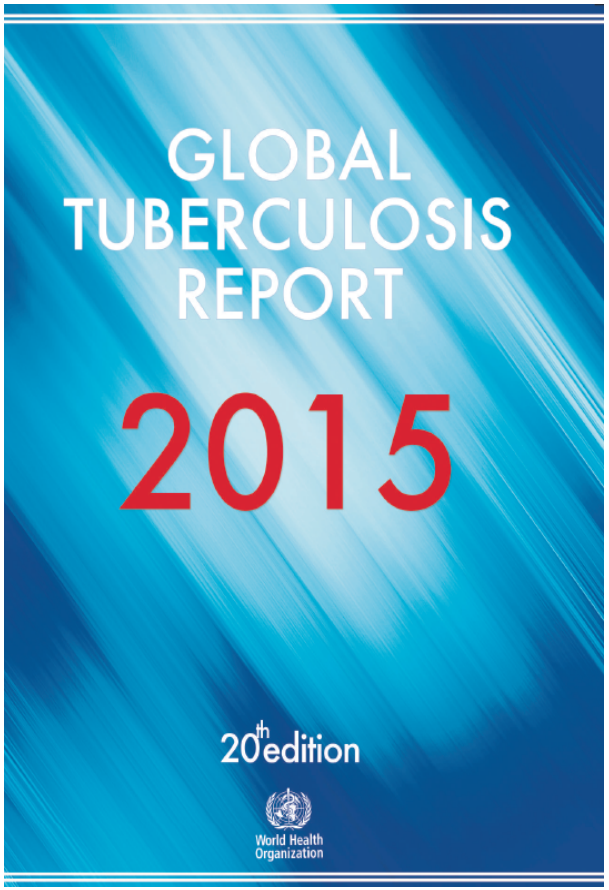
Mycobactéries : Nouveautés de l'année 2015

S.DIROU
Service de Pneumologie
CHU Nantes

Aucun conflit d’intérêt

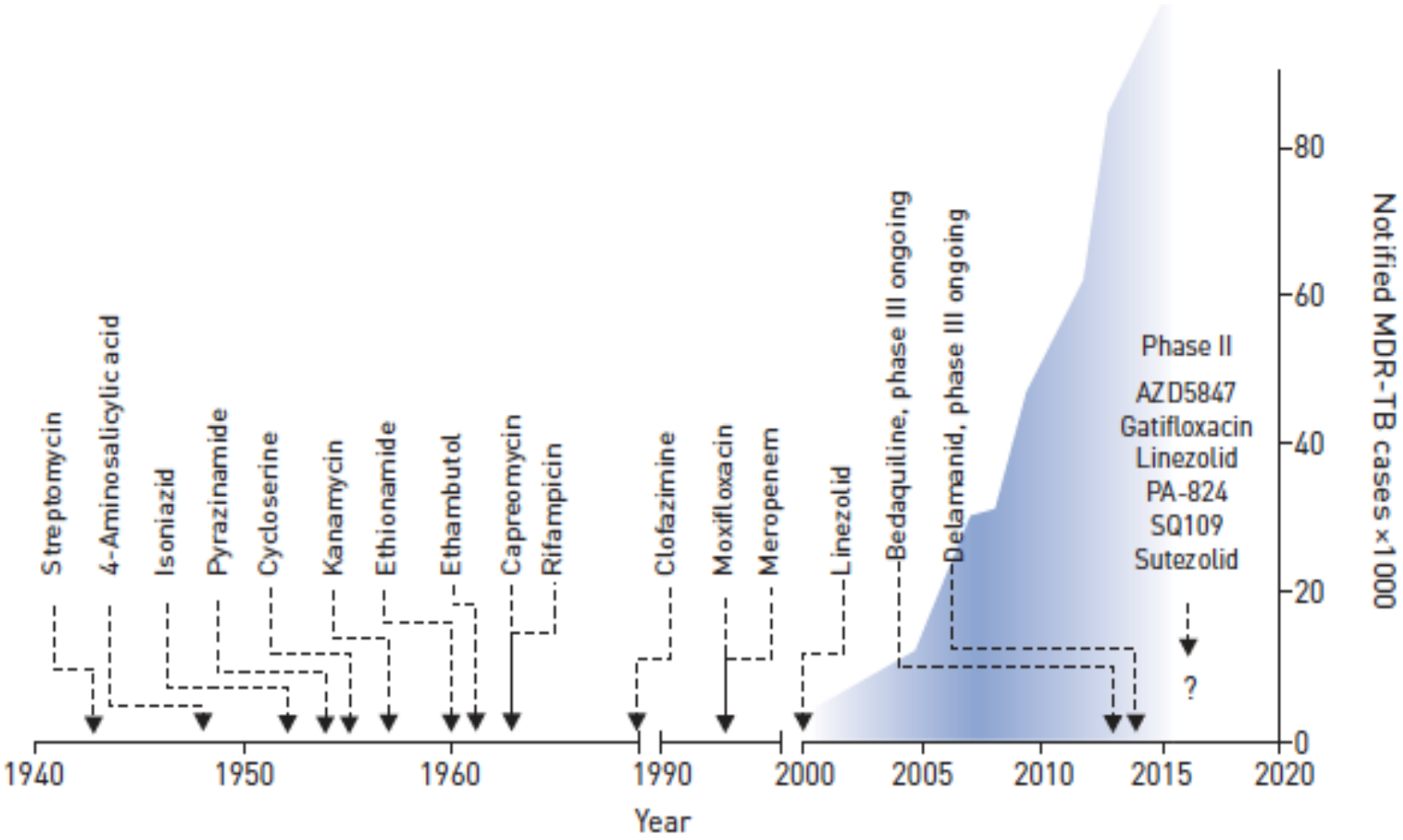
Tuberculose : chiffres clés de l'OMS



World Health Organization

13 millions de cas prévalents
-> Prévalence TB = 42% moins importante qu'en 1990
9,6 millions de cas incidents incl. 0,48 million de MDR-TB
MDR TB = 3.3% des nouveaux cas et 20% chez patients déjà traités
9,7% des MDR TB = XDR TB
Seulement 50% des cas MDR TB sont traités avec succès (≥ 75% dans certains pays)

Evolution des traitements



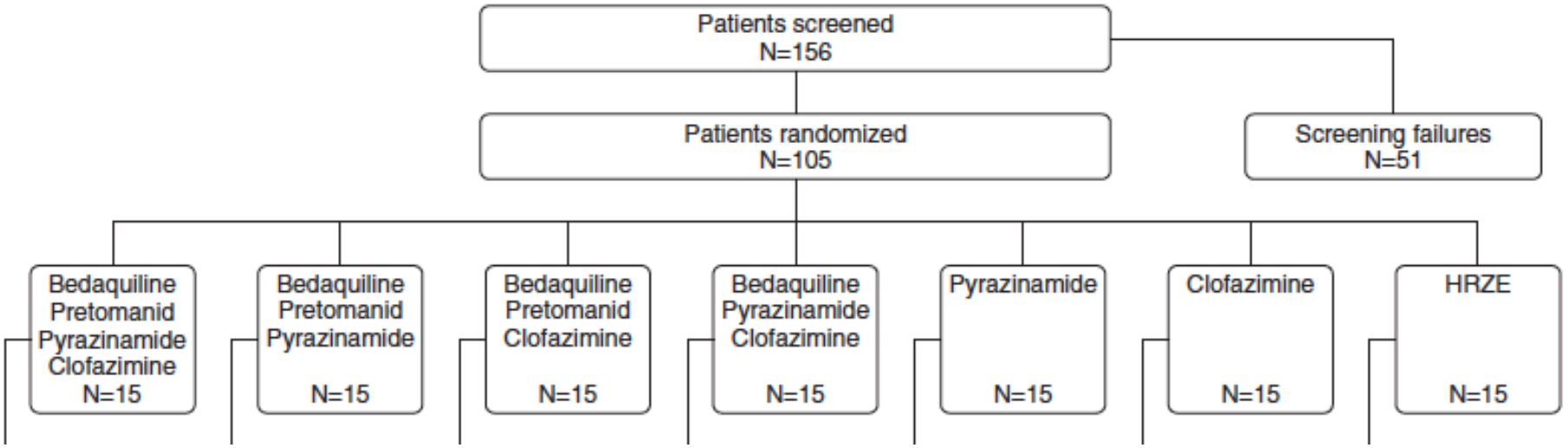
Eur Respir J 2015; 45: 1119–1131 | DOI: 10.1183/09031936.00162314

Phase 2a

Bactericidal Activity of Pyrazinamide and Clofazimine Alone and in Combinations with Pretomanid and Bedaquiline

Andreas H. Diacon[1,2], Rodney Dawson[3], Florian von Groote-Bidlingmaier[2], Gregory Symons[3], Amour Venter[4], Peter R. Donald[5], Christo van Niekerk[6], Daniel Everitt[7], Jane Hutchings[6], Divan A. Burger[8,9], Robert Schall[8,9], and Carl M. Mendel[7]

AJRCCM 2015



Drug Regimen	Period		
	0–14 d	0–2 d	7–14 d
B-Pa-Z-C			
n	13	13	13
log_{10}CFU/ml sputum, mean (95% CI)	0.115 (0.039 to 0.189)	0.161 (0.042 to 0.279)	0.085 (−0.013 to 0.175)
B-Pa-Z			
n	12	12	12
log_{10}CFU/ml sputum, mean (95% CI)	0.167 (0.075 to 0.257)	0.196 (0.061 to 0.330)	0.146 (0.033 to 0.248)
B-Pa-C			
n	15	15	15
log_{10}CFU/ml sputum, mean (95% CI)	0.076 (0.005 to 0.145)	0.062 (−0.045 to 0.161)	0.085 (−0.006 to 0.182)
B-Z-C			
n	13	13	13
log_{10}CFU/ml sputum, mean (95% CI)	0.124 (0.035 to 0.214)	0.132 (0.008 to 0.262)	0.118 (−0.017 to 0.250)
Z			
n	15	15	15
log_{10}CFU/ml sputum, mean (95% CI)	0.036 (−0.026 to 0.099)	0.080 (−0.028 to 0.209)	0.022 (−0.058 to 0.101)
C			
n	14	14	14
log_{10}CFU/ml sputum, mean (95% CI)	−0.017 (−0.085 to 0.053)	0.018 (−0.089 to 0.125)	−0.038 (−0.130 to 0.046)
HRZE			
n	15	15	15
log_{10}CFU/ml sputum, mean (95% CI)	0.151 (0.071 to 0.232)	0.141 (0.039 to 0.251)	0.157 (0.048 to 0.267)

61,9% des patients ont présenté des effets indésirables (grade 3 ou 4 chez 6,7%)

Bactericidal Activity of Pyrazinamide and Clofazimine Alone and in Combinations with Pretomanid and Bedaquiline

Andreas H. Diacon[1,2], Rodney Dawson[3], Florian von Groote-Bidlingmaier[2], Gregory Symons[3], Amour Venter[4], Peter R. Donald[5], Christo van Niekerk[6], Daniel Everitt[7], Jane Hutchings[6], Divan A. Burger[8,9], Robert Schall[8,9], and Carl M. Mendel[7]

AJRCCM 2015

Association Bedaquiline Pa824 et Pyrazinamide a une activité bactéricide précoce similaire au traitement standard

Pas de résistance connue à ce jour

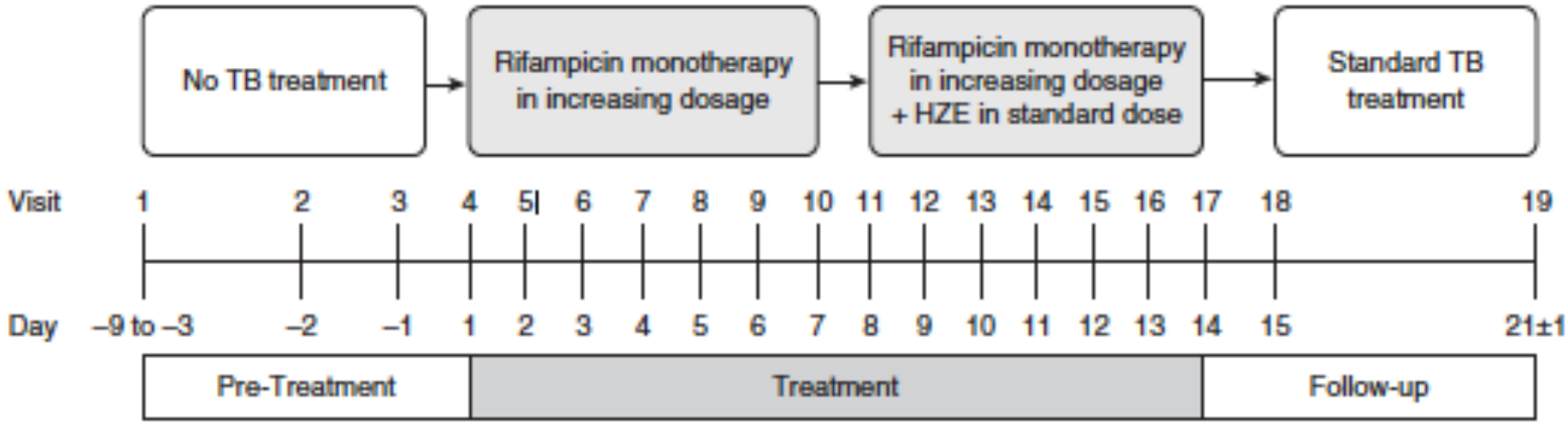
Phase 2a

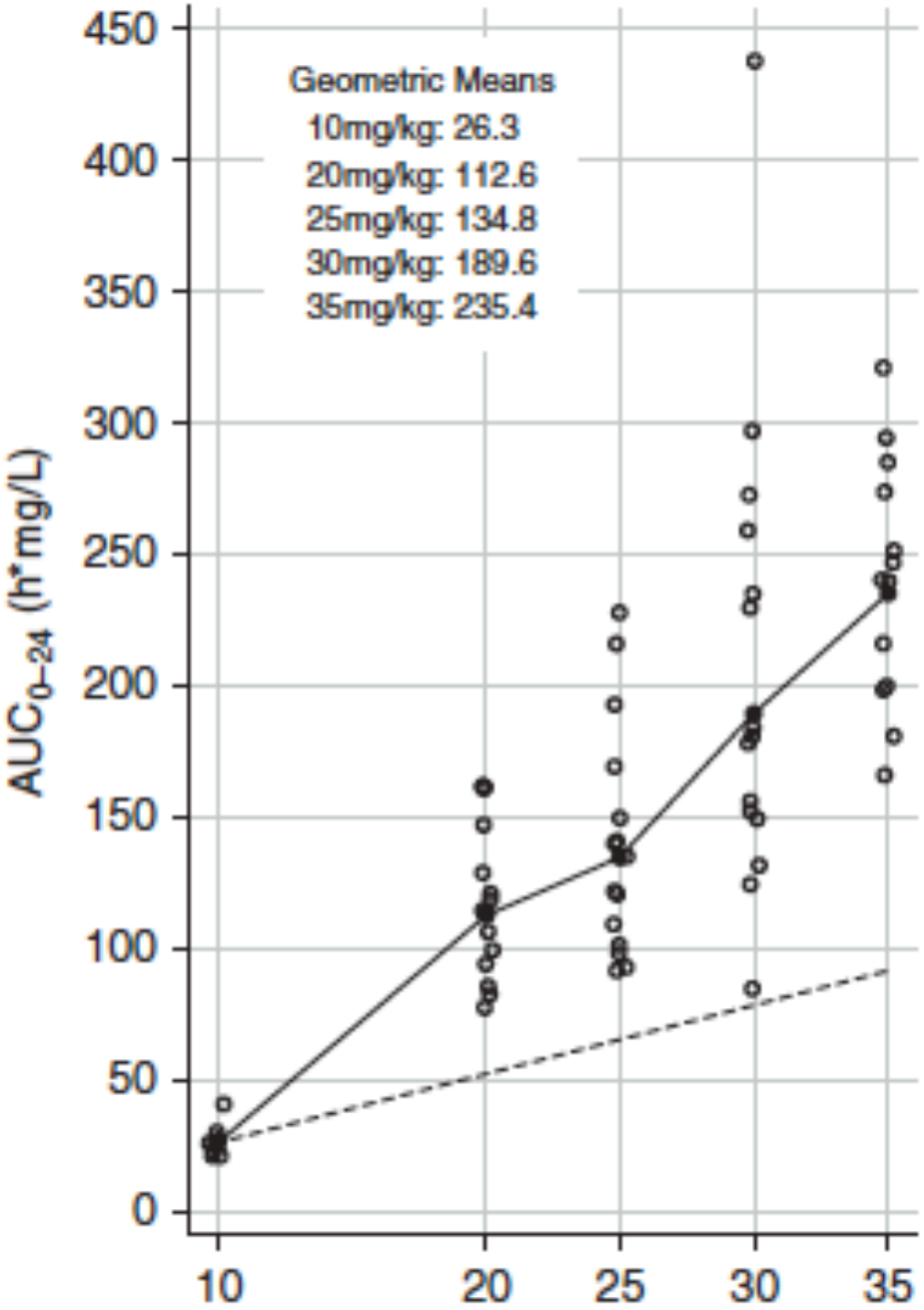
A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

Martin J. Boeree[1,2], Andreas H. Diacon[3,4], Rodney Dawson[5,6], Kim Narunsky[5,6], Jeannine du Bois[4], Amour Venter[3], Patrick P. J. Phillips[7], Stephen H. Gillespie[8], Timothy D. McHugh[9], Michael Hoelscher[10,11], Norbert Heinrich[10,11], Sunita Rehal[7], Dick van Soolingen[12,13], Jakko van Ingen[12], Cecile Magis-Escurra[1], David Burger[14], Georgette Plemper van Balen[1], and Rob E. Aarnoutse[14]; on behalf of the PanACEA Consortium

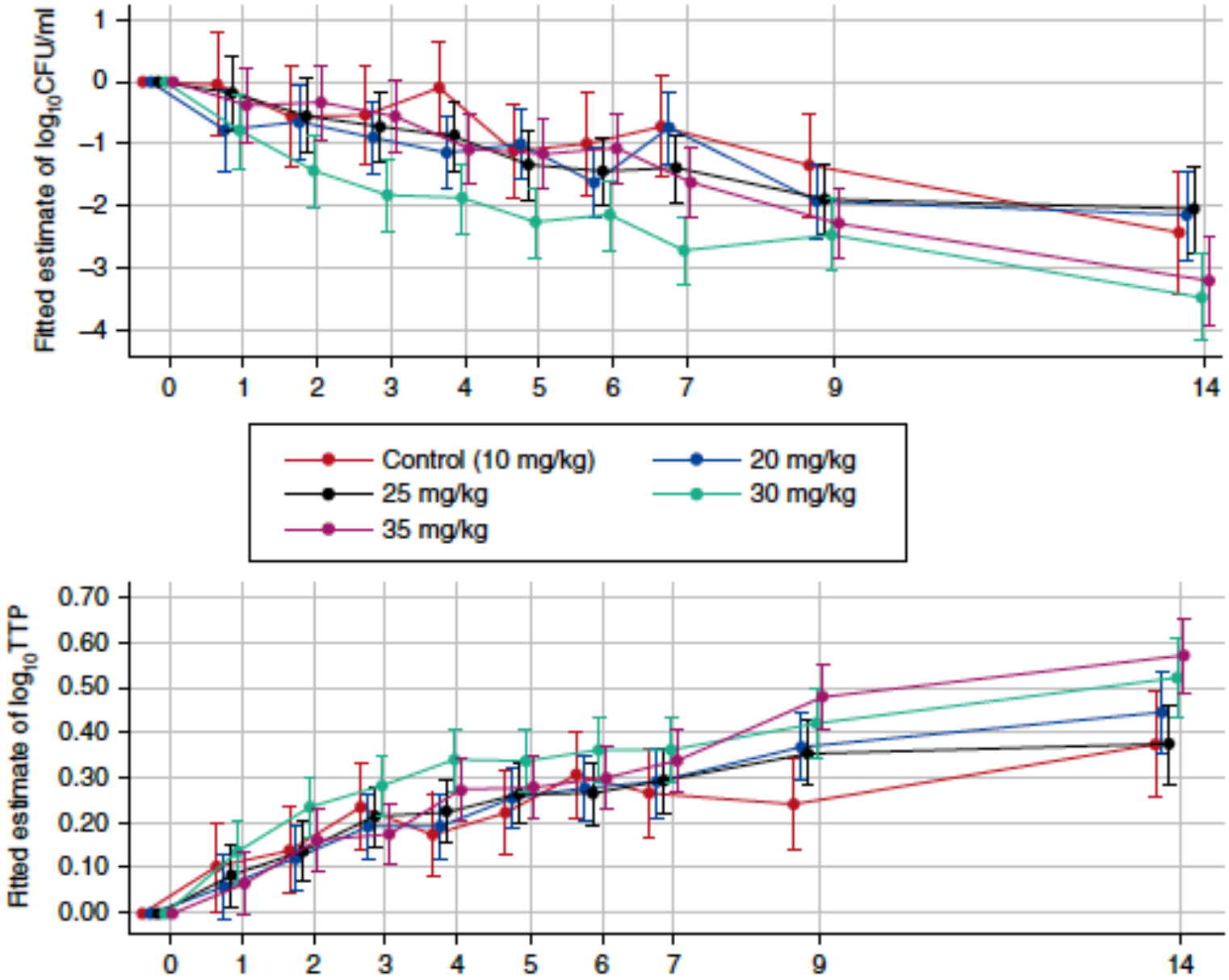
American Journal of Respiratory and Critical Care Medicine Volume 191 Number 9 | May 1 2015

68 patients d'Afrique du Sud





Boeree et al., AJRCCM 2015



Boeree et al., AJRCCM 2015

Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

Boeree et al., AJRCCM 2015

A Dose-Ranging Trial to Optimize the Dose of Rifampin in the Treatment of Tuberculosis

Martin J. Boeree[1,2], Andreas H. Diacon[3,4], Rodney Dawson[5,6], Kim Narunsky[5,6], Jeannine du Bois[4], Amour Venter[3], Patrick P. J. Phillips[7], Stephen H. Gillespie[8], Timothy D. McHugh[9], Michael Hoelscher[10,11], Norbert Heinrich[10,11], Sunita Rehal[7], Dick van Soolingen[12,13], Jakko van Ingen[12], Cecile Magis-Escurra[1], David Burger[14], Georgette Plemper van Balen[1], and Rob E. Aarnoutse[14]; on behalf of the PanACEA Consortium

American Journal of Respiratory and Critical Care Medicine Volume 191 Number 9 | May 1 2015

•Rifampicine à fortes doses (jusqu'à 35mg/kg)

- bien tolérée pendant 14 jours
- quantité de substance circulante x 10
- effect bactéricide plus rapide

•2 essais de phase 2b en cours

-NCT00760149(Rifampicine à la dose de 15 et 20mg/kg pendant 2mois)

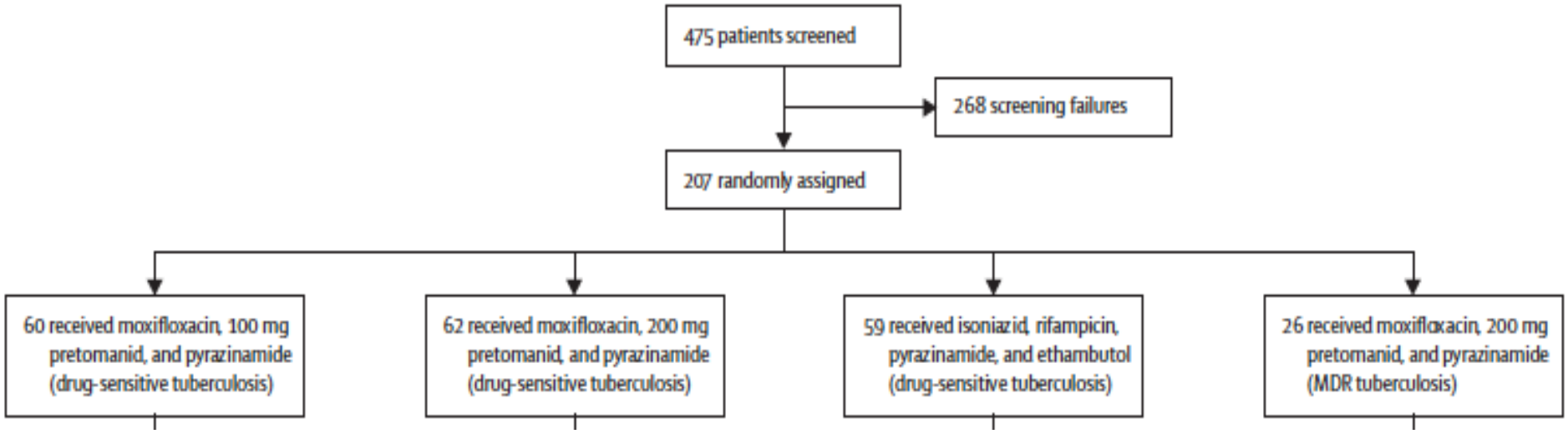
-NCT01785186(Rifampicine 20mg/kg et 35mg/kg en association différente)

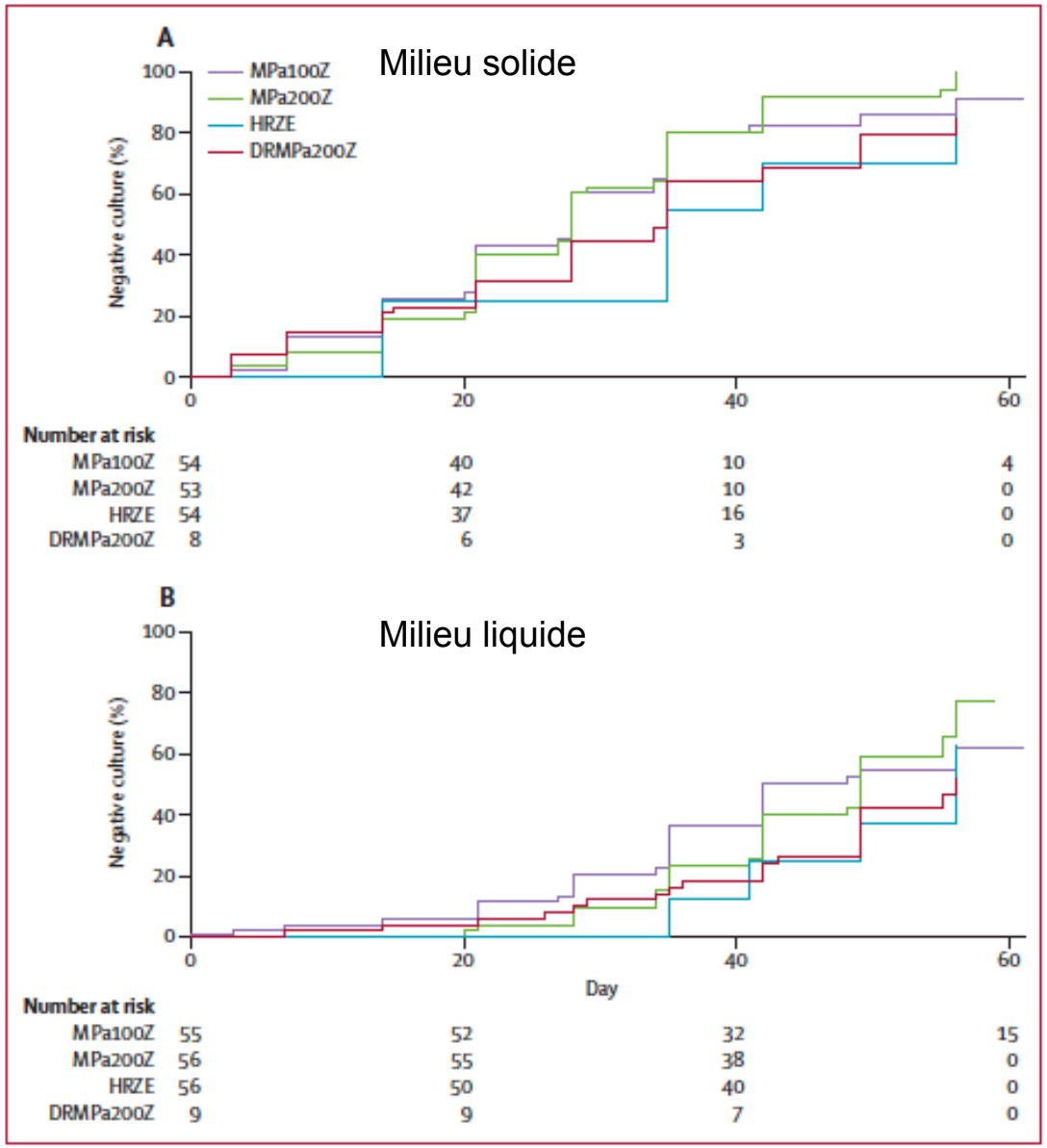
Phase 2b

Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis

Rodney Dawson, Andreas H Diacon, Daniel Everitt, Christo van Niekerk, Peter R Donald, Divan A Burger, Robert Schall, Melvin Spigelman, Almari Conradie, Kathleen Eisenach, Amour Venter, Prudence Ive, Liesl Page-Shipp, Ebrahim Variava, Klaus Reither, Nyanda E Ntinginya, Alexander Pym, Florian von Groote-Bidlingmaier, Carl M Mendel

www.thelancet.com **Vol 385 May 2, 2015**





Pas de différence significative concernant les effets secondaires

Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis

Rodney Dawson, Andreas H Diacon, Daniel Everitt, Christo van Niekerk, Peter R Donald, Divan A Burger, Robert Schall, Melvin Spigelman, Almari Conradie, Kathleen Eisenach, Amour Venter, Prudence Ive, Liesl Page-Shipp, Ebrahim Variava, Klaus Reither, Nyanda E Ntinginya, Alexander Pym, Florian von Groote-Bidlingmaier, Carl M Mendel

www.thelancet.com **Vol 385 May 2, 2015**

Combinaison thérapeutique intéressante

- pas de rifampicine
- pas de traitement IV
- efficace dans la tuberculose sensible et MDR
- plus bas coût pour prise en charge MDR TB

A retrospective review comparing treatment outcomes of adjuvant lung resection for drug-resistant tuberculosis in patients with and without human immunodeficiency virus co-infection

Gerard R. Alexander[a,*] and Bruce Biccard[a,b]

European Journal of Cardio-Thoracic Surgery (2015) 1–7

Jusqu'à 90% de guérison de la MDR TB après chirurgie

	XDR-TB		
	HIV-positive (n = 9)	HIV-negative (n = 4)	P-value
Cure	7 (77.8%)	1 (25%)	0.2168
Conversion	2 (22.2%)	3 (75%)	0.2168
Treatment failure	0	0	
Protocol morbidity	2 (22.2%)	1 (25%)	1.0000
Mortality	0	0	

	MDR-TB		
	HIV-positive (n = 19)	HIV-negative (n = 17)	P-value
Cure	12 (63.2%)	15 (88.2%)	0.1279
Conversion	6	2 (11.8%)	0.2357
Treatment failure	1	0	1.0000
Protocol morbidity	1 (5.3%)	1 (5.9%)	1.0000
Mortality	0	0	

Biomarkers on patient T cells diagnose active tuberculosis and monitor treatment response

Toidi Adekambi,[1] Chris C. Ibegbu,[1,2] Stephanie Cagle,[3] Ameeta S. Kalokhe,[1,3] Yun F. Wang,[4,5] Yijuan Hu,[6] Cheryl L. Day,[1,7] Susan M. Ray,[3] and Jyothi Rengarajan[1,3]

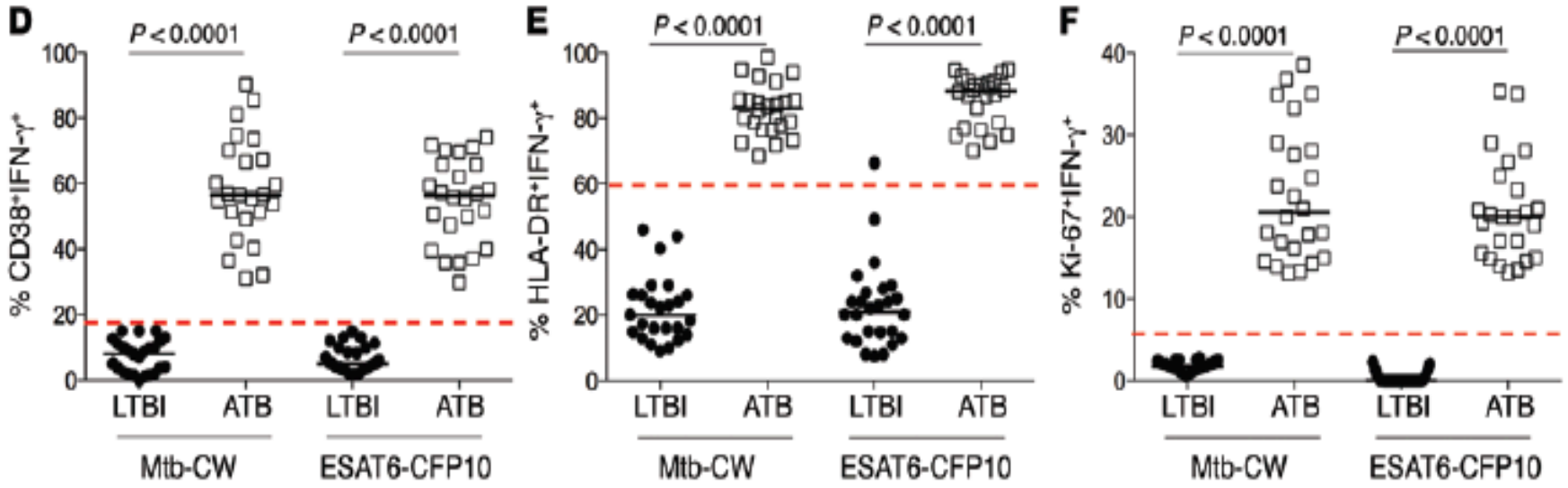
J Clin Invest. 2015;125(5):1827–1838. doi:10.1172/JCI77990.

Biomarkers on patient T cells diagnose active tuberculosis and monitor treatment response

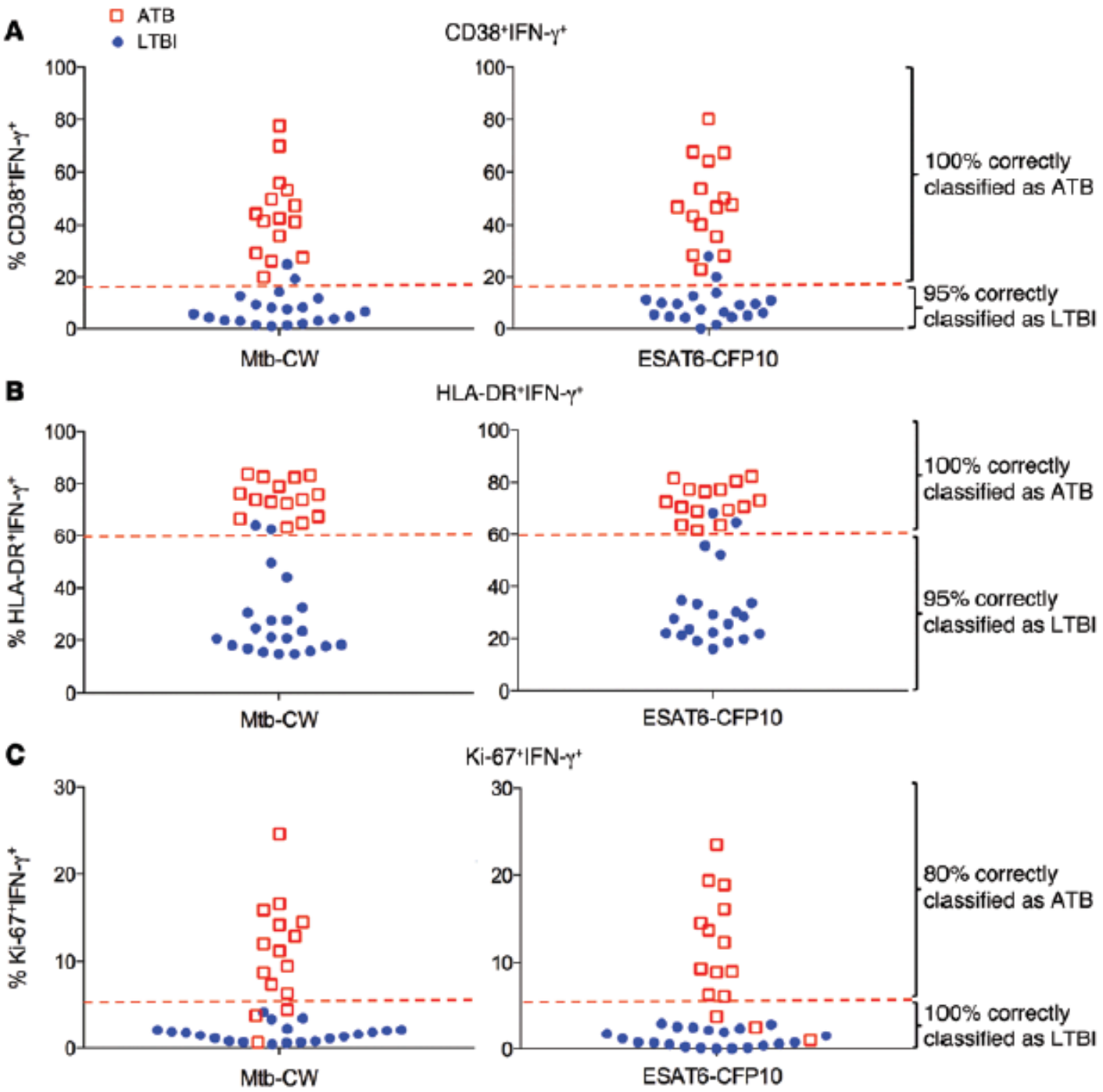
Toidi Adekambi,[1] Chris C. Ibegbu,[1,2] Stephanie Cagle,[3] Ameeta S. Kalokhe,[1,3] Yun F. Wang,[4,5] Yijuan Hu,[6] Cheryl L. Day,[1,7] Susan M. Ray,[3] and Jyothi Rengarajan[1,3]

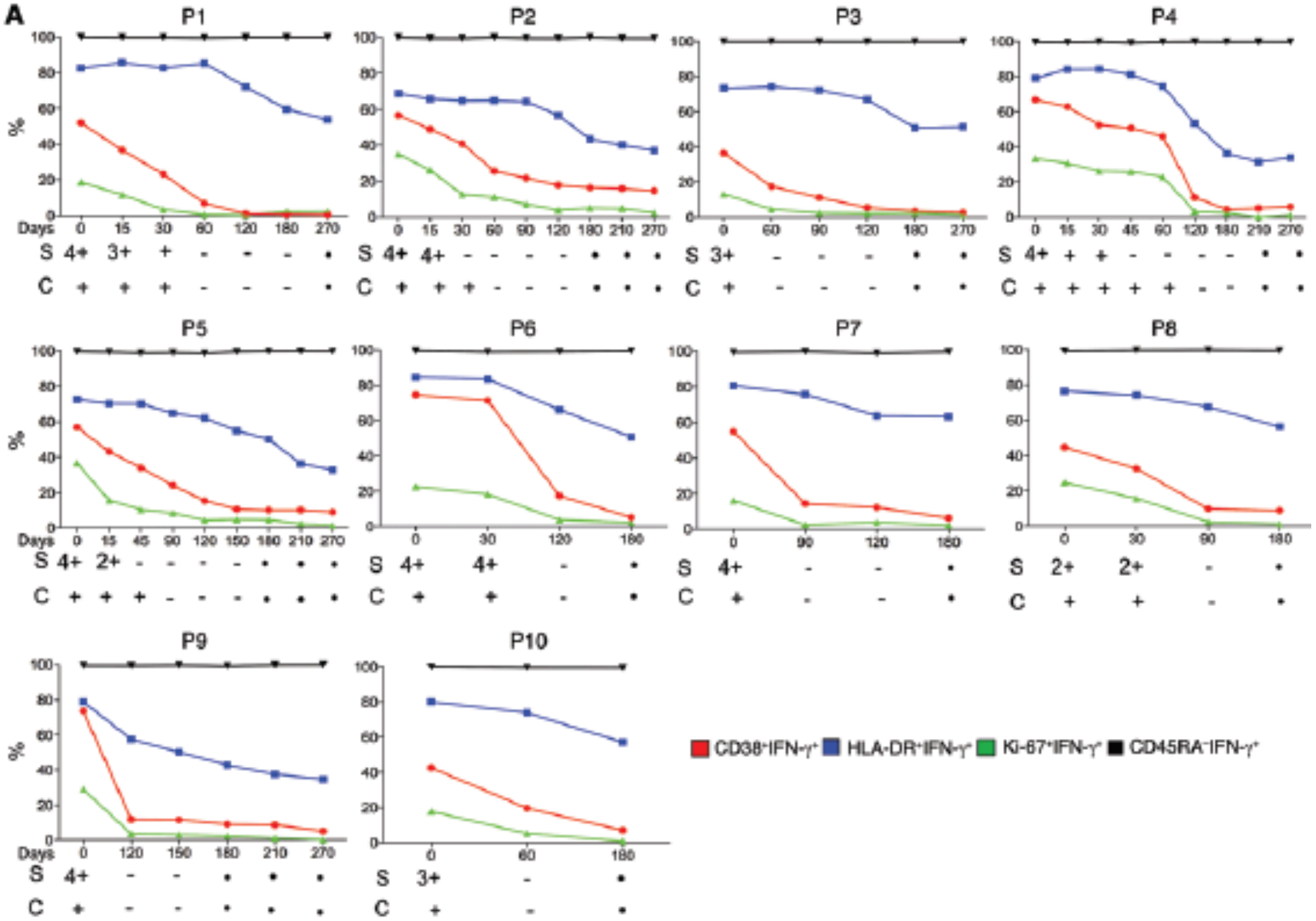
J Clin Invest. 2015;125(5):1827–1838. doi:10.1172/JCI77990.

CD38+ IFN-γ⁺ **HLA-DR-IFN-γ⁺** **Ki-67-IFN-γ⁺**



Les patients ayant une tuberculose maladie ont des cellules T exprimant significativement plus de marqueurs CD38, HLA DR et Ki 67


A
ATB
LTBI
CD38+IFN-γ+
% CD38+IFN-γ+
100
80
60
40
20
0
Mtb-CW
ESAT6-CFP10
100% correctly classified as ATB
95% correctly classified as LTBI
B
HLA-DR+IFN-γ+
% HLA-DR+IFN-γ+
100
80
60
40
20
0
Mtb-CW
ESAT6-CFP10
100% correctly classified as ATB
95% correctly classified as LTBI
C
Ki-67+IFN-γ+
% Ki-67+IFN-γ+
30
20
10
0
Mtb-CW
ESAT6-CFP10
80% correctly classified as ATB
100% correctly classified as LTBI


A
P1
P2
P3
P4
P5
P6
P7
P8
P9
P10
%
Days
S
C
CD38+IFN-γ+
HLA-DR+IFN-γ+
Ki-67+IFN-γ+
CD45RA-IFN-γ+

Mycobactéries non tuberculeuses

Preliminary Results of Bedaquiline as Salvage Therapy for Patients With Nontuberculous Mycobacterial Lung Disease

Julie V. Philley, MD; Richard J. Wallace Jr, MD, FCCP; Jeana L. Benwill, MD; Varsha Taskar, MD; Barbara A. Brown-Elliott, MS, MT(ASCP)SM; Foram Thakkar, MBBS; Timothy R. Aksamit, MD, FCCP; and David E. Griffith, MD, FCCP

CHEST 2015; 148(2):499-506

10 patients, Texas
Echec de traitement d'une infection à *Mycobacterium abscessus* ou *M. avium complex*
Souches résistantes aux macrolides (80%)
Bedaquiline 400mg/j sur les 2 premières semaines puis 200mg/j 3x/sem
6 mois de traitement

- Amélioration des symptômes chez 90% des patients (9/10) : toux, expectoration, poids
- Amélioration des signes radiologiques chez 40% des patients
- ≥ 1 culture négative chez 50% des patients
- Peu d'effets secondaires (nausées)

- Amélioration des symptômes chez 90% des patients (9/10) : toux, expectoration, poids
- Amélioration des signes radiologiques chez 40% des patients
- ≥ 1 culture négative chez 50% des patients
- Peu d'effets secondaires (nausées)

Patient No.	Baseline (at the Start of Therapy)	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1 Mab	4+	3+	1+	2+	3+	1+	2+
2 Mab	1+	3+	1+	35 colonies	37 colonies	16 colonies	3+
3							ies
4							
5							
6							
7 MAC	4+	4+	30 colonies	Negative	Negative	…[a]	…[a]
8 MAC	4+	1+	Negative	3+	4+	4+	4+
9 MAC	4+	2+	3+	1 colony	4 colonies	1+	4 colonies
10 MAC	30 colonies	8 colonies	Negative	1+	Negative	9 colonies	Negative

Preuve de concept : Bedaquiline utilisée en dehors de la tuberculose

Résultats décevants

Long Term Follow Up Of *Mycobacterium Avium* Complex Lung Disease In Patients Treated With Regimens Including Clofazimine and/or Rifampin

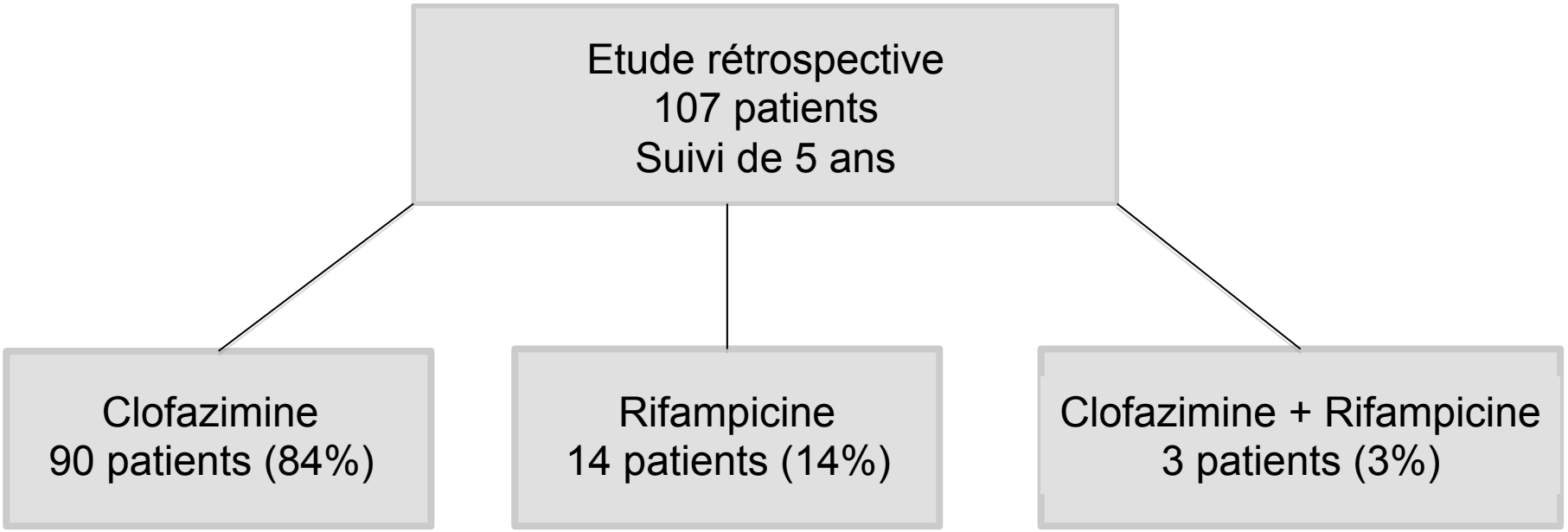
Julie Jarand MD[1], J. Paul Davis MD[1], Robert L. Cowie MD[1], Stephen K. Field MD[1], Dina A. Fisher MD[1]

Chest 2015

Long Term Follow Up Of *Mycobacterium Avium* Complex Lung Disease In Patients Treated With Regimens Including Clofazimine and/or Rifampin

Julie Jarand MD[1], J. Paul Davis MD[1], Robert L. Cowie MD[1], Stephen K. Field MD[1], Dina A. Fisher MD[1]

Chest 2015



Azithromycine 250mg/j 5j/sem
Ethambutol 15-18mg/kg/j
Clofazimine 100mg/j ou Rifampicine 450mg/j si <50kg ou 600mg/j si >50kg

	All patients (n=107)	Clofazimine (n= 90)	Rifampin (n= 14)
Microbiology			
Conversion (%)	102 (95%)	90 (100%)	10 (71%) *
Average time to first negative culture ± SD (range); months	4.5 ± 4.2 (0-30)	4.4 ± 3.5 (0-20)	5.9 ± 8.6 (1-30)
Average length of treatment after sputum conversion ± SD (range); months	8.7 ± 5.4 (0-39)	8.5 ± 4.6 (0-33)	8.5 ± 4.4 (2-14)
Microbiologic relapse	52 (49%)	44 (49%)	7 (50%)
Continual treatment	4 (4%)	0 (0%)	2 (14%)
Re-treatment**	38 (36%)	33 (37%)	4 (29%)

Conversion de la culture : 2 cultures négatives à la suite ou 1 culture négative sans autre crachat

Pas de différence significative sur les effets indésirables
Arrêt Ethambutol ++
Arrêt Clofazimine chez 6,5% des patients

American Osteopathic College of Dermatology

	No re-treatment (n=65)	Re-treatment (n=38)	P value*
Cavitation (n=25)	16 (25%)	9 (24%)	1.000
Smear positive (n=50)	33 (51%)	17 (45%)	0.683
Bilateral disease (n=77)	46 (71%)	31 (82%)	0.250
Received clofazimine (n=90)	57 (88%)	33 (87%)	1.000
Received rifampin (n=12)	8 (12%)	4 (11%)	1.000
Treated ≥ 12 months post culture conversion (n=28)	21 (32%)	7 (18%)	0.170

	No re-treatment (n=65)	Re-treatment (n=38)	P value*
Cavitation (n=25)	16 (25%)	9 (24%)	1.000
Smear positive (n=50)	33 (51%)	17 (45%)	0.683
Bilateral disease (n=77)	46 (71%)	31 (82%)	0.250
Received clofazimine (n=90)	57 (88%)	33 (87%)	1.000
Received rifampin (n=12)	8 (12%)	4 (11%)	1.000
Treated ≥ 12 months post culture conversion (n=28)	21 (32%)	7 (18%)	0.170

Long Term Follow Up Of *Mycobacterium Avium* Complex Lung Disease In Patients Treated With Regimens Including Clofazimine and/or Rifampin

Julie Jarand MD[1], J. Paul Davis MD[1], Robert L. Cowie MD[1], Stephen K. Field MD[1], Dina A. Fisher MD[1]

Chest 2015

Efficacité Clofazimine : alternative à la Rifampicine ?

Peu d'effets secondaires (≠ *Tang et al., CID 2015*)

Recommandations ATS/IDSA 2007 : traitement poursuivi ≥ 12mois après négativation de la culture
➔ Evite rechute et re-traitement ?

Etude rétrospective

Intermittent Antibiotic Therapy for Nodular Bronchiectatic *Mycobacterium avium* Complex Lung Disease

Byeong-Ho Jeong[1*], Kyeongman Jeon[1*], Hye Yun Park[1], Su-Young Kim[1], Kyung Soo Lee[2], Hee Jae Huh[3], Chang-Seok Ki[3], Nam Yong Lee[3], Sung Jae Shin[4], Charles L. Daley[5], and Won-Jung Koh[1]

Am J Respir Crit Care Med Vol 191, Iss 1, pp 96–103, Jan 1, 2015

Intermittent Antibiotic Therapy for Nodular Bronchiectatic *Mycobacterium avium* Complex Lung Disease

Byeong-Ho Jeong[1*], Kyeongman Jeon[1*], Hye Yun Park[1], Su-Young Kim[1], Kyung Soo Lee[2], Hee Jae Huh[3], Chang-Seok Ki[3], Nam Yong Lee[3], Sung Jae Shin[4], Charles L. Daley[5], and Won-Jung Koh[1]

Am J Respir Crit Care Med Vol 191, Iss 1, pp 96–103, Jan 1, 2015

Traitement journalier
Azithromycine 250mg
ou Clarithromycine 1g
Ethambutol 15mg/kg
Rifampicine 450 à 600mg/j

Traitement intermittent
Azithromycine 500mg
ou Clarithromycine 1g
Ethambutol 25mg/kg
Rifampicine 600mg 3/sem

TDM avant et à 12 mois de traitement
BK crachat à 1,2, 6mois puis /3mois
Conversion de la culture si 3 cultures négatives à la suite

	Daily Therapy (*n* = 99)	Intermittent Therapy (*n* = 118)	*P* Value
Improvement of symptom	74 (75%)	97 (82%)	0.181
Improvement of HRCT	67 (68%)	86 (73%)	0.402
Sputum culture conversion	75 (76%)	79 (67%)	0.154
Time of sputum culture conversion, d	34 (27–63)	35 (28–83)	0.149

	Daily Therapy (*n* = 99)	Intermittent Therapy (*n* = 118)	*P* Value
Early discontinuation of antibiotic treatment	15 (15%)	13 (11%)	0.366
Dose reduction of CLR	11/95 (12%)	1/26 (4%)	0.458
Change from AZM to CLR	0/12 (0%)	3/116 (3%)	NA
Discontinuation of RIF or RFB	4/99 (4%)	7/118 (6%)	0.527
Discontinuation of EMB	24/99 (24%)	1/118 (1%)	<0.001
Discontinuation of streptomycin	4/60 (7%)	—	NA
Total	46/99 (46%)*	25/118 (21%)	<0.001

Intermittent Antibiotic Therapy for Nodular Bronchiectatic *Mycobacterium avium* Complex Lung Disease

Byeong-Ho Jeong[1*], Kyeongman Jeon[1*], Hye Yun Park[1], Su-Young Kim[1], Kyung Soo Lee[2], Hee Jae Huh[3], Chang-Seok Ki[3], Nam Yong Lee[3], Sung Jae Shin[4], Charles L. Daley[5], and Won-Jung Koh[1]

Am J Respir Crit Care Med Vol 191, Iss 1, pp 96–103, Jan 1, 2015

Traitement intermittent = piste intéressante concernant la tolérance
Mais l'observance?

Meilleur taux de négativation de la culture avec le traitement quotidien (76% vs 67%)

Etude non randomisée et non contrôlée