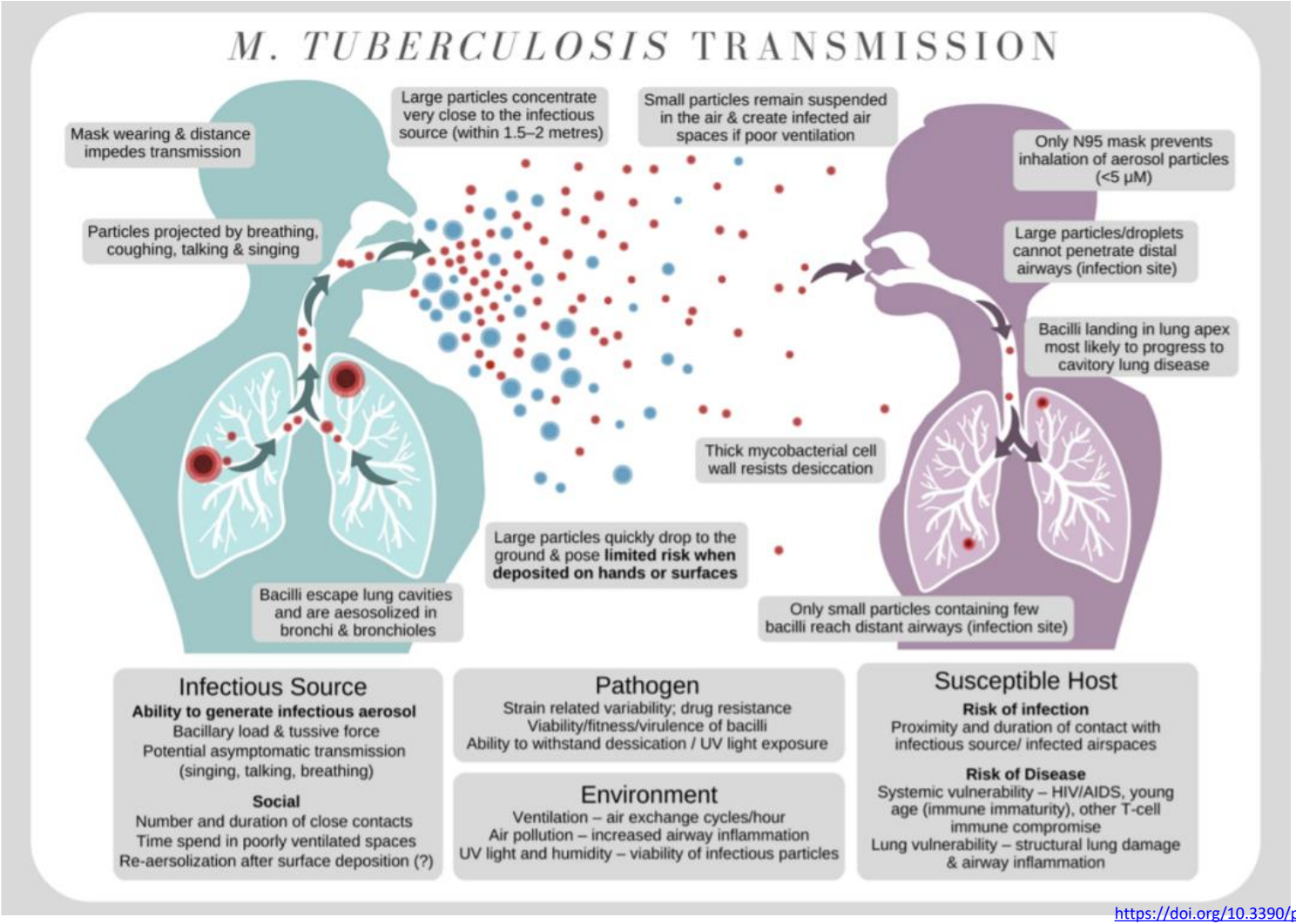
Tuberculose

Pr Elisabeth Botelho-Nevers

Service d'Infectiologie, CHU de Saint-Etienne
Inserm CIC 1408- Axe Vaccinologie, I-Reivac, Covireivac
Team GIMAP, CIRI, Inserm, U1111, CNRS, UMR530
Chaire Prévention, Vaccination, Contrôle de l'Infection PRESAGE

Diplôme Universitaire de Thérapeutiques Anti-Infectieuses
Université Grenoble Alpes
1ère session – Janvier 2024

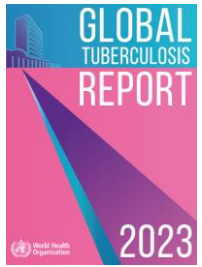


https://doi.org/10.3390/pathogens11111228

DONNÉES ÉPIDEMIOLOGIQUES

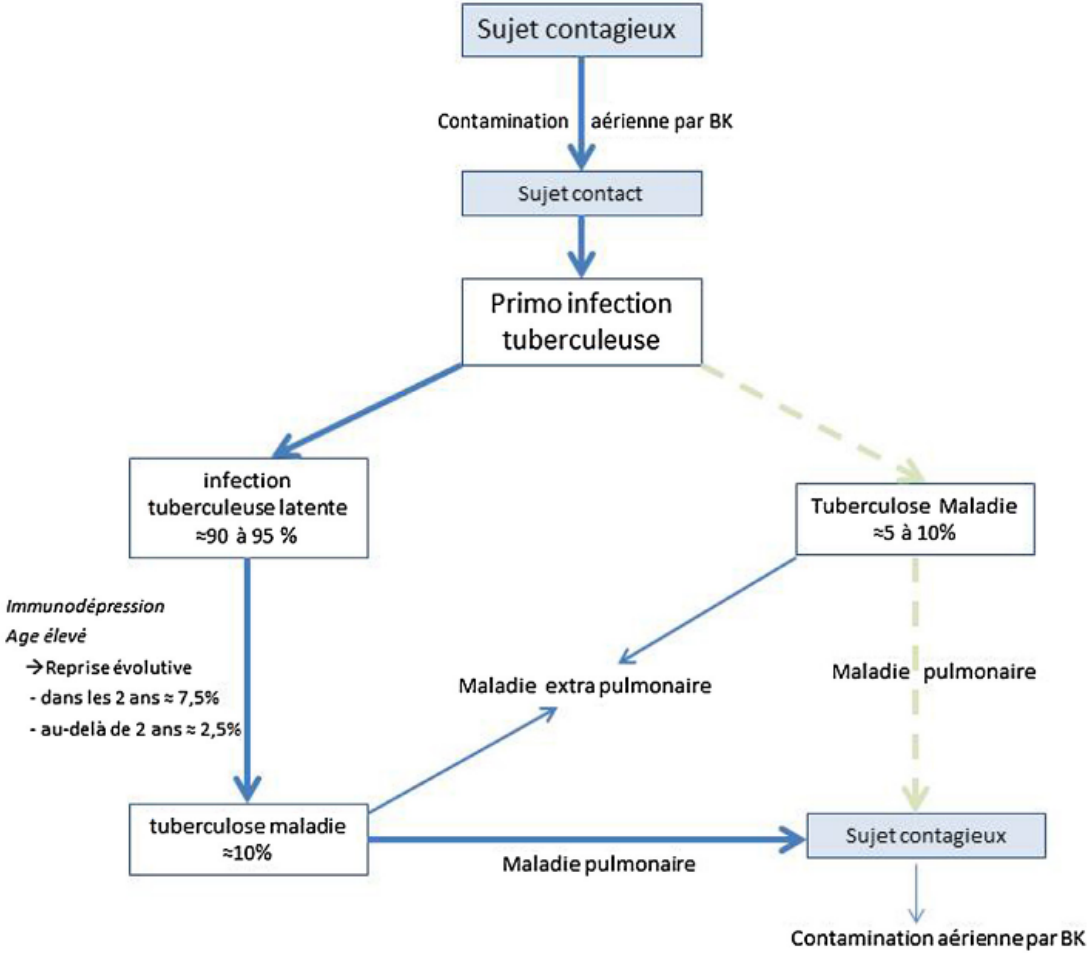
Quelques faits marquants

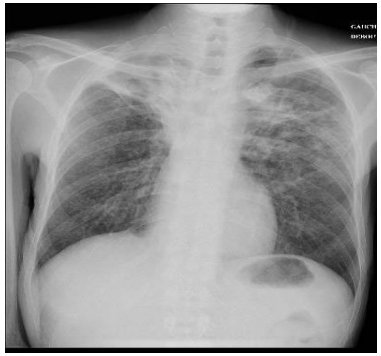
- Environ ¼ de la population mondiale a été infecté par la tuberculose.
- 5 (-10%) d'entre eux feront une tuberculose maladie dans leur vie, risque accru dans les 2 ans
- En l'absence de traitement à 5 ans, 50% des patients avec une tuberculose pulmonaire BAAR+ décédent. Avec un traitement recommandé 85% guerison
- En l'absence de traitement, une personne ayant une tuberculose pulmonaire active contagieuse peut infecter en moyenne 10 à 15 autres personnes/ an
- 2ère cause infectieuse de mortalité dans le monde en 2022

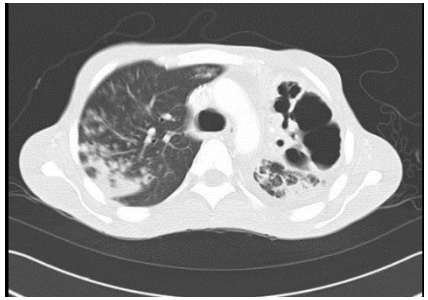


https://iris.who.int/bitstream/handle/10665/373828/9789240083851-eng.pdf?sequence=1

https://www.has-sante.fr/upload/docs/application/pdf/2023-09/evaluation_des_strategies_de_depistage_et_de_reperage_precoce_de_la_tuberculose_pulmonaire_-_note_de_2023-09-07_09-30-39_346.pdf







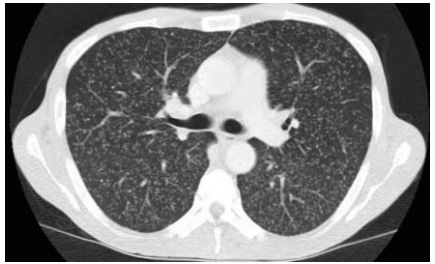
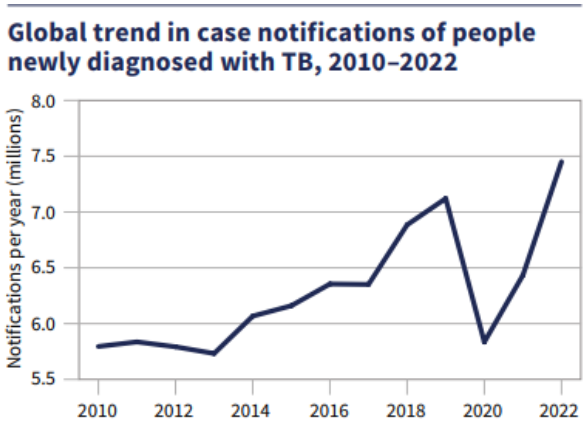


Fig. 1. Histoire naturelle de la tuberculose. BK : bacille de Koch.

Quelques faits marquants

- Impact de la pandémie COVID-19



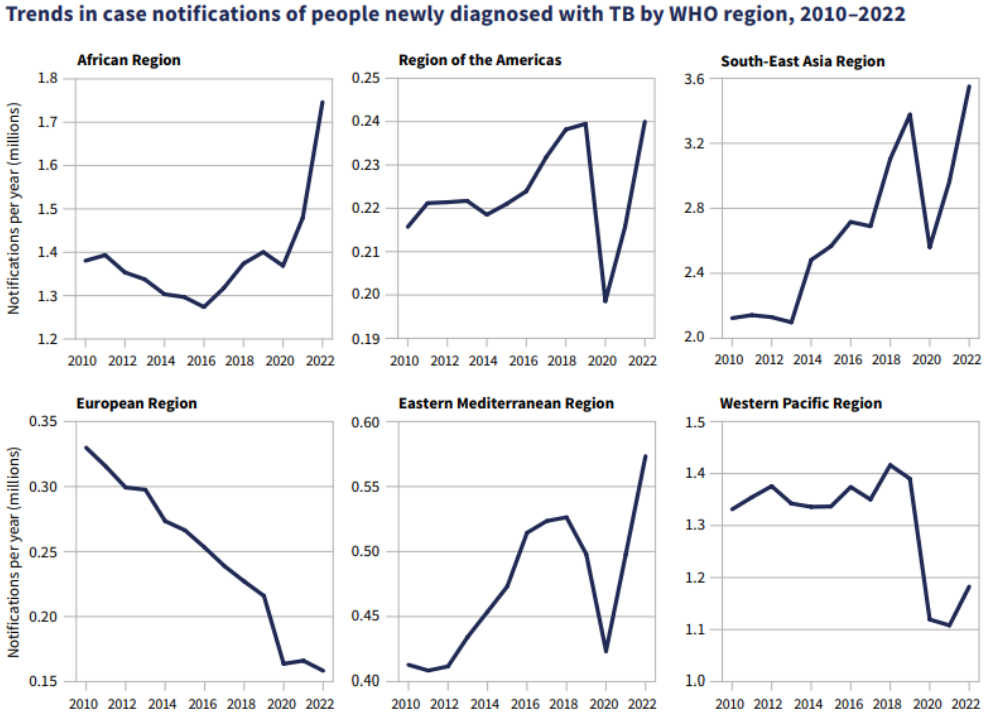
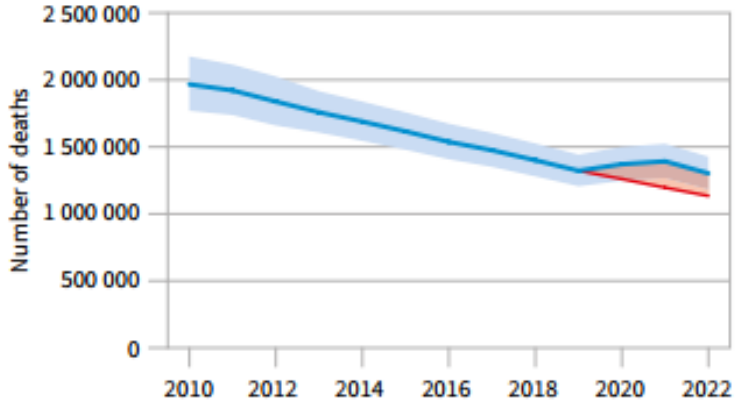


FIG. 6

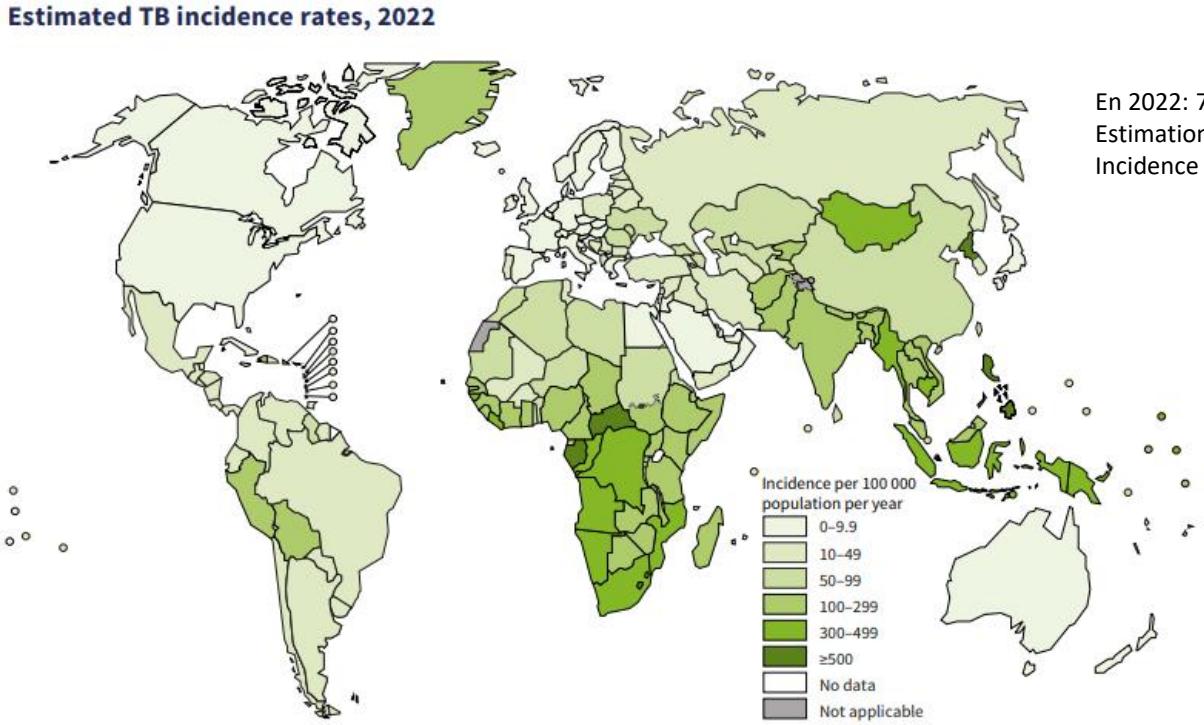
Estimated number of excess TB deaths during the COVID-19 pandemic and its aftermath

The **blue** shaded area represents the 95% uncertainty interval of the actual number of deaths estimated to have been caused by TB; the **red** line shows the estimated number of deaths that would have been caused by TB in the absence of the COVID-19 pandemic; the **red** shaded area shows the excess number of deaths caused by TB due to disruptions associated with the COVID-19 pandemic.



≈2020-2022: 1 million de morts en excès

Quelques faits marquants



En 2022: 7,5 millions de cas diagnostiqués
Estimation de 10,6 millions infections (95% UI: 9.9–11.4 millions)
Incidence estimée est de 133/100 000 (95% UI: 124–143) en 2022.

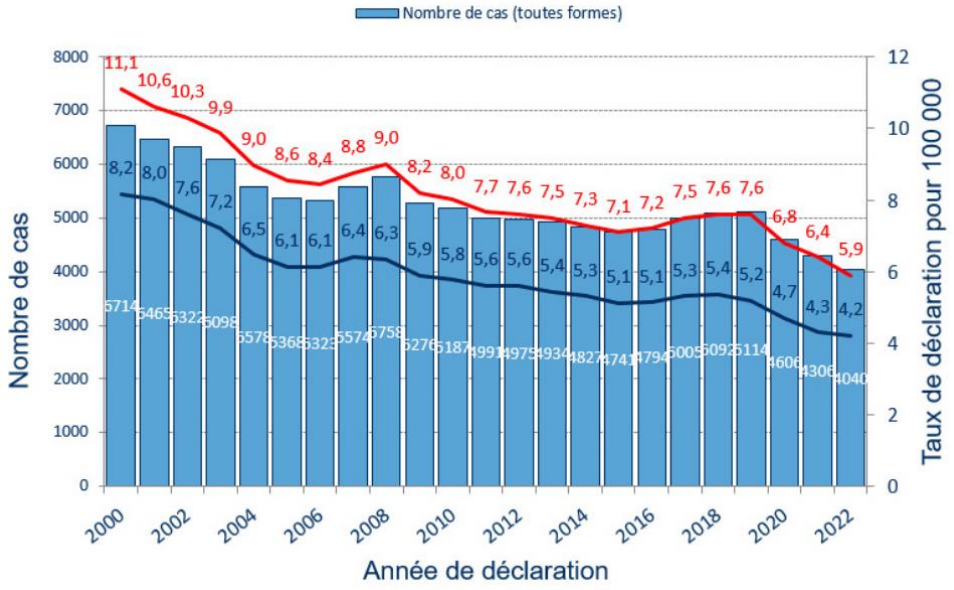
Disparités populationnelles

- Population générale : 6,8 / 100 000
- Migrants : 34 / 100 000
- Sans domicile fixe : 170 / 100 000
- Détenus : 64 / 100 000

Disparités territoriales

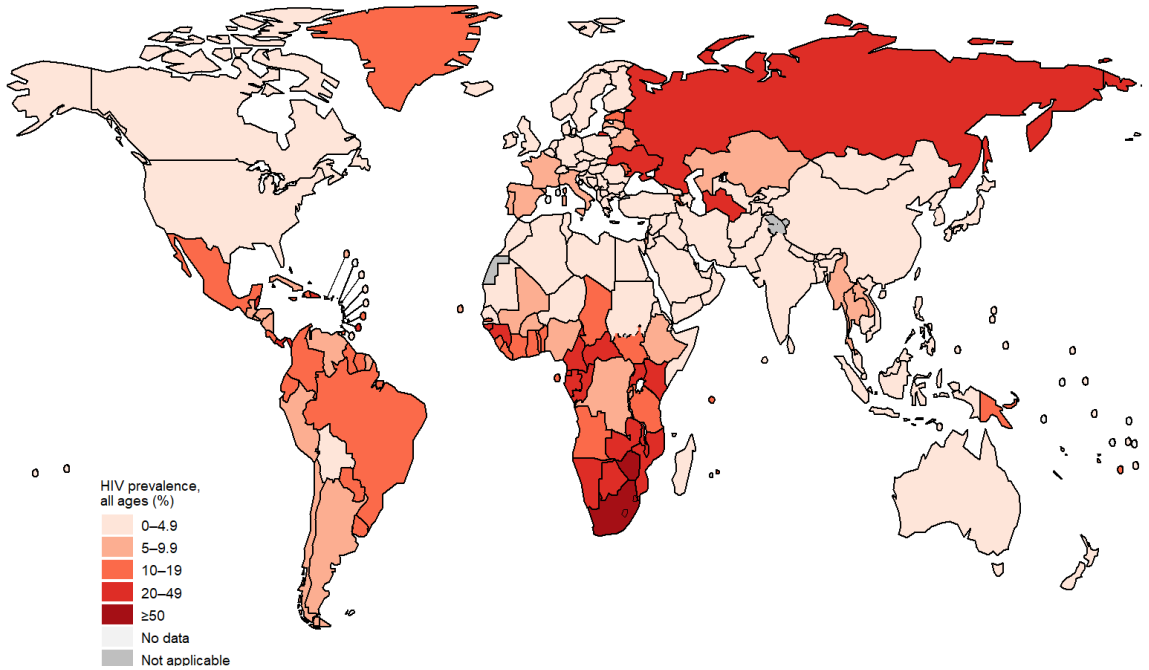
- Guyane : 22,5 / 100 000
- Ile-de-France : 14,3 / 100 000
- Mayotte : 15,1 / 100 000
- Seine-Saint-Denis : incidence ≥ 4 fois le niveau national (23,8 / 100 000)

Figure 2. Tuberculose en France : les chiffres 2020 (9)



https://www.has-sante.fr/upload/docs/application/pdf/2023-09/evaluation_des_strategies_de_depistage_et_de_reperage_precoce_de_la_tuberculose_pulmonaire_-_note_de_2023-09-07_09-30-39_346.pdf

Poids de la co-infection VIH

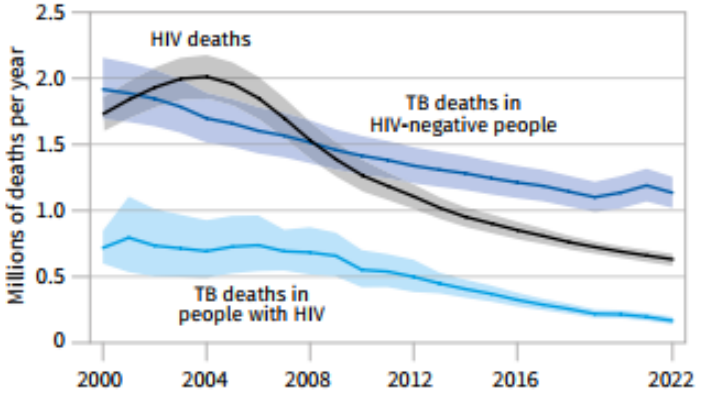


Mortalité de la Tuberculose

FIG. 7

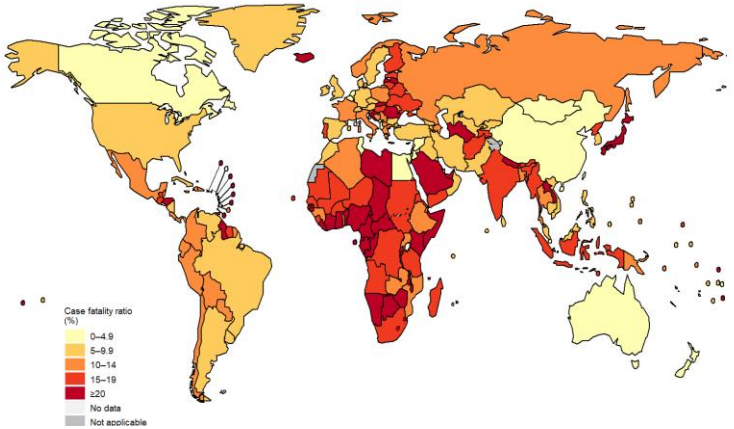
Global trends in the estimated number of deaths caused by TB and HIV (in millions),[a,b] 2000–2022

Shaded areas represent 95% uncertainty intervals.



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2022 that have been published by UNAIDS are available at http://www.unaids.org/en/ (accessed 15 August 2023). For TB, the estimates for 2022 are those published in this report.

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



≈ 1.30 million décès (95% UI: 1.18–1.43 million)

Résistance aux anti-tuberculeux

Extensively drug-resistant TB (XDR-TB): 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 (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).

MDR/RR-TB: refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid.

Pre-extensively drug-resistant TB (pre-XDR-TB): 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).

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.

Avant 2022

Tuberculose ultra-résistante:

- Résistance aux FQ
- ET Résistance à un agent injectable: capréomycine, kanamycine, amikacine

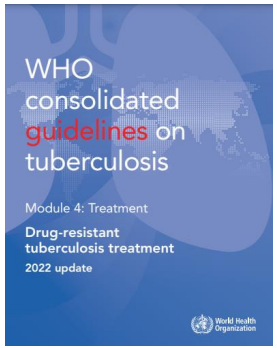
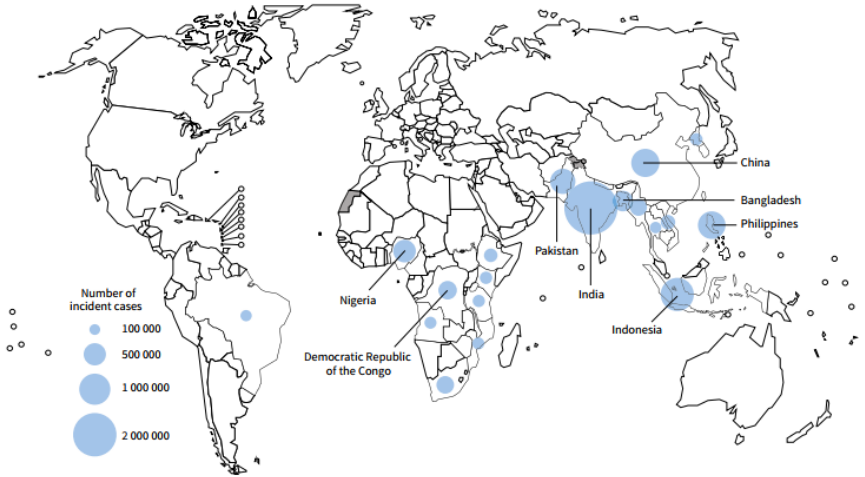


Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

Estimated number of incident TB cases in 2022, for countries with at least 100 000 incident cases[a]



- Seules 2/5 personnes avec une tuberculose pharmacorésistante environ ont eu accès au traitement en 2022.
- En 2022, 3.3% (95% UI: 2.6–4.0%) des nouveaux cas de TB ont une MDR/RR-TB et 17% (95% UI: 11–23%) parmi ceux pré-traités

Estimated number of people who developed MDR/RR-TB (incident cases) in 2022, for countries with at least 1000 incident cases[a]

[a] The eight countries ranked in descending order of the total number of RR-TB incident cases in 2022 are India, the Philippines, the Russian Federation, Indonesia, China, Pakistan, Myanmar and Nigeria.

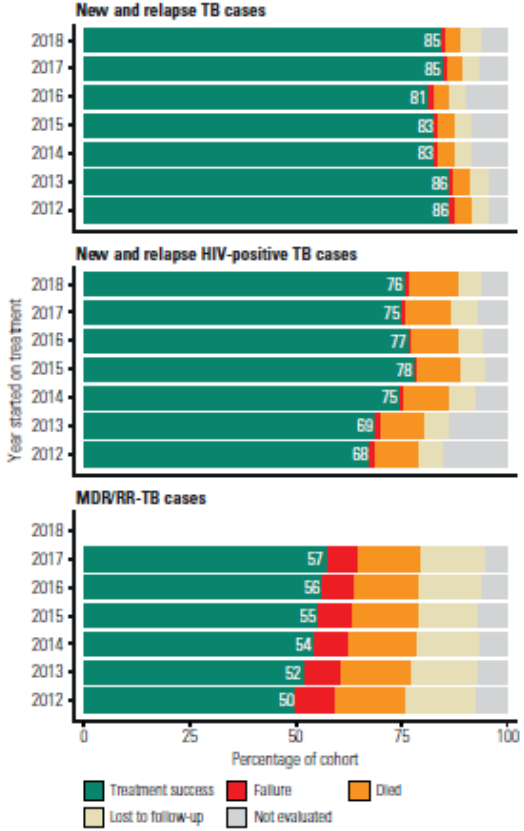
≈410 000 personnes (95% UI: 370 000– 450 000) ont developpé un MDR/RR-TB en 2022

Résistance aux anti-tuberculeux

Impact majeur sur la mortalité liée à la tuberculose

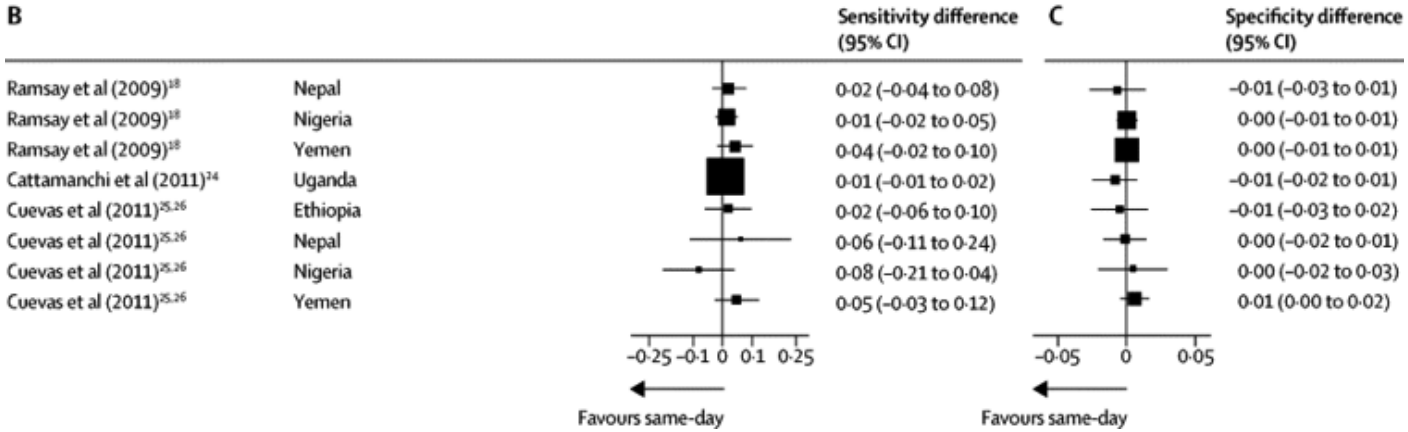
FIG. 5.30

Treatment outcomes for new and relapse TB cases, new and relapse HIV-positive TB cases, and MDR/RR-TB cases, globally[a], 2012–2018



PERFORMANCES DES TESTS DIAGNOSTIQUES

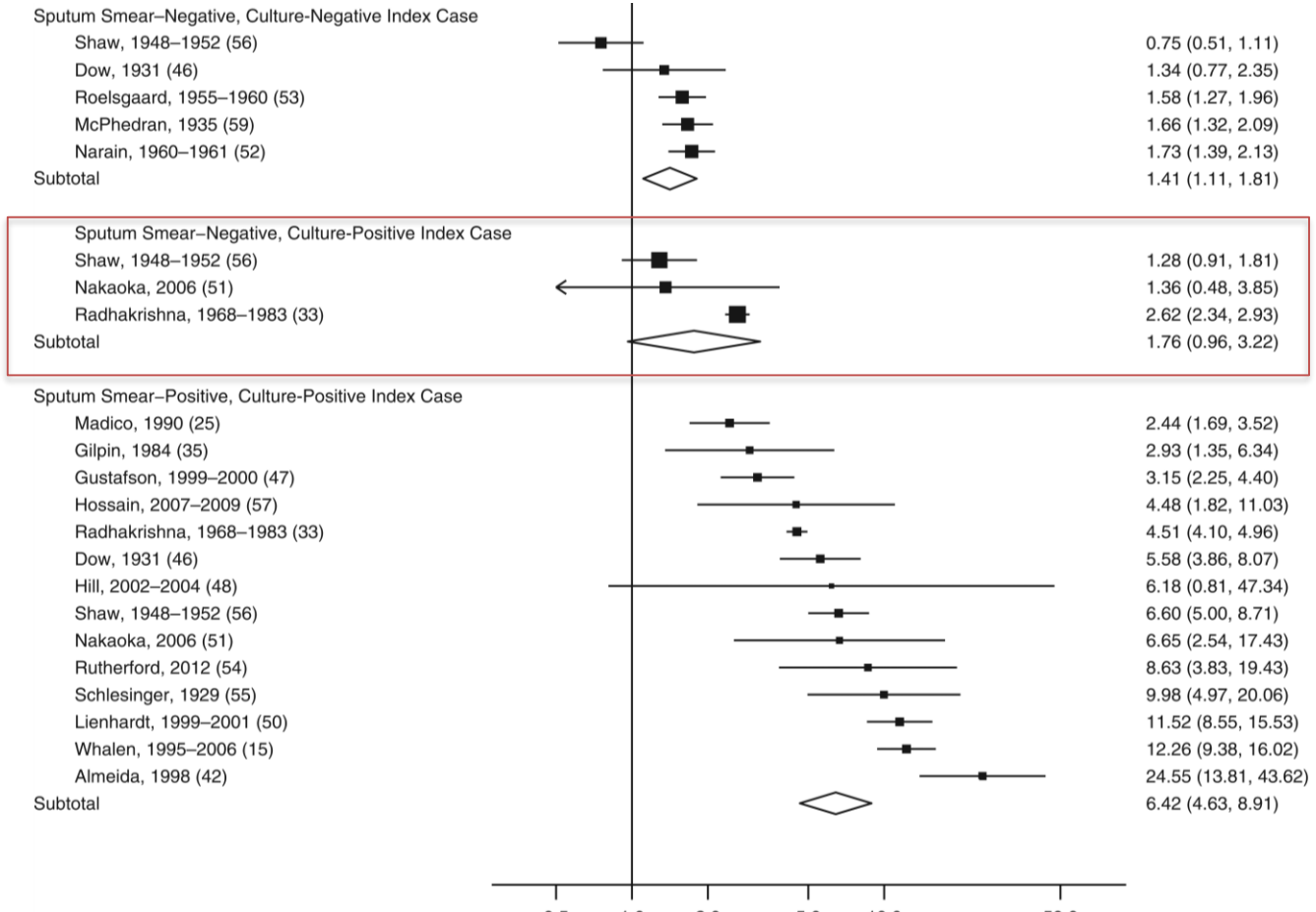
A propos des crachats



Davis et al. Lancet Infectious Diseases 2013

Sensibilité de l'examen des crachats 2 crachats le même jour versus 1 crachat deux jours de suite

Crachats et risque de transmission (Martinez et al. American journal of epidemiology 2017)



Adénosine déaminase

	TB neuro-méningée	Péricardite	Tuberculose péritonéale	Pleurésie
Sensibilité	89 %	95 %	82 %	93 %
Spécificité	91 %	84 %	79 %	87,3 %
VPP	89 %	72 %	86 %	21 %
VPN	88 %	98 %	74 %	99 %

Concentration élevée en faveur dune tuberculose

Pormohammad et al. J Infection 2017
Pandie et al. BMC medicine 2014
Young-Lee Journal of Infection 2015
Blakiston JCM 2018

PCR Gene Xpert

	Neuro-méningée	Péricardite	Tuberculose péritonéale	Pleurésie	Génito-urinaire	GGS	Os
Se	71 %	66 %	59 %	51 %	83 %	87 %	92 %
Spé	98 %	96 %	98 %	99 %	99 %	79-86%	82 %

La prévalence de la maladie affecte la sensibilité et la spécificité.
En zone de faible prévalence, réduction de la sensibilité…

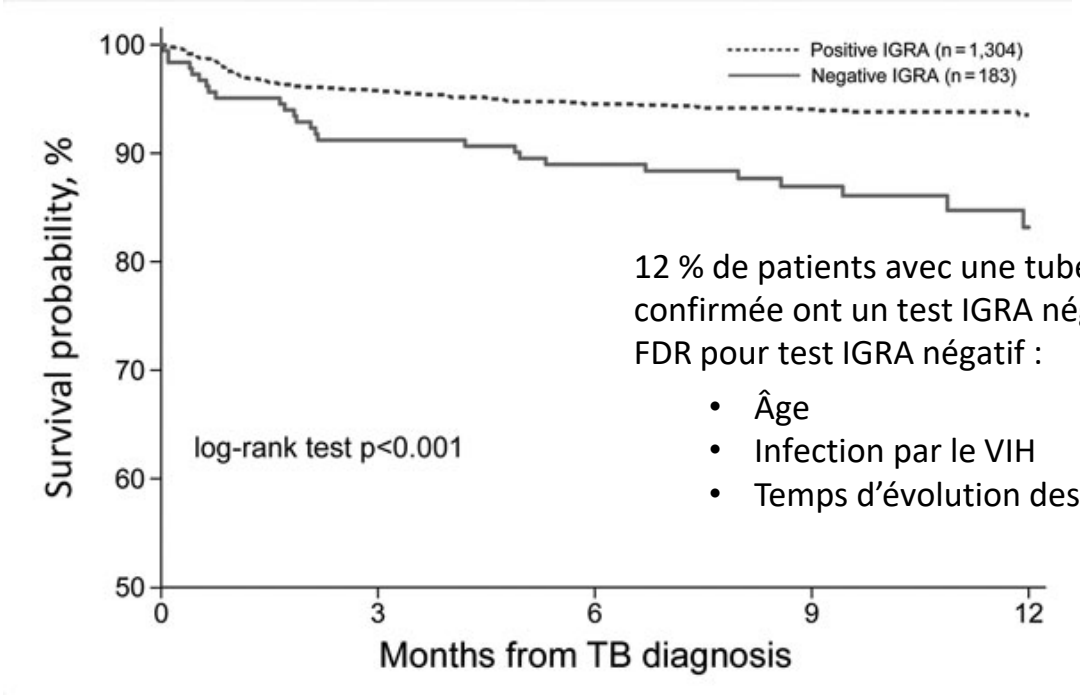
Méta-analyse Cochrane Juillet 2018

Test IGRA:
diagnostic de tuberculose maladie

Sensibilité	88 %
Spécificité	60 %
VPP	81 %
VPN	70 %

Du et al. Scientific reports 2018

Test IGRA: trop souvent négatif en cas de tuberculose maladie



12 % de patients avec une tuberculose confirmée ont un test IGRA négatif
FDR pour test IGRA négatif :

- Âge
- Infection par le VIH
- Temps d'évolution des signes cliniques

N'Guyen Emerging Infectious Diseases 2018

Surveillance

Surveillance minimale du traitement d'une tuberculose pulmonaire.

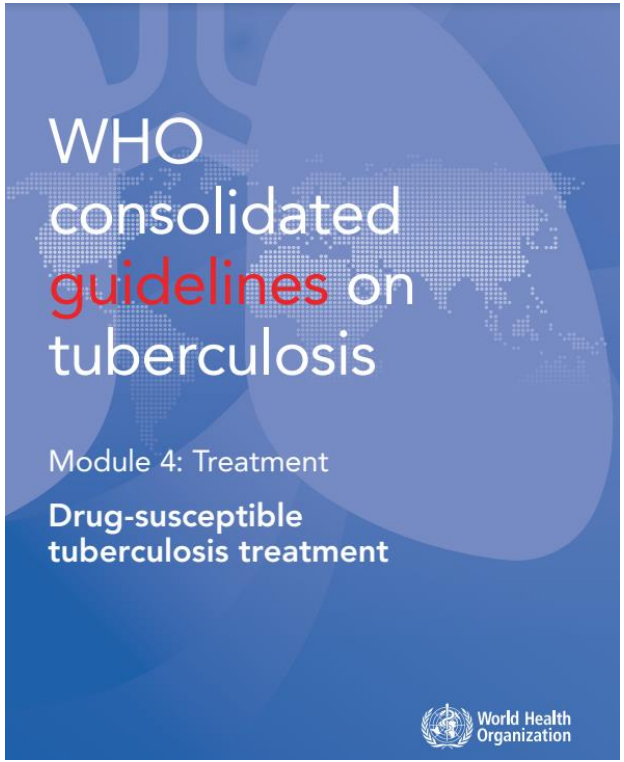
	Initial	J 10-15	J 30	M2	M4	M6	M9	M12-18
Consultation	∴	∴	∴	∴	∴	∴	∴	∴
Bactériologie	∴	❖		∴		∴ si expectoration		
Radio thorax	∴	∴	∴	∴ si expectoration	∴	∴	∴	∴
Transaminases	∴	∴	∴	∴				
Uricémie	∴			si anomalie				
Créatinémie	∴							

❖ L'examen bactériologique précoce entre le 10e et 15e jour de traitement est indiqué chez les malades hospitalisés en isolement afin de vérifier la négativation de l'examen micoscopique.

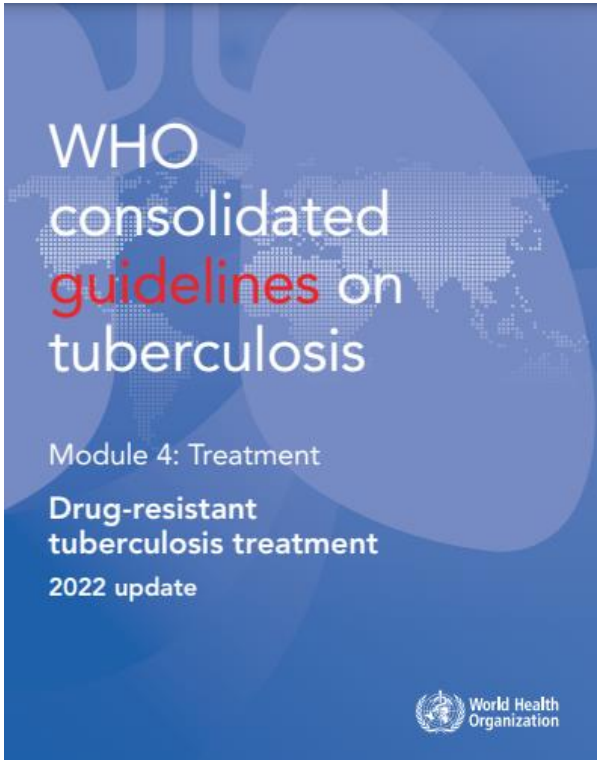
Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

PRISE EN CHARGE THÉRAPEUTIQUE

Prise en charge thérapeutique



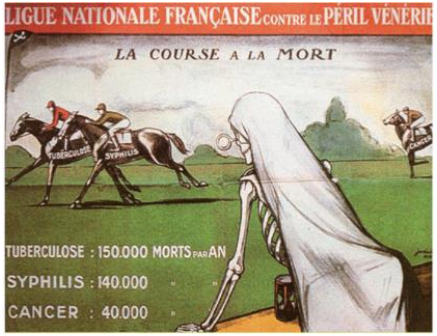
https://www.who.int/publications/i/item/9789240048126



https://www.who.int/publications/i/item/9789240063129

Un peu d’histoire

- 1890: identification de *Mycobacterium tuberculosis* par Robert Koch.
- Juillet 1921:
  - Première utilisation du BCG par voie orale
  - Vaccination rapidement déployée chez les nouveaux-nés
- 1944: premier traitement antibiotique disponible

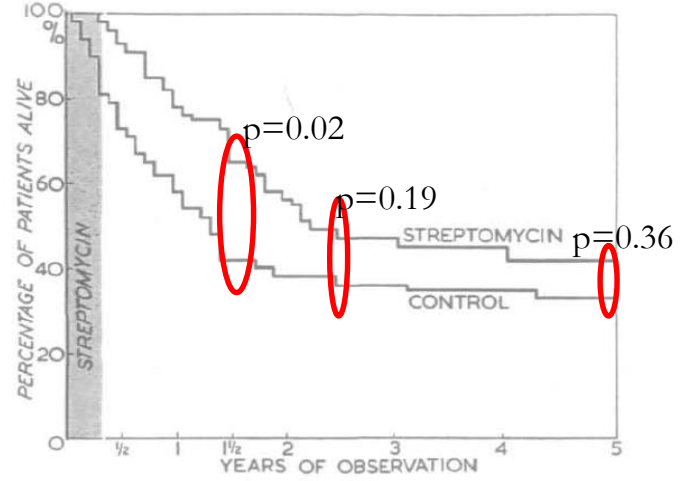


A FIVE-YEAR ASSESSMENT OF PATIENTS IN A CONTROLLED TRIAL OF STREPTOMYCIN IN PULMONARY TUBERCULOSIS[1]

Report to the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council

1954

By WALLACE FOX, IAN SUTHERLAND, AND THE LATE MARC DANIELS



Percentage survival in streptomycin and control series for a five-year period (55 streptomycin and 52 control patients).

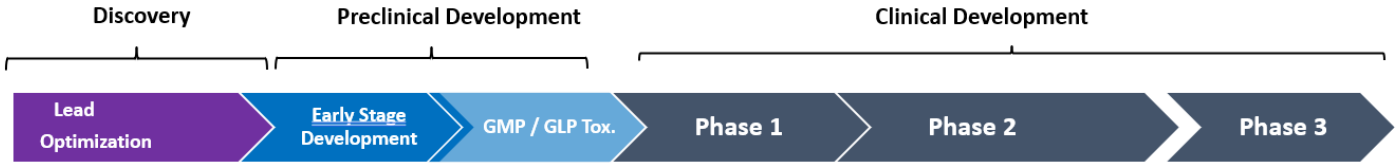
Antituberculeux (abréviations)	**Année de découverte**
Streptomycine (SM)	1944
Acide para-aminosalicylique (PAS ou P)	1945
Thioacétazone (TB1 ou T)	1946
Néomycine	1949
Viomycine (VM ou V)	1951
Isoniazide (INH ou H)	**1952**
Pyrazinamide (PZA ou Z)	**1952**
Thiocarbanilide	1953
D-cyclosérine (CS ou C)	1955
Ethionamide (ETA ou ET)	1956
kanamycine (KM ou K)	1957
Ethambutol (EMB ou E)	**1961**
Capréomycine (CM ou Cm)	1962
Prothionamide	1963
Rifampicine (RMP ou R)	**1967**
Amikacine	1972
Ofloxacine (fluoroquinolone)	1985

Linezolide 2001
Moxifloxacine 2001
Bédaquiline 2014
Delamanide 2016
Pretomanide 2020

Antibiotiques	Activité sur les bacilles			Proportion de mutants résistants au sein d'une population sensible	Apport dans le traitement
	À multiplication active (caverne) ~10^8 bacilles	À multiplication lente			
		À pH acide (macrophage) ~10^5 bacilles	À pH neutre (foyers caséeux) ~10^5 bacilles		
Isoniazide (INH)	++	+	0	10^{-6}	Antibiotique le plus rapidement bactéricide
Rifampicine (RMP)	++	+	+	10^{-7}	18 mois -> 9 mois
Pyrazinamide (PZA)	0	++	0	> 10^{-5}	9 mois -> 6 mois
Éthambutol (EMB)	±	±	0	10^{-6}	Empêche sélection de RMP-R si résistance primaire à INH

+, ++ : activité bactéricide ; ± : activité bactériostatique ; 0 : pas d'activité.

2023 Global New TB Drug Pipeline[1] Updated 11/1/2023



Lead Optimization

- Indazole sulfonamides
- Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors
- Mtb energy metabolism
- Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP
- Oxazolidinones
- DnaE1 / Nargenicin analogs

Early Stage Development

- FIM-253
- TBD10 (MK-3854)
- CLB-073*
- SPR720*
- MPL-447*
- JSF-3285*
- CPZEN-45*
- NTB-3119*
- MBX-4888A (1810)*
- FNDR-20364*

GMP / GLP Tox.

- GSK-839*
- OTB-658

Phase 1

- TBD09 (MK-7762)
- GSK-286*
- TBAJ-587
- TBI-223
- Macozinone* (PBTZ-169)

Phase 2

- Telacebec* (Q203)
- Alpibectir (BVL-GSK098)*
- TBAJ-876
- Sanfetrinem
- Delpazolid, Sutezolid, Tedizolid
- BTZ-043*
- TBA-7371*
- Quabodepistat (OPC-167832*)
- Ganfeborole (GSK-656*/070)
- Pyrifazimine (TBI-166)
- SQ-109*

Phase 3

- Sudapyridine (WX-081)

Regulatory Market Approvals

- Bedaquiline*
- Delamanid*
- Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

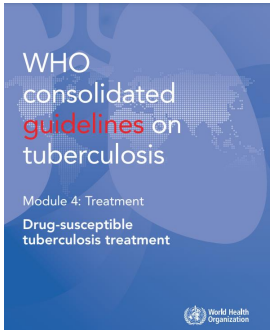
WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2023

TUBERCULOSE SENSIBLE

Treatment of drug-susceptible TB using 6-month regimen



Recommendation 1.

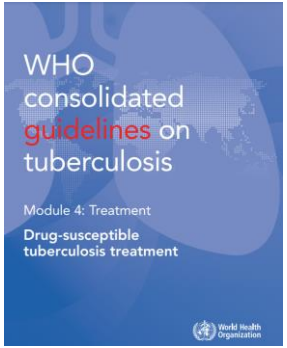
New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (strong recommendation, high certainty of evidence)

Recommendation 4.

The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB (conditional recommendation, low certainty of evidence)

Tuberculose sensible

- Rifampicine/ isoniazide/ éthambuthol /pyrazinamide 2 mois puis Rifampicine/ isoniazide 4 mois
  - Prise quotidienne
  - Préférer les associations
- Indication de Vit B6: femmes enceintes, allaitantes, infection VIH, éthylisme, diabète, malnutrition, insuffisance rénale.

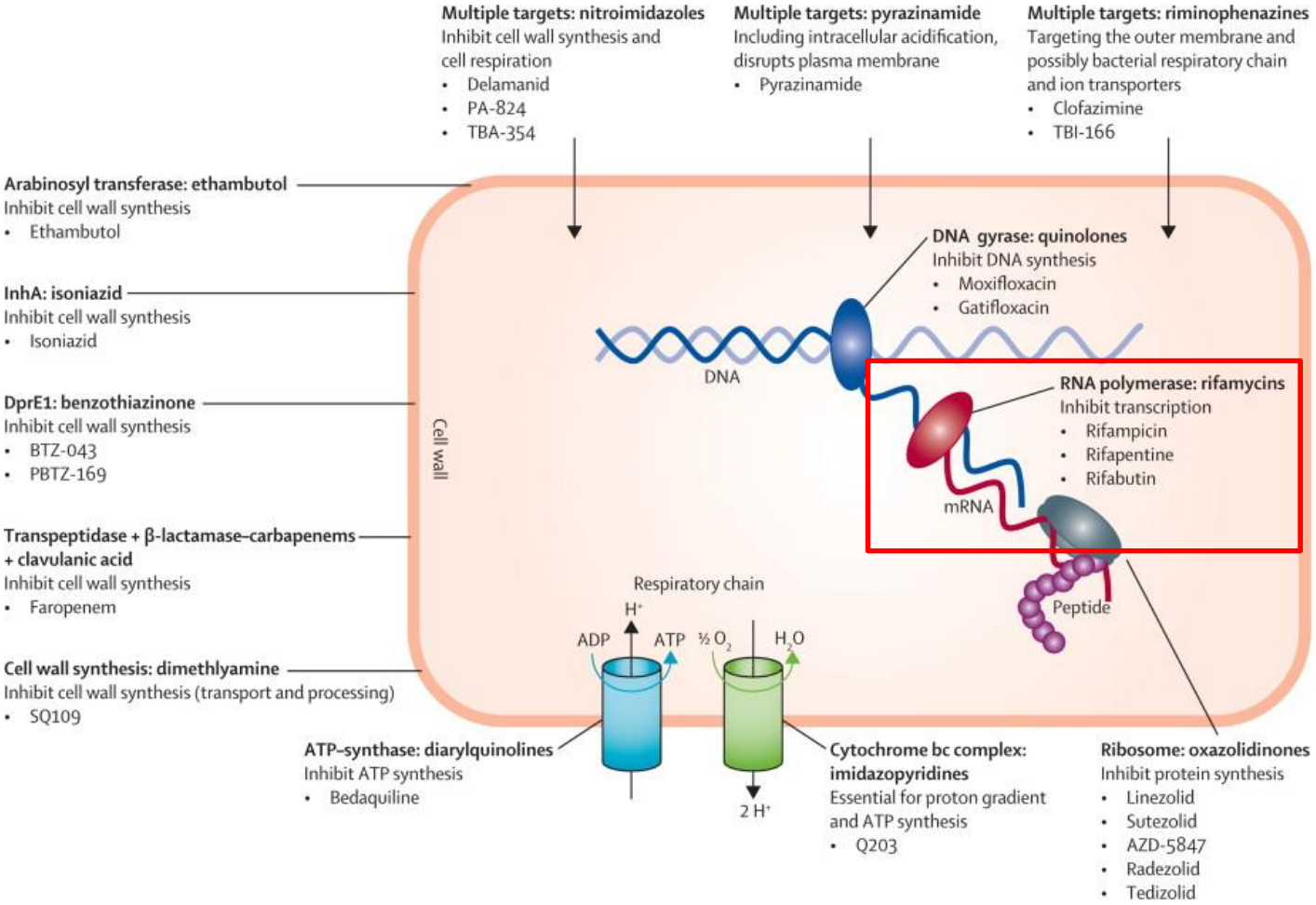


Recommendation 10.

In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used (strong recommendation, moderate certainty of evidence).

Recommendation 11.

In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (conditional recommendation, very low certainty of evidence).


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
InhA: isoniazid
Inhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
Cell wall
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

Rifampicine

- **Posologie 10 mg/kg/j**
- **Bactéricide**, elle est active sur les bacilles des cavernes, du caséum solide et sur les bacilles intra-macrophagiques: activité stérilisante
- La molécule est un **puissant inducteur enzymatique** microsomal, provoquant d'importantes interactions médicamenteuses, en particulier avec les oestroprogestatifs, les anticoagulants oraux,…
- La rifampicine colore les excrétas (larmes, urines, sperme) en rouge orange (prévenir les porteurs de lentilles).
- Elle peut induire des phénomènes immuno-allergiques (thrombopénie, anémie hémolytique, insuffisance rénale aiguë par TNIA), surtout lors des prises discontinues du médicament.
- **Rifabutine (Ansatipine®): 450 à 600 mg/j si tuberculose-R**

Received: 1 November 2021 | Revised: 4 February 2022 | Accepted: 7 February 2022
DOI: 10.1002/phar.2672

REVIEW OF THERAPEUTICS

PHARMACOTHERAPY accp

Systematic review of drug–drug interactions between rifamycins and anticoagulant and antiplatelet agents and considerations for management

Conan MacDougall[1] | Theora Canonica[2] | Chris Keh[3] | Binh An P. Phan[4] | Janice Louie[5]

Interaction importante avec les AVK
Baisse de l'AUC de NACO

Mais augmentation du risque hémorragique sous NACO
Possibilité d'utiliser la rifabutine

Original Investigation

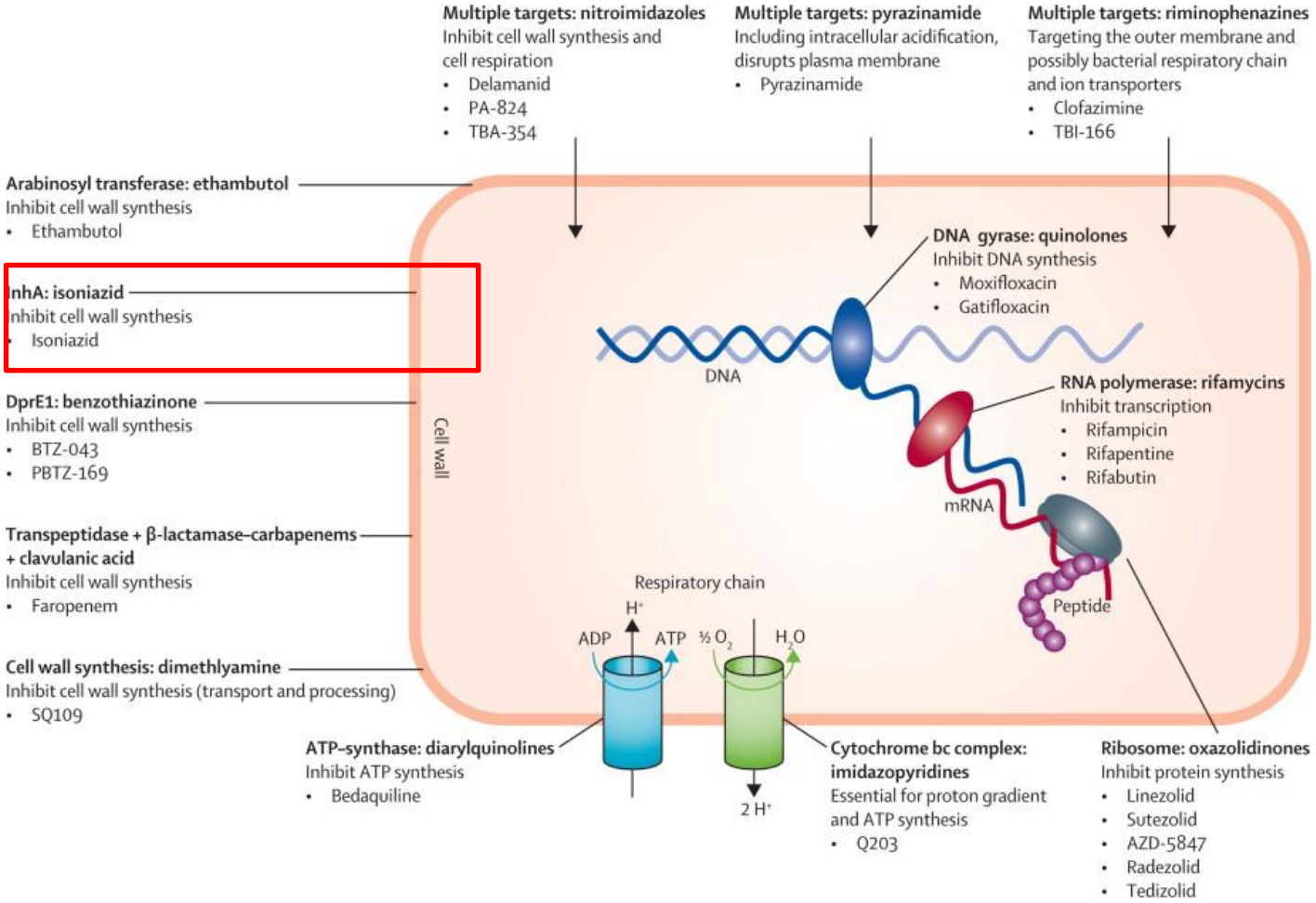
October 3, 2017

Association Between Use of Non–Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation

Shang-Hung Chang, MD, PhD[1,2,3]; I-Jun Chou, MD[3,4]; Yung-Hsin Yeh, MD[1,3]; et al

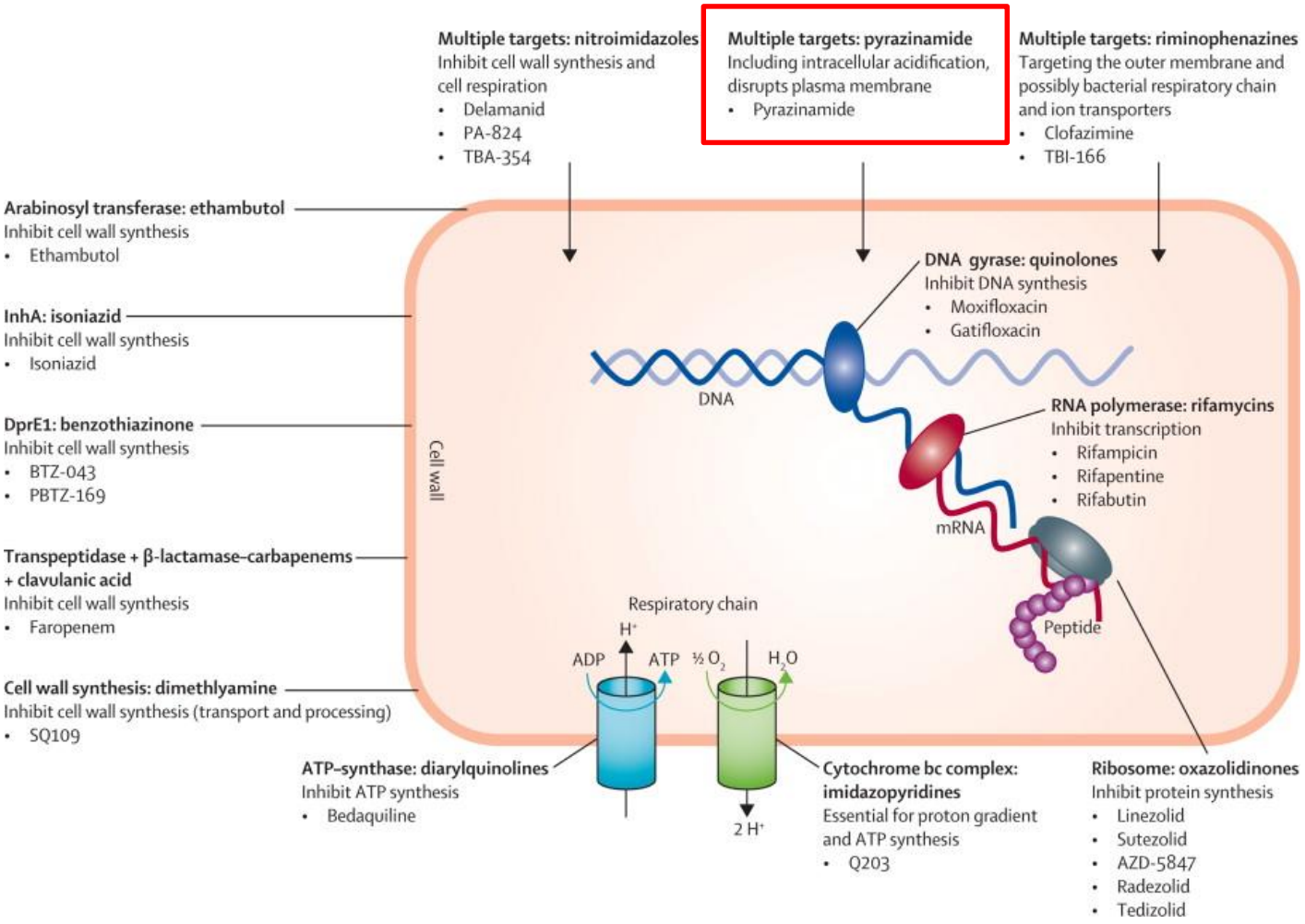
Author Affiliations | Article Information

JAMA. 2017;318(13):1250-1259. doi:10.1001/jama.2017.13883


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
nhA: isoniazid
nhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
Cell wall
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

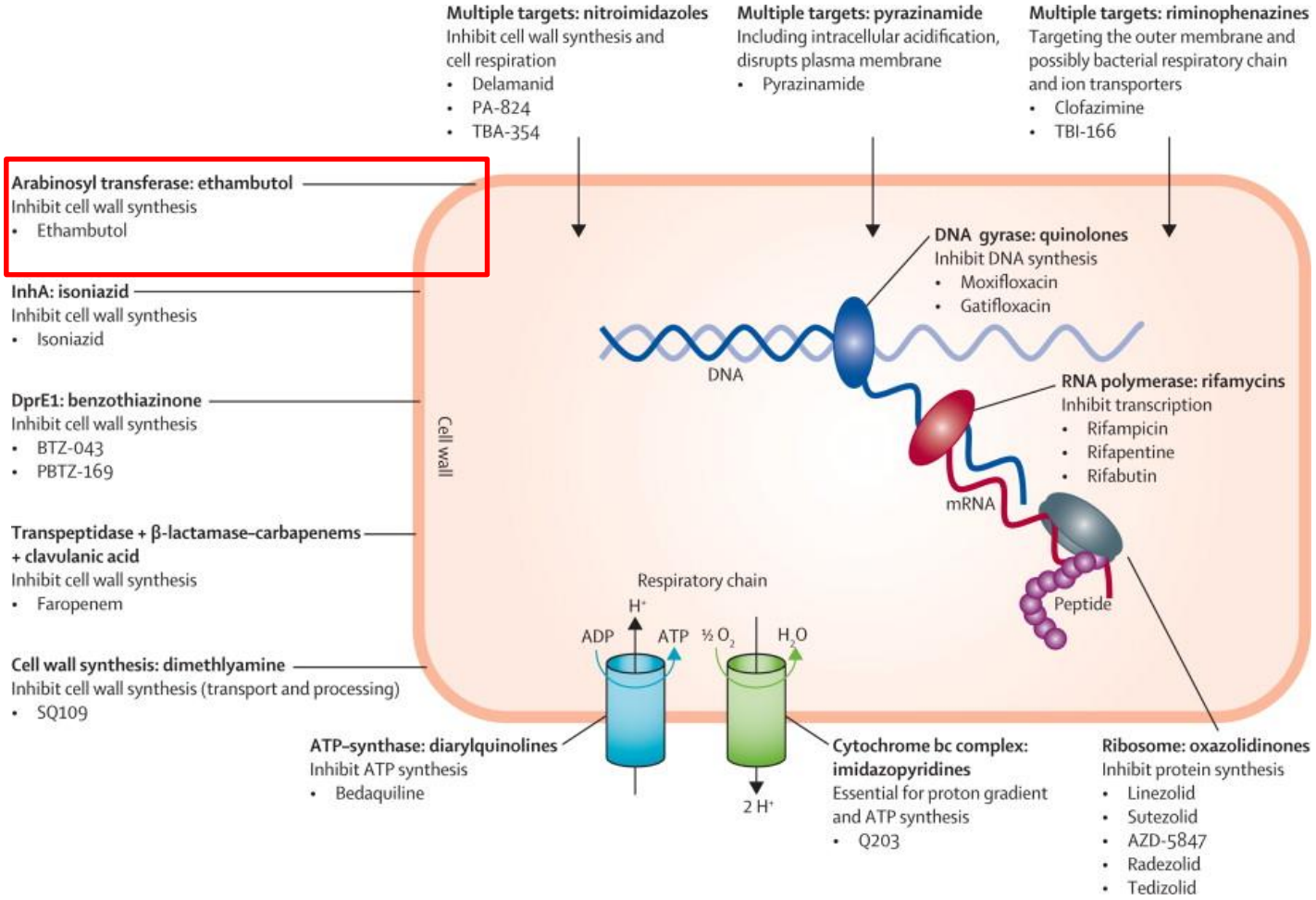
Isoniazide

- Puissamment et rapidement **bactéricide**
- Posologie de **3-6 mg/kg/j** (acétyleurs lents-rapides)
- L'isoniazide est actif sur les bacilles des cavernes et à un moindre degré sur les bacilles intramacrophagiques.
- Il n'a pas d'activité sur les bacilles du caséum solide.
- ***Principaux effets secondaires***: nausées, simple élévation des transaminases ou hépatite médicamenteuse dose-dépendante, polynévrites sensitivo-motrices (surtout en cas de carence en vit B6), troubles neuropsychiques, névralgies cervico-brachiales (syndrome épaule-main) et syndromes rhumatoïdes.
- La supplémentation en pyridoxine (vitamine B6) recommandée pour limiter la toxicité neurologique de l'INH chez le patient dénutri


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
InhA: isoniazid
Inhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
Cell wall
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

Pyrazinamide

- Posologie de **25 à 30 mg/kg/j**.
- Il est contre-indiqué en cas d'insuffisance hépatocellulaire ou d'insuffisance rénale.
- **Bactéricide**, il est uniquement actif sur les bacilles intramacrophagiques et son activité à ce niveau est forte, détruisant les bacilles quiescents pouvant rester plusieurs années dans les macrophages: stérilisant
- Il évite donc les rechutes et **a permis de raccourcir le traitement antituberculeux à 6 mois+++.**
- Ce médicament a une toxicité hépatique, dose dépendante, moindre que celle de celle de l'isoniazide.
- Il provoque une **hyperuricémie,** (l'absence d'hyperuricémie doit faire douter de la prise du traitement), le plus souvent asymptomatique et ne nécessitant un traitement spécifique qu'en cas de signes cliniques (arthralgies, crises de goutte).
- Photosensibilisation


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
InhA: isoniazid
Inhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Cell wall
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

Éthambutol

- Posologie de 20 à 25 mg/kg/j.
- Ce médicament est **bactériostatique** et agit sur les bacilles des cavernes et sur les bacilles intramacrophagiques mais n'a pas d'action sur les bacilles du caséum solide.
- Mais prévient la multirésistance +++
- La principale complication est ophtalmologique, avec névrite optique rétrobulbaire se manifestant initialement par un trouble de la vision des couleurs (dyschromatopsie) puis par une baisse de l'acuité visuelle (surtout pour des doses ≥ 25 mg/kg/j, en cas d' éthylisme chronique, ou chez l'insuffisant rénal).
- Cela impose une consultation d'ophtalmologie avant la mise en route du traitement, puis tous les mois tant que le médicament est poursuivi.

OBJECTIVES OF ANTITUBERCULOSIS THERAPY

Treatment of tuberculosis is focused on both curing the individual patient and minimizing the transmission of *Mycobacterium tuberculosis* to other persons; successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides.

The objectives of tuberculosis therapy are:

1. To reduce the bacillary population rapidly thereby decreasing severity of the disease, preventing death and halting transmission of *M. tuberculosis*;
2. To eradicate persisting bacilli in order to achieve durable cure (prevent relapse) after completion of therapy; and
3. To prevent acquisition of drug resistance during therapy.

Dosages des anti-tuberculeux

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

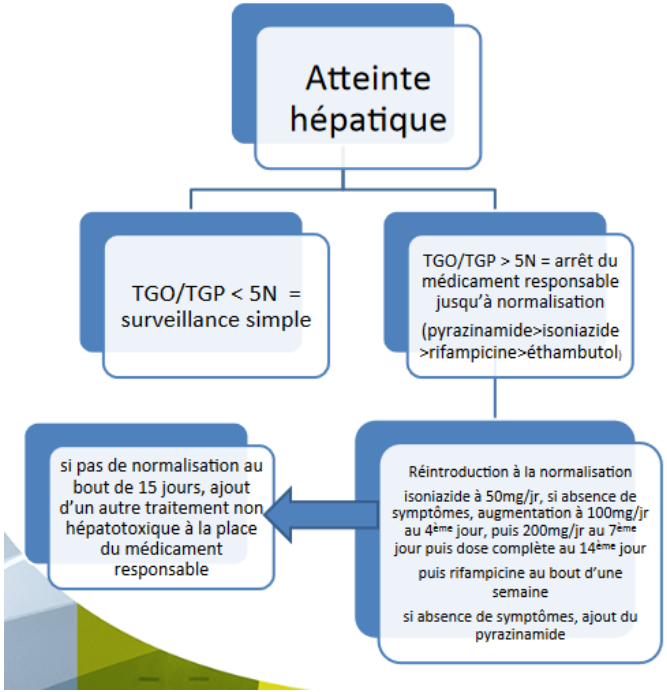
Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

Poor response to tuberculosis treatment despite adherence and fully drug-susceptible *Mycobacterium tuberculosis* strain
Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption
Drug–drug interactions
Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
HIV infection
Diabetes mellitus
Treatment using second-line drugs

Abbreviation: HIV, human immunodeficiency virus.

Toxicité hépatique



TROUBLES HEPATIQUES		
TGO/TGP < 5N **TGO/TGP > 5N**	Atteinte modérée : surveillance Arrêt du traitement jusqu'à normalisation des constantes	! si normalisation trop longue, ajout d'un antituberculeux non hépatotoxique
Cytolyse **Cholestase**	Isoniazide ou pyrazinamide rifampicine	! si réaction d'hypersensibilité associée : rifampicine
Délai d'apparition précoce **Délai d'apparition Tardif**	Isoniazide Pyrazinamide ou rifampicine	
Responsabilité reconnue de l'isoniazide • adaptation des posologies en fonction des concentrations sériques • réintroduction croissante • si cytolyse persistante : arrêt définitif de l'isoniazide		
Responsabilité reconnue de la rifampicine : • arrêt complet de la rifampicine sans réintroduction possible		
Responsabilité reconnue du pyrazinamide : • arrêt du pyrazinamide sans réintroduction possible		

Raccourcir la durée de traitement ?

Rifapentine + Moxifloxacine + isoniazide + Pyrazinamide 4 mois non inférieur à SOC 6 mois

Attention Rifapentine + isoniazide + ethambuthol + pyrazinamide inférieur au SOC 6 mois

NEJM 6 May 2021

RESEARCH SUMMARY

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

CLINICAL PROBLEM

The standard treatment of drug-susceptible pulmonary tuberculosis is a 6-month course of a daily rifamycin-based antimicrobial regimen. A more potent regimen with improved rifamycin exposure might shorten treatment duration, potentially improving adherence and reducing adverse effects and costs.

CLINICAL TRIAL

Design: A randomized, open-label, noninferiority trial of two 4-month rifapentine-containing regimens, as compared with a standard 6-month rifampin-containing regimen, for the treatment of drug-susceptible tuberculosis.

Intervention: 2516 participants 12 years of age or older with newly diagnosed tuberculosis were randomly assigned to a 6-month control regimen, a 4-month regimen in which rifampin was replaced with rifapentine (rifapentine group), or a 4-month regimen in which rifampin was replaced with rifapentine and ethambutol with moxifloxacin (rifapentine–moxifloxacin group). The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug.

RESULTS

Efficacy: The rifapentine–moxifloxacin regimen, but not the rifapentine regimen, was shown to be noninferior to the control regimen.

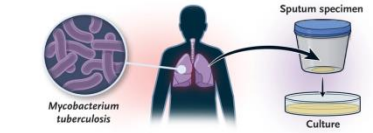
Safety: The percentages of patients who had adverse events of grade 3 or higher or who discontinued the assigned regimen prematurely did not differ significantly between the rifapentine–moxifloxacin group and the control group but were lower in the rifapentine group than in the control group.

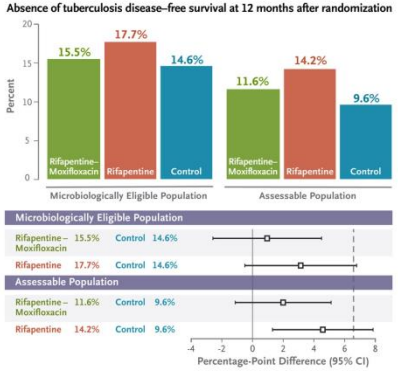
LIMITATIONS AND REMAINING QUESTIONS

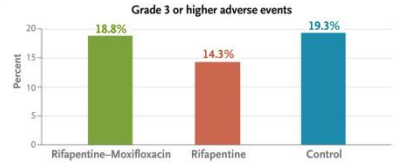
Further study is required to understand the following:

- How the trial regimens perform in HIV-coinfected patients
- Whether the shorter treatment duration offsets the likely higher cost of the rifapentine–moxifloxacin regimen

Links: Full article | NEJM Quick Take | Editorial







CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.

Raccourcir encore la durée de traitement encore ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., Irawaty Djaharuddin, M.D., Jani J.R. Sugiri, M.D., Rholine S. Veto, M.D., Christine Sekaggya-Wiltshire, Ph.D., Anchalee Avihingsanon, M.D., Rohit Sarin, M.D., Padmasayee Papineni, F.R.C.P., Andrew J. Nunn, M.Sc., and Angela M. Crook, Ph.D., for the TRUNCATE-TB Trial Team*

20 février 2023

Essai randomisé de non infériorité comparant quadrithérapie standard avec 4 autres stratégies en 8 semaines de traitement

Critère de jugement composite: décès à 96 semaines, traitement toujours en cours, TB active à 96 semaines

Evaluation à 8 semaines:

Si patient symptomatique: poursuite 4 semaines de plus

Si symptomatique à 12 Semaines: switch vers traitement standard

B. Rifampicin-linezolid arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Rifampicin	35mg/kg (rounded to nearest 150mg, maximum 2100mg)*			
Isoniazid	150mg	225mg	300mg	375mg
Pyrazinamide	800mg	1200mg	1600mg	2000mg
Ethambutol	550mg	825mg	1100mg	1375mg
Linezolid	600mg			

C. Rifampicin-clofazimine arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Rifampicin	35mg/kg (rounded to nearest 150mg, maximum 2100mg)			
Isoniazid	150mg	225mg	300mg	375mg
Pyrazinamide	800mg	1200mg	1600mg	2000mg
Ethambutol	550mg	825mg	1100mg	1375mg
Clofazimine	200mg			

D. Rifapentine-linezolid arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Isoniazid	5mg/kg rounded to nearest 100mg		300mg	
Pyrazinamide	25mg/kg rounded to nearest 500mg	1000mg	1500mg	2000mg
Rifapentine	1200mg			
Linezolid	600mg			
Levofloxacin	1000mg			

E. Bedaquiline-linezolid arm

For 8 weeks

DRUG	<40KG	40KG- 54KG	55KG - 70KG	≥71KG
Bedaquiline	400 mg once daily for 2 weeks then 200mg three times a week			
Isoniazid	5mg/kg rounded to nearest 100mg		300mg	
Pyrazinamide	25mg/kg rounded to nearest 500mg	1000mg	1500mg	2000mg
Ethambutol	15mg/kg (rounded to nearest 100mg, maximum 1600mg)			
Linezolid	600mg			

Table 2. Primary Efficacy Outcome.*

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment Adjusted Difference (97.5% CI)†	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment Adjusted Difference (97.5% CI)†
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (–3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
No evaluation at wk 96 and insufficient evidence of disease clearance when last seen	0	1 (0.5)	—	1 (0.5)	—
Outcomes classified as unassessable — no. (%)	1 (0.6)	1 (0.5)	—	2 (1.1)	—
Single positive culture at wk 96 but no other evidence of active disease‖	0	1 (0.5)	—	0	—
Death from a cause that was definitively unrelated to tuberculosis**	1 (0.6)	0	—	0	—
No evaluation at wk 96 and sufficient evidence of disease clearance when last seen	0	0	—	2 (1.1)	—
No primary outcome or outcome classified as unassessable — no. (%)	173 (95.6)	162 (88.0)	—	176 (93.1)	—
Assessable population††					
Primary outcome — no./total no. (%)	7/180 (3.9)	21/183 (11.5)	7.5 (1.7 to 13.2)	11/187 (5.9)	0.8 (–3.4 to 5.1)
Per-protocol population‡‡					
Primary outcome — no./total no. (%)	6/177 (3.4)	17/160 (10.6)	6.9 (0.9 to 12.8)	9/176 (5.1)	0.9 (–3.3 to 5.1)

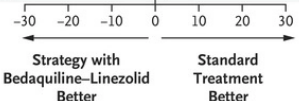
Non-inferiority met

Strategy with Rifampin–Linezolid Better

Standard Treatment Better

B Primary Outcome in Strategy Group with Initial Bedaquiline–Linezolid Regimen vs. Standard-Treatment Group

Subgroup	Strategy with Bedaquiline–Linezolid *no. of participants with event/total no. (%)*	Standard Treatment *no. of participants with event/total no. (%)*	Difference (95% CI) *percentage points*
Sex			
Male	5/116 (4.3)	5/119 (4.2)	0.1 (–4.4 to 4.6)
Female	6/73 (8.2)	2/62 (3.2)	3.6 (–3.9 to 11.2)
Age			
18–34 yr	4/95 (4.2)	5/104 (4.8)	–1.8 (–7.0 to 3.4)
35–65 yr	7/94 (7.4)	2/77 (2.6)	4.8 (–1.1 to 10.7)
Country			
Indonesia or Philippines	6/145 (4.1)	4/139 (2.9)	1.3 (–3.0 to 5.5)
Uganda	4/27 (14.8)	2/28 (7.1)	7.7 (–8.8 to 24.1)
India or Thailand	1/17 (5.9)	1/14 (7.1)	–1.3 (–18.8 to 16.3)
Education			
0–7 yr	3/48 (6.3)	4/49 (8.2)	–2.4 (–12.1 to 7.3)
≥8 yr	8/141 (5.7)	3/132 (2.3)	2.8 (–1.6 to 7.3)
Smoking status			
Never	8/107 (7.5)	2/89 (2.2)	3.7 (–2.2 to 9.5)
Current or former	3/82 (3.7)	5/92 (5.4)	–1.0 (–7.0 to 5.0)
Body-mass index			
<18.5	4/76 (5.3)	5/79 (6.3)	–1.3 (–8.5 to 6.0)
≥18.5	7/113 (6.2)	2/102 (2)	3.3 (–2.0 to 8.6)
Cavitation on chest radiograph			
Absent	5/81 (6.2)	1/87 (1.1)	3.4 (–2.4 to 9.2)
Present	6/108 (5.6)	6/94 (6.4)	–0.6 (–7.0 to 5.9)
Proportion of lung affected on chest radiograph			
≤50%	8/151 (5.3)	3/140 (2.1)	2.8 (–1.0 to 6.6)
>50%	3/38 (7.9)	4/41 (9.8)	–2.2 (–14.4 to 10.1)
WHO smear grade			
Negative	1/50 (2.0)	1/46 (2.2)	0.9 (–16.8 to 18.7)
Scanty or 1+	4/77 (5.2)	0/65	6.4 (–18.7 to 31.6)
2+ or 3+	6/62 (9.7)	5/69 (7.2)	2.0 (–9.8 to 13.8)
Grade on MRC breathlessness scale			
Grade 1	3/112 (2.7)	3/106 (2.8)	1.1 (–3.0 to 5.2)
Grade 2 or higher	8/77 (10.4)	4/75 (5.3)	3.5 (–5.0 to 11.9)
Relapse risk			
Low	1/50 (2.0)	2/47 (4.3)	–0.8 (–7.3 to 5.6)
Intermediate or high	10/139 (7.2)	5/134 (3.7)	2.6 (–2.6 to 7.8)



Strategy with Bedaquiline–Linezolid Better

Standard Treatment Better

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)

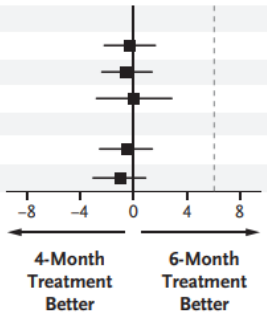


Figure 2. Unadjusted Analysis of the Primary Efficacy and Key Secondary Outcomes in the Trial Populations.

The primary efficacy outcome was unfavorable status by 72 weeks, which was defined as a composite of treatment failure (treatment extension, change, or restart or tuberculosis recurrence), loss to follow-up during treatment, or death, with the exclusion of all the participants who had undergone randomization but did not complete 4 months of treatment (modified intention-to-treat population). The per-protocol population included all the participants in the modified intention-to-treat population except those who had not adhered to the trial regimen. The intention-to-treat population included all the participants who had undergone randomization. Differences have been carried to one decimal place because of the small values. The prespecified margin for noninferiority in the primary efficacy analysis was 6 percentage points (dashed line). The key secondary analysis was unfavorable status at 72 weeks as assessed among the 958 participants who had been independently adjudicated as having tuberculosis at baseline.

Recommandations
Tuberculose pulmonaire

RT1 Devant une suspicion de tuberculose pulmonaire, des précautions complémentaires Air doivent être mises en place dès l'entrée dans l'établissement. **A**

RT2 Devant une suspicion de tuberculose pulmonaire, pour laquelle les examens microscopiques sont négatifs, il est possible de lever les précautions complémentaires Air sauf si :

- la clinique et l'imagerie thoracique sont en faveur d'une tuberculose pulmonaire active ;
- le patient est au contact d'un sujet immunodéprimé (essentiellement VIH+ ou sous immuno-modulateurs) ;
- il existe un risque de tuberculose multirésistante aux antibiotiques (RT5). **C**

RT3 Devant une suspicion de tuberculose pulmonaire, il faut attendre d'avoir les résultats négatifs de trois examens microscopiques d'expectoration ou de tubage gastrique avant de réaliser une fibroscopie bronchique. **C**

RT4 La durée des précautions Air en cas de tuberculose pulmonaire active contagieuse (examen microscopique positif ou conviction clinique) est d'au moins 15 jours à partir de la mise en route du traitement. **C**

RT5 En cas de forte suspicion ou de diagnostic de tuberculose multirésistante aux antibiotiques, il faut immédiatement mettre en place les précautions complémentaires Air, et s'assurer de leur maintien pendant toute la durée de l'hospitalisation. **C**

https://www.sf2h.net/wp-content/uploads/2013/03/SF2H_recommandations_air-ou-gouttelettes_2013.pdf

TUBERCULOSE RÉSISTANTE

Table 3.1. Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

Tuberculose résistante

Situations	Molécules	durée
Résistance uniquement à l'isoniazide	Rifampicine/ pyrazinamide/ ethambuthol/ lévofloxacine	6 mois
Résistance à la Rifampicine et tuberculose multi-résistante	Bédaquilline Linézolide **Moxifloxacine (si souche sensible)** **Pretomanid** **Bédaquiline (6 mois)** **Lévofloxacine ou Moxifloxacine** **Clofazimine (4 mois)** **Ethionamide** **Ethambuthol** **Isoniazide** **Pyrazinamide**	6 mois Plus de 14 ans Pas d'atteinte du SNC Pas de femmes enceintes 9 mois

Section 1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)

1.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

Section 2. The 9-month all-oral regimen for MDR/RR-TB (NEW)

2.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*

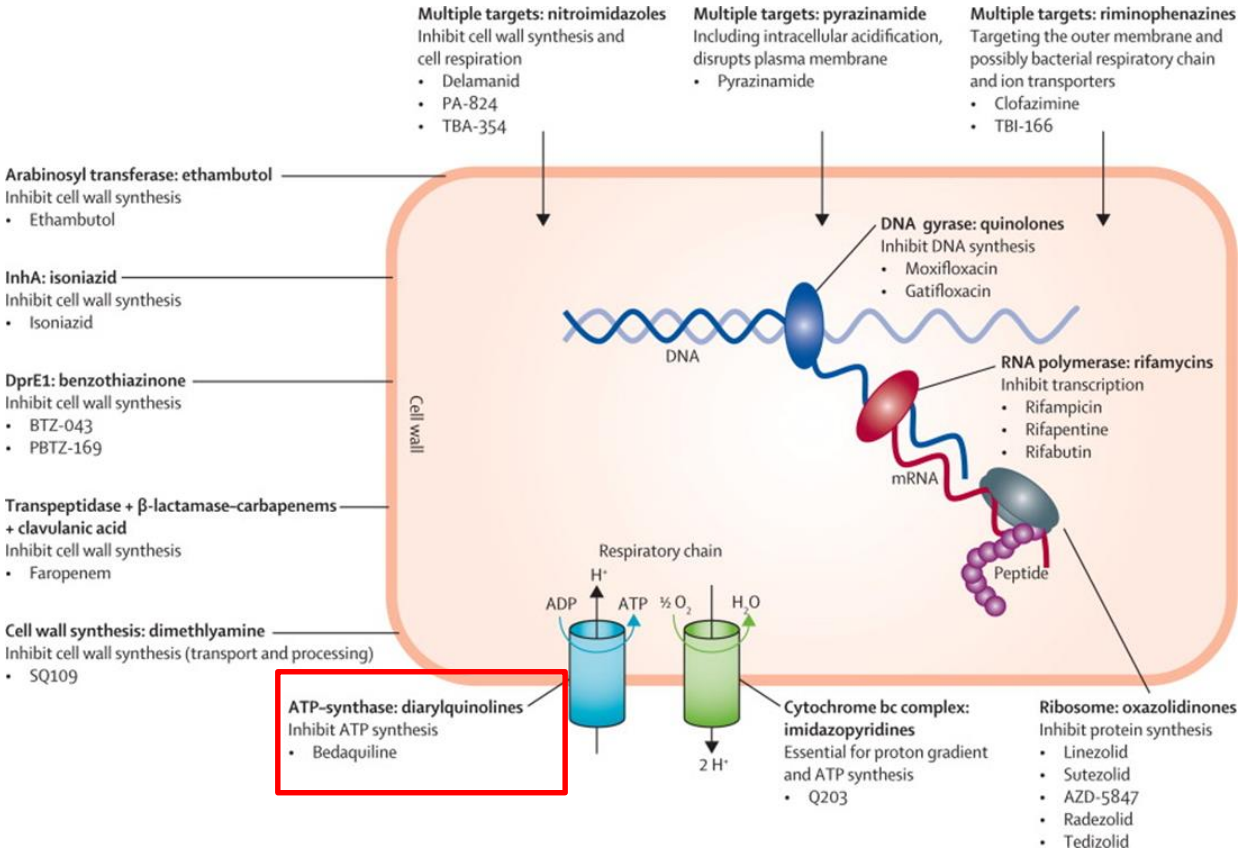
Remarks

1. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).

Section 3. Longer regimens for MDR/RR-TB

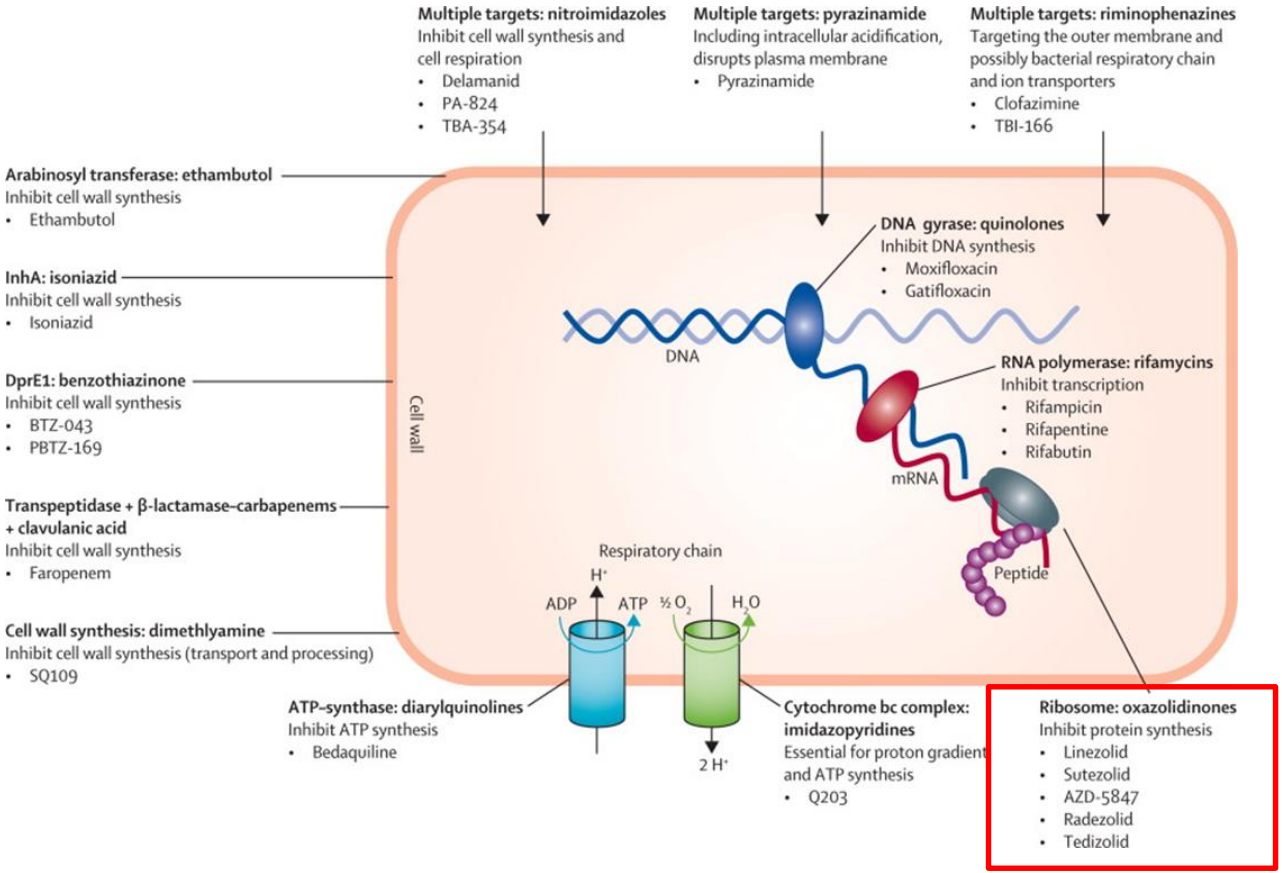
Recommendations

No.	Recommendation
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
InhA: isoniazid
Inhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
Cell wall
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

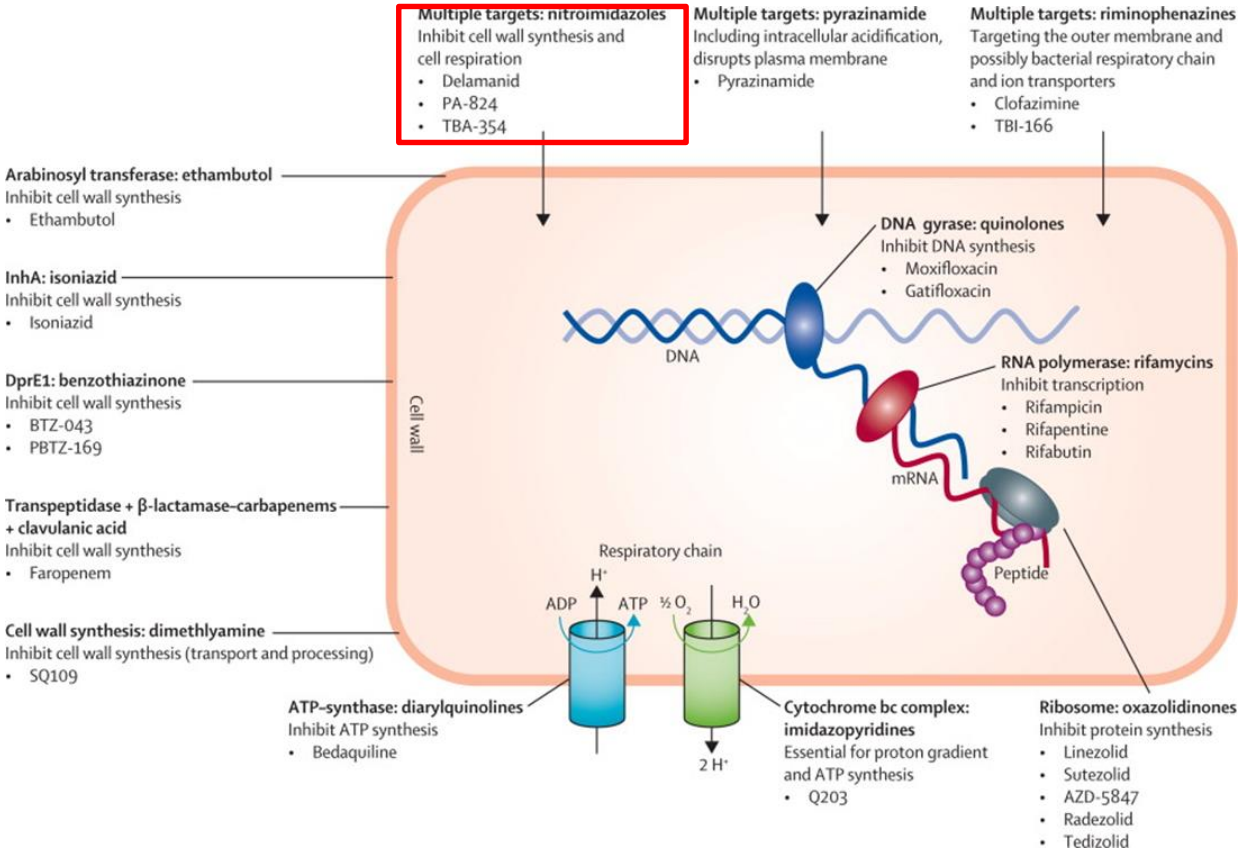
Bédaquilline

- Premier représentant de la famille des diarylquinolines
- Activité bactéricide sur les bacilles tuberculeux en réplication et dormants. La bedaquiline inhibe spécifiquement l'adénosine 5'-triphosphate (ATP) synthase, une enzyme essentielle à la production d'énergie chez *Mycobacterium tuberculosis*.
- ASMR III
- Posologies: Semaine 1 à 2 : 400 mg (4 comprimés de 100 mg) une fois par jour - Semaine 3 à 24 : 200 mg (2 comprimés de 100 mg) : trois fois par semaine (avec un intervalle d'au moins 48 heures entre chaque prise). La durée de traitement est de 24 semaines.
- pris par voie orale avec de la nourriture, car l'administration avec la nourriture augmente la biodisponibilité orale d'environ deux fois
- Attention à l'allongement du QT


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
InhA: isoniazid
Inhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
Cell wall
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

Linézolide

- Oxazolidone
- 600mg dans la tuberculose
- Biodisponibilité proche de 100 %
- Myélotoxicité (thrombopénie, anémie, pancytopénie) possible, apparaissant après 15 jours de traitement et en cas d'antécédent d'anémie, de granulopénie, de thrombopénie ou en cas d'insuffisance rénale
- Syndrome sérotoninergique
- Acidose lactique par cytotoxicité mitochondriale
- Neuropathies optiques ou périphériques lors de traitements prolongés


Multiple targets: nitroimidazoles
Inhibit cell wall synthesis and cell respiration
• Delamanid
• PA-824
• TBA-354
Multiple targets: pyrazinamide
Including intracellular acidification, disrupts plasma membrane
• Pyrazinamide
Multiple targets: riminophenazines
Targeting the outer membrane and possibly bacterial respiratory chain and ion transporters
• Clofazimine
• TBI-166
Arabinosyl transferase: ethambutol
Inhibit cell wall synthesis
• Ethambutol
InhA: isoniazid
Inhibit cell wall synthesis
• Isoniazid
DprE1: benzothiazinone
Inhibit cell wall synthesis
• BTZ-043
• PBTZ-169
Transpeptidase + β-lactamase–carbapenems + clavulanic acid
Inhibit cell wall synthesis
• Faropenem
Cell wall synthesis: dimethlyamine
Inhibit cell wall synthesis (transport and processing)
• SQ109
Cell wall
DNA gyrase: quinolones
Inhibit DNA synthesis
• Moxifloxacin
• Gatifloxacin
DNA
RNA polymerase: rifamycins
Inhibit transcription
• Rifampicin
• Rifapentine
• Rifabutin
mRNA
Peptide
Respiratory chain
H+
ADP
ATP
½ O2
H2O
2 H+
ATP–synthase: diarylquinolines
Inhibit ATP synthesis
• Bedaquiline
Cytochrome bc complex: imidazopyridines
Essential for proton gradient and ATP synthesis
• Q203
Ribosome: oxazolidinones
Inhibit protein synthesis
• Linezolid
• Sutezolid
• AZD-5847
• Radezolid
• Tedizolid

Delamanide /Prétonamide

- Nitro-imidazolés
- Deux mécanismes d'action:
  - Inhibition de la synthèse de la paroi bactérienne (inhibition de la synthèse de l'acide mycolique)
  - Empoisonnement respiratoire: stress oxydatif?
- Delamanid 100 mg deux fois par jour avec prise alimentaire
- Pretomanide 200 mg par jour en une prise avec prise alimentaire
- Résistance à l'un n'implique pas résistance à l'autre composant

J Antimicrob Chemother 2022; **77**: 880–902
https://doi.org/10.1093/jac/dkab505 Advance Access publication 28 January 2022

Journal of Antimicrobial Chemotherapy

Delamanid or pretomanid? A Solomonic judgement!

Saskia E. Mudde[1]*, Anna M. Upton[2], Anne Lenaerts[3], Hannelore I. Bax[1,4] and Jurriaan E. M. De Steenwinkel[1]

[1]Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Evotec, Princeton, New Jersey, USA; [3]Mycobacteria Research Laboratories, Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO, USA; [4]Department of Internal Medicine, Section of Infectious Diseases, Erasmus University Medical Center, Rotterdam, The Netherlands

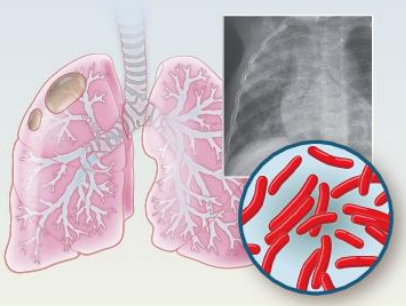
*Corresponding author. E-mail: s.e.mudde@erasmusmc.nl

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients
with confirmed tuberculosis



Three-drug regimen (26 wk)

Bedaquiline

Pretomanid
(recently approved)

Linezolid

XDR tuberculosis
N=71
(65%)

Nonresponsive or treatment-intolerant MDR tuberculosis
N=38
(34%)

Clinical resolution at 6 mo after therapy

90% of all patients had favorable outcomes
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

F. Conradie et al. 10.1056/NEJMoa1901814

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

Francesca Conradie, M.B., B.Ch., Tatevik R. Bagdasaryan, M.D., Sergey Borisov, M.D., Pauline Howell, M.D., Lali Mikiashvili, M.D., Nosipho Ngubane, M.D., Anastasia Samoilova, M.D., Sergey Skornykova, M.D., Elena Tudor, M.D., Ebrahim Variava, M.D., Petr Yablonskiy, Ph.D., Daniel Everitt, M.D., et al., for the ZeNix Trial Team*

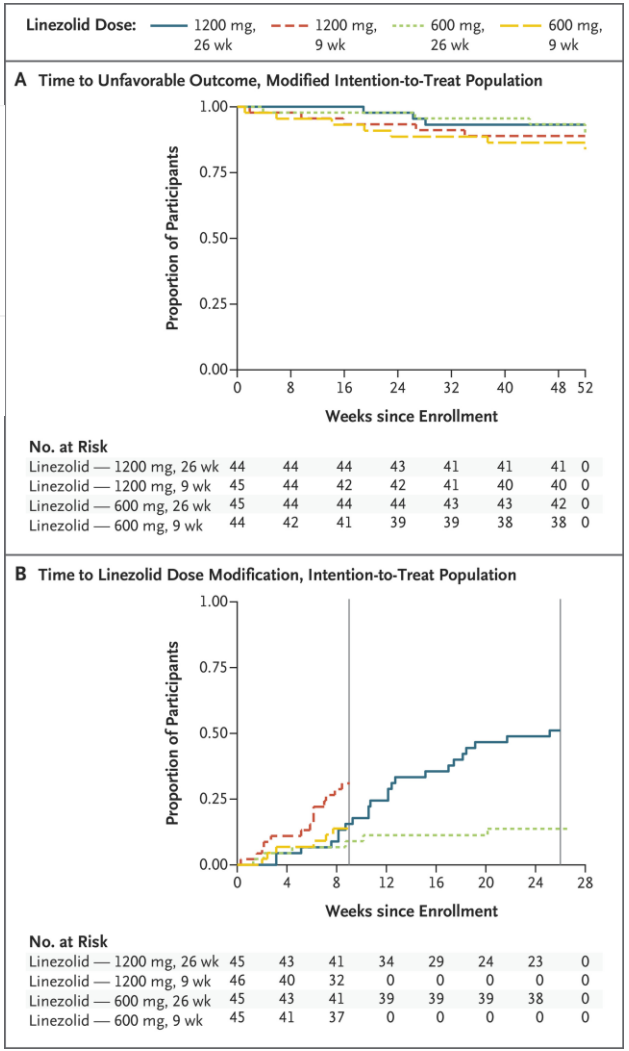
Article Figures/Media Metrics

21 References 15 Citing Articles Letters

September 1, 2022
N Engl J Med 2022; 387:810-823
DOI: 10.1056/NEJMoa2119430

Réduction de la posologie de linézolide à 600 mg/jour non inférieur pendant 26 semaines à la dose de 1200 mg
Moins de myélosuppression et moins de neuropathie périphérique

20 % de patients VIH
42 % de TB XDR



Effets secondaires et tuberculose multi-résistante

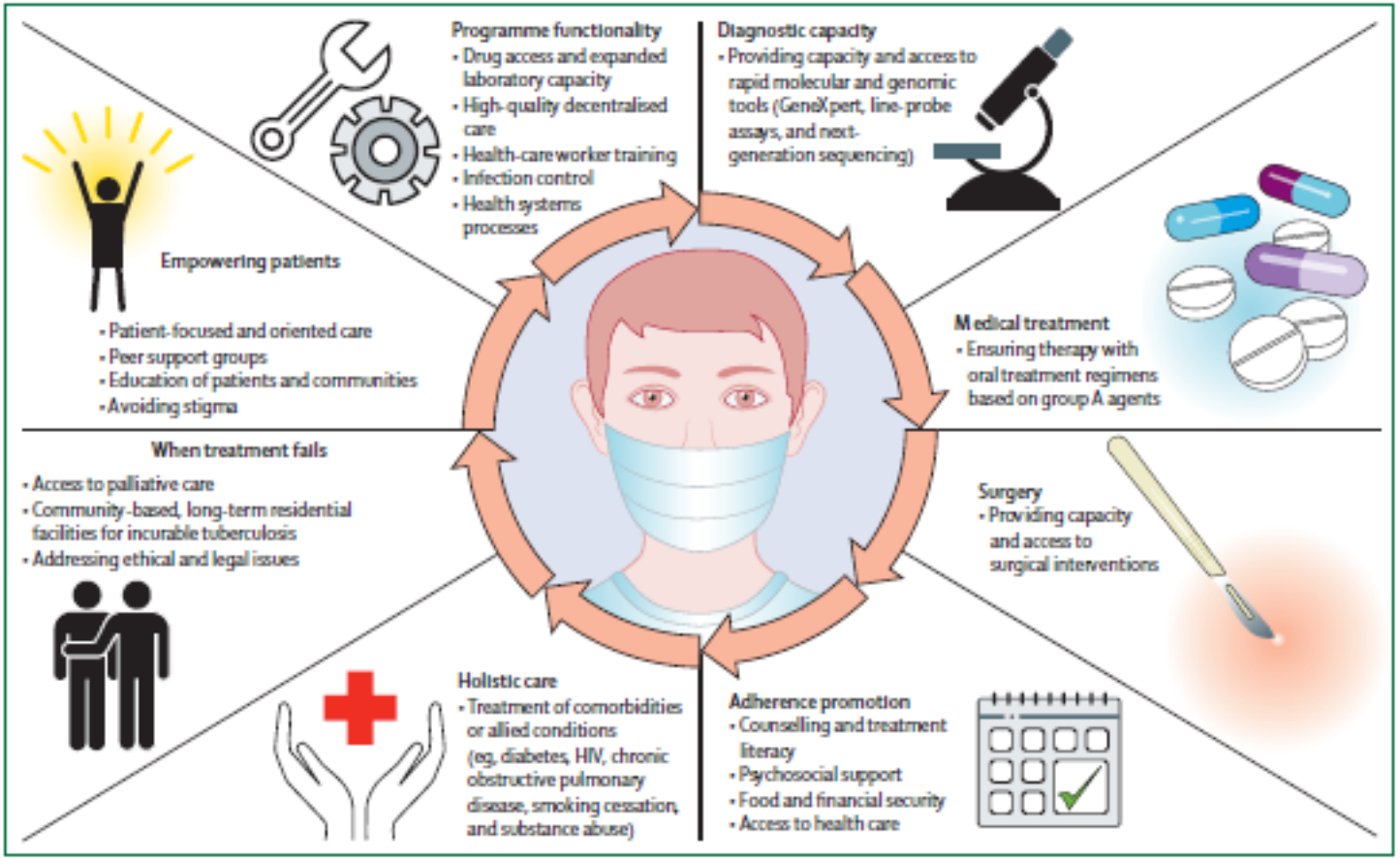
Table 6. Incidence Rate of Clinically Relevant Adverse Events of Special Interest Among Patients During Exposure to a Drug of Interest

Clinically Relevant[a] Adverse Event of Interest	Drug of Interest	Person-Months of Exposure to Drug of Interest	Patients With at Least 1 Occurrence of a Clinically Relevant AESI,[a] (n/N, %)	Incidence of Clinically Relevant AESI/1000 Person-Months[a] (95% Confidence Interval)
QT prolongation	Bedaquiline or delamanid	19 543	50/2296 (2.2)	2.6 (1.9–3.4)
Hearing loss	Kanamycin, amikacin, capreomycin	4936	182/925 (19.7)	36.9 (31.9–42.6)
Hearing loss or acute renal failure or electrolyte depletion	Kanamycin, amikacin, capreomycin	5864	340/925 (36.8)	72.8 (66.0–80.0)
Peripheral neuropathy or optic neuritis or myelosuppression	Linezolid	23 660	507/1826 (27.8)	22.8 (20.9–24.8)

Safety of treatment regimens containing bedaquiline and delamanid in the endTB cohort Hewison et al. CID Janvier 2022

Table 2.2. Summary of adverse events associated with linezolid and ethionamide

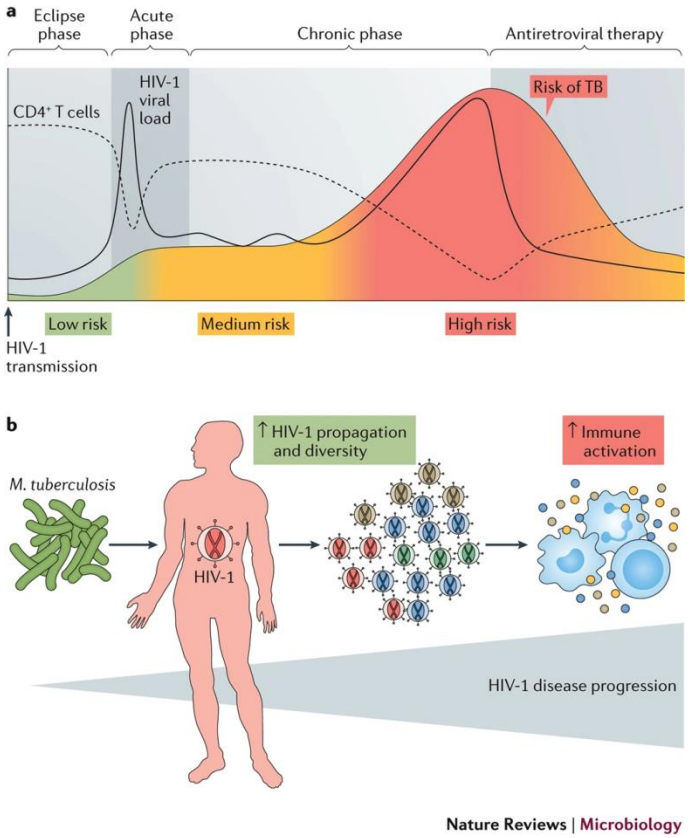
Linezolid adverse events	Ethionamide adverse events
• Myelosuppression (anaemia, decreased level of white blood cells or decreased level of platelets) • Peripheral or optic neuropathy – these conditions may be irreversible, and linezolid should be stopped if they develop • Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test • Diarrhoea and nausea	• Gastrointestinal upset and anorexia (sometimes intolerable) – symptoms are moderated by food or by taking at bedtime • Hepatotoxicity • Endocrine effects (e.g. gynaecomastia, hair loss, acne, impotence, menstrual irregularity and reversible hypothyroidism) • Neurotoxicity – patients taking ethionamide should take high doses of vitamin B6

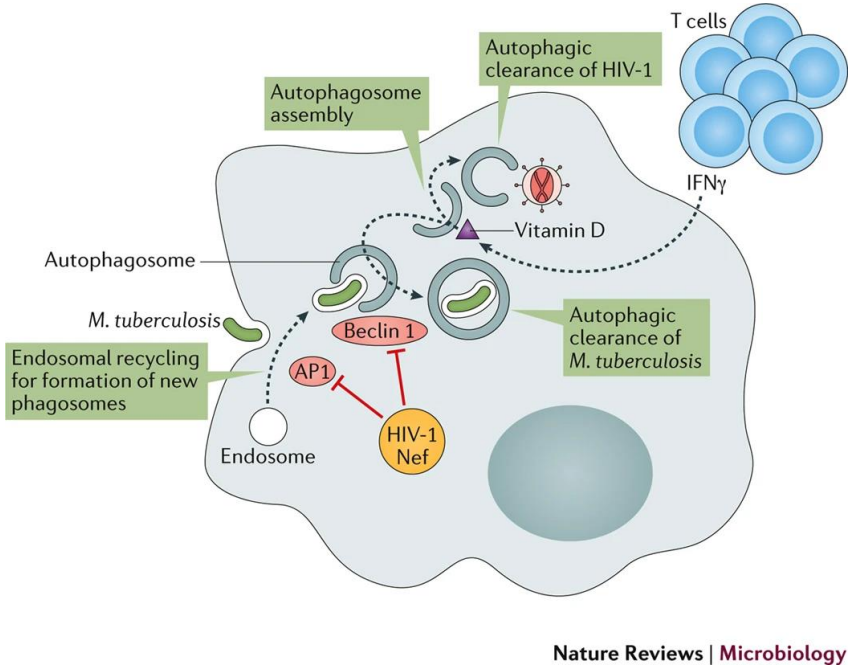


Lange et al. Lancet 2019

TUBERCULOSE ET VIH

Tuberculose et VIH





Bell et al. Nature Reviews Microbiology 2017

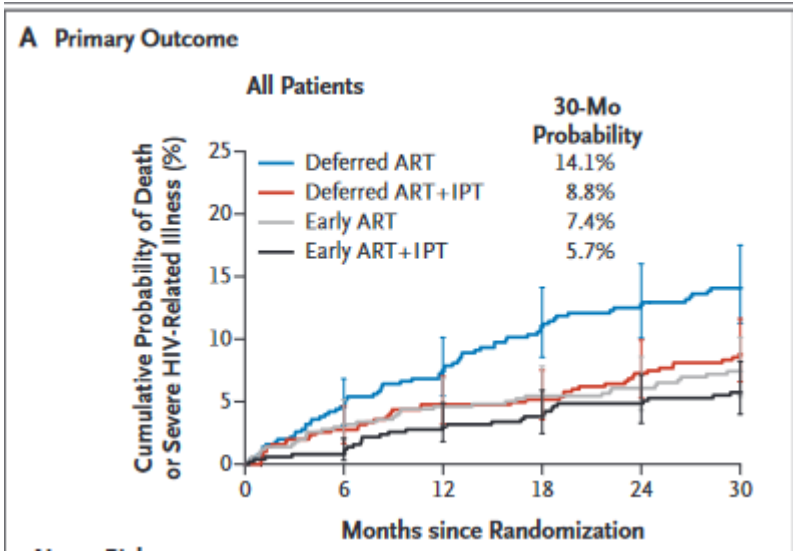
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group*

ABSTRACT



Effet d'un traitement antirétroviral précoce associé à 6 mois d'isoniazide sur la mortalité toute cause, infections bactériennes, cancers classant SIDA ou non

N Engl J Med 2015;373:808-22.
DOI: 10.1056/NEJMoa1507198

The NEW ENGLAND JOURNAL of MEDICINE

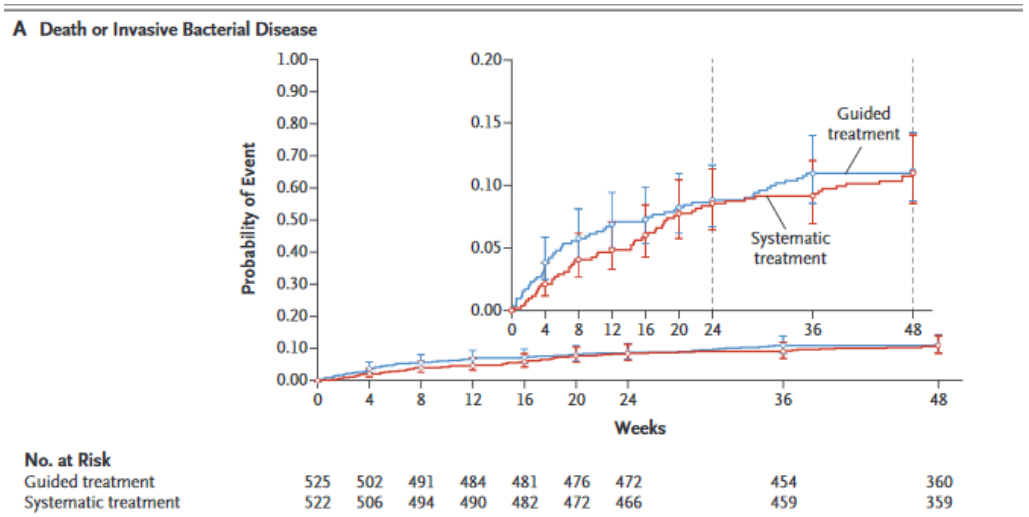
ESTABLISHED IN 1812 JUNE 18, 2020 VOL. 382 NO. 25

Systematic or Test-Guided Treatment for Tuberculosis in HIV-Infected Adults

F.-X. Blanc, A.D. Badje, M. Bonnet, D. Gabillard, E. Messou, C. Muzoora, S. Samreth, B.D. Nguyen, L. Borand, A. Domergue, D. Rapoud, N. Natukunda, S. Thai, S. Juchet, S.P. Eholié, S.D. Lawn,* S.K. Domoua, X. Anglaret, and D. Laureillard, for the STATIS ANRS 12290 Trial Team†

Traitement empirique de la tuberculose chez les patients infectés par le VIH avec moins de 100 CD4/mm3 vers traitement guidé

N Engl J Med 2020;382:2397-410.
DOI: 10.1056/NEJMoa1910708



Dépistage basé sur Xpert MTB/RIF test, urinary lipoarabinomannan test, and chest radiography

ORIGINAL ARTICLE

Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

G. Meintjes, C. Stek, L. Blumenthal, F. Thienemann, C. Schutz, J. Buyze, R. Ravinetto, H. van Loen, A. Nair, A. Jackson, R. Colebunders, G. Maartens, R.J. Wilkinson, and L. Lynen, for the PredART Trial Team

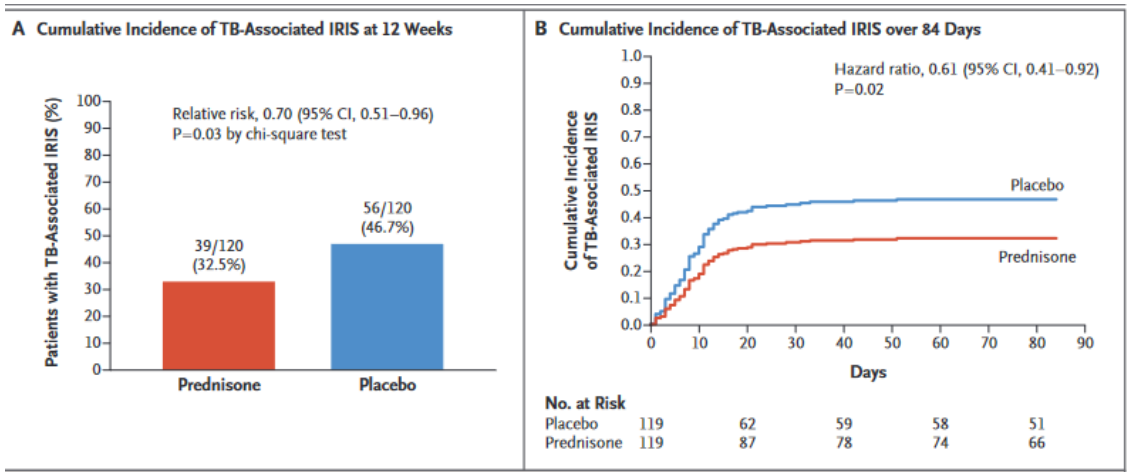


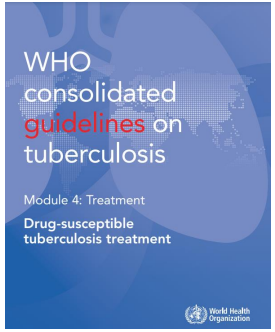
Figure 2. Cumulative Incidence of Paradoxical TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS).

Panel A shows the cumulative incidence of the primary end point of paradoxical TB-associated IRIS at 12 weeks. If paradoxical TB-associated IRIS had not developed before a patient died, withdrew, or was lost to follow-up, the patient was considered not to have had the syndrome. Panel B shows the cumulative incidence of TB-associated IRIS over 84 days. Diagnosis of TB-associated IRIS was determined according to the International Network for the Study of HIV-associated IRIS criteria.[14] Day 0 is the day ART was initiated.

N Engl J Med 2018;379:1915-25.
DOI: 10.1056/NEJMoa1800762

Recommendation 8.

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



Recommendation 9.

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents (strong recommendation, low to moderate certainty of evidence;

Children and infants (strong recommendation, very low certainty of evidence)

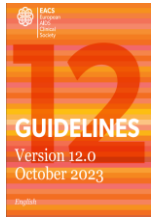
[a] Except when signs and symptoms of meningitis are present.

- https://www.hiv-druginteractions.org/

Recommandations de l'EACS

When to start ART in Persons with Opportunistic Infections (OIs)

	Initiation of ART	Comments
General recommendation	As soon as possible within 2 weeks after starting treatment for the opportunistic infection	
TB meningitis	In persons with CD4 < 50 cells/μL, ART should be initiated within the first 2 weeks after initiation of TB treatment, if close monitoring and optimal TB treatment can be ensured ART initiation should be delayed for 4 weeks in all other cases	Corticosteroids are recommended as adjuvant treatment Where very close monitoring and optimal treatment are available, ART could be initiated early in selected cases
Prevention		
Tuberculosis		
paradoxical IRIS	Prophylactic prednisone (40 mg qd po for 2 weeks, followed by 20 mg qd po for 2 weeks) may be considered as it reduced the risk of TB-IRIS by 30% in persons with CD4 cell count < 100 cells/μL and no TB meningitis or rifampin resistance who started anti-TB treatment within 30 days prior to ART	
Treatment		
In general, OI-IRIS resolve within a few weeks with continuation of specific treatment for the OI, without discontinuing ART and without anti-inflammatory treatment. In life-threatening or other cases where anti-inflammatory treatment is contemplated by the physician, corticosteroids or non-steroidal anti-inflammatory agents can be used. However, little or no data support their use or specific administration schedules in the specific conditions		
TB-IRIS	**Prednisone** 1.5 mg/kg/day po for 2 weeks, then 0.75 mg/kg/day for 2 weeks	



TUBERCULOSE LATENTE

Tableau 4 – Modalités de dépistage d'une ITL dans les pays à revenus élevés et à faible incidence de la tuberculose, à partir des données de la littérature (Source : ECDC /OMS).

Groupe cible	Tests	Commentaires
Personnes vaccinées par le BCG	IGRA	L'IDR est affectée par une vaccination antérieure par le BCG alors que les IGRA ne le sont pas
Enfants âgés de moins de 5 ans	IGRA ou IDR	Performances élevées des IGRA chez les enfants âgés de moins de 5 ans
Personnes vivants avec le VIH	IGRA	
Personnes vulnérables*	IGRA	Une seule visite, commodité
Personnes migrantes	IGRA ou IDR	Les IGRA ne nécessitent qu'une seule visite et ne sont pas affectés par une vaccination antérieure par le BCG

*Personnes vulnérables : Sans-abris, détenus, usagers de drogues

Indications de dépistage ITL (HCSP 2019)

Enfants jusqu'à 18 ans	Vivant au domicile d'un patient Contact de courte durée pour un enfant de moins de 5 ans Contact même de courte durée sur immunodépression
Migrants	Moins de 18 ans Vivant avec des enfants de moins de 18 ans Si immunodépression, si travaille en collectivité d'enfants, ou structures de soins
Professionnels de santé à l'embauche	Pas de suivi
PVVIH	Quelque soit le niveau de CD4
Instauration d'anti-TNF	
Candidats à une transplantation d'organes	
Patients dialysés chroniques	

Recos HCSP 2019

Le traitement de première intention des ITL, lorsque la souche de tuberculose est présumée sensible, repose chez l'adulte et chez l'enfant sur l'association des antituberculeux isoniazide et rifampicine pendant 3 mois.

Les alternatives possibles sont isoniazide 6 mois ou rifampicine 4 mois. L'association isoniazide et rifapentine permet une réduction de la durée du traitement, mais la rifapentine n'est pas disponible en France actuellement.

- En cas de contact avec une tuberculose à bacilles résistant à l'INH, le schéma de première intention est une monothérapie par rifampicine pendant 4 mois.
- L'administration d'un traitement antituberculeux préventif chez un sujet contact d'une tuberculose multi-résistante relève d'un avis d'experts comme cela est préconisé par le rapport du HCSP de 2014 sur la tuberculose à bacilles résistant [92]. L'aide du Groupe thérapeutique multidisciplinaire animé par le CNR-MyRMA qui proposera une attitude personnalisée en fonction (a) des résultats de l'enquête autour du cas et (b) des résultats cliniques, biologiques et radiologiques du cas index et du cas contact peut être sollicitée. En tout état de cause, tous les cas d'ITL au contact d'une tuberculose MDR ou XDR doivent faire l'objet d'une attention particulière et d'un suivi clinique au-delà de deux ans.

Merci de votre attention