2019台灣胸腔暨重症加護醫學會夏季會

2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

Latent Tuberculosis Infection: Current Aspects and Future Directions

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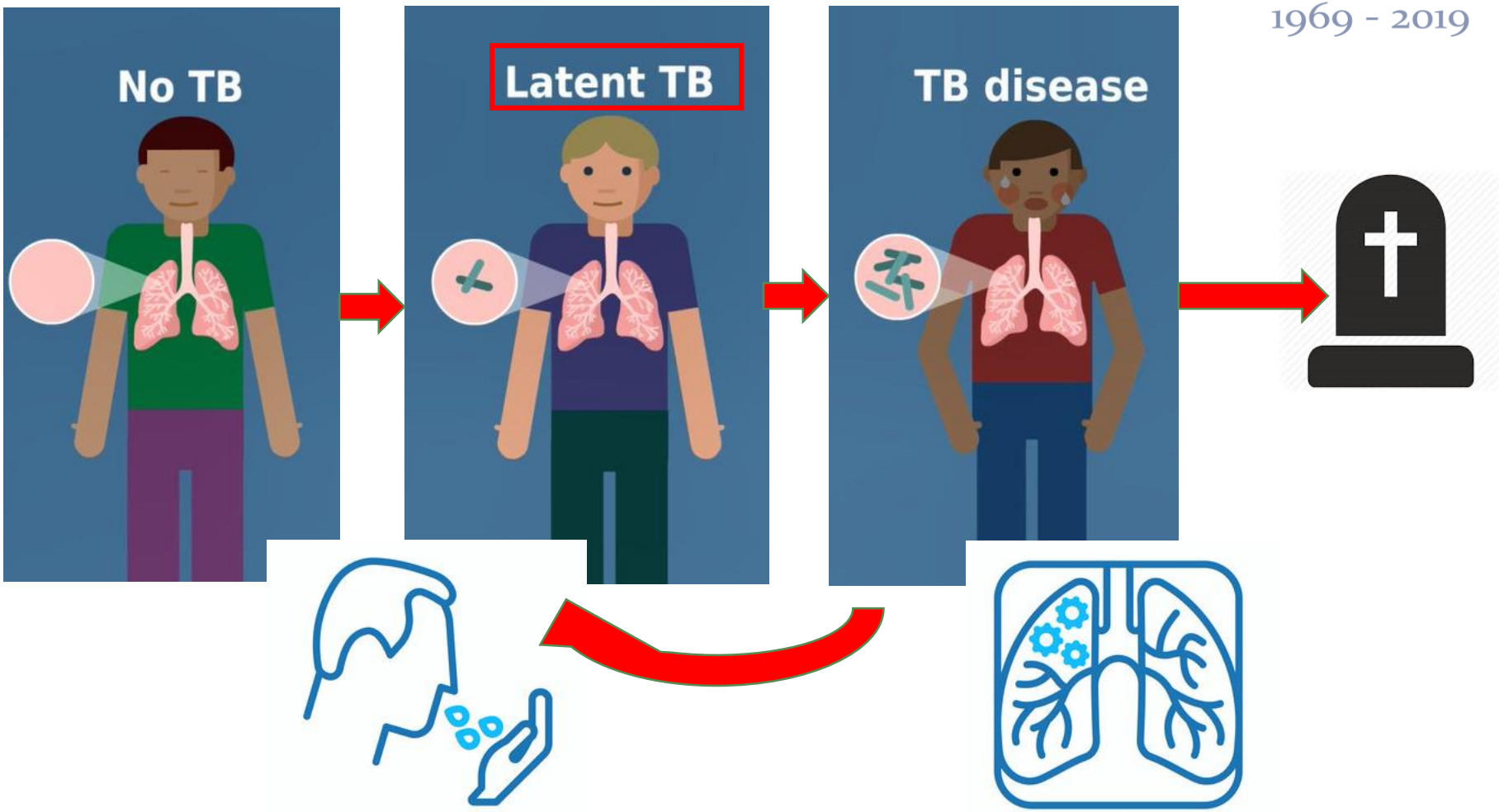
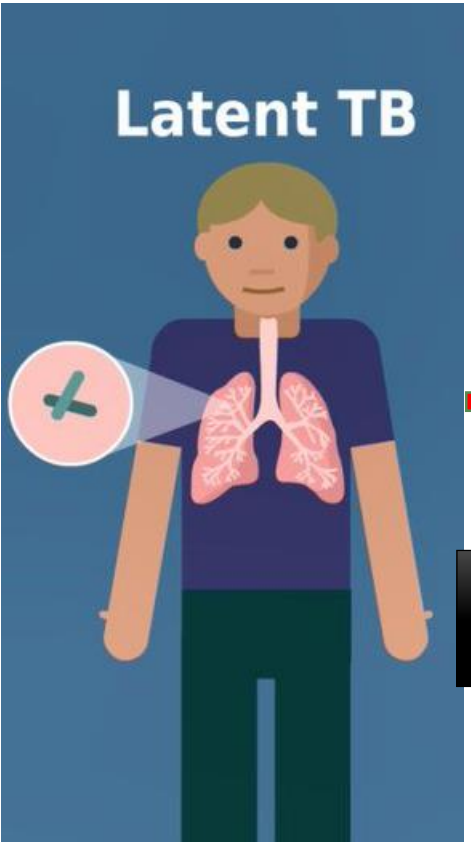
Outline

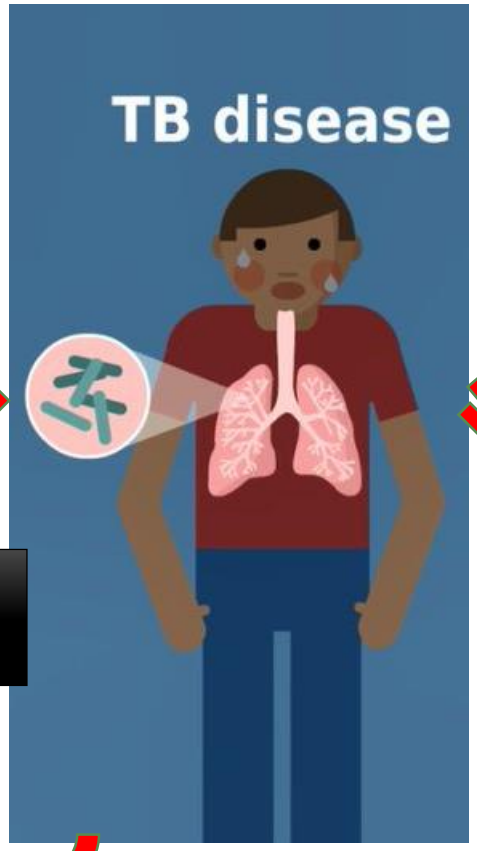
- Latent tuberculosis infection (LTBI): Overview
- Diagnostic Tool Current/Future: Newer generation IGRA
- Treatment Regimens and Side-effects Issues: Systemic drug reactions in weekly isoniazid and rifapentine (3HP) regimen
- Factors associated with SDRs in 3HP regimen: maybe not the same as we thought

TB Natural History



TB Clinical History



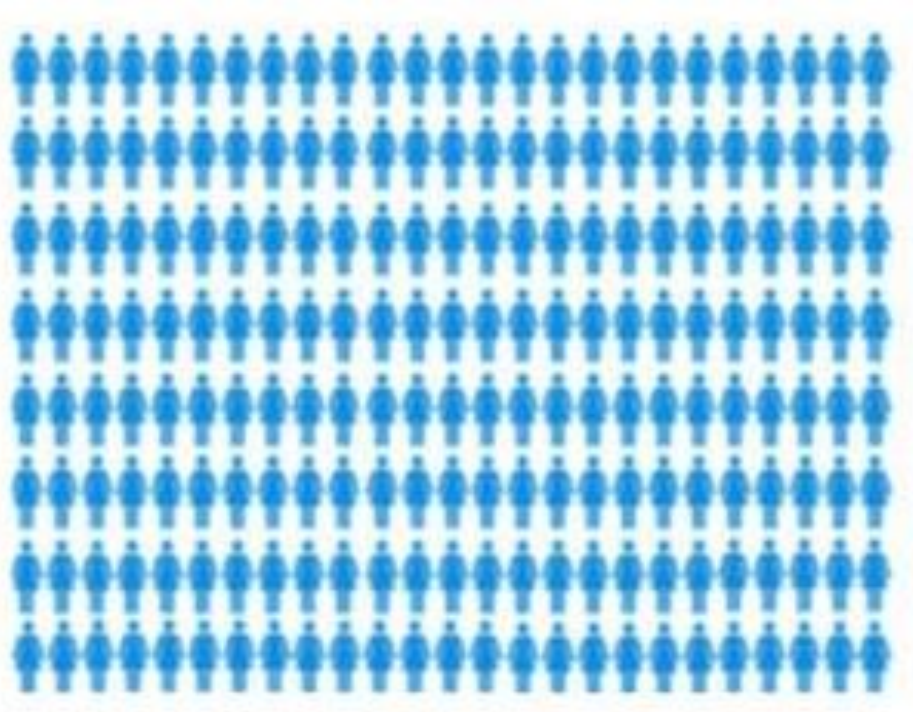


Anti-TB treatment

LTBI treatment

Why Target LTBI?

LTBI (2 billion)



Active TB (10 million)

In 2017, the estimated global prevalence of LTBI and active TB was 2 billions vs 10 millions

Definition of LTBI

A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB

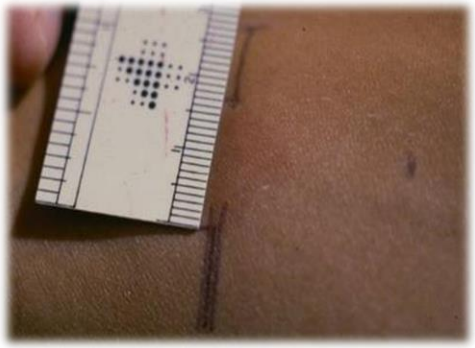
World Health Organization

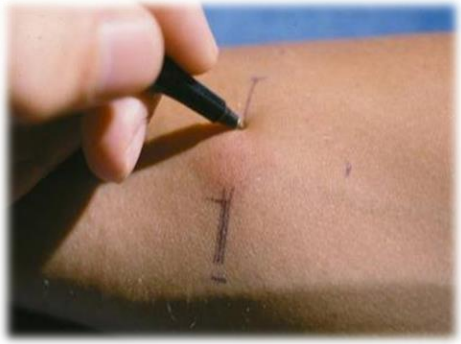
Diagnosis of LTBI

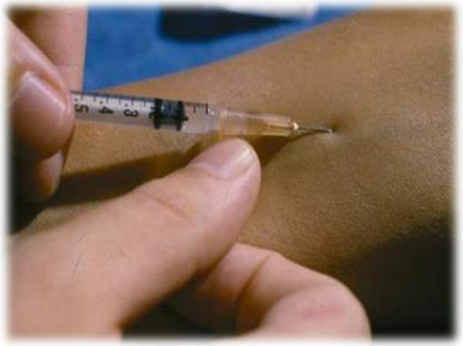
- Tuberculin skin test

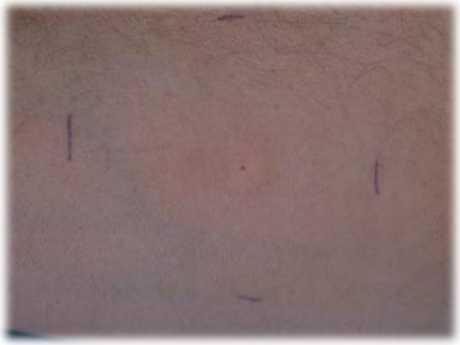
- Interferon-gamma release assay

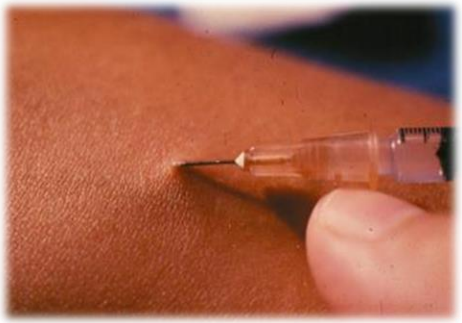
Tuberculin Skin Test

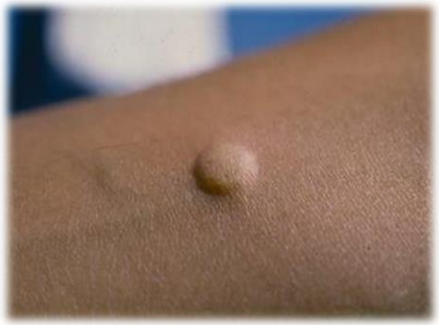


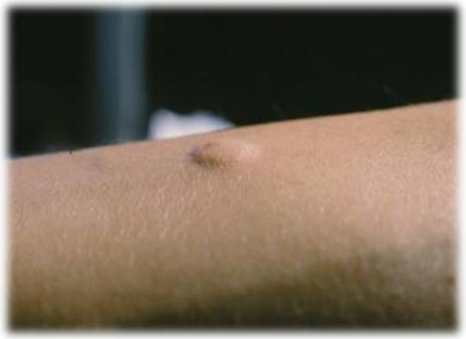












WIKIPEDIA
The Free Encyclopedia

Purified protein derivative (**PPD**) is a poorly defined, complex mixture of antigens. Tests based upon PPD are relatively unspecific since many of its proteins are found in different mycobacterial species

Interferon-gamma release assay

	QFT-GIT	T-Spot
Initial Process	Process whole blood within 16 hours	Process peripheral blood mononuclear cells (PBMCs) within 8 hours-30 hours
***M. tuberculosis* Antigen**	Single mixture of synthetic peptides representing ESAT-6, CFP-10 & TB7.7.	Separate mixtures of synthetic peptides representing ESAT-6 & CFP-10
Measurement	IFN-g concentration	Number of IFN-g producing cells (**spots**)
Possible Results	Positive, negative, indeterminate	Positive, negative, borderline, invalid

https://www.cdc.gov/

TABLE 2 Considerations for selection of latent tuberculosis infection (LTBI) testing method

Target group	Preferred test	Reason
Children under 5 years of age	TST	Children's immune system, difficulty of drawing blood, little data on performance of IGRAs in young children
Vulnerable and hard-to-reach populations[#]	IGRA	No need for a second visit to read the test result
Immunocompromised patients (including PLHIV)	Combination of TST and IGRA (parallel testing)[¶]	LTBI tests are less sensitive in immunocompromised people In order not to miss *Mycobacterium tuberculosis*-infected people who may face significant adverse health effects due to TB, a more inclusive approach is advisable
Migrant populations	IGRA or TST acceptable (IGRA for large numbers)	No need for a second visit to read the IGRA result
BCG-vaccinated people	IGRA	TST may be affected by prior vaccination with BCG

Complementary LTBI diagnostic tools

Rosales-Klintz S et al. Eur Respir J 2018

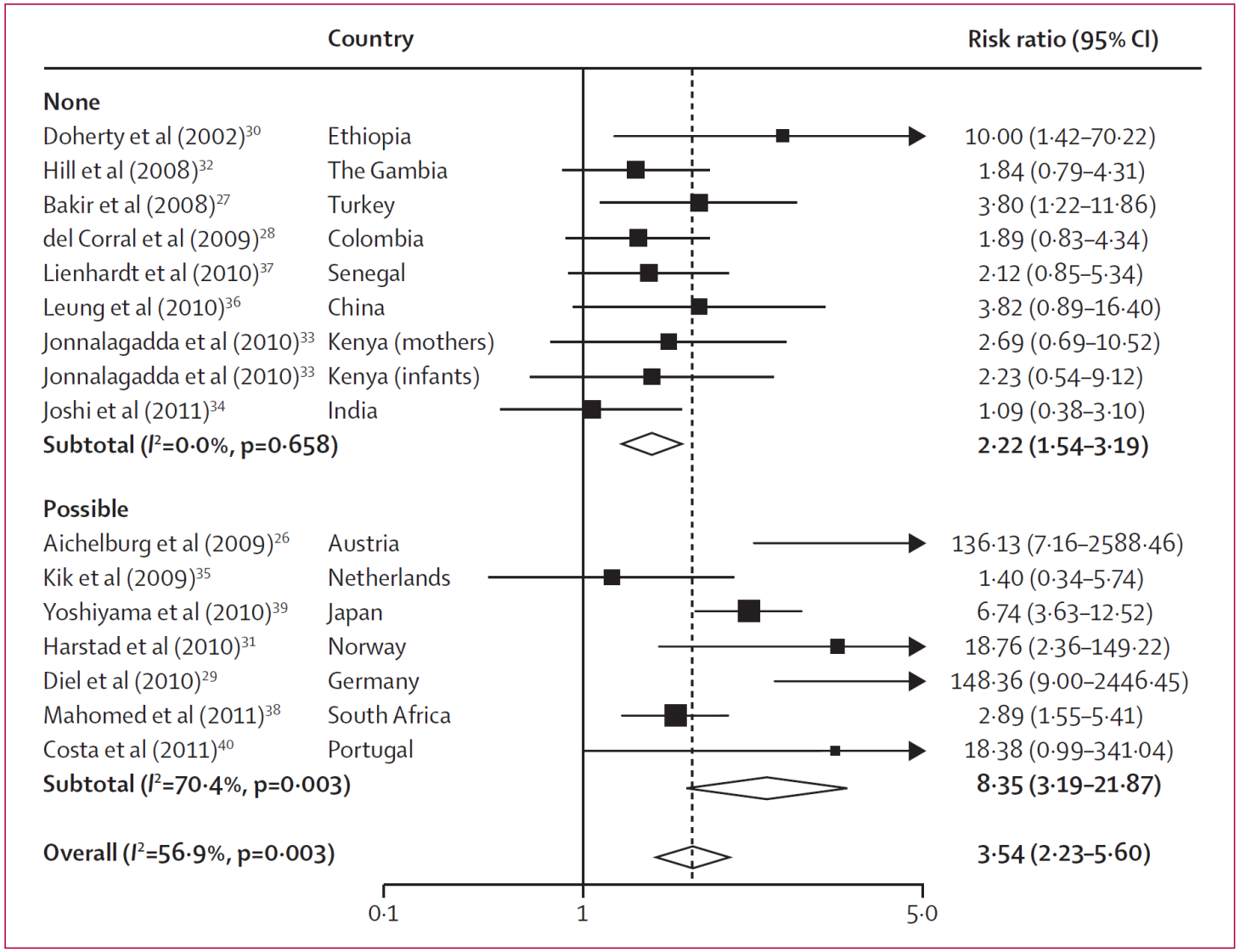


Figure 3: **Unadjusted cumulative incidence risk ratios for positive versus negative interferon-γ release assay (IGRA) results, by possibility of incorporation bias**

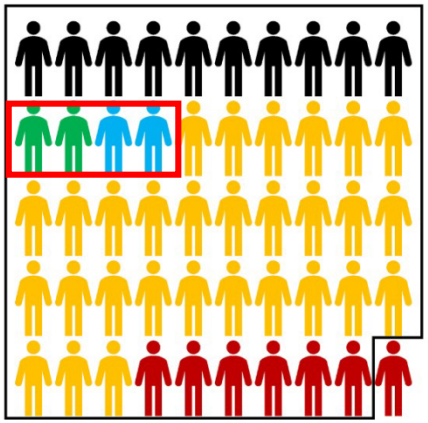
Rangaka MX et al. Lancet Infect Dis 2012

Suboptimal performance of IGRA in predicting TB risk

Distribution of TB Disease Among Risk Groups (in Canada)

1969 - 2019

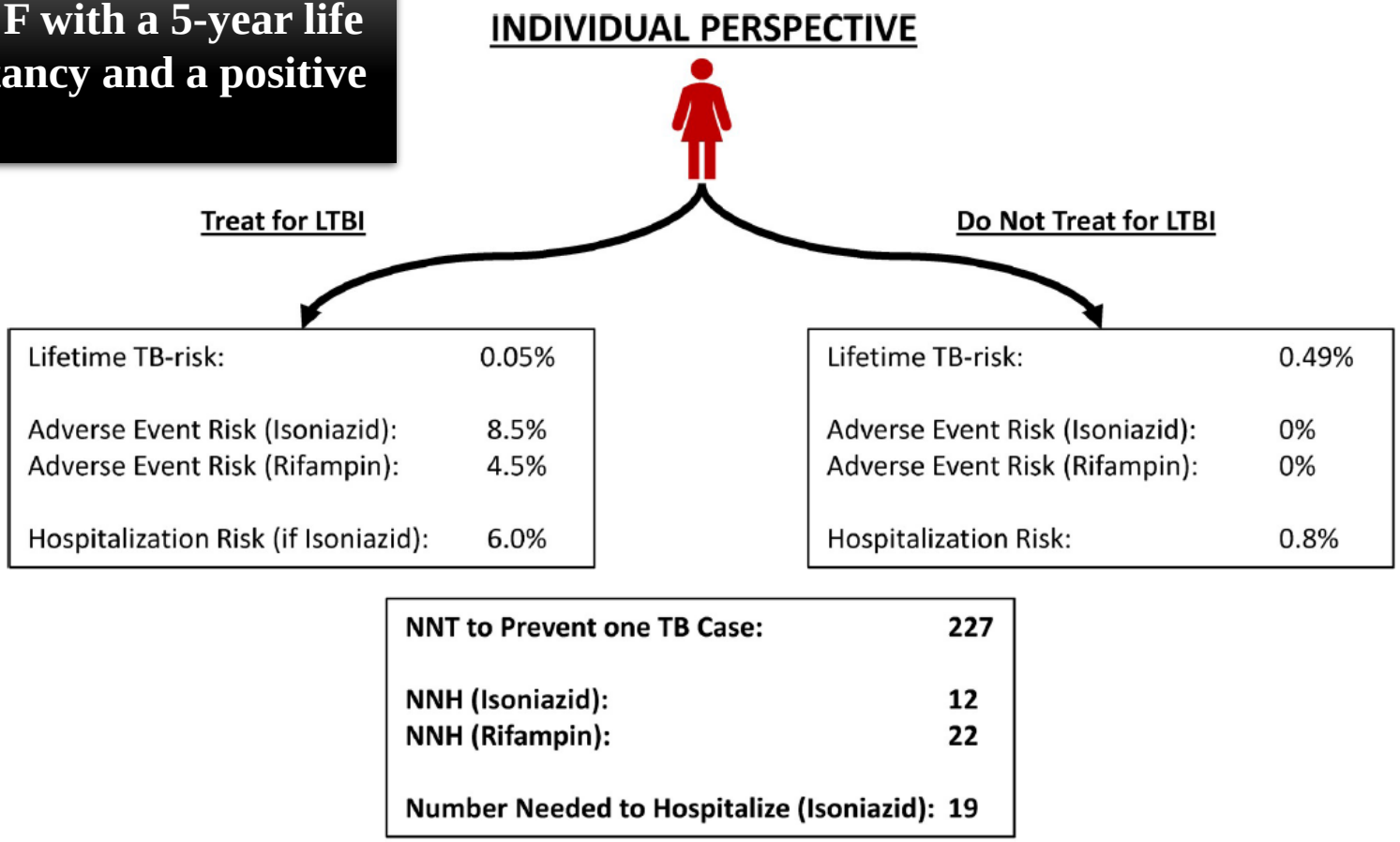
- Reflective of recent transmission due TB contact (contacts with newly acquired infection)
- Currently have a WHO recommendation for LTBI screening/treatment (e.g. HIV, dialysis, transplant)
- In some jurisdictions, carry additional recommendations for LTBI screening/treatment (e.g. steroids, biologics, cancers)
- Aged < 65 years with no WHO recommendation for LTBI screening/treatment; must be treated for LTBI to eliminate TB
- Aged ≥ 65 years with no WHO recommendation for LTBI screening/treatment; must be treated for LTBI to eliminate TB



Campbel JR et al. Plos Med 2019

Treatment for All LTBI?

75 y/o F with a 5-year life expectancy and a positive IGRA



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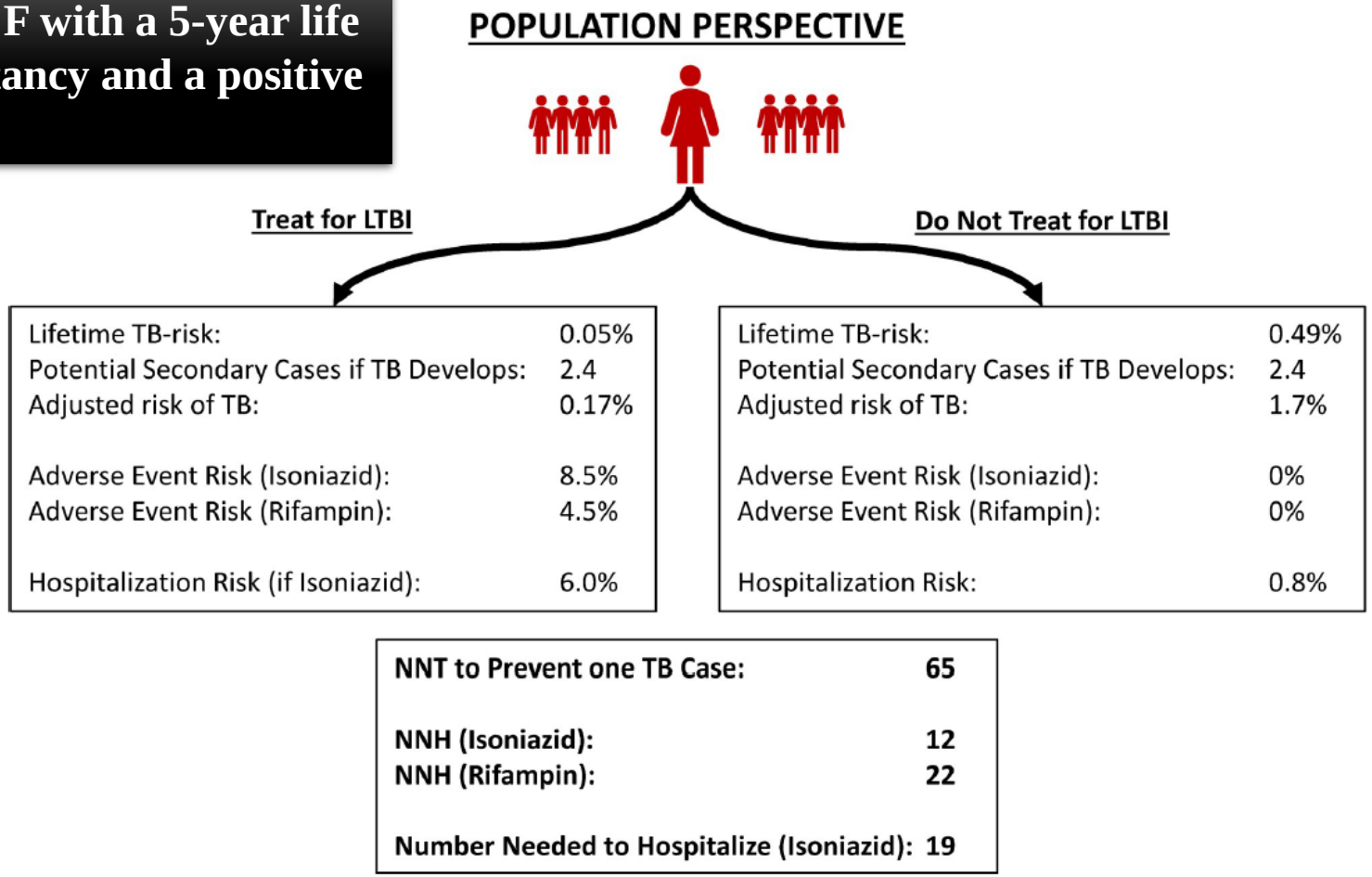
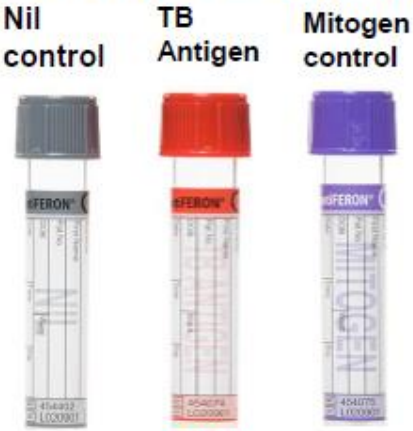


Campbell JR et al. Plos Med 2019

Newer Diagnostic and Prediction Tools For LTBI

Newer Generation of QuantiFERON

QuantiFERON® TB Gold In tube

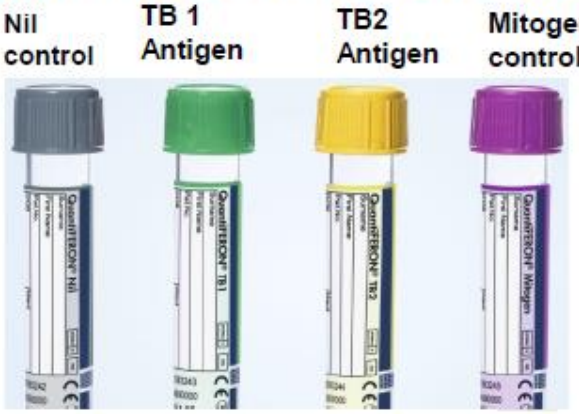


Cells stimulated: none | CD4+ T-Cells | All

Polypeptide Antigens: Long peptides (MHC class II) •ESAT-6 •CFP-10 •TB7.7

Positive: TB Antigen-Nil>0.35 IU/ml

QuantiFERON® TB Gold Plus

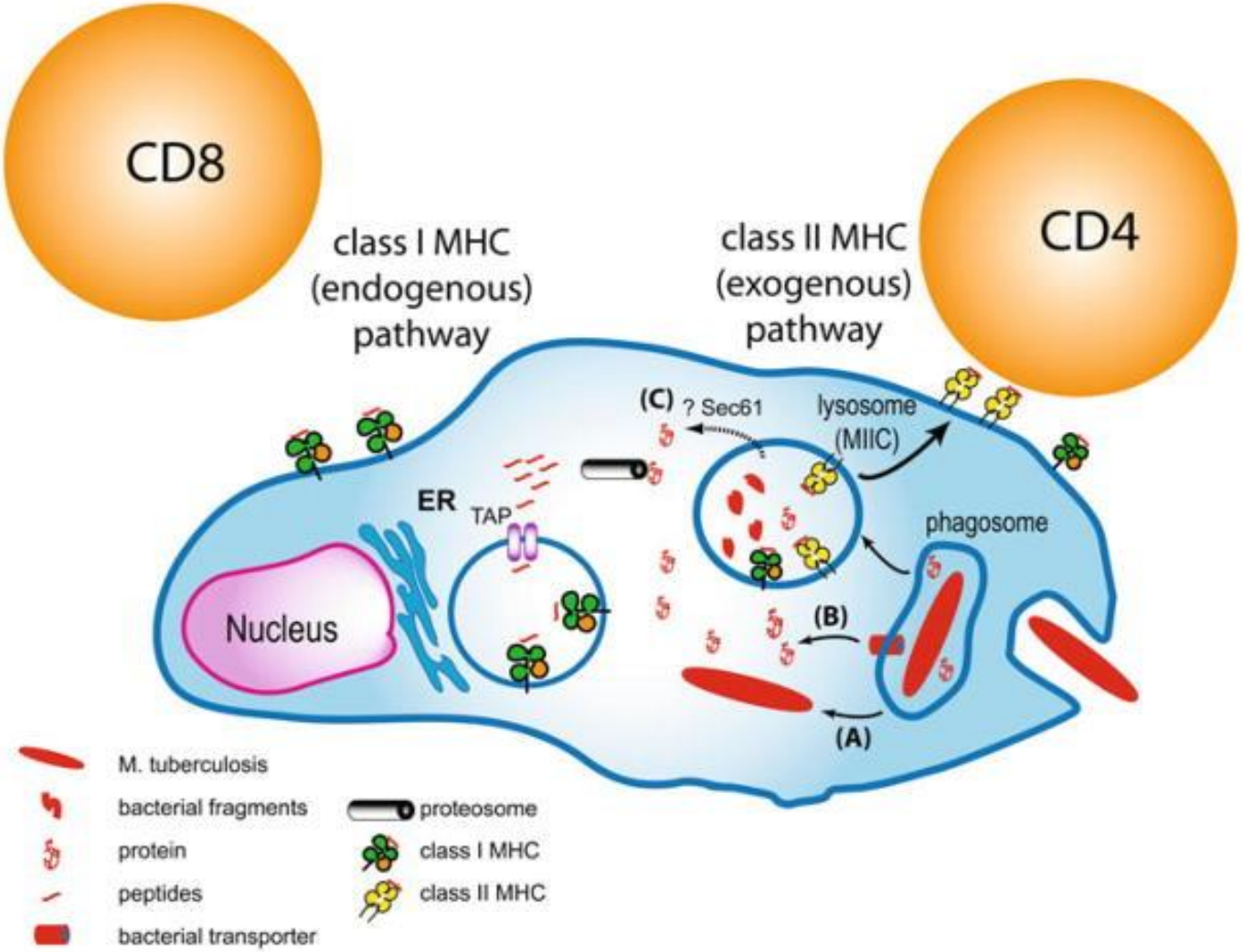


Cells stimulated: none | CD4+ T-Cells | CD4+ and CD8+ T-Cells | All

Polypeptide Antigens: Long peptides (MHC class II) •ESAT-6 •CFP-10 •TB7.7 ✗ + Additional 6 short peptides (MHC class I) •ESAT-6 •CFP-10 •TB7.7 ✗

Positive: Either tube (TB1 or TB2) Antigen-Nil>0.35 IU/ml

https://www.qiagen.com



1969 - 2019

M.tb-specific CD8 lymphocytes have been 1.detected in patients with LTBI as well as those with active TB 2.detected more often in active TB than LTBI 3.correlated with recent exposure

Rozot V et al. Eur J Immunol 2013
Day CL et al. J Immunol 2011

First evaluation of QuantiFERON-TB Gold Plus performance in contact screening

Lucia Barcellini[1], Emanuele Borroni[1], James Brown[2], Enrico Brunetti[3], Daniela Campisi[4], Paola F. Castellotti[4], Luigi R. Codecasa[4], Federica Cugnata[5], Clelia Di Serio[5], Maurizio Ferrarese[4], Delia Goletti[6], Marc Lipman[2], Paola M.V. Rancoita[5], Giulia Russo[1], Marina Tadolini[7], Elisa Vanino[7] and Daniela M. Cirillo[1]

TABLE 2 Test results

QFT-GIT results	Subjects	QFT-Plus results		Positive results per tube		QTF-Plus IFN-γ concentrations IU·mL^{-1}	
		Negative	Positive	TB1	TB2	TB1-nil	TB2-nil
Negative	63	51 (80.95)	12 (19.05)	10[#]	10[¶]	0.01 (−0.01–0.17)	0.04 (0–0.23)
Positive	56	0	56 (100)	56	56	10.60 (2.94–16.57)	11.00 (3.32–17.75)
Total	119	51 (42.86)	68 (57.14)	66	66	0.74 (0.01–9.65)	0.67 (0.04–8.94)

Data are presented as n, n (%) or median (interquartile range). [#]: two were positive to TB1 only; [¶]: two were positive to TB2 only. QFT-GIT: QuantiFERON-TB Gold in Tube; QFT-Plus: QuantiFERON-TB Plus; IFN: interferon.

Among 119 contacts, 56 were QFT-GIT (+) and 68 were QFT-Plus (+)
12 were QFT-GIT (-) but QFT-Plus (+)

Barcellini L et al. Eur Respir J 2016

TABLE 3 QuantiFERON-TB Plus (QFT-Plus) and QuantiFERON-TB Gold in Tube (QFT-GIT) discordant results

Sample	BCG scar	TST diameter of induration mm	QFT-GIT	QFT-Plus TB1[#] IU·mL^{-1}	QFT-Plus TB2[¶] IU·mL^{-1}	Index case smear status	Relationship to index case	Immunosuppression
C1	Yes	20	Negative	1.83	0.51	Positive	Household, primary caregiver	Prednisone treatment
C11	Yes	7	Negative[+]	0.49	0.83	Positive	Boyfriend	No
C15	No	21	Negative[+]	0.11	0.48	Positive	Employer (index case: housemaid)	No
C17	Yes	10	Negative	0.38	0.41	Negative	Household, sister	No
C39	Yes	20	Negative	0.83	0.88	Positive	Hospital close contact (sharing the same room)	Cancer
C53	Yes	20	Negative	0.3	0.58	Positive	Colleague, daily journey to work	No
C63	Yes	16	Negative	0.74	0.67	Negative	Household	No
C69	Yes	14	Negative	0.52	0.29	Positive	Household	No
C75	Yes	11	Negative	0.81	0.9	Positive	Household	No
C78	No	11	Negative	1.88	1.93	Positive	Colleague (sharing the same room)	No
C91	Yes	14	Negative	0.36	0.1	Negative	Household	No
C98	Yes	20	Negative	1.65	1.14	Positive	Household	Pregnant

Barcellini L et al. Eur Respir J 2016

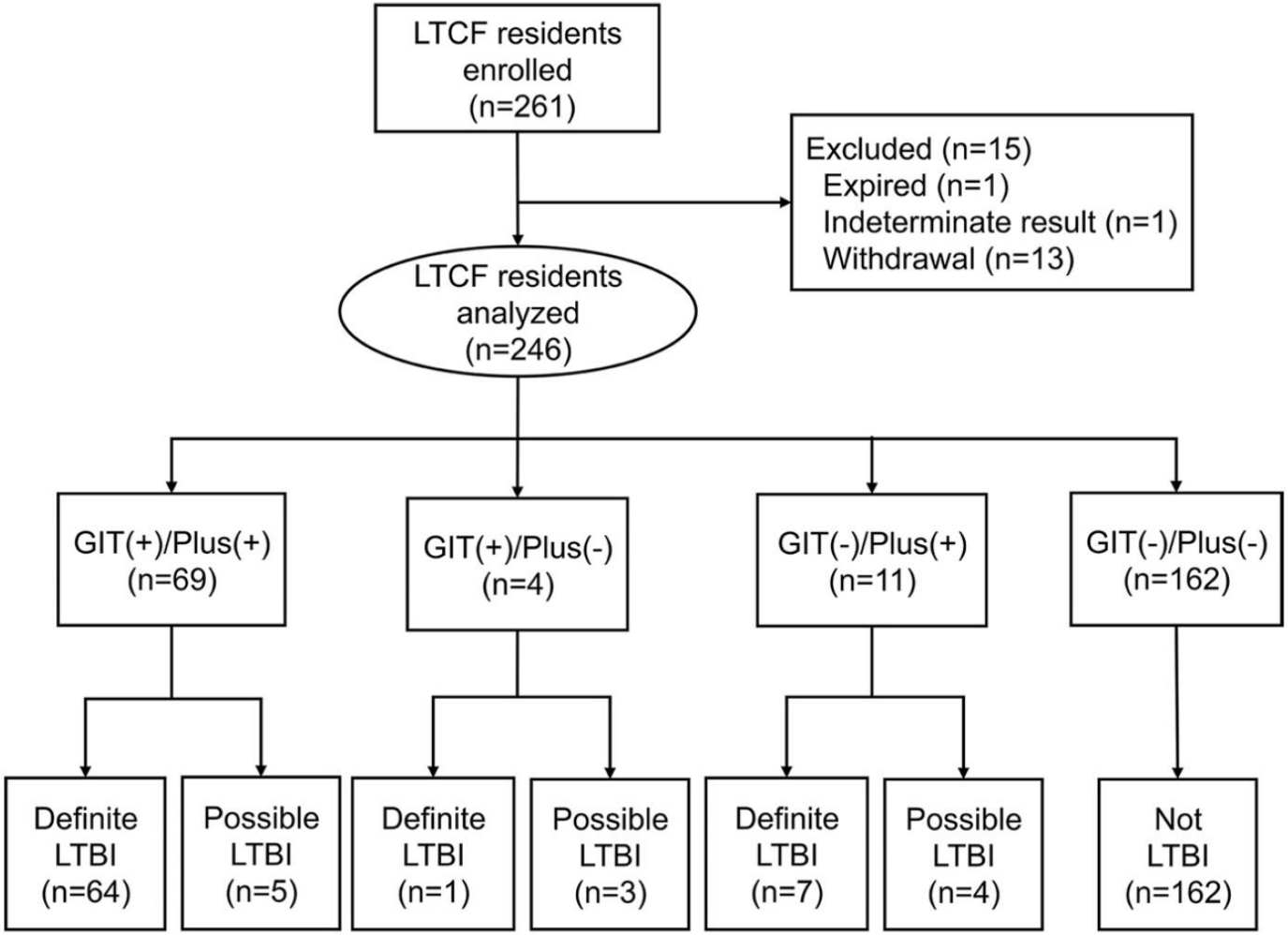


FIG 1 Flow diagram of the study participants.

99.3% agreement between QFT-GIT and QFT-Plus

Chien JY et al. J Clin Microbiol 2018

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TABLE 6 Backward stepwise multivariate logistic regression for predicting TB2–TB1 >0.6 IU·mL^{-1}

	OR (95% CI)	p-value
Country of birth		
Non-European	1	
European	3.46 (1.03–11.69)	0.0453
Sleeping proximity to the index case		
Different room	1	
Same room	5.90 (1.83–18.97)	0.0029

TB2−TB1 values >0.6 IU·mL−1 were significantly associated with proximity to the index case

Barcellini L et al. Eur Respir J 2016

Monitoring Treatment Response

TABLE 1 Interferon-γ test quantitative and qualitative results

	0 months	3 months	6 months
Quantitative data			
TB1 (surrogate $CD4^+$ T-cell response) $IU \cdot mL^{-1}$	6.40±8.92	2.56±3.28*	2.33±3.06
TB2 (CD4 and CD8 response) $IU \cdot mL^{-1}$	8.98±16.25	4.50±7.53*	3.23±4.95
TB2-TB1 (surrogate $CD8^+$ T-cell response) $IU \cdot mL^{-1}$	2.58±8.45	1.93±5.12	0.91±2.85*
Qualitative data			
TB1 positive/negative/indeterminate	35/2/1	31/7/0	26/11/1
TB2 positive/negative/indeterminate	36/1/1	32/6/0	32/5/1
TB1 or TB2 positive/negative/indeterminate	36/1/1	32/6/0	32/5/1

Quantitative data are presented as mean±SD. TB1: QFT-Plus Tube 1; TB2: QFT-Plus Tube 2. *: $p<0.05$ compared to prior value.

CD8 T cell response declines with therapy

Kamada A et al. Eur Respir J 2017

Research Questions

- Taiwan local data were not readily available

- CD8 response and TB status

Materials and Methods

- **Study Design and Duration**
  - ➢Prospective study
  - ➢National Taiwan University Hospital and National Taiwan University Hospital Hsin-Chu Branch from Jan 2017 to December 2017

Study Population

- **Inclusion**
  - Adult patients: 20 ≤ age ≤ 90
  - **TB group**: culture- or histology-confirmed (based on caseating granulomatous inflammation) active TB
  - **LTBI group**: those close contacts of TB with positive QFT-GIT
  - **Uninfected group**: those close contacts of TB with negative QFT-GIT

Demographic data

	All (n=336)	Contacts (n=223)	Uninfected (n=118)	LTBI (n=105)	P (LTBI vs. Uninfected)	TB (n=113)	P (TB vs. Contacts)
Age	43.3±19.0	37.2±17.4	31.3±14.1	43.7±18.4	<0.001	55.5±16.1	<0.001
BMI	22.8±3.54	23.3±3.54	23.2±3.49	23.3±3.61	0.766	22.0±3.39	0.002
Men	176 (56.1)	112 (54.1)	69 (58.5)	49 (46.7)	0.078	64 (59.8)	0.116
DM	29 (8.6)	4 (1.8)	1 (0.9)	3 (2.9)	0.344	25 (21.1)	<0.001
ESRD	2 (0.6)	0	0	0	NA	2 (1.8)	0.113
Cancer	18 (5.4)	0	0	0	NA	18 (15.9)	<0.001
Smoking	64 (19.0)	35 (15.7)	9 (7.6)	26 (24.8)	<0.001	29 (25.7)	0.028
Index Case							
Sm+	NA	210 (94.2)	108 (91.5)	102 (97.1)	0.074	NA	NA
Cavitation	NA	60 (26.9)	21 (17.8)	39 (37.1)	0.001	NA	NA
Exposure							
HHs, same house	NA	28 (12.6)	12 (10.2)	16 (15.2)	0.254	NA	NA
HHs, same room	NA	17 (7.6)	6 (5.1)	11 (10.5)	0.130	NA	NA
Same classroom	NA	94 (42.2)	69 (58.5)	25 (23.8)	<0.001	NA	NA
Same office	NA	37 (16.6)	13 (11.2)	24 (22.9)	0.018	NA	NA
Other	NA	47 (21.1)	18 (15.3)	29 (27.6)	0.024	NA	NA
TB1-Nil (IU/ml)	1.23±2.22	0.97±1.86	0.03±0.23	2.03±2.28	<0.001	1.74±2.73	0.008
TB2-Nil (IU/ml)	1.43±2.46	1.04±1.96	0.05±0.03	2.15±2.40	<0.001	2.21±3.09	<0.001
TB2-TB1 (IU/ml)	0.15±1.24	-0.02±1.03	0.02±0.01	-0.05±1.47	0.575	**0.47±1.53**	**0.003**
CD8>0.6	42 (12.5)	18 (8.1)	4 (3.4)	14 (13.3)	**0.012**	**24 (21.2)**	**0.001**

N=300 (89.3%) concordance rate

Lee MR et al. J Infect 2019

Culture-Diagnosed VS Histology -Diagnosed TB

	TB (n=113)	Cul+ (n=81)	His+ (n=32)	P (Cul+ vs. His+)	P (Cul+ vs. LTBI)
Age	55.5±16.1	56.2±16.3	53.6±15.6	0.438	<0.001
BMI	22.0±3.39	22.0±3.29	22.0±3.69	0.998	0.01
Men	64 (59.8)	55 (67.9)	15 (46.9)	0.038	0.004
Comorbidity					
DM	25 (21.1)	21 (25.9)	4 (12.5)	0.140	<0.001
ESRD	2 (1.8)	2(2.5)	0	1.000	0.190
Cancer	18 (15.9)	10 (12.4)	8 (25)	0.100	<0.001
Smoking	29 (25.7)	21 (25.9)	8 (25)	0.919	0.856
TB1-Nil (IU/ml)	1.74±2.73	1.77±2.50	1.67±3.30	0.868	0.461
TB2-Nil (IU/ml)	2.21±3.09	2.39±2.99	1.73±3.32	0.311	0.542
TB2-TB1 (IU/ml)	**0.47±1.53**	**0.63±1.74**	**0.07±0.67**	**0.016**	**0.004**
CD8>0.6	**24 (21.2)**	**21 (25.9)**	**3 (9.4)**	**0.073**	**0.029**

Lee MR et al. J Infect 2019

Clinical characteristics of contacts with discordant QFT-GIT and QFT-Plus

	QFT-GIT	QFT-Plus TB1	QFT-Plus TB2	TB2 – TB1	Index Cavitation	Relationship	Exposure
	QFT-GIT (-) QFT-Plus (+)						
	Neg (-0.14)	Pos (0.74)	Pos (1.51)	0.77	No	colleague	same dormitory
	Neg (0.01)	Neg (0.05)	Pos (1.04)	0.99	No	classmate	same classroom
	Neg (0.02)	Pos (0.53)	Pos (1.38)	0.85	Yes	colleague	same dormitory
	Neg (0.02)	Pos (1.30)	Neg (0.04)	-1.26	No	classmate	same classroom
N=9	Neg (0.16)	Neg (0.19)	Pos (0.42)	0.23	Yes	colleague	same office
	Neg (0.26)	Neg (0.24)	Pos (0.54)	0.30	No	husband	same room
	Neg (0.29)	Neg (0.16)	Pos (0.40)	0.24	No	classmate	same classroom
	Neg (0.29)	Pos (0.71)	Neg (0.23)	-0.48	No	daughter	same house
	Neg (0.32)	Pos (0.43)	Neg (0.27)	-0.16	Yes	colleague	same office
	QFT-GIT (+) QFT-Plus (-)						
	Pos (1.33)	Neg (0.16)	Neg (0.34)	0.18	Yes	wife	same room
	Pos (1.08)	Neg (0.19)	Neg (0.34)	0.15	No	son	same house
	Pos (0.99)	Neg (0.08)	Neg (0.16)	0.08	Yes	classmate	same classroom
	Pos (0.94)	Neg (0.00)	Neg (0.02)	0.02	No	classmate	same classroom
	Pos (0.86)	Neg (0.11)	Neg (0.09)	-0.02	Yes	sister	different house
N=12	Pos (0.80)	Neg (0.13)	Neg (0.22)	0.09	No	son	same house
	Pos (0.68)	Neg (0.09)	Neg (0.17)	0.08	No	husband	same room
	Pos (0.47)	Neg (-0.44)	Neg (-0.49)	-0.05	No	father	same house
	Pos (0.37)	Neg (0.13)	Neg (0.04)	-0.09	No	classmate	same classroom
	Pos (0.36)	Neg (0.09)	Neg (0.12)	0.03	Yes	classmate	same classroom
	Pos (0.36)	Neg (0.14)	Neg (0.24)	0.10	No	classmate	same classroom
	Pos (0.36)	Neg (0.14)	Neg (0.09)	-0.05	Yes	classmate	same classroom

Clinical characteristics of active TB with discordant QFT-GIT and QFT-Plus

QFT-GIT	QFT-Plus TB1	QFT-Plus TB2	TB2 – TB1	Sex	Age	Comorbidity	Acid-fast stain	Diagnosis
QFT-GIT (-) QFT-Plus (+)								
Neg (-0.01)	Neg (0.03)	Pos (0.49)	0.46	Male	51	DM, ESRD	Neg	Culture
Neg (0.19)	Neg (0.21)	Pos (0.73)	0.52	Female	70	Nil	1+	Culture
Neg (0.19)	Neg (0.14)	Pos (0.53)	0.39	Male	77	DM	Neg	Culture
Neg (0.22)	Pos (0.72)	Neg (1.45)	0.73	Male	64	Nil	Neg	Culture
Neg (0.23)	Pos (0.36)	Pos (0.73)	0.37	Male	81	DM	2+	Culture
Neg (0.24)	Pos (0.55)	Pos (0.86)	0.31	Female	29	Nil	4+	Culture
Neg (0.24)	Pos (0.45)	Pos (0.46)	0.01	Male	56	DM, cancer	Neg	Culture
Neg (0.24)	Pos (0.35)	Pos (1.48)	1.13	Male	62	Cancer	Neg	Culture
Neg (0.31)	Pos (1.05)	Pos (0.91)	-0.14	Female	57	DM	1+	Culture
QFT-GIT (+) QFT-Plus (-)								
Pos (0.60)	Neg (0.07)	Neg (0.06)	-0.01	Male	67	Nil	Neg	Culture
Pos (0.47)	Neg (0.14)	Neg (0.16)	0.02	Female	29	Nil	Neg	Culture
Pos (0.43)	Neg (0.15)	Neg (0.14)	-0.01	Male	60	DM	Neg	Histology
Pos (0.40)	Neg (0.13)	Neg (0.20)	0.07	Male	60	Nil	Neg	Culture
Pos (0.39)	Neg (0.11)	Neg (0.12)	0.01	Male	79	Nil	Neg	Culture
Pos (0.35)	Neg (0.08)	Neg (0.06)	-0.02	Male	81	Cancer	1+	Culture

N=9

N=6

QFT-GIT and QFT-Plus results of all contacts according to contact type

	Household, same house (n=28)	Household, same room (n=17)	Classmates, same classroom (n=94)	Colleagues, same office (n=37)	Other (n=47)
TB1 – Nil (IU/ml)	1.41 ± 2.39	0.97 ± 1.16	0.40 ± 1.25	1.46 ± 1.99	1.46 ± 2.33
TB2 – Nil (IU/ml)	1.76 ± 2.91	1.33 ± 1.46	0.37 ± 1.13	1.59 ± 2.22	1.40 ± 2.18
CD8 (IU/ml)	0.19 ± 1.08	**0.35 ± 0.52**	-0.09 ± 1.17	-0.06 ± 0.86	-0.08 ± 0.93
CD8 >0.6 IU/ml	5 (17.9)	2 (11.8)	3 (3.2)	2 (5.4)	6 (12.8)
QFT-GIT (+)	16 (57.1)	11 (64.7)	25 (26.6)	24 (64.9)	29 (61.7)
QFT-Plus (+)	14 (50.0)	10 (58.8)	23 (24.5)	25 (67.6)	30 (63.8)

The CD8 response was higher in contacts living with index case in the same room compared with others (0.35 ±0.52 IU/ml vs. −0.05 ±1.05 IU/ml, p = 0.010)

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CD8 Response after TB Treatment

	Before Tx	After 2-months Tx	P value
All (n=43)	0.63±1.80	0.42±1.32	0.371
2nd month culture conversion (n=38)	0.66±1.89	0.41±1.33	0.331
2nd month culture persistence (n=5)	0.39±0.93	0.53±1.40	0.560
Initial smear positive (n=14)	1.38±2.83	0.84±2.24	0.379
Initial smear negative (n=29)	0.27±0.87	0.22±0.38	0.817

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Discussion

- QFT-Plus CD8 response (TB2 – TB1) :
  - active TB > LTBI and uninfected contacts
  - culture-confirmed TB > histology-confirmed TB

- CD8 response: TB2 minus TB1, as a potential biomarker for TB disease status and exposure intensity

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TB2 Tube

- Only six (2.7% of all contacts) cases were QFT-GIT negative but QFT-Plus positive according to positivity of **TB2 tube** results

- The incremental gain of TB2 tube, therefore, was limited in contact evaluation

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QFT-Plus Performance

- 12 contacts were QFT-GIT positive but QFT-Plus negative

- **A potential serious drawback for clinical utility of QFT-Plus**

(The removal of original TB-7.7 from QFT-Plus)

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QFT-Plus in Active TB

- Sensitivity in our study was considerably lower
- Elderly population (median: 59) low smear positivity rate (22.1%) and high proportion of histology-confirmed TB (28.3%)
- Utilization of QFT-Plus in the setting of active TB should be cautious

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Second-Generation IGRA

	T-SPOT.*TB*		QFT-GIT		ESAT, CFP-10, and Rv3615c		CFP-10, Rv3615c, and Rv3879c	
	n/N	Estimate (95% CI)	n/N	Estimate (95% CI)	n/N	Estimate (95% CI)	n/N	Estimate (95% CI)
Sensitivity for active tuberculosis								
All	253/311	81·4% (76·6–85·3)	220/327	67·3% (62·0–72·1)	273/306	89·2% (85·2–92·2)	263/299	88·0% (83·8–91·2)
Culture-confirmed tuberculosis	185/218	84·9% (79·5–89·0)	163/231	70·6% (64·4–76·1)	203/216	94·0% (90·0–96·4)	197/211	93·4% (89·2–96·0)
Highly probable tuberculosis*	68/93	73·1% (63·3–81·1)	57/96	59·4% (49·4–68·7)	70/90	77·8% (68·2–85·1)	66/88	75·0% (65·0–82·9)
Smear-positive tuberculosis†	45/55	81·8% (69·7–89·8)	42/56	75·0% (62·3–84·5)	48/51	94·1% (84·1–98·0)	47/50	94·0% (83·8–97·9)
Smear-negative tuberculosis†‡	169/206	82·0% (76·2–86·7)	148/222	66·7% (60·2–72·5)	183/207	88·4% (83·3–92·1)	176/202	87·1% (81·8–91·1)
Pulmonary tuberculosis	79/105	75·2% (66·2–82·5)	79/115	68·7% (59·7–76·5)	88/100	88·0% (80·2–93·0)	85/97	87·6% (79·6–92·8)
Extrapulmonary tuberculosis	141/169	83·4% (77·1–88·3)	113/171	66·1% (58·7–72·8)	148/167	88·6% (82·9–92·6)	142/164	86·6% (80·5–91·0)
Specificity for active tuberculosis								
Active tuberculosis excluded	319/370	86·2% (82·3–89·4)	304/378	80·4% (76·1–84·1)	296/370	80·0% (75·6–83·8)	296/372	79·6% (75·2–83·4)
Active tuberculosis excluded, TST negative, no risk factors for LTBI	87/93	93·5% (86·6–97·0)	85/91	93·4% (86·4–96·9)	84/92	91·3% (83·8–95·5)	84/93	90·3% (82·6–94·8)

Commercially available IGRAs do not have sufficient accuracy for diagnostic evaluation of suspected tuberculosis

Second-generation tests, however, might have sufficiently high sensitivity, low negative likelihood ratio, and correspondingly high negative predictive value in low-incidence settings to facilitate prompt rule-out of tuberculosis

Latent Tuberculosis Infection Therapy

Recommended LTBI Regimens

	Drug regimen	Dose per kg body weight	Maximum dose
9H	Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7–15 mg)	300 mg
4R	Daily rifampicin alone for 3–4 months	Adults, 10 mg Children, 15 mg (range, 10–20 mg)	600 mg
3HR	Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
3HP	Weekly rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg > 50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

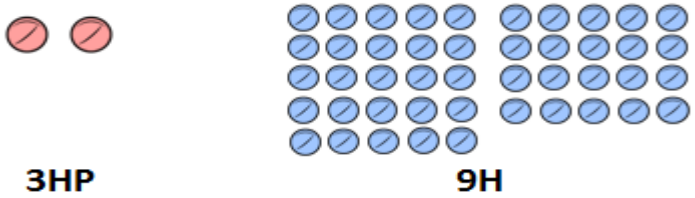
Latent tuberculosis infection Updated and consolidated guidelines for programmatic management WHO 2018

3HP (Weekly Isoniazid and Rifapentine)

- Advantage

Convenience (12 doses)

12 : 270

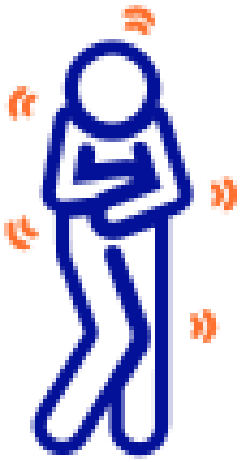


Good Evidence (≈ 9H)

- Disadvantage

Systemic drug reactions

A median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours.



The NEW ENGLAND JOURNAL of MEDICINE

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- 2019

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

PREVENT TB Study

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		

Sterling TR et al. N Engl J Med 2011

本來一切都很美好，但是...

PREVENT TB Study

Outcome	Isoniazid Only (N=3759)	Combination Therapy (N=4040)	P value
Permanent discontinuation--- no./ total no. (%)			
For any reason	1160/3745 (31.0)	713/3986 (17.9)	<0.001
Because of an adverse event	139/3745 (3.7)	**196/3986 (4.9)**	**0.009**
Death ---no./ total no. (%)	39/3745 (1.0)	31/3986 (0.8)	0.22
Attribution --- no. (%)¶			
Related to drug	206 (5.5)	**332 (8.2)**	**<0.001**
Hepatotoxicity‖	103 (2.7)	18 (0.4)	<0.001
Rash	21 (0.6)	31 (0.8)	0.26
Possible hypersensitivity**	17 (0.5)	**152 (3.8)**	**<0.001**
Other drug reaction	65 (1.7)	**131 (3.2)**	**<0.001**
Not related to drug	410 (10.9)	226 (5.6)	<0.001

Post-hoc analysis

	3HP (n = 138)	9H (n = 15)
Cutaneous[a]	23 (17%)	9 (60%)
Severe	3	1
Nonsevere	20	8
Flu-like[b]	**87 (63%)**	**2 (13%)**
Severe	6	0
Nonsevere	81	2
Gastrointenstinal[c]	7 (5%)	1 (7%)
Severe	2	0
Nonsevere	5	1
Respiratory[d]	5 (4%)	0 (0%)
Severe	1	0
Nonsevere	4	0
Not defined[e]	16 (12%)	3 (20%)
Severe	1	0
Nonsevere	15	3

Rifamycin flu-like syndrome?

Sterling TR et al. N Engl J Med 2011
Sterling TR et al. Clin Infect Dis 2015

Taiwan Data

Table 5
Adverse drug reactions (ADRs) other than hepatotoxicity.

Variables	3HP (n = 132)	9H (n = 131)
Any ADR other than hepatotoxicity,[a] n (%)	65 (49.2)	33 (25.2)
Gr. III	3 (2.3)	0 (0)
Gr. II[b]	17 (12.9)	5 (3.8)
Systemic drug reactions,[c] n (%)	5 (3.8)	0 (0)
Any flu-like symptoms,[a] n (%)	54 (40.9)	22 (16.8)
Fatigue	23 (17.4)	14 (10.7)
Dizziness	10 (7.6)	7 (5.3)
Nausea	12 (9.1)	9 (6.9)
Vomiting[d]	10 (7.6)	1 (0.8)
Fever[a]	17 (12.9)*	1 (0.8)
Chills	6 (4.5)	1 (0.8)
Hot flushes[e]	8 (6.1)	1 (0.8)
Headache[d]	10 (7.6)	1 (0.8)
Myalgia	3 (2.3)	0 (0)
Dyspnea	2 (1.5)	2 (1.5)
Cutaneous reaction, n (%)	14 (10.6)	9 (6.9)
Hypersomnia, n (%)	9 (6.8)	5 (3.8)
Abdominal pain, n (%)	4 (3.0)	3 (2.3)
Diarrhea, n (%)	2 (1.5)	3 (2.3)
Others,[f] n (%)	13 (9.8)#	4 (3.1)##
Risk of Grade 2 and 3 ADRs other than hepatotoxicity in different subgroups		
Age ≥35 vs. < 35	22.0% vs. 12.1%	2.4% vs. 4.4%
Men vs. Women	8.6% vs. 25.5%[g]	5.6% vs. 1.7%
Body-mass index < 18.5 vs. ≥18.5	14.3% vs. 15.3%	0% vs. 4.4%

SDRs, flu-like symptoms…

Sun HY et al. **Tuberculosis** (Edinb) 2018

Clinical Scenario

- 52 y/o M, close contact of smear-positive TB
- IGRA positive, CXR: negative for active TB
- Start LTBI treatment
- Systemic drug reactions (SDR) (Flu-like symptoms, myalgia, arthralgia) after 3HP
- Reluctant to continue on 3HP due to side-effects

Clinical Questions

- **Q1.** What is the causative agent of systemic drug reactions?
- **Q2.** What are the risk factors for developing SDR?
- **Q3.** What can we do to prevent or avoid SDRs?

Study Design

- Prospective, multicenter, observational study
- Close contacts with index patients (AFS (+) pulmonary TB) between September 2016 and August 2018
- National Taiwan University Hospital in northern Taiwan and Kaohsiung Medical University Hospital in southern Taiwan—and their four branch hospitals (Hsin-Chu, Siaogang, Ta-Tung, Ping-Tung)
- Single nucleotide polymorphism (SNP) cohort and pharmacokinetic (PK) cohort

Inclusion Criteria

(1) Aged ≥ 12 years

(2) In close contact with patients diagnosed with AFS (+) pulmonary TB

(3) Diagnosed with LTBI using either a tuberculin skin test (TST) or QuantiFERON-TB Gold in-tube assay (QFT; Cellestis / Qiagen, Carnegie, Australia)

3HP regimen

- Weekly RPT (900 mg for participants with body weight >50.0 kg; 750 mg for 32.1–50.0 kg; 600 mg for 25.1–32.0 kg; and 450 mg for 14.1–25.0 kg) plus

- INH (15 mg/kg, rounded up to nearest 50 mg; maximum 900 mg) for a total of 12 doses

Study Protocol

	Baseline	Week 4	Week 8
SNP cohort	SNPs of *N-acetyltransferase 2* (*NAT2*), *cytochrome P450 2E1* (*CYP2E1*), and *arylacetamide deacetylase* (*AADAC*)		
PK cohort	SNPs of drug-metabolising enzymes, including *NAT2*, *CYP2E1*, and *AADAC*	Concentrations of RPT, INH, and their metabolites (25-desacetyl-rifapentine [DeAcRPT] and acetyl-isoniazid [AcINH]) at either 23–25 hours (C24, preferred) or 5–7 hours (C6, Tmax of RPT) or both	Concentrations of RPT, INH, and their metabolites (DeAcRPT and AcINH) at either 23–25 hours (C24) or 5–7 hours (C6, Tmax of RPT) or both

SNP

4th wk C6

4th wk C24

8th wk C6

8th wk C24

Outcome

- Primary endpoint: development of SDRs during 3HP treatment, defined as AEs that met either of the following:

(1) hypotension (SBP <90 mm Hg), urticaria, angioedema, acute bronchospasm, or conjunctivitis plus

(2) >4 of the following symptoms occurring concurrently (>1 of which had to be grade 2 or higher): weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills

Outcome

- The probability of AEs to the study drugs was determined using the Naranjo algorithm. A Naranjo score of 5–8 indicates probable AEs, whereas a score of ≧9 indicates definite AEs

不良反應與藥物相關性之評估 Naranjo Algorithm	是	否	不知
(1) 以前是否有關於此種不良反應確定的研究報告？	+1	0	0
(2) 此種不良反應是否發生於服藥之後？	+2	-1	0
(3) 當停藥或服用此藥之解藥，不良反應是否減輕？	+1	0	0
(4) 停藥一段時間再重新服用此藥，同樣的不良反應是否再度發生？	+2	-1	0
(5) 有沒有其他原因（此藥物以外）可以引起同樣之不良反應？	-1	+2	0
(6) 當給予安慰劑時，此項不良反應是否會再度發生？	-1	+1	0
(7) 此藥物的血中濃度是否達到中毒劑量？	+1	0	0
(8) 對此病人而言，藥物劑量與不良反應的程度是否成正向關係？	+1	0	0
(9) 病人過去對同樣或類似藥物是否也產生同樣的不良反應？	+1	0	0
(10) 此項不良反應是否有客觀的證據證明是藥品引起的	+1	0	0
總分 _____；判斷屬於下列何者：			
_____ ≤0 分，存疑； _____ 1-4 分，可能； _____ 5-8 分，極有可能； _____ ≥9 分，確定			

Naranjo CA, Sellers EM, Sandor P et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45

Results

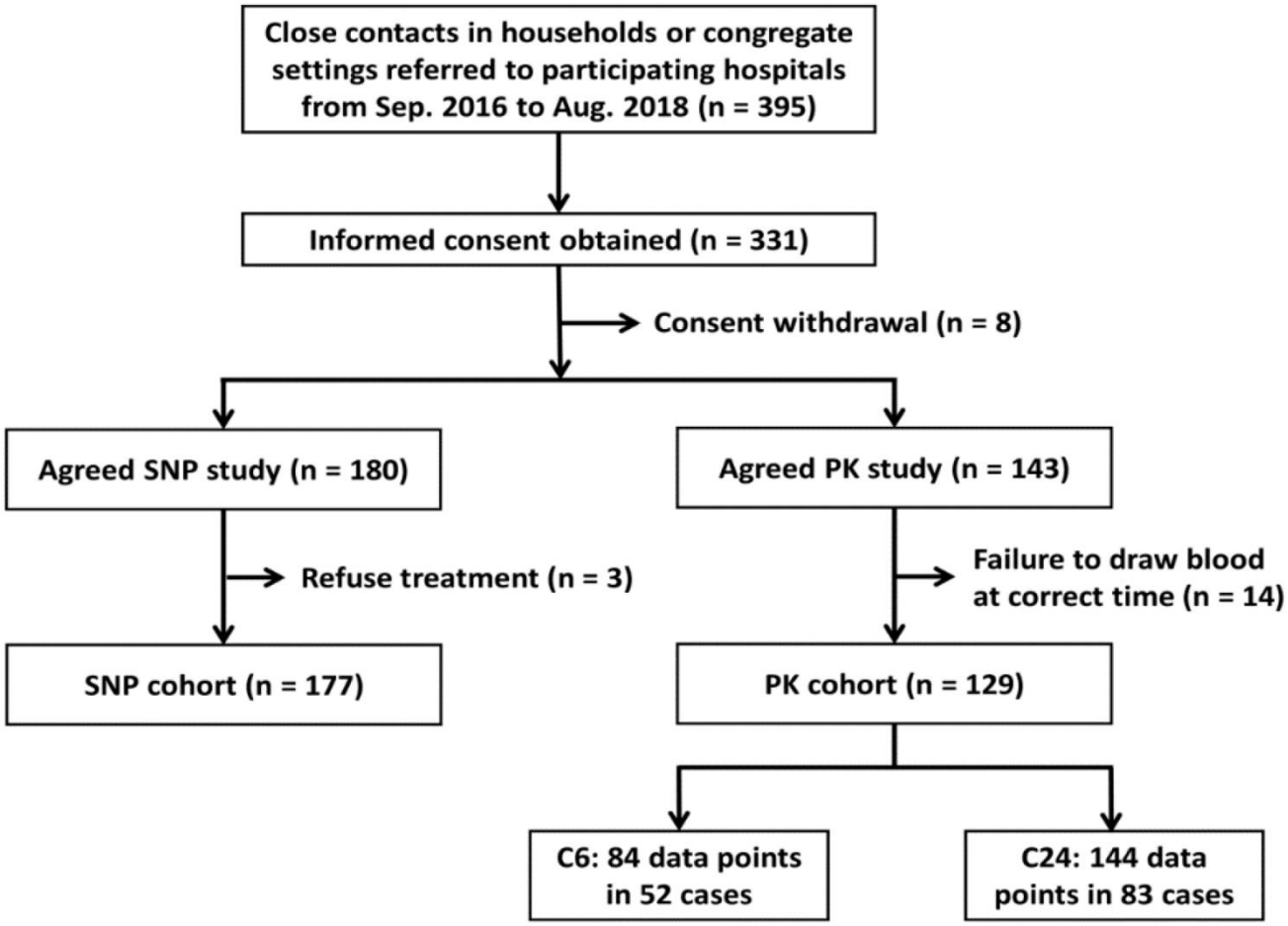

Figure 1. Case enrollment (PK: pharmacokinetic; SNP: single-nucleotide polymorphism).

Clinical Characteristics

	SNP group (N=177)	SDR (N=14)	No SDR (N=163)	*P* value	PK group (n=129)	SDR (N=13)	No SDR (N=116)	*P* value
Age (year)	37.1 ± 17.8	46.6 ± 14.5	36.3 ± 17.9	0.038	48.8 ± 17.2	51.6 ± 12.7	48.5 ± 17.6	0.533
≤35	94 (53%)	2 (14%)	92 (56%)	0.002	30 (23%)	2 (15%)	28 (24%)	0.868
35 ~ 55	44 (25%)	8 (57%)	36 (22%)		46 (36%)	5 (38%)	41 (35%)	
>55	39 (22%)	4 (29%)	35 (21%)		53 (41%)	6 (46%)	47 (41%)	
Female sex	83 (47%)	6 (43%)	77 (47%)	0.753	67 (52%)	6 (46%)	61 (53%)	0.660
Household contact	38 (21%)	2 (13%)	36 (22%)	0.737	53 (41%)	5 (38%)	48 (41%)	>0.999
Height (cm)	165.8 ± 8.3	165.1 ± 8.8	165.9 ± 8.2	0.729	164.3 ± 9.0	163.7 ± 7.5	164.4 ± 9.1	0.788
Weight (kg)	64.0 ± 11.9	65.7 ± 12.0	63.8 ± 10.9	0.568	65.5 ± 12.1	63.1 ± 9.4	65.8 ± 12.4	0.444
Body-mass index (kg/m^2)	23.2 ± 3.52	24.1 ± 3.22	23.1 ± 3.55	0.334	24.2 ± 3.36	23.45 ± 2.23	24.26 ± 3.46	0.413
Current smoker	20 (11%)	4 (29%)	16 (80%)	0.057	28 (22%)	5 (38%)	23 (20%)	0.154
eGFR (mL/min/1.73m^2)				0.005				0.670
<60	14 (8%)	0	14 (9%)		6 (5%)	1 (8%)	5 (4%)	
60 ~ 90	54 (31%)	10 (71%)	44 (27%)		47 (36%)	4 (31%)	43 (37%)	
≥90	109 (62%)	4 (29%)	105 (66%)		77 (59%)	8 (62%)	68 (59%)	
Comorbidity								
HBV infection	3 (2%)	0	3 (2%)	>0.999	7 (5%)	1 (8%)	6 (5%)	0.534

Lee MR et al. J Clin Med 2019

Table 1. Clinical characteristics and laboratory data

	SNP group (N=177)	SDR (N=14)	No SDR (N=163)	*P* value	PK group (n=129)	SDR (N=13)	No SDR (N=116)	*P* value
HCV infection	2 (1%)	0	2 (1%)	>0.999	3 (2%)	0	3 (3%)	>0.999
Diabetes mellitus	3 (2%)	0	3 (2%)	>0.999	11 (9%)	2 (15%)	9 (8%)	0.306
Malignancy	1 (1%)	1 (7%)	0	0.079	6 (5%)	2 (15%)	4 (3%)	0.112
Autoimmune	1 (1%)	0	1 (1%)	>0.999	1 (1%)	1 (8%)	0	0.100
Asthma	0	0	0		1 (1%)	0	1 (1%)	>0.999
Hypertension	5 (3%)	2 (14%)	3 (2%)	0.051	25 (19%)	5 (38%)	20 (17%)	0.130
Anti-hypertensive medication	5 (3%)	2 (14%)	3 (2%)	0.051	19 (15%)	4 (31%)	15 (13%)	0.101
Isoniazid dose (mg/kg)	14.2 ± 2.1	13.8 ± 2.0	14.3 ± 2.1	0.483	14.0 ± 2.2	14.3 ± 1.9	13.9 ± 2.2	0.512
Rifapentine dose (mg/kg)	14.2 ± 2.1	13.8 ± 2.0	14.3 ± 2.1	0.454	14.0 ± 2.2	14.3 ± 1.9	13.9 ± 2.2	0.512
Hemoglobin (g/dL)	14.0 ± 1.6	14.2 ± 1.5	14.0 ± 1.6	0.643	14.0 ± 1.5	13.8 ± 1.6	14.1 ± 1.5	0.560
Leukocyte (K/uL)	6.44 ± 1.77	6.78 ± 1.42	6.41 ± 1.80	0.448	6.81 ± 1.85	6.98 ± 1.44	6.78 ± 1.90	0.732
Platelet (K/uL)	258 ± 56	253 ± 57	259 ± 56	0.705	270 ± 58	280 ± 45	269 ± 59	0.511
ALT (U/L)	23.0 ± 28.0	27.6 ± 30.8	22.6 ± 27.9	0.526	23.7 ± 18.9	27.2 ± 11.1	23.3 ± 19.6	0.290
Total bilirubin (mg/dL)	0.65 ± 0.28	0.63 ± 0.38	0.66 ± 0.27	0.823	0.63 ± 0.22	0.70 ± 0.25	0.62 ± 0.22	0.215
Creatinine (mg/dL)	0.82 ± 0.20	0.83 ± 0.16	0.82 ± 0.20	0.754	0.84 ± 0.29	0.83 ± 0.18	0.84 ± 0.30	0.876
Treatment completion	159 (90%)	4 (29%)	155 (95%)	<0.0001	107 (83%)	4 (31%)	103 (89%)	<0.0001

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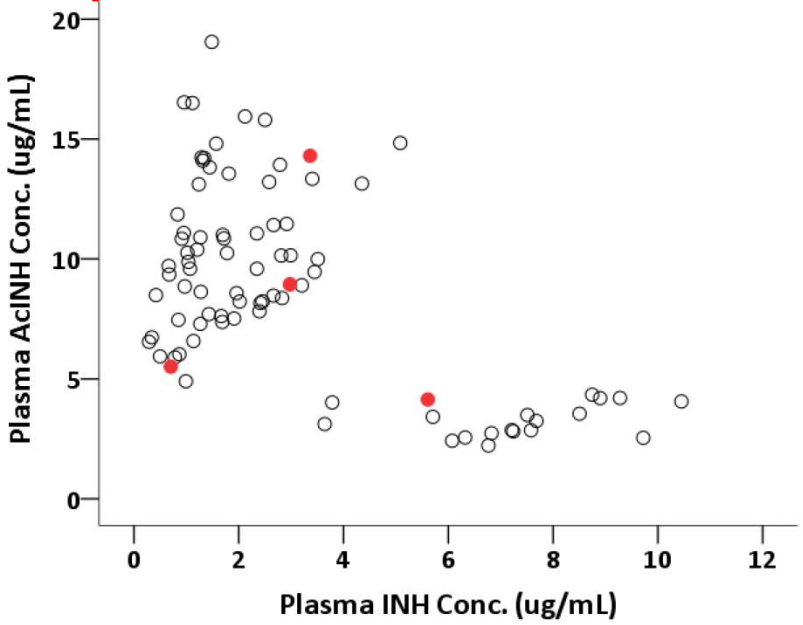
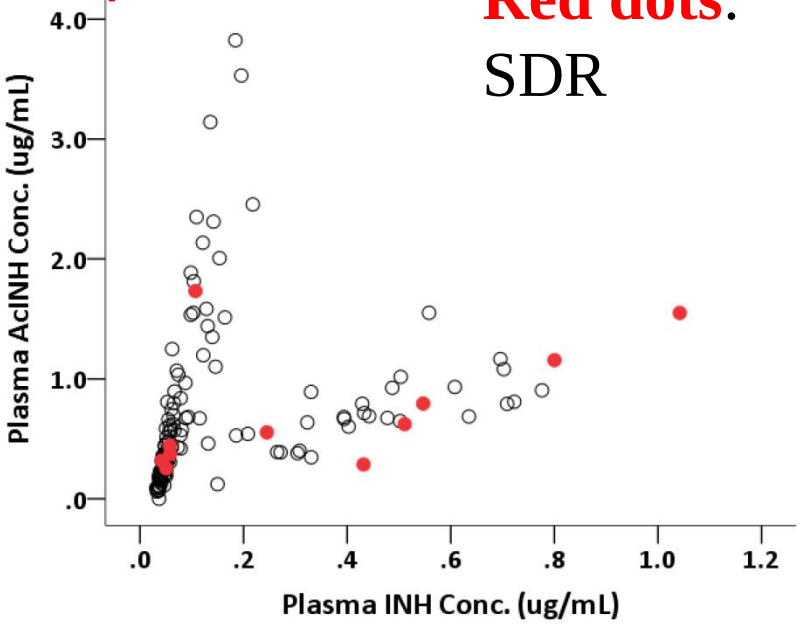
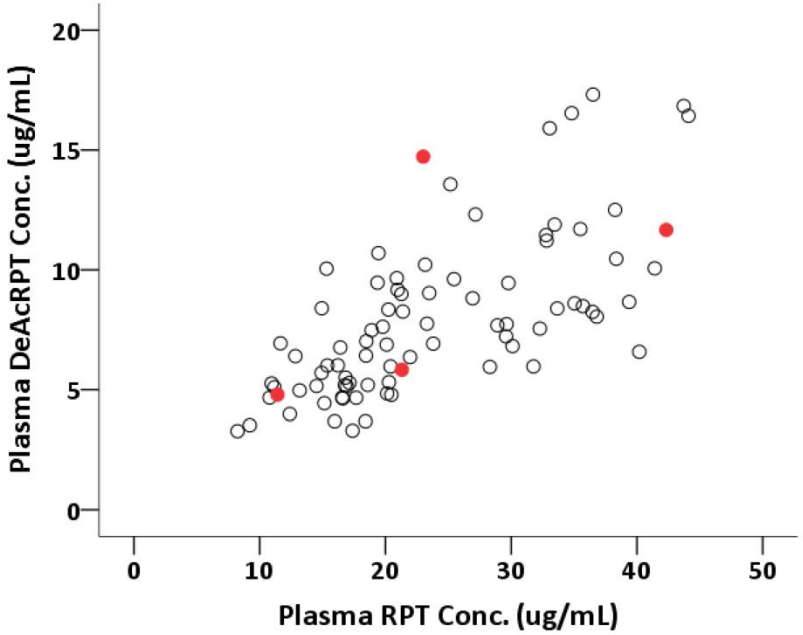
C6 V

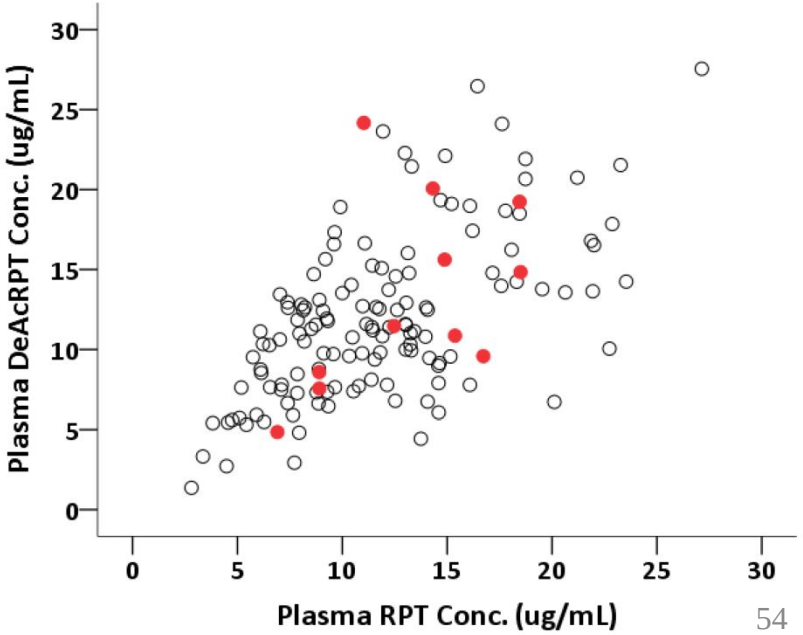


C24 V



Red dots: SDR





Lee MR et al. J Clin Med 2019

Participants experiencing systemic drug reaction during 3HP therapy in the PK cohort

Age/Sex	BW (kg)/BH (cm)	Adverse Reactions	Severity (Grade)	Comorbidity & Medication	Risk Allele in *NAT2/CYP2E1* *	INH/RPT Conc. # [Sampling Week]	Onset (Week)	Time of Onset/Duration (h)	Outcome of 3HP
66.3/F	50.0/149	fever, chills, malaise, myalgia, headache	2	Lung adenocarcinoma under gefitinib	1/2	**C24: 0.11/18.5** [3]	3	7/29	Stop
64.4/M	62.5/170	fever, myalgia, chills, weakness, sweating	2	HTN under amlodipine & olmesartan	2/1	**C6: 5.61/21.3** [4]	3	6/18	Stop
59.8/F	59.5/154	fever, chills, dyspnea, angioedema, malaise	3	Breast cancer, cured	2/2	**C24: 0.51/16.7** [3]	3	4/>100	Stop
56.7/M	73.0/175	shock (BP 90/60 mmHg), fever, flush, myalgia, dyspnea, rash	3	HTN under lercanidipine	2/2	**C24: 1.04/8.9** [3]	3	5/47	Stop
53.4/F	63.0/160	fever, chills, dizziness, myalgia, dizziness	2	Nil	1/1	**C6: 2.98/11.4** [4]	3	9/15	Stop
51.4/M	74.0/167	shock (BP 85/67 mmHg), dizziness, vomiting	2	DM, HTN	2/1	**C24: 0.80/8.9** [3]	3	3/47	Stop
50.5/M	72.0/168	shock (BP 88/63 mmHg), fever, nausea, vomiting, dizziness, sweating	2	HTN under bisoprolol & olmesartan	2/0	**C24: 0.25/6.9** [7]	7	1/8	Stop
33.9/F	47.0/158	shock (BP 82/57 mmHg), fever, headache, nausea, vomiting, malaise	3	Nil	2/0	**C24: 0.43/15.4** [3]	3	1/88	Stop
20.6/F	53.0/162	shock, fever, chills, headache, myalgia, nausea	3	Nil	1/1	**C6: 3.36/42.3** [4] **C24: 0.06/18.4** [4]	3	2/30	Stop
60.9/M	62.0/161	fever, myalgia, nausea, vomiting dizziness	2	DM, HTN amlodipine & valsartan	0/1	**C24: 0.06/11.0** [3]	3	6/28	Complete
55.9/F	60.0/163	fever, chills, myalgia, malaise, headache	3	AS under celecoxib	0/0	C24: 0.04/14.3 [4]	3	5/76	Complete
53.7/M	76.5/174	fever, chills, dizziness, malaise, nausea	2	HBV carrier not Tx	2/1	**C24: 0.55/14.9** [6]	6	3/16	Complete
43.8/M	67.5/167	fever, myalgia, dizziness, tachypnea, malaise	2	Nil	1/0	C6: 0.70/23.0 [4]	4	1/27	Complete

Generalized Estimating Equation Model in the PK Cohort

Outcome: SDR

C24 data	OR	95% CI	P value
Plasma INH	**1.61**	**1.15-2.25**	**0.006**
Plasma RPT	1.01	1.00-1.02	0.218

C6 data	OR	95% CI	P value
Plasma INH	1.00	0.98-1.02	0.990
Plasma RPT	1.00	0.99-1.01	0.996

Plasma INH level, but not RPT level, was associated with a higher risk of SDR development at C24

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Association of NAT2/CYP2E1 SNPs with systemic drug reactions in SNP cohort

		Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)*	*P* value
Genotype model					
NAT2 rs1041983	CC	Ref		Ref	
	CT	0.85 (0.14-5.29)	0.101	0.87 (0.14-5.46)	0.132
	TT	7.67 (1.51-39.0)	**0.0006**	6.78 (1.31-35.1)	**0.002**
CYP2E1 rs2070673	TT	Ref		Ref	
	TA	0.84 (0.20-3.52)	0.815	0.89 (0.21-3.77)	0.869
	AA	3.21 (0.79-15.0)	0.103	3.28 (0.78-13.8)	0.105
Dominant model					
NAT2 rs1041983	CC	Ref		Ref	
	CT+TT	2.41 (0.51-11.3)	0.265	2.36 (0.50-11.2)	0.280
CYP2E1 rs2070673	TT	Ref		Ref	
	TA+AA	1.43 (0.42-4.84)	0.568	1.49 (0.43-5.16)	0.534
Recessive model					
NAT2 rs1041983	CC+CT	Ref		Ref	
	TT	8.47 (2.55-28.1)	**0.0005**	7.38 (2.17-25.1)	**0.001**
CYP2E1 rs2070673	TT+TA	Ref		Ref	
	AA	3.51 (1.05-11.7)	**0.041**	3.49 (1.02-12.0)	**0.047**

Lee MR et al. J Clin Med 2019

Validation of NAT2/CYP2E1 SNPs with systemic drug reactions in PK cohort

		Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)*	*P* value
Genotype model					
NAT2 rs1041983	CC	Ref		Ref	
	CT	1.09 (0.19-6.28)	0.925	1.11 (0.19-6.51)	0.338
	TT	4.52 (0.86-23.8)	**0.075**	4.44 (0.81-24.4)	**0.024**
CYP2E1 rs2070673	TT	Ref		Ref	
	TA	1.84 (0.49-6.94)	0.807	2.02 (0.52-7.78)	0.772
	AA	2.53 (0.51-12.5)	0.383	2.85 (0.55-14.9)	0.346
Dominant model					
NAT2 rs1041983	CC	Ref		Ref	
	CT+TT	2.13 (0.45-10.2)	0.343	2.05 (0.42-10.0)	0.375
CYP2E1 rs2070673	TT	Ref		Ref	
	TA+AA	2.03 (0.59-6.96)	0.262	2.23 (0.63-7.86)	0.213
Recessive model					
NAT2 rs1041983	CC+CT	Ref		Ref	
	TT	4.23 (1.30-13.8)	**0.017**	4.14 (1.24-13.8)	**0.021**
CYP2E1 rs2070673	TT+TA	Ref		Ref	
	AA	1.84 (0.46-7.41)	0.392	1.98 (0.47-8.35)	0.355

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First Drug re-challenge			Second Drug re-challenge		
First drug	Number re-challenged	Tolerated	Second drug	Number re-challenged	Tolerated
INH	20	Yes (n=3)[a] (15%)	---	0	--
		No (n=17)[b] (85%)	RPT[c]	5	Yes (n=3) (60%)
					No (n=2) (40%)
RPT[d]	51	Yes (n=36) (71%)	INH[e]	12	Yes (n=2) (17%)
					No (n=10) (83%)
		No (n=15) (29%)	INH[f]	7	Yes (n=3) (43%)
					No (n=4) (57%)
INH + RPT[g]	2	Yes (n=0)			
		No (n=2) (100%)			
Total	**73**	**Yes (n=39) (53%)**		**24**	**Yes (n=8) (33%)**

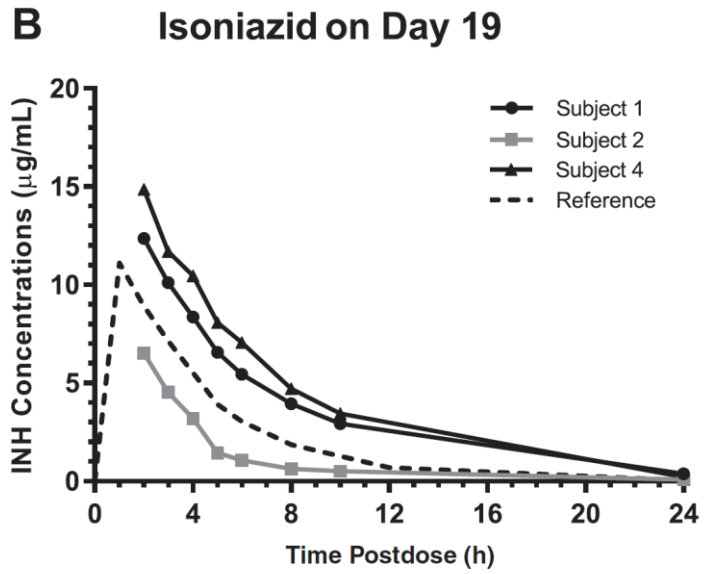
In Prevent Study, RPT is better tolerated than INH

Sterling TR et al. N Engl J Med 2011

Drug-drug interaction with dolutegravir and 3HP

Table 1. Demographic Information and N-Acetyltransferase 2 Status of Enrolled Subjects

Subject	Age, y	Sex	Weight, kg	BMI, kg/m^2	Race/Ethnicity	NAT2 Genotype	Predicted NAT2 Phenotype
1	21	Male	74.3	26.3	White	*5B/*6A	Slow √
2 No SDR	42	Male	93.9	29.6	Black	*13A/*6B or *4/*6A	Intermediate
3[a] withdraw	42	Male	74.4	23.9	White	*5B/*6A	Slow
4	44	Female	80.1	28.2	White/Hispanic	*6A/*6A	Slow √



Four subjects

Subject 1 and 4 developed SDR

Isoniazid AUC 67% and 92% higher than reference data in subject 1 and 4

Brooks KM et al. Clin Infect Dis 2018

Flu-like syndrome- Rifamycin and Isoniazid

Total cases	TB status	Incident cases (%)	RMP Dosage	Concomitant drugs	Onset after starting Tx
49 [3]	Active TB	8 (16%)	1200 mg BIW	INH, pyridoxine	2.5-4 hr
115 [4]	Active TB	9 (8%)	900 mg BIW	INH	NA
119 [4]	Active TB	5 (4%)	600 mg BIW	INH	NA
115 [4]	Active TB	25 (22%)	900 mg QW	INH	NA
117 [4]	Active TB	12 (10%)	600 mg QW	INH	NA
116 [5]	Active TB	32 (55%)	900-1200 mg QW (22.1-24.4 mg/kg)	EMB, PZA	NA
94 [5]	Active TB	23 (24%)	900 mg QW (21.5 mg/kg)	INH	NA
96 [5]	Active TB	11 (11%)	600 mg QW (13.7 mg/kg)	INH	NA
68 [6]	Active TB	15 (22%)	900-1200 mg BIW	EMB	1~6M: 13%; 6~12M: 7%; 13~18M: 1%
72 [6]	Active TB	36 (50%)	900-1200 mg QW	EMB	1~6M: 26%; 6~12M: 24%
77 [6]	Active TB	31 (40%)	450 mg/day, then 900-1200 mg QW	EMB	1~6M: 12%; 6~12M: 18%; 13~18M: 10%
288 [7]	Active TB	2 (0.7%)	600 mg BIW	INH	NA
530 [8]	Active TB	2 (0.3%)	600 mg/day	INH, EMB	Mean: 30 days
8 [9]	RA	1 (12.5%)	600 mg/day 8wks, then 900 mg/day 8wks, then 1200 mg/day	NA	4th weeks
2868 [10]	Active TB	12 (0.4%)	600 mg/day	INH, EMB, PZA	Mean: 36 days
667 [11]	Leprosy	54 (8.1%)	600 mg/day	DDS, CFZ	NA
3893 [12]	LTBI	87 (2.2%)	600-900 mg QW	INH	Usually at 3rd dose
207 [13]	LTBI	2 (1%)	600-900 mg QW	INH	Usually at 3rd dose

Total cases	TB status	Incident cases (%)	Mean age (yr)	Sex	HIV	INH Dosage	Concomitant drugs	Mean onset after starting Tx (days)	Duration of symptoms
112 [22]	Active TB	11 (9.8)	NA	NA	NA	300 mg/day (15 mg/kg/day)	RMP	NA	NA
814 [23]	Active TB	8 (1.0)	66	M: 5 F: 3	negative	300 mg/day	RMP	21 days	12 hrs

INH reports: proven with re-challenge

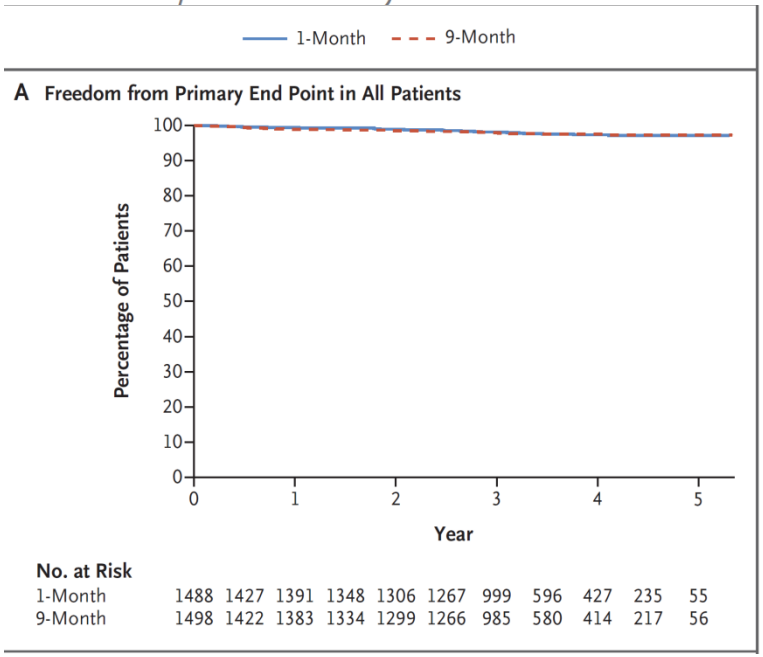
Rifamycins frequently co-administered with INH

BRIEF TB Study

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

4 weeks of rifapentine (at a dose of 300 mg daily for a weight of <35 kg, 450 mg daily for a weight of 35 to 45 kg, and 600 mg for a weight of >45 kg) plus isoniazid at a dose of 300 mg daily (1-month group)



Swindells S et al. N Engl J Med 2019

Table 3. Adverse Events of Grade 3 or Greater.*

Adverse Event	1-Month Group (N=1488)				9-Month Group (N=1498)			
	Grade 3	Grade 4	Grade 5	Grades 3–5	Grade 3	Grade 4	Grade 5	Grades 3–5
	number of patients (percent)							
Targeted adverse event†	34	9	1	44 (3)	32	20	0	52 (3)
Serious adverse event	41	22	12	75 (5)	49	25	19	93 (6)
Any systemic event	101	9	1	111 (7)	123	12	0	135 (9)
Any adverse event	198	47	5	250 (17)	213	59	2	274 (18)
Hematologic event	41	22	0	63 (4)	36	21	0	57 (4)
Thrombocytopenia	0	3	0	3 (<1)	4	1	0	5 (<1)
Anemia	6	14	0	20 (1)	8	18	0	26 (2)
Neutropenia	28	8	0	36 (2)	16	2	0	18 (1)
Hepatic event	19	9	0	28 (2)	24	18	0	42 (3)
Gastrointestinal event	29	1	1	31 (2)	22	2	0	24 (2)
Dermatologic event	8	0	0	8 (1)	11	0	0	11 (1)
Neurologic event	12	2	0	14 (1)	25	4	1	30 (2)

Supplemental Table S3.1 New Signs/Symptoms and Laboratory Events of Grade 3 or Higher from "Random. date, step 1 (STEP Table)" through November 17, 2017.

	Treatment Group											
	INH (N=1498)				RPT (N=1488)				All (N=2986)			
	Grade			Number	Grade			Number	Grade			Number
Sign/Symptom/Lab Event	3	4	5	subjects	3	4	5	subjects	3	4	5	subjects
Any General Body	123	12	0	135	101	9	1	111	224	21	1	246
Abn Phys Appearance/Characteristic, Specify	0	0	0	0	1	0	0	1	1	0	0	1
Ache	0	0	0	0	3	0	0	3	3	0	0	3
Asthenia	0	0	0	0	1	0	0	1	1	0	0	1
Chills	0	0	0	0	1	0	0	1	1	0	0	1
Fatigue	1	1	0	2	9	0	0	9	10	1	0	11
Fever	13	1	0	14	7	0	0	7	20	1	0	21
Malaise	0	0	0	0	2	0	0	2	2	0	0	2
Night Sweats	1	0	0	1	0	0	0	0	1	0	0	1
Pain	39	1	0	40	34	2	0	36	73	3	0	76
Sweats	0	0	0	0	1	0	0	1	1	0	0	1
Tenderness	2	0	0	2	2	0	0	2	4	0	0	4
Wasting	1	0	0	1	0	0	0	0	1	0	0	1
Weight Loss	85	9	0	94	55	7	1	63	140	16	1	157

1 HP therapy-> much less SDRs

Swindells S et al. N Engl J Med 2019

Take Home Message

- CD8 response by QFT-Plus: a potential direction for differentiating TB disease status
- CD8 response appeared to escalate as disease status progressed
- Isoniazid may played a more important role than generallly perceived in 3HP-related SDRs
- NAT2 genotype may be used for risk stratification of 3HP-related SDRs

1969 - 2019

Thanks for Your Attention!