Les traitements courts de l'infection latente : vraiment?

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CLAT 67 Alsace Nord

Journées des CLAT – 23 et 24 septembre 2024

Problème de santé publique mondiale

- Tuberculose maladie : 10 M de cas par an[1].
- Plus d'un million de décès imputable chaque année[1].
- 2,2% des tuberculoses diagnostiquées en Europe (≈220 000 cas)[1].

WHO, 2023 annual report

L’infection latente, le réservoir

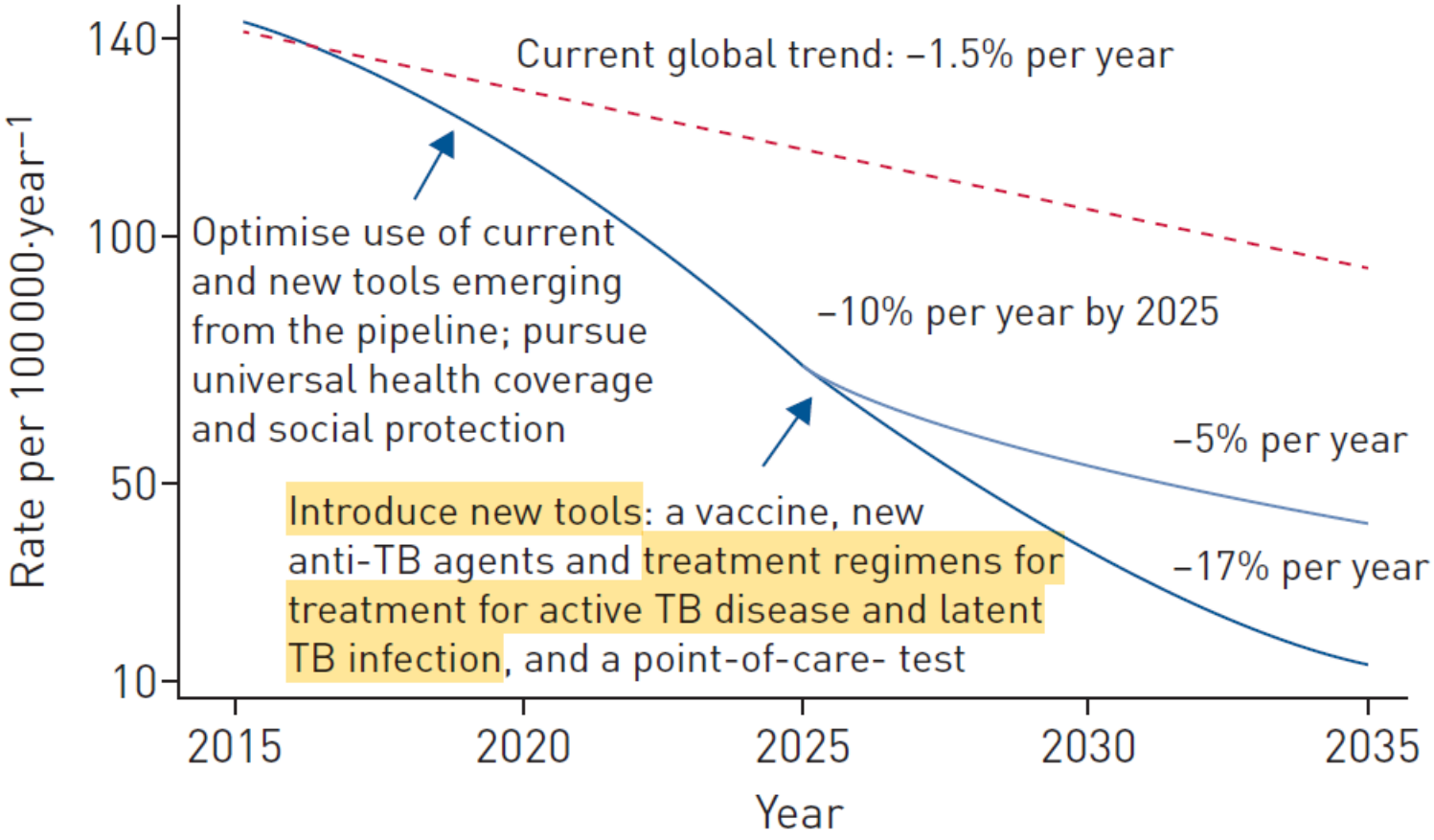
- Définition : Immunodiagnostic positif sans signe clinique ni radiologique de tuberculose[1].
- Infection tuberculeuse latente: 24,8% de la population mondiale[2].

	Estimates of LTBI
Africa	33,6 (24,4-42,9)
The Americas	13,7 (11-16,3)
Eastern Mediterranean	24 (19,4-28,5)
Europe	12,2 (9,8-14,5)
South-East Asia	36 (25,3-46,7)
Western Pacific	20,7 (16,8-24,5)

HCSP, Enquête autour d’un cas, 2013
Cohen A et al, Eur Respir J, 2019

Matteelli A et al, Eur Respir Rev, 2018

End TB Strategy



Isoniazide

- USA 1957-1960, sujets contacts intra-familiaux, 25033 cas.
- Isoniazide 5 mg/kg/jour pendant **12 mois**.
- Réduction de l'incidence sous traitement.

TABLE 24

ONE HUNDRED AND THREE CASES OF ACTIVE PULMONARY TUBERCULOSIS DEVELOPING AFTER THE START OF THE TRIAL, BY STAGE OF DISEASE

Stage of Disease	During Medication Year		After Medication Year	
	Placebo	Isoniazid	Placebo	Isoniazid
Total.....	62	14	17	10
Minimal.....	12	2	5	3
Moderately advanced.....	36	7	9	5
Far advanced.....	14	5	3	2

-77%

Ferebee S and Mount F, Am J Respir Med, 1962

Isoniazide

- France, 1959-1969.
- Virage tuberculinique récent, pas de signe clinique ou radiographique de tuberculose, pas de BCG préalable.
- Isoniazide 5-15 mg/kg/jour pour une durée ≥ 5 mois.

	Incidence à 10 ans
Isoniazide	0,99%
Placebo	2,72%

-66% à 10 ans de suivi.

Debré R et al, Int J Epidemiol, 1973

Isoniazide

Choice of Drugs, Dosage, and Duration of Preventive Treatment

Isoniazid has been proved to be an effective agent for preventive treatment in tuberculosis; it is relatively free from side-effects, and is cheap. Isoniazid should be given in the dosage of 5 mg. per kilogram per day, usually for twelve to eighteen months. In certain self-limited situations, such as pregnancy or in children with measles, the duration may be considerably reduced; but in some instances, much longer administration of isoniazid is indicated. There is a possibility that adminis-

Corpe R et al, Am Rev Respir Dis, 1965

Les problèmes : l'observance

Table 2. Percentage of participants by regimen and weeks completed and complied

Duration	Product	No. of weeks completed (complied)			
		12	24	36	52
12 weeks	Isoniazid	95 (87)			
	Placebo	97 (91)			
24 weeks	Isoniazid	94 (84)	93 (78)		
	Placebo	96 (87)	95 (82)		
52 weeks	Isoniazid	93 (84)	91 (79)	89 (73)	88 (68)
	Placebo	95 (87)	93 (79)	91 (74)	90 (69)

28000 IDR+ avec lésions fibrotiques.
INH 300 mg/jour 3/6/12 mois.

IUAT, Bull World Health Organization, 1982

Isoniazide: durée et efficacité

Table 4. Efficacy of various durations of isoniazid therapy compared with placebo: all assigned participants

Regimen	No. of participants entering regimen	Cumulative no. of cases	5-Year incidence[a]	Percentage reduction	Relative risk
Placebo	6990	97[b]	14.3	0	4.0
12-I	6956	76	11.3	21	3.1
24-I	6965	34[b]	5.0	65	1.4
52-I	6919	24[c]	3.6	75	1.0

[a] Culture-positive tuberculosis per 1000 persons at risk.
[b] Includes 1 case during the first 6 months of pill-taking.
[c] Includes 2 cases during the first 6 months of pill-taking.

Population : IDR positive, lésions fibrotiques à l'imagerie.

Bull World Health Organ, 1982

Isoniazide: durée et efficacité –observance complète

- Traitement historique.
- 5 mg/kg/j

Table 6. Efficacy of various durations of isoniazid therapy compared with placebo for ''completer-compliers''

Regimen	No. of participants	No. of cases	Incidence[a]	Percentage reduction	Relative risk
Placebo	5616	83	15.0	0	13.6
12-I	6039	61	10.4	31	9.4
24-I	5437	25	4.7	69	4.3
52-I	4543	5	1.1	93	1.0

[a] Culture-positive tuberculosis per 1000 persons at risk.

Population : IDR positive, lésions fibrotiques à l'imagerie.

Bull World Health Organ, 1982
Am J Respir Crit Care Med, 2000

Isoniazide

- INH 12 mois vs placebo.
- Sujets contacts intrafamiliaux.
- **Bénéfice quasi-maximal pour une durée de 9-10 mois.**

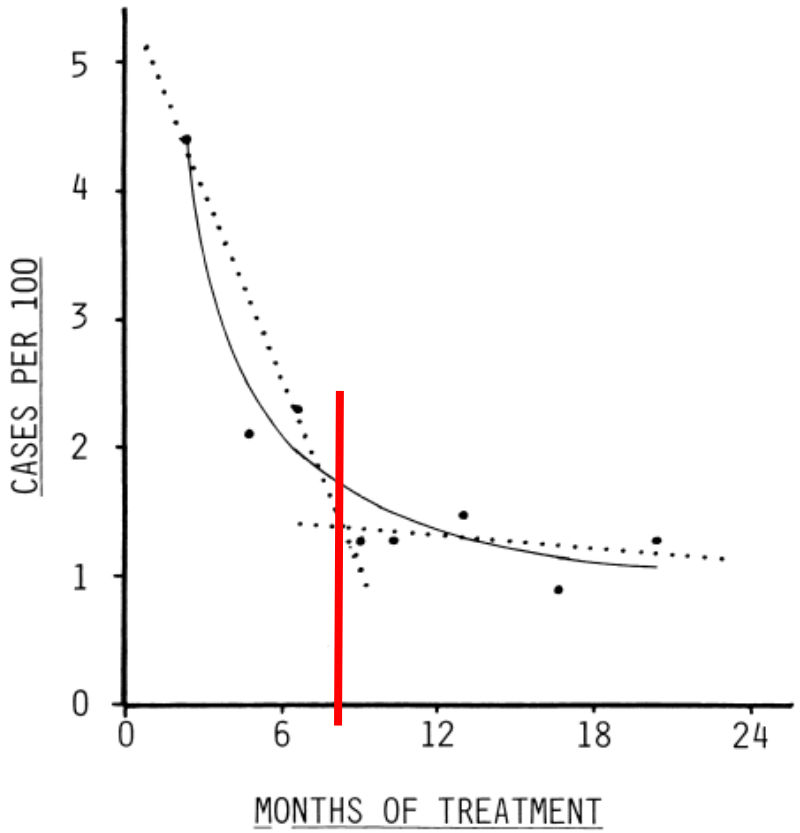
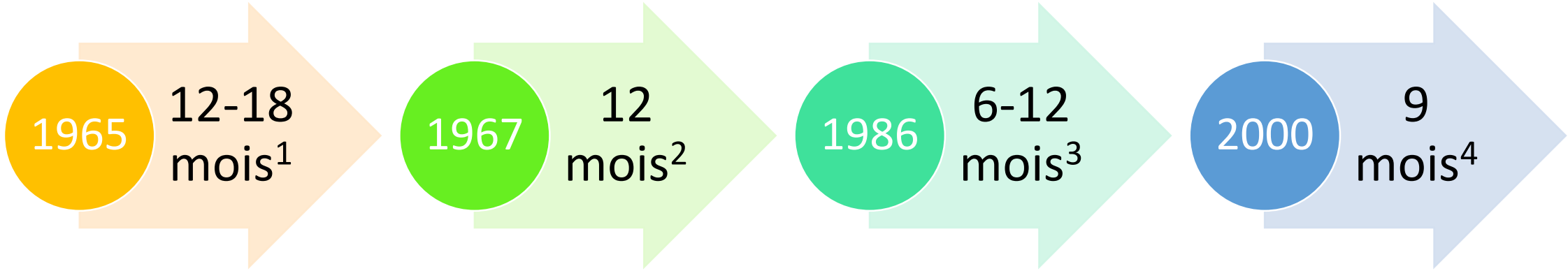


Figure Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve ($y = a + b/x$); and dotted lines, the calculated values based on the first four and last five observations ($y = a + bx$).

Comstock G et al, Am Rev Respir Dis, 1979

Traitement



1.Corpe R et al, Am Rev Respir Dis, 1965
2.Am Thorac Soc, Am Rev Respir Dis, 1967
3.Am Thorac Soc, Am Rev Respir Dis, 1986
4.Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000

Les problèmes : l'observance

INH 9 mois

	Type d'étude	Effectif	Traitement complet
Sterling T et al, 2011[1]	RCT	3745	**69%**
Menzies D et al, 2018[2]	RCT	2989	**57%**
Ronald L et al, 2020[3]	Retrospective	9684	**36,9%**

Sterling T et al, New Eng J Med, 2011; Menzies D et al, New Eng J Med, 2018; Ronald L et al, Eur Respir J, 2020

Isoniazide et Rifampicine: non infériorité.

INH+RMP 3 mois.

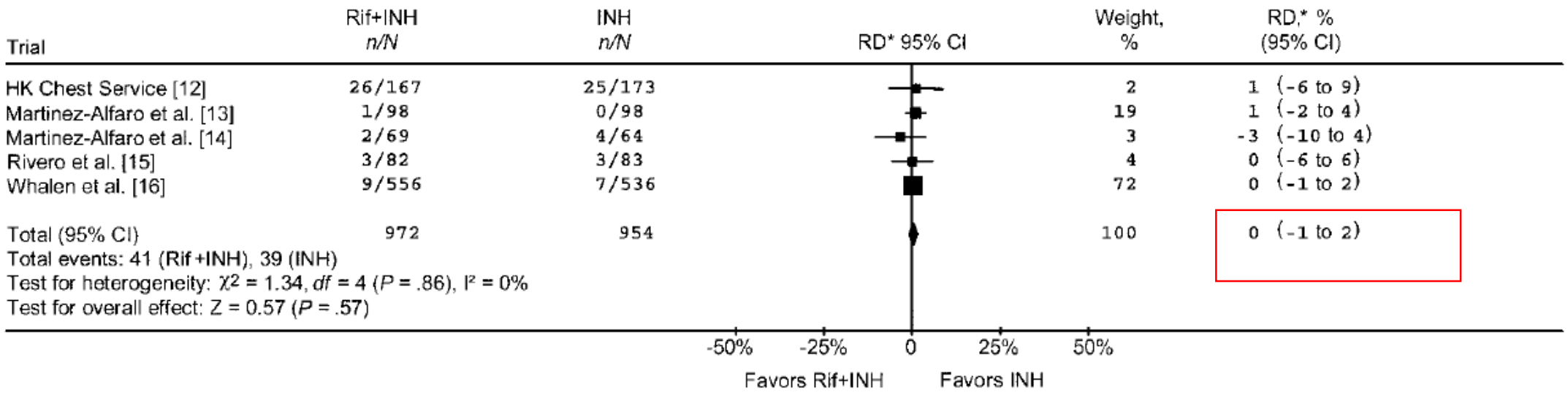


Figure 2. Pooled risk difference (RD) for development of active tuberculosis. HK, Hong Kong; I^2, percentage of total variation across the studies that is the result of heterogeneity rather than chance; INH, isoniazid; *n/N*, total no. of trial participants who developed tuberculosis/total no. of trial participants who received the regimen specified; Rif, rifampin; weight, contribution of the study to the overall result. *, RDs pooled using a random-effects model.

HKCS, Am Rev Respir Dis, 1992
Ena J, Clin Infect Dis, 2005

Pyrazinamide dans l'ITL

- RMP + PZA 2 mois
- Efficacité similaire par rapport à INH 12 mois et meilleure observance[1].
- Plus d'hépatotoxicité+++[2,3,4].
- Disparait des recommandations américaines de 2003[4].

Gordin F et al, JAMA, 2000
Jasmer R et al, Ann Intern Med, 2002
Stout J et al, AJRCCM, 2002
Schechter M et al, AJRCCM, 2006
Morb Mortal Wkly Rep 2003

Rifampicine seule

- 3443 ITL, 9 pays.
- Rifampicine 10 mg/kg/j 4 mois vs Isoniazide 5 mg/kg/j 9 mois.
- Efficacité similaire à 2 ans et 3 mois.

Table 3. Primary End Point of Occurrence of Active Tuberculosis among All Participants.*

Variable	Isoniazid	Rifampin	Rate Difference (95% CI)	P Value
Modified intention-to-treat analysis				
No. of participants	3416	3443	—	—
Completed 28 mo of follow-up — no. (%)	3138 (91.9)	3178 (92.3)	0.4 (−0.9 to 1.7)	0.57
Total person-yr of follow-up	7652	7732	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis†	9	8	—	—
Microbiologically confirmed active tuberculosis	4	4	—	—
Clinically diagnosed tuberculosis‡	5	4	—	—
No. of cases of active tuberculosis per 100 person-yr (95% CI)				
Confirmed cases	0.05 (0.02 to 0.14)	0.05 (0.02 to 0.14)	<0.01 (−0.14 to 0.16)	0.76
Confirmed or clinically diagnosed cases	0.11 (0.05 to 0.21)	0.10 (0.05 to 0.21)	<0.01 (−0.23 to 0.22)	0.98
Per-protocol analysis				
No. of participants	1931	2411	—	—
Total no. of person-yr of follow-up	4423	5503	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis	5	5	—	—
Microbiologically confirmed active tuberculosis	1	3	—	—
Clinically diagnosed tuberculosis‡	4	2	—	—
No. of confirmed or clinically diagnosed cases of active tuberculosis per 100 person-yr (95% CI)	0.11 (0.05 to 0.27)	0.09 (0.04 to 0.22)	−0.02 (−0.30 to 0.26)	0.77

Menzies D et al, New Eng J Med, 2018

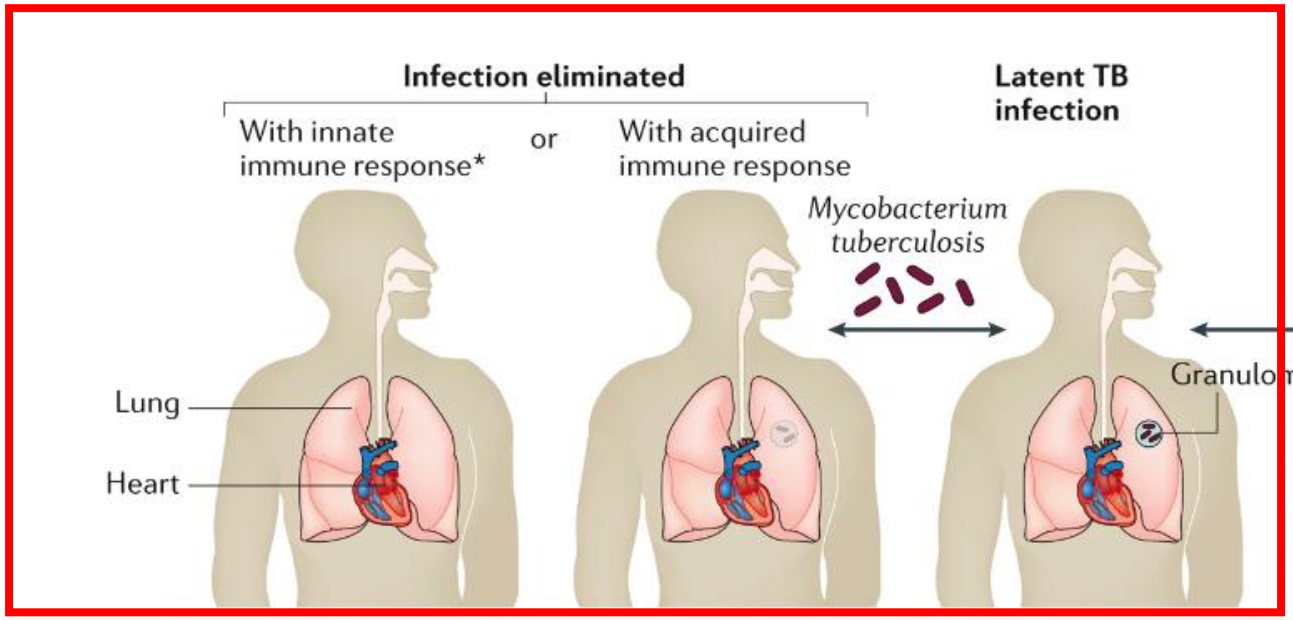
Observance: isoniazide vs rifampicine seul

TABLE 2 Frequencies of latent tuberculosis infection (LTBI) treatment completion and severe hepatic events, and mean direct health system costs during LTBI treatment[#], stratified by patient age group and co-morbidity[¶,+,§]

	With co-morbidity by age years				No co-morbidity by age years				All patients
	0–19	20–34	35–64	≥65	0–19	20–34	35–64	≥65	
Number of people n									
R	8	20	87	106	55	289	280	30	875
H	132	228	356	183	2164	2777	3434	410	9684
Treatment completion %									
R	28.6	30.0	18.7	16.4	61.6	66.8	63.5	39.4	53.5
H	19.4	22.1	28.2	27.7	33.8	25.3	28.3	34.0	36.9
Severe adverse events hepatic n (%)[f]									
R	0	0	0	1 (0.9)	0	0	0	0	1 (0.1)
H	0	1 (0.4)	2 (0.6)	2 (1.1)	2 (0.09)	2 (0.07)	5 (0.2)	1 (0.2)	15 (0.2)
TB drug costs mean CAD									
R	212	170	225	265	252	257	267	281	256
H	152	74	80	68	182	75	80	77	102
Other costs mean CAD									
R	12089	4571	9651	8587	341	223	591	8558	2793
H	2540	5813	13090	25280	556	660	2227	8491	2593

[#]: patients starting LTBI treatment with H or R in Quebec between 2003 and 2007 (N=10559). [¶]: Co-morbidity defined as having one or more hospitalisations in the year before LTBI treatment start. [+]: Treatment completion for 9H was 270 doses dispensed in 12 months and for 4R was 120 doses dispensed in 6 months. [§]: Costs during LTBI treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 12 months for H and 6 months for R). Costs reported in 2011 Canadian dollars (CAD; rounded to the nearest dollar). "Other costs" include all *Régie de l'assurance maladie du Québec*-paid costs, except those for TB drugs (*i.e.* sum of hospitalisations, emergency department visits, hospital day procedures, physician billing, and non-TB drugs dispensed). [f]: Included liver transplants (n=2) and hospitalisations ending in death (n=1), all occurring in H patients.

Ronald L et al, Eur Respir J, 2020



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Nature Reviews | Disease Primers

Pai M et al, Nature reviews, 2016

Schémas validés[1,2]

	Posologie	Durée
Isoniazide	5 mg/kg/j	6 à 9 mois
Isoniazide + Rifampicine	5 mg/kg/j 10 mg/kg/j	3 mois
Rifampicine	10 mg/kg/j	4 mois

1.European Centre for Disease Prevention and Control. Programmatic management of latent tuberculosis infection in the European Union. Stockholm: ECDC; 2018.
2.HCSP, Mai 2019

Rifapentine

Rifapentine 900 mg + Isoniazide
15-25 mg/kg
3 MOIS

Table 2. Number of Subjects with Tuberculosis and Event Rates.*

Population and Study Group	No. of Subjects	Subjects with Tuberculosis			Difference in Cumulative Rate†	Upper Limit of 95% CI for Difference in Cumulative Rate
		no.	*no. per patient-yr*	*cumulative rate*	*percentage points*	
Modified intention-to-treat analysis						
Isoniazid only	3745	15	0.16	0.43	−0.24	0.01
Combination therapy	3986	7	0.07	0.19		
Per-protocol analysis						
Isoniazid only	2585	8	0.11	0.32	−0.19	0.06
Combination therapy	3273	4	0.05	0.13		

* Combination therapy consisted of 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg). Isoniazid-only therapy consisted of 9 months of self-administered daily isoniazid (300 mg). Data are shown for a period up to 33 months after study enrollment.
† The difference is the rate in the combination-therapy group minus the rate in the isoniazid-only group.

Sterling T et al, New Eng J Med, 2011

Rifapentine: schéma 1 mois.

3000 HIV+
Rifapentine 300-600 mg/jour
+ Isoniazide 300 mg/jour
1 MOIS.

Table 2. Univariate Analysis of Risk Factors for the Primary End Point.*

Variable	1-Month Group		9-Month Group		Difference in Incidence Rate (95% CI)†
	no. of events/ person-yr	*incidence rate/ 100 person-yr*	*no. of events/ person-yr*	*incidence rate/ 100 person-yr*	
All patients	32/4926	0.65	33/4896	0.67	−0.02 (−0.35 to 0.30)
Per-protocol analysis	31/4876	0.64	29/4718	0.61	0.02 (−0.30 to 0.34)
Status on tuberculin skin test or IGRA					
Positive	10/1110	0.90	11/1137	0.97	−0.07 (−0.87 to 0.73)
Negative or unknown	22/3815	0.58	22/3759	0.59	−0.01 (−0.35 to 0.34)
Receipt of antiretroviral therapy at entry					
Yes	13/2381	0.55	15/2387	0.63	−0.08 (−0.52 to 0.35)
No	19/2545	0.75	18/2508	0.72	0.03 (−0.44 to 0.50)
Screening CD4+ count					
≤250 cells/mm^3	12/621	1.93	8/628	1.28	0.66 (−0.75 to 2.06)
>250 cells/mm^3	20/4304	0.47	25/4268	0.59	−0.12 (−0.43 to 0.19)
Sex					
Male	11/2303	0.48	15/2293	0.65	−0.18 (−0.61 to 0.26)
Female	21/2623	0.80	18/2603	0.69	0.11 (−0.36 to 0.58)

* The primary end point was a diagnosis of tuberculosis or death from tuberculosis or an unknown cause.
† This difference is the incidence rate in the 1-month group minus the rate in the 9-month group, so negative values indicate a lower risk in the 1-month group.

Swindells S et al, New Eng J Med, 2019

Observance: amélioration avec le schéma court.

560 3HP et 773 4R.
Rétrospectif, 2016-2018.

	Schéma	Traitement complet	RR multivarié
18-49 ans	**3HP**	**79%**	1.17 (1.08-1.27)
	4R	68%	
≥ 50 ans	**3HP**	**87%**	1.35 (1.19-1.52)
	4R	64%	

H: Isoniazide; P: rifapentine.

Haas M et al, Clin Infect Dis, 2021

Conclusion

- Ce n’est pas un mythe : on peut traiter une infection latente < 3-6 mois.
- Antituberculeux stérilisateurs+++ (rifampicine, rifapentine)
- Accessibilité à la rifapentine.