Tuberculose : du neuf pour cette vieille maladie ?

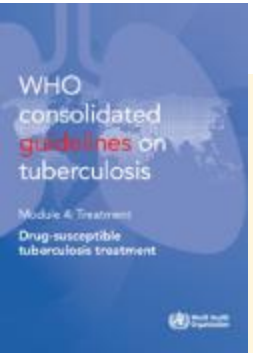
JRPI 2023

Macha TETART

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) : Aucune

Sommaire : ACTUALITES THERAPEUTIQUES

- **Recommandations thérapeutiques (NEWS 2022)**
- **Le modèle de la tuberculose multi résistante**
- **Des espoirs aussi pour la tuberculose multi S ?**
- **Spécificités chez PVVIH**



Traitement

- **Quadrithérapie INH(H)+RMP(R)+EMB(E)+PZA(Z) 2 mois puis bithérapie HR pendant 4 mois**

- **Rationnel de la polychimiothérapie :**

  Bacilles extra-cellulaires = Contagiosité & symptomatologie

  → *Rifampicine & Isoniazide*

  Bacilles intracellulaires quiescents = Dans les macrophages

  → *Rifampicine & Pyrazinamide*

  Bacilles extracellulaires au sein du caséum = risque de rechute

  → *Rifampicine*

Review > Int J Tuberc Lung Dis. 1999 Oct;3(10 Suppl 2):S231-79.

Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications

W Fox [1], G A Ellard, D A Mitchison

- **Formulation combinée** :
  Rifater® + Ethambutol puis Rifinah 300/150mg®

Traitement de 4 mois possible *… avec P

Patients aged 12 years or older with pulmonary DS-TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM).
(Conditional recommendation, moderate certainty of evidence) – **new recommendation**

EUROPEAN RESPIRATORY JOURNAL
CORRESPONDENCE
L. GUGLIELMETTI ET AL.

Rifapentine access in Europe: growing concerns over key tuberculosis treatment component

Régime de 4 mois avec Rifapentine : Study 31

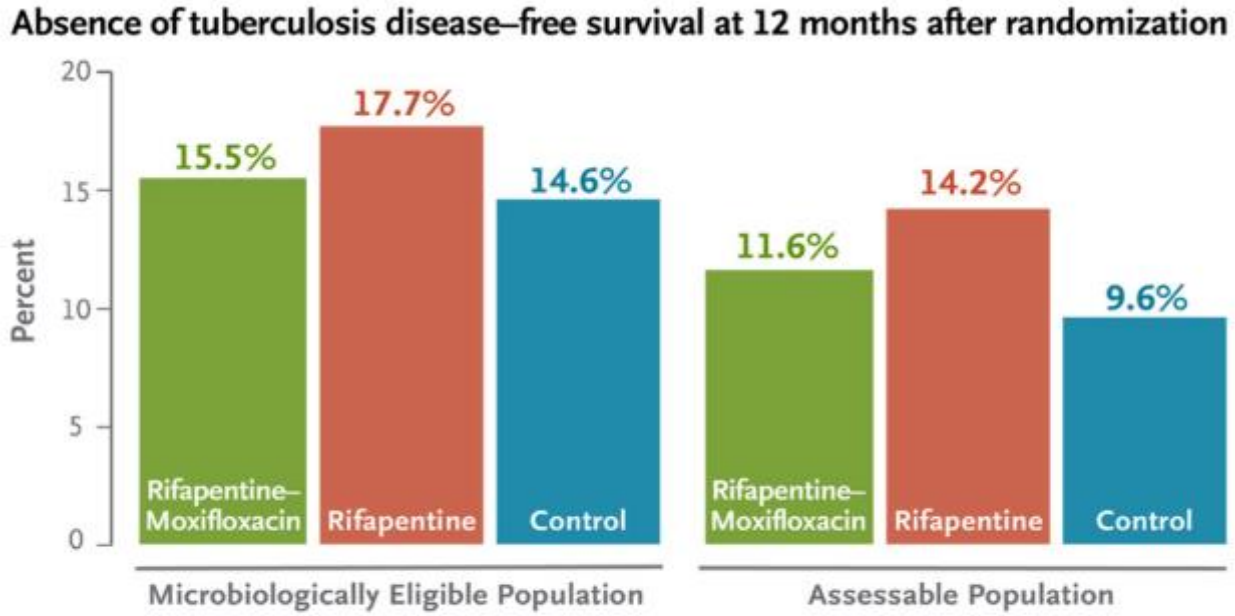
- Phase III, 13 pays, 2516 participants
- Tuberculose multi sensible, > 12 ans, > 40 kg

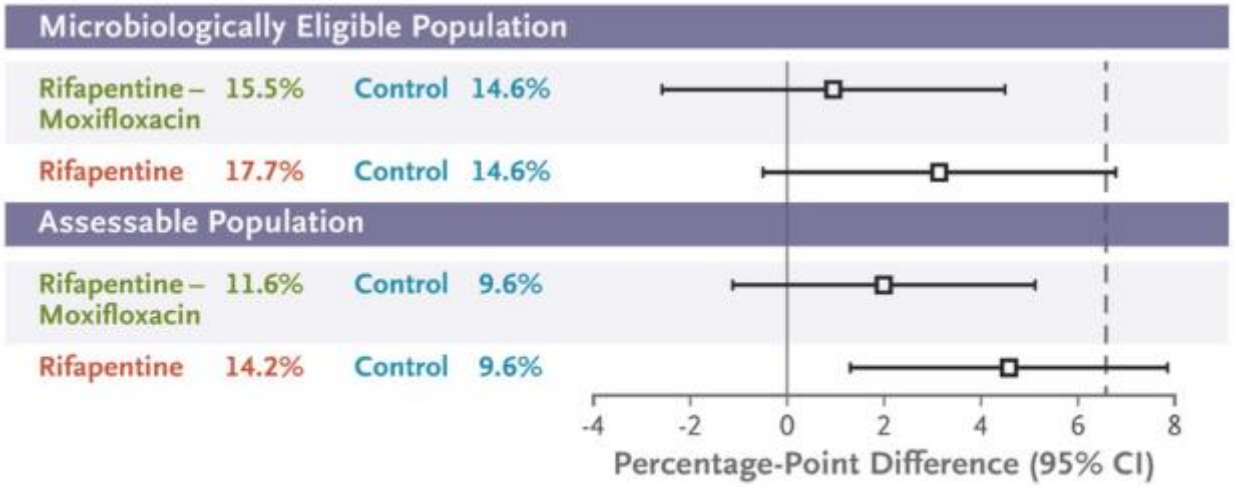
Bras vert : 4 mois Rifapentine + Moxifloxacin

Non inférieur !

Bras saumon : 4 mois Rifapentine

Bras bleu : régime standard





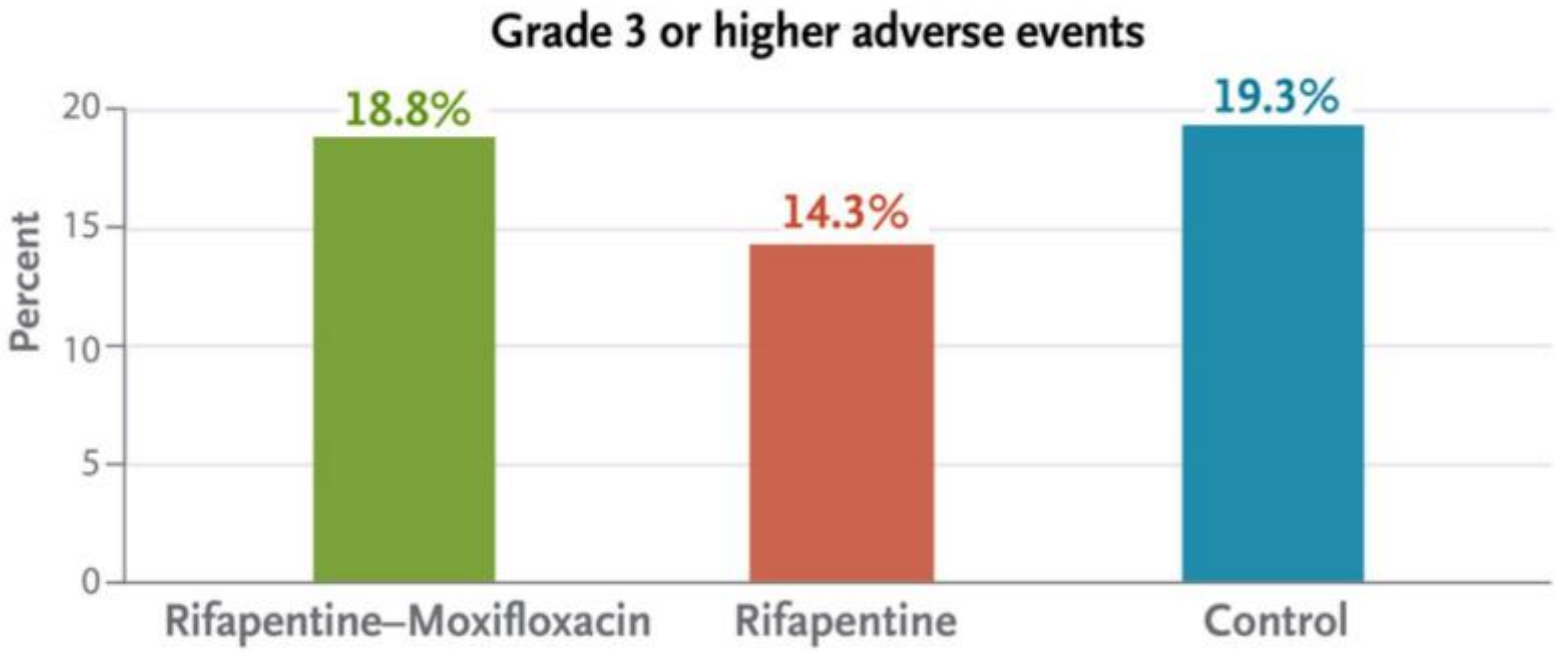
ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Susan E. Dorman, M.D., Payam Nahid, M.D., M.P.H., Ekaterina V. Kurbatova, M.D., Ph.D., M.P.H., Patrick P.J. Phillips, Ph.D., Kia Bryant, M.P.H., Kelly E. Dooley, M.D., Ph.D., Melissa Engle, C.R.T., C.C.R.C., Stefan V. Goldberg, M.D., Ha T.T. Phan, Dr.P.H., M.D., James Hakim, M.D., John L. Johnson, M.D., Madeleine Lourens, M.B., Ch.B., Ph.D., et al. for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

The NEW ENGLAND JOURNAL of MEDICINE

Régime de 4 mois avec Rifapentine : Study 31



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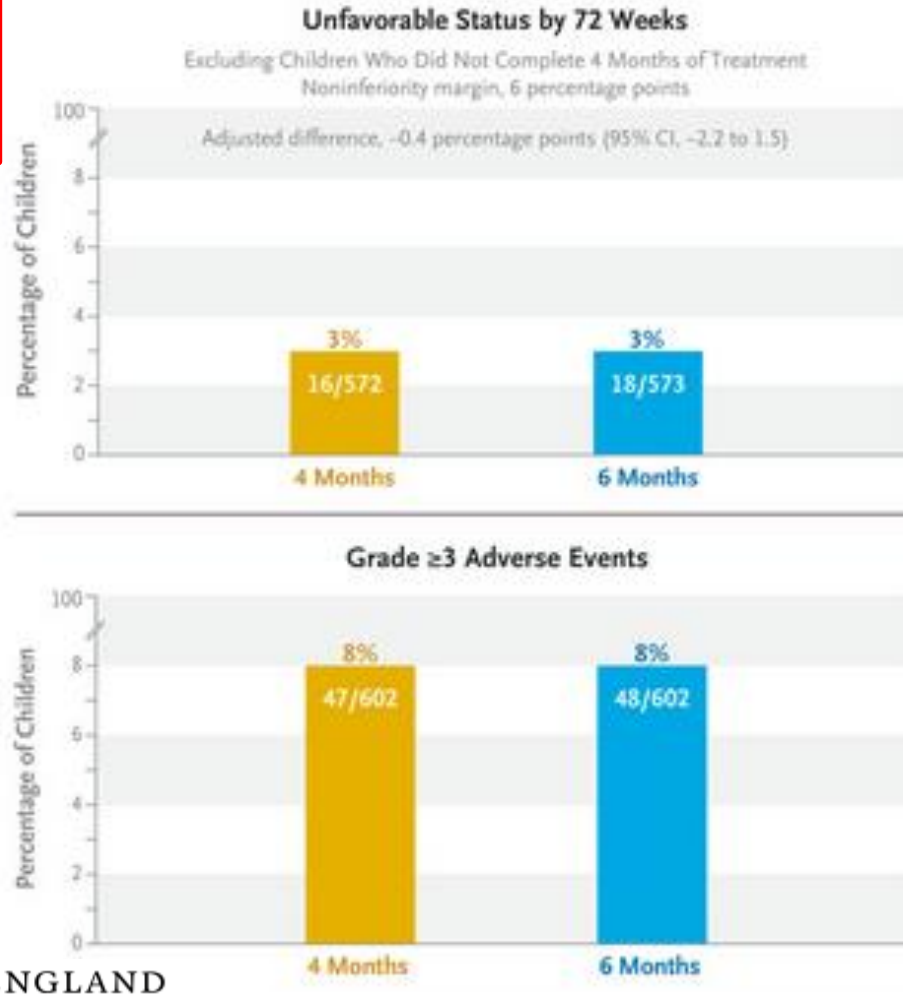
Âge plus petit, durée plus petite !

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.

< de 16 ans
tuberculose sensible
de forme non sévère

2 HRZ(E)/ 2HR
non inférieur
même taux d'E2



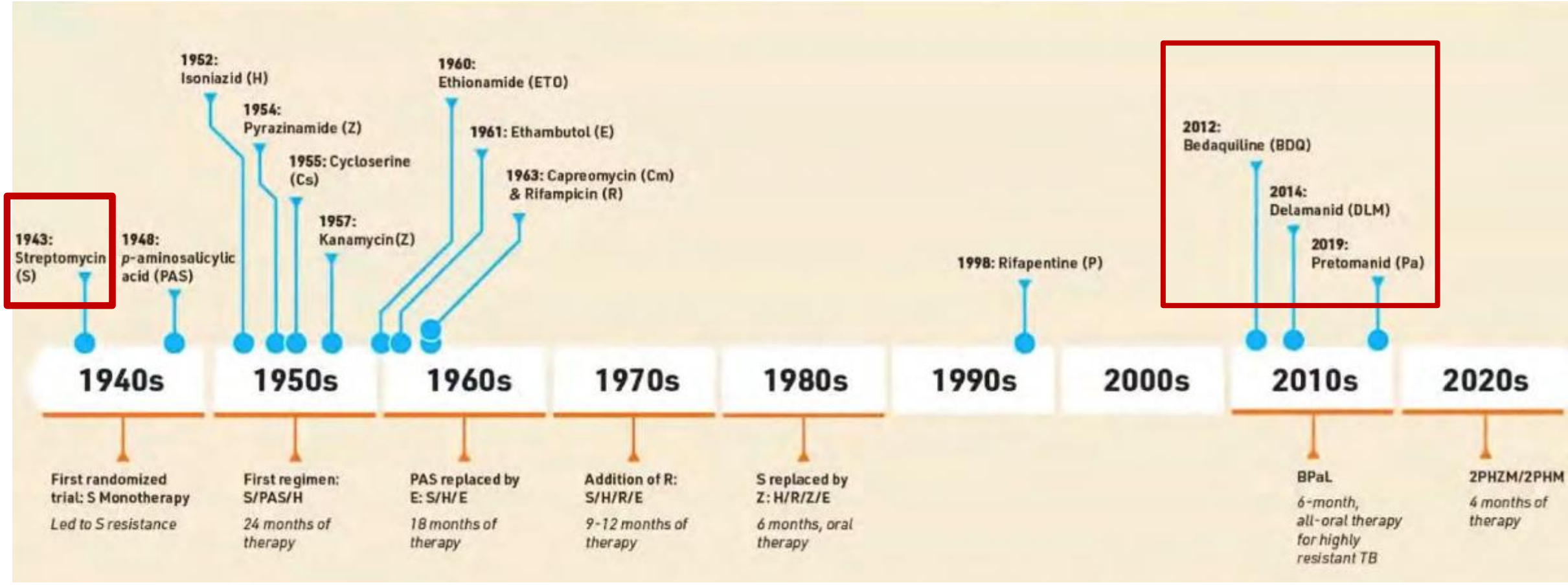
ORIGINAL ARTICLE

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Anna Turkova, M.R.C.P.C.H., Genevieve H. Wills, M.Sc., Eric Wobudeya, M.Med., Chishala Chabala, M.Med., Megan Palmer, M.B., Ch.B., M.Med., Aarti Kinikar, M.D., Syed Hissar, M.D., M.P.H., Louise Choo, Ph.D., Philippa Musoke, Ph.D., Veronica Mulenga, M.Med., M.Sc., Vidya Mave, M.D., M.P.H.&T.M., Bency Joseph, M.B., B.S., M.P.H., et al., for the SHINE Trial Team*

The NEW ENGLAND JOURNAL of MEDICINE

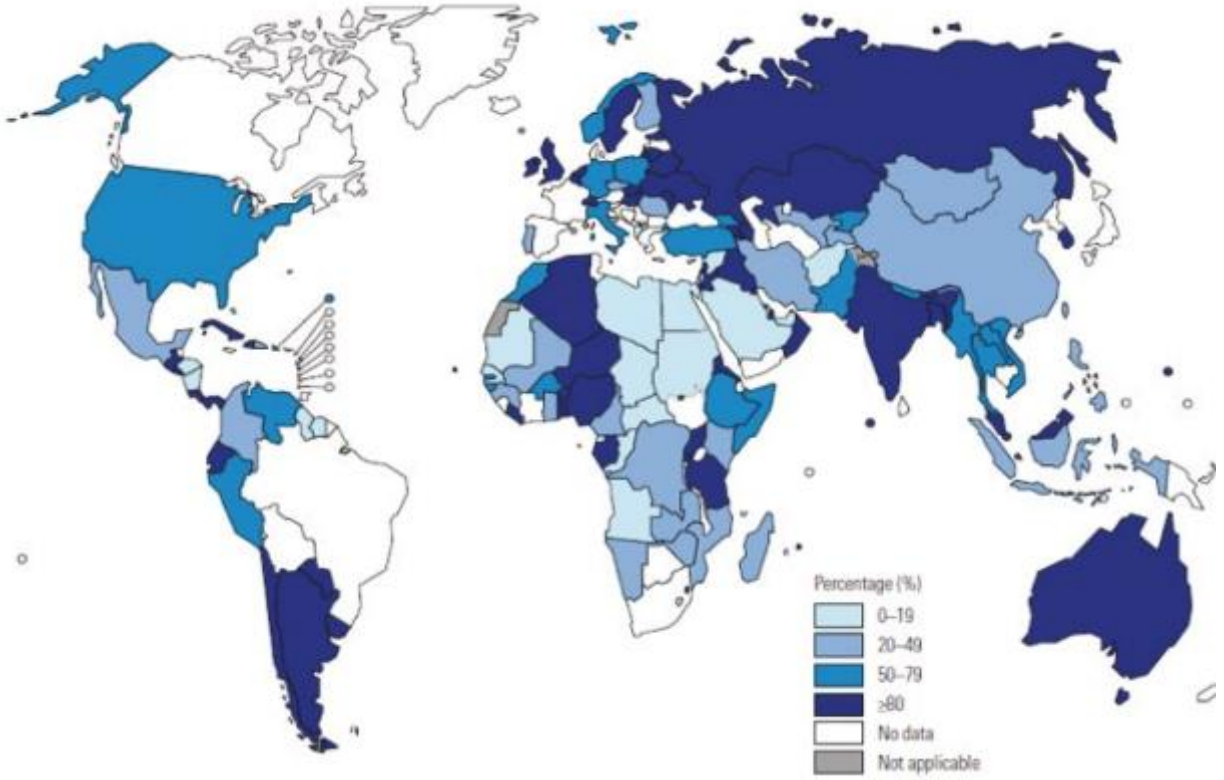
Frise TB Alliance



BLIGNY <3	Mode d'action	Posologie / Délivrance	Effets secondaires / Surveillance	Dosage
Bedaquiline = Sirturo	Inhibe ATP synthase mycobactérienne	400 mg/j pendant 15 jours puis 200 mg x3/sem , avec le repas	QT ! CPK, lipase, interactions CYP450	Bichat !
Pretomanide = Dovprela	Paroi (nitroimidazolés)	200mg avec repas	Digestif	
Linezolide = Zyvoxid	Oxalinodones inhibe su 50S du ribosome	600mg/J	Neuropathie, Myélotoxicité, Vision des couleurs	Pic : 12 à 20mg/L, Creux : <2mg/L
Delamanide	Nitroimidazolés	100mg x 2/J	Hep, alu, K, Mg, Ca, QT ! Interact CYP450	non
Ethionamide = Tracetor	Synthese de l acide mycolique des parois	+ Supplément B6 et PP 250 mg puis augmention par 250mg tous les 7J	Hépatique, TSH Psy	
Clofazimine = Lamprene	bactériostatique	100mg/J	Pigmentation peau, hép, neuro, QT	Pic : 0,5 à 2 mg/L Creux : 0,1 à 0,5mg/L
Cycloserine	Oxalinidones également	250mg pendant 7 jours puis 500mg/J + Supplémentat B6 et PP	Suivi neuro-psy	Pic : 20 à 35mg/L, Creux : <5mg/L (si bien toléré jusque 12)

Définitions

- **MDR : R Rifampicine ET Isoniazide**
- **Pré-XDR : MDR + R au moins 1 fluoroquinolone (Levo ou Moxiflo)**
- **XDR : Pré-XDR + 1 molécule des antibiotiques du groupe A (Bédaquiline ou Linezolide)**



Meeting report
of the WHO expert consultation
on the definition of extensively
drug-resistant tuberculosis,

27-29 October 2020

World Health Organization

Recommandations

Résistance H : RIF+PZA+ETM+FLQ 6 mois

Résistance R = régime MDR

MDR mais FQ S : BPaLM 6 mois sous conditions
(bedaquiline, pretomanid, linezolid, moxifloxacine)

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

Recommandations

- Si contre-indications au BPaLM (<14 ans, femmes enceintes ou allaitantes) non exposés au traitement 2ème intention > 1 mois

4–6 $Bdq_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E

***Initial phase:* 4–6 $Bdq_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto**

***Continuation phase:* 5 Lfx/Mfx-Cfz-Z-E**

- **Alternatives :** TTT complexe IV 18 M…

	Molécules
Groupe A	- Levofloxacine ou Moxifloxacine - Bedaquiline - Linezolide
Groupe B	- Clofazimine - Cycloserine
Groupe C	- Ethambutol - Delamanide - Pyrazinamide - Amikacine - Imipenem/Cilastine ou Meropénème - Ethionamide ou Prothionamide - Para-aminosalicylic acid

The NEW ENGLAND JOURNAL of MEDICINE

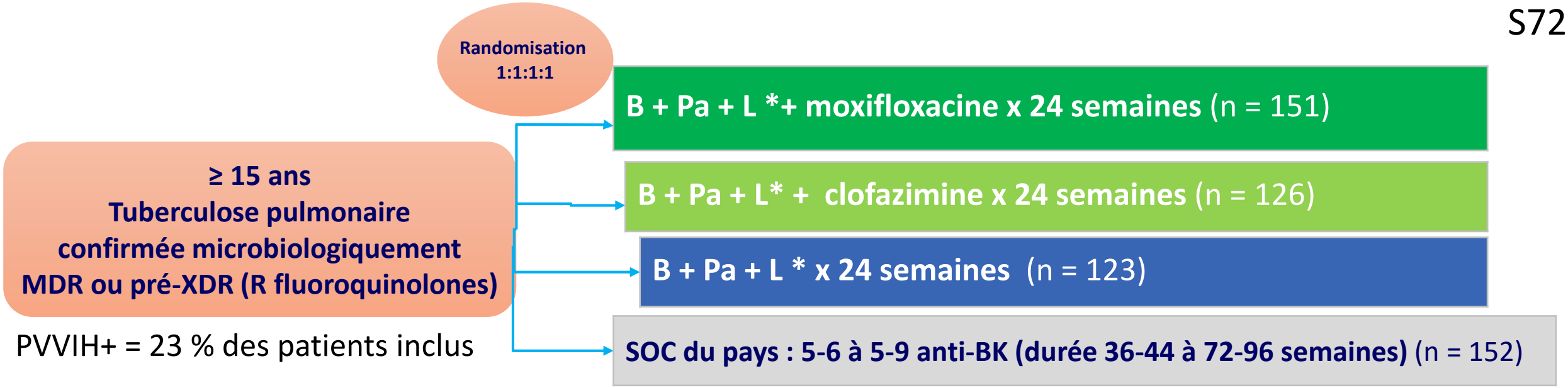
A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Sarah K. Meredith, M.Sc., Chen-Yuan Chiang, Dr.Philos., Francesca Conradie, M.B., Ch.B., Doljinsuren Dalai, M.D., Armand van Deun, Ph.D., Phan-Thuong Dat, Ph.D., Ngoc Lan, Ph.D., Iqbal Master, M.B., Ch.B., Tesfamariam Mebrahtu, M.D., Daniel Meressa, M.D., et al., for the STREAM Study Collaborators*

Essai TB-PRACTECAL

- Essai randomisé, en ouvert, 3 pays (Biélorussie, Ouzbékistan, Afrique du Sud)

S72



* linézolide 600 mg/j x 16 semaines puis 300 mg/j x 8 semaines

- Critère de jugement principal
  - % avec évolution défavorable à S72 post-randomisation (échec traitement, décès, arrêt du traitement, rechute, perdu de vue)
  - Borne de non-infériorité = 12 %

Nyang'Wa BT, CROI 2022, Abs. 79

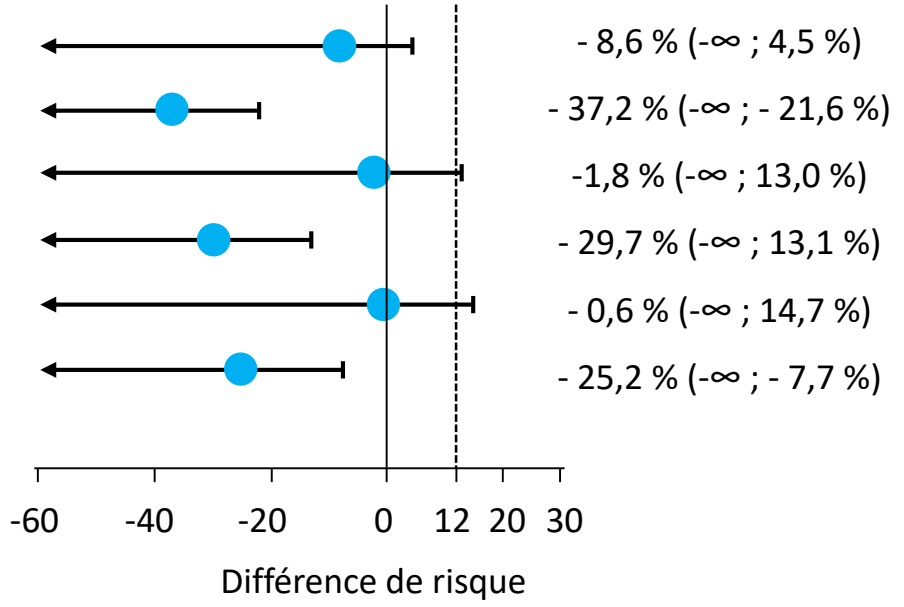
Essai TB-PRACTECAL

ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

December 22, 2022
N Engl J Med 2022; 387:2331-2343
DOI: 10.1056/NEJMoa2117166

	Bras contrôle	Bras d'investigation	Différence de risque (IC 98,3 % unilatéral)
BPaLM per protocole	4/33 (12,1 %)	2/57 (3,5 %)	- 8,6 % (-∞ ; 4,5 %)
BPaLM ITTm	32/66 (48,5 %)	7/62 (11,3 %)	- 37,2 % (-∞ ; - 21,6 %)
BPaLC per protocole	4/33 (12,1 %)	6/58 (10,3 %)	-1,8 % (-∞ ; 13,0 %)
BPaLC ITTm	32/66 (48,5 %)	12/64 (18,8 %)	- 29,7 % (-∞ ; 13,1 %)
BPaL per protocole	4/33 (12,1 %)	6/52 (11,5 %)	- 0,6 % (-∞ ; 14,7 %)
BPaL mITT m	32/66 (48,5 %)	14/60 (23,3 %)	- 25,2 % (-∞ ; - 7,7 %)



B = bédaquiline ; Pa = prétomanide ; L = linézolide ;
M = moxifloxacine ; C = clofazimine

Essai TB-PRACTECAL

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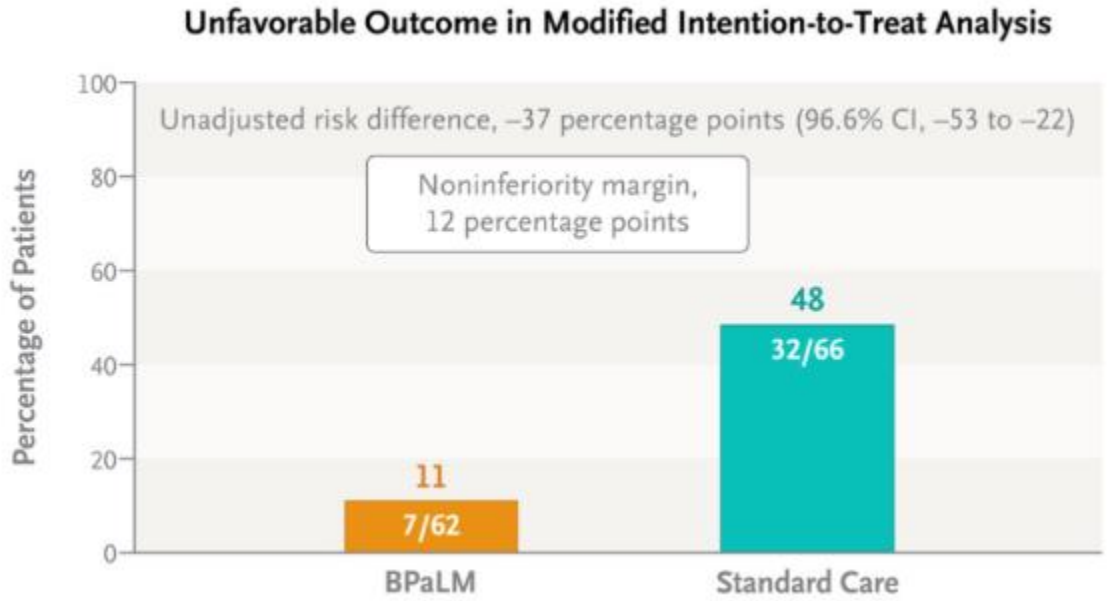
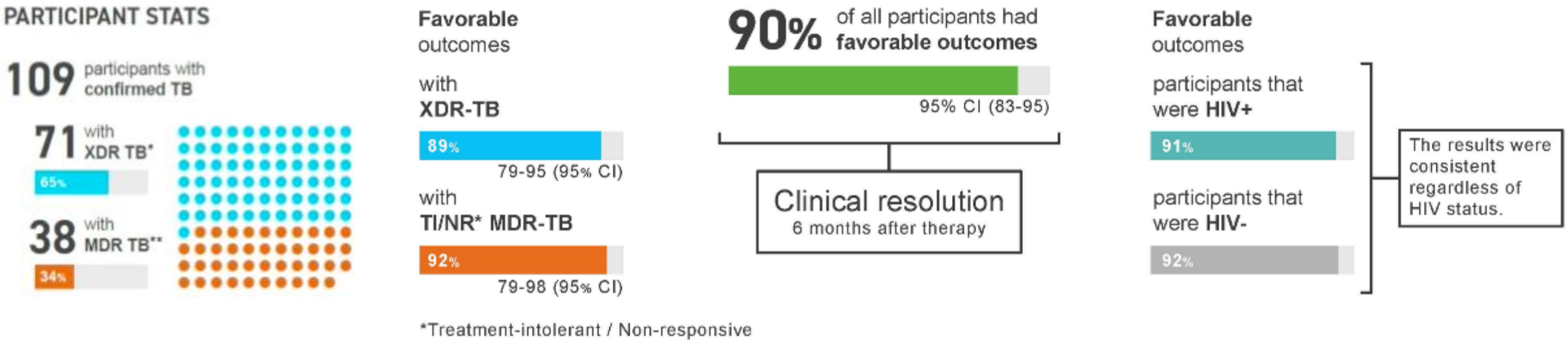


EIG ou EI ≥ grade 3

	%
SOC	58,9 %
BPaLM	**19,4 %**
BPaLC	31,9 %
BPaL	21,7 %

- **Conclusions**
  - Tous les bras avec BPaL pendant 24 semaines sont très efficaces et bien tolérés
  - BPaLM est le traitement le plus efficace et le mieux toléré

Shortening Success : Nix-TB



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

ORIGINAL ARTICLE

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

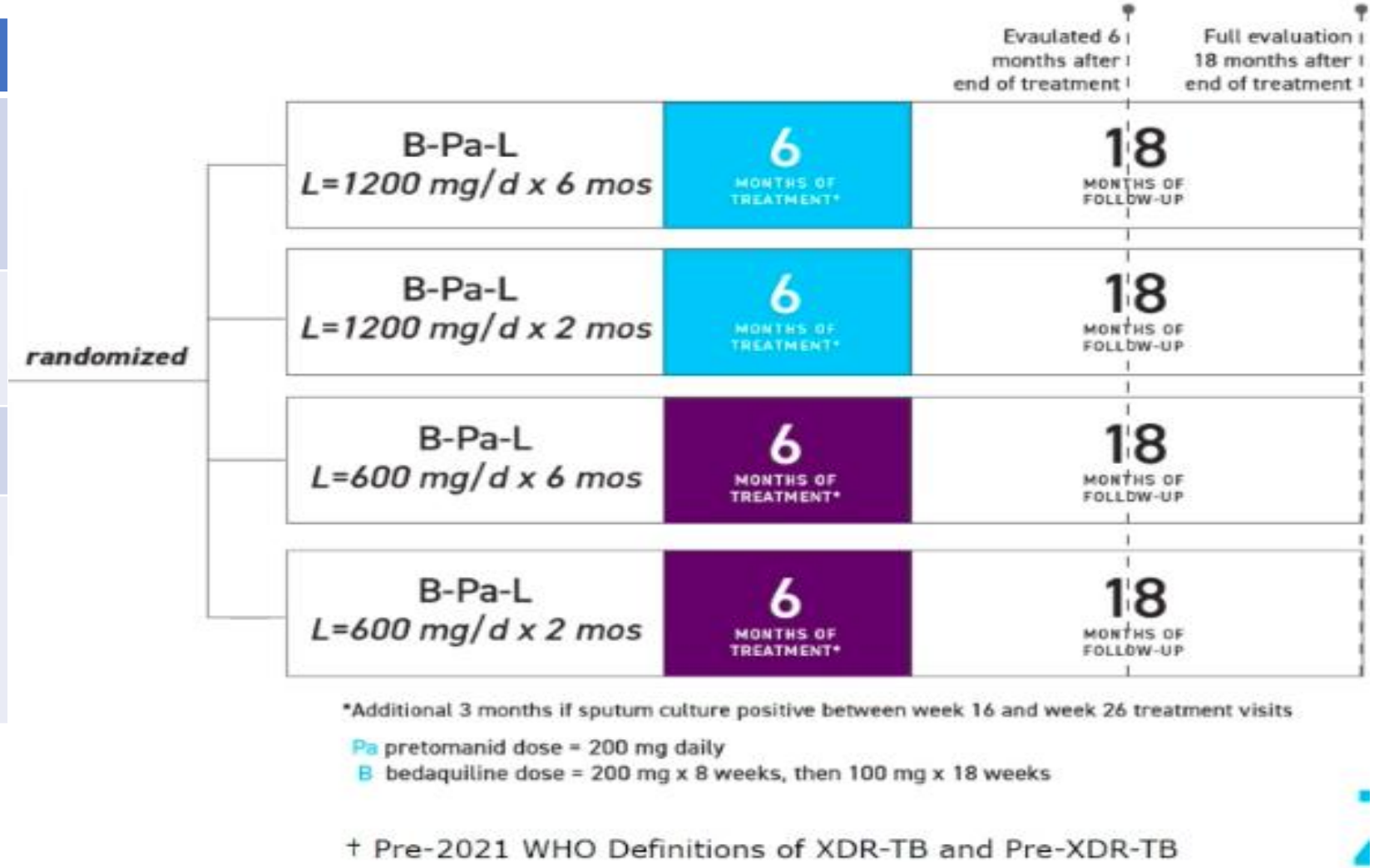
Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., et al., for the Nix-TB Trial Team*

The NEW ENGLAND JOURNAL of MEDICINE

March 5, 2020
N Engl J Med 2020; 382:893-902
DOI: 10.1056/NEJMoa1901814
Chinese Translation 中文翻译

ZeNix : Linezolide Optimization Trial

ZeNix : phase III
Bedaquiline + Pretonamid + **Linezolide mais dose et durée variables en aveugle**
Afrique du Sud, Russie, Géorgie, Moldavie
BK XDR ou échec/intolérance MDR
Critère de jugement : échec bactériologique, rechute, ou échec clinique



ZeNix : Linezolide Optimization Trial

MDR-TB = 26%, Pré-XR = 47%, XR = 41%

ZeNix N=181	Efficacité	Neuropathie	Myélo-suppression	Modification, interruption
1200L6M (n=45)	**93%**	38%	29%	51%
1200L2M (n=46)	**89%**	24%	15%	28%
600L6M (n=45)	**91%**	**24%**	**13%**	**13%**
600L2M (n=45)	**84%**	13%	16%	13%

ORIGINAL ARTICLE

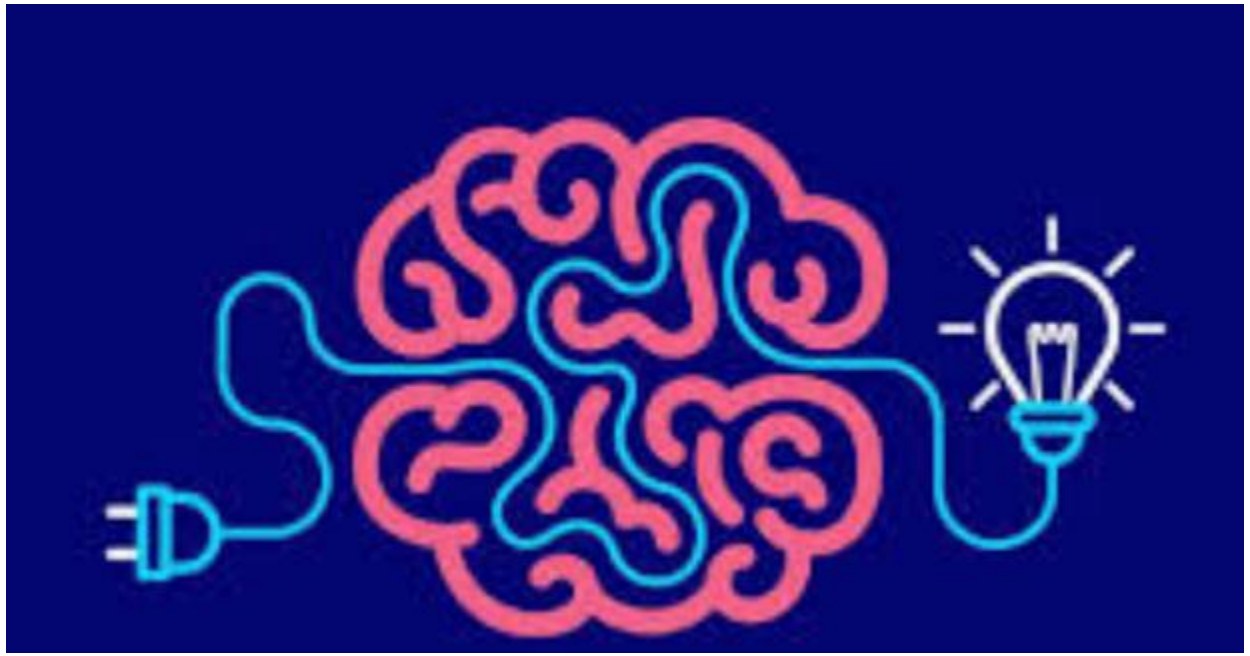
The NEW ENGLAND JOURNAL of MEDICINE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

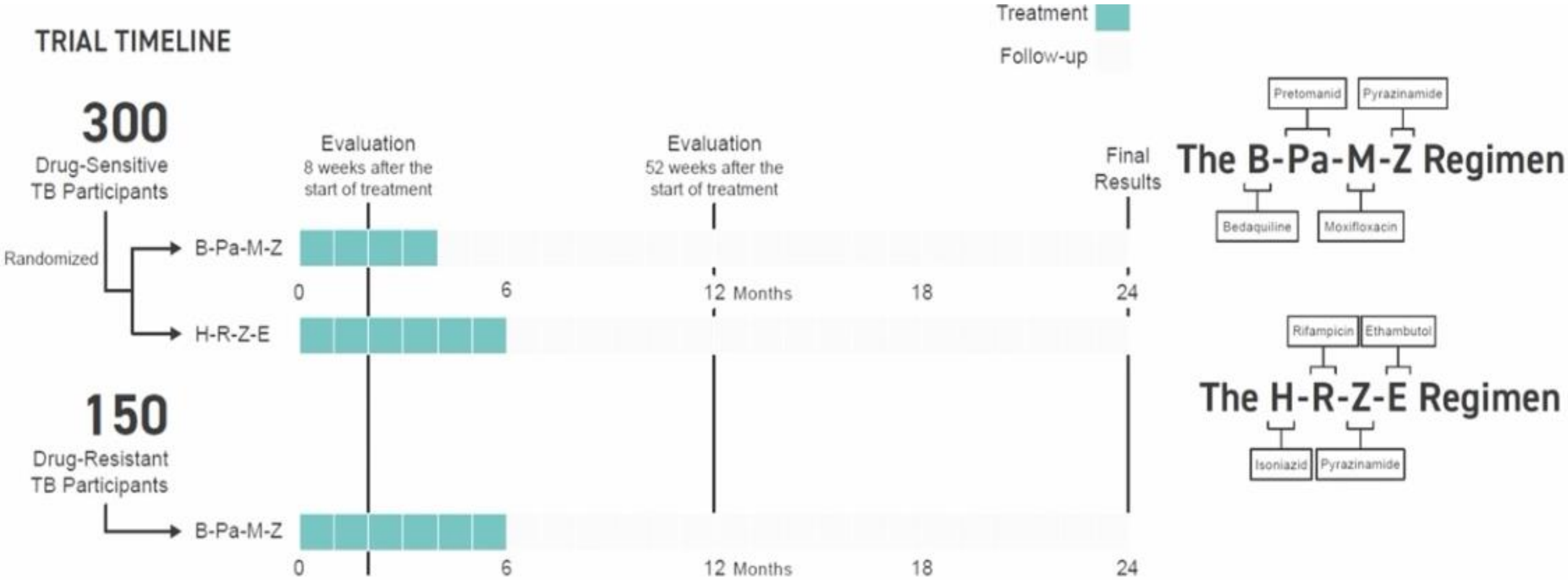
Francesca Conradie, M.B., B.Ch., Tatevik R. Bagdasaryan, M.D., Sergey Borisov, M.D., Pauline Howell, M.D., Lali Mikiashvili, M.D., Nosipho Ngubane, M.D., Anastasia Samoilova, M.D., Sergey Skornykova, M.D., Elena Tudor, M.D., Ebrahim Variava, M.D., Petr Yablonskiy, Ph.D., Daniel Everitt, M.D., et al.,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

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

Peut-on étendre ce modèle au traitement de la tuberculose multisensible ?



SIMPLICI- TB



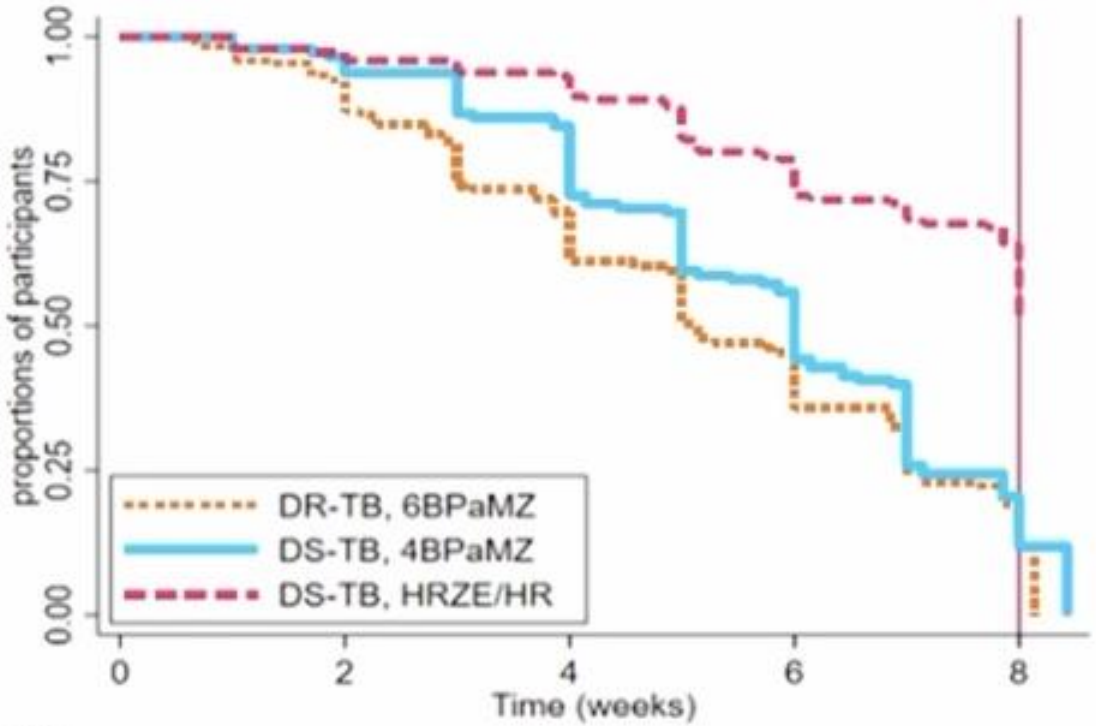
BPaMZ Dosing: Bedaquiline (B) at a dose of 200 mg daily for eight weeks followed by 100 mg daily to end of treatment, together with daily pretomanid (Pa) 200mg, moxifloxacin (M) 400mg and pyrazinamide (Z) 1500mg

SIMPLICI- TB

TB Alliance

Parameter		2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=152) n (%)
Median Age (years) - IQR		34.0 (26.0, 46.0)	35.0 (25.0, 45.0)	35.0 (26.0, 47.0)
Male sex – n (%)		118 (77.1%)	112 (74.7%)	94 (61.8%)
Race	White	25 (16.3%)	29 (19.3%)	31 (20.4%)
	Black	119 (77.8%)	108 (72.0%)	82 (54.0%)
	Mixed	6 (3.9%)	5 (3.3%)	26 (17.1%)
	Asian	3 (2.0%)	8 (5.3%)	13 (8.6%)
HIV positive – n (%)		27 (17.6%)	25 (16.7%)	35 (23.0%)
Median BMI - (kg/m^2)		18.7 (17.2, 20.4)	19.3 (17.6, 21.4)	19.3 (17.1, 22.2)
WHO Smear grade				
	1+	28 (18.3%)	20 (13.3%)	37 (24.3%)
	2+	53 (34.6%)	49 (32.7%)	47 (30.9%)
	3+	72 (47.1%)	81 (54.0%)	67 (44.1%)
Median time to positive sputum culture at baseline (IQR)		5.0 (4.2, 6.5)	4.6 (3.9, 6.2)	6.2 (4.7, 8.9)
Cavities in chest XR				
	Absent	37 (24.2%)	31 (20.7%)	31 (20.4%)
	Unilateral	76 (49.7%)	75 (50.0%)	70 (46.0%)
	Bilateral	40 (26.1%)	44 (29.3%)	50 (32.9%)

SIMPLICI- TB



Number at risk

DR-TB, 6BPaMZ	133	122	90	57	24
DS-TB, 4BPaMZ	145	139	119	77	26
DS-TB, HRZE/HR	148	143	136	114	93

HAZARD RATIO

4BPaMZ is superior
Culture negative by 8 weeks is more likely with BPAMZ

*2.17-3.96 (95%CI)

PROPORTION OF PTS CULTURE NEGATIVE AT WEEK 8

Drug-Sensitive TB

HRZE

4BPaMZ

Drug-Resistant TB

6BPaMZ

SIMPLICI- TB

	DS-TB		DR-TB
	2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=152) n (%)
Unassessable	9	6	19
Total assessable	144	144	133
Favorable	134 (93.1%)	120 (83.3%)	111 (83.5%)
Unfavorable	10 (6.9%)	24 (16.7%)	22 (16.5%)
95% CI for Favorable	87.6% to 96.6%	76.2% to 89.0%	83.1% to 89.8%
(Risk difference) unadjusted	9.72%		
Two-sided 95% CI (unadjusted)	(2.35% to **17.09%**)		

SIMPLICI- TB

TB Alliance

Status	Outcome		DS-TB 2HRZE/4HR (N=153) n (%)	DS-TB 4BPaMZ (N=150) n (%)	DR-TB 6BPaMZ (N=152) n (%)
	Total Assessable (%)		144 (94.1%)	144 (96.0%)	133 (87.5%)
Favorable	Culture negative status at 52 weeks post randomisation		134	120	111
	Total Favorable (% of assessable)		134 (93.1%)	120 (83.3%)	111 (83.5%)
Unfavorable	During treatment	Death (Non-violent)	1	2	2
		Withdrawn (AE)	1	14	14
		Withdrawn (Investigator/Sponsor decision)	2	1	5
		Withdrawn (Participant decision)	2	3	0
		Withdrawn (Treatment failure)	2	0	0
	Post treatment	Confirmed relapse at 52 weeks post randomisation	1	2	1
		Re-treatment	1	2	0
	Total Unfavorable (% of assessable)		10 (6.9%)	24 (16.7%)	22 (16.5%)

SIMPLICI- TB

TB Alliance

	DS-TB		DR-TB
	2HRZE/4HR (N=153) n (%)	4BPaMZ (N=150) n (%)	6BPaMZ (N=149) n (%)
Any TEAE	144 (94.1%)	139 (92.7%)	142 (95.3%)
Any grade ≥ 3 TEAE	61 (39.9%)	68 (45.3%)	47 (31.5%)
Any study drug-related TEAE	99 (64.7%)	119 (79.3%)	123 (82.6%)
Any serious TEAE	7 (4.6%)	17 (11.3%)	16 (10.7%)
Any TEAE leading to study drug discontinuation	3 (2.0%)	17 (11.3%)	16 (10.7%)
Any TEAE leading to study drug interruption	14 (9.2%)	15 (10.0%)	23 (15.4%)
Any TEAE leading to death	1 (0.6%)	3 (2.0%)	2 (1.3%)

Total number of participants ALT and or AST ≥ 3X ULN	17 (11.1%)	24 (16.0%)	21 (14.1%)
3 - 8 x ULN	14 (9.2%)	12 (8.0%)	12 (8.1%)
>8 x ULN	3 (2.0%)	12 (8.0%)	9 (6.0%)

SIMPLICI-TB

- BPaMZ pendant 4 mois permet une négativation des cultures plus importante que régime standard à 8 semaines (HR>2)
- Mais non infériorité non prouvée versus HRZE à S52

Pas si **Simple**

TRUNCATE

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., Erina 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., et al., for the TRUNCATE-TB Trial Team*

Selected inclusion criteria

- Age 18 to 65 years
- Clinical symptoms consistent with pulmonary TB and/or evidence of pulmonary TB on CXR
- Sputum Xpert MTB/RIF positive

Selected exclusion criteria

- Rifampicin resistance on Xpert MTB/RIF
- Previous active TB disease
- Extra-pulmonary TB
- Severe clinical PTB
- Sputum smear 3+ *
- Cavity size >4cm on screening CXR*
- HIV positive*
- Poorly-controlled diabetes
- Cardiac disease
- Severe chronic lung disease
- Peripheral neuropathy

*Removed/modified in stage 3 of trial

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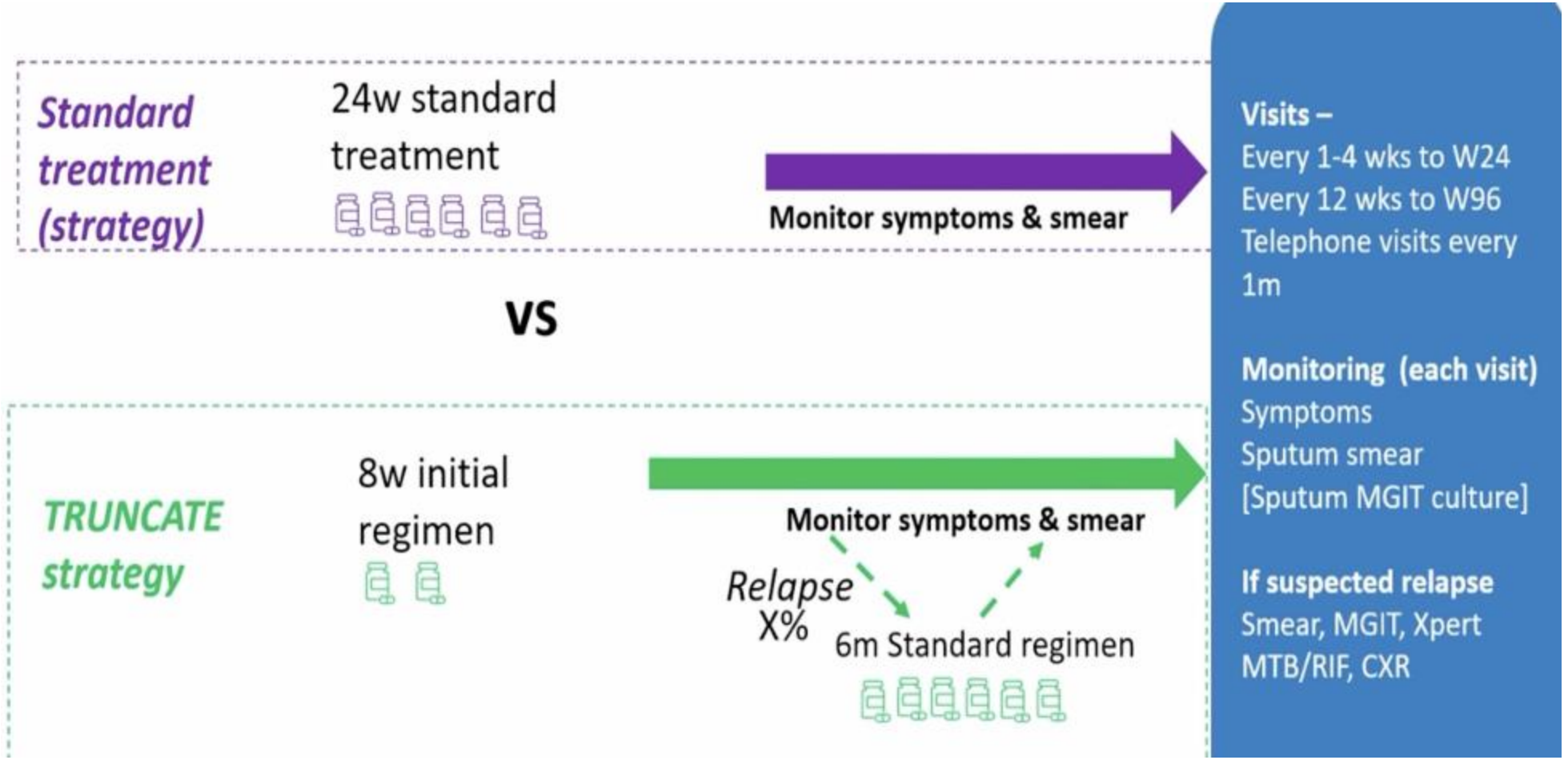
ORIGINAL ARTICLE

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erina 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., et al., for the TRUNCATE-TB Trial Team*



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Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

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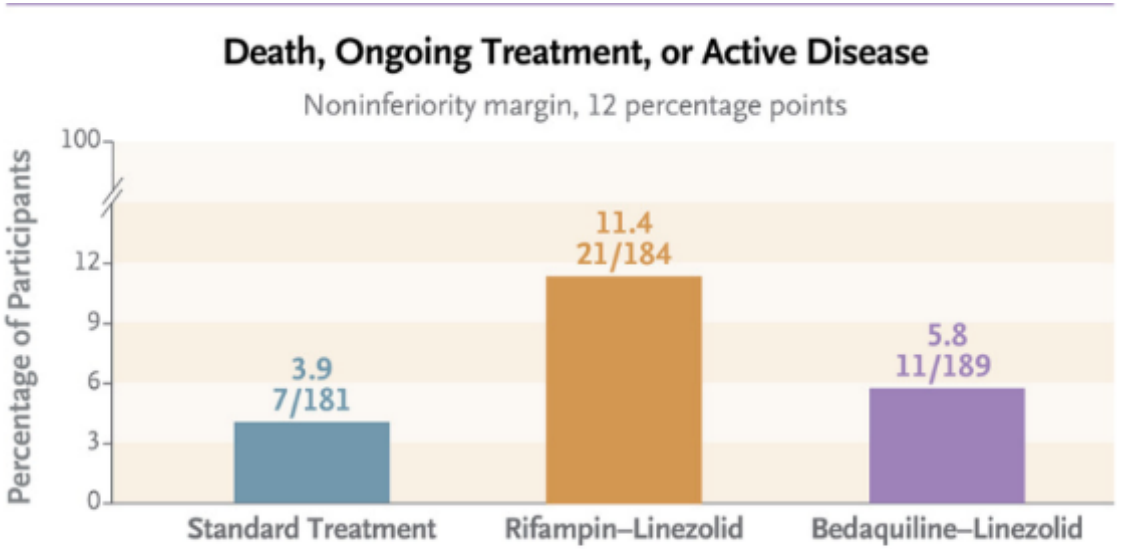
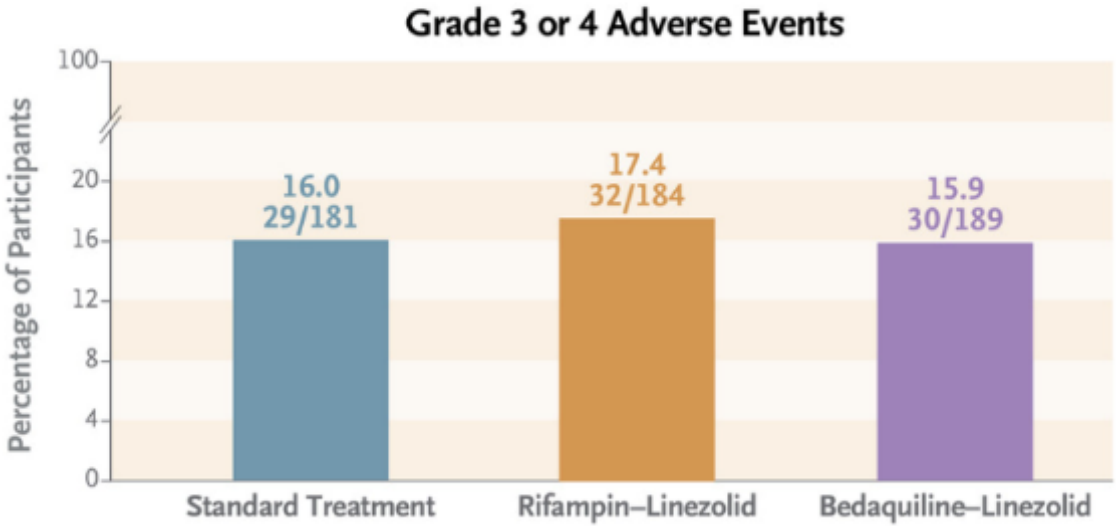




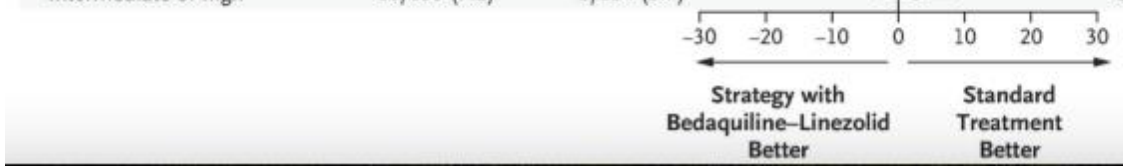
TRUNCATE

- Critère de jugement principal

- évalué à S 96
- composite : †□, évolution défavorable (clinique/ bactériologique/ radiographique)

- Puis analyse bayésienne
  → évaluer les probabilités de réussite avec marge de non-infériorité = 20%

Subgroup	Strategy with Bedaquiline–Linezolid	Standard Treatment	Difference (95% CI)
	no. of participants with event/total no. (%)		*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)



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	Probability of unfavourable outcome < 20%		
	24 wk Standard treatment (N=181)	8wk hRIF/LZD (N=184)	8wk BDQ/LZD (N=189)
All participants	1	0.052	0.989
Smear grade			
Negative	1	0.819	0.994
Scanty/1+	1	0.433	0.956
2+	0.994	0	0.779
3+	0.964	0.265	0.31
Xpert MTB/RIF burden			
Very low/low	1	0.913	0.996
Medium	1	0.019	0.994
High	0.94	0.001	0.062
CXR % lung affected			
< 25%	1	0.808	0.987
25-50%	1	0.015	0.897
> 50%	0.99	0.13	0.785

>0.8

0.5 to 0.8

<0.5

Paton N, Cousins C, Suresh C et al. NEJM published online 20 Feb 2023: DOI: 10.1056/NEJMoa2212537

Rifampicine à hautes doses ?

- Phase II : 180 patients atteints de tuberculose pulmonaire bacillifère
- Tester 3 posologies de RIF en traitement d'attaque
- Clairance bactérienne plus rapide
- Tolérance similaire à 10, 15 ou 20 mg/kg

Efficacy and Safety of High-Dose Rifampin in Pulmonary Tuberculosis. A Randomized Controlled Trial

Gustavo E. Velásquez [1,2], Meredith B. Brooks [2], Julia M. Coit [2], Henry Pertinez [3,4], Dante Vargas Vásquez Epifanio Sánchez Garavito [6], Roger I. Calderón [7], Judith Jiménez [7], Karen Tintaya [7], Charles A. Peloquin [8], E

ATS Journals

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Sherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Mungofa, M.P.H., Nasir A. Shah, M.B., B.S., et al., for the RIFAQUIN Trial Team*

The NEW ENGLAND JOURNAL of MEDICINE

October 23, 2014

N Engl J Med 2014; 371:1599-1608

DOI: 10.1056/NEJMoa1314210

RIFASHORT

NEJM Evidence

ORIGINAL ARTICLE

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

Authors: Amina Jindani, M.D., Daniel Atwine, Ph.D., Daniel Grint, Ph.D., Boubacar Bah, M.D., Jack Adams, B.Sc., Eduardo Rómulo Ticona, Ph.D., Bhabana Shrestha, M.D., +38, for RIFASHORT Study Group* Author Info & Affiliations

Published August 22, 2023 | NEJM Evid 2023;2(9) | DOI: 10.1056/EVIDoa2300054 | VOL. 2 NO. 9

PAS de non-infériorité 4M vs 6M

(a)$2HR_{1200}ZE/2HR_{1200}$

(b) $2HR_{1800}ZE/2HR_{1800}$

(c) [2HRZE/4HR]

Unfavorable outcomes:		**Risk difference, experimental-control (95% confidence interval)**
(a)	19/186 (10.2%)	3.1 (-1.6 to 7.9)
(b)	25/186 (13.4%)	6.3 (1.1 to 11.5)
(c)	13/187 (7%)	NA

Primary Safety Outcome:
The four-month high dose rifampicin regimens were safe.

	Any grade 3 or 4 AEs	Any serious AEs	Deaths
(a)	10 (4.5%)	3 (1.3%)	8 (3.6%)
(b)	10 (4.4%)	3 (1.3%)	3 (1.3%)
(c)	9 (4.0%)	3 (1.3%)	5 (2.2%)

RIFASHORT

NEJM Evidence

ORIGINAL ARTICLE

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

Authors: Amina Jindani, M.D., Daniel Atwine, Ph.D., Daniel Grint, Ph.D., Boubacar Bah, M.D., Jack Adams, B.Sc., Eduardo Rómulo Ticona, Ph.D., Bhabana Shrestha, M.D., +38, for RIFASHORT Study Group* Author Info & Affiliations

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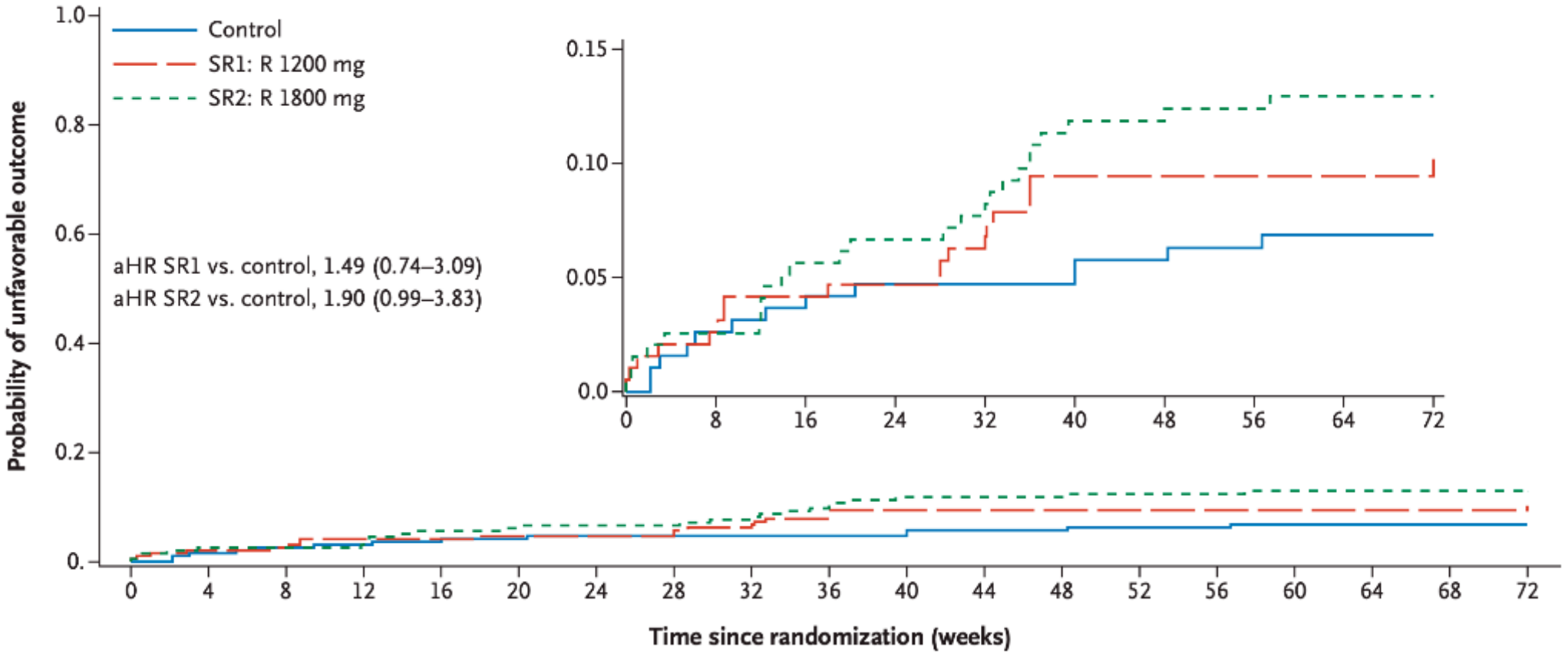
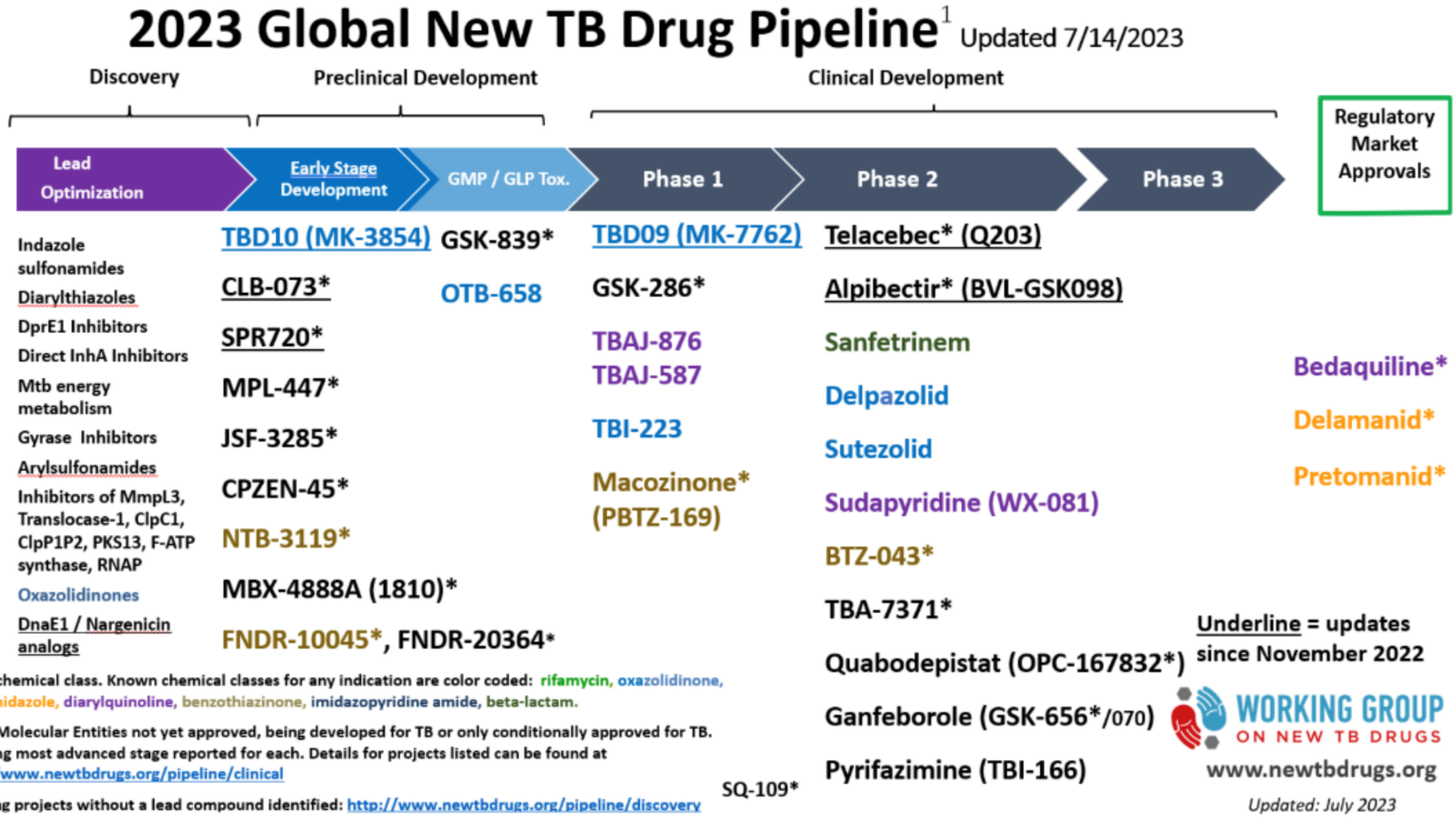


Ajout du Pretonamid

- AJRCCM 2023
- Négativation des cultures + rapide
- Toxicité hépatique +++

Beaucoup d'espoirs en tuberculose…

Telacebec (Q203), a New Antituberculosis Agent
The NEW ENGLAND JOURNAL of MEDICINE



Initiation des ARV chez VIH+BK

EACS European AIDS Clinical Society

Version 11.1
October 2022

	Initiation of ART	Comments
General recommendation	As soon as possible within 2 weeks after starting treatment for the opportunistic infection	
Tuberculosis	As soon as possible within two weeks of starting TB treatment, regardless of CD4 count	For details, see ART in TB/HIV Co-infection section, page 20
- TB meningitis	ART should be delayed for 4 weeks, but can be initiated within the first 2 weeks in persons with TB meningitis and CD4 < 50 (100) cells/μL	Corticosteroids are recommended as adjuvant treatment for TB meningitis
Cryptococcal meningitis	Defer initiation of ART for at least 4 weeks (WHO recommends a delay of 4-6 weeks and some specialists recommend a delay of 6-10 weeks in severe cryptococcal meningitis)	Corticosteroids are not recommended as adjuvant treatment

Initiation des ARV chez co inf VIH/BK

EACS European AIDS Clinical Society

Version 11.1
October 2022

Tuberculosis	
paradoxical IRIS	Simultaneous initiation of ART and prophylactic prednisone in persons with CD4 cell count < 100 cells/μL, who started anti-TB treatment within 30 days prior to ART, may reduce risk of TB-IRIS by 30%. **Prednisone** dose: 40 mg qd po for 2 weeks, followed by 20 mg qd po for 2 weeks

November 15, 2018
N Engl J Med 2018; 379:1915-1925
DOI: 10.1056/NEJMoa1800762

Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

Graeme Meintjes, M.B., Ch.B., Ph.D., Carl Stek, M.D., Lisette Blumenthal, M.B., Ch.B., Friedrich Thienemann, M.D., Charlotte Schutz, M.B., Ch.B., Jozefien Buyze, Ph.D., Raffaella Ravinetto, Pharm.D., Ph.D., Harry van Loen, M.Sc., Amy Nair, M.Sc., Amanda Jackson, B.Sc., Robert Colebunders, M.D., Ph.D., Gary Maartens, M.B., Ch.B., et al., for the PredART Trial Team

- Pas de quadrithérapie antituberculeuse systématique sur toute découverte de VIH avec CD4 < 100

June 18, 2020
N Engl J Med 2020; 382:2397-2410
DOI: 10.1056/NEJMoa1910708

ORIGINAL ARTICLE

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

François-Xavier Blanc, M.D., Ph.D., Anani D. Badje, M.D., Ph.D., Maryline Bonnet, M.D., Ph.D., Delphine Gabillard, M.Sc., Eugène Messou, M.D., Conrad Muzoora, M.D., Sovannarith Samreth, M.D., Bang D. Nguyen, M.D., Laurence Borand, Pharm.D., Ph.D., Anais Domergue, M.Sc., Delphine Rapoud, Ph.D., Naome Natukunda, M.D., et al., for the STATIS ANRS 12290 Trial Team†

Take home messages

- **Tuberculose multi sensible :**
  . Régime traditionnel déjà très efficace
  . Régime de 4 mois avec RFP et MFX non inférieur
  . Régime de 4 mois OK pour les <16 ans
  . Beaucoup d'essais ne trouvent pas mieux ! Mais des pistes …

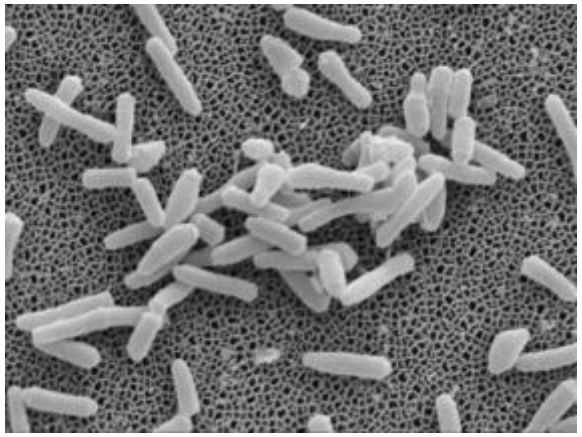
- **Tuberculose multi résistante :**
  . Régime oral BPaLM de 6 mois révolutionnaire
  . Extension du régime BPaL +/- X à tous les BK MDR/XDR ?
  . Nombreuses molécules à venir prometteuses…

Hold your breath – Siniatkina - 2015

Merci pour votre écoute

Complexe *Mycobacterium tuberculosis*

- bacille aérobie strict, immobile, de 2 à 5 µm
- paroi riche en acides mycoliques



M. tuberculosis
M. bovis
M. africanum
M. microti
M. mungi
M. caprae
M. orygis
M. canettii
M. pinnipedii

Epidemiologie TB mondiale / européenne

- Monde
  - Nouveaux cas : 10.6 millions en 2021
  - Décès : 1,6 millions en 2021, dont 200 000 chez PVVIH
  - 8 pays concentrent 75% des cas !
- Europe
  - concentre seulement 3%
  - 166 000 cas étaient déclarés en 2021 (33 000 en UE), soit incidence 7,4 cas/10^5 habitants/an

  Global report WHO 2022, ECDC 2023 (data 2021)

Epidémiologie TM en France

- **7.7 pour 100 000 à l'échelle nationale** mais,
  16 pour 100 000 en Ile de France,
  202 pour 100 000 parmi SDF
  76 pour 100 000 parmi détenus
- 63% de personnes nées hors de France
- 2% de multi-résistance
- Risque de 5 à 15% de développer une TM :
  62% dans les 2 ans, 83% dans les 5 ans

Attention l'OFII ne fait plus de dépistage systématique des primo-arrivants (décret du 2/11/2016) !

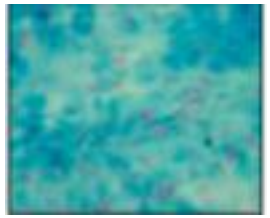
BEH 7/4/2020 La tuberculose en France Jean-Paul Guthmann et al

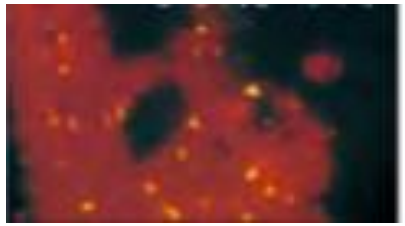
Risques spécifiques aux enfants

	Risque de maladie pulmonaire ou lymphatique	Risque de méningite ou disséminée
< 12 mois	35%	15%
12-24 mois	15%	3%
5 à 10 ans	2%	<0,5%

OUTILS DIAGNOSTIQUES

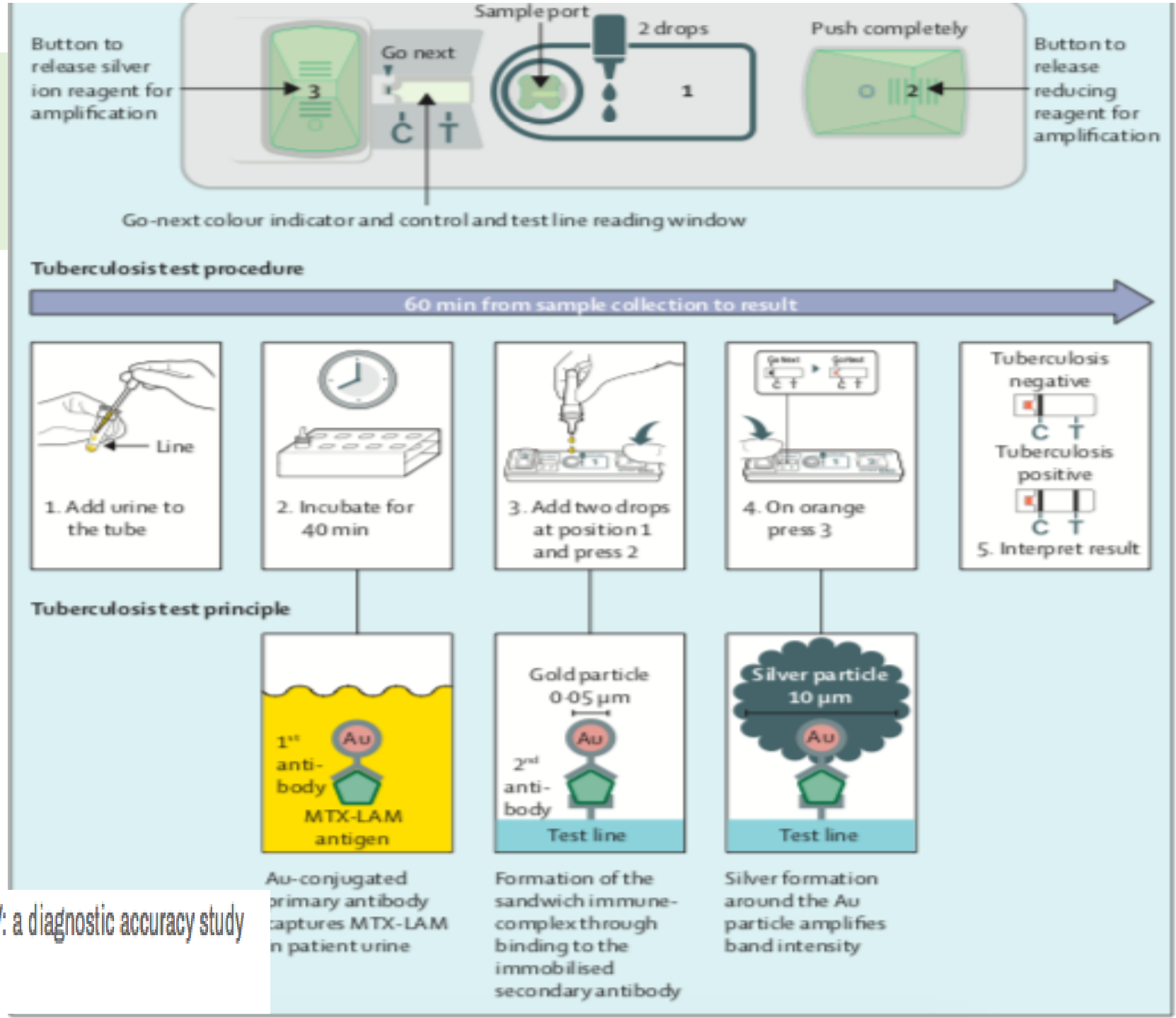
- Examen direct





- PCR BK : le débat de la VPP !
- Culture
  - milieu liquide (10 jours si ED+, 28 jours si ED-)
  - milieu solide = référence (21jours si ED+, 42 jours si ED-)

Fujilam : en pratique

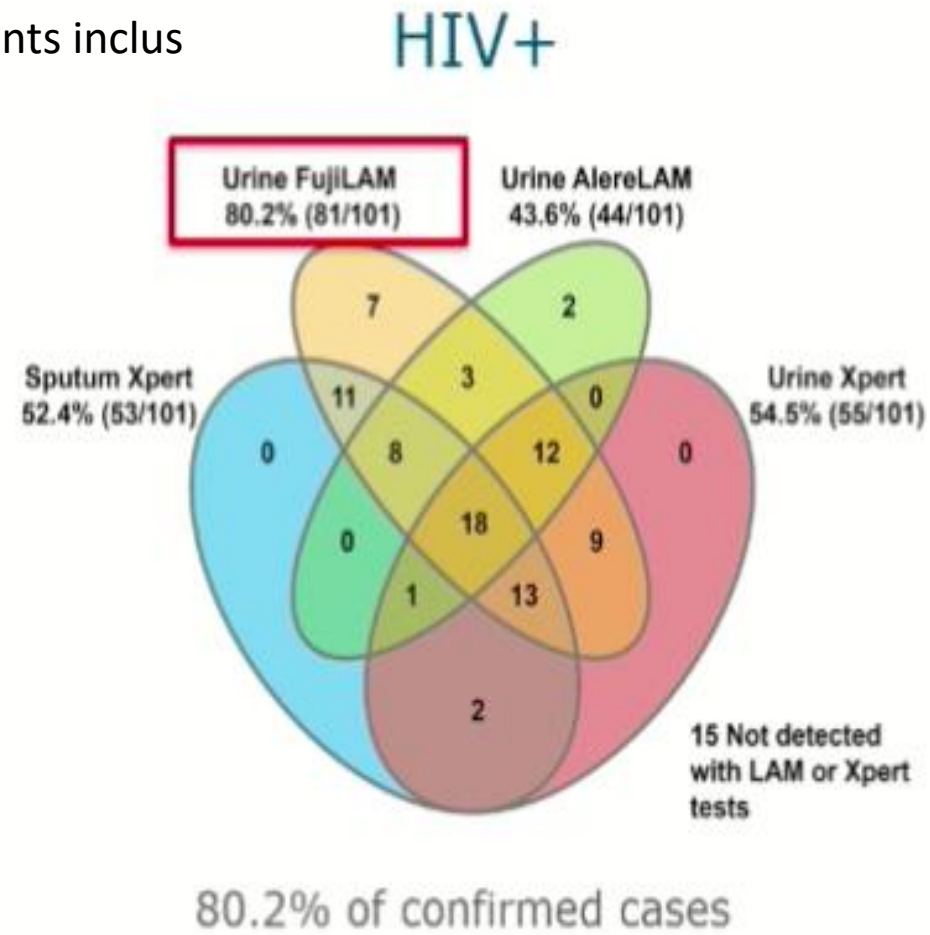


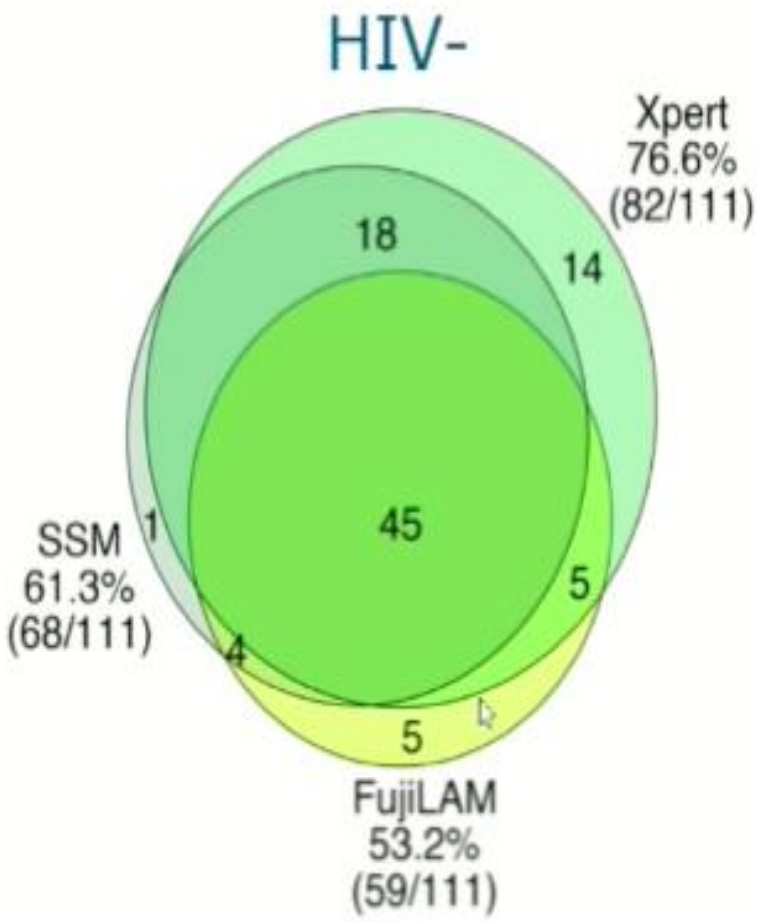
Novel lipoarabinomannan point-of-care tuberculosis test for people with HIV: a diagnostic accuracy study

Lancet Infect Dis. 2019 Aug; 19(8): 852–861.

Fujilam : rendement selon statut VIH

983 patients inclus

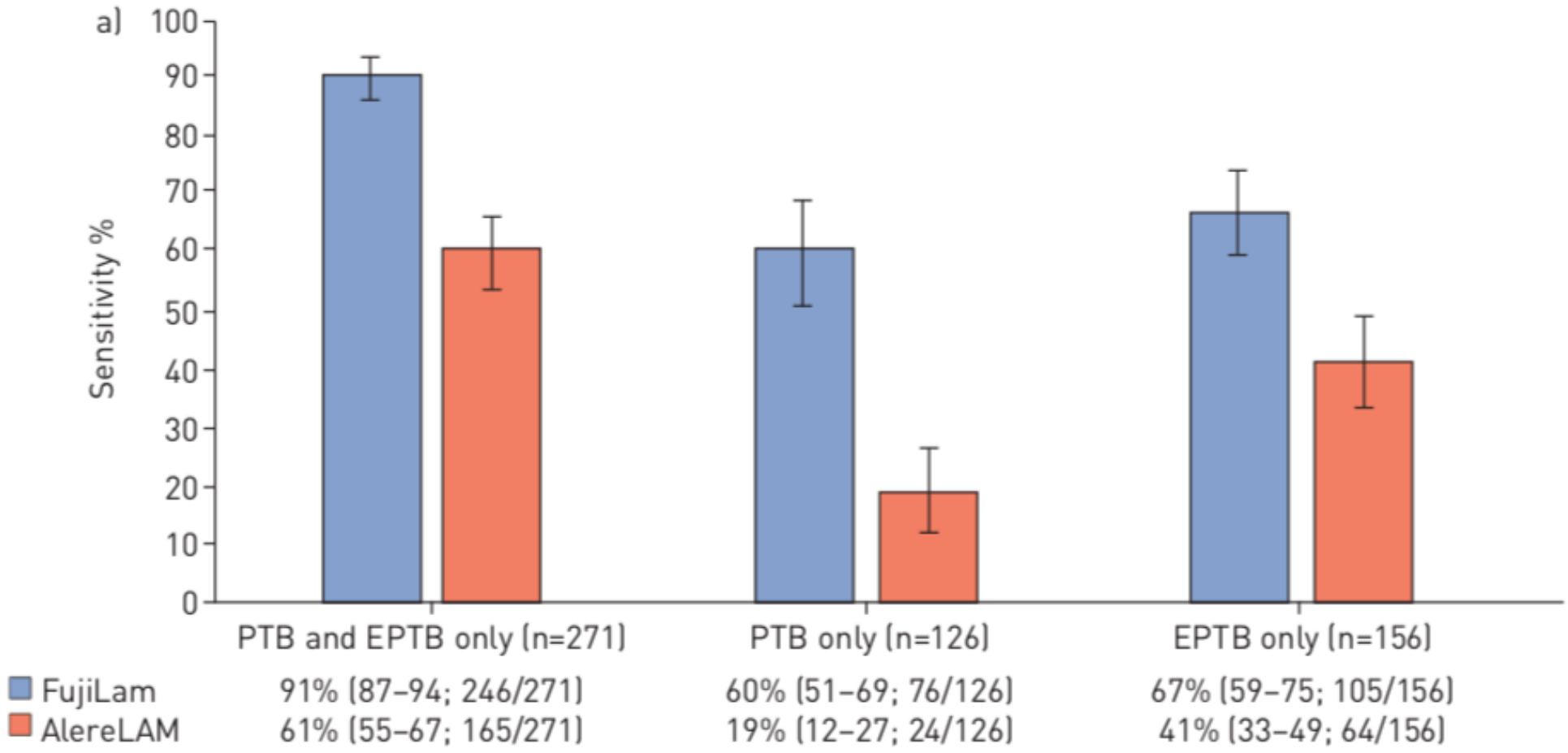




"SILVAMP TB LAM" Rapid Urine Tuberculosis Test Predicts Mortality in Patients Hospitalized With Human Immunodeficiency Virus in South Africa

Clin Infect Dis. 2020 Oct 15; 71(8): 1973–1976.

Fujilam : rendement selon atteinte chez VIH+



Diagnostic sensitivity of SILVAMP TB-LAM (FujiLAM) point-of-care urine assay for extra-pulmonary tuberculosis in people living with HIV

Eur Respir J. 2020 Feb; 55(2): 1901259.

Une solution pour accélérer ?

- Deeplex Myc-TB (Genoscreen, Lille, France)
- Permet de prédire la sensibilité à 13 drogues
(dont linezolid, bedaquiline, et clofazimine)
et permet l'identification des espèces.
- En ciblant 18 régions
(rpoB, katG, fabG1, ahpC, inhA, pncA, embB, gidB, rpsL,
gyrA, gyrB, ethA, eis, rrs, tlyA, rplC, rrl, rv0678)

Drug	Locus	Deeplex®-MycTB assay			pDST			Hain MTBDR*plus/sl*		
		R	R (minority mutation)	S	R	S	Concordance	R	S	Concordance
RIF	*rpoB*	8	0	31	7[#]	32[#]	38/39[#] (97.4%)	8[ff]	31	39/39 (100%)
INH	*katG/fabG1/ahpC/inhA*	6	2	31	8[¶]	31[¶]	37/39[¶] (94.9%)	4[###] 3	34 34	37/38 (97.4%) (*katG*) 37/37 (100%) (*inhA*)
PZA	*pncA*	4	1	34	4	35[+]	38/39[+] (97.4%)			
EMB	*embB*	4	0	35	3[§]	36[§]	38/39[§] (97.4%)	1	2	3/3 (100%)
SM	*gidB/rpsL/rrs*	5	2	32	ND	ND	ND			
FQ	*gyrA/gyrB*	0	4	35	0[ƒ]	12[ƒ]	8/12[ƒ] (66.7%)	0[¶¶] 0	39 39	35/39 (89.7%) (*gyrA*) 39/39 (100%) (*gyrB*)
ETH/PTH	*inhA/fabG1/inhA*	3	0	36	5[ψψ]	3[ψψ]	6/8[¶¶] (75.0%)	3	34	37/37 (100%)
KAN only	*eis*	1	0	38	0[¶¶]	4[¶¶]	4/4[++] (100%)			
KAN AMI CAP	*rrs*	1	0	38	1[++]	7[++]	8/8[++] (100%)	1	38	39/39 (100%)
CAP only	*tlyA*	0	0	39	0	5	5/5[§§] (100%)			
LIN	*rplC/rrl*	0	0	39	0	2	2/2 (100%)			
BDQ CFZ	*Rv0678*	0	0	39	0	2	2/2 (100%)			

EUROPEAN RESPIRATORY *journal*

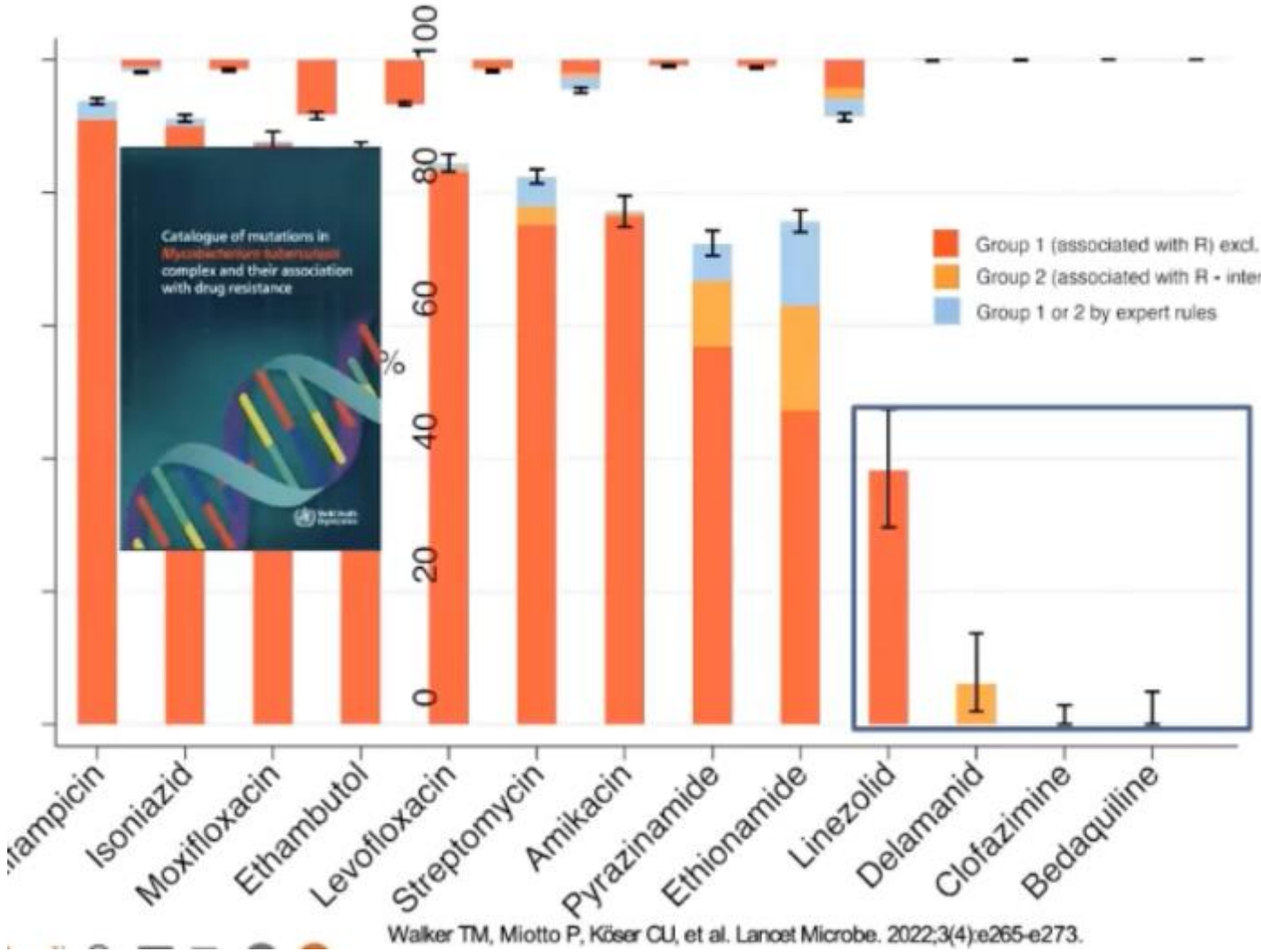
Rapid genomic first- and second-line drug resistance prediction from clinical *Mycobacterium tuberculosis* specimens using Deeplex-MycTB

THE LANCET
Infectious Diseases

Clinical implications of molecular drug resistance testing for *Mycobacterium tuberculosis*: a 2023 TBnet/RESIST-TB consensus statement

José Domínguez, PhD • Prof Martin J Boeree, MD • Prof Emmanuelle Cambau, MD • Dumitru Chesov, MD • Francesca Conradie, MD • Vivian Cox, MD • et al. Show all authors • Show footnotes

Translating NGS to action: WHO mutation catalogue



Walker TM, Miotto P, Köser CU, et al. Lancet Microbe. 2022;3(4):e265-e273.

Data from 52.000TB strains da 67 countries

Traitement pour tous: bénéfices individuels

- **Critères d'inclusion** : adultes HIV + > 500 CD4/mm^3

Traitement ARV immédiat

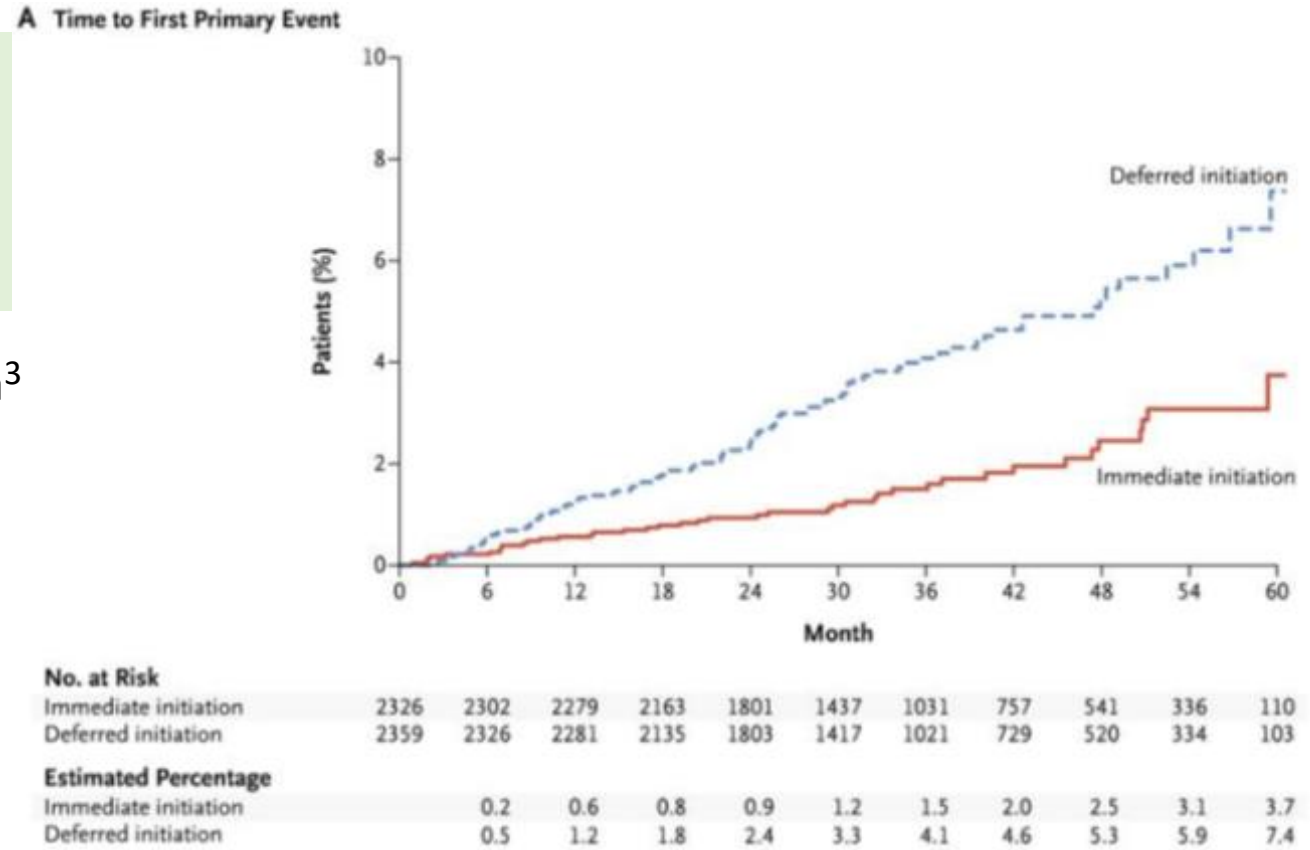
VS `

Traitement ARV différé (en médiane 3 ans) si :

CD4 <350/mm3 ou stade SIDA ou autres
(ex : grossesse)

- **Critère de jugement principal composite** : évènement grave attribuable au VIH ou non (dont le décès toute cause)

- 4685 patients suivis pendant une médiane de 3 ans



Randomized Controlled Trial > N Engl J Med. 2015 Aug 27;373(9):795-807.
doi: 10.1056/NEJMoa1506816. Epub 2015 Jul 20.

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

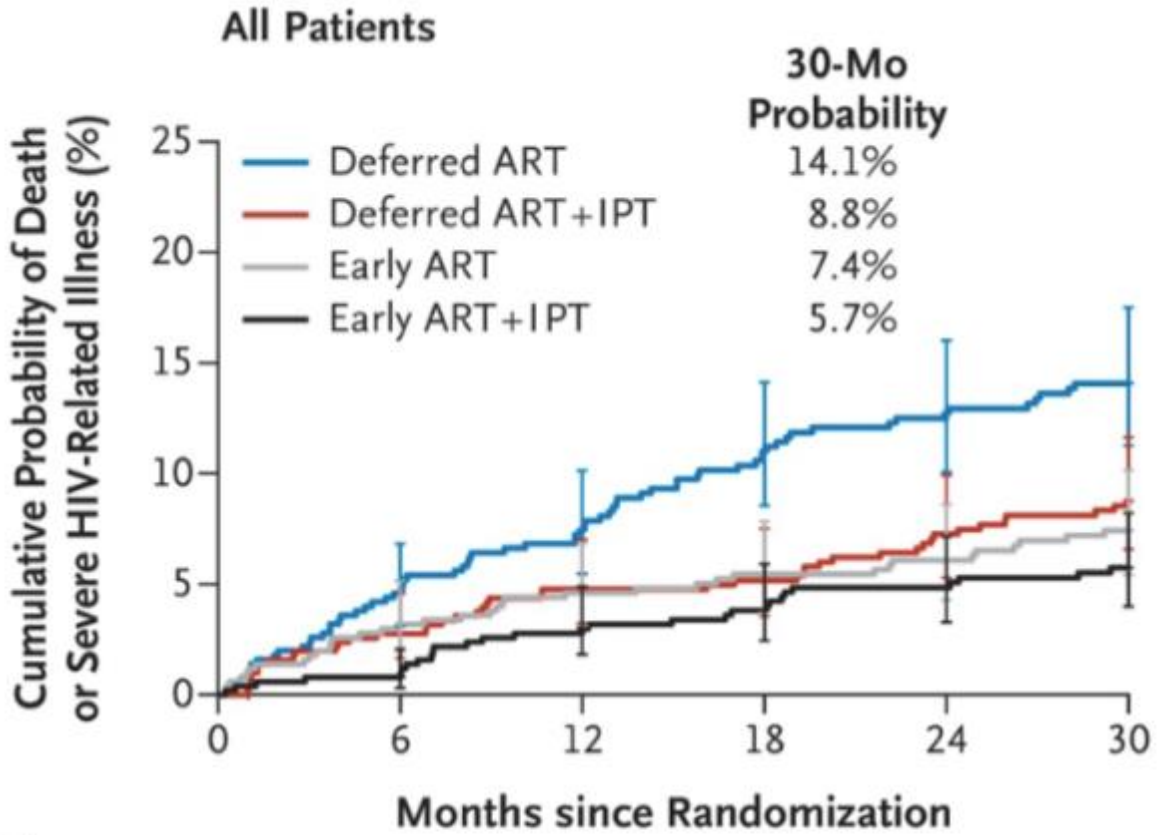
INSIGHT START Study Group; Jens D Lundgren, Abdel G Babiker, Fred Gordin, Sean Emery,

Traitement pour tous: bénéfices individuels

- **Critères d'inclusion** : VIH-1, CD4+ >800 /mm^3 sans critères de traitement immédiat

- **4 groupes**:
  ARV différés,
  ARV différés + Isoniazide,
  ARV immmédiats,
  ARV immmédiats + Isoniazide

- **Critère de jugement principal composite** : SIDA, cancer, infection bactérienne invasive, mort de toute cause à 30 mois



No. at Risk

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

Randomized Controlled Trial > N Engl J Med. 2015 Aug 27;373(9):808-22.
doi: 10.1056/NEJMoa1507198. Epub 2015 Jul 20.

A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

TEMPRANO ANRS 12136 Study Group; Christine Danel, Raoul Moh, Delphine Gabillard,

Traitement pour tous : bénéfices individuels

- Au décours de la publication de ces 2 essais :

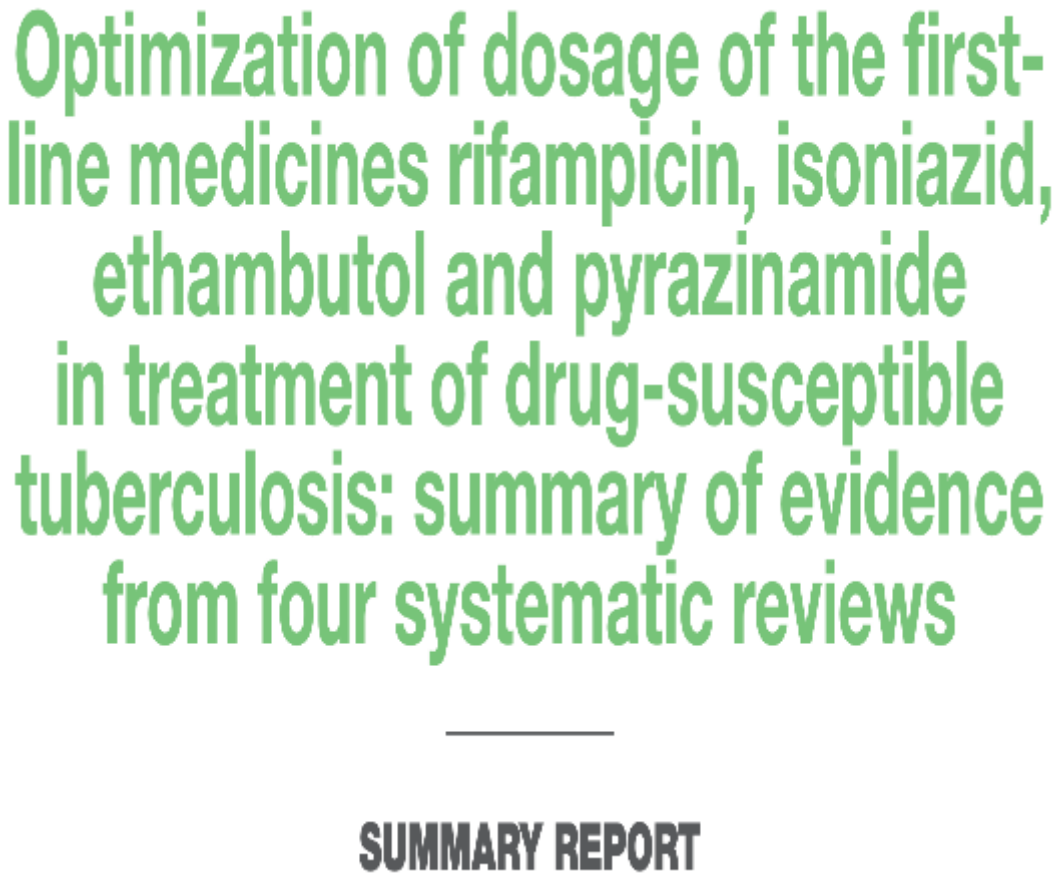
→ EACS et OMS publient en 2015 de nouvelles recommandations
→ "toute personne infectée par le VIH devrait commencer le traitement antirétroviral le plus tôt possible après le diagnostic"

En pratique

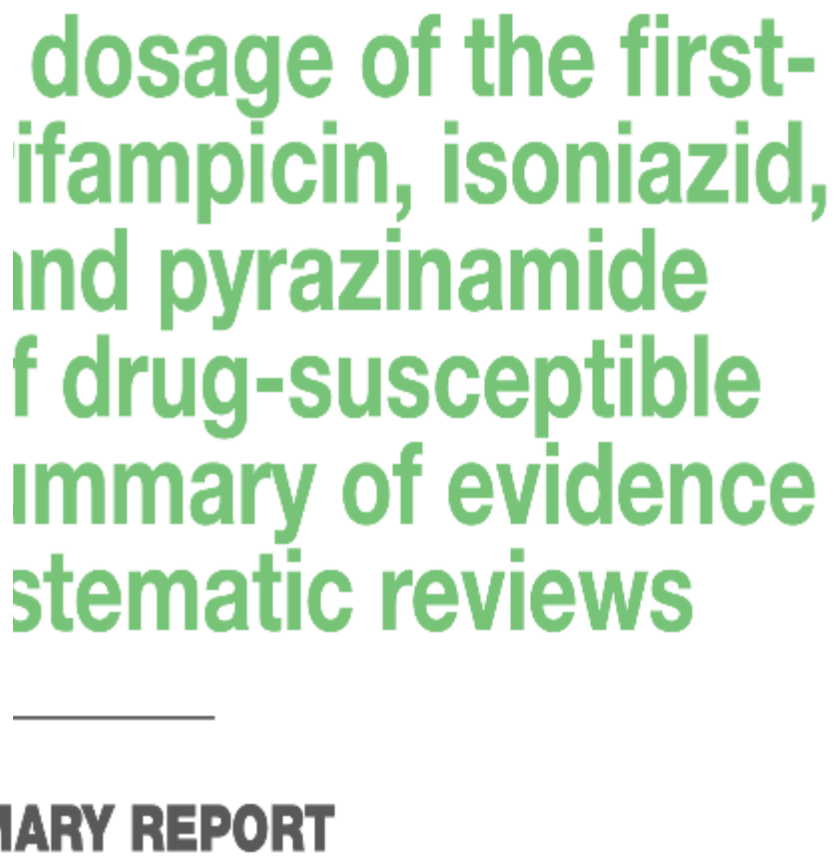
- **INNTI** → Efavirenz : augmenté à 600mg

- **II** → Raltegravir à 400mg x 2 par jour
  → Dolutegravir *à 2*dose (50mg x 2)*
  →~~Bictegravir~~
  →~~ Cabotegravir~~

- **IP** → Darunavir/r => Rifabutine à dose réduite



There was no evidence of higher



s at RIF
00, [0.97–
3.5%], 4
) mg/kg
2.9% [–
(RR 0.98,
rticipants).

Medicine	Weight-based dose	Formulation (mg)	Formulation type	25 to <30 kg	30 to <35 kg	35 to <50 kg	50 to <65 kg	65 kg +
				tablets	tablets	tablets	tablets	tablets
FDC (HR)		75/150	FDC	2	3	4	4	5
FDC (HRE)		75/150/275	FDC	2	3	4	4	5
FDC (HRZE)		75/150/400/275	FDC	2	3	4	4	5
Isoniazid (H)	4–6 mg/kg	300	Loose	0.5	1	1	1	1.25
Rifampicin (R)	8–12 mg/kg	300	Loose	1	1.5	2	2	2.5
Ethambutol (E)	15–25 mg/kg	400	Loose	1.5	2	3	3	4
Pyrazinamide (Z)	20–30 mg/kg	400	Loose	2	3	4	4	5

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.

D’autres essais encore en cours dans tub MDR

- BEAT TB (Afrique du Sud, >6A dont femmes enceintes)
  Non publié, mais résultats montrés à l’Union 2022

Interventions

- Bdq-**Dlm**-Lnz-Lfx **or** Cfz for 6mo
- SOC 9mo South Africa (Bdq-2Lnz-Lfx-Cfz-Pza-Etb-HdH)

Clinical Infectious Diseases
MAJOR ARTICLE

Bedaquiline, Delamanid, Linezolid, and Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis

Chandrasekaran Padmapriyadarsini, Vikram Vohra, Anuj Bhatnagar, Rajesh Solanki, Rathinam Sridhar, Lalitkumar Anande, M. Muthuvenjatachini, Meera Bhatia Rana, Dharathi Jeyashenpa, Gaurav Taneja, S. Babaji, Prashant Shah, N. Saravanan, Vijay Chavan, Hemanth Kumar, Chinnaiyan Ponnaraja, Viktoriya Livchits, Monica Bahl, Umesh Akasi, K. S. Sachdeva, and Soumya Swaminathan; for the BEAT India Team*

Am J Respir Crit Care Med. 2022 May 15; 205(10): 1142–1144.
Published online 2022 Mar 23. doi: 10.1164/rccm.202202-0393ED

Treatments of Multidrug-Resistant Tuberculosis: Light at the End of the Tunnel

Comparative effectiveness of adding delamanid to a multidrug-resistant tuberculosis regimen comprised of three drugs likely to be effective

Carly A. Rodriguez[1,2*], Sara Lodi[3], C. Robert Horsburgh[1,3,4,5], Carole D. Mitnick[2,6,7], Mathieu Bastard[8], Helena Huerga[8], Uzma Khan[9], Michael Rich[6,7], Kwonjune J. Seung[6,7], Sidney Atwood[2], Md Manzur-ul-Alam[10], Nara Melikyan[8], Stephanie Mpinda[11], Zaw Myint[12], Yugandran Naidoo[13], Ofelya Petrosyan[14], Naseem Salahuddin[15], Samreen Sarfaraz[15], Stalz Charles Vilbrun[16], Kalkidan Yae[17], Jay Achar[18], Saman Ahmed[19], Elena Algozhina[20], Jude Beauchamp[21], Sara de Guadelupe Perea Moreno[22], Munara Gulanbaeva[23], Marika Gergedava[24], Cut Yulia Indah Sari[25], Catherine Hewison[26✉], Palwasha Khan[9✉], Molly F. Franke[2✉]

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Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes

https://www.infectiologie.com/UserFiles/File/jni/2021/com/jni2021-st7-02-bonnet.pdf