JN 25es Journées Nationales d'Infectiologie
DEAUVILLE et la région Normandie
du mercredi 12 au vendredi 14 juin 2024

Best of Mycobactériose

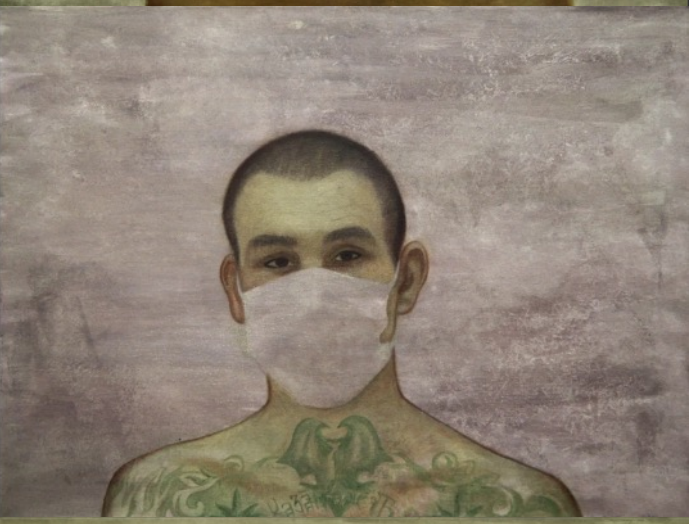
LORENZO GUGLIELMETTI

Déclarations d’intérêt (2014-2023)

Affiliation à un laboratoire de recherche qui a reçu des financements de la part de:

- J&J
- TB Alliance
- Viatris

TOP 10



TOP 10

Tuberculosis (TB)

- Treatment
  - DS-TB (RIFASHORT, SimpliciTB)
  - HR-TB (INHindsight)
  - RR-TB (TB-PRACTECAL & BPaLM availability)
  - Meningitis (Dexamethasone in HIV-positive)
- Prevention
  - RR-TB (V-QUIN & TB-CHAMP)

(DS = drug-susceptible; HR = isoniazid-resistant; RR = rifampicin-resistant)

RIFASHORT trial

NEJM Evidence

Published August 22, 2023
NEJM Evid 2023; 2 (9)
DOI: 10.1056/EVIDoa2300054

ORIGINAL ARTICLE

Four-Month High-Dose Rifampicin Regimens for Pulmonary Tuberculosis

Amina Jindani, M.D.,[1] Daniel Atwine, Ph.D.,[2,3] Daniel Grint, Ph.D.,[4] Boubacar Bah, M.D.,[5] Jack Adams, B.Sc.,[1]

- Open-label, Phase 3, randomized, controlled, non-inferiority trail
- 672 DS-TB patients: a) **HRZE 6** months, b) **HRZE 4** months with **R 1200** mg/d (SR1) or c) **HRZE 4** months with **R 1800** mg/d (SR2)
- Noninferiority margin: 8%; sequence of ordered tests starting with SR2.

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 — no. (%)	174 (93.0)	167 (89.8)	161 (86.6)
Unfavorable			
Participants with outcome — no. (%)	13 (7.0)	19 (10.2)	25 (13.4)
Adjusted percentage point difference from control (90% CI)		3.1 (–1.6 to 7.9)	6.3 (1.1 to 11.5)

Table 3. Laboratory-Defined and Clinical Adverse Events According to Treatment Group.*

Participants Experiencing	Control (n=224)	Study Regimen 1 (n=223)	Study Regimen 2 (n=225)
Primary safety outcome			
Grade 3 or 4 adverse event — no. (%)	9 (4.0)	10 (4.5)	10 (4.4)
Percentage point difference from control (95% CI)		0.5 (–3.3 to 4.2)	0.4 (–3.3 to 4.2)
Secondary safety outcome			
Grade 1–4 adverse event — no. (%)	120 (53.6)	109 (48.9)	115 (51.1)
Percentage point difference from control (95% CI)		–4.7 (–13.9 to 4.6)	–2.5 (–11.7 to 6.8)

- Four-month high-dose rifampicin regimens **not non-inferior** to the 6-month standard regimen
- High-dose rifampicin **well tolerated**

DS-TB = drug-susceptible TB; HRZE = isoniazid, rifampicin, pyrazinamide, ethambutol.

SimpliciTB trial

www.thelancet.com/infection **Published online May 17, 2024** https://doi.org/10.1016/S1473-3099(24)00223-8

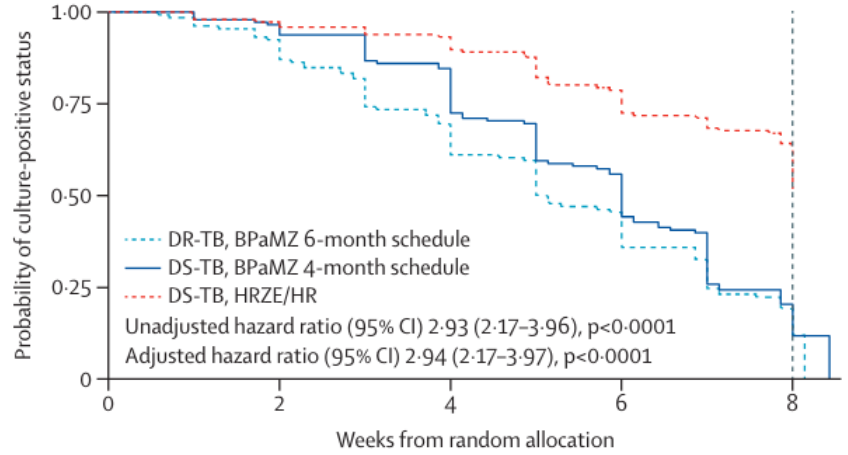
Bedaquiline-pretomanid-moxifloxacin-pyrazinamide for drug-sensitive and drug-resistant pulmonary tuberculosis treatment: a phase 2c, open-label, multicentre, partially randomised controlled trial

Muge Cevik, Lindsay C Thompson, Caryn Upton, Valéria Cavalcanti Rolla, Mookho Malahleha, Blandina Mmbaga, Nosipho Ngubane,

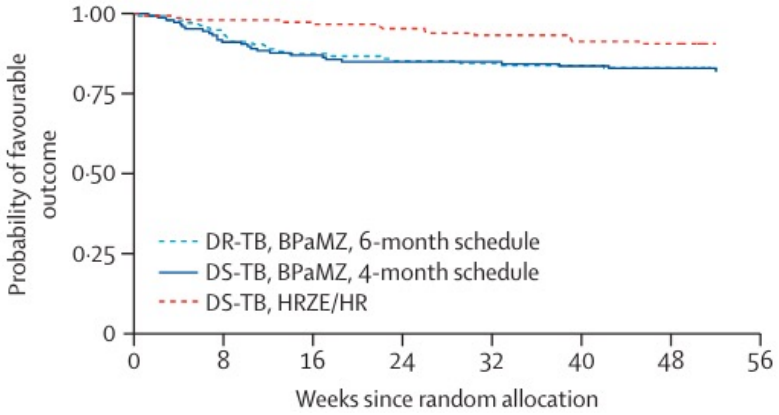
- Partially-randomised, controlled, Phase 2c, open-label clinical trial
- 455 participants, including 303 DS-TB: **4** months of **BPaMZ** (n=150) or **6** months of **HRZE** (n=153)

- **BPaMZ did not meet the key efficacy endpoint** due to adverse events resulting in treatment withdrawal
- These results **confirm the liver toxicity of** the **PaMZ** combination (STAND trial)

Primary efficacy analysis in the mITT population—time to culture-negative status by 8 weeks



Time to unfavourable status at week 52 (mITT)



BPaMZ = bedaquiline, pretomanid, moxifloxacin, pyrazinamide.

INHindsight trial

American Journal of Respiratory and Critical Care Medicine Volume 201 Number 11 | June 1 2020

Early Bactericidal Activity of Different Isoniazid Doses for Drug-Resistant Tuberculosis (INHindsight): A Randomized, Open-Label Clinical Trial

Kelly E. Dooley[1], Sachiko Miyahara[2], Florian von Groote-Bidlingmaier[3], Xin Sun[2], Richard Hafner[4],

Am J Respir Crit Care Med. 2024 Apr 2. doi: 10.1164/rccm.202311-2004OC. Online ahead of print.

High-Dose Isoniazid Lacks EARLY Bactericidal Activity Against Isoniazid-resistant Tuberculosis Mediated by katG Mutations: A Randomized, Phase 2 Clinical Trial

Kamunkhwala Gausi [1] [2], Elisa H Ignatius [3], Veronique De Jager [4], Caryn Upton [5], Soyeon Kim [6],

- Phase 2a early bactericidal activity (EBA) trial
- Smear-positive pulmonary TB
- First stage (2020): 43 **HR-TB with *inhA* mutation**, treated with **H 5 mg/kg** (n=13), **H 10 mg/kg** (n=14), or **H 15 mg/kg** (n=16), compared to 16 DS-TB controls.
- Second stage (2024): 21 **HR-TB with *katG* mutation** treated with **H 15 or 20 mg/kg**.

- **H 10–15 mg/kg daily** had **similar activity** against **HR-TB with *inhA* mutations** to **H 5 mg/kg** on **DS-TB**
- **H 20 mg/kg** had **no EBA on HR-TB with *katG* mutations**, except in a subset of slow acetylators

H = isoniazid; HR-TB = isoniazid-resistant TB.

BPaLM for RR-TB treatment

www.thelancet.com/respiratory Vol 12 February 2024

Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial

Bern-Thomas Nyang'wa, Catherine Berry, Emil Kazounis, Ilaria Motta, Nargiza Parpieva, Zinaida Tigay, Ronelle Moodliar, Matthew Dodd,

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Research Note

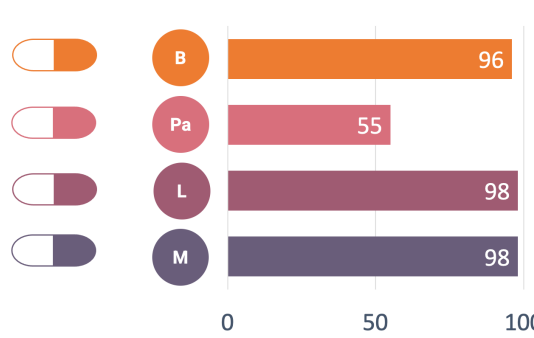
Availability of drugs and resistance testing for bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaL(M)) regimen for rifampicin-resistant tuberculosis in Europe

Gunar Günther [1, 2, x], Lorenzo Guglielmetti [3, 4, x], Yousra Kherabi [5, 6], Raquel Duarte [7, 8, 9, 10],

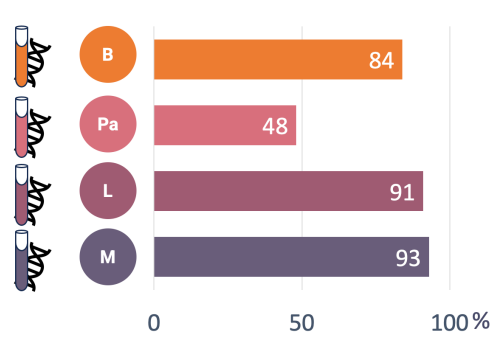
- Final results of the multi-arm, multi-stage Phase 2/3 randomized controlled open-label trial
- Confirms **non-inferiority of 6-month BPaLM** (N=151) compared to long, individualized treatment (N=152)
- **BPaLM** also **better tolerated**
- Confirms 2022 WHO recommendations

Representatives from 44/54 countries of the WHO Europe region

52% of participating countries have access to all the drugs



48% have access to DST for all the drugs



BPaLM = bedaquiline, pretomanid, linezolid, moxifloxacin.

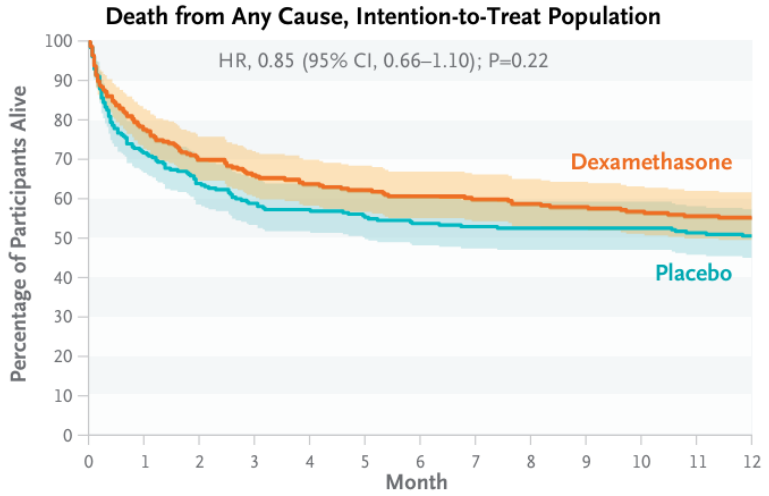
Dexamethasone in HIV-positive TB meningitis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2023 VOL. 389 NO. 15

Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults

Joseph Donovan, Ph.D., Nguyen D. Bang, Ph.D., Darma Imran, M.D., Ho D.T. Nghia, Ph.D., Erlina Burhan, Ph.D.,

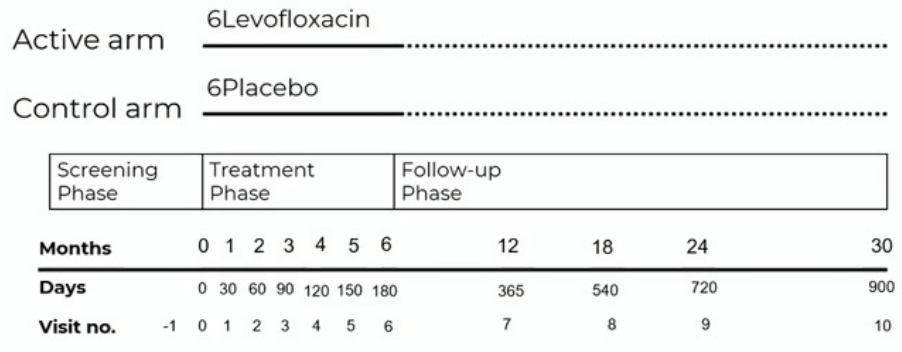


- Double-blind, randomized, placebo-controlled, Phase III trial
- 520 adults with **TB meningitis** treated with HRZE plus **dexamethasone** (IV + oral) or placebo
- 51.9% presented with a CD4 <50, 49.0% had not previously received ART

- The **addition of dexamethasone did not reduce** 12-month all-cause **mortality**
- One fourth of the participants received open-label glucocorticoids during the trial
- Study may be underpowererd to detect difference and/or benefit may be higher in specific subgroups (i.e. higher inflammation)

Preventive treatment for RR-TB contacts

TRIAL DESIGN



- **V-QUIN & TB-CHAMP**
- Phase III, double-blind, randomized, placebo-controlled trials
- 2041 TST-positive **adult** (V-QUIN) and 927 **children** (TB-CHAMP) household contacts of RR-TB patients
- Intervention: **Levofloxacin (Lfx) daily for 6 months**

- Efficacy: meta-analysis of the studies shows **60% overall reduction of incident cases**
- Safety: more grade 1-2 (not 3/4) AEs in adults, well tolerated in children
- No selection of drug resistance reported
- **Lfx prophylaxis recommended by WHO** for all contacts of RR-TB cases

Unpublished; presented at 2023 Union World TB Conference; AEs = adverse events.

TOP 10

TOP 10

Non-tuberculous mycobacteria (NTM)

- Treatment
  - Treatment duration and long-term survival in MAC-PD
  - Clofazimine *vs* rifampicin in MAC-PD regimens

MAC-PD = pulmonary *M. avium* disease

Treatment duration & MAC-PD mortality

Clinical Infectious Diseases

MAJOR ARTICLE

CID 2023:77 (1 July)

Impact of Treatment on Long-Term Survival of Patients With *Mycobacterium avium* Complex Pulmonary Disease

Joong-Yub Kim,[1,2] Yunhee Choi,[3] JiWon Park,[3] Jin Mo Goo,[4] Taek Soo Kim,[5] Moon-Woo Seong,[5] Nakwon Kwak,[1,2] and Jae-Joon Yim[1,2]

- Retrospective cohort of 486 adult patients treated for MAC-PD
- **Treatment exposure divided into four time intervals:** <6, ≥6 to <12, ≥12 to <18, and ≥18 months.
- Time-varying multivariable Cox proportional hazards models for all-cause mortality

Table 3. Time-Varying Multivariable Cox Proportional Hazards Model of Survival by Treatment Duration in Patients With *Mycobacterium avium* Complex Pulmonary Disease

		aHR (95% CI) by Treatment Duration							
Patient Population	Patients, No.	<6 m	6–12 m	*P* Value	12–18 m	*P* Value	≥18 m	*P* Value	*P* Value for Trend
Total study population	486	Reference	0.50 (.22–1.18)	.11	0.54 (.24–1.21)	.13	0.32 (.15–.71)	.005	.007
Subgroup									
Noncavitary	266	Reference	1.05 (.25–4.41)	.95	0.46 (.11–1.92)	.29	0.79 (.24–2.58)	.70	.61
Cavitary	220	Reference	0.30 (.09–.995)	.049	0.49 (.16–1.55)	.22	0.17 (.05–.57)	.004	.008
Negative AFB smear	379	Reference	0.48 (.16–1.43)	.19	0.51 (.18–1.41)	.19	0.40 (.16–.98)	.045	.06
Positive AFB smear	107	Reference	0.53 (.10–2.73)	.45	0.17 (.03–1.10)	.06	0.13 (.02–.84)	.03	.04

Abbreviations: AFB, acid-fast bacilli; aHR, adjusted hazard ratio; CI, confidence interval.

Long-term antimicrobial treatment should be considered in patients with progressive MAC-PD, especially in the presence of cavities or positive sputum smears.

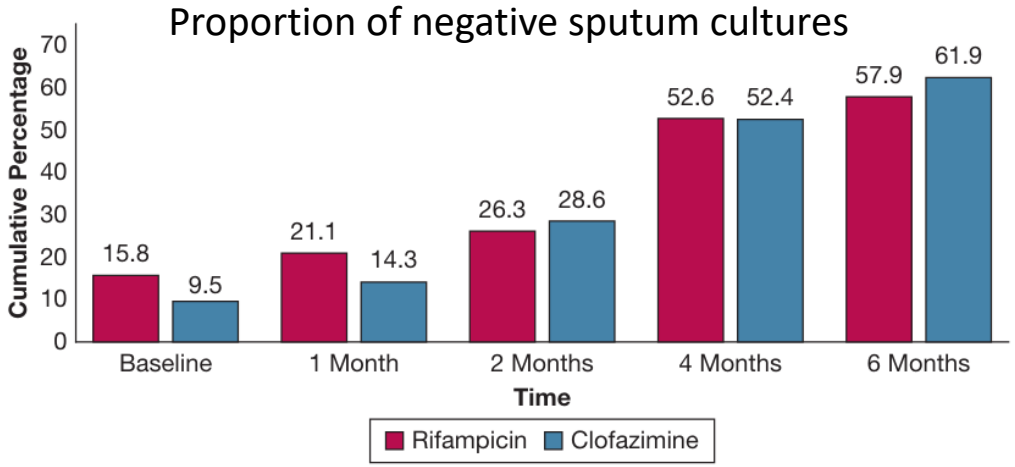
Clofazimine (Cfz) vs rifampicin (R) in MAC-PD

CHEST [165#5 CHEST MAY 2024]

Safety and Efficacy of Clofazimine as an Alternative for Rifampicin in *Mycobacterium avium* Complex Pulmonary Disease Treatment

Outcomes of a Randomized Trial

Sanne M. H. Zweijpfenning, MD; Rob Aarnoutse, PharmD; Martin J. Boeree, MD; Cecile Magis-Escurra, MD, PhD; Ralf Stemkens, PharmD; Bram Geurts, MD; Jakko van Ingen, MD, and Wouter Hoefsloot, MD, PhD



- Open-label, randomized, controlled Phase III clinical trial
- **Macrolide, ethambutol + R** (n=19) **or Cfz** (n=21)
- Study discontinuation similar (26% vs 33%)
- Safety: diarrhea more frequent in Cfz arm, arthralgia more frequent in R arm; no difference in QT prolongation

- **Clofazimine-ethambutol-macrolide** showed **similar efficacy to standard regimen**
- Individual patient characteristics and interactions to be considered to choose MAC-PD regimen
- (underpowered: initial sample size 124)

MERCI
Questions?

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

PARIS Cimi Centre d'Immunologie et des Maladies Infectieuses

SANTÉ SORBONNE UNIVERSITÉ

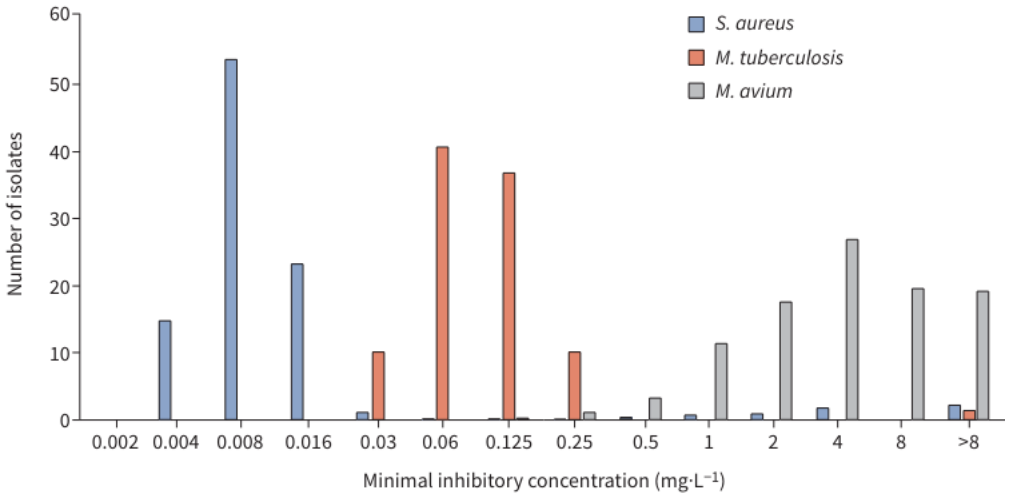
CENTRE NATIONAL DE REFERENCE DES MYCOBACTERIES et de la résistance des mycobactéries aux antituberculeux
CNR-MyRMA

Rifamycins in MAC-PD treatment

Eur Respir J 2024; 63: 2302210

Rifampicin has no role in treatment of *Mycobacterium avium* complex pulmonary disease and bactericidal sterilising drugs are needed: a viewpoint

Jakko van Ingen [1], Wouter Hoefsloot [2], Véronique Dartois[3,4] and Thomas Dick[3,4,5]



- the role of rifampicin in the treatment of MAC-PD is questionable and not supported by
- PK-PD science; its in vitro activity is low, PK-PD targets cannot be attained by safe and tolerable doses
- and preclinical (as well as clinical) studies suggest that it does not add any activity to the ethambutol/
- azithromycin backbone and does not prevent the emergence of macrolide resistance. Its negative
- pharmacokinetic interactions with macrolides are another important reason to reconsider its place in
- treatment regimens.