Tuberculose pulmonaire : quid d'un traitement plus court ?

Loïc KASSEGNE

CLAT Alsace Nord

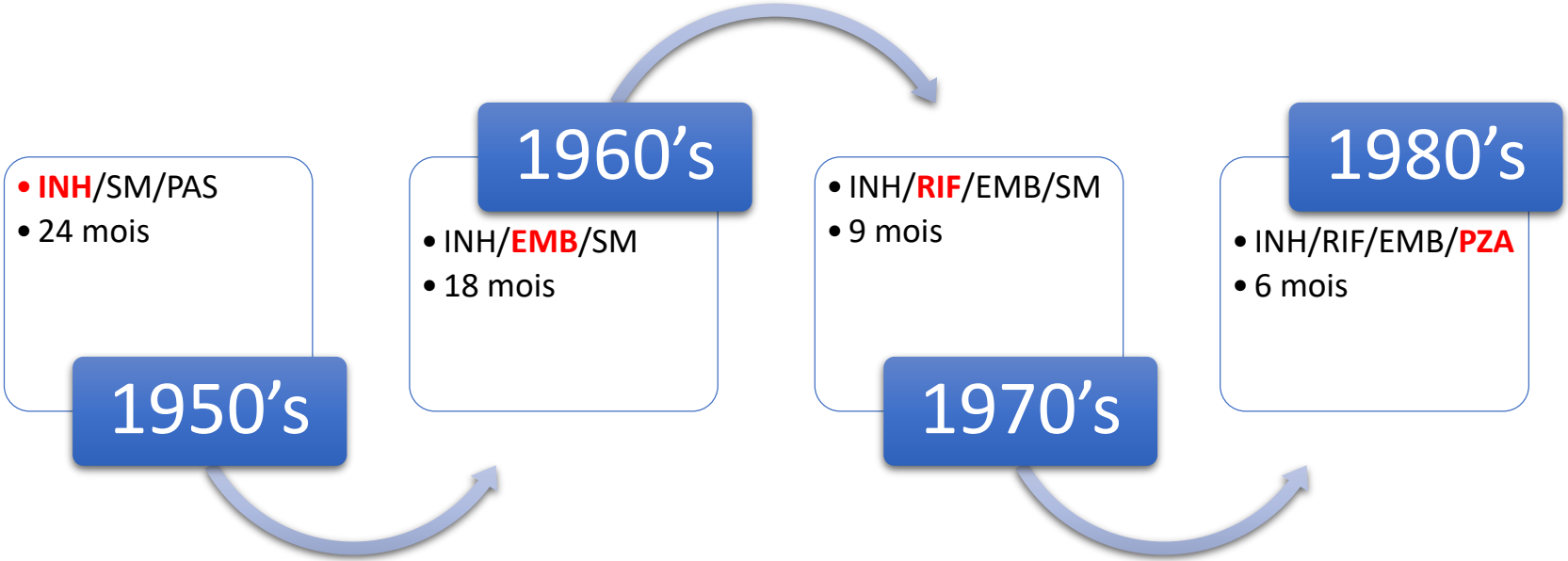
Journées des CLAT – 23 et 24 septembre 2024

Contexte

	MOLECULES	POSOLOGIE	DUREE
ATTAQUE	ISONIAZIDE RIFAMPICINE PYRAZINAMIDE ETHAMBUTOL	4-6 mg/kg 8-12 mg/kg 25-30 mg/kg 15-20 mg/kg	2 mois
ENTRETIEN	ISONIAZIDE RIFAMPICINE	4-6 mg/kg 8-12 mg/kg	4 mois

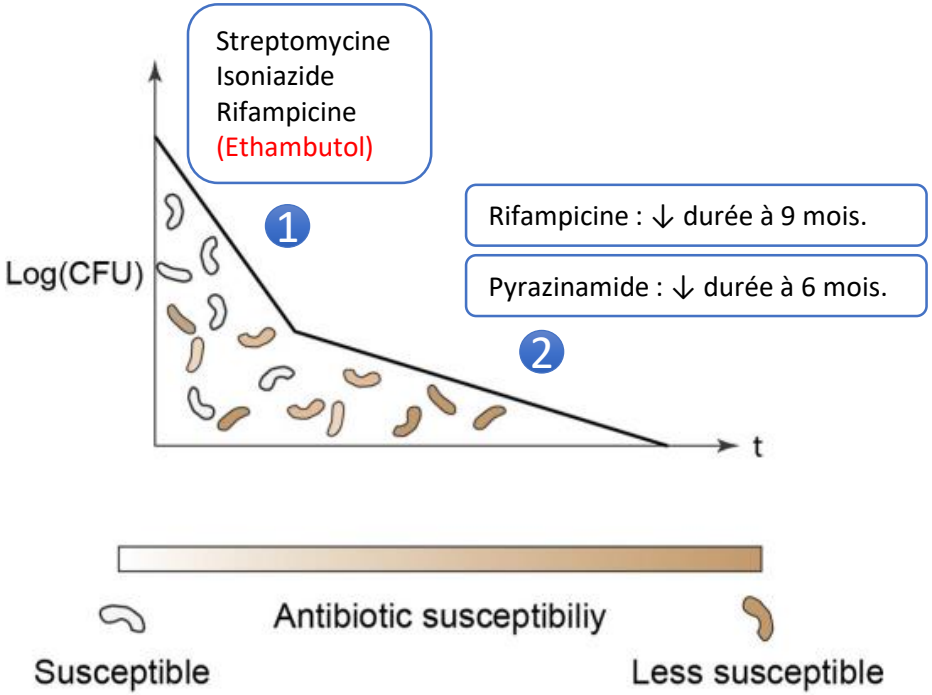
SPLF, Rev Mal Respir, 2004

Contexte



Grosset, J. H. (1989). Present Status of Chemotherapy for Tuberculosis. Clinical Infectious Diseases.

Evolution sous traitement



Phase 1:

- Bactéries à haut métabolisme.
- Risque : résistance.
- Anti-tuberculeux bactéricides.

Phase 2:

- Bactéries à faible/très faible métabolisme.
- Risque : rechute à bacilles sensibles.
- Anti-tuberculeux stérilisateurs.

Martinecz A et al, Plos Comput Biol, 2023

Contexte

- Augmentation des cas de tuberculose à la fin des années 80[1].
- Explosion du nombre de tuberculoses à bacilles multirésistants avec traitement moins efficace, mal toléré et très long[2].
- Nécessité de nouvelles molécules.

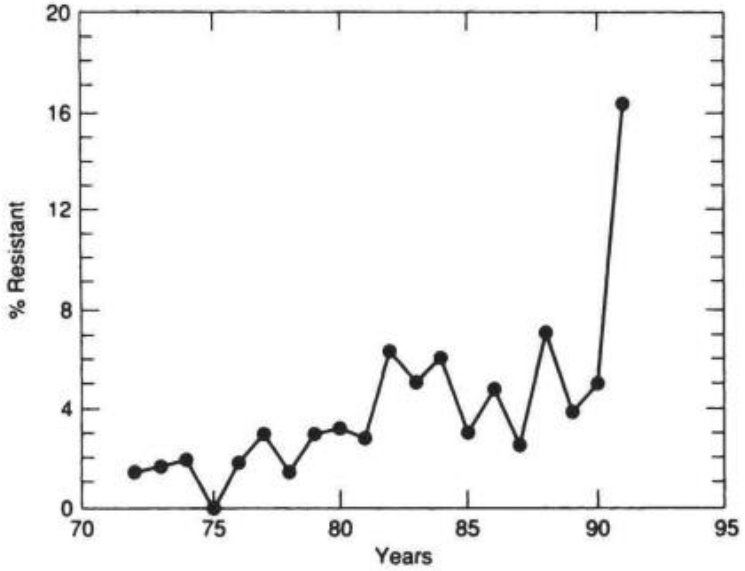
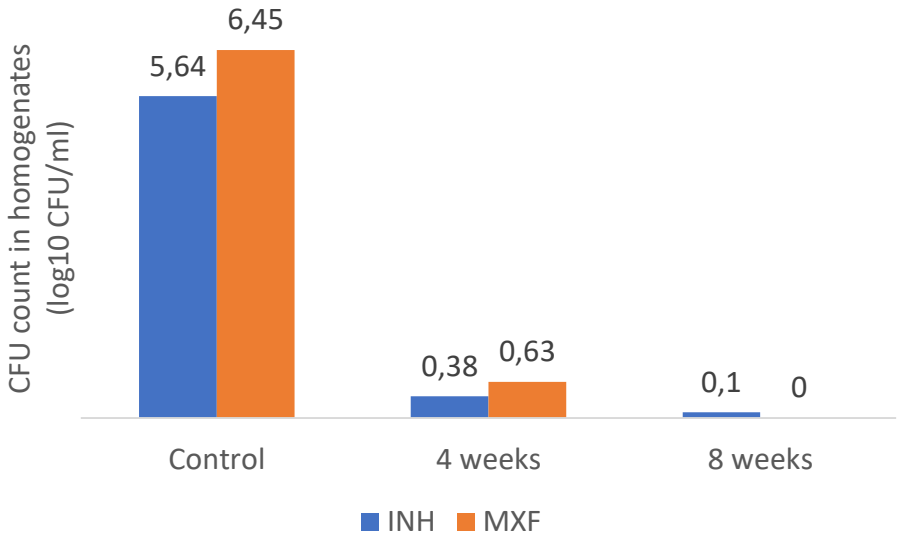


FIGURE 1. Combined isoniazid and rifampin resistance.

Raviglione M, Tuberculosis, Feb 2003
Neville K et al, Chest, Jan 1994

Fluoroquinolones

- Très efficace *in vitro* et *in vivo*[1].
- Molécule orale.
- Meilleure tolérance que les antibiotiques de seconde ligne.
- Amélioration du pronostic des tuberculoses MDR[2].



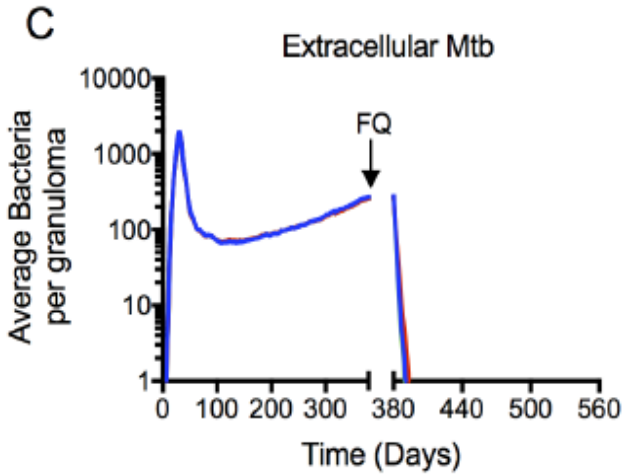
Miyazaki E et al, AAC, 1999
Aung K et al, Int J Tuberc Lung Dis, 2014

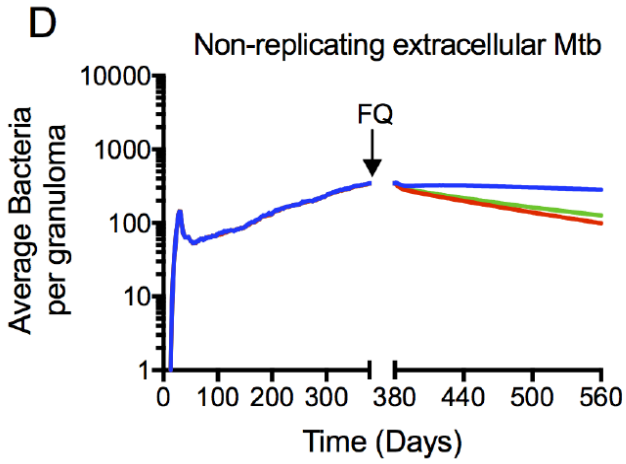
Fluoroquinolones: des résultats décevants.

Etude	Nombre	Caractéristique	Intervention	Culture positive à 2 mois	Rechute à 18-24 mois
Gillespie et al, NEJM, 2014	1931	71% cavité 7% VIH	4 RHZM 4 RZEM 2RHZE, 4RH	Bras 1 et 2 : **11,5%** Bras contrôle: **12,8%** RR 0,89 95% CI [0,69-1,16]	**15%** (RHZM) **20%** (RZEM) Contrôle 8%
Jindani et al, NEJM, 2014	827	65% cavité 27% VIH	2 RMZE, 2RPTM 2 RMZE, 4RPTM 2 RHZE, 4RH		**18,2%** **3,2%** **4,9%**
Merle C et al, NEJM, 2014	1836	49,8-52,1% cavité 0% VIH	4 RHZG 6 RHZE	14% 16,5%	**14,6%** **7,1%**

Fluoroquinolones

Les fluoroquinolones:
- Très bactéricide.
- Peu stérilisateur.





Pienaar, Plos Comput Biol, 2017

Fortes doses de rifampicine

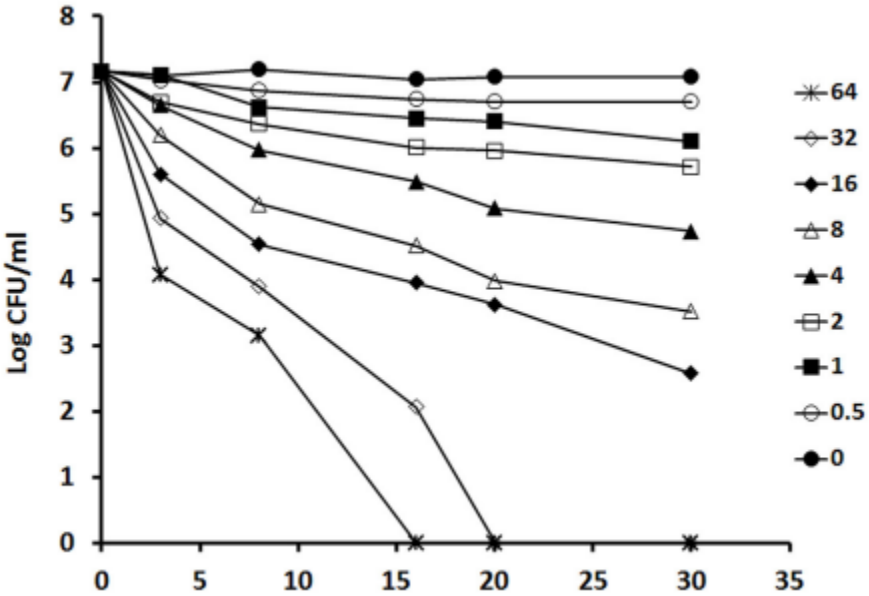


TABLE 4 | Organ CFU counts after 8 weeks of steroid treatment.

Positive culture from	R10HZ	R50HZ
Spleen only	11	0
Lung only	5	0
Both organs	5	0
Neither organs*	3	28
Total	24	28
Relapse (%)	87.5	0

*R10HZ, Rifampicin 10 mg/kg, Isoniazid 25 mg/kg, Pyrazinamide 150 mg/kg for 14 weeks; R50HZ, Rifampicin 50 mg/kg, Isoniazid 25 mg/kg, Pyrazinamide 150 mg/kg for 14 weeks. *Plate and broth count negative.*

Hu Y et al, Frontiers Microbiol, 2015
Liu Y et al, J Antimicrob Chemother, 2018

Rifapentine

- Synthèse en 1965
- Aussi (voir plus) efficace que la rifampicine vis-à-vis des bacilles quiescents[1].
- Pharmacocinétique plus favorable[2].
- Bonne tolérance jusqu'à 20 mg/kg[3].

	Rifampicine (600 mg)	Rifapentine (600mg)	Rifapentine (1200 mg)
C_{max}	10-12 mg/l	18-20 mg/l	28-30 mg/l
$t_{1/2}$	3-4 h	13-16h	
Liaison protéique	80%	> 95%	

1 Sarathy J et al, Antimicrob Agents Chemother, 2017
2 Weiner M et al, AJRCCM, 2004
3 Dooley KA et al, Clin Pharmacol Ther, 2012

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

- 2343 DS-TB pulmonaire ≥ 12 ans ,
- 26% Caverne
- 8% VIH
- 26% Examen direct très positif

	Contrôle	Rifapentine	
		R1	R2
Attaque : 2 mois	Isoniazide Rifampicine Ethambutol Pyrazinamide	Isoniazide **Rifapentine** Ethambutol Pyrazinamide	Isoniazide **Rifapentine** **Moxifloxacine** Pyrazinamide
Entretien : 2 à 4 mois	Isoniazide Rifampicine	Isoniazide Rifapentine	Isoniazide Rifapentine Moxifloxacine
Durée totale	6 mois	4 mois	4 mois

Dorman S et al, New Eng J Med, 2021

Outcome	Microbiologically Eligible Population				Assessable Population			
	Control (N=768)	Rifapentine–Moxifloxacin (N=791)	Rifapentine (N=784)	Total (N=2343)	Control (N=726)	Rifapentine–Moxifloxacin (N=756)	Rifapentine (N=752)	Total (N=2234)
Favorable								
Participants with outcome — no. (%)	656 (85.4)	668 (84.5)	645 (82.3)	1969 (84.0)	656 (90.4)	668 (88.4)	645 (85.8)	1969 (88.1)
Adjusted difference from control — percentage points (95% CI)	NA	1.0 (–2.6 to 4.5)	3.0 (–0.6 to 6.6)	NA	NA	2.0 (–1.1 to 5.1)	4.4 (1.2 to 7.7)	NA
Participant had negative culture at month 12 — no. (%)	643 (83.7)	656 (82.9)	636 (81.1)	1935 (82.6)	643 (88.6)	656 (86.8)	636 (84.6)	1935 (86.6)
Participant was seen at month 12 but no sputum was produced or cultures were contaminated but without evidence of *M. tuberculosis* — no. (%)	13 (1.7)	12 (1.5)	9 (1.1)	34 (1.5)	13 (1.8)	12 (1.6)	9 (1.2)	34 (1.5)
Unfavorable								
Participants with outcome — no. (%)	112 (14.6)	123 (15.5)	139 (17.7)	374 (16.0)	70 (9.6)	88 (11.6)	107 (14.2)	265 (11.9)
Outcome related to tuberculosis — no. (%)	24 (3.1)	45 (5.7)	75 (9.6)	144 (6.1)	24 (3.3)	45 (6.0)	75 (10.0)	144 (6.4)
Two consecutive positive cultures at or after week 17†	11 (1.4)	34 (4.3)	63 (8.0)	108 (4.6)	11 (1.5)	34 (4.5)	63 (8.4)	108 (4.8)
Participant not seen at month 12 but had positive culture when last seen	11 (1.4)	3 (0.4)	4 (0.5)	18 (0.8)	11 (1.5)	3 (0.4)	4 (0.5)	18 (0.8)
Clinical diagnosis of tuberculosis recurrence and treatment restarted	2 (0.3)	8 (1.0)	8 (1.0)	18 (0.8)	2 (0.3)	8 (1.1)	8 (1.1)	18 (0.8)

Dorman S et al, New Eng J Med, 2021

Recommandations

Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[8] (conditional recommendation, moderate certainty of evidence) – new recommendation.

World Health Organization, 2022

Fortes doses de rifampicine

SR1 : $R_{1200}HZE$
SR2 : $R_{1800}HZE$
} 4 mois

Control: $R_{600}HZE$ 6 mois

- Posologies in vivo (modèles murins) nécessaires ≥ 30 mg/kg/jour[1].
- Pas plus d'effets secondaires pour des posologies jusqu'à 50 mg/kg/jour[2,3].
- Pas de non infériorité démontrée statistiquement[4].

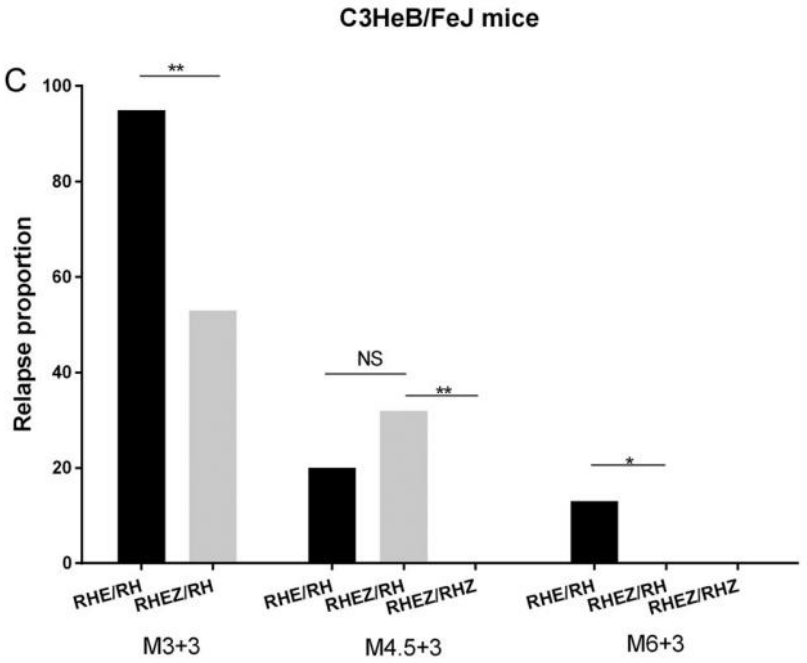
Table 2. Primary and Key Secondary Outcome Analyses

mITT-M primary analysis assessable outcomes	Control (N=187)	Study regimen 1 (N=186)	Study regimen 2 (N=186)
Favorable			
Participants with outcome - n (%)	174 (93.0)	167 (89.8)	161 (86.6)
Unfavorable			
Participants with outcome - n (%)	13 (7.0)	19 (10.2)	25 (13.4)
Adjusted risk difference to control (95% CI)		3.1 (-1.6 to 7.9)	6.3 (1.1 to 11.5)
Death during the treatment phase	3 (1.6)	4 (2.2)	0
Post-treatment death, TB a plausible cause	0	1 (0.5)	0
Lost to follow-up during the treatment phase	2 (1.1)	0	1 (0.5)
Withdrew from the trial during the treatment phase[1]	3 (1.6)	2 (1.1)	5 (2.7)
Change in treatment due to adverse event[2]	1 (0.5)	2 (1.1)	7 (3.8)
Two consecutive positive cultures after completing treatment	2 (1.1)	9 (4.8)	9 (4.8)
Retreated for TB due to clinical signs and symptoms without two consecutive positive cultures	2 (1.1)	1 (0.5)	3 (1.6)

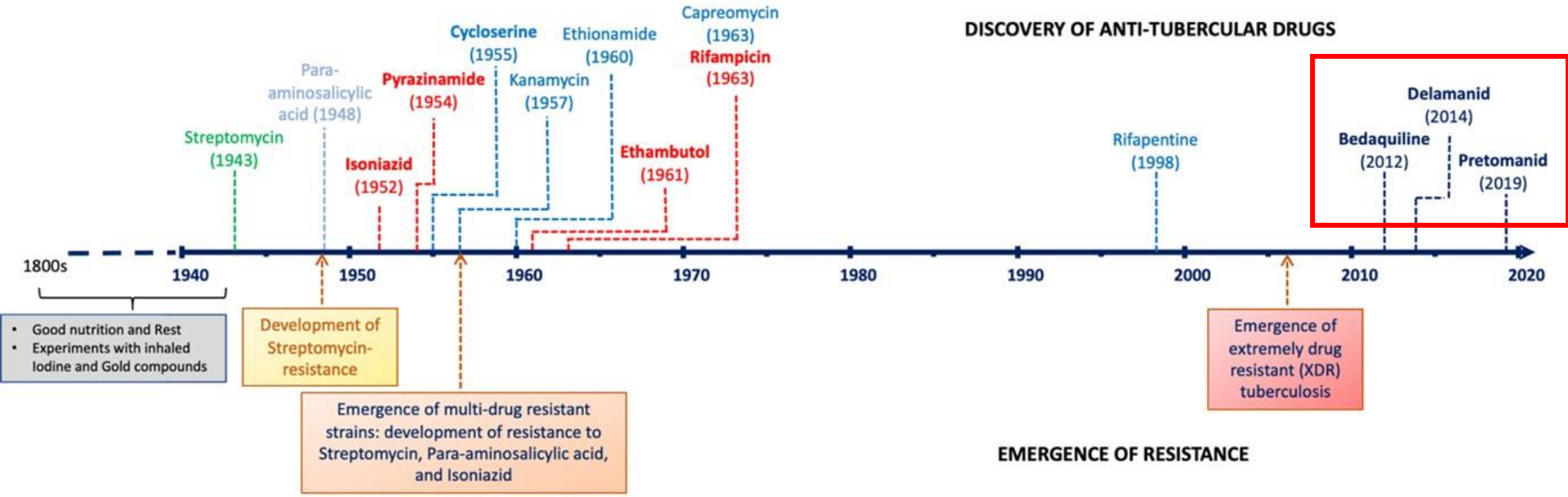
1 Liu Y et al, J Antimicrob Chemother, 2018;
2 Boeree M et al, AJRCCM, 2015;
3 Te Brake L et al, Eur Respir J, 2021
4 Jindani A et al, New Eng J Med, 2023

Prolonger le Pyrazinamide

- Arrêt du PZA après 2 mois car aucun gain sur le taux de rechute[1].
- Baisse du risque de rechute en prolongeant le PZA en modèle murin[2].



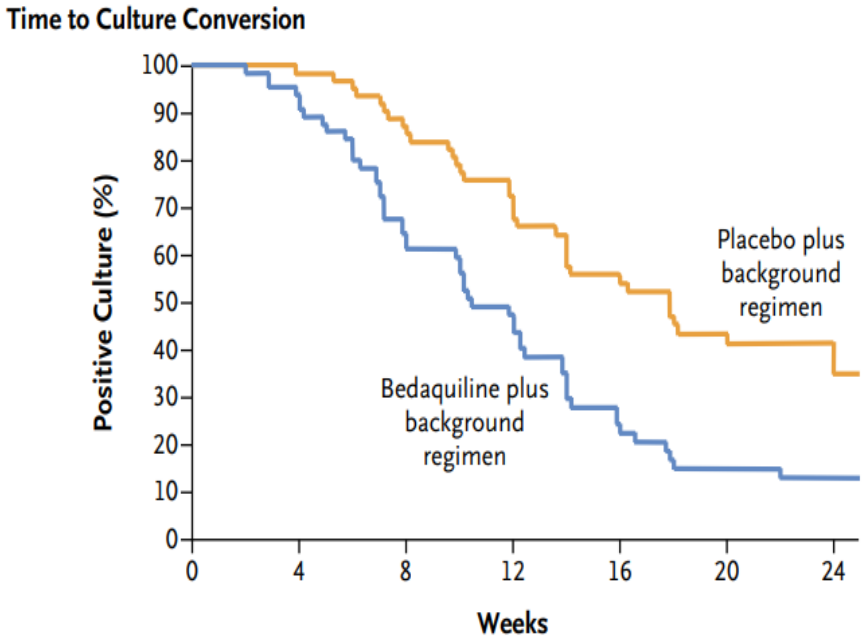
Am Rev Respir Dis, 1991
Lanoix J-P, AAC, 2016



https://www.tballiance.org/content/drugs-regimens-transforming-tb-drug-development

Bédaquiline

- Famille des diarylquinolines[1]
- Molécule clé dans le schéma MDR[2].
- Possible baisse de la durée de traitement quand associée au traitement standard, modèle murin[3]



1-Andries K et al, Science, Jan 2005
2-Diacon A et al, New Eng J Med, Aug 2014
3-Ibrahim M et al, AJRCCM, 2009

Bédaquiline & Rifampicine

93% des cas ont eu un traitement de 2 mois[4].

- Famille des diarylquinolines[1]
- Molécule clé dans le schéma MDR[2].
- 5,8% d'issue défavorable quand associé à la rifampicine forte dose et linézolide[4].

	Traitement standard (n=181)	Rifampicine et Linézolide (n=184)	Rifampicine, Bedaquiline-Linézolide (n=189)
Schéma	Isoniazide **Rifampicine$_{10}$** Pyrazinamide Ethambutol	Isoniazide **Rifampicine$_{20\text{-}35}$** Pyrazinamide Ethambutol **Linézolide**	Isoniazide **Rifampicine$_{20\text{-}35}$** Pyrazinamide Ethambutol **Bédaquiline** **Linézolide**
Durée	6 mois	≥ 2 mois	≥ 2 mois
Critère composite*	7 (3,9%)	21 (11,4%)	11 (5,8%)

*Critère composite : mort, traitement en cours ou maladie active à 2 ans.

1-Andries K et al, Science, Jan 2005
2-Diacon A et al, New Eng J Med, Aug 2014
3-Ibrahim M et al, AJRCCM, 2009
4-Paton N et al, New Eng J Med, 2023

Prétomanide

- Antibiotique de la famille des nitroimidazolés.
- Efficace sur les bacilles fortement métaboliques (modestement) et sur les bacilles quiescents.
- Inclus dans le schéma oral 6 mois des tuberculoses ≥ MDR[1,2] (BPaLM).

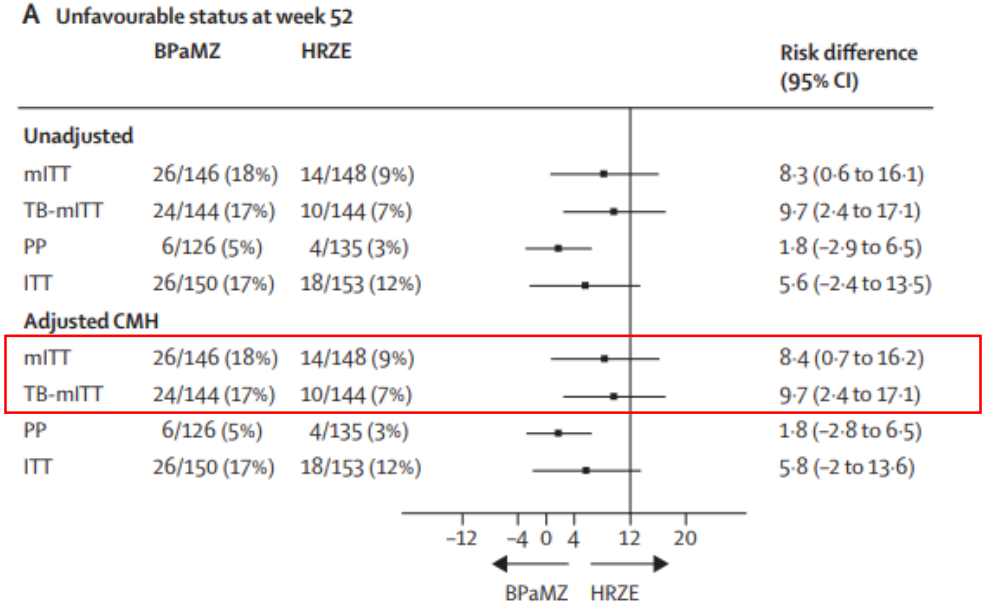
Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population		Modified Intention-to-Treat Population	
	Standard-Care Group (N=73)	BPaLM Group (N=72)	Standard-Care Group (N=66)	BPaLM Group (N=62)
Favorable outcome — no. (%)	34 (47)	55 (76)	34 (52)	55 (89)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)	32 (48)	7 (11)
Death — no. (%)	2 (3)	0	2 (3)	0
Early discontinuation — no. (%)	35 (48)	15 (21)	28 (42)	5 (8)
Adherence issues — no./total no. (%)	3/35 (9)	0	3/28 (11)	0
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)	17/28 (61)	5/5 (100)
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)	0	0
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	6/28 (21)	0
Other reason — no./total no. (%)†	2/35 (6)	0	2/28 (7)	0
Treatment failure — no.	0	0	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)	2 (3)	2 (3)
Recurrence — no.	0	0	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)	—	−37 (−53 to −22)

Nyang'wa B et al, New Eng J Med, Dec 2022
World Health Organ, WHO consolidated guidelines on tuberculosis. Module 4: treatment—drug-resistant tuberculosis treatment, 2022 update

Bédaquiline & Prétomanide

- Etude contrôlée randomisée, 303 TB sensible.
- BPZM 4 mois vs RHZE 6 mois.
- Taux d'issue défavorable après 52 semaines : échec, rechute ou arrêt de traitement.
- **Absence de non-infériorité (marge de 12%).**



B: Bedaquiline, P: pretomanide; Z: pyrazinamide; M: moxifloxacine

Cevik M et al, Lancet Infect Dis, 2024

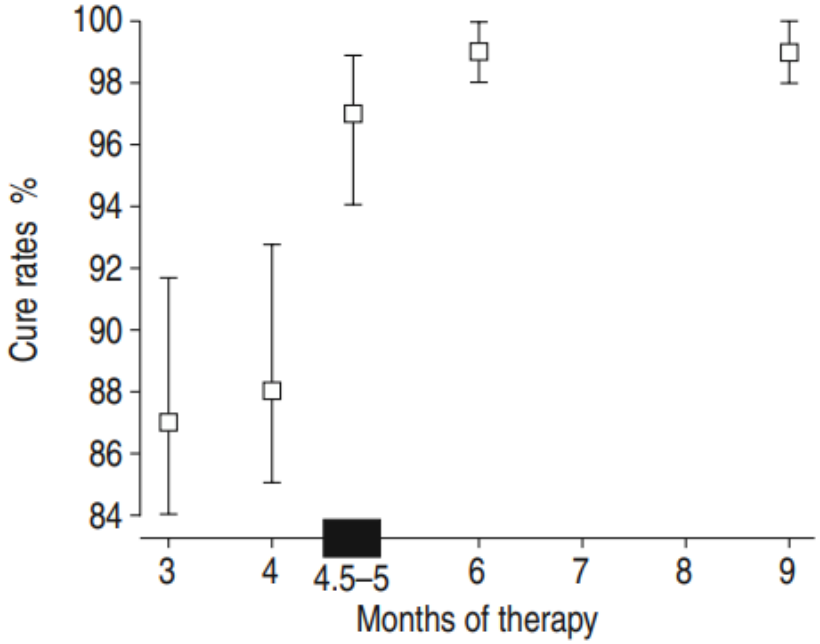
Bédaquiline & Prétomanide

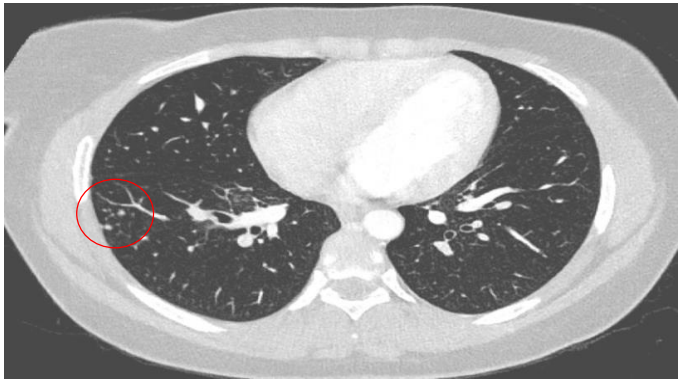
- RCT, 303 DS-TB
- BPZM 4 mois vs RHZE 6 mois.
- Taux d'issue défavorable après 52 semaines : échec, rechute ou arrêt de traitement.
- **Plus d'arrêt de traitement : plus d'effets secondaires++ hépatiques.**

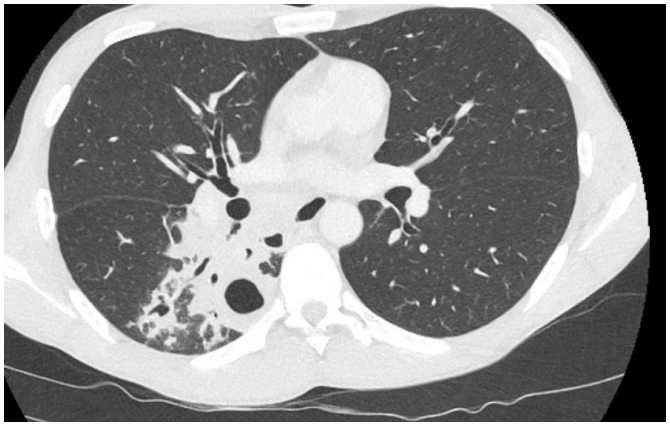
	DS-TB		
	2HRZE/4HR (N=153)	4BPaMZ (N=150)	Total (N=303)
Screen Failures	-	-	-
Received at least one dose of treatment (Safety)	153	150	303
Discontinued treatment (% of enrolled)†	11 (7.2%)	21 (14.0%)	32 (10.6%)
Completed treatment	142 (92.8%)	129 (86.0%)	271 (89.4%)
Discontinued follow-up (% of enrolled)†	8 (5.2%)	8 (5.3%)	16 (5.3%)
Completed follow-up	134 (87.6%)	121 (80.7%)	255 (84.2%)
Completion or discontinuation of treatment*			

Cevik M et al, Lancet Infect Dis, 2024

Paucibacillarité







Iseman M, Eur Respir J, 2002

SPUTUM-SMEAR-NEGATIVE PULMONARY TUBERCULOSIS

CONTROLLED TRIAL OF 3-MONTH AND 2-MONTH REGIMENS OF CHEMOTHERAPY

First Report

Hong Kong Chest Service, Tuberculosis Research Centre, Madras, India, and British Medical Research Council

- 1072 imageries évocatrices de TB ED négatif, 64% culture négative.
- RHZS 2 ou 3 mois vs SPH/S2H2 12 mois.

	Culture pré-thérapeutique	
	Négative	**Positive**
RHZ 2 mois	1% (2/175)	16% (12/73)
RHZ 3 mois	1% (3/168)	7% (5/74)

R: rifampicine; H: isoniazide; Z : pyrazinamide; S: streptomycine; P: PAS

Hong Kong Chest Service, Lancet, June 1979

A Controlled Trial of 3-Month, 4-Month, and 6-Month Regimens of Chemotherapy for Sputum-smear-negative Pulmonary Tuberculosis

Results at 5 Years[1,2]

Culture positive (n=459):

- RHZS tous les jours pendant 4 mois.
- 2% d'excavation
- **3% de rechute à 5 ans.**

Culture négative (n=1034):

- RHZS tous les jours pendant 3 mois.
- 1% d'excavation
- **6% de rechute à 5 ans.**

British Medical Research Council, Am Rev Respir Dis, 1989

Recommandation

Culture-Negative Pulmonary Tuberculosis in Adults

PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients with paucibacillary tuberculosis (ie, smear negative, culture negative)?

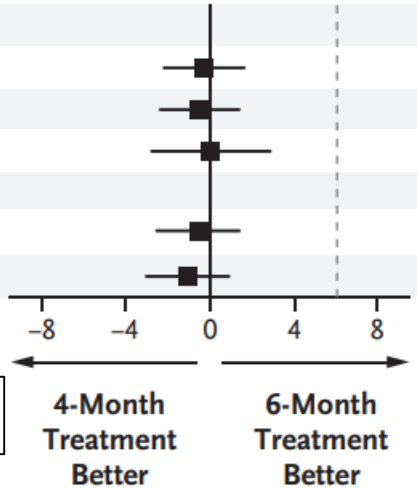
Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-uninfected adult patients with AFB smear- and culture-negative pulmonary tuberculosis *(conditional recommendation; very low certainty in the evidence)*.

Nahid P et al, Clin Infect Dis, 2016

Tuberculose « paucibacillaire » de l'enfant

2016-2018
RHZE 4 mois vs 6 mois
1204 enfants
7% culture positive

	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)



Primary outcome : unfavorable status (échec, rechute) by 72 weeks.

Tuberculose paucibacillaire : examen direct négatif, un seul lobe atteint, pas de cavité, pas de miliaire, pas d'épanchement pleural, pas d'adénopathie, pas d'atteinte bronchique.

Turkova A et al, New Eng J Med, March 2022

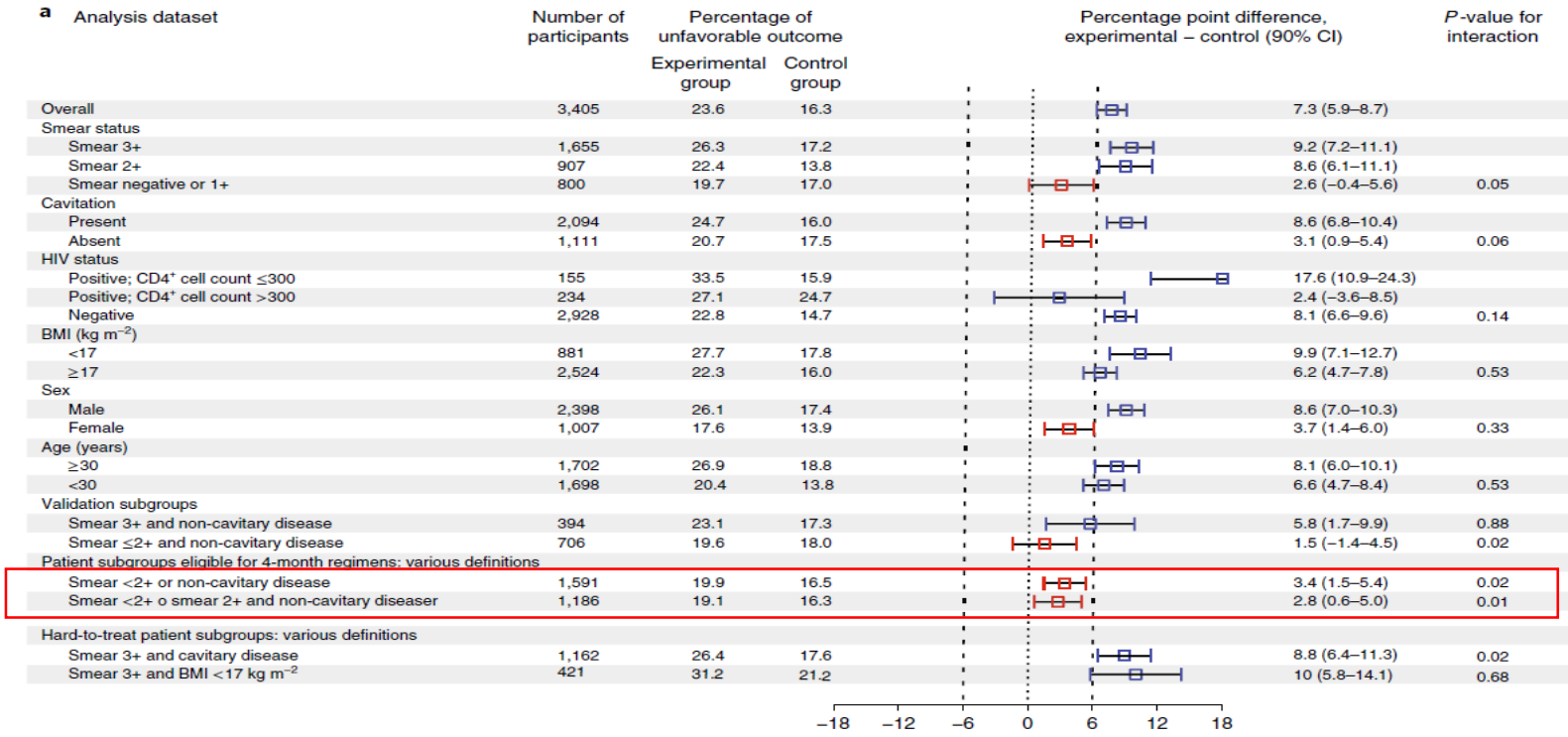
Recommandations

Recommendation 7.

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used (strong recommendation, moderate certainty of evidence) – new recommendation.

World Health Organization, 2022

Schéma 4 mois fluoroquinolones: sous-groupes



a Analysis dataset	Number of participants	Percentage of unfavorable outcome		Percentage point difference, experimental – control (90% CI)	*P*-value for interaction
		Experimental group	Control group		
Overall	3,405	23.6	16.3	7.3 (5.9–8.7)	
Smear status					
Smear 3+	1,655	26.3	17.2	9.2 (7.2–11.1)	
Smear 2+	907	22.4	13.8	8.6 (6.1–11.1)	
Smear negative or 1+	800	19.7	17.0	2.6 (−0.4–5.6)	0.05
Cavitation					
Present	2,094	24.7	16.0	8.6 (6.8–10.4)	
Absent	1,111	20.7	17.5	3.1 (0.9–5.4)	0.06
HIV status					
Positive; $CD4^+$ cell count ≤300	155	33.5	15.9	17.6 (10.9–24.3)	
Positive; $CD4^+$ cell count >300	234	27.1	24.7	2.4 (−3.6–8.5)	
Negative	2,928	22.8	14.7	8.1 (6.6–9.6)	0.14
BMI (kg m^{-2})					
<17	881	27.7	17.8	9.9 (7.1–12.7)	
≥17	2,524	22.3	16.0	6.2 (4.7–7.8)	0.53
Sex					
Male	2,398	26.1	17.4	8.6 (7.0–10.3)	
Female	1,007	17.6	13.9	3.7 (1.4–6.0)	0.33
Age (years)					
≥30	1,702	26.9	18.8	8.1 (6.0–10.1)	
<30	1,698	20.4	13.8	6.6 (4.7–8.4)	0.53
Validation subgroups					
Smear 3+ and non-cavitary disease	394	23.1	17.3	5.8 (1.7–9.9)	0.88
Smear ≤2+ and non-cavitary disease	706	19.6	18.0	1.5 (−1.4–4.5)	0.02
Patient subgroups eligible for 4-month regimens: various definitions					
Smear <2+ or non-cavitary disease	1,591	19.9	16.5	3.4 (1.5–5.4)	0.02
Smear <2+ o smear 2+ and non-cavitary diseaser	1,186	19.1	16.3	2.8 (0.6–5.0)	0.01
Hard-to-treat patient subgroups: various definitions					
Smear 3+ and cavitary disease	1,162	26.4	17.6	8.8 (6.4–11.3)	0.02
Smear 3+ and BMI <17 kg m^{-2}	421	31.2	21.2	10 (5.8–14.1)	0.68

Imperial M et al, Nature med, 2018

Shortening Treatment in Adults with Noncavitary Tuberculosis and 2-Month Culture Conversion

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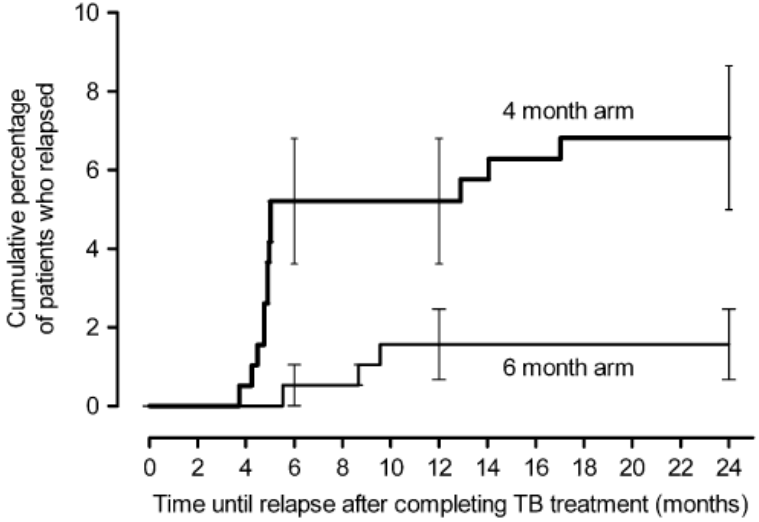

Number at Risk

6 Month Arm	193	193	191	190	187	184	182
4 Month Arm	193	193	192	181	178	174	173

- 396 PTB non cavitaire, multicentrique.
- 4 mois si évolution favorable et expectoration négative à 2 mois. Sinon, 6 mois.
- A 24 mois, taux de rechute: 7% vs 1,6%.

Johnson J et al, AJRCCM, 2009

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TABLE 1. BASELINE CHARACTERISTICS OF ENROLLED PATIENTS BY STUDY ARM (N = 394)*

Baseline Characteristics	4-Month Arm (*n* = 196)	6-Month Arm (*n* = 198)
Male, n (%)	119 (61)	120 (61)
Age, yr	31.2 (10)	30.3 (10)
Weight, kg	55.8 (10)	55.2 (10)
Body mass index, kg/m^2	20.6 (3)	20.3 (3)
Hemoglobin, g/dl	13.2 (2)	13.4 (2)
Chest radiograph—extent of disease,† n (%)		
Normal to minimal disease	77 (39)	91 (46)
Moderately advanced disease	94 (48)	91 (46)
Far advanced disease	25 (13)	16 (8)
Bilateral disease on chest radiograph	85 (43)	70 (35)
Highest sputum AFB smear grade, n (%)		
Negative	74 (38)	67 (34)
1+ to 2+	43 (22)	56 (28)
3+ to 4+	79 (40.3)	75 (37.9)
Time after inoculation in liquid media until positive sputum culture, d	11.0 (7)	10.0 (7)

Definition of abbreviation: AFB = acid fast bacillus.
* Values are mean (SD) unless otherwise noted.
† According to the scheme of the U.S. National Respiratory and Disease Association (25).

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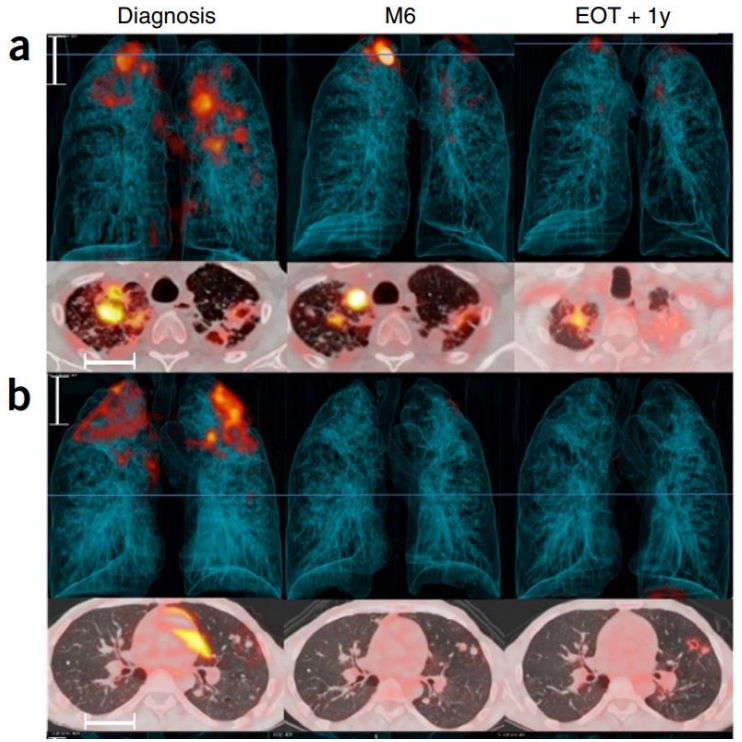
Autres pistes

- TEP scanner : AUC 0,8 pour prédire l'échec ou la rechute[1] (>80% de réduction de l'activité totale).
- Génomique[2]: score TB22 prédictif d'une guérison AUC 0,94.
- ARN 16s[3]: 67,9% des patients guéris et 100% des rechutes bien classées à 6 mois.

Malherbe S et al, Nature medicine, 2016



1 Cross G et al, J Infect Dis, 2023
2Heyckendorf J et al, Eur Respir J, 2021
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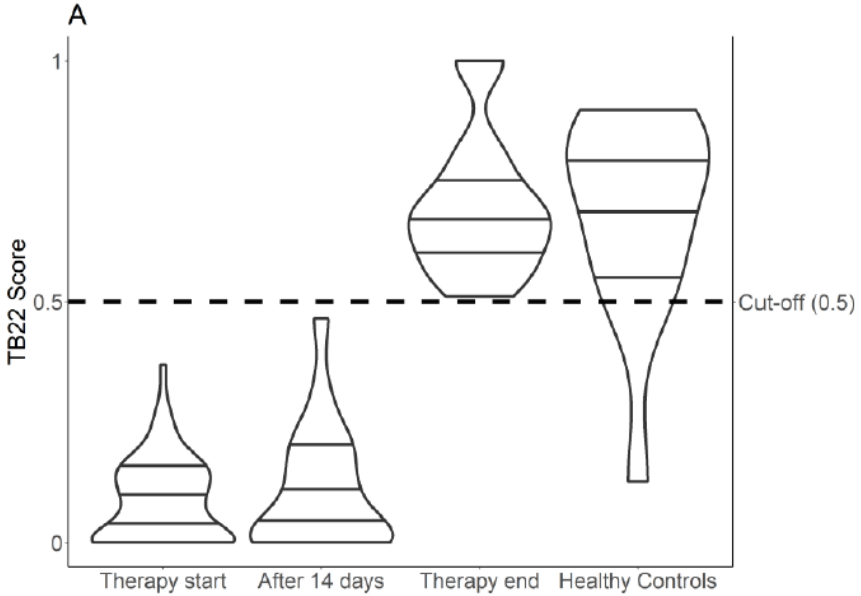

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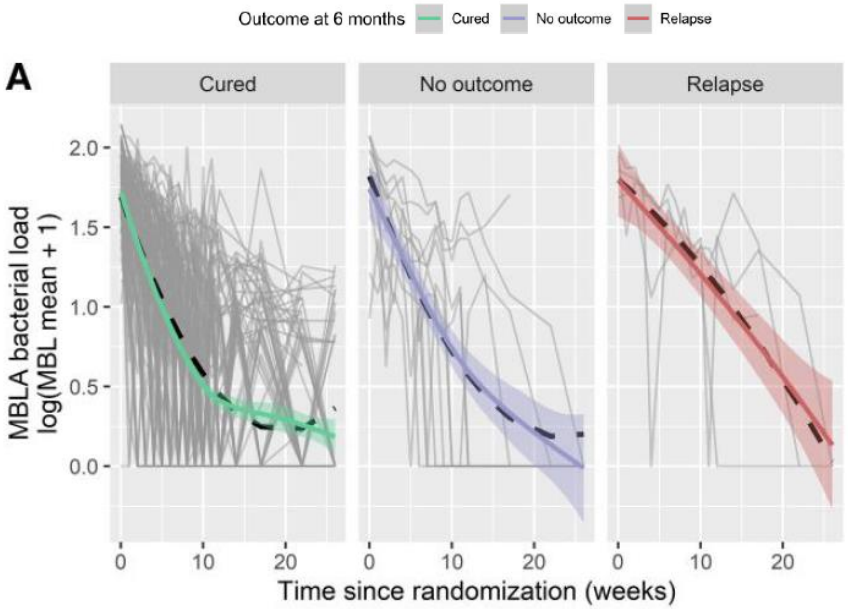

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Conclusion

- Oui, c’est déjà une réalité : 4 mois avec la moxifloxacine et la rifapentine mais non accessible en France.
- Oui, cela semble possible, soit:
  - En augmentant les capacités stérilisatrices du schéma: rifampicine forte dose, rifapentine, anti tuberculeux de seconde ligne.
  - En différenciant les tuberculoses :
    - Au début de traitement (bactériologie, imagerie) → tuberculose paucibacillaire.
    - Ou en cours de traitement (pet scanner, génomique, ARN 16S) → hyperrépondeurs.