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Supplementary information

Anti-tuberculosis treatment strategies and drug development: challenges and priorities

In the format provided by the authors and unedited

Supplementary Table 1: approved 1st, 2nd and 3rd line agents recommended for treatment of active TB (*)

Disease indication	Drug or drug class	Year of discovery/approval	Route of administration	Comments
Drug susceptible TB	Isoniazid (INH)	1952/1952	Oral	Administered as 2 months of INH-PZA-RIF-EMB (intensive phase, approved as Rifater drug combination in 1994) followed by 4 months of INH-RIF (continuation phase).
	Pyrazinamide (PZA)	1952/1953	Oral	
	Rifampicin (RIF)	1966/1974	Oral	
	Ethambutol (EMB)	1961/1968	Oral	
	Rifapentine (RPT)	1965/1998	Oral	
Multidrug resistant (MDR) TB (resistant to INH and RIF) (**)	Fluoroquinolones (levofloxacin, moxifloxacin)	1987/1998, 1991/1999	Oral	
	Aminoglycosides (streptomycin, amikacin)	1946/1947, 1971/1993	Injectable (i.m or i.v.)	Gradually replaced with bedaquiline where available [1]
	Rifabutin (RBT)	1975/1992	Oral	5-10% of RIF-resistant strains are susceptible to and can be treated with RBT
	Capreomycin	1960/1973	Injectable (i.m or i.v.)	
	Pyrazinamide	1952/1953	Oral	
	Ethambutol	1961/1968	Oral	
	Thioamides (ethionamide, prothionamide)	1956/1968	Oral	Date of discovery/approval of prothionamide not available
	Para-amino-salicylate	1944/1950	Oral	
	Cycloserine	1954/1968	Oral	
	Bedaquiline	2004/2012	Oral	
	Nitroimidazole delamanid	2006/2014	Oral	Approved by the EMEA but not the FDA for treatment of MDR-TB
Extensively drug resistant (XDR) TB (resistant to INH, RIF, fluoroquinolones and one injectable) (**)	Nitroimidazole pretomanid	2000/2019	Oral	FDA-approved for highly drug resistant forms of TB in combination with bedaquiline and linezolid
	Clofazimine	1954/1969	Oral	Approved for the treatment of leprosy in 1969; approved for off-label compassionate use (expanded access) against TB
	Linezolid	Mid-1990s/ 2000	Oral	Approved for off-label use only against TB
	MDR-TB drugs as appropriate based on drug susceptibility profile			

(*) See [5] for a recent and comprehensive review.

(**) A 3 to 5 drug regimen is optimized based on the individual's drug susceptibility profile. i.m.: intramuscular; i.v. : intravenous; EMEA: European Medicines Evaluation Agency

Supplementary Table 2: proposed biomarkers of progression from LTBI to active TB

Study type / methodology	Discovery or validation cohorts	Study outcome	references
Immunodiagnostics			
Various interferon-γ release assays (IGRA) used as a baseline "Target Product Profile" by the WHO (*) to benchmark improvements in sensitivity and specificity of new markers	Multiple large cohorts in UK, South Africa, Norway, 10 European countries, and Germany	Limited sensitivity and specificity of IGRAs to predict incipient TB among subjects with LTBI.	6-10 11
IGRA versus tuberculin skin test	Meta-analysis of 15 studies across 4 continents	Highlights the comparable predictive ability of both tests, the limited predictive value of a single test and the need for longitudinal testing to improve accuracy and facilitate interpretation	12
Transcriptomics			
Clinical blood transcriptomics	Compiled analysis of multiple cohorts	Systematic comparison and evaluation of 17 and 7 blood signatures, respectively, of incipient TB, and identification of best performing signatures	13,14,15
Whole blood RNA sequencing	47 progressors and 107 matched controls from Adolescent Cohort Study or ACS [16]	16-gene signature (ZAK16) of risk of progression in the 12 months preceding TB diagnosis	17
Blood transcriptomics of 11 genes selected from ZAK16, by RT-qPCR	2 validation cohorts: (1) 820 HIV-positive subjects, and (2) 764 RISK-positive and 1,784 RISK-negative participants	Validation of an 11-gene signature (RISK11) for diagnosis of symptomatic tuberculosis, and for short-term prediction of incident tuberculosis: RISK11 identified prevalent tuberculosis and predicted risk of progression to incident tuberculosis within 15 months in HIV-positive subjects	18,19 (**)
Blood-based transcriptomics linked to PET/CT findings	10 likely progressors identified by PET/CT among 35	Transcripts of the classical complement pathway and Fcγ receptor 1 overabundant in subclinical stages of disease; validated in HIV-negative cohort from Zak *et al*. [17]	20

	HIV-positive subjects with LTBI		
Whole blood RNAseq, plasma proteome and purified T cell gene expression analysis	44 progressors and 107 matched controls from ACS	Longitudinal blood transcriptional analysis complemented with proteomic analysis of plasma and T cell responses, indicating orchestrated changes that precede progression to TB disease.	[21]
Whole blood RNA sequencing	12 progressors and 48 non-progressors	A 3-gene signature (ROE3) for short term risk of progression within 90 days in HIV-negative subjects (BATF2, GBP5, and SCARF1)	[22]
Whole blood RNA sequencing and RT-qPCR	79 progressors and 328 matched non-progressors from ACS	2- and 4-gene signatures of risk to progression in 3 to 24 months preceding TB diagnosis	[23 24]
Blood RNA sequencing and RT-qPCR in adolescents	43 progressors among 144 adolescents with LTBI [(***)]	Validation of a 3-gene signature – initially discovered to distinguish active TB from healthy individuals – to predict risk of progression to active TB	[25,26]
RNAseq of peripheral blood mononuclear cells	16 progressors and 21 non-progressors for the new signature discovery set	Evaluated the predictive performance of six published signatures on the transcriptional profiles of peripheral blood mononuclear cells from progressors and non-progressors during a five-year follow-up, and derived a new 29-gene signature that predicts progression up to 5 years prior to disease development	[27]
Blood transcriptomics by RT-qPCR	ACS as discovery cohort; 7 large validation cohorts	A 6-gene transcriptomic signature of TB disease risk, validated by blind application using microfluidic qRT-PCR to samples from seven different cohorts	[28]
Blood transcriptomic analyses of human, mouse, and macaque samples	ACS (46 progressors and 107 matched controls), mouse: 16 progressors,13 controllers, 10 naïve; macaque: 8 progressors, 4 controllers, 4 naïve.	From [21] and [28], identified differentially expressed genes in controllers and progressors across species, and defined a TB risk signature gene in humans, mice and macaques	[29]
Genetics			
Genome Wide Association Study	2175 early progressors and 1827 non-	Identified variants of monocyte-specific regulatory element in 3q23	[30]

	progressing household contacts		
Epigenetics and proteomics in monocytes and granulocytes	8 active TB and 8 LTBI	Pilot study linking DNA methylome, transcriptome and proteome to distinguish LTBI from active TB	[31]
Proteomics			
Highly multiplexed proteomic assay (SOMAscan) to quantify 3,000 human proteins in plasma	ACS (44 progressors and 107 matched controls) for discovery; 1,948 HIV-negative household TB contacts for validation	Identified a 5-protein signature, TB Risk Model 5 (TRM5), and 3-protein signature, 3-protein pair-ratio (3PR) with excellent predictive value within 6 months of active TB diagnosis	[32]
Imaging			
PET-CT imaging	35 HIV-positive subjects with LTBI	10 subjects with subclinical TB identified by PET/CT, progression to active TB not assessed	[33]
PET/MRI imaging	30 household contacts of active TB index cases	Identified abnormalities in asymptomatic patients indicative of subclinical TB; no significant correlation between presence of PET/MRI abnormalities (SUVmax values) and initial quantitative IGRA values	[34]
PET-CT/MRI across species	Not included, study compilation	Exhaustive review covering PET, MRI and/or CT imaging in mouse, rabbit, and non-human primate models, and in TB patients, as (i) a tool to study and predict progression to active disease, (ii) a biomarker of treatment response and relapse, (iii) a patient stratification tool for clinical trials, and (iv) a modality to measure vaccine efficacy.	[35]

(*) https://apps.who.int/iris/bitstream/handle/10665/259176/WHOHTM-TB-2017.18-eng.pdf?sequence=1

(**) see appendix to [15] for a comparison of individual signature performance to the WHO Target Product Profile criteria

(***) this was the validation cohort. The discovery cohort in [26] included n = 1023 samples

Supplementary Table 3: Selected animal models used to evaluate drug efficacy against active TB and/or penetration at the site of disease

Species and Model	Relative cost/Duration	Compound requirements (*)	Major Read-out(s)	Strengths	Limitations	References
Zebrafish (larvae)	+ / 1-2 weeks	≤ 1 mg	Survival, fluorescence as a surrogate of CFU	Amenable to medium throughput drug screening	Absence of pulmonary site of infection	36,37
BALB/c acute model of low dose aerosol infection	++ / 2 months	≤ 1 g	Δ lung CFU of treated versus control in the fast-replicating phase of infection	Rapid, low cost, modest space requirements; large body of published data available as benchmark	Lack of necrotic lesions and cavities	38,39
BALB/c chronic model of low dose aerosol infection	++/ 3 months	≤ 1 g	Δ lung CFU of treated versus control in the slow/non-replicating phase of infection			
BALB/c relapse model	+++/8-12 months	6-10 g	Δ lung CFU, relapse rate following varying treatment durations	Exhaustive body of data available with single drugs and drug combinations; Reasonably predicts relapse in patients		
C3HeB/FeJ necrotic lesion model	+++ / 4-6 months	1-3 g	Δ lung CFU and relapse rates; site-of-disease pharmacokinetics	Presence of large necrotic lesions; pathology variability delivers bimodal response of drug efficacy in necrotic versus cellular lesions (two models in one)	Large sample size required due to varying pathology; model is very sensitive to strain and inoculum size (inter-lab reproducibility is a challenge)	40-43
Guinea pig model	+++ / 4-5 months	10-20 g	Δ lung CFU	Presence of cellular, caseating and calcified granulomas	Limited body of efficacy data to estimate the predictive value of the model; used more frequently to evaluate vaccine than drug efficacy	44-46
Rabbit cavitary model	+++ / 5-6 months	20-200 g	single lesion CFU; site-of-disease pharmacokinetics	Presence of cellular, necrotic, cavitating granulomas and open cavities	Not validated for efficacy studies of drug regimens	47-50

Marmoset model of active TB	++++ / 5-6 months	10-20 g	single lesion CFU; corresponding ^{18}FDG uptake by PET as a measure of lesion-associated inflammation; volume of disease by CT	Recapitulates major human pathology features; PET-CT read out allows for longitudinal evaluation and reduced numbers of animals; small animal size (~ 500 g)	Cost, bioethics, model validation still in progress	[51,52]
Macaque model of active TB	+++++ / 6-12 months	50-300 g	Same as above; relapse following SIV infection	Same as above; ability to co-infect macaques with SIV to model HIV co-infection	Cost, space requirements, bioethics	[53-55]

(*) conservative estimates based on average sample size, average human equivalent dose, and treatment duration recorded in the literature; CFU: colony forming unit; PET: positron emission tomography; ^{18}FDG: fluoro-deoxy-glucose (PET tracer); CT: computerized tomography; NHP: non-human primate; SIV: Simian Immunodeficiency Virus.

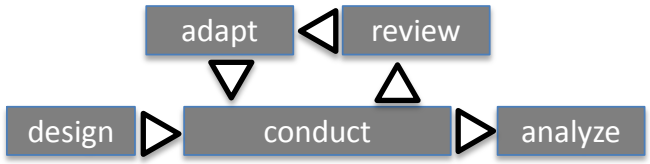
Supplementary Box 1 | Propose, apply, and endorse new clinical trial designs to improve the pace of regimen development

Adaptive trial designs rely on accumulated data and interim analyses to make preplanned adaptations, such as stopping an arm early for futility or safety and increasing allocation ratios to best performing arms. They are usually more efficient and informative than traditional fixed designs, offer savings in time, resources, and sample size [2]. One such adaptive design applied to TB trials is the Multi-Arm Multi-Stage (MAMS) concept, under which multiple treatment options are compared simultaneously, against a control arm. These can either be different drug combinations, doses, or treatment durations. Through interim analyses with predetermined adaptation rules, randomization can be adjusted to reallocate patients to most effective or least toxic regimens [3]. MAMS has been applied to inventive Phase II trials such as TRUNCATE-TB (https://www.newtbdrugs.org/pipeline/trials/truncate-tb).

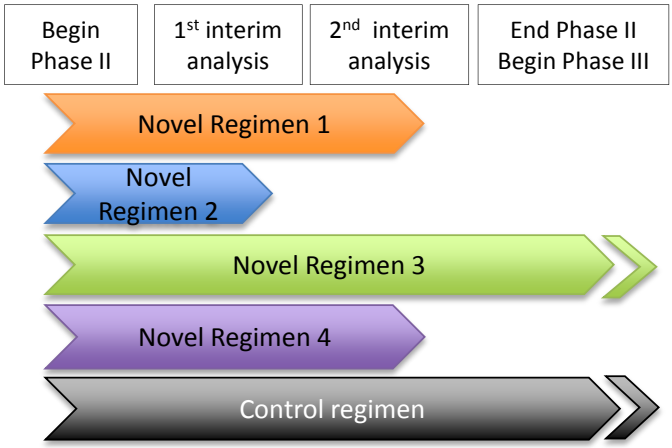
A new Phase IIC trial design has been created specifically in the context of TB to accelerate regimen development: the Selection Trial with Extended Post-treatment follow-up (STEP) [4]. Experimental regimens are given for the duration for which they will be studied in phase III and patients are followed for clinical outcomes of treatment failure and relapse for a total of 12 months from randomization. Collection of clinical outcome data in a relatively small number of participants over only 12 months provides information about the likelihood of success of each arm in a phase III trial. MAMS and STEP can be sequentially combined to accelerate both Phase II and III trials.

In the figure below, the adaptive design principle (a), MAMS (b), STEP (c) and a two stage STEP-to-STEP (d) schematic designs are shown. In the STEP-to-STEP stage 1, two new regimens are compared side-by-side to the standard of care, leading to go/no go decisions and if appropriate, the selection of best performing new combination at the completion of the 12-month follow up. In stage 2, different durations of the selected regimen are tested to identify the shortest treatment duration delivering non-inferiority results.

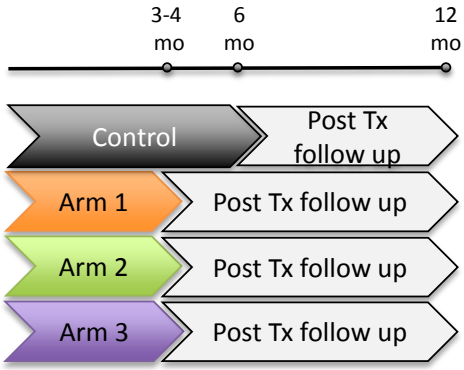
a Adaptive trial design



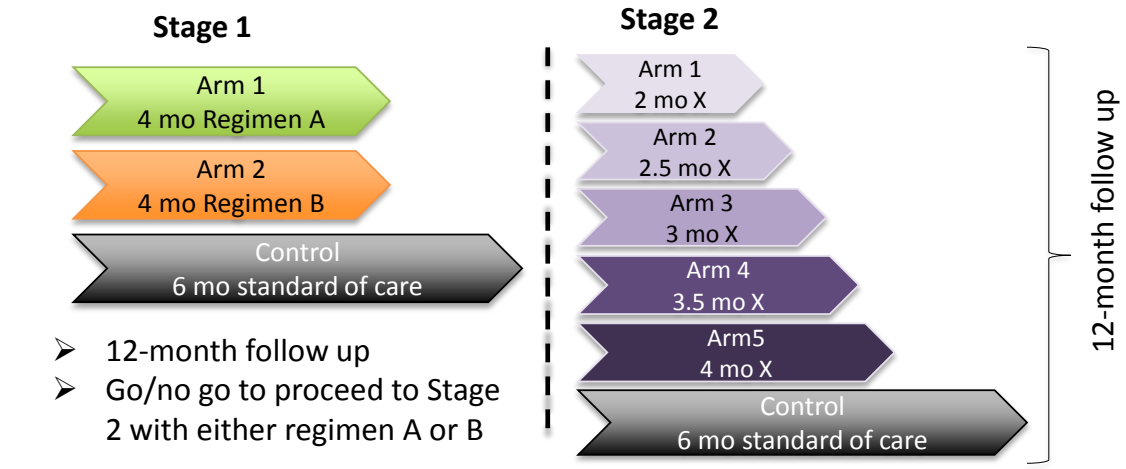
b MAMS design



c STEP design



d STEP to STEP design



- 12-month follow up
- Go/no go to proceed to Stage 2 with either regimen A or B

Panel c reprinted from ref 4, CC BY 4.0

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