different LAI agents may introduce operational complexities, because different compounds may have different treatment coverage periods (e.g. one monthly and another quarterly), making the administration timing and overall clinic schedule more complex to manage programmatically. These issues emphasize the need, when developing LAI products, to prioritize a strong safety profile, high potency (to reduce the number of agents required), and synchronized pharmacological coverage and washout periods.

1.1.5 TRP minimal and optimal requirements for LAI

This document addresses TRPs for LAI regimens for TPT and for treatment of TB disease. TRPs specify the main characteristics of new treatment regimens. For each of these characteristics, requirements are defined and provided as either:

- minimal – the lowest acceptable output for a characteristic; or
- optimal – the most favourable, realistically achievable target.

These definitions are detailed in Table 1.1. The expectation is that any developed regimens will meet the minimal requirements and as many of the optimal requirements as possible. However, the criteria are indicative rather than absolute, because potential trade-offs on performance, cost, impact and operational characteristics would need to be considered for WHO policy. Where a regimen does not meet minimal or optimal requirements, WHO would still review data on the regimen; however, falling short of the requirements may lower the strength of a recommendation (e.g. where the magnitude of desirable effects is judged to be small or trivial) and thus reduce the uptake of a new regimen.

Table 1.1. TRP terminology

Term	Definition
Characteristic	Specific attribute or specification that is measurable.
Minimal requirement	For a specific characteristic, it refers to the lowest acceptable output for that characteristic. To be acceptable, regimens should generally meet the minimal requirements.
Optimal requirement	For a specific characteristic, it provides the most favourable output for that characteristic that is believed to be realistically achievable. Meeting the optimal requirements will provide the greatest impact for end users, clinicians and patients. Ideally, developers would design and develop their solutions to meet the optimal requirements.

TRP: target regimen profile.

Sometimes, minimal and optimal requirements are set in reference to existing comparator regimens (e.g. being safer than the comparator regimen). The comparator regimen is the relevant benchmark regimen to which the requirements for a certain characteristic may be compared (e.g. efficacy should be at least as good as the contemporary comparator regimen that aligns with programmatic feasibility across diverse settings). It is the regimen that should be provided to patients in the comparator arm of randomized trials or nonrandomized comparisons. Typically, the comparator regimen would be based on the latest WHO recommendations for the respective indication. Note that this comparator is expected to be an all-oral treatment regimen.

In the case of multidrug regimens, some TRP attributes may be more relevant to a specific component of the regimen (e.g. dosing interval flexibility) while others may apply to the whole regimen (e.g. target population).

To complement the TRPs, WHO has developed guidance on evidence generation (GEG) on new TB regimens for treatment *(15)*, and a GEG for TPT is currently in development. The TRPs describe *what* the minimal and optimal requirements for each regimen characteristic are, whereas the GEG provides more detailed guidance on *how* the achievement of these requirements could or should be measured in clinical trials or other studies, from the perspective of evidence needed to inform WHO policy-making. Although the GEG documents are tailored to the more usual oral regimens, many of the suggested measurements are also applicable to LAI regimens. As the field develops, more details pertinent to LAIs may be added to the dedicated GEG document.

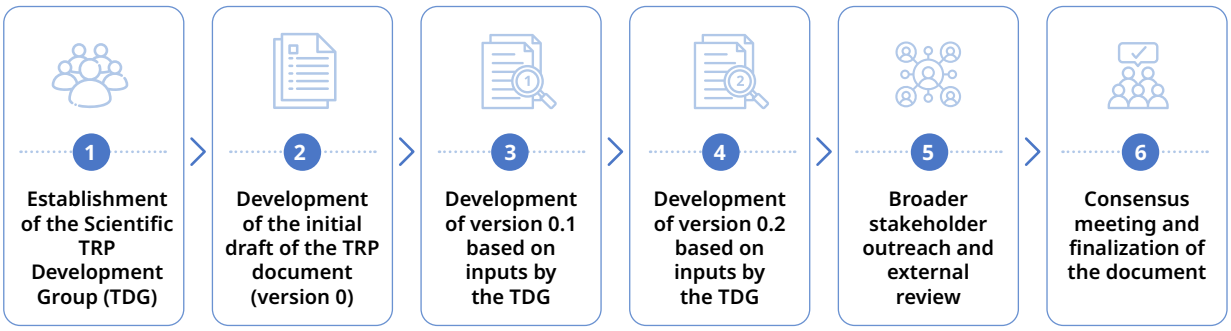
1.2 Objective and target audience

The overall objective of these WHO TRPs for LAIs for TB treatment and TPT is to align developers' performance and operational targets for new regimens with the needs of end users, in line with the current trends in science. The target audience comprises the pharmaceutical industry, academia, research institutions, product development partners, TB-affected communities, nongovernmental organizations (NGOs), civil society organizations (CSOs) and donors. These TRPs will describe minimal and optimal requirements across key characteristics for LAIs.

2. Methodology

Fig. 2.1 provides a high-level overview of the development process of the TB LAI TRPs. This chapter describes key activities in relation to these TRPs.

Fig. 2.1. Overview of the development process of the TB LAI TRPs



LAI: long-acting injectable; TB: tuberculosis; TDG: Scientific TRP Development Group; TRP: target regimen profile.

2.1 Establishment of the Scientific TRP Development Group for TB LAIs

In May 2025, WHO constituted a Scientific TRP Development Group (TDG) for TB LAIs that included leading scientists and experts, public health officials, regulators, those involved in the development of WHO policy recommendations, and representatives of in-country end users. The TDG served to support the entire TRP development process by reviewing drafts at several stages, contributing to discussions during meetings and providing direct input into the drafting process. The full list of TDG members can be found in Annex 1. All TDG members completed the WHO declaration of interest form; the declarations were presented to the whole group ahead of discussions and are summarized in Annex 4. A WHO Steering Group oversaw the scope of the target regimen profiles and supported the planning, development, review and publication of this document. Its members were WHO staff from headquarters departments, the Regulation and Prequalification Department and the WHO regional offices, and they are listed in the Acknowledgements. Samuel Schumacher and Fuad Mirzayev served as the responsible technical officers. WHO regional offices also contributed through the regional stakeholder workshops described in section 2.4, and the ethics review committees of the WHO Regional Office for South-East Asia and the WHO Regional Office for the Western Pacific granted the ethics clearances for the stakeholder surveys.

2.2 Landscape analysis

LAIs hold transformative potential for the programmatic management of TB, HIV and malaria. HIV leads the way with approved therapies, such as cabotegravir long-acting (CAB-LA), rilpivirine long-acting (RPV-LA) and lenacapavir; these therapies demonstrate high efficacy, including over 90% viral suppression *(5, 16, 17)*. In TB, LAIs are in early stages of development but show promise for both TPT and the treatment of TB disease. For malaria, LAI candidates remain in preclinical or early clinical phases *(18)*, primarily targeting prevention. Although LAIs offer significant promise for improving adherence and treatment outcomes, challenges remain, particularly regarding cost, delivery logistics and the limited availability of robust clinical data on their use in LMIC. Realizing the full impact of LAIs will require sustained research investment; community engagement and community-based delivery models; careful assessment of health system capacities, including cold-chain management; training for injection-based delivery; pharmacovigilance, especially in settings with constrained resources; and enabling of policy and regulatory support through frameworks that prioritize equitable access.

The research is advancing on long-acting formulations of existing TB drugs, with a focus on both TPT *(19)* and treatment of TB disease. Recent preclinical studies of LAI for TB have shown promising results. For instance, a long-acting formulation of bedaquiline demonstrated sustained antimicrobial activity for up to 12 days in a mouse model *(20)* and a Phase 1 clinical trial was launched to evaluate bedaquiline LAI *(21)*. This has relevance and potential for curative TB treatments.

The appeal of LAIs lies in their ability to reduce the number and frequency of dosing, which could make therapy more acceptable and significantly improve quality of life and adherence compared with current daily oral regimens and potentially revolutionize TB care by streamlining complex treatment protocols. Efforts to drive this innovation are underway but only one TB LAI candidate has currently entered human clinical trials, for TPT *(22)*; all other current efforts are at the preclinical or formulation stage. Early animal studies suggest that LAIs for TPT may have a dual mechanism of action; that is, both treating and preventing TB infection *(23)*.

Several development efforts are ongoing, with a particular focus on equitable access in LMIC, where the TB burden is highest (see Table 2.1 for a non-exhaustive overview).

Table 2.1. Overview of development work on LAIs

Preclinical (formulation and animal models)	
Medincell + iM4TB / ERA4TB	Developing long-acting macozinone formulations for TB treatment.
Centre of Excellence for Long-acting Therapeutics, University of Liverpool *(24)*	Working on LAI formulations of TB drugs – including rifapentine, isoniazid and sorfequiline – for TB prevention and treatment. Rifapentine LAI is expected to enter Phase 1 in 2026. A sorfequiline LAI development is a collaboration with Johns Hopkins University and the TB Alliance.
University of North Carolina, TB Alliance and Gates Foundation	Investigating LAI rifabutin and other agents using an in situ forming implant (ISFI) platform.
University of Southern Denmark and Gates Foundation	LAIs for treatment using three different substances against TB. The project focuses on injection suspensions and the determination of appropriate stabilization methods and particle size to achieve a release period of 4–6 months for the three substances.

Clinical development	
Janssen Pharmaceuticals	Phase 1 trial: A single ascending dose, single-centre study, to assess pharmacokinetics, safety and tolerability of a single IM dose of bedaquiline long-acting injection formulation in healthy participants.
Enabling technology / intellectual property	
MPP and Extentus Pharma Ltd. (previously Tandem Nano)	Extentus's nano-formulation platform for rifapentine and isoniazid LAIs is licensed to MPP for potential use in TB and other diseases.
Cross-disease initiatives, including TB	
Unitaid / LONGEVITY Project (MPP, Imperial College London, University of Liverpool, Johns Hopkins University, Clinton Health Access Initiative and Tandem Nano)	Focus on accelerating access to LAIs for malaria, hepatitis C and TB (including rifapentine and isoniazid, as mentioned above in this table).
LEAP TB Working Group	Engaged in advocacy, TPP development and prioritization of TB LAI candidates.

IM: intramuscular; LAI: long-acting injectable; LEAP: Long-Acting/Extended-Release Antiretroviral Research; MPP: Medicines Patent Pool; TB: tuberculosis; TPP: target product profile.

Significant challenges remain. Many existing TB drugs have PK (high target exposure or rapid clearance, or both) or physicochemical properties that make them unsuitable for long-acting formulations *(25)*, because they would require unsuitable injection volumes or injection frequency, narrowing the list of viable candidates. Drugs with substantial genetic variability in metabolism by geography (e.g. isoniazid) will be less preferred for consideration as LAI, and will need to be considered in combination with other characteristics. Injectable use as part of TB treatment has largely declined in recent years, with newer, oral treatments that are safer and much more tolerable being preferred. Thus, staff experience in administering injections as part of TB care may have decreased over time. On the implementation side, issues such as the need for trained health care personnel and high delivery costs may pose significant obstacles to large-scale deployment for the use of LAIs in resource-limited settings. Regulatory pathways for TB LAIs remain underdeveloped, and countries may require substantial guidance to evaluate pharmacovigilance and injection-site safety. Moreover, to date there are limited data from clinical trials on the safety of TB LAIs, and effectiveness data are not yet available; in addition, if initial trials exclude children, pregnant women and people with comorbidities, such evidence gaps will affect real-world application. Transitioning adult LAI formulations to paediatric use offers a major opportunity to bypass the long timelines associated with traditional drug development. When the core delivery system is already validated, the focus shifts to establishing appropriate weight-based dosing through PK/pharmacodynamic (PD) modelling rather than developing new formulations. Provided the safety profile in adults is well-characterized and lacks paediatric-specific risks, this extrapolation pathway could substantially fast-track the delivery of long-acting interventions to children.

2.3 Consultative process supporting the development of draft TRPs

The development of the TRP document involved several structured steps, aligned with WHO guidance.[3]

WHO convened a TDG on LAIs (see Annex 1 for the list of members), composed of leading trialists, scientists, national TB programme (NTP) officers and public health officials, people with lived experience of TB, civil society representatives and regulators. Standard WHO procedures for declaring conflicts of interest and confidentiality undertakings were followed for all members of the TDG (see Annex 4). The TDG supported the entire development process of the TRP document from 2025 until its completion in mid-2026. TDG members reviewed an initial draft of the TRP document prepared by the WHO Secretariat and provided direct input on successive versions of the document. They also participated in online discussions at various stages of the document's development, as well as one in-person meeting in November 2025. The discussion also benefited from the results of quantitative surveys and qualitative studies (key informant interviews and focus group discussions) conducted by partners (see Section 2.4).

To gather input from a broader span of stakeholders than those represented in the TDG, the document underwent a month of public commentary during April–May 2026. The consultation was open to all interested parties rather than to a defined list of stakeholders, and comments were received from a range of respondents, including pharmaceutical manufacturers. Comments provided by the public were integrated into a subsequent version of the document, which was reviewed by the TDG and a group of external reviewers who have profiles similar to those of the TDG members. Outstanding issues where there was perceived divergence of opinion were discussed during a final online consensus meeting of the TDG held on 29 June – 2 July 2026.

2.4 Stakeholder surveys

Summary of stakeholder surveys undertaken by the Treatment Action Group

In 2025, WHO, in collaboration with the Treatment Action Group (TAG), conducted a survey to assess global perspectives on LAI medicines for TB. This research, which was also supported by the London School of Hygiene & Tropical Medicine (LSHTM), gathered insights from country programmes, technical partners and civil society representatives during regional workshops across the WHO regions of South-East Asia, Western Pacific and Europe. Ethics clearance was obtained from the various regional WHO ethics committees (WPRO and SEARO), LSHTM and the WCG (see Annex 2). The findings highlighted robust stakeholder support for the development and adoption of LAI medicines for both TB prevention and treatment, noting the significant potential of LAIs to enhance treatment adherence across diverse clinical settings.

The analysis integrated data from two distinct surveys comprising 310 participants: 102 health care providers and policy-makers, and 208 community members and patients. The sample was diverse, featuring civil society representatives (39%), clinicians and health workers (25%), and individuals with lived experience of TB (19%). Geographically, the data reflected a global perspective with strong representation from the WHO regions of Africa (33%), Europe (25%) and South-East Asia (15%). Regional representation varied between the two surveys, with Survey 1 drawing more from the WHO Western Pacific Region and Survey 2

[3] W*HO target product profiles, preferred product characteristics, and target regimen profiles: standard procedure*. 2nd ed. Geneva: World Health Organization (internal unpublished document; WHO/SCI/RFH/ERP/2024.1). 2024.

from the Region of the Americas and the African Region; however, the combined results provide a broad and nuanced understanding of stakeholder needs worldwide.

A majority of respondents (83%) expressed definite or probable interest in adopting LAIs for TB treatment in place of daily oral regimens, while only 8% showed reluctance. This high level of acceptance was remarkably consistent across all stakeholder groups and geographical regions, signalling that LAIs are viewed as a promising alternative modality. Notably, despite measurable reluctance, positive attitudes towards LAI persisted even among individuals who had previously experienced injection-related side-effects. Furthermore, 65% of respondents supported the use of LAIs in their own children, suggesting that the perceived benefits of long-acting formulations outweigh concerns about administration for paediatric populations. Although the findings generally indicate enthusiasm for LAIs, the eventual formulation and design of the LAI package will confirm or modify the level of acceptance.

Stakeholder preferences consistently emphasized the need for shorter treatment durations and a reduction in the total number of injections required, with a particular interest in co-formulation strategies to simplify the patient experience. Collectively, these insights provide essential evidence for guiding WHO TRPs and prioritizing LAI drug development. By aligning technological innovation with the specific needs of patients and providers, the development of LAIs can be strategically directed to transform the TB care continuum. The complete report on the surveys, detailing the methodology and full analysis, is provided in Annex 2.

These findings should be interpreted with several limitations in mind. Both surveys relied on convenience samples of self-selected respondents recruited through country programmes, technical partners and civil society networks, so participants were likely to be more familiar with, and more favourably disposed towards, LAIs than the wider population of people affected by TB or front-line providers. Civil society representatives were overrepresented compared with clinicians and people with lived experience, and regional coverage was uneven. The surveys also captured stated preferences and hypothetical intentions rather than observed behaviour. Acceptability expressed before any LAI product is available may not predict real-world uptake once concrete regimen attributes (e.g. injection volume, pain, dosing schedule and price) are known.

Summary of TAG-performed focus group study

The TAG coordinated a mixed-methods study to explore community perspectives on LAIs for both TB treatment and TPT between August and September 2025. The study was conducted in two phases, the first being an online, multilingual survey of TB community networks, designed to capture anonymous data on acceptability, preferences and prior experiences with TB medications; this survey generated 208 responses from 45 countries. Respondents included civil society representatives (46%, *n*=95), people with lived experience of TB (29%, *n*=60), clinicians or health workers (24%, *n*=50) and researchers (1%, *n*=3). In total, 53% (*n*=110) of participants reported prior awareness of LAIs for TB, while 38% (*n*=79) had prior TB treatment or TPT experience, of whom 27% (*n*=21) had received injectable TB medication. The second phase convened four regionally organized group discussions, involving a total of 14 participants who had taken part in the survey described above, to deepen understanding of community priorities, trade-offs and contextual factors that could influence uptake of LAIs.

Across both surveys (310 responses), 82% (*n*=256) of respondents expressed favourable interest in adopting LAIs for TB treatment. However, prior experience with TB injectables significantly reduced acceptance: 52% of previously injected respondents reported they would

likely not choose an LAI regimen, compared with 13% among those without such experience. Preferences strongly favoured a shorter, simplified regimen. For TB treatment, 69% (*n*=215) preferred a 3-month LAI regimen over the standard 6-month oral regimen; this figure rose to 80% (*n*=249) when total injections were reduced from four to two. Trade-off scenarios demonstrated that minimizing the total number of injections was a priority. For TPT, acceptance was high, with 79% (*n*=246) preferring a single-dose LAI over a 1-month oral regimen. LAI use for children was viewed favourably by 65% (*n*=126), though negative perceptions increased among those with prior injection experience.

There was a significant preference for minimizing the number of injections per visit. Although respondents favoured shorter total treatment timelines, they were willing to accept longer durations (e.g. 4 months vs 3 months) if it meant fewer injections per session. Initially, respondents preferred SC over IM delivery when queried on technology type; however, regimen-specific trade-offs suggest that visit rhythm and total duration are more influential than the specific route of administration, with key caveats such as concerns about where on the body LAIs are administered and associated privacy (e.g. deep gluteal injections). LAIs may serve as a stigma-mitigation tool by reducing the frequency of clinic visits and eliminating the need for daily oral medication within households or workplaces. Although there is a baseline preference for local community-level clinics (51%), patients indicated a willingness to travel to centralized district hospitals (54%) if it resulted in less frequent visits or a shorter overall regimen. Concerns about persistence of side-effects were prominent. Participants emphasized the need for treatment agency, including the flexibility to switch back to oral regimens if side-effects become intolerable. The complete report, detailing the methodology and full analysis, is provided in Annex 2.

As with the stakeholder surveys, the results of the focus groups had important limitations. The four focus group discussions drew on only 14 participants, limiting how far the findings can be generalized across settings and populations. Respondents came predominantly from civil society and community networks, and participation required internet access and familiarity with the survey languages. The trade-off scenarios measured preferences under hypothetical conditions; although they are useful for prioritizing regimen characteristics, they cannot substitute for evidence on acceptability, adherence and effectiveness generated once LAI regimens are used in practice.

Summary of the Philippines pilot and GLINT initiative LAI stakeholder and user acceptability study

Between April and August 2024, the Gates Medical Research Institute supported a two-stage, mixed-methods study on LAI for pan-TB treatment in one urban and one semiurban site in the Philippines *(26)*. Subsequently, the GLINT (Global Leadership and INsight for TB injectables) initiative led by FHI 360 expanded this work to Indonesia, South Africa and the United Republic of Tanzania, allowing assessment of stakeholder preferences and acceptability across multiple settings, and providing important additional evidence to inform development of the TRPs. The end-user research focused on treatment of TB disease and did not cover the full set of TRP characteristics. Nine characteristics were outside its scope: indication and testing; duration of coverage; dosing interval flexibility; number of component drugs; safety and safety monitoring; drug-related tolerability; drug–drug interactions; propensity to develop resistance to TB medicines; and stability or shelf life and storage requirements. At the time of writing, the GLINT multicountry research had not been published. The findings summarized here are drawn from reports prepared for WHO in 2026 (FHI 360, unpublished data).

The study findings were intended to inform developers on the acceptability and preferences for LAI TB treatments. The methods employed included key informant interviews with 15 national and regional TB experts, followed by surveys with TB patients, survivors and care providers (*n* = ~350), also incorporating a discrete choice experiment to assess likely trade-offs between different LAI characteristics. Experts interviewed were receptive to new TB treatment regimens and were optimistic about the ability of the health system to implement LAIs for TB treatment; the reported anticipated barriers to adoption mostly centred on logistics (cost, supply chain and distribution) and patient apprehension about injections. The study compared three treatment scenarios: two injections monthly for 4 months; four shots as a one-time treatment; and a 1-month daily oral lead-in, followed by two injections 3 months apart. The two multi-visit scenarios were both preferred over the one-time four-injection treatment. The survey respondents also found the four shots at one time treatment to be less acceptable (59%) than the other two options (78%), suggesting a preference for fewer injections per visit. The survey identified characteristics that:

- favoured the decision to choose an LAI treatment – a one-time encounter with fewer shots, no oral lead-in, mild pain and administration at a local clinic; and
- were unfavourable to the decision to choose an LAI treatment – a 2-month oral lead-in, multiple cycles of injection, multiple injections (3+) per encounter, injection-site pain requiring medication and deep muscle gluteal injection.

Overall, building patient familiarity with an injectable and ensuring a less painful experience seemed to be important. Delivery of LAI at a local health centre was broadly preferred across TB patients, TB survivors and TB care providers.

Building on the initial Philippines pilot, the GLINT initiative subsequently expanded stakeholder consultations and acceptability research to Indonesia, South Africa and United Republic of Tanzania, generating a broader evidence base across diverse geographical, epidemiological and health system contexts. Findings were generally consistent across countries, demonstrating a strong interest in LAI technologies that reduce pill burden and simplify treatment delivery; at the same time, the findings highlighted the importance of patient acceptability, injection burden, tolerability, service-delivery preferences and health system feasibility. Common themes included preferences for decentralized delivery at local health facilities, fewer injections per encounter, avoidance of prolonged oral lead-in periods, and the preservation of patient choice where possible. Preferences in South Africa differed most from those in the other countries. Greater familiarity with long-acting injectables for HIV prevention and treatment in that setting is likely to have shaped user expectations and acceptability. Although some regional variation in preferences was observed, the broader findings largely reinforced those from the Philippines pilot and helped to inform refinement of the final TRP characteristics and implementation considerations.

2.5 Consensus meeting

A 4-day virtual consensus meeting (29 June to 2 July 2026) represented the final stage in the development of WHO TRPs for LAI formulations for TB prevention and treatment. The meeting brought together experts from clinical research, pharmacology, implementation science, regulatory agencies and NTPs, and representatives from civil society and affected communities; the aims were to review evidence, stakeholder preferences and draft TRP requirements, and to achieve consensus on the key characteristics that should guide future LAI development. The meeting was attended by the members of the TDG, together with the alternative members, technical resource persons and observers listed in Annex 1. Consensus on the requirements

was reached by the members of the TDG alone; a closed session restricted to them was held for that purpose, as shown in the agenda in Annex 3. Two members who declared interests deemed to conflict with the subject of the discussion took part as observers and did not participate in decision-making (see Annex 4).

Participants reviewed findings from stakeholder consultations, patient and provider surveys, and focused group discussions. The findings consistently highlighted the potential of LAIs to reduce pill burden, improve treatment adherence and enhance patient convenience, while also underscoring the importance of acceptability, patient choice, injection burden and decentralized delivery. These perspectives were incorporated into the refinement of both prevention and treatment TRPs. The requirements set out in sections 4 and 5 were determined by consensus of the TRP Development Group. The end-user research informed and corroborated those judgements; it was not used as the sole basis for any individual requirement.

The group reached broad consensus on the overall vision for LAI products – the products should support person-centred, community-based care; minimize treatment burden; and offer meaningful advantages over existing oral regimens. Discussions focused on balancing ambition with feasibility, and ensuring that optimal targets remain transformative while minimum requirements remain achievable within the anticipated development horizon.

For TPT, consensus emerged around prioritizing highly simplified regimens that minimize the number of encounters, injections, monitoring requirements and reliance on oral lead-in therapy. For TB treatment, discussions recognized the greater complexity of achieving fully injectable regimens; they supported a pragmatic approach that allows intermediate and hybrid strategies during product development, while maintaining the long-term goal of shorter, simplified and more patient-friendly treatment regimens.

Across both prevention and treatment, participants emphasized the importance of flexibility in routes of administration, preserving patient choice wherever possible, and ensuring that implementation requirements do not undermine access or scalability. There was strong support for delivery at the lowest feasible level of the health system and for minimizing additional monitoring and operational burdens on patients and programmes.

The meeting also included extensive discussion on regulatory considerations and evidence generation. Participants acknowledged the need for continued dialogue with regulatory authorities to define appropriate development pathways for LAI products, particularly when formulations are based on oral compounds that have already been approved. Although opportunities for streamlined development were recognized, the consensus was that requirements will need to remain evidence driven and be assessed on a case-by-case basis. The group further highlighted the need for future GEG, including PK/PD considerations, implementation research, safety monitoring and assessment of real-world effectiveness.

Overall, the meeting achieved its objective of reviewing and refining the draft TRPs and obtaining expert consensus on the remaining outstanding issues. The discussions substantially strengthened the document's technical content and provided clear direction for finalization.



3. Definitions of characteristics and related considerations

Table 3.1 provides the definitions and some related considerations for the regimen characteristics used in the subsequent sections. Characteristics apply to the regimen as a whole, unless specifically indicated for individual drugs. Box 3.1 explains how to distinguish between dosing encounters, treatment duration and duration of coverage.

Table 3.1. Definitions of regimen characteristics and related considerations

Characteristic	Definition and related considerations
1. Target population	People with TB infection or disease for whom the regimen described in a given TRP is intended. Vulnerable populations of interest may have specific needs that differ from those of the general population. Such groups include children, pregnant and breastfeeding women, people living with HIV, and people with other conditions such as undernutrition and diabetes.
2. Indication and testing	The specific indication of a given TRP (i.e. for TPT or for TB treatment) and related needs for testing (e.g. DST, or test for infection or disease).
3. Number of encounters for LAIs administration	The number of times a person needs to encounter the health system or the community health worker during treatment to receive a dose of LAIs.
4. Duration of coverage [single drug]	This is a PK metric. It refers to the duration over which injection of an individual long-acting drug is considered to lead to a safe and clinically effective drug concentration in plasma or at the site of the disease. The duration of coverage for regimens containing multiple LAIs with varying duration of coverage needs to be considered. Duration of coverage determines the **dosing frequency**; that is, the frequency at which injections need to be given (e.g. if duration of coverage is 1 month, the dosing frequency is 1 time per month).
5. Treatment duration	This is a clinical metric. It refers to the total duration of treatment administration; that is, the time between the first and the last dose encounters. After provision of the last dose, further care, monitoring and follow-up (e.g. for assessment of symptom resolution, cure and AEs) also needs consideration for programmatic implementation, but is not considered part of the treatment duration characteristic.[a]

Characteristic	Definition and related considerations
6. Dosing interval flexibility [single drug]	Dosing interval flexibility refers to the permissible variation in the timing of sequential injectable dosing encounters – that is, how much earlier or later a subsequent dose can be administered after the preceding dose without compromising safety or efficacy. It reflects the extent to which the drug's PK profile can accommodate real-world variability in patient attendance, provider availability and health system capacity. Although duration of coverage defines the target re-dosing interval (e.g. every 2 months), dosing interval flexibility defines the acceptable window around that target. For example, a regimen with 2-month coverage and ±2 weeks of flexibility would allow the next dosing encounter to occur safely between weeks 6 and 10. This flexibility must address two distinct clinical risks. If a patient presents late, drug concentrations must remain above the minimum effective or inhibitory threshold for long enough to avoid subtherapeutic exposure and reduce the risk of selecting drug-resistant mutants. Conversely, if a patient presents early, overlapping exposure from the previous and subsequent doses must not result in peak plasma concentrations that increase the risk of toxicity. An optimal formulation should therefore provide a dosing window within which modest delays or early administration do not meaningfully compromise efficacy, promote resistance or increase toxicity. This is particularly important for multidrug regimens and for implementation in settings where follow-up schedules, clinic capacity, travel constraints or access to care may vary. By allowing safe flexibility around dosing encounters, the regimen reduces the burden of "perfect timing" on both patients and providers, supports adherence and helps programmes to maintain treatment effectiveness without jeopardizing the patient's likelihood of cure.
7. Number of component drugs	This is the number of component drugs included to make up a regimen. The same number may be considered for use for the total duration; alternatively, a different number of component drugs may be considered for the regimens that have intensive and continuation phases of treatment.
8. Formulation and number of injections per dosing encounter	**Formulation** is the way in which the active drug is combined with other chemical substances to yield the final product, including whether multiple drugs are co-formulated such that two or more drugs can be delivered in a single injection. **Number of injections per encounter** is the number of injections delivered each time a person receives a dose of the LAI regimen. One dose may need to be split into more than one injection if the volume is too large.
9. Combination with oral TB medications	Combination with oral TB medications may be considered for various reasons and thus may be implemented using different regimen models using several possible strategies. These two scenarios assume the same medicines exist and are used in oral and LAI formulations. • **Oral lead-in to test the regimen for potential AEs.** Patients take the oral formulation of the medicines in the LAI regimen for a short period. The goal is to assess the safety and tolerability of the regimen and any potential systemic reactions in the individual before committing to a non-reversible long-acting dose that remains in the body for months and cannot be easily removed. • **Oral lead-in to cover for the slowly increasing drug concentration** – ***time to reach therapeutic levels*.** Patients take the oral formulation before or alongside the first injection. The goal is to bridge the time it takes for the LAI to reach adequate concentration levels. The timing of this lead-in largely depends on the LAI chemistry and delivery methods.

Characteristic	Definition and related considerations
	The following two scenarios can take place with different medicines in oral and LAI formulations. • **Oral intensive phase with LAI continuation phase.** The intensive phase includes a combination of oral and LAI medication, with the LAIs being continued in the continuation phase without the oral medications. This scenario: – could allow the inclusion of LAIs in a hybrid regimen if the number of drugs available as LAIs is insufficient on its own; and – would permit the use of existing, highly effective oral medications if they are not available as LAIs to bring down the bacillary burden in the first months of treatment, while at the same time preserving some of the important benefits of LAIs (in particular, in the later stages of treatment when patients tend to feel better and adherence can become challenging). • **Concurrent use of LAIs and oral formulations of medicines throughout the regimen** would not be expected to yield the same benefits as the above-described scenarios because high levels of adherence to take medications daily would still be required. However, this option may still have some value; for example, if the LAI use provides for a significant decrease in the pill burden or helps to avoid gastrointestinal disturbance, or if the oral route is not viable or is suboptimal for certain drugs (e.g. due to the PK properties of the drug, the importance of avoiding first-pass metabolism, or issues related to bioavailability or other formulation-related constraints). Although fully LAI-based regimens offer the most transformative potential in terms of adherence and programmatic use, regimens that combine LAIs with oral agents can still offer partial advantages, especially in the transitional period as technologies, formulations and delivery systems mature.
10. Route of administration and injection volume [single drug]	**Route of administration** refers to the way by which a pharmaceutical agent is delivered into the body to achieve systemic or local effect. For LAIs, the route of administration is typically either IM or SC, while lead-in or companion drugs may be given orally. Implants and depot tablets are outside the scope of these TRPs. The selected route constrains the permissible **injection volume**: IM administration generally accommodates larger volumes (2–5 mL in adults) compared with SC (0.5–2 mL in adults), depending on the individual and injection site, owing to differences in tissue capacity and absorption kinetics. However, the maximum injectable volume is further influenced by the anatomical site selected (e.g. gluteal vs deltoid for IM) and individual patient factors (e.g. tissue composition, nutrition status and tolerability).
11. Setting of treatment administration	This refers to the physical, organizational and procedural environment in which a treatment is delivered to a patient. The setting can have significant implications for resource use, patient acceptance, well-being, treatment completion, safety and the overall burden on the health system. Typical settings for treatment administration are inpatient (hospital), outpatient or ambulatory care, primary care, home-based care and self-administration. Implementation models usually prioritize decentralized and community-based delivery where feasible, including differentiated service-delivery approaches to reduce patient burden and improve equitable access.

Characteristic	Definition and related considerations
12. Efficacy and effectiveness	**Efficacy** refers to the extent to which a treatment produces a beneficial outcome under ideal, controlled conditions; it is typically demonstrated in explanatory RCTs. **Effectiveness** refers to the extent to which a treatment achieves the desired outcomes in real-world conditions, where factors such as patient quality of life, adherence, comorbidities, health system variability and social determinants of health come into play; it may be demonstrated in pragmatic RCTs. For regimens to treat **TB disease**, efficacy and effectiveness is evidenced by durable cure; that is, a relapse-free cure (typically 12 months after treatment completion under controlled clinical trial conditions) or the treatment success rate (cure and completion), taking into account challenges such as loss to follow-up, drug resistance and health system limitations. For **TPT** regimens, efficacy and effectiveness relate to the ability to avert the occurrence of disease arising from infections that were present at the time of TPT administration, typically evaluated based on incidence of TB disease over the next 2–5 years.
13. Safety and safety monitoring	**Safety**: This is the incidence and seriousness of AEs observed with the use of the regimen, including injection-related reactions. **Safety monitoring**: This is the frequency and type of clinical and laboratory monitoring required to ensure the safe use of the regimen.
14. Drug-related tolerability	Drug tolerability is defined by the FDA as "the degree to which overt AEs can be tolerated by patients" *(27)*. The tolerability profile of a given drug or regimen is of comparative importance to its efficacy and safety, because it largely determines acceptability and adherence to treatment, and ultimately treatment success or failure. Tolerability is a key characteristic to consider because it has a direct impact on quality of life, patient acceptability, treatment intake and risk of treatment discontinuation. Measures of tolerability include the proportion of patients interrupting or discontinuing treatment owing to AEs, and the occurrence of lower grade AEs that may not cause imminent danger to patients but may have a detrimental effect on their quality of life.
15. Injection-related tolerability	This is a critical determinant of regimen acceptance, because the discomfort of an injection must be weighed against the persistent burden of daily oral medication. Although health care providers and patients anticipate a degree of localized reaction, the targets emphasize that these symptoms (e.g. mild pain, redness, itching or swelling) should remain manageable and non-cumulative. A key requirement is that subsequent injections do not exacerbate previous reactions to the point of rendering those reactions as non-manageable, ensuring that tolerability remains stable throughout the treatment course. The timeframe for symptom resolution is a primary differentiator between minimal and optimal profiles.
16. Drug–drug interactions [single drug/regimen]	This refers to DDIs with other medications, including those used to treat the most frequent comorbidities.
17. Propensity to develop resistance to TB medicines	This parameter assesses the potential of an LAI candidate to select resistant *M. tuberculosis* strains. Regimens should be structured so that included drugs protect each other against the emergence of resistance. Cross-resistance with existing TB medicines should be evaluated, but its presence should not automatically preclude LAI development when the formulation offers clear advantages for TB treatment or prevention. It is crucial to minimize the risk of undermining both current and future therapeutic options, while allowing innovation in formulation and delivery. Studies have estimated the in vitro frequency of mutations that confer resistance to various TB medications. The in vivo risk of clinical resistance also depends on drug exposure, host immunity, bacterial population size and treatment adherence; therefore, laboratory estimates do not directly reflect clinical incidence.

Characteristic	Definition and related considerations
	Novel regimens should be based on combinations of drugs that have different targets from one another (i.e. different classes of drugs with different modes of action and mechanisms of resistance). Drugs included in the multidrug therapy may have different PK/PD properties as well as bactericidal or sterilization capacity, and may be acting on different compartments within a lesion *(28)*. Hence, some of the drugs may be considered as "protective" to other drugs, to avoid any risk of intermittent monotherapy that may generate drug resistance. Companion drugs should, where possible, be synergistic in activity at the lesion site and should have a half-life that is well matched with the core drugs, to reduce the risk of functional monotherapy. The propensity to develop resistance to different antimicrobials could be measured in clinical trials of TB disease by comparing resistance patterns in bacilli isolated at baseline to those isolated at later stages. In TPT studies, this propensity can be assessed by comparing the resistance pattern of the strains in individuals who develop TB to the one in the presumed source case (if isolates are not genetically identical, then it is likely that the source case was different and interpretation of differences in the resistance pattern is not meaningful).
18. Stability or shelf life and storage requirements [single drug]	The period of time (usually in years) during which a product remains stable at a given temperature and humidity, which influences its storage requirements.

AE: adverse event; DDI: drug–drug interaction; DST: drug susceptibility testing; FDA: United States Food and Drug Administration; HIV: human immunodeficiency virus; IM: intramuscular; LAI: long-acting injectable; *M. tuberculosis*: *Mycobacterium tuberculosis*; PD: pharmacodynamic; PK: pharmacokinetic; RCT: randomized controlled trial; SC: subcutaneous; TB: tuberculosis; TPT: TB preventive treatment; TRP: target regimen profile.

[a] In the context of LAIs, treatment duration can conceptually be divided into two distinct parts: the duration of the engagement between the patient and the health system for the actual treatment administration, and the duration of the treatment's continued clinical effectiveness after the last dose is given. The latter, in the case of LAI-based treatments, is dependent on another LAI-specific attribute; namely, the duration of coverage. To maintain consistency between different regimens and avoid the complexity related to the potentially variable duration of coverage, the treatment duration characteristic is presented as the total duration of treatment administration (i.e. from the first event of treatment administration to the last one, oral or injectable).

Box 3.1. Distinguishing dosing encounters, treatment duration and duration of coverage

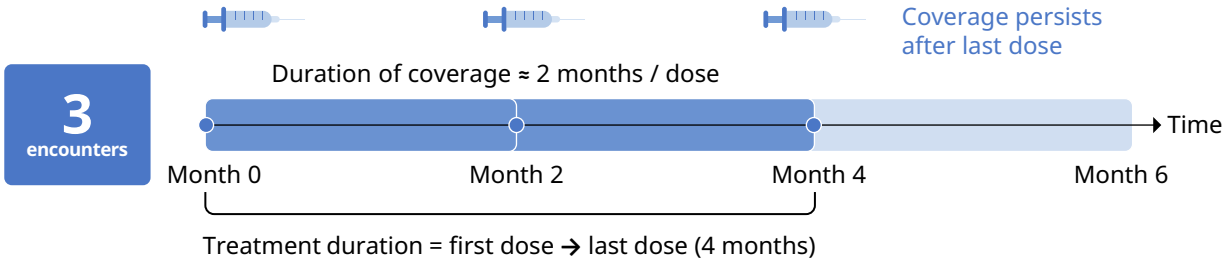
These three attributes – dosing encounters, treatment duration and duration of coverage – are distinct and should not be conflated:

- Number of dosing encounters – how many times a person attends to receive an injection (a programmatic count).
- Treatment duration – the time from the first to the last dosing encounter (a clinical metric); it excludes post-treatment follow-up.
- Duration of coverage – the period over which a single injection maintains effective drug concentrations (a PK metric); it extends beyond the last encounter as the drug clears (the "PK tail").

Treatment of TB disease

A regimen given in three dosing encounters – at months 0, 2 and 4, with each injection providing 2 months of coverage – has a treatment duration of 4 months (first dose at month 0 to last dose at month 4). Because the final encounter maintains effective concentrations for an additional 2 months, the total effective pharmacological coverage extends to the 6th month, 2 months beyond the last clinical contact (Fig. 3.1).

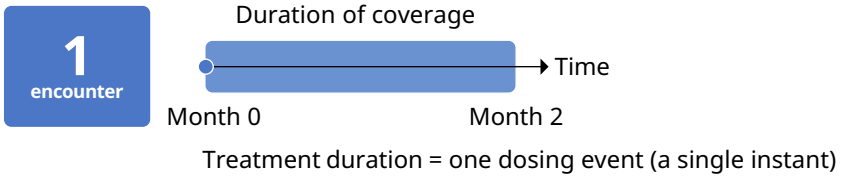
Fig. 3.1. Treatment of TB disease – treatment duration and duration of coverage



TB preventive treatment

The optimal target of a single dosing event is the simplest case of the same idea: the treatment duration is a single instant, while the duration of coverage is the period over which that one injection remains effective (Fig. 3.2).

Fig. 3.2. TB preventive treatment – treatment duration and duration of coverage





4. LAIs for TB preventive treatment

Table 4.1 describes the minimal and optimal requirements for each characteristic of an LAI TPT regimen, and provides explanatory notes, including trade-offs between these requirements.

Table 4.1. Requirements for regimen characteristics for LAIs for TB preventive treatment

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Target population	Adults and adolescents in whom TPT is recommended, including household contacts of people with TB and people living with HIV	All individuals recognized as being at increased risk of TB disease, including children, and pregnant and breastfeeding women	TPT is currently not systematically recommended for ALL people with an increased risk of developing TB. Indication is based on an assessment of risk of progression from infection to disease, and consideration of the risk–benefit profile of TPT. The latest WHO guidelines *(11)* recommend TPT for: • children aged ≥12 months, adolescents and adults living with HIV; • household contacts of people with bacteriologically confirmed pulmonary TB, regardless of age, HIV status and rifampicin-susceptibility status of the index case; and • other people at increased risk – namely, those who are initiating anti-TNF treatment, receiving dialysis, preparing for an organ or haematological transplant or have silicosis; or those who are prisoners, health workers, immigrants from countries with a high TB burden, homeless people or people who use drugs. Current evidence does not yet support a recommendation for the systematic testing for TB infection and TPT in people whose only risk is diabetes, harmful use of alcohol, tobacco smoking, being underweight or living in an area with a high prevalence of TB. Optimally, the LAI TPT would have a better safety profile and more favourable risk–benefit profile than currently available oral TPT options, justifying its wider use for prevention among populations in whom oral TPT is not currently systematically recommended. Broader use of LAI TPT will depend on reliable safety data. TPT regimens based on H, HP, HR, R and Lfx are currently recommended in all populations at increased risk. There should be a similar expectation for the widespread use of LAI regimens, regardless of age, comorbidity, pregnancy or breastfeeding status.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			The minimal requirements can still be satisfied if there is insufficient evidence on the safety of the drug in some populations (e.g. children, and pregnant and breastfeeding women); the LAI will not be intended for use in these subgroups until sufficient evidence is available. If clinical data are not available on dosing and safety in children and pregnant and breastfeeding women, explicit plans for the generation of such evidence should be in place. Efficacy trials in these populations are not necessarily required, given that efficacy can be extrapolated from other populations. **Children**: PK and safety studies will be needed in infants, children and adolescents for optimal requirements. TB regimen developers should consider initiating paediatric studies as soon as early studies of the drug show promising efficacy and safety, to allow for development of suitable paediatric formulations for dosing in trials involving young children *(29)*. The FDA generally requires submission of an initial paediatric study plan no later than 60 days after the end-of-Phase-2 meeting or another date agreed upon between the FDA and the sponsor *(30)*. These requirements are waived by the FDA for orphan drug designations (the drugs for treatment of TB disease usually qualify for the orphan drug designation because TB is a rare disease in the USA). The EMA requires the provision of plans for paediatric studies at the conclusion of Phase 2 studies at the latest. **Pregnant and breastfeeding women**: In pregnant women at increased risk of TB, the benefits of TPT usually outweigh the harms. In pregnant women, the drugs used in most current TPT regimens cross the placenta, but do not appear to have harmful effects on the fetus. Formulations should be safe for use in pregnancy and during breastfeeding *(31–33)*. Non-clinical developmental, DART and reproductive toxicology studies should be initiated early, because Phase 1 and early Phase 2 trial data are collected to support the inclusion of pregnant and breastfeeding women in pre-licensure trials. Clinical development plans should include pregnant and breastfeeding women. There is little justification for the exclusion of breastfeeding women in research studies if PK studies suggest that the levels of TPT drug(s) in breast milk are not harmful for the child. The assumption of inclusion should otherwise apply to breastfeeding women. The exclusion of pregnant women might be supported by evidence-based rationale from developmental and reproductive toxicity studies *(34)*. Additional considerations will be needed for special populations (e.g. older people; and people living with HIV, diabetes or other comorbidities).

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Indication and testing	The LAI is indicated as TPT, at least for people presumed to be infected with a rifampicin-susceptible *M. tuberculosis* strain	The LAI is indicated as TPT, regardless of whether the *M. tuberculosis* strain is presumed to be rifampicin-susceptible or rifampicin-resistant	If LAIs contain rifamycins, the DST pattern in the presumed source case would ideally be obtained before starting a contact of the source case on TPT as a minimal requirement. When required, a single, rapid, molecular test for rifampicin resistance would be carried out on the source case. Under the optimal requirements, the LAI would ideally contain novel compound(s) to which resistance is rare in circulating *M. tuberculosis* strains or that are not known to be cross-resistant to currently used drugs. These compounds may be from among those in the currently recommended TB treatment or TPT regimens. DST of the source case would not usually be required for TPT initiation because the frequency of resistance to the new drug and the likelihood of generating resistance would both be low. Use of LAI TPT in these situations would need a clear policy for use when DST is unavailable. As a general principle, for people aged 5 years and older exposed to a TB case, as well as other people at increased risk, a positive test of TB infection is recommended before starting TPT (people living with HIV do not need to be tested before starting TPT). Currently recommended tests for infection are IGRAs, TSTs and new antigen-based skin tests (TBSTs). The need to confirm infection before TPT becomes less important as the drugs used become safer and the inconvenience in TPT delivery – including cost – is removed, enhancing the benefit-to-risk ratio. Screening to exclude TB disease (symptomatic or asymptomatic) is needed to assess eligibility for TPT with LAI, for both the minimal and optimal scenarios, to avoid the inadvertent use of TPT in people with TB disease. Screening algorithms that employ tests of higher sensitivity (e.g. chest radiography) to exclude TB disease are preferred. Details of appropriate screening strategies must be clearly explained at the time of scale-up.
Number of encounters for LAIs administration	Two	One	Results from surveys and focus group discussions highlighted the overarching importance of limiting the number of visits to a health centre as a top priority for people receiving preventive or curative treatment for TB. Ideally, one encounter would be sufficient to administer the full course of LAI TPT. However, it may be that initial LAI products developed for this indication require two encounters spaced a few weeks apart.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Duration of coverage [single drug]	The duration of coverage needs to be aligned to the effective duration of the equivalent TPT regimen given as LAI		The duration of coverage that a single LAI injection will provide is an important determinant of dosing frequency and TPT duration. Given that the aim is to have only one LAI encounter, the duration of coverage needs to align with the duration of the existing effective TPT regimen. Thus, the LAI TPT regimen may require more than a single injection or encounter, and therefore require trade-offs with other optimal requirements. Current trials are evaluating one-drug oral TPT regimens lasting 4–6 days; along with other ongoing studies of LAIs, these trials will provide evidence that may inform the operationalization of this requirement.
Treatment duration	Up to 1 month	One dosing encounter	The current shortest duration for an oral TPT regimen recommended by WHO is 1 month with daily dosing. Shortening this duration would require a drug or a drug combination of sufficient potency and persistence to provide a long duration of coverage, such that a relatively short period of adequate coverage would be sufficient to achieve efficacy. In the surveys conducted to inform this TRP, 79% of respondents preferred a single injection TPT given at a single encounter to a 1-month oral TPT, with 6% being neutral and 15% preferring the oral TPT option. The **minimal target** is 1 month. The **optimal target** is to achieve adequate coverage for a TPT regimen with one LAI dosing encounter.
Dosing interval flexibility [single drug]	Dosing interval ±2 days from the scheduled dose	Dosing interval ±4 days from the scheduled dose	For TPT, the requirement for dosing interval flexibility follows the same pharmacological principles and durations as those detailed in the treatment section: maintaining a "forgiveness window" via a robust PK tail to accommodate programmatic delays. However, a longer delay than for treatment may be permissible in TPT, given that there is less concern about the generation of drug resistance when the bacillary load is smaller. The delay was maximized at 4 days as this is a reasonable expectation of the length of the PK tail that can maintain preventive effect, and it is expected that a person's engagement for a TPT regimen would not last more than a few months. However, the applicability of this concept depends on the regimen model. Dosing interval flexibility requirements are only applicable if the LAI regimen does not fulfil the optimal requirement of one LAI encounter.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Number of component drugs	Two	One	Recommended TPT regimens are currently composed of one or two drugs. This number should not be exceeded in LAI TPT regimens. Having one drug was considered optimal because it is more likely to be safe and cheaper than two drugs. The minimal requirement of two drugs was judged to be acceptable, based on the principles of oral TPT. A combination of two drugs may provide benefits over one drug alone (e.g. maximizing efficacy and durability, and enabling a shorter duration of effective treatment). Any drug combination should not increase the toxicity of the individual drugs in the regimen to a degree that would impede patient management or wide-scale implementation. New compounds used in the regimen should have minimal cross-resistance with existing drugs used to treat TB (especially the older drugs to which resistance is more widespread).
Formulation and number of injections per dosing encounter	Up to two injections	One injection	For the immediate future, it is expected that each component drug would require one injection when an LAI dose is administered. However, co-formulation of drugs in a single vial or in a prefilled syringe may in future reduce the number of injections needed to complete a regimen, facilitating the administration of a regimen and making it more convenient for the person taking the regimen. For drugs that can be used for both TPT and TB treatment, it may be preferable not to have a co-formulation so that the same product can be used in different clinical scenarios. Additionally, co-formulation may complicate LAI administration when the ratio of dosages needed for the individual components to achieve their therapeutic window differs by weight band; this would thus necessitate a separate paediatric formulation. The formulation should provide for the maximal adult dose and one vial per patient. In case the volume to be injected exceeds the minimal requirement, the dose can be given in two injections at different sites at the same encounter.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Combination with oral TB medications	No oral lead-in No combination with oral medicines		Given that TPT aims to treat a smaller bacterial load in the infected person than in someone with TB disease, a loading dose with an oral lead-in may be less important. It is likely that adequate serum concentration levels will be reached rapidly after an LAI dose. In TPT, an oral lead-in could only be justified to assess the safety and tolerability of the LAI compound before administering it in a long-acting form that remains in the body for months and cannot be easily removed. However, an oral lead-in would be a significant barrier to uptake, considering that the shortest oral TPT regimen is only 1 month long. Moreover, a treatment challenge of 1–2 days may be insufficient to evoke ADRs that develop later during treatment. The principle of having no oral lead-in for TPT underscores the critical importance that compounds formulated as LAI for TPT have a very good safety profile, including new drugs not previously used to treat TB. However, in the development pathway it is understood that an oral lead-in may be used in initial studies. Aside from oral lead-in, there is no place for a hybrid TPT regimen composed of LAI and companion oral drugs.
Route of administration and injection volume [single drug]	IM or SC Maximum injection volume: SC: ≤2 mL for adults (adjusted for children) IM: ≤5 mL	IM or SC Maximum injection volume: SC: ≤1 mL for adults (adjusted for children) IM: ≤3 mL	There may be lower tolerability to higher volumes in people who do not have TB disease. If the volume to be injected exceeds the minimum requirement, the dose can be administered in two injections at different sites during the same encounter. Acceptability of the gluteal injection site varied across geographies. Dosage may vary according to body weight. Tolerability depends not only on the volume injected and the route, but also on formulation properties such as viscosity.
Setting of treatment administration	Injections administered by a health worker, at the lowest level of health service		For both the minimal and optimal requirements, it should be possible and is preferable to administer the LAI at the lowest level of the health service, in the community or a person's home, by a health worker authorized to give injections. Given the need to administer the LAI by a qualified health worker and the expectation that TPT would be completed in 1–2 encounters and not usually repeated, self-administration is not considered an option. Also, self-administration is likely to require additional studies and a more complex regulatory pathway.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Efficacy and effectiveness	The LAI regimen efficacy is as good as current oral TPT regimens	LAI regimen efficacy is as good as current oral TPT regimens and its effectiveness is better than that of current oral TPT regimens	Currently recommended oral TPT regimens have an efficacy of about 60–90%, compared with no treatment, under trial conditions. As a minimum, the efficacy of LAI regimens should not be lower than currently recommended oral TPT regimens. Ideally, effectiveness would be superior in the main target population(s). Under programmatic conditions, adherence to oral TPT and completion of treatment are problematic, and TPT effectiveness is expected to be lower than in trials. LAIs bear the promise of overcoming the commonplace interruption of oral medication and are therefore expected to enhance effectiveness.
Safety and safety monitoring	The incidence and severity of AEs (non-injection-related) should be no worse than those with the recommended oral TPT regimens No more than one routine monitoring visit with a health worker for drug toxicity and no laboratory monitoring is needed, except in certain populations (e.g. people with pre-existing liver disease, renal disease or diabetes)	The incidence and severity of AEs (non-injection-related) should be lower than with the recommended oral TPT regimens No routine clinical or laboratory monitoring for drug toxicity is needed, except in certain populations (e.g. people with pre-existing liver disease, renal disease or diabetes)	The LAI formulations should not present any additional safety issues over and above the standard safety requirements related to the administration of an injectable. For both the minimal and optimal scenarios, the target product should not require any additional medication to allay toxicity (e.g. pyridoxine). Given that it is unlikely that the injected depot could be removed, it is important for manufacturers to provide instructions on the management of toxicity associated with the LAI. Hepatotoxicity and clinical hepatitis are serious AEs associated with the drugs that are currently recommended for TPT, either alone or in combination. Neuropathy is a frequent AE with isoniazid *(11)*. Hypersensitivity may occur to any new or old medication. Serious AEs and AEs of special interest are priorities for monitoring. If the LAI dose is incomplete (e.g. only 1 of a 2-injection TPT regimen is administered) the manufacturer should provide guidance on how to complete TPT with the standard medication. If the LAI medicine is available in oral form, this may simplify continuation.
Drug-related tolerability	Drug-related tolerability should be comparable to oral TPT regimens	Drug-related tolerability should be better than with oral TPT regimens	Tolerability is of paramount importance. Because TPT is given to individuals who are usually symptom-free, healthy and do not consider themselves to be ill, any discomfort or AE should be avoided.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Injection-related tolerability	The injection should cause only mild or moderate localized reactions	The injection should cause only mild localized reactions	Injection reactions would typically consist of redness, itching, swelling or mild induration, and pain or discomfort that resolves after a few days. A person given an injection is likely to endure more discomfort than when receiving an oral dose of medication, but this needs to be balanced with the inconvenience of taking oral medication for 1 month or more. Tolerability depends not only on the volume injected and the route, but also on formulation properties such as viscosity. Ideally, the administration of an LAI should require no or only minimal adjustment to food intake, and no co-medication to prevent reactions.
Drug–drug interactions [single drug/ regimen]	The LAI (or regimen) should have no greater amount of DDI with often co-administered drugs than with currently preferred SoC treatments; any DDI should be of a magnitude and type that can be reasonably compensated for or managed	It should be possible to use the LAI (or regimen) with other medications while maintaining safety and efficacy, without adjustment of dose or frequency and without the need for active laboratory monitoring	The novel drugs in the regimen should have minimal or no DDI with other drugs that are often co-administered; for example: • ART regimen(s); • drugs that are a substrate for and induce or inhibit P450 liver enzymes; • proarrhythmic drugs that prolong the QT/ QTc interval; • oral contraceptives; • antidiabetes drugs; • immunosuppressive drugs; • opioid substitution; • hepatitis C drugs; and • anticonvulsant drugs. ART regimens may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, CYP3A and UGT1A1) or that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; and ritonavir, CYP3A). Such regimens may need to be modified to permit their use with TB treatment.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Propensity to develop resistance to TB medicines	Potential for the acquisition or amplification of resistance during or after LAI treatment to one or more drugs in the regimen is *comparable to or lower than* with oral TPT	Potential for the acquisition or amplification of resistance during or after LAI treatment to one or more drugs in the regimen is *comparable to or lower than* with oral TPT Fewer than two gene targets are linked to the development of resistance There is no cross-resistance with existing drugs for single-agent LAIs	To date, there is no empirical evidence that the use of isoniazid or rifamycins for TPT in the absence of TB disease is associated with the generation of resistance to TB drugs in a community *(35, 36)*. TB infection is characterized by a low bacillary load, reducing the likelihood of the emergence of resistance. However, it is possible that TPT may be inadvertently given to someone with undiagnosed TB disease, some of whom may be asymptomatic. Bearing in mind the technical difficulties in expressing the potential for the acquisition or amplification of resistance during or after LAI treatment, some measurable markers that are known to correlate with in vitro mutations are proposed. However, these may not be clinically or preclinically demonstrable. Although this characteristic is primarily focused on the risk of generating drug-resistant *M. tuberculosis* strains, attention should also be given to the risk of creating resistance to other bacterial flora in the body with the use of broad-spectrum antimicrobial agents used in TB care.
Stability or shelf life and storage requirements [single drug]	No cold chain required All LAI component drugs are stable for ≥2 years in climate zones 3 and 4, and freezingconditions	No cold chain required All LAI component drugs are stable for ≥3 years in climate zones 3 and 4, and freezingconditions	Any drugs for oral lead-in should be stable to heat, humidity and light, with a shelf life of ≥5 years under ideal conditions. Factors to consider are whether a drug is stable in light-blocking containers or is sensitive to light.

ADR: adverse drug reaction; AE: adverse event; ART: antiretroviral therapy; DART: developmental and reproductive toxicology; DDI: drug–drug interaction; DST: drug susceptibility testing; ECG: electrocardiogram; EMA: European Medicines Agency; FDA: United States Food and Drug Administration; H: isoniazid; HIV: human immunodeficiency virus; HP: isoniazid and rifapentine; HR: isoniazid and rifampicin; IGRA: interferon gamma release assay; IM: intramuscular; LAI: long-acting injectable; Lfx: levofloxacin; *M. tuberculosis*: *Mycobacterium tuberculosis*; PK: pharmacokinetic; QT/QTc: time from the start of the Q wave to the end of the T wave on an ECG (the small "c" refers to a correction of the interval); R: rifampicin; SC: subcutaneous; SoC: standard of care; TB: tuberculosis; TBST: TB antigen-based skin test; TNF: tumour-necrosis factor; TPT: TB preventive treatment; TRP: target regimen profile; TST: tuberculin skin test; USA: United States of America; WHO: World Health Organization.



5. LAIs for the treatment of TB disease

Table 5.1 describes the minimal and optimal requirements for each characteristic of an LAI-based regimen for the treatment of active TB, and provides explanatory notes, including trade-offs between these requirements.

Table 5.1. Requirements for regimen characteristics for LAIs for the treatment of TB disease

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Target population	Adults and adolescents with pulmonary TB disease, including people living with HIV and people with other comorbidities, such as diabetes	All groups, irrespective of severity and site of disease (including pulmonary and extrapulmonary disease), across the full age spectrum, including children, adolescents and older people, pregnant or breastfeeding women, people living with HIV and people with other comorbidities, such as diabetes	Non-severe forms of EPTB – such as mild lymph node TB, pleural effusion or peripheral joint TB – are typically managed identically to pulmonary TB because drug penetration to the site of disease is generally adequate and standard regimens are effective. Conversely, severe forms of EPTB – such as TB meningitis, pericarditis or spinal disease – may require special approaches or regimen modifications. Plans to generate evidence should be in place if clinical data are not available on dosing and safety in children, pregnant women and breastfeeding women. However, efficacy trials in these populations are not necessarily required, because efficacy can often be extrapolated from other populations. **Children**: PK and safety studies will be needed in infants, children and adolescents for optimal requirements. TB regimen developers should consider initiating paediatric studies as soon as early studies of the drug show promising efficacy and safety, to allow for the development of suitable paediatric formulations for dosing in trials involving young children *(29)*. The FDA generally requires submission of an initial paediatric study plan no later than 60 days after the end-of-Phase-2 meeting or another date agreed upon between the FDA and the sponsor *(30)*. These requirements are waived by the FDA for orphan drug designations (drugs for treatment of TB disease usually qualify for the orphan drug designation because TB is a rare disease in the USA). The EMA requires the provision of plans for paediatric studies at the conclusion of Phase 2 studies at the latest.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
			Pregnant and breastfeeding women: Formulations should be safe for use in pregnancy and during breastfeeding *(30, 31, 33)*. Non-clinical developmental, DART and reproductive toxicology studies should be initiated early, when Phase 1 and early Phase 2 trial data are collected, to support the inclusion of pregnant and breastfeeding women in pre-licensure trials. Clinical development plans should include pregnant and breastfeeding women. There is little justification for the exclusion of breastfeeding women in research studies if PK studies suggest that the levels of TB drug(s) in breast milk are not harmful for the child. The assumption of inclusion should otherwise apply to breastfeeding women. The exclusion of pregnant women might be supported by evidence-based rationale from DART studies *(34)*. Additional considerations will be needed for special populations (e.g. older people; and people living with HIV, diabetes or other comorbidities).
Indication and testing	The regimen is indicated for patients with TB disease caused by RS *M. tuberculosis* strains	The regimen is indicated for patients with TB disease caused by RS and RR *M. tuberculosis* strains	**Minimal**: RS-TB, as this could in principle be used for about 95% of patients globally (based on their resistance pattern) within the context of recommended DST for rifampicin at the time of TB diagnosis, using WHO-recommended rapid molecular tests if the regimen includes LAIs from the rifamycin family. **Optimal**: A regimen meeting the optimal requirements could be used for most patients. It could be started empirically so that treatment could begin without delay while testing for susceptibility to component drugs is sought. Although the minimal requirement targets RS-TB for maximum global impact, the initial entry point for LAI regimens will depend on how effectively safety, cost and implementation feasibility can be addressed at scale. Historically, regulatory pathways that accelerate approvals for conditions with high unmet needs, together with the prioritization of investigative drugs as LAIs, have favoured RR-TB as an earlier indication. However, an entry through RS-TB treatment remains equally plausible if these implementation constraints are sufficiently resolved, given the far larger population that would benefit. By using novel drug classes outside the rifamycin family, LAI regimens can achieve universal applicability across RS-TB and RR-TB, with efficacy independent of circulating rifampicin resistance patterns. This would allow for empirical initiation of treatment and reduce the diagnostic burden at the point of care.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Number of encounters for LAIs administration	Three	One or two	A single encounter with LAI administration for TB treatment is an aspirational, potentially distant goal, but a highly desired optimal requirement. Results from surveys and focus group discussions highlighted the importance of limiting the number of visits to health centres for dosing encounters as a priority for people receiving preventive or curative TB treatment.
Duration of coverage [single drug]	≥2 months	≥4 months	This is a PK metric. The duration of stable, clinically effective drug concentrations in serum or at the site of the disease that a single LAI injection maintains at or above the MIC required for clinical efficacy is an important determinant of dosing frequency, treatment duration and overall PK coverage duration. Given current technologies and the properties of candidate drugs, a single drug's duration of coverage of ≥2 months appears feasible. The survey and focus group results also indicate a desire for 2 months of coverage by both health care providers and the affected community. For large-scale implementation, the number of health facility visits should be kept to a minimum. The differing coverage durations across LAIs may complicate the scheduling of visits and increase the number of visits. To mitigate the complexity caused by varying coverage durations, product development should prioritize harmonized release profiles. In the absence of perfectly matched durations, clinical implementation should favour a "synchronized encounter" model based on the shortest-acting component (e.g. a 2-monthly cycle) to ensure predictable patient follow-up and prevent the decoupling of the combination therapy, which could lead to monotherapy and subsequent resistance. The challenge of mismatched dosing is already visible in the HIV landscape, which serves as a cautionary example for TB regimen design. The experience with HIV LAIs (e.g. the 2-month cycle of cabotegravir vs the 6-month cycle of lenacapavir) highlights the risk of dosing friction. If these 2 agents were required as a combination therapy (as is mandatory for TB), the patient would be forced into a "lowest common denominator" schedule. They would have to visit the clinic every 2 months to receive cabotegravir, essentially wasting the 6-month convenience of lenacapavir. For TB treatment, where combination therapy is an SoC, any mismatch in duration of coverage between component drugs does not just increase visit frequency, it creates a dangerous window for functional monotherapy. Therefore, optimal regimens must prioritize agents that can be harmonized into a single, synchronized dosing encounter (e.g. all components administered every 4 months).

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Treatment duration	≤4 months	≤2 months	This is a clinical metric. It refers to the total time elapsed from the first dosing encounter (including any oral lead-in) to the completion of the therapeutic course. It defines the patient's "time on treatment". Targets are based on the assumption that 4–6 months of effective PK treatment coverage would be required to achieve sufficient regimen efficacy. If a regimen requires a period of oral lead-in, that period is counted towards the target treatment duration. When the treatment duration is achieved via multiple encounters, the final injection provides a "therapeutic tail" of coverage that extends beyond the final health care interaction. This ensures that the patient remains protected by effective drug concentrations during the transition to the post-treatment follow-up phase. The **minimal target** of ≤4 months could be achieved in a variety of ways; for example: • 1 month could be achieved with a 1-month oral lead-in, followed by a single dosing encounter with LAIs; • 2 months could be achieved with 2 dosing encounters with LAIs with 2 months duration of coverage (or 3 months if including a 1-month oral lead-in period); or • 4 months could be achieved with 3 dosing encounters with LAIs (months 0, 2 and 4), each with a 2-month duration of coverage. In the last scenario, although the patient's clinical interaction ends at the 4th month, the total effective PK coverage extends to 6 months. The **optimal target** is set to ≤2 months. This could be achieved if the regimen combines LAIs (potentially with an oral lead-in or in combination with oral medicines) with a sufficiently long duration of coverage and sufficiently high potency, such that a period of effective PK coverage is adequate to achieve sufficient efficacy.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Dosing interval flexibility [single drug]	Dosing interval ±2 days from the scheduled dose	Dosing interval ±4 days from the scheduled dose	The product should maintain therapeutic drug concentrations over an extended period following a single injection, with a PK profile characterized by a potential gradual rise to peak concentration and a prolonged decline ("PK tail"). This slow-release profile of LAIs should enable a dosing interval flexibility of ±2 to 4 days around the target re-dosing point, without compromising efficacy or safety. The formulation should provide sufficient dosing interval flexibility; that is, a period during which suboptimal dosing (either delayed or early) does not lead to significant drops below the minimum effective concentration or increase the risk of drug resistance or dose overlap, thereby increasing the risk of toxicity. This flexibility is critical for accommodating programmatic realities (e.g. variability in patient follow-up and health system capacity) and enhancing patient adherence, particularly in settings with limited health care access. Dosing flexibility shifts the burden of "perfect timing" away from the patient and the provider. It allows the programme to accommodate flexible dosing encounter schedules with multidrug regimens without jeopardizing the patient's cure.
Number of component drugs	Three or four drugs (either oral or LAI) throughout the regimen (possibly a decrease in the number of component drugs in the maintenance phase of treatment)		A minimum of 3–4 medicines was considered likely to be required to ensure high efficacy and short duration, and to minimize the risk of developing drug resistance *(2)*. Conversely, it is desirable to limit the number of component drugs in an LAI regimen to minimize the number of injections and safety risks, and to facilitate co-formulation if possible. Current regimens recommended for DS-TB (HRZE or HPMZ) and MDR/RR-TB (BPaLM or BPaLC) are effective 4-drug regimens, and the BPaLM regimen without moxifloxacin is an effective 3-drug regimen (BPaL) for pre-XDR-TB in non-severe cases. Developers should ensure that the new compounds comprising the regimen offer minimal cross-resistance, and that the combination does not increase the toxicity of the individual drugs in the regimen. Although 3 or 4 drugs may be required during the intensive phase of treatment, 2 drugs may be sufficient during the maintenance phase to achieve adequate efficacy, as evident from the 2HRZE/4HR regimen.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Formulation and number of injections per dosing encounter	Three or four separate injections (one per drug)	One or two injections (with each injection containing 2 or more co-formulated drugs)	Co-formulation of LAI means that several drugs are included in a single vial or prefilled syringe. Co-formulation of drugs in a single vial may, in the future, reduce the number of injections needed to complete a regimen. In the immediate future, it is expected that 1 drug component would require 1 injection (unless a higher dose requires it to be split into 2 injections) when an LAI dose is administered. Where multiple LAIs are used within a treatment regimen, a staggered or harmonized dosing schedule may be needed to simplify programmatic implementation. Ideally, there should be no or minimal adjustment to food and no need for co-medication adjustments for both the LAI and oral lead-in components. Oral drugs should be available in paediatric forms (dispersible, scored tablets that are palatable) and FDCs. In the survey and qualitative work presented by the GLINT team, respondents generally considered 1–2 injections per visit acceptable, whereas 4 injections in a single visit were less acceptable; this reinforced the need for LAI-based regimens to be paired with fewer injections and good tolerability. The minimal requirement of 3–4 injections acknowledges that the development of LAI for TB treatment is still in early stages, with the optimal requirement of 1–2 co-formulated injections representing the intended direction of product development.
Combination with oral TB medications	If required, an oral lead-in will be given for no longer than **1 month** LAIs may be combined with oral TB medicines	No oral lead-in No combination with oral medicines	Setting "no oral lead-in" as the optimal requirement reflects a deliberate prioritization of simplicity, with fewer encounters and reduced treatment burden. However, a short oral lead-in can confer an important safety advantage: because oral medication can be stopped immediately, hypersensitivity, intolerance or systemic AEs can be identified and managed before a long-acting dose that cannot be withdrawn is given. The optimal requirement, therefore, presumes a compound whose safety and reversibility profile is sufficiently well established that this safeguard is not needed; where this is not the case, a short oral lead-in (see Section 6.2) remains an appropriate, and at times preferable, design choice. In patients with severe forms of disease, some clinicians may prefer to extend the lead-in duration. Although fully LAI-based regimens offer the most transformative potential, hybrid models including oral medicines represent an essential transitional step. They enable the immediate use of LAI technology as it matures, providing clinicians with a "modular" approach to TB care that can be tailored to the patient's resistance profile and the health system's capacity. These hybrid models may depend on the LAI's availability, its PK profile and the clinical objective. Hybrid regimens can reduce the complexity of treatment by converting a 10-pill-a-day regimen into a 2-pill-a-day regimen plus LAI. For some drugs with poor bioavailability or high GI toxicity, the LAI route can be a viable way to achieve effective PK levels.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Route of administration and injection volume [single drug]	IM or SC Maximum injection volume: SC: ≤2 mL for adults (adjusted for children) IM: ≤5 mL	IM or SC Maximum injection volume: SC: ≤1 mL for adults (adjusted for children) IM: ≤3 mL	In the survey conducted by the GLINT team, SC administration raised acceptability concerns, mainly owing to injection-site pain and visible subdermal bumps, particularly when bumps might persist or occur in multiple sites, although preferences between SC and IM routes were not uniform across settings. The choice between SC and IM administration is often dictated by the drug's formulation (e.g. oil-based vs aqueous) and the desired release profile. IM typically allows faster onset and slightly larger volumes, but requires deeper penetration and specific anatomical sites (e.g. gluteal or deltoid). SC tissue has a lower capacity for large volumes and may be prone to local injection-site reactions. High volumes are often cited by health care providers as a barrier to implementation owing to the increased time required for administration, and the increased risk of pain and discomfort. In some settings, there may be cultural sensitivities regarding the gluteal area as the injection site. Where IM administration is required, it is equally important to preserve patient choice and agency in selecting the injection site among clinically appropriate options (e.g. gluteal, deltoid or vastus lateralis), considering personal comfort, cultural considerations, lifestyle and prior injection experience. Acceptability of the gluteal injection site varied across geographies; conversely, TB is frequently a disease of poverty and malnutrition, and large muscle groups may be preferable. This creates a specific physiological challenge for LAI administration because malnourished patients often have significant muscle wasting and minimal SC fat. This reduces the "reservoir" capacity for LAI deposits. Dosage may vary according to body weight.
Setting of treatment administration	Injections administered by a health worker, at the lowest level of the health service		The desirable TB treatment setting is community or primary care based, enabling patient-centred, decentralized care and the safe, effective and equitable delivery of treatment. For both the minimal and optimal requirements, LAI administration should be possible and preferred at the lowest level of health service (including community settings or the person's home) by a health worker authorized to give injections. Specialized outpatient or inpatient services remain warranted for the treatment of DR-TB or for severely ill or otherwise complex cases. Self-administration was not considered an option at this stage and is also likely to require additional studies and a more complex regulatory pathway.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Efficacy and effectiveness	The LAI regimen efficacy is *as good as* the comparator (SoC) regimens	The LAI regimen efficacy is *as good as* the current comparator (SoC) regimens and the effectiveness is *better*	The current standard regimens for the treatment of RS-TB and most types of RR-TB achieve about 90% efficacy under trial conditions. The effectiveness of recommended all-oral regimens is reduced under programmatic conditions for various reasons, notably adherence challenges and care discontinuation. Given that such challenges are expected to decrease with the use of LAIs, the "efficacy–effectiveness gap" is also expected to narrow for LAI-based regimens. Thus, under optimal conditions, the expectation would be greater *effectiveness* than current comparator regimens. For optimal performance, developers should assess regimen attributes expected to drive higher real-world effectiveness, including treatment completion, adherence, number of encounters and injections, and overall implementation feasibility. Although effectiveness is ultimately measured in routine use, these surrogate indicators should be evaluated during product development as predictors of improved effectiveness.
Safety and safety monitoring	The incidence and severity of AEs should be *equal to or lower than* with the comparator (SoC) regimens Clinical and laboratory monitoring for drug toxicity should be at least as frequent as that with the comparator (SoC) regimens, except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes)	The incidence and severity of AEs should be *lower than* with the comparator (SoC) regimens Clinical and laboratory monitoring for drug toxicity should be less frequent than that with the comparator (SoC) regimens, except in specific populations (e.g. pre-existing liver disease, renal disease or diabetes)	The current standard 6-month regimen for TB has known safety issues with the component drugs, most notably hepatotoxicity *(37)*. The proportion of patients experiencing Grade 3 or 4 treatment emergent AEs when treated with HRZE was 19–25% in the 6-month HRZE control arms of the REMox trial *(38)*, the Study 31 trial (2HPMZ/2HPM) *(39)* and the PaMZ Phase 2B trial *(40)*. Among participants receiving the 4-month HPMZ regimen in Study 31, 19% experienced Grade 3 or higher AEs *(41)*. The persistence of drug exposure may warrant safety monitoring that extends beyond the dosing encounter and across the coverage period. The LAI formulations would ideally have no clinically or programmatically meaningful increase in AEs and should not present any additional safety requirements beyond those required for standard injections.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Drug-related tolerability	*Tolerability* should be *comparable to that of* the SoC	*Tolerability* should be *better than that of* the SoC	The survey findings revealed that although systemic drug-related tolerability is a concern, it does not significantly deter stakeholder interest in LAIs. A majority of participants, including those with prior experience of systemic side-effects during TB treatment, maintained a positive outlook on transitioning to LAIs. This suggests that the benefits of reduced pill burden, treatment duration, fewer interactions with the health system and enhanced adherence are often perceived to outweigh the risks of drug-related AEs. However, the "slowly reversible" nature of systemic effects remains a pivotal factor. The survey data indicate that interest in LAIs is sensitive to symptom duration and the severity of side-effects; stakeholders expressed a specific concern about scenarios in which systemic AEs might remain at constant levels or take longer to resolve than with oral medications.
Injection-related tolerability	The injection should cause only mild or moderate reactions	The injection should cause only mild reactions	The feedback from surveys and focus group discussions suggests that the duration of mild symptoms is less critical than the severity of the pain itself. Stakeholders indicated a greater "appetite" for mild, lingering symptoms (extending 2–3 days) if it meant avoiding severe injection-site reactions that could interfere with daily functioning. Ultimately, the tolerability of LAIs is evaluated by their impact on a patient's quality of life compared with the management of oral drug AEs. For many, the brief localized discomfort of an injection is preferable to the systemic side-effects or the complex scheduling often required to minimize symptoms associated with daily oral regimens. Therefore, the goal is to ensure that injection-site reactions remain localized and transient, thereby providing a net benefit for both adherence and daily lived experience. Injection-related tolerability depends not only on the volume injected and the route, but also on formulation properties such as viscosity.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Drug–drug interactions [single drug/ regimen]	The LAI (or regimen) should have no greater amount of DDI with often co-administered drugs than the SoC treatment or predictable DDIs of a magnitude that can be compensated If predictable adjustments need to be made to the drugs for the other (non-TB) condition, this may be acceptable	It should be possible to use the LAI (or regimen) with other medications while maintaining safety and efficacy, without adjustment of dose or frequency and without the need for active laboratory monitoring	The prolonged systemic presence and non-retrievable nature of LAIs mean that DDIs are not temporary; they are "locked in" for the duration of the PK profile. Therefore, the regimen must allow for the safe introduction of or transition to other medications, without the risk of metabolic interference or cumulative toxicity. The novel drugs in the regimen should have minimal or no DDI with other drugs that are often co-administered with TB treatment (e.g. ART or HIV prevention, with either LAI or oral drugs). HIV medicines may include drugs that are substrates of P450 or other metabolizing enzymes (e.g. dolutegravir, cabotegravir, CYP3A and UGT1A1) or that inhibit or induce P450 enzymes (e.g. efavirenz, CYP2B6; and ritonavir, CYP3A). Such regimens may need to be modified to permit their use with LAI for TB treatment, or they must be compatible with current oral ART (e.g. dolutegravir) and LAI-HIV PrEP/ treatment (e.g. cabotegravir or lenacapavir). Given that certain drugs increase the risk of QT/QTc prolongation, where feasible, regimens combining several of these drugs should be avoided unless there are data to support the safety of concomitant use. Regulatory guidance on QT/ QTc prolongation by non-antiarrhythmic drugs is available *(42)*. Potential toxic effects of accompanying drugs should also be investigated.
Propensity to develop resistance to TB medicines	Potential for the acquisition or amplification of resistance during or after TB treatment to one or more drugs in the regimen is *comparable to* the SoC	Potential for the acquisition or amplification of resistance during or after TB treatment to one or more drugs in the regimen is *lower than* with the SoC	Drug resistance observed during TB treatment regimen development should be studied intensively, and developers should make expertise available for DST development and population-based surveillance of genomic mutations. Regimen developers should transfer high-quality data and technology on active pharmaceutical ingredients (e.g. MIC distribution or mutation sites of resistant strains) to facilitate the development of suitable DST for the novel regimen components. Where possible, this should take place early in the clinical development pathway (see Section 5). Useful benchmarks for the expected magnitude of on-treatment resistance acquisition can be drawn from experience with oral regimens. For example, one study found that among patients receiving HRZE with strong treatment support, 2.1% acquired resistance during or after treatment with one or more drugs in the regimen *(43)*, whereas another study reported no acquisition of drug resistance (0/768) *(39)*. These oral regimen data provide a reference point against which LAI performance can be assessed, while also highlighting the specific aspects – adherence-driven subtherapeutic exposure and interpatient PK variability – where LAI formulations may offer meaningful improvements. Accordingly, the LAI regimen should exhibit robust PK predictability and limited intersubject variability, to ensure sustained drug concentrations above target levels and thereby minimize the risk of resistance emergence relative to what has been observed with oral therapy.

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes
Stability or shelf life and storage requirements [single drug]	No cold chain required	No cold chain required	Any drugs for oral lead-in should be stable to heat, humidity and light, with a shelf life of ≥5 years.
	All LAI component drugs are stable for ≥2 years in climate zones 3 and 4 and freezing conditions	All LAI component drugs are stable for ≥3 years in climate zones 3 and 4 and freezing conditions	Factors to consider are whether a drug is stable in light-blocking containers or is sensitive to light.

AE: adverse event; ART: antiretroviral therapy; BPaL: bedaquiline, pretomanid and linezolid; BPaLC: bedaquiline, pretomanid, linezolid and clofazimine; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; DART: developmental and reproductive toxicology; DDI: drug–drug interaction; DR-TB: drug-resistant TB; DS-TB: drug-susceptible TB; DST: drug susceptibility testing; ECG: electrocardiogram; EMA: European Medicines Agency; EPTB: extrapulmonary TB; FDA: United States Food and Drug Administration; FDC: fixed-dose combination; GI: gastrointestinal; GLINT: Global Leadership and INsight for TB injectables; HIV: human immunodeficiency virus; HPMZ: isoniazid, rifapentine, moxifloxacin and pyrazinamide; HR: isoniazid and rifampicin; HRZE: isoniazid, rifampicin, pyrazinamide and ethambutol; IM: intramuscular; LAI: long-acting injectable; *M. tuberculosis*: *Mycobacterium tuberculosis*; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; MIC: minimum inhibitory concentration; PaMZ: pretomanid, moxifloxacin and pyrazinamide; PK: pharmacokinetic; PrEP: pre-exposure prophylaxis; QT/QTc: time from the start of the Q wave to the end of the T wave on an ECG (the small "c" refers to a correction of the interval); RR: rifampicin resistant; RS: rifampicin susceptible; SC: subcutaneous; SoC: standard of care; TB: tuberculosis; USA: United States of America; WHO: World Health Organization; pre-XDR-TB: pre-extensively drug-resistant TB; XDR-TB: extensively drug-resistant TB.



6. Trade-offs between characteristics

During the development of LAI-based regimens, there may be a need to make difficult decisions because optimizing one characteristic is often at odds with optimizing another.

The TRPs detailed in this document describe requirements for various characteristics of LAI-based regimens for TB prevention and treatment, such as the efficacy of treatment, safety and the potential for acquisition of drug resistance. Thus, regimen developers may have to decide to prioritize one characteristic over another.

The trade-offs are not symmetrical. Some attributes should not be traded away for convenience; examples include efficacy (i.e. durable, relapse-free cure or durable prevention of disease), safety and the preservation of existing TB medicines against resistance. Other attributes usually allow more latitude; examples include dosing frequency, dosing interval flexibility, route and the number of dosing encounters. The minimal and optimal targets set for each characteristic make these priorities explicit: a candidate regimen should meet most of the minimal requirements and as many of the optimal requirements as possible.

6.1 Injection volume versus number of dosing events

A central trade-off in the development of the LAI formulation concerns the relationship between injection volume and the number of dosing instances required to achieve adequate therapeutic coverage.

A **single, high-payload injection** can extend the duration of coverage and reduce the total number of encounters. However, achieving prolonged exposure typically requires a higher drug concentration or a larger injection volume, or both. Increasing the injection volume is associated with decreased tolerability at the injection site. Mechanical distension of muscle or SC tissue may cause intense pain, persistent pressure sensation, swelling and general discomfort. Larger volumes also increase the risk of localized tissue reactions, including sterile abscesses, granulomas and palpable nodules that can persist for weeks. In addition, higher total drug payloads amplify the inherent irreversibility of LAIs; in contrast to oral therapy, the injected drug cannot be withdrawn if systemic toxicity occurs, potentially prolonging AEs.

An alternative strategy is to use **several smaller injections** or to administer lower volumes. Distributing the total payload reduces the mechanical strain at each injection site and may decrease the incidence and severity of local AEs. Smaller depots can also provide a more gradual PK profile, potentially improving tolerability. However, this approach increases the number of injections per encounter or the total number of encounters, thereby diminishing some of the core programmatic and adherence advantages of LAIs. In surveys, potential recipients of LAIs see minimizing encounters as a highly desirable feature of LAI-based regimens.

The acceptable balance depends on predefined minimum requirements for injection volume and tolerability. Although fewer dosing instances are desirable for adherence and operational simplicity, the injection volume must not exceed thresholds that result in intolerable pain or unacceptable local reactions – characteristics identified as important in the survey and focus group discussions.

Injection volume is influenced by multiple factors, including the active compound, required dose, formulation chemistry and release characteristics. Importantly, the maximum feasible injection volume depends on the route of administration. Generally, SC administration accommodates smaller volumes than IM administration. Therefore, a strategic preference for SC delivery (e.g. to enable decentralization or potential self-administration) may require adjustments in drug concentration, total dose per injection or dosing frequency.

6.2 Combination with oral TB medications versus an exclusively LAI regimen

Another key strategic decision in designing an LAI regimen is whether to implement an oral lead-in phase or adopt an exclusively injectable regimen from the outset. An exclusively LAI-based approach maximizes simplicity because it minimizes ongoing pill burden, reduces daily adherence demands and limits repeated interaction with the health system. This approach may also simplify procurement and supply. From a patient perspective, receiving an injection and returning to normal activities without continued daily dosing is appealing, and may reduce stigma and treatment fatigue.

An oral lead-in may provide an important safety advantage over a fully injectable regimen. Because oral therapy can be discontinued immediately, it allows early action when drug-related hypersensitivity, intolerance or systemic AEs occur. In contrast, once a long-acting injection formulation has been administered, it cannot be removed. This reversibility is particularly relevant for compounds with known toxicity risks or limited post-marketing safety data. An oral lead-in may also serve a strategic role in structuring the regimen. In regimens requiring prolonged total coverage, an initial oral phase could reduce the number of LAI injections required, potentially enabling a single LAI encounter. This may improve acceptability and reduce the risk of treatment interruption if patients do not return for subsequent injections, particularly once they become asymptomatic but may still harbour viable bacilli and remain at increased risk of relapse or resistance development.

An alternative is an LAI–oral hybrid model (concurrent or phased use of LAIs and oral drugs). This approach partially compromises the conceptual simplicity of a fully injectable regimen, but offers practical advantages. It can substantially reduce the total pill burden while ensuring inclusion of a sufficient number of effective drugs in multidrug regimens, especially where there are not yet enough agents available in LAI formulation. Additionally, hybrid approaches may facilitate gradual implementation, allowing patients and health care providers to become familiar with LAIs, and reducing apprehension associated with exclusive reliance on LAIs.

6.3 Efficacy versus tolerability in TPT

In TPT, the acceptable balance between efficacy and tolerability differs fundamentally from that in TB disease. Because TPT is typically offered to individuals who feel well and do not perceive themselves as being ill, tolerance for toxicity, injection-related pain or procedural inconvenience is inherently low.

LAI regimens for TPT must, at a minimum, demonstrate efficacy that is comparable to current SoC oral regimens. However, pursuing marginal gains in efficacy at the expense of increased systemic toxicity, larger injection volumes, greater pain or reduced convenience may be unacceptable from a patient or programmatic perspective. In this context, incremental improvements in protective efficacy may not justify a deterioration in safety profile or user experience.

For TPT, tolerability, injection-related comfort and simplicity are not secondary attributes but central determinants of overall value. Optimizing efficacy beyond established standards must not compromise the safety, acceptability and risk–benefit balance required for TPT in otherwise healthy populations.

6.4 Number of drugs in the continuation phase

In treatment regimens with both an intensive and a continuation phase, the total number of drugs maintained during the continuation phase presents a strategic trade-off. Reducing the number of component drugs may simplify administration, decrease cumulative toxicity and lessen the injection burden. However, maintaining multiple active agents throughout treatment strengthens protection against resistance amplification and may improve robustness of cure, particularly in patients with a high bacillary burden or cavitary disease. Hence, decisions about the number of drugs in the continuation phase must balance regimen simplicity and tolerability against microbiological safety and the prevention of resistance.

6.5 Formulation chemistry and reversibility

The choice of LAI formulation platform introduces additional trade-offs related to reversibility. Certain technologies (e.g. removable implants or in situ forming systems) may permit physical removal of the drug depot in cases of severe AEs or intolerance. This offers an important safety advantage over LAIs, particularly for compounds with uncertain long-term tolerability. Currently, the development of these technologies for TB prevention and treatment lags behind that of LAIs.

In contrast, conventional IM depot injections cannot be removed once administered. Drug release continues for the full intended coverage period, limiting options for mitigating systemic toxicity. Although IM formulations may be operationally simpler or more scalable, they inherently sacrifice reversibility. Selection of formulation chemistry must therefore balance implementation feasibility, safety assurance and risk management.



7. Cross-cutting aspects

Although the TPPs indicate the attributes to consider during the *developmental* stage, these attributes should not be disconnected from the factors to consider during the *implementation* stage within the overall framework of TB-oriented activities. LAI implementation strategies should preserve patient autonomy, by providing clear pathways for informed consent, treatment choice and transition back to oral regimens when clinically appropriate. Aside from costs, it will take time for LAI products to become available at scale. In the meantime, work should continue on developing better oral treatments for people who need them or who prefer not to receive injections. The TRPs detailed in this document present a series of characteristics that are considered essential for LAI-based treatments of TB, such as efficacy, safety, toxicity, drug–drug interactions and potential for the acquisition of drug resistance. Alongside these characteristics, there are cross-cutting aspects that need to be considered; this section discusses each of those aspects.

7.1 Efficacy, effectiveness and trial design considerations for TB regimens

The central value proposition of LAIs is to shift the burden of adherence from the patient (daily pill taking) to the drug delivery system. LAIs reduce the risk of adherence-related failures, where missed daily doses lead to subtherapeutic drug levels and resistance. However, missing an LAI dose is more consequential because the dose provides coverage for a longer period. This tension is most acute in active TB treatment, where resistance poses a direct threat; it also remains critical in TPT unless the goal of a "one-shot" regimen is achieved.

In clinical trial designs for LAIs, the tension between adherence gains and the consequences of a missed dose requires a shift towards pragmatic, implementation-focused trial protocols. For TB treatment trials, the consequences of missing an LAI dose during the period when drug levels slowly decline make it more important to track patients carefully, to prevent the emergence of drug resistance. Hence, this is an important subject for investigation.

For prevention trials, which involve healthy participants, the design must incorporate acceptability and preference endpoints. Researchers must determine whether the physical burden of an injection outweighs or balances the convenience of one or two visits and daily pill taking.

In both contexts, the trial design must transition from measuring pure biological efficacy to measuring real-world effectiveness, which is ultimately what matters, taking into account whether the health system can maintain adherence without the intensive, artificial incentives typical of a trial environment. To this end, developers should investigate, within efficacy trials, the implementation features most likely to determine programmatic performance; for example, the number of encounters and adherence patterns. Trials are encouraged

to include children and pregnant and breastfeeding women by design, with the necessary safeguards in place.

Separate from how efficacy and effectiveness are demonstrated in trials is the question of what evidence regulators will require to approve an LAI. An important consideration in developing LAI formulations for TB is the extent to which existing evidence for corresponding oral formulations can be used to support regulatory approval. Where efficacy and safety have already been established for an oral product, leveraging existing data could facilitate the development of LAI formulations, and potentially reduce the time and resources required to bring them to patients.

Approaches that integrate existing evidence may be particularly relevant for LAI formulations of compounds with well-characterized efficacy, safety and PK/PD profiles. In such cases, development programmes may be able to draw on data from existing oral formulations while generating additional evidence specific to the LAI formulation. This additional evidence would probably include characterization of PK/PD relationships, evaluation of the safety profile associated with the route of administration, and assessment of any formulation-specific risks, including injection-site reactions and effects related to excipients (i.e. inactive substances formulated alongside the active ingredient in a medication).

The applicability of such approaches will depend on multiple factors, including the intended indication, the degree to which exposure–response relationships are understood, the similarity of exposures achieved by the LAI and oral formulations, the availability of supporting non-clinical and clinical data, and the overall safety profile of the product. Consequently, evidence requirements will probably vary between products and indications, and regulatory authorities will need to consider the requirements on a case-by-case basis. Additional studies on acceptability, quality of life, feasibility and real-world cost–effectiveness of LAIs compared with oral regimens are important to inform policy development. Trial designs should allow for a switch to an oral regimen if, for any reason, a patient cannot continue an LAI-based regimen.

As the field evolves, continued collaboration among developers, researchers, regulatory agencies and public health stakeholders will be important to define appropriate and efficient development pathways for LAI products for TB prevention and treatment. Establishing clear regulatory expectations can support innovation while ensuring that standards for quality, safety and efficacy are maintained.

7.2 Overall treatment burden

LAIs should strive to reduce the negative experience of treatment that is lengthy and repetitive and involves taking multiple pills. The evaluation of trials of LAIs for prevention and treatment of TB should not focus solely on severe AEs or laboratory findings; rather, it should include other elements of treatment burden that matter to patients (e.g. quality of life, tolerability and mild-to-moderate AEs that may affect adherence to and acceptability of interventions). Hence, there is a need to solicit input from patients, communities and stakeholders, to explicitly incorporate patient-reported outcomes (e.g. measures of acceptability, stigma, time costs and treatment agency) alongside other clinical and programmatic outcomes in both pivotal and implementation studies, to ensure relevance and improve treatment uptake. There is a need to derive a suitable metric to capture the different dimensions of treatment burden in regimens that include LAIs and those that do not. Studies focused on real-world and implementation contexts would be better suited to capturing these aspects of care *(44)*.

7.3 Scalability, equitable access and transparent pricing

The cost and resources required for an LAI-containing regimen should be weighed against considerations of equity, non-discrimination and transparency; the goal should be affordable access for all, ensuring that vulnerable and marginalized groups do not bear disproportionate costs. Drug developers should ensure that any resulting products are quality assured, affordable, widely available in a timely manner and supplied in sufficient quantities to meet the needs of affected populations, including children and pregnant and breastfeeding women. Scalability needs to be built into the development of LAIs from the very start, because the intervention needs to work at scale with good geographical access if it is to make a difference in global TB prevention and care.

WHO will give due consideration to whether there are pathways towards equitable access to quality-assured versions of the desired formulations *(45)*. The quality of medicines can be assured through WHO prequalification or a similar assessment by the WHO listed authority *(46)*. Ultimately, quality-assured formulations of the regimen, or its individual components, are expected to be widely available in countries soon after a recommendation is made. Developers, including manufacturers of generics, should commit to prioritizing in-country registration and sales in TB-endemic countries, and in countries where there is a high incidence (either subnationally or within vulnerable populations), at the lowest sustainable price. Price setting should be transparent and be justified through transparent disclosure of the R&D costs (including clinical trial costs and public subsidies received), with a verifiable estimate of the manufacturing cost, expected sales and demand volume, and profit margin calculations.

To achieve earlier and simplified regimen development, and to ensure that products are fit-for-purpose and can meet the needs of affected communities (particularly in low-resource areas), developers should work within open collaborative models for TB R&D, enabling the sharing of research knowledge, materials (e.g. reference products and active pharmaceutical ingredients), intellectual property (e.g. using mechanisms such as the Medicines Patent Pool) and data. Developers are encouraged to grant nonexclusive voluntary licensing with technology transfer provisions (including sharing of all relevant data for rapid generic approval) for all LMIC, and for vulnerable populations in high-income countries, at the earliest feasible stage of clinical development; they are also encouraged to include the development of paediatric formulations from the very beginning of the process. With necessary controls, developers should allow their drugs to be tested and studied in combination with other drugs from other developers, including in the analyses required to allow for future development of fixed-dose combinations (FDCs), where therapeutically relevant and feasible. In addition, affected communities should be consulted and involved in the late stages of the drug or regimen research, to ensure that the final product and use-case are driven by gaps in care, and the needs and priorities of patients.

Given the significant role of public financing for TB research and innovation, new products should be appropriately priced to reflect overall investments by global actors, including governments, philanthropists, and other research and product sponsors. Any resulting product should provide a public return on investment, and should be linked to public-health-driven priority-setting and application of the core principles of affordability, effectiveness, efficiency and equity – as identified in resolutions WHA66.22 *(47)* and WHA69.23 *(48)*. New regimens and their component drugs should aim to be cost neutral, or even cost saving, to health programmes and systems, when considering both drug and nondrug costs. The price of medicines is determined by many factors, including production costs, margins to recover development costs and profit margins. Those margins are highly dependent on the volume and speed of product uptake; hence, the margin should be modest and reasonable, given the public health context. Furthermore, there should be

collective efforts to ensure accelerated development, commercialization and scale-up of affordable generic versions of drugs and formulations included in target regimens.

In the case of TPT, the uptake of which still depends on programmatic efforts to create demand, pricing should not present an additional barrier to scale-up. Lessons from recent experience with scaling up the 3-month regimen of weekly isoniazid and rifapentine should be taken into account *(49)*. In the case of TB treatment, a single, lowest sustainable price for LMIC that accounts for the full cost of the regimen should be prioritized at the point of introduction. Further information should be gained from recent experiences introducing new drugs and replacing older regimens for drug-resistant TB with shorter regimens containing newer drugs.

7.4 Cost considerations

7.4.1 Purpose and scope

This section draws on existing economic modelling studies to inform cost targets for LAI TB regimens for prevention and treatment. The analysis includes WHO-commissioned models for previous TPP exercises, research by key modelling groups known to WHO for TB economic evaluation, and recently published models examining regimen characteristics relevant to LAI development. Where LAI-specific models were available, these were included directly; where such models were unavailable, relevant studies were reviewed to inform estimates of the potential economic value of LAI formulations.

7.4.2 TB preventive treatment

No studies have yet addressed the cost–effectiveness of LAI-based TPT regimens. Therefore, existing cost–effectiveness models for oral TPT were reviewed to gain insights into how LAI-based regimens may affect outcomes and cost. A cost–effectiveness analysis using bottom-up micro-costing in Brazil and South Africa compared the WHO TPT TPPs with 6-month isoniazid (6H, drug cost of US$ 3.70) *(50)*. Cost-neutral drug cost thresholds, defined as the maximum drug prices that would result in no additional cost relative to the SoC, were US$ 26 in Brazil and US$ 27 in South Africa for a 3-month regimen, and US$ 53 in Brazil and US$ 142 in South Africa for a 1-month regimen. Primary savings resulted from fewer follow-up visits and higher completion rates. It was determined that single-dose LAI-based TPT regimens would add extra value by eliminating adherence monitoring and ensuring completion, which was not reflected in these oral regimen models; thus, cost-neutral prices would be expected to be higher than the values given in the article. Another study analysed the scale-up of TPT using 3HP (a 12-week regimen of weekly isoniazid and rifapentine) across 29 high-incidence countries *(51)*. Contact investigation was a major cost driver, accounting for 39–70% of costs by age group; this cost driver would remain unchanged for LAI regimens. However, costs for visits, monitoring and AEs during TPT (estimated at US$ 39 in Brazil and US$ 32 in South Africa per person for 6H, reducing to US$ 16 and US$ 11, respectively, for a 1-month oral regimen) could be further reduced with LAI formulations that ensure completion through a single or fewer administrations.

A study of paediatric TPT with integrated case-finding and contact management in nine sub-Saharan African countries used real-world data from 146 sites *(52)*. TPT completion rates varied widely, from 33% to 93% at baseline, improving to 83% to 99% with the intervention. This variation in completion rates was a key factor in the differences in cost–effectiveness across settings. The finding that poor completion reduced cost–effectiveness underscores the main value of LAI formulations, which can guarantee treatment completion through fewer administrations.

7.4.3 Treatment of TB disease

Two modelling studies provide evidence for LAI treatment regimens. One study used a mathematical cohort model to assess the effects of a hypothetical oral pan-TB LAI regimen in India, the Philippines and South Africa over a 10-year time horizon *(53)*. The model also evaluated a single-dose LAI version of this regimen, aligning with optimal targets in the pan-TB TRP. The LAI-based regimen increased initial cure rates from about 69–71% to 82%. Compared with the SoC, pan-TB LAI reduced mortality by 58–63% and transmission by 33–39%. These improvements were driven mainly by the elimination of non-adherence and treatment discontinuation. The model identified cost-neutral price thresholds for pan-TB LAI, using HRZE (isoniazid, rifampicin, pyrazinamide and ethambutol) for RS-TB and BPaL[M] (bedaquiline, pretomanid and linezolid [and moxifloxacin]) for RR-TB as comparators. From a health system perspective, thresholds for pan-TB LAI were US$ 160 in India, US$ 210 in the Philippines and US$ 310 in South Africa. From a societal perspective, including patient-borne costs, thresholds increased to US$ 200, US$ 290 and US$ 390, respectively. These figures provide reasonable upper bounds for the cost-neutral pricing of an LAI-based regimen, assuming perfect adherence and single-dose administration.

The second study used a microsimulation model to examine LAI treatment of people living with HIV and drug-susceptible TB in South Africa *(54)*. The model compared a 2-month oral lead-in followed by a single LAI injection to a 6-month daily oral regimen, using both a 24-month and a lifetime horizon. The LAI approach reduced treatment disengagement from 20.9% to 12.9% over 6 months; it also reduced TB mortality from 21.3% to 16.6% over 24 months, and from 24.5% to 19.9% over a lifetime. With the LAI regimen priced at US$ 199.80 versus US$ 50.40 for the SoC, the incremental cost–effectiveness ratio was US$ 2230 per year of life saved over 24 months and US$ 520 per year of life saved over a lifetime, both below the opportunity-cost-based threshold of US$ 3000 per year of life saved. At 24 months, the cost-effective price ceiling for the LAI regimen was US$ 200. These results indicate that LAI treatment could be particularly valuable where treatment disengagement is high, although its applicability to HIV-negative populations would require further research.

7.4.4 Key considerations

At their introduction, LAI-based regimens are expected to be costlier than equivalent oral treatments, given that they will employ a novel technology and require new consumables (e.g. syringes), different storage requirements and waste management, longer contact time for an encounter, community engagement activities and more highly trained professionals. However, some of these costs are expected to be offset by savings from the smaller amount of active pharmaceutical ingredient needed to deliver the total dose as an LAI. From a programmatic perspective, LAIs are also expected to lower costs for both the individual on treatment and health services, given that fewer encounters will be needed to complete treatment or to follow up in case of interruption. Although evidence remains limited, current evidence suggests that LAI formulations can be cost effective or cost saving at prices above those of current oral regimens, with thresholds that depend on country income, health system costs and baseline treatment completion rates. The economic case for LAI regimens rests on their potential to address two main cost drivers in TB care: suboptimal treatment completion and health care delivery costs associated with prolonged oral regimens that require multiple clinic visits for monitoring and adherence support. Additional benefits, such as fewer AEs or elimination of the need for facility visits for injections, may further reduce costs. However, important evidence gaps remain. There are currently no LAI-specific TPT economic models, and LAI modelling is limited and has not yet been explored for use in community-screening contexts. Efforts are underway to address these gaps. Further research is needed on parameters for which costs remain uncertain, including the price

of LAI formulations, cold-chain and storage requirements, the number of encounters and injections required, injection-delivery infrastructure and training requirements.

Future economic models could further explore key LAI characteristics such as duration of protection, dosing frequency and oral lead-in requirements.

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Annex 1. List of members of the Scientific Target Regimen Profiles Development Group

Role	Last name	First name	Institution
Member	Angami	Ketho	ARK Foundation, India
Member	Ashesh	Ashna	Survivors Against TB, India
Member	Bizzini	Alain	Swissmedic, Switzerland
Member	Campbell	Michael	Clinton Health Access Initiative, USA
Member	Cavaleri	Marco	European Medicines Agency, Netherlands (Kingdom of the)
Member	Churchyard	Gavin	Aurum Institute, South Africa
Member	Davies	Gerry	University of Liverpool, United Kingdom
Member	Dooley	Kelly	Vanderbilt University Medical Center, USA
Member	Faisal	Sobia	Greenstar Social Marketing, Pakistan
Member	Fox	Greg	University of Sydney, Australia
Member	Gler	Maria Tarcela (Maricel)	Makati Medical Center, the Philippines
Member	Hesseling	Anneke	Stellenbosch University, South Africa
Member	Kendall	Emily	Johns Hopkins University, USA
Member	Kityo	Cissy	Joint Clinical Research Centre, Uganda
Member	Lange	Christoph	Borstel Institute, Germany
Member	McConnell	Erin	Treatment Action Group, USA
Member	Meintjes	Graeme	University of Cape Town, South Africa
Member	Ndjeka	Norbert	NTP, South Africa
Member	Nuermberger	Eric	Johns Hopkins University School of Medicine, USA
Member	Owen	Andrew	University of Liverpool, United Kingdom
Member	Pal	Arnab	Clinton Health Access Initiative, USA
Member	Salazar-Austin	Nicole	Johns Hopkins University School of Medicine, USA
Member	Sekadde	Moorine	Ministry of Health, Uganda
Member	Semete-Makokotlela	Boitumelo	South African Health Products Regulatory Authority, South Africa

Role	Last name	First name	Institution
Member	Singh	Urvashi	NTP, India
Member	Svensson	Elin	Uppsala University, Sweden
Member	Wei	Ningyi	National Institutes for Food and Drug Control, China
Member	Zhao	Yanlin	NTP, China
Alternative member	Di Meco	Eugenia	European Medicines Agency, Netherlands (Kingdom of the)
Alternative member	Mattoo	Sanjay	NTP, India
Technical resource person	Kim	Chaelin	LSHTM, United Kingdom
Technical resource person	McQuaid	Finn	LSHTM, United Kingdom
Observer	Brigden	Grania	Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland
Observer	Chauhan	Sandeep	National Tuberculosis Elimination Programme, India
Observer	Flood	Debra	Gates Foundation, USA
Observer	Holtzman	David	Gates Medical Research Institute, USA
Observer	Lienhardt	Christian	French National Research Institute for Sustainable Development, France
Observer	Perrin	Christophe	Médecins Sans Frontières, Switzerland
Observer	Scott	Cherise	Unitaid, Switzerland
Observer	Spigelman	Mel	TB Alliance, USA
Observer	Sun	Eugene	TB Alliance, USA
Observer	Waning	Brenda	Global Drug Facility, Switzerland
Observer	Wells	Charles	Gates Medical Research Institute, USA

LSHTM: London School of Hygiene & Tropical Medicine; NTP: national TB programme; TB: tuberculosis; United Kingdom: United Kingdom of Great Britain and Northern Ireland; USA: United States of America



Annex 2. Report on community perspectives on long-acting injectables for tuberculosis: mixed-methods analysis

This report was prepared by Erin McConnell (Treatment Action Group) with Nora West (Consultant) and Chaelin Kim (Consultant, London School of Hygiene & Tropical Medicine); and reviewed by Mike Frick (Treatment Action Group).

A2.1 Background and rationale

Long-acting technologies (LATs), including long-acting injectable (LAI) treatments, represent a potential gamechanger for treating many diseases. LAIs for tuberculosis (TB) prevention and treatment *(1–4)* could offer an alternative to current standard oral regimens that require daily dosing over weeks or months. Despite the promise of LAIs, historical community experiences and concerns with injectables for TB must be addressed in the context of new technologies to ensure maximal impact *(5)*. Community and stakeholder input on the ideal characteristics of any new intervention or technology, particularly LAIs to prevent and treat TB, is critical to their successful introduction *(6)*. It is imperative to ensure that new treatment approaches meet the needs and mitigate concerns of patients, health care providers and health systems.

The overall aim of this study was to gather community perspectives on the preferred characteristics of LAIs for TB and factors that may affect community acceptance and uptake (e.g. health facility preferences, route of administration, side-effects, drug interactions and timing). In addition, the study collected information on community impressions and existing awareness of LAIs for TB treatment, including lingering negative associations related to injectable aminoglycoside agents; these findings will need to be addressed during development of other injectables. This information is intended to inform an addendum to World Health Organization (WHO) target regimen profiles (TRPs) for the prevention and treatment of TB focused on LAIs, and to help drug developers design LAIs that are acceptable to people affected by TB.

A2.2 Study design

The study used a mixed-methods approach to understand community perceptions around LAIs. In the initial phase, an online survey was developed to assess community perceptions and acceptance of LAIs for TB. In the second phase, four regionally organized

focus group discussions were conducted to probe survey findings and generate qualitative data to inform the development of the WHO TRPs for LAIs for TB, and to identify further areas for investigation in advance of LAI introduction.

Phase 1: Community survey

An online survey (administered via Google Forms™) was developed and disseminated to collect anonymous data on preferences for and the acceptability of LAIs for TB prevention and treatment. Survey questions were designed to align with and build off the WHO-led survey of TB service providers conducted in early 2025 (Table A2.1, Survey 1). The survey was designed and reviewed in English, then translated into French, Russian and Spanish for dissemination. Survey recruitment was conducted via email and listservs to civil society and community partners, and organizations affiliated with Treatment Action Group (TAG), as well as their community partners and networks. Recruitment was supplemented with purposive snowball sampling through regional networks, and direct outreach to community representatives serving marginalized and hard-to-reach population groups. The online community survey was open for participation in June 2025 and resulted in 208 completed surveys from 45 countries across all WHO regions (Table A2.1, Survey 2).

Those who were eligible were:

- adults aged 18 years and older;
- individuals living in a high TB burden country; and
- individuals living in high TB burden communities.

The sample size was up to 200 participants.

Phase 2: Focus group discussions

Once survey data had been analysed, focus group discussions were organized to further explore Phase 1 findings and better understand how LAI preferences were being considered among community respondents. Separate focus group discussions were held for participants in four WHO-defined regional groupings: the African Region, the Region of the Americas, the Western Pacific and South-East Asia regions, and the European and Eastern Mediterranean regions. A focus group facilitation guide was developed to further explore preferences and concerns for LAIs identified from the Phase 1 survey. Participants were asked to give consent in advance of the discussion via Google Forms.

Those who were eligible were:

- adults aged 18 years and older;
- individuals living in a high TB burden country who previously participated in the Phase 1 survey; and
- individuals proficient in the English language.

Recruitment to join the survey was conducted via email, and only individuals demonstrating proficient English and who had indicated willingness in the survey (Phase 1) to be contacted for a focus group were contacted. Targeted outreach was used for regions with limited potential participants (e.g. Eastern Europe and Central Asia, WHO Region of the Americas).

The sample size was up to 10 participants per focus group (*n*=up to 40 in total).

Limitations

The analysis of Phases 1 and 2 faced inherent limitations:

- *Geographical scope:* Despite disseminating the survey broadly and conducting purposive outreach within TB community networks to ensure global representation, some regions and contexts were underrepresented in the data (e.g. South America, Francophone Africa, the Middle East and North Africa).
- *Language barriers:* The survey was available in English, French, Russian and Spanish, limiting responses to those proficient in these languages. The focus groups were conducted exclusively in English, limiting participation to those proficient in English from each region.
- *Selection bias:* The sampling strategy focused on community groups, networks and individuals already engaged in existing regional or global TB networks. Both the survey and the focus groups were conducted electronically, and were therefore accessible only to people with internet access. The focus group was conducted to accommodate Eastern Time (GMT –5), which may have influenced who was available to participate.
- *Gender bias:* Despite recruiting broadly from survey respondents to ensure equitable gender representation in focus groups, male participants were underrepresented in the focus group discussions. Across both the survey and the focus groups, gender minorities were not meaningfully represented.
- *Age bias:* The survey and focus group eligibility began at 18 years of age; thus, younger populations that may benefit from LAIs were not represented in the survey findings.

A2.3 Data analysis

Survey

The analysis of survey data employed descriptive statistics and visual representations to examine preferences across stakeholder groups. Participant characteristics were summarized using descriptive statistics for each variable type. Categorical variables, including demographic characteristics (gender, age groups, education level and employment), were analysed for frequencies and percentages. Key demographic subgroups were stratified using prespecified categories for stakeholder affiliation, geographical region, and previous experience with TB treatment or TB injections (or both).

The results from the TAG-led community survey (Survey 2, Table A2.1) were combined, where possible, with responses from the related WHO-led survey targeting national TB programme (NTP) managers, civil society members and health workers (Survey 1, Table A2.1). Both surveys queried trade-off and preference considerations, with Survey 2 building upon the questions in Survey 1 to gain a deeper understanding of community perceptions around LAIs. For all questions where the answer choices were identical between Surveys 1 and 2, the data were analysed and reported together.

Focus group discussions

Focus group transcripts were analysed using a modified framework analysis *(5)*. Focus group discussions were transcribed, deidentified and analytically coded in ATLAS.ti

software *(7)* and charted into thematic categories, situated within three a priori chosen categories of interest: LAI treatment characteristic preferences, barriers and facilitators to LAI acceptance, and community-specific considerations for implementation. Findings were initially summarized by region; once they had been thematically charted, findings were further compared across regions. When regional differences were present, this was noted in the results. Representative quotes from the focus groups are presented with narrative text. Specific thematic areas that were highlighted followed the overarching areas of inquiry in focus group conversations. All participants were assigned pseudonyms; thus, any names included do not reflect real names. This study received ethics approval from the WCG Institutional Review Board (IRB Protocol: 20252075) and the London School of Hygiene & Tropical Medicine Research Ethics Committee (LSHTM Ethics Ref: 33795).

A2.4 Results

Survey demographics

The community survey closed with 208 completed submissions representing a diversity of countries, geographical regions, target populations, knowledge of LAIs and experience with TB treatment.

Respondents from civil society made up the largest share of stakeholder affiliation (46%, *n*=95), followed by individuals with TB experience (29%, *n*=60), clinicians and health workers (24%, *n*=50) and researchers (1%, *n*=3). Respondents came from 45 countries from all six WHO regions (Table A2.1, Survey 2). There was broad age representation, with near equal numbers of respondents aged 35–44 (28%, *n*=59) and 45–54 (27%, *n*=57), followed by 26–34 (22%, *n*=46), 55–64 (11%, *n*=23), 18–25 (7% *n*=15) and 65+ (4%, *n*=8). Gender representation was fairly equal between female (51%, *n*=107) and male (47%, *n*=98) respondents, with gender minorities making up 1.4% (*n*=3) of all respondents.

About half of all respondents (53%, *n*=110) reported existing awareness of LAIs for TB. Given the history of negative associations around injectable aminoglycosides for treatment of drug-resistant TB (DR-TB), respondents were asked about previous experience with TB treatment and injectables for TB: 38% (*n*=79) of respondents had previous experience with TB treatment *or* TB preventive treatment (TPT). Of those, 27% (*n*=21 of 79) had experience taking injectables as part of their TB regimens.

Table A2.1. Survey participant demographics

Category	Name	Survey 1: NTPs, CSOs and health workers (led by WHO) *n* (%)	Survey 2: Community survey (led by TAG) *n* (%)	Total *n* (%)
Primary role	Civil society	26 (25%)	95 (46%)	121 (39%)
	Clinician/health worker	26 (25%)	50 (24%)	76 (25%)
	Person with TB experience	0 (0%)	60 (29%)	60 (19%)
	Multilateral organization or NGO	18 (18%)	0 (0%)	18 (6%)
	NTP staff	16 (16%)	0 (0%)	16 (5%)
	Laboratory	11 (11%)	0 (0%)	11 (4%)
	Researcher	5 (5%)	3 (1%)	8 (3%)

Category	Name	Survey 1: NTPs, CSOs and health workers (led by WHO) *n* (%)	Survey 2: Community survey (led by TAG) *n* (%)	Total *n* (%)
WHO region	African	11 (11%)	91 (44%)	102 (33%)
	European	27 (26%)	49 (24%)	76 (25%)
	South-East Asia	17 (17%)	30 (14%)	47 (15%)
	Western Pacific	34 (33%)	6 (3%)	40 (13%)
	Americas	3 (3%)	30 (14%)	33 (11%)
	Eastern Mediterranean	0 (0%)	2 (1%)	2 (1%)
	Global	10 (10%)	0 (0%)	10 (3%)
	Overall total	**102 (100%)**	**208 (100%)**	**310 (100%)**

CSO: civil society organization; NGO: nongovernmental organization; NTP: national TB programme; TAG: Treatment Action Group; TB: tuberculosis; WHO: World Health Organization.

Surveys detailed here include the community and civil society focused survey (Survey 2) described in the text above, as well as a parallel survey focused on NTPs and clinicians (Survey 1). When questions aligned, data were analysed collectively to understand preferences across the larger TB community.

Focus group demographics

Table A2.2. Focus group participant demographics

WHO region (and number)	Mean age range (years)	Gender
African (n=4)	55–64	Male (*n*=1) Female (*n*=3)
Western Pacific and South-East Asia (n=5)	35–44	Male (*n*=1) Female (*n*=4)
Americas (n=3)	35–44	Male (*n*=1) Female (*n*=2)
European and Eastern Mediterranean (n=2)	45–54	Male (*n*=0) Female (*n*=2)

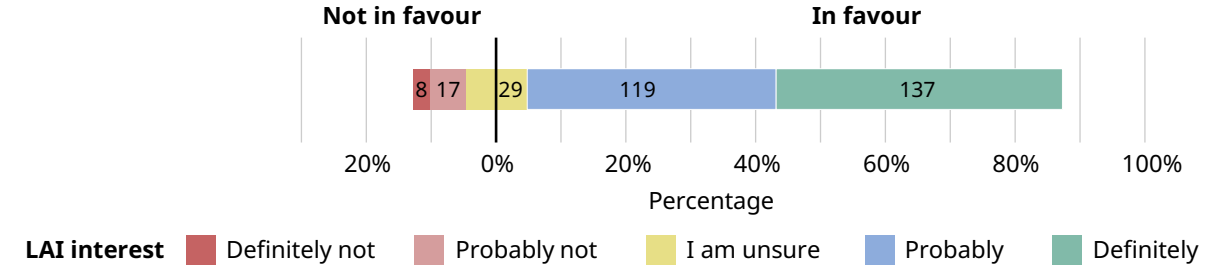
WHO: World Health Organization.

Four focus groups were conducted with community representatives who had participated in the Phase 1 community survey. Participants were selected to balance lived experiences and demographics across each focus group region. Focus group topics included LAIs for children, preferred location for treatment administration, and trade-off concerns between LAIs and oral regimens. Each focus group had two to five participants, with a mean age range of 35–44 years across all groups (Table A2.2). Male participants made up 21% (*n*=3) of all participants, compared with 79% (*n*=11) female participants. No participants from gender minorities participated in the focus groups.

LAI treatment acceptability

Overall acceptability of injectables for TB prevention or treatment (or both)

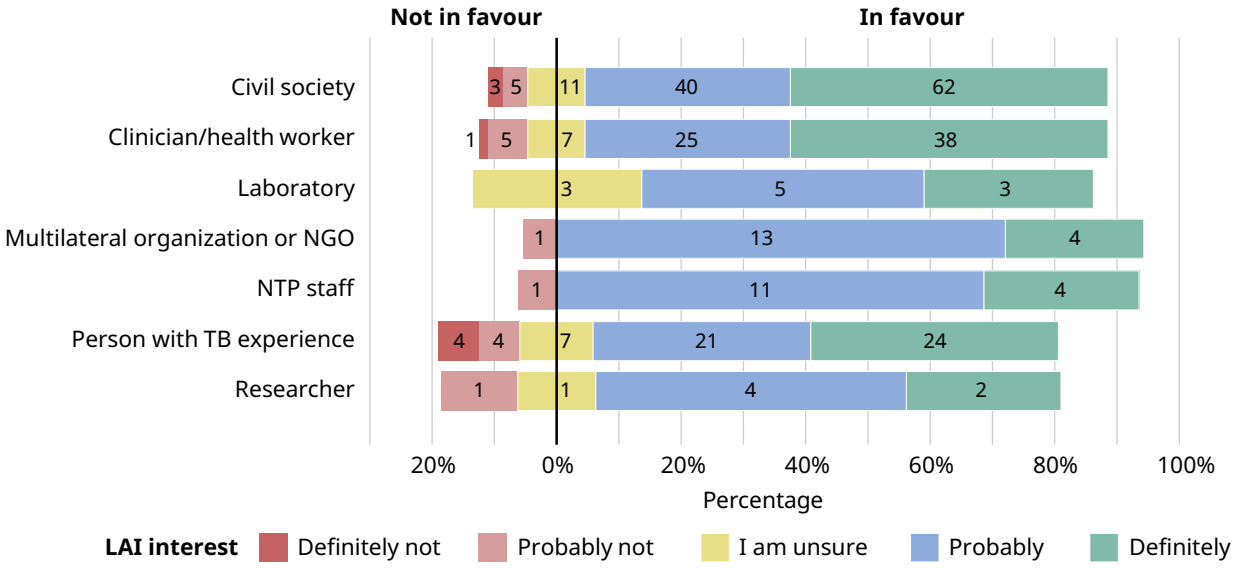
Fig. A2.1. Interest in LAI for TB adoption (Surveys 1 and 2 combined)



LAI: long-acting injectable; TB: tuberculosis.

Survey respondents and focus group participants were largely supportive of LAIs for TB, with 82% (*n*=256) of all survey respondents reporting net favourable interest in LAIs for TB (Fig. A2.1). An additional 9% (*n*=29) indicated a neutral or undecided position and 8% (*n*=25) reported net unfavourable interest. Among civil society and people with TB experience, there was a slight decrease in favourable interest in LAIs for TB as compared with other respondent groups (Fig. A2.2). This difference may be attributable to differences between programme and implementation considerations, and experiential considerations of TB-affected communities.

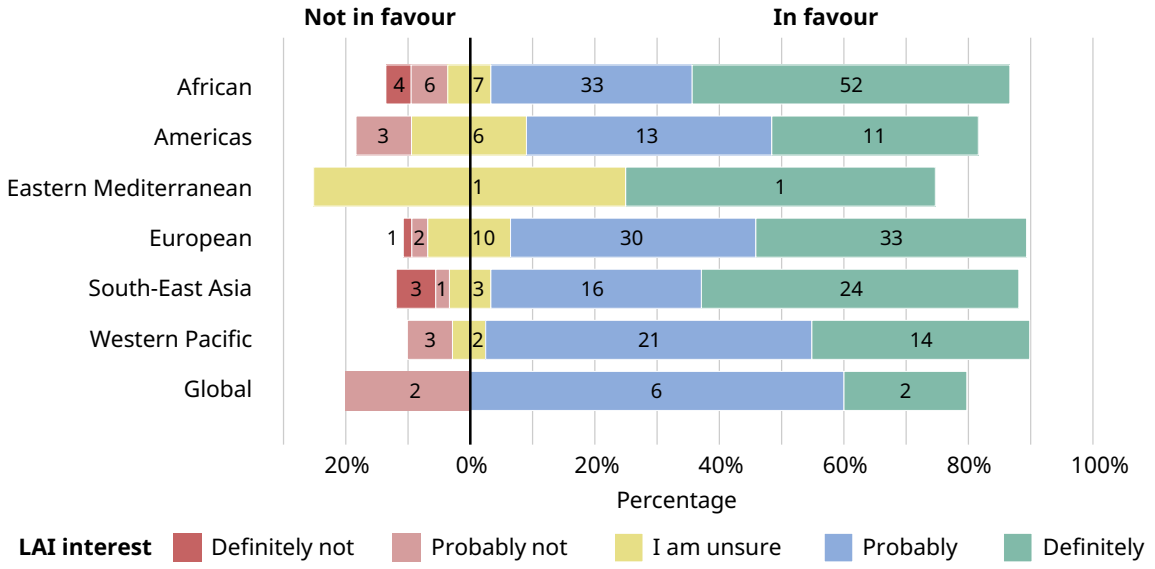
Fig. A2.2. Interest in LAI for TB adoption by primary associations or identification (or both) (Surveys 1 and 2 combined)



LAI: long-acting injectable; NGO: nongovernmental organization; NTP: national TB programme; TB: tuberculosis.

Acceptability of LAIs followed similar patterns across regions; with some variability between regions most respondents reported a favourable interest in LAIs (Fig. A2.3).

Fig. A2.3. Interest in adopting LAIs for TB by WHO region (Surveys 1 and 2 combined)



LAI: long-acting injectable; TB: tuberculosis; WHO: World Health Organization.

Within the focus groups, acceptability of injections in general varied by region, with participants from the WHO African Region and the Region of the Americas being more likely to endorse LAIs overall, often citing pill burden for both other comorbid conditions and TB itself. However, important caveats for certain groups (e.g. urban vs rural) influenced overall perceptions and acceptability of LAIs in each region.

> *I think this [LAIs] will be a great milestone because most of the time, people have complained of having to swallow a lot of pills once they have TB. So, if the injections are there, they are receiving them once every 3 months or every 2 months. I think that can also be a relief [from] swallowing a lot of pills. And this has also affected the adherence to [TB] treatment because people will reluctantly not take the pills if they don't have food. But if it is an injection, sometimes people will not directly think of getting food now, uh, because they will say the injection, I can get the injection, then find food, because the injection will be acting slowly as compared to the pills, which I cannot swallow on an empty stomach.*
> *Quote 1*

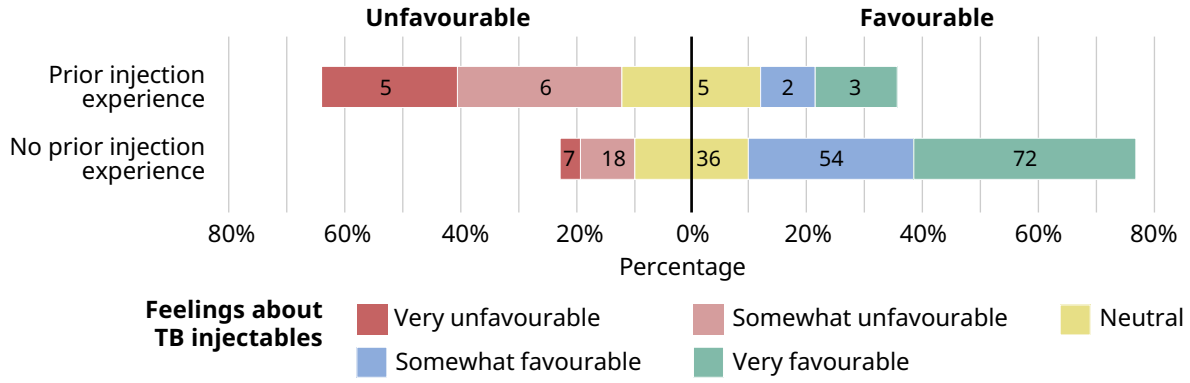
> *So, in general, it depends. It depends on the situation because, of course, I fully support the point of view of the previous speaker that, normally, injections are painful. Yeah? But at the same time, well, for instance, when there is the alternative, well, now I'm speaking about myself. If I have the alternative, well, for instance, of having one injection instead of having uh, um, well, 20 pills. Well, for instance, I would definitely prefer having this, uh, injection because for me, it's more convenient. That's again, uh, depending on people.*
> *Quote 2*

Participants in the WHO African Region did not bring up multidrug-resistant TB (MDR-TB), but did note historical negative memories of anti-TB injectables for MDR-TB treatment (i.e. aminoglycoside agents) causing severe symptoms including hearing loss. Participants from other regions had discussions around existing historical memories of MDR-TB injection frequency and side-effects, though some participants stated this may be less of a concern for younger generations.

> *At the same time, if coming back to those times when people with TB didn't have any opportunity to choose while having TB treatment. They had only the choice of having injections, and at that particular time, the injections were painful, and at the same time, they had lots of adverse effects. And now, uh, if, um, thinking retrospectively, um, if the let me say so that new generation, I mean, of people with TB, um, have the experience of communicating with people with TB who had bad consequences of treating a TB with injections, it might potentially influence their decision. And, well, we should always keep this thing in mind.*
> *Quote 3*

The impact of historical negative experiences with anti-TB injectables was borne out in survey results. Respondents with prior injection experience in TB treatment reported higher opposition to and lower acceptance of LAIs for TB. Among 21 people with prior injection experience, 52% (*n*=11) expressed that they definitely or probably would *not* receive an LAI for TB as compared with 13% (*n*=25) of the 187 people who had no prior experience with injectables (Fig. A2.4). The higher opposition among respondents with prior injection experience underscores the potential challenges of lingering negative association around historic TB injectables when introducing LAIs.

Fig. A2.4. Perception of LAIs for TB by prior injection experience in TB treatment



LAI: long-acting injectable; TB: tuberculosis.

Differences in acceptability among men and women

Focus group participants discussed how the acceptability of LAIs may differ between men and women, with some participants raising concerns about men's willingness to get an LAI injection in the buttocks versus the arm. Considerations around the age of men receiving LAIs – with older men potentially being less comfortable – were also described.

> *Uh, men with the ladies [females administering injections]. And, of course, at that point, they have lost weight, so their clothes kind of fall off, uh, uh, when they they they they they can't keep holding to it, uh, or the pain of the injection. So, uh, it's to me, it's those two issues, uh, the concerns, the part of the body. Uh, they would prefer the arms like other vaccines. That would be very comfortable.*
> *Quote 4*

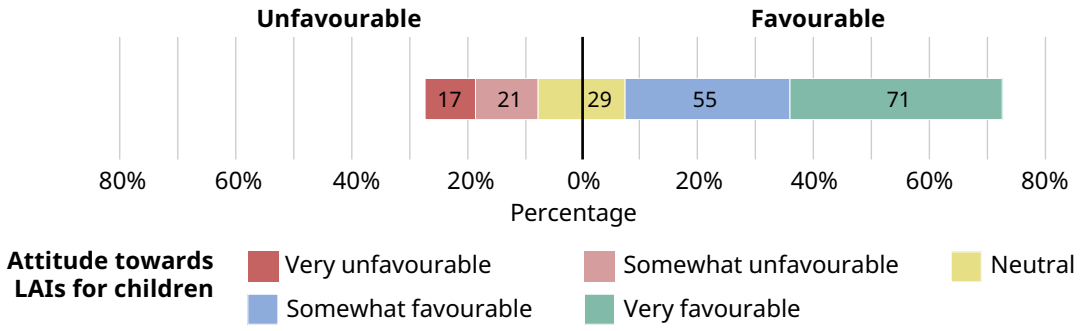
Some focus group participants noted their perception that women are more engaged with the health system in their region (for various reasons, including work burden and lifetime interactions with the health system – e.g. women come for other types of services such as prenatal care). These participants expressed a belief that women may therefore be more likely to be interested in an LAI. However, this dynamic is highly influenced by cultural or

contextual factors that shape gendered access to care – factors that vary among regions, with different effects on LAI acceptability and access in each context.

Given the underrepresentation of males in the focus groups and the male-specific concerns raised, further exploration of LAI acceptability by gender is warranted.

Adult acceptability of injectables for TB prevention or treatment (or both) for children

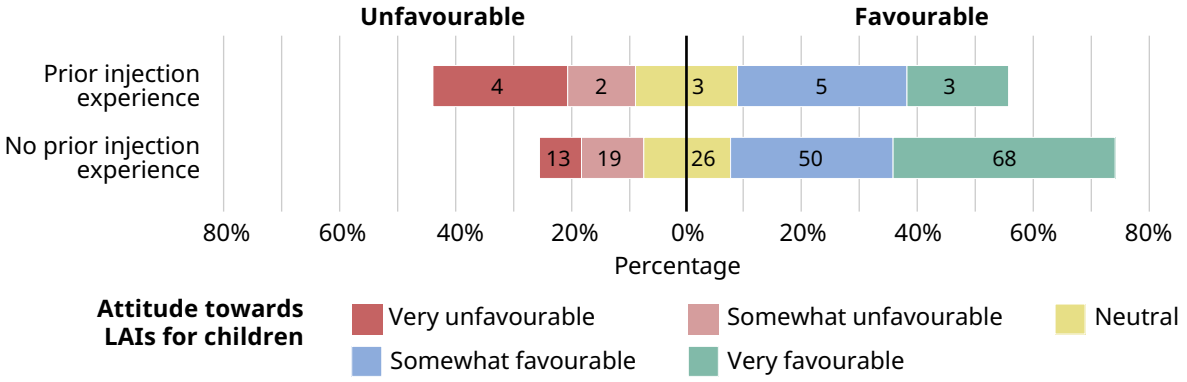
Fig. A2.5. Adult or parental favourability of LAIs for treatment or prevention of TB in children



LAI: long-acting injectable; TB: tuberculosis.

The community survey explored adult or parental willingness to adopt LAIs for TB prevention and treatment in children. Overall, most (65%, *n*=126) respondents felt favourably towards their child being treated with LAIs (Fig. A2.5). When stratified by prior experience with injectables for TB, those with prior experience reported higher unfavourability towards LAIs for TB (35% of responses) compared with 18% unfavourability among respondents without prior injectables experience (Fig. A2.6). This suggests that the negative perception of historical anti-TB injectables within the TB community may influence overall acceptability of LAIs, particularly in communities with a greater burden of DR-TB.

Fig. A2.6. Adult or parental favourability of LAIs for treatment or prevention of TB in children by prior respondent experience with injections for TB treatment



LAI: long-acting injectable; TB: tuberculosis.

In focus group discussions, participant feelings about the acceptability of LAIs for children were largely favourable. Participants expressed that it is challenging to deal with pain and injection site reactions for children of any age. Most participants acknowledged that younger children do not like injections, and some participants said that it can be hard for older children to accept a vaccine. At the same time, participants described the difficulty for parents

in administering oral medications and ensuring that the full dose is taken, making LAIs largely acceptable for treatment or prevention of TB in children.

> *But if, um, I do know that my kids might not like injections, but they would get them, um, because it would be easier. And especially because of what I would have to do here, which would be crushing pills, um, you know, and I think the options I would have that, that, uh, people in my country have for treating their kids, there's just not many of them. So, I would definitely be interested in injectables because crushing pills is just not great. It's not accurate.*
> *Quote 5*

Some participants also spoke about how although children, particularly younger children, may dislike injections in the moment, administering an injection is faster and shorter in duration than giving pills daily.

> *And if there is an, uh, an injection for treating TB, it will be great, I think, because it will be, okay, just a few quiet minutes of crying and screaming, some yelling. That's right. But you will be sure that they receive those in the dose, and on time.*
> *Quote 6*

Trade-offs

Unique preference scenarios were designed and included in the survey to understand and explore personal preferences and stakeholder priorities around different LAI characteristics. Seven trade-off scenarios were examined in the Phase 1 surveys:

1. Standard of care (SoC) (6-month oral regimen) versus LAI regimen without co-formulation (3-month regimen, with 1-month oral lead-in, followed by 4 shots monthly for 2 months).
2. SoC versus LAI regimen with co-formulation (2 shots monthly for 2 months).
3. Coverage duration versus number of injections; that is, fewer injections monthly versus more injections on a 2-monthly schedule.
4. Subcutaneous (SC) injections monthly versus intramuscular (IM) injections 2-monthly.
5. Injections at local clinics monthly versus at central hospitals 2-monthly.
6. A single injection appointment for continuation phase versus two monthly injection appointments.
7. TPT SoC (1-month oral regimen) versus a single LAI injection(s) appointment.

Survey findings on trade-offs were explored in greater detail in focus groups. When asked about trade-offs (e.g. longer oral lead-in, fewer total injections and frequency), many focus group participants raised questions about the efficacy of treatments. This suggests that treatment efficacy is of high concern for people being treated for TB and is central to assessing individual preferences for potential LAIs, regardless of their characteristics.

Table A2.3. Combined treatment preference summary from Surveys 1 and 2

Treatment preference scenario	Option A preferred *n* (%)	Neutral *n* (%)	Option B preferred *n* (%)
TB treatment			
A: 6-month daily oral (SoC) B: 3-month (1-month oral lead-in + 4 monthly injections for 2 months)	61 (20%)	34 (11%)	215 (69%)
A: 6-month daily oral (SoC) B: 3-month (1-month oral lead-in + 2 monthly co-formulated injections for 2 months)	44 (14%)	17 (6%)	249 (80%)
A: 4-month (3 monthly injections) B: 3-month (6 injections given on months 1 and 3)	141 (45%)	50 (16%)	119 (38%)
A: 4-month (3 SC monthly injections) B: 3-month (3 IM injections given on months 1 and 3)	81 (26%)	31 (10%)	198 (64%)
A: 4-month (monthly injections at local clinic visits) B: 3-month (injections at district hospital visits on months 1 and 3)	108 (35%)	36 (12%)	166 (53%)
A: 3-month (1-month oral lead-in + 2 monthly injections) B: 3-month (2-month oral lead-in + 1 injection visit)	141 (45%)	36 (12%)	133 (43%)
TPT			
A: 1-month oral prevention (SoC) B: Single prevention injection given at 1 visit	46 (15%)	18 (6%)	246 (79%)

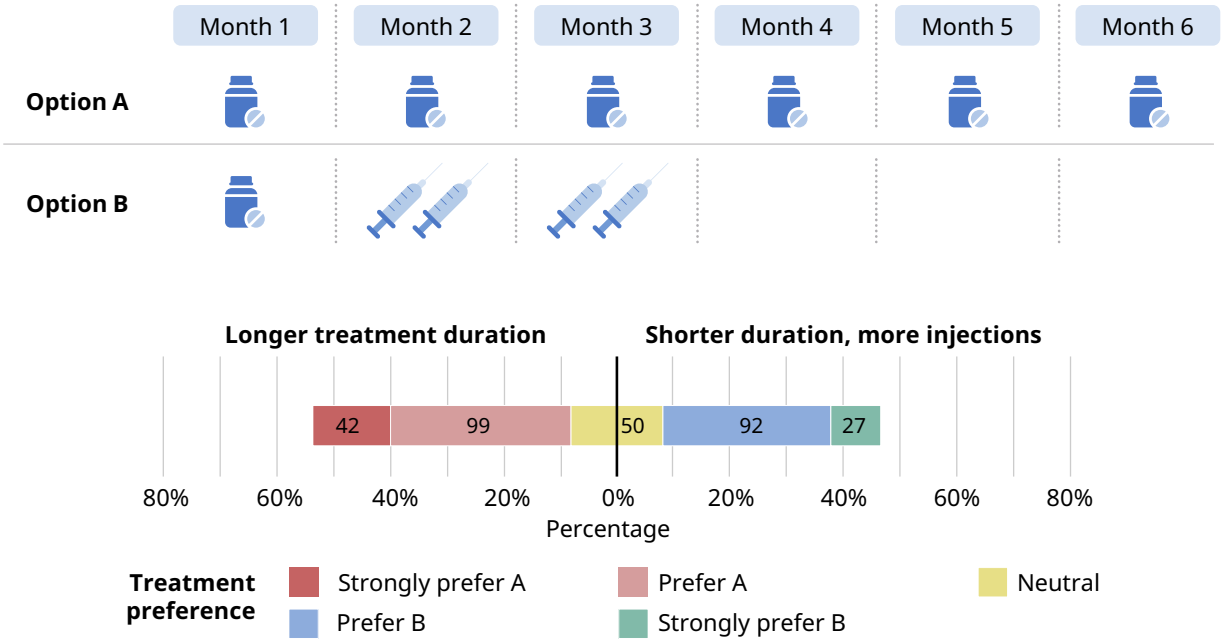
IM: intramuscular; SC: subcutaneous; SoC: standard of care; TB: tuberculosis; TPT: TB preventive treatment.

SoC versus LAIs

Comparing a 6-month daily oral regimen (SoC TB treatment) to a 3-month LAI regimen with 1-month oral lead-in with four monthly injections for 2 months (no co-formulation), 69% of all respondents preferred the LAI option while only 20% of respondents preferred the standard oral regimen. This suggests strong support for an LAI regimen that shortens overall treatment timelines and reduces pill burden. When a 3-month co-formulated LAI regimen (with 1-month oral lead-in and two monthly co-formulated injections for 2 months) was compared with the SoC, preference for the LAI regimen rose 11 points to 80%. The large increase in support for the co-formulated LAI regimen indicates community and other stakeholder interest in minimizing the overall number of injections alongside reducing treatment times and pill burdens.

Asked about coverage duration versus number of injections (i.e. fewer injections monthly vs more injections on a 2-monthly schedule), 45% of respondents preferred a longer treatment duration with fewer injections (e.g. a 4-month regimen with 3 monthly injections) compared with 38% of respondents preferring a shorter duration with more injections (a 3-month regimen with 6 injections on months 1 and 3) (Fig. A2.7). Preference varied across stakeholders, but clinicians or health workers and civil society respondents favoured fewer injections with longer treatment duration, suggesting a higher priority among advocates and health care providers for reducing the number of injections per visit; this aligned with findings from other trade-offs (see above).

Fig. A2.7. Preference for longer duration of treatment coverage with fewer injections versus shorter duration with more injections



The findings from the three scenarios described above suggest that reducing the total number of injections and the time in treatment are high priorities for TB stakeholders; thus, reducing the total number of injections represents a key aim for acceptability of LAI regimens. Further exploration of the trade-off between number of injections and time in treatment is required to identify the ideal balance between each parameter.

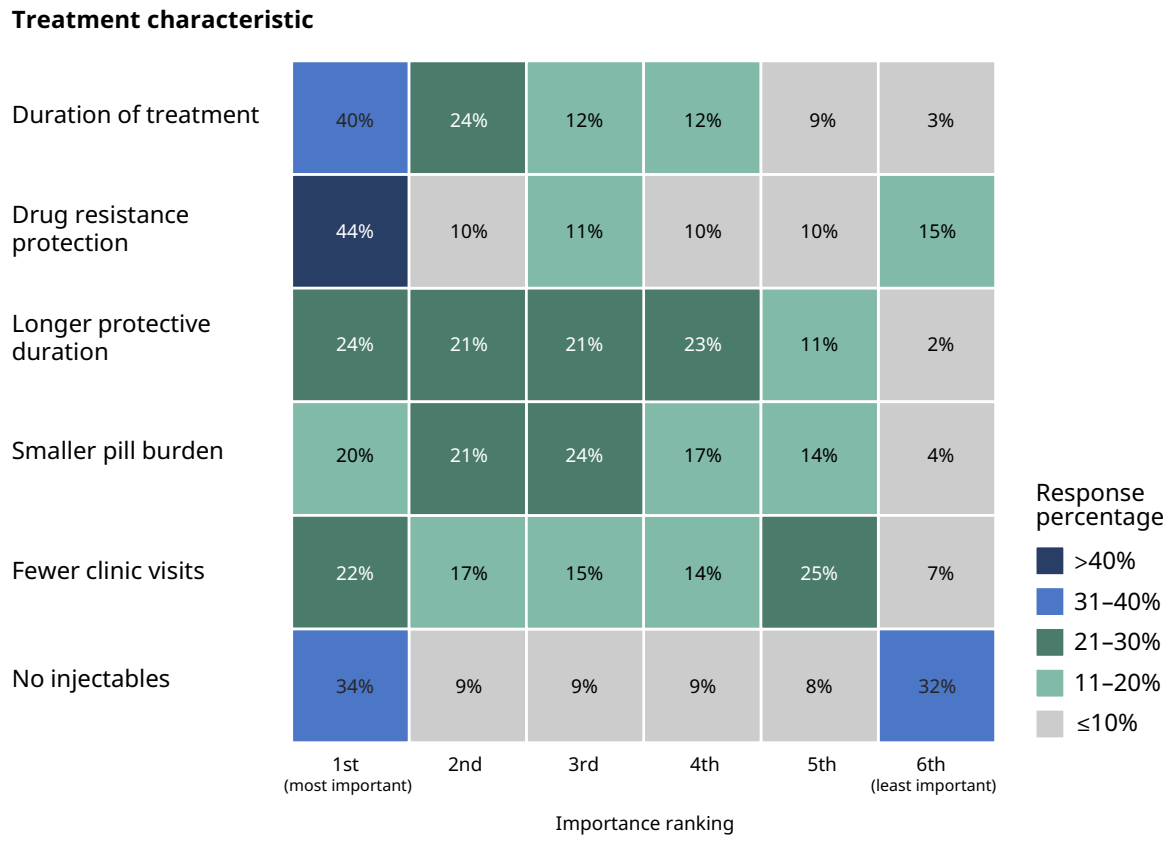
Aligned with the findings from the TB treatment preferences, respondents indicated a strong preference for a single LAI injection for TPT (79%) over a 1-month oral regimen (15%) – an option that showcases the strong potential LAIs have for TPT.

When directly asked about which LAT characteristics were of highest priority, community survey respondents reported that protection against drug resistance was the most important (44%), followed by duration of treatment (40%); longer protective duration, fewer clinic visits and smaller pill burden were secondary priorities (Fig. A2.8). For the option of LATs not featuring injectables, there was a near equal split between “most important” and “least important”. This is in line with earlier analysis, which revealed the impact of negative history of injectables for TB on LAI acceptance while also underscoring an appetite for LATs in general.

Focus group participants stressed that options and information were most critical to successful implementation of any LAIs. Across WHO regions, participants described how health workers were likely to influence their choice, noting that it was likely that a health worker (per their role) had determined a specific course of treatment before discussing it with the individual. In an expanding landscape of TB prevention and treatment options, a common request was that there be clear information on trade-offs and that there be an option for making individual decisions, whether for adults, children or other subgroups.

Options

Fig. A2.8. Prioritization and preferences of LAT treatment characteristics in overall acceptability and uptake of LATs



LAT: long-acting technology.

> *One thing, like, I really want for other people who have had TB or have TB is just options. And, um, so, you know, if we're viewing this as another option, I think that's a great way to do it. And, um, the other thing is, of course, you know, please remember children, and please remember people who are pregnant. Um, these are populations that always get left out. I feel very strongly about it, obviously.*
> *Quote 7*

Stigma

The impact of new LAI regimens on stigma was described across the focus groups. One common theme was that LAI regimens that result in fewer visits to a health centre could mean people are less seen at health centres collecting pills.

> *A patient will go to the medical department for injections. How to say – not so often. It means that the risk of receiving stigma and discrimination from medical staff, people or somebody from his environment [community]. That is why less visits, risk of meeting somebody who will stigmatize him.*
> *Quote 8*

Other participants raised the issue that reducing or eliminating the duration of taking oral medication in the home or work could reduce family and community-based stigma. However, the nuances of this dynamic between regions were not explored in depth in the focus groups. Further investigation into the potential impact of LAIs on stigma is required.

> *It gives them the right to privacy, and getting injections gives them space to do other chores as well as to reduce the cost of frequent visits to the facility. So that also, uh, uh, gives them time to manage their households. So, most of the women here will prefer injections because they provide that privacy and respect and dignity, and no one can stigmatize them or blame them.*
> *Quote 9*

IM versus SC injections

When the preference for injection route – IM or SC – was explored, 64% of respondents preferred IM (3-month treatment with 3 IM injections given 2-monthly) over SC (4-month treatment with 3 SC injections given monthly). However, because the IM option featured both a shorter treatment duration and fewer injections, it is difficult to draw conclusions specific to SC versus IM injection preferences (Fig. A2.9). A separate ranking question in the community survey considered technology type independently of treatment duration and dosing frequency; 45% of respondents ranked SC injectables as their first or second choice, compared with 37% for IM injectables. Overall, 86% ranked SC injectables among their top three choices compared with 55% for IM injectables (Fig. A2.10). The preference for SC injectables when considered outside of hypothetical treatment duration and number of injections, but IM when associated with shorter treatment and fewer injections, suggests that treatment duration and number of clinic visits are of higher importance in determining LAI preferences than the specific injection site.

Fig. A2.9. Preference for SC injections with monthly visits versus IM injection with 2-monthly visits (Survey 2)

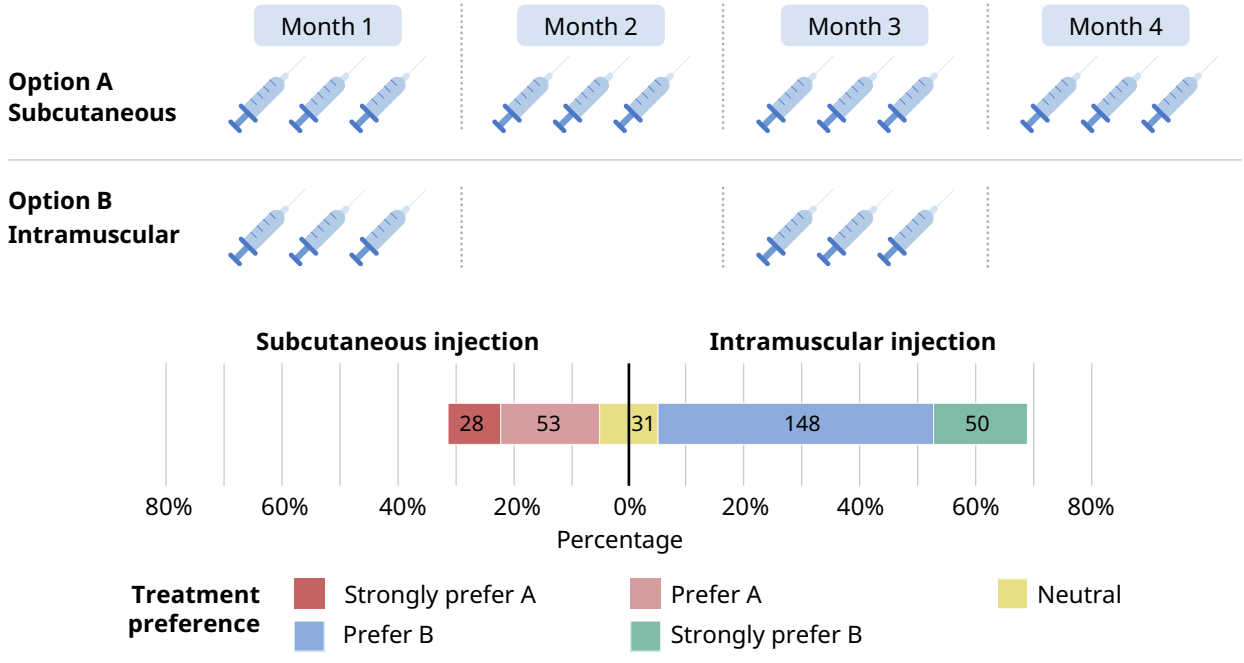
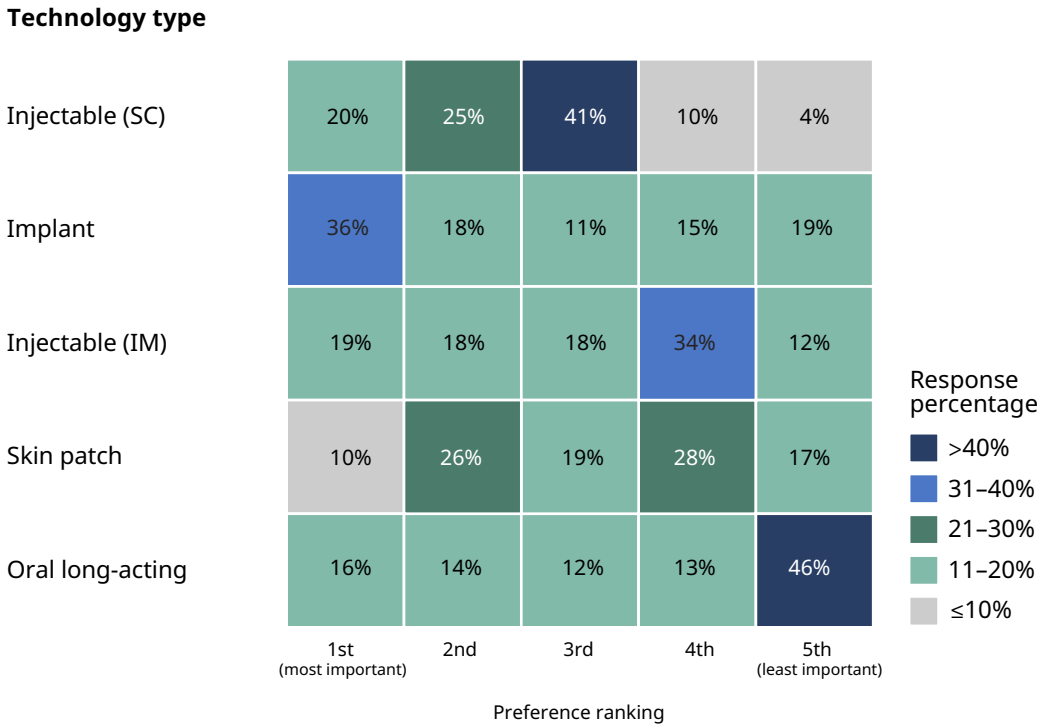


Fig. A2.10. Preference rankings for LATs for TB



IM: intramuscular; LAT: long-acting technology; SC: subcutaneous; TB: tuberculosis.

When injection sites were raised in focus groups, participant responses were primarily focused on minimizing pain associated with injections.

> *Less painful? Every time is better.*
> *Quote 10*

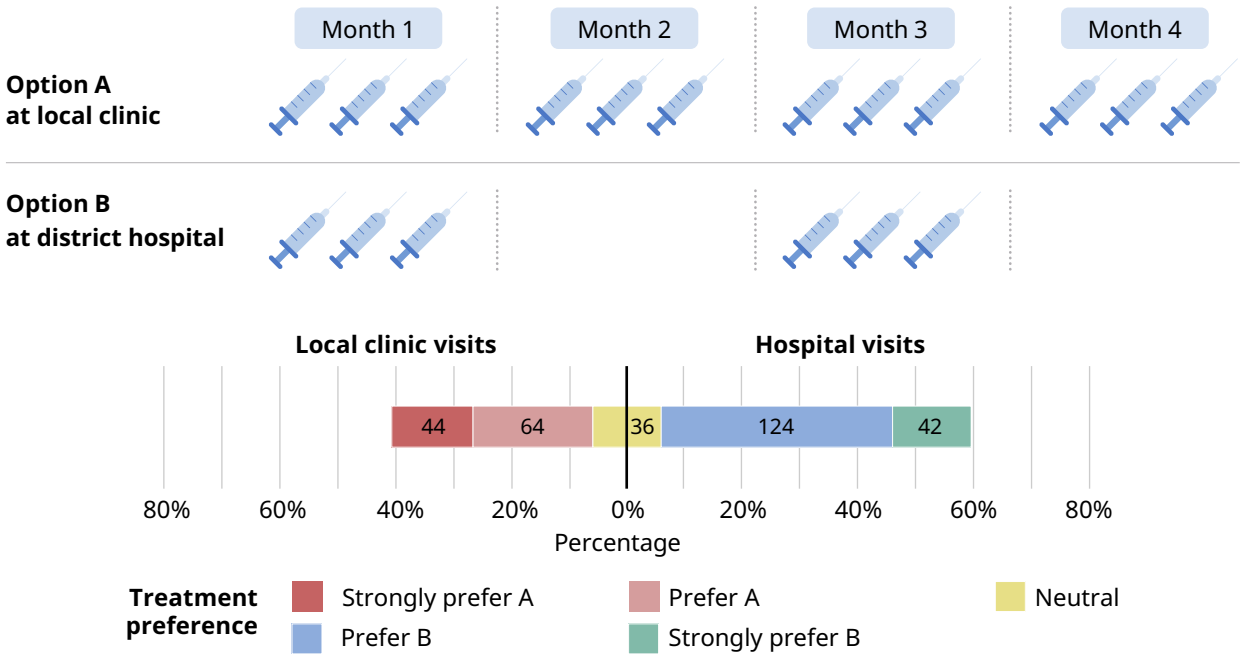
Other participants described how the duration of the pain may not be unfamiliar to people, but the severity of pain and how long the pain lasts is the most important consideration. This is in line with survey findings that suggest the highest priority for affected communities in assessing injections is not the *type* of injection, but the side-effects of an injection and, by extension, the severity of pain from administration. Focus group participants suggested that the associated pain of LAI treatment will have an outsized impact on acceptability.

> *It depends on how painful. If it's the that is derived from the then penetrating the muscle, then that one, they can easily bear because they are used to it … but if it is a pain from the drug getting into the muscles and the pain persists, after the administration, then they might prefer to go back to the pills.*
> *Quote 11*

Location of LAI treatment

When asked about receiving LAI treatment at a local clinic monthly (4-month regimen) versus at central district hospitals 2-monthly (3-month regimen), 54% of respondents preferred the district hospitals (Fig. A2.11). However, the query did not isolate location of treatment from considerations about preferences for number of visits, visit rhythm (i.e. monthly vs 2-monthly) or overall regimen length. As such, respondent preference for the district hospital in the scenario described (Fig. A2.11) may reflect interest in a shorter treatment duration, in less frequent clinical visits, or in receiving treatment at a district hospital over a local clinic.

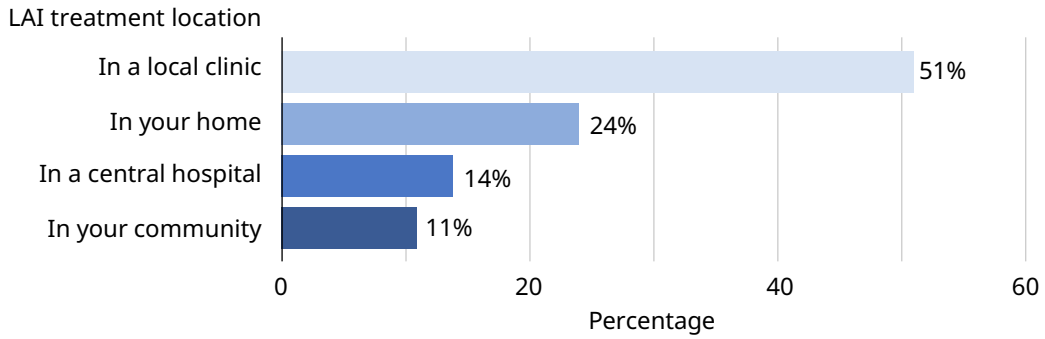
Fig. A2.11. Preference for receiving LAIs for TB in local clinics on a monthly schedule versus regional hospitals on a 2-monthly schedule, regardless of injection type (Surveys 1 + 2)



LAI: long-acting injectable; TB: tuberculosis.

When community survey respondents were asked to rank preferences for where they would want to receive LAI treatment *independent* of number of visits or injections required, 51% of respondents preferred local clinics compared with 14% preferring central district hospitals (Fig. A2.12). This suggests that when an LAI is regimen agnostic, respondents prefer to receive care closer to their communities (e.g. at local clinics).

Fig. A2.12. Overall preference for location of LAI treatment regardless of injection type and treatment schedule

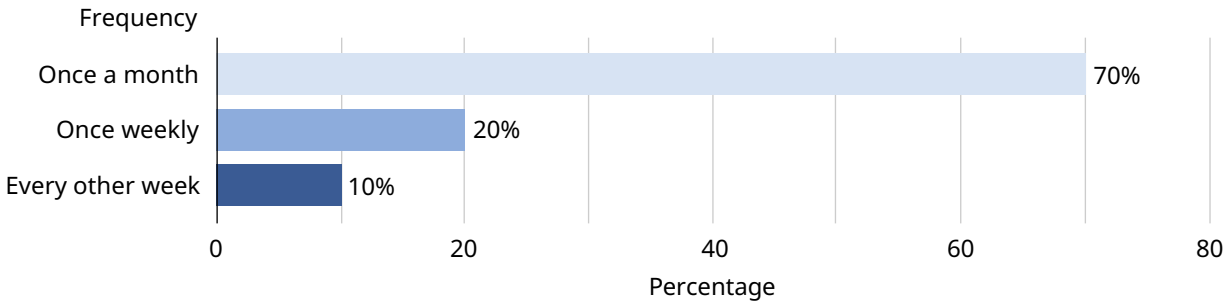


LAI: long-acting injectable; TB: tuberculosis.

Despite this strong preference for receiving care closer to home (Fig. A2.12), when considerations such as regimen duration and number of visits are included (Fig. A2.11), respondents prioritized shorter treatment durations or fewer clinic visits over a central location of care (e.g. local clinics). This finding is supported by the rankings of LAI characteristic priorities (Fig. A2.8), in which "duration of treatment" and "fewer clinic visits" were high priorities for respondents. When asked about how often they would be willing to visit their treatment provider regardless of location, most (70%) preferred monthly visits, with 20%

indicating a willingness to go once a week, and 10% a willingness to go fortnightly; 2-monthly options were not discussed (Fig. A2.13). Taken together, these findings indicate that patients are willing to accept less convenient locations in exchange for shorter treatment durations and fewer total visits.

Fig. A2.13. Preference or willingness for timing of required clinical visits for LAI treatment, regardless of treatment location



LAI: long-acting injectable; TB: tuberculosis.

Focus group participants expressed mixed feelings about the best location for LAI treatment (e.g. health centre, hospital, community location or home-based). Some participants noted that a community location would minimize travel costs. Others described how, in their respective health systems, receiving LAIs at community clinics would be an unlikely option because all TB care is administered through a pre-existing, fixed TB clinic system. Some participants from the WHO Americas, European and Eastern Mediterranean regions raised a preference for oral regimens with video directly observed therapy (DOT) over an LAI regimen, because they felt that oral regimens can be more convenient than needing to take time away from work, childcare and other responsibilities for LAI treatment. This suggests that personal conveniences will be a consideration in LAI acceptance and how easily LAIs can be integrated into existing routines or structures. Participants did not raise interest in DOT for self-administration of LAIs, but this should be explored in greater detail in future studies.

> *That's actually a lot and big, it's kind of a pain. If I could take the pills by myself and on a, you know, DOT, you know, if they can watch me take it, and I can do it from my home, video DOT is way more convenient. For me personally, and I know a lot of working people, having a doctor's appointment every month would be a pain. So, if for me, it would be the treatment I can take at home versus the treatment I have to go in for, and however it would be.*
> *Quote 12*

LAI treatment side-effects

Within focus groups, the side-effects of LAIs compared with pill-based TB treatment or prevention were raised by participants as an important consideration. If side-effects are too severe, there were concerns that after one injection or a series of injections, someone might not return for additional injections.

> *If the side-effect is [bad], then people might not have a repeat, [come to] a repeat visit if the injection is over a period of time. We have had that problem with TB, with side-effects when people can't work properly... so they stop [treatment] immediately because they don't want to be sicker than they are [due to side-effects].*
> *Quote 13*

Other discussions around side-effects included timing of an injection versus taking a pill, which could influence when side-effects are experienced; also, that there may be less control of side-effects with administration of an LAI.

> *I was on pills. And I could kind of take them at a time, like, right after work, and then I would have the side-effects, like, at night. And so I could time that a little bit better once I figured out what was going on. Whereas, you know, if you're on the clinic schedule or whatever and going back to work, you might not have that option. Like, if you have a morning appointment or whatever, that's all they have available. Quote 14*

The discussion of side-effects also focused on ensuring that patients have information to make an informed choice about what will work best for their lives (e.g. pills vs injection vs a combination), and whether or how easy it would be to switch to a pill-only based regimen if LAI side-effects were too significant. Participants raised concerns about how much agency individuals on LAIs would have over side-effects, timing and even mode of treatment (e.g. switching from LAI to oral), and the impact of that situation on acceptability.

> *People then, after they are taking the long-acting injectable, don't feel comfortable and want to change the mode of transmission from the injection to taking the pills, or the other way around. Is that possible for people to do that? Quote 15*

A2.5 Summary

Taken together, the findings from the surveys and the focus group discussions underscored strong existing interest in and support for LAIs for treatment of TB. Support was consistent across all groups engaged in the TB field including TB-affected communities, health workers, NTPs and civil society. Although the history of anti-TB injectables still influences community perceptions of LAIs, support for LAIs was found even among those with prior experience of TB injectables.

Overall, community respondents favoured shorter treatment durations, fewer injections, minimal associated pain in the design of LAIs and personal modesty during treatment (i.e. there was resistance to injections in the buttocks or other culturally sensitive areas of the body), with less importance placed on the route of administration or location of treatment. There was particularly strong interest in LAIs for TB prevention, demonstrating the strong potential of future LAIs to overcome adherence concerns associated with existing oral TPT regimens.

The insights gleaned from the focus groups revealed that although LAIs represent a promising alternative to daily oral regimens, the acceptability, implementation and success of LAIs will depend on careful consideration of diverse community needs, preferences and contextual factors that differ across regions. Although participants from the WHO African and Americas regions demonstrated strong support for LAIs and recognized their promise in reducing daily pill burden and improving adherence, the support was not unconditional. In line with survey findings, participants highlighted key concerns and historical experiences with injectable TB treatments, particularly for MDR-TB.

Several key themes emerged as being crucial for LAI acceptance and implementation. Side-effects stood out as a pivotal concern that could determine whether patients continue with LAI treatment. Participants emphasized the need for clear information about potential

adverse effects and the flexibility to switch between treatment modalities if needed. Stigma mitigation was identified as a potential benefit of LAIs, because needing fewer clinic visits could reduce visibility within communities and health care settings; however, this must be balanced against the logistical challenges of attending clinics for injections.

The findings highlighted the critical trade-offs that must be addressed in LAI development and implementation to support community acceptability and uptake. Early consideration and inclusion of community perspectives and voices in the LAI development pathway are vital for ensuring that future LAIs carry the potential to meaningfully meet the needs of TB-affected communities. LAIs hold significant promise as an innovation that could improve treatment adherence and reduce pill burden, but their success requires a nuanced, person-centred approach to implementation.

References for Annex 2

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Annex 3. Consensus meeting agenda

Members of the Scientific Target Regimen Profiles Development Group met virtually over 4 days, from 29 June to 2 July 2026, from 12:00 to 15:00 Geneva time each day, to reach consensus on the target regimen profiles for long-acting injectables (LAIs) for tuberculosis (TB) prevention and treatment. Alternative members, technical resource persons and observers also attended; the closed session shown in the agenda was restricted to members of the group.

The objectives of the meeting were to:

- review and discuss additional survey evidence;
- review and achieve consensus on the TRP tables for prevention and treatment; and
- review and achieve consensus on the section on trade-offs and cross-cutting aspects.

The expected outcome was clear direction allowing the World Health Organization (WHO) to finalize the target regimen profiles (TRP) document; in particular, to reach consensus on revisions to the minimal and optimal requirements.

Table A3.1. Meeting agenda

Time	Item	Presenter
Monday, 29 June. Session 1: Welcome, introduction, objectives of the meeting and surveys. Moderators: Fuad Mirzayev and Dennis Falzon		
12:00–12:10	Welcome and introduction to the meeting	Tereza Kasaeva
12:10–12:20	Meeting objectives and agenda	Samuel Schumacher
12:20–12:30	Declarations of interest	Dennis Falzon
12:30–13:00	Reminder on characteristics and notes on feedback received	Fuad Mirzayev
13:00–13:45	GLINT study findings	Emily Namey
13:45–14:00	Summary of results from prior surveys and focus group discussions, and reflections on the GLINT results	Erin McConnell
14:00–14:30	Questions and discussion on survey results, and general discussion	All
14:30	Adjourn	
Tuesday, 30 June. Session 2: Prevention TRP. Moderator: Dennis Falzon		
12:00–15:00	Discussion on characteristics for TRPs for LAIs for TB prevention	All
15:00	Adjourn	

Time	Item	Presenter
Wednesday, 1 July. Session 3: Treatment TRP. Moderator: Fuad Mirzayev		
12:00–15:00	Discussion on characteristics for TRPs for LAIs for the treatment of TB disease	All
15:00	Adjourn	
Thursday, 2 July. Session 4: Other parts of the TRP document. Moderators: Fuad Mirzayev and Dennis Falzon		
12:00–14:45	Trade-offs and cross-cutting topics	All
	Next steps	Samuel Schumacher
	Closed session (members of the Scientific TRP Development Group only)	
14:45–15:00	Meeting closure	Matteo Zignol

LAI: long-acting injectable; TB: tuberculosis; TRP: target regimen profile.



Annex 4. Summary of declarations of interest and management of conflicts

This annex summarizes the declarations of interest (DOIs) and management of conflicts for the Scientific Target Regimen Profiles Development Group (TDG), which developed the target regimen profiles (TRPs) for long-acting injectable (LAI) regimens for tuberculosis (TB) preventive treatment (TPT) and TB treatment.

The DOI assessment period was from 2024 to 2026.

Thirty experts with a wide range of technical and programmatic expertise were invited to participate (see list of members in Annex 1). The experts included representatives from academia, research institutions, product development partnerships, civil society and national TB programmes (NTPs).

All invited experts completed and submitted their DOI and confidentiality undertaking forms.

On review of the completed DOIs, the following 10 experts declared interests that required further consideration:

1. Ashna Ashesh
2. Gavin Churchyard
3. Geraint (Gerry) Rhys Davies
4. Greg Fox
5. Maria Tarcela Gler
6. Anneke Hesseling
7. Emily Kendall
8. Graeme Meintjes
9. Eric Nuermberger
10. Elin Svensson

Table A4.1. Participants with potential conflicts of interest

Expert name	Ashna Ashesh
Conflict disclosed	**(5b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of the meeting or work** Ms Ashesh is a steering committee member of the ReLAY Track of FAST-TB. ReLAY's focus is on helping prioritize clinical research that aligns with the global realities of TB care and accelerating the introduction of more effective regimens that dramatically improve outcomes for TB patients.
Assessment	The disclosed conflict supports a broader TB research strategy, not specifically linked to LAIs or any product that is under review.
Conclusion	No significant conflict of interest.
Expert name	**Gavin Churchyard**
Conflict disclosed	**(1b) Consulting, including service as a technical or other advisor** Dr Churchyard has received an honorarium (US$ 1500) as a member of the Janssen advisory board on LAIs for TPT. This has now ceased. **(2a) Research support, including grants, collaborations, sponsorships and other funding** The expert has received salary support from the NIH/DAIDS/ACTG of approximately US$ 13 500, until the United States Government funding cut. While this support has now ceased, the research activities are still ongoing. **(6e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?** Dr Churchyard disclosed that he is supporting Janssen in developing a protocol, as a protocol co-chair, to evaluate long-acting bedaquiline (ongoing activity). This is expected to be submitted to the NIH/DAIDS/ACTG for approval, and if approved, the project will start in the third quarter of 2026.
Assessment	Although previous funding has ended, the ongoing collaboration with Janssen represents a direct involvement in a commercial LAI product, which is currently under review and thus represents a potential perception of conflict.
Conclusion	Dr Churchyard may participate as a member of the group with observer status, due to the active protocol development role. He should refrain from participating in the decision-making processes on TRP characteristics.
Expert name	**Geraint (Gerry) Rhys Davies**
Conflict disclosed	**(2a) Research support, including grants, collaborations, sponsorships and other funding** In 2024, Dr Davies was a co-investigator on a research grant funded by ViiV Healthcare, awarded to the University of Liverpool Department of Pharmacology, totalling £374 574. He receives no personal salary or other benefits from this grant. The study focuses on the pharmacokinetic interaction between high-dose rifampicin and dolutegravir. (**6e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?** 2011–2017: Academic coordinator of PreDiCT-TB consortium (EU funded, public funding only; no direct funding from industry for him or his institution). Since 2017: Academic partner in PanACEA clinical trials consortium (no pharmaceutical funding to him or his institutions). Since 2020: Academic partner in UNITE4TB consortium (EU funded with industry partners; no direct funding from industry). Attended GSK and Janssen advisory meetings with no payment or benefits received.

Assessment	Dr Davies' involvement in publicly funded consortia and his role as a co-investigator on a ViiV Healthcare funded grant, without receiving personal financial benefits, indicates no direct financial conflict of interest. His advisory meeting participation was unpaid.
Conclusion	No significant competing interests.
Expert name	**Greg Fox**
Conflict disclosed	**(2b) Non-monetary support valued at more than US$ 1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)** Dr Fox received an in-kind contribution of US$ 30 000 from Sanofi Pharmaceuticals for the medications to support the research project (clinical trial). There was no personal benefit and no financial contribution. The trial has now finished.
Assessment	The disclosed in-kind contribution of US$ 30 000 from Sanofi Pharmaceuticals provided for a clinical trial on rifapentine, which is not a subject of the TRP update and the support is no longer active.
Conclusion	No significant conflict of interest.
Expert name	**Maria Tarcela Gler**
Conflict disclosed	**(1b) Consulting, including service as a technical or other advisor** **(2a) Research support, including grants, collaborations, sponsorships and other funding** Dr Gler received research support of US$ 2000 from the Gates Medical Research Institute for a qualitative study describing three patient scenarios related to potential LAIs for TB treatment.
Assessment	Although the topic is relevant to the TRP, the amount received is considered insignificant.
Conclusion	No significant competing interests.
Expert name	**Anneke Hesseling**
Conflict disclosed	**(1b) Consulting, including service as a technical or other advisor** Technical advisor for GSK on the ganfeborole clinical development plan, on a once-off basis. **(2a) Research support, including grants, collaborations, sponsorships and other funding** Stellenbosch University receives US$ 750 000 for several investigator-initiated research studies, including with the NIH IMPAACT network, TBTC and Unitaid. The support is ongoing.
Assessment	Dr Hesseling is an academic at Stellenbosch University, a leading teaching and academic institution in South Africa. The university receives annual grants for several investigator-initiated research studies, including from the NIH IMPAACT network, TBTC, Unitaid, British Medical Research Council/Wellcome Trust, and the South African Medical Research Council. These studies focus on therapeutic trials and diagnostics in childhood TB, and although these subgroups may be discussed, this is not a key focus of the TDG. Ganfeborole trial, Phase 2, is focused on early bactericidal activity of oral GSK3036656 in combination with delamanid or bedaquiline, delamanid in combination with bedaquiline, or standard of care in male and female participants aged 18 to 65 years. This study is not directly linked to the primary focus of TRPs of LAIs.
Conclusion	No significant competing interests were identified as the disclosure is not in conflict with the scope of the work of the TDG.

Expert name	Emily Kendall
Conflict disclosed	**(2a) Research support, including grants, collaborations, sponsorships and other funding** Dr Kendall is currently involved in research activities funded by the Gates Foundation and the NIH (USA). As principal investigator for the Gates Foundation, she leads grants on i) modelling resistance risks and diagnostic needs for a pan-TB regimen, and ii) supporting a cohort study to understand the true burden of TB among people with trace Xpert® MTB/RIF Ultra management and guide their clinical management. For the NIH, she is the principal investigator on projects investigating i) the prevalence and incidence of TB among people with trace Xpert Ultra results during community-wide screening; and ii) the implementation and effect of two different approaches to mass digital chest X-ray screening for TB in Uganda. The expert is a co-investigator in modelling roles on NIH grants studying a variety of new TB diagnostics (the R2D2 project) and studying active case-finding for recurrent TB after successful completion of initial treatment. The amount of funding has not been disclosed.
Assessment	The disclosed funding is for research that is non-commercial and not related to LAIs.
Conclusion	No significant conflict of interest.
Expert name	**Graeme Meintjes**
Conflict disclosed	**(1b) Consulting, including service as a technical or other advisor** Dr Meintjes received an honorarium of US$ 5000 for his service as an independent consultant; this has now ceased. He also served as an independent consultant for the Gates Medical Research Institute without financial compensation; this has also ceased.
Assessment	The disclosed funding has ended and was unrelated to LAIs.
Conclusion	No significant conflict of interest.
Expert name	**Eric Nuermberger**
Conflict disclosed	**(1b) Consulting, including service as a technical or other advisor** Dr Nuermberger served on an advisory board for Janssen on two occasions, once in 2021 and once in 2024, receiving a total of US$ 8175. In each case, he served as a consultant in a virtual advisory board meeting to evaluate clinical practice and unmet needs in the prevention and treatment of TB, and provided feedback and advice regarding interpretation of preclinical data, clinical trial designs and target product profiles. **(2a) Research support, including grants, collaborations, sponsorships and other funding** He received research support from Janssen in 2022, and from the Gates Medical Research Institute in 2024. In addition, he is currently receiving support from the TB Alliance; the amount is not specified. He served as principal investigator for these research grants and contracts awarded to Johns Hopkins University. **(4a) Patents, trademarks or copyrights (including pending applications)** The expert is an inventor on a patent application for LAI formulations of diarylquinoline drugs for the prevention and treatment of TB.
Assessment	Dr Nuermberger's 2024 advisory role with Janssen, a developer of LAIs, represents a recent and directly relevant financial relationship. Although the advisory role has now ended, its timing and compensation raise concerns, as the advisory work aligns closely with the TRP meeting's focus. Additionally, he is listed as an inventor on a patent application for LAI formulations of diarylquinoline drugs for the prevention and treatment of TB, a topic that is the subject of the TRP meeting.

Conclusion	Given the direct relevance of both the recent financial relationship and the intellectual property interest to the TRP meeting's topic, Dr Nuermberger will be part of the group as an observer.
Expert name	**Elin Svensson**
Conflict disclosed	**(2a) Research support, including grants, collaborations, sponsorships and other funding** The research unit has received one-time funding of €60 000 from Janssen Pharmaceuticals and US$ 200 000 ongoing from the TB Alliance.
Assessment	Dr Svensson received one-time funding (€60 000) from Janssen Pharmaceuticals to support a research project focused on improving QT correction methods in TB patients and developing a new type of pharmacometric model for TB outcomes. This funding was used to cover the salary of one of her students. She also receives ongoing funding (US$ 200 000) from the TB Alliance for pharmacometrics analyses related to the IMPAACT-TB Alliance pediatric study of pretomanid and for assisting with population pharmacokinetic modelling of TBAJ-876 to inform the design of a drug–drug interaction study. This support is being used to cover a PhD student's salary. Both activities are conducted within Dr Svensson's research unit and are directly related to her academic work. There are no personal or financial interests that could compromise her objectivity in contributing to the review of LAIs. The disclosed relationships do not represent a significant competing interest.
Conclusion	No significant competing interests were identified as the disclosure is not in conflict with the scope of the work of the TDG.

ACTG: Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections; AIDS: acquired immunodeficiency syndrome; DAIDS: Division of AIDS; EU: European Union; FAST-TB: Facilitating Accelerated Science and Translation for TB Regimen Development; GSK: GlaxoSmithKline; HIV: human immunodeficiency virus; IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Network; LAI: long-acting injectable; NIH: National Institutes of Health; QT: time from the start of the Q wave to the end of the T wave on an electrocardiogram; ReLAY: Research to Translate and Yield Evidence into Practice; TB: tuberculosis; TBTC: TB Trials Consortium; TDG: Scientific TRP Development Group; TPT: TB preventive treatment; TRP: target regimen profile; USA: United States of America.

For further information, please contact:
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