潛伏結核全都治
Latent TB Infection
Treat for All
速克伏 3HP短程治療處方介紹

疾病管制署
慢性傳染病組

Outlines

- Experiences of Adverse Effects with 9H in Taiwan
- Introduction of a Shorter Regimen for LTBI Treatment
- Monitor and Surveillance of Adverse Events
- Choosing a Regimen for Treatment of LTBI

這要從2008年跟我們一起一路走來的LTBI合作醫師說起

EXPERIENCES OF ADVERSE EFFECTS WITH 9H IN TAIWAN

CI & LTBI Treatment

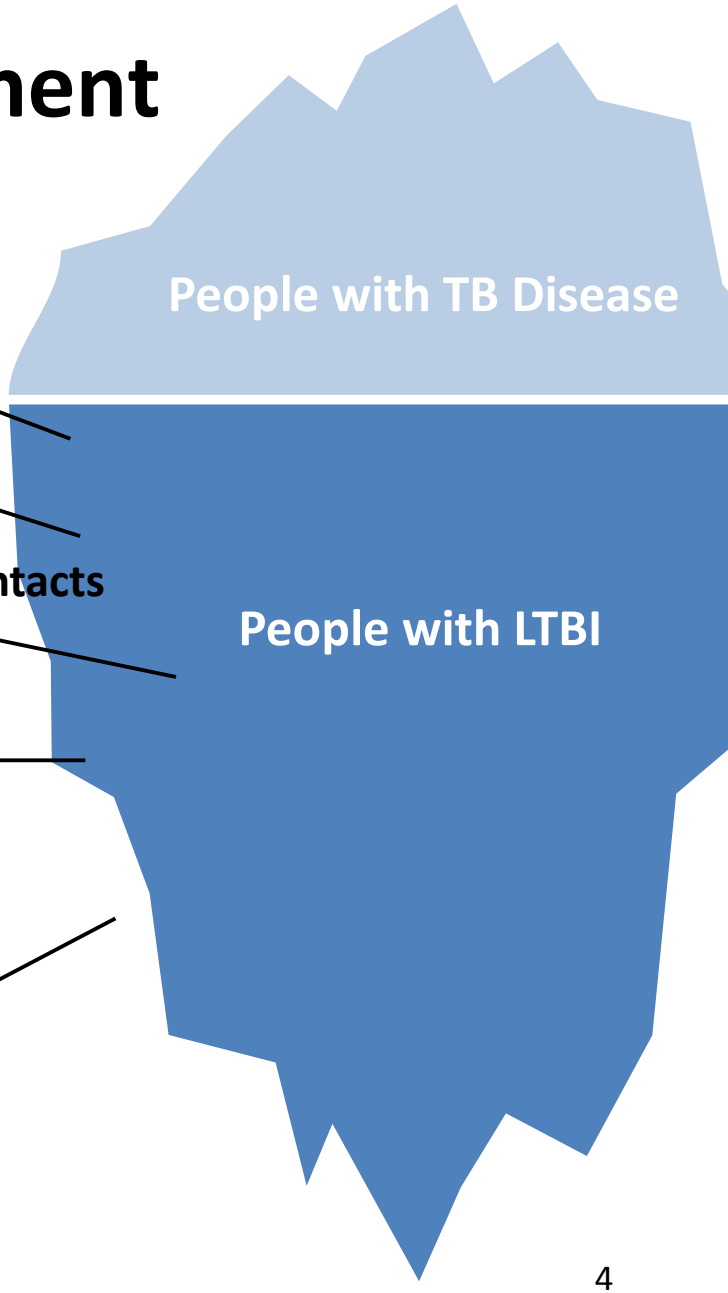
2007 **Increase contact exam. willingness:** Copayment subsidy by the TCDC

2008 **LTBI treatment for contacts <13 y/o**

2010 -2012 **Provide IGRA and LTBI treatment for contacts of all age groups (in 11 townships only)**

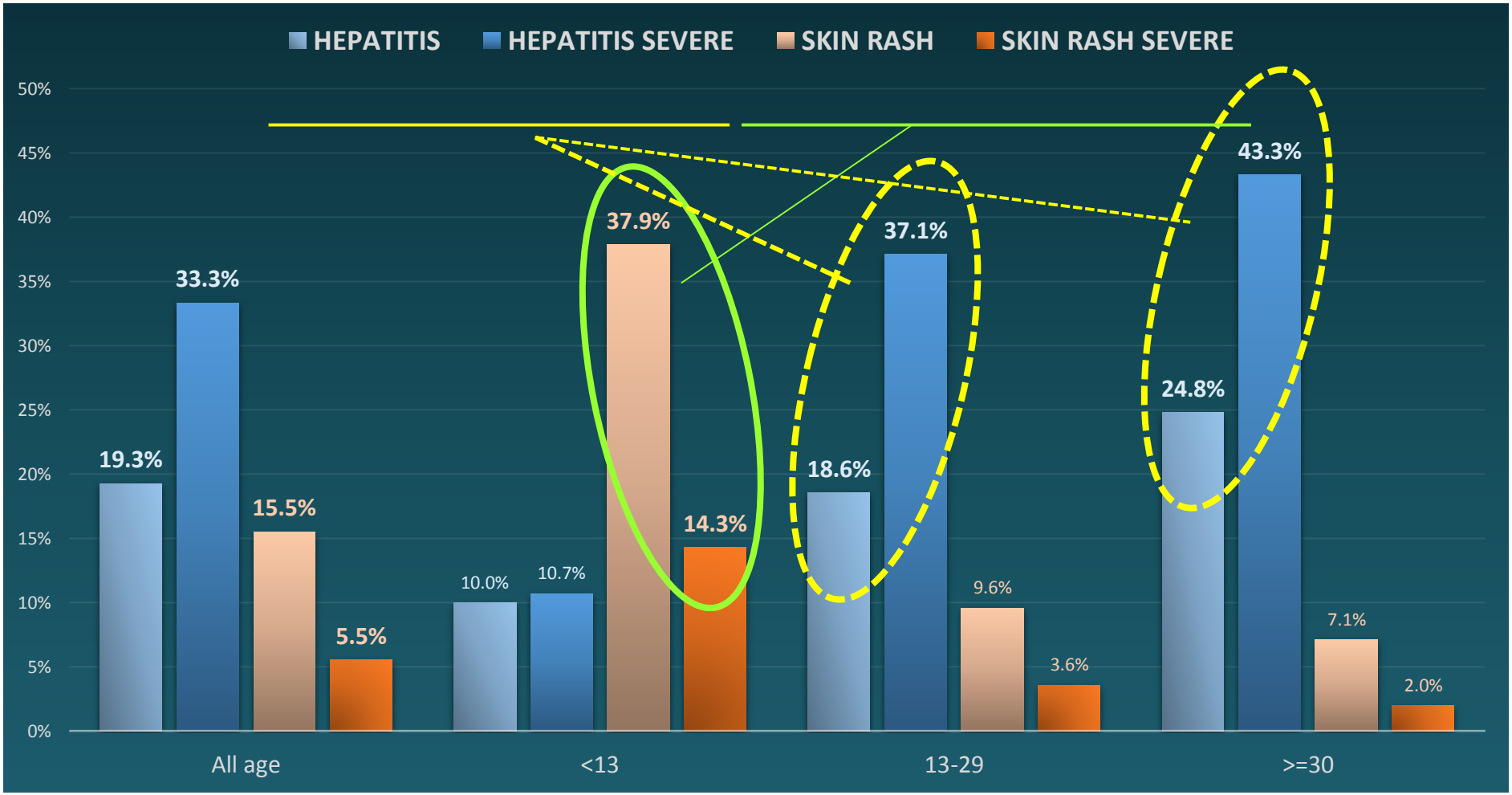
2012 **Expansion of LTBI treatment target :** ≧13 y/o to birth cohort younger than 1986 in household, school & congregate settings

2015 **Provide IGRA and LTBI treatment for contacts of all age groups (in 6 counties/ cities only)**



潛伏結核感染治療期間因不良反應而永久停藥比率

依年齡分層, 9H



肝炎及嚴重肝炎 (ATS) 在13歲以上分別為56%, 68%

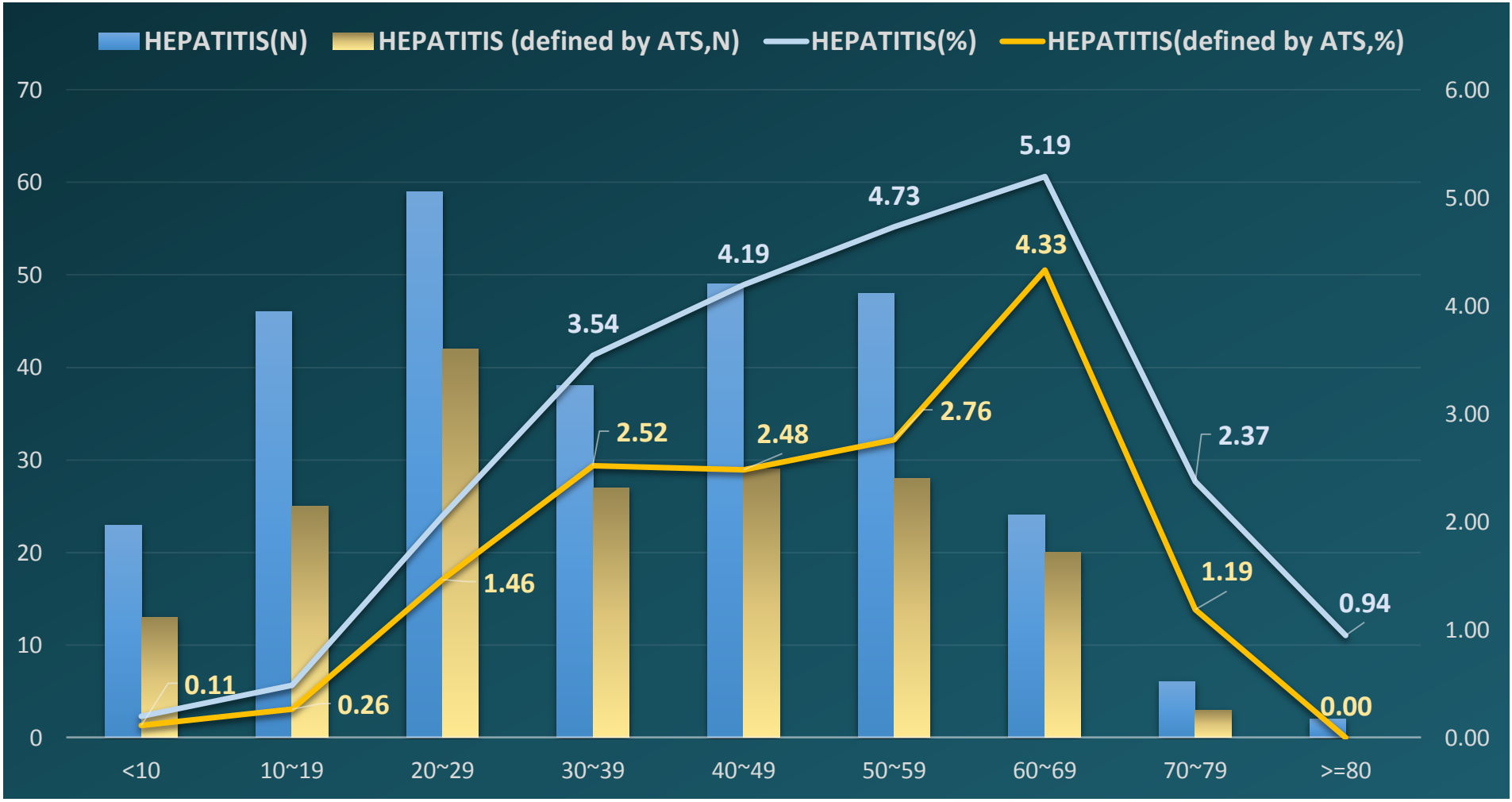
<13歲則以皮膚相關癢疹為最多(53%)

因肝炎導致住院:0.56‰(16/28,353)，沒有因不良反應導致死亡

MOHW103-CDC-C-315-000302

潛伏結核感染治療期間因肝炎而永久停藥比率

依年齡分層, 9H



肝炎(n=295)在30歲以上會有3-5%的發生率, trend test: p<0.001

若為嚴重肝炎 (n=187,即符合美國胸腔暨重症醫學會建議的肝炎標準)，

則<10歲的發生率為1‰，20歲達1%，30歲達2-4%, trend test: p<0.001。

9H vs. 3HP (速克伏)處方

INTRODUCTION OF A SHORTER REGIMEN FOR LTBI TREATMENT

WHO Recommendation for LTBI Management

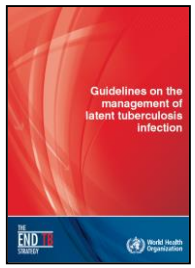


TABLE 3.7

WHO recommendations for the management of latent TB infection, by country group

COUNTRY GROUP	AT RISK POPULATIONS	TESTING ALGORITHM	TREATMENT OPTIONS
High-income and upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population	Strongly recommended for the following risk groups: 1) People living with HIV; 2) Adults and children who are household or close contacts of pulmonary TB cases; 3) Clinical indications – patients with silicosis; patients initiating anti-TNF treatment; patients on dialysis; transplant patients.	Exclude active TB using TB investigations. A positive IGRA or TST test result is required to diagnose LTBI.	6 months daily isoniazid 9 months daily isoniazid 3 months weekly rifapentine plus isoniazid 3 to 4 months daily isoniazid plus rifampicin 3 to 4 months daily rifampicin
Resource-limited and other middle-income countries with an estimated TB incidence rate of more than 100 per 100 000 population	1) People living with HIV; 2) Children under 5 years of age who are household contacts of a TB case.	Exclude active TB using TB investigations. An LTBI test is not required prior to LTBI treatment, but is encouraged for people living with HIV. IGRA should not replace TST.	6 months daily isoniazid

Comparison of Efficacy and Hepatotoxicity among LTBI Regimens

TABLE 3 Standard random effects meta-analysis comparison of efficacy and hepatotoxicity among various treatment regimens for treatment of latent tuberculosis (TB) infection

每種LTBI治療都可以有效降低TB發病

Comparator	Intervention	Development of incident TB	Hepatotoxicity
Placebo	Isoniazid 6 months	0.61 (0.48–0.77)	0.99 (0.42–2.32)
Placebo	Isoniazid 12–72 months	0.53 (0.41–0.69)	0.59 (0.23–1.55)
Placebo	Rifampicin 3–4 months	0.48 (0.26–0.87)	
Placebo	Rifampicin and isoniazid 3–4 months	0.52 (0.33–0.84)	
Isoniazid 6 month	Rifampicin 3–4 months	0.78 (0.41–1.46)	0.03 (0.00–0.48)
Isoniazid 6 month	Rifampicin and isoniazid 3–4 months	0.89 (0.65–1.23)	0.89 (0.52–1.55)
Isoniazid 6 month	3 month weekly rifapentine plus isoniazid[#]	1.09 (0.60–1.99)	1.00 (0.50–1.99)
Isoniazid 9 month	3 month weekly rifapentine plus isoniazid	0.44 (0.18–1.07)	0.16 (0.10–0.27)

VS

Data are presented as odds ratios with 95% confidence intervals. [#]: exclusively among people living with HIV.

但不同處方肝毒性的確有差異

ERJ 2015 Management of latent Mycobacterium tuberculosis infection: WHO guidelines for low tuberculosis burden countries

Current Regimens for LTBI

Regimen	Efficacy / Effectiveness	Tolerability Drug discontinue AE/ Hepatotoxicity	Comments
9 INH (9H) Daily	90% / 25-88% median:60% **台灣 73– 94%***	0-31% 0.1-3.8% **台灣肝炎 0.1-4.3%***	6 and 12 months well-studied; 30-60% completion **台灣 60-80%***
3 INH + rifapentine (3HP) once-weekly	90% (estimated) 90% (estimated) 與九個月無差別	4.9% 0.4% **台灣 3.0- 9.3% , 0-1 % ******	82% completion Directly-observed **台灣 90-97%****
3 INH + rifampin daily	--- 41-59%	0-5.1% 0-5.1%	An alternative Hepatoxicity
4 rifampin daily	--- 46-50% (3 months)	1.9-14% 0-0.7% 台灣收容人研究*** 2-6%, 肝炎 0%	An alternative When INH R, Not in HIV+ 台灣完成率86%***

Curtsey of Dr. ME Villarino/ MOHW103-CDC-C-315-000302/ MOHW104-CDC-C-114-123201/ IJTLD 2012;16(5):633-8.

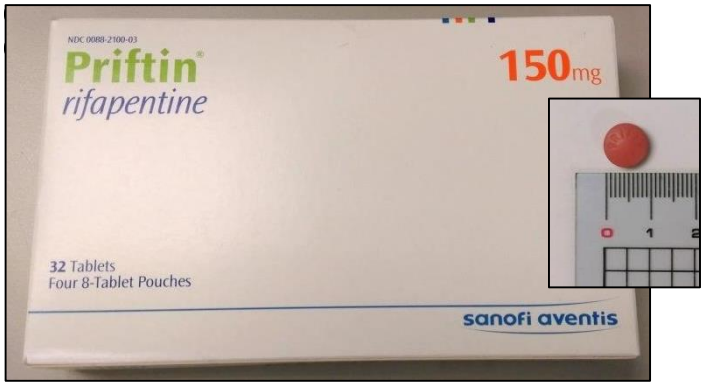
潛伏結核全都治計畫
2016年全面推行

增加短程治療處方之選擇
短程處方須以傳統都治方式執行

短程處方(3HP速克伏)

once weekly x 3 months =

only 12 doses



900mg Isoniazid (INH) +
900mg Rifapentine (RPT)

Priftin® – Taiwan Status

Rifapentine 150mg

美國FDA適應症

肺結核(1988)

潛伏結核(2014)

台灣FDA已註冊但尚未核可

2016年

疾病管制署專案進口

使用於非INH非RMP抗藥的

傳染性肺結核病人之

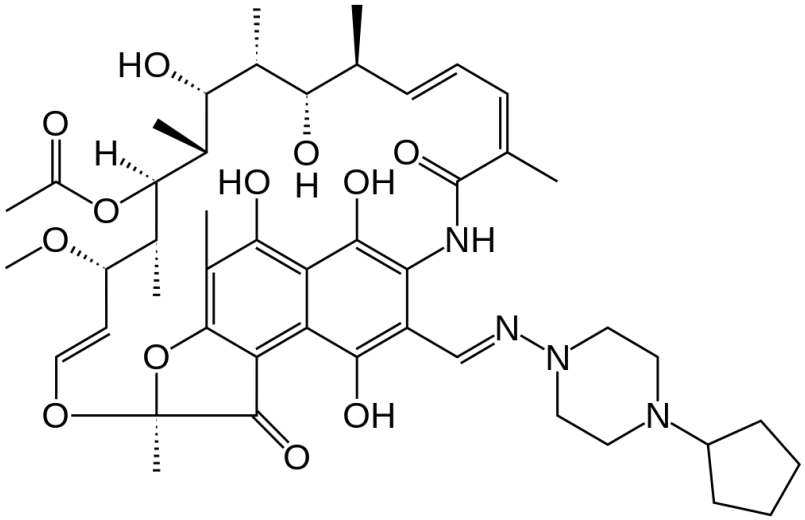
LTBI(+)接觸者

3個月的

潛伏結核感染

短期治療處方

Against Mycobacteria by Inhibiting Bacterial DNA-dependent RNA Polymerase

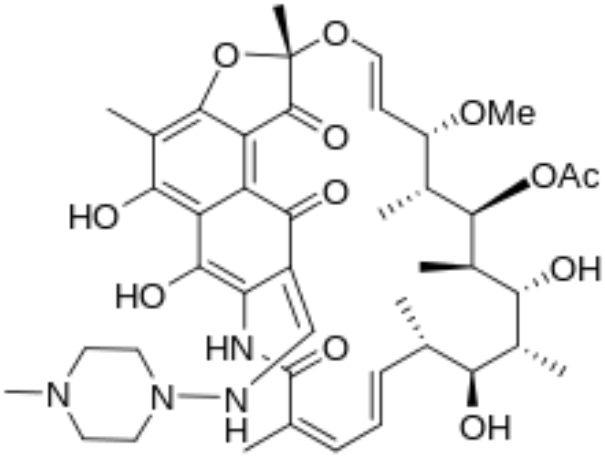


$C_{47}H_{64}N_4O_{12}$

RPT

$C_{43}H_{58}N_4O_{12}$

RMP



- RPT/RMP 會活化CYP450之3A4 與 2C8/9，經由**CYP450代謝的藥物**與RPT/RMP合併使用的話, 可能導致這些藥物的**血中濃度降低, 療效減低**。
- 使用RPT/RMP，**體液或某些身體組織可能變橘紅色**。
- RPT/RMP 抑制荷爾蒙避孕藥的效用，**建議採用其他有效避孕方式**。

異 RPT 跟RMP哪裡不一樣?

- RPT 半衰期比RMP長得多 (>12 h vs 2-3 h)
- RPT 與高脂餐點一起服用可增加血清濃度但RMP是空腹服用吸收才會好
  - Consumption with food (especially **lipid-rich meal) increases the peak serum concentration** of RPT (40-50% Cmax & AUC), in contrast to RMP that needs to be taken in a fasting state (also INH).

Prifin USPI, Dec 2014

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

NEJM

對大部分的國家來說，

嚴格執行**9個月DOPT非常困難**。

3個月的短程處方，效果不輸傳統治療，

完治率卻更高！更可以用有限的人力進行全都治。

Morbidity and Mortality Weekly Report

Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection

MMWR / December 9, 2011 / Vol. 60 / No. 48

US CDC

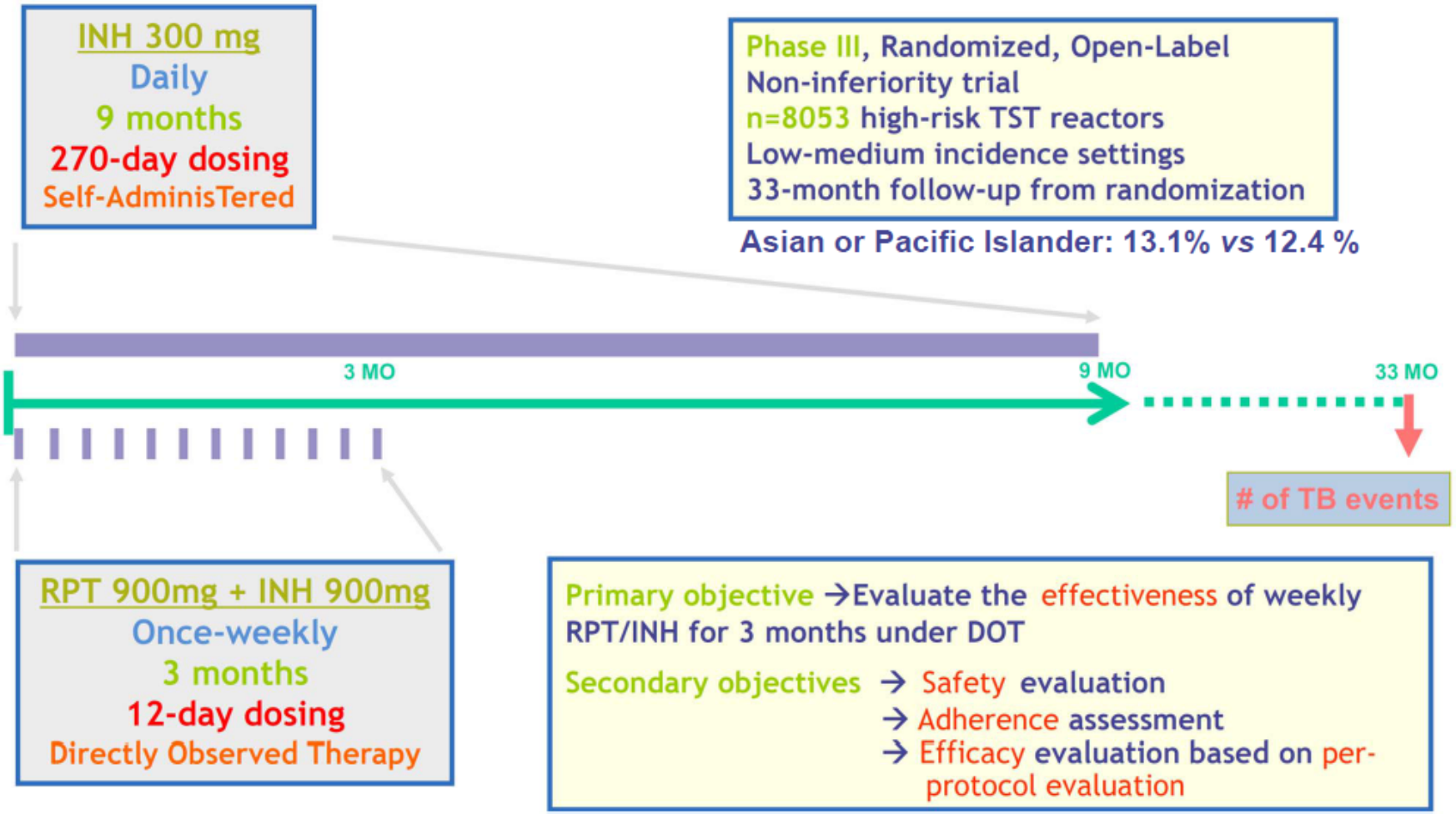
亦於2011/12/9正式宣布，

建議使用12doses的INH+RPT短程處方，

利用完整的DOPT來達成高完治率的目標。

The PREVENT TB Study (TBTC 26)

-TBTC S26 Design



Sterling TR et al. *N Engl J Med*. 2011;365:2155-66
Shepardson D et al. *Int J Tuberc Lung Dis*. 2013;17:1531-7
Morb Mort Wkly Rep 2011;60:1650-1653

Demographic Characteristics
in mITT Populations

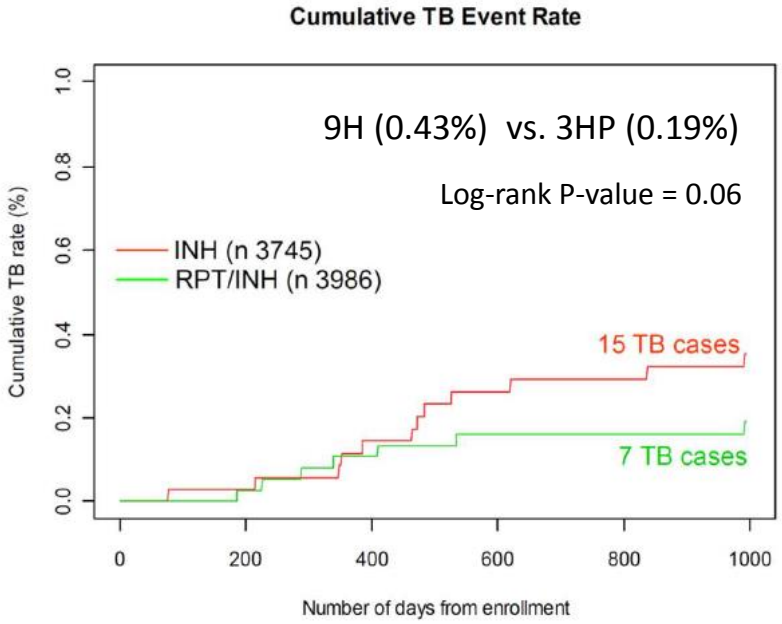
Characteristic	9H傳統治療 (N=3,745)	**3HP短程處方** (N=3,986)
Age (median,IQR)	36 (25-46)	37 (25-47)
Unemployed	390 (10)	424 (11)
Hx of alcohol at enrollment	1888 (50)	1929 (48)
Jail/prison ever	175 (5)	221 (6)
Hx of IVDU at enrollment	135 (4)	149 (4)
Current smoker	1034 (28)	1112 (28)
Close contact for LTBI	2609 (70)	2857 (72)
HCV* * Excluded when AST >=5 x UNL	97 (3)	99 (3)
HBV*	60 (2)	42 (1)

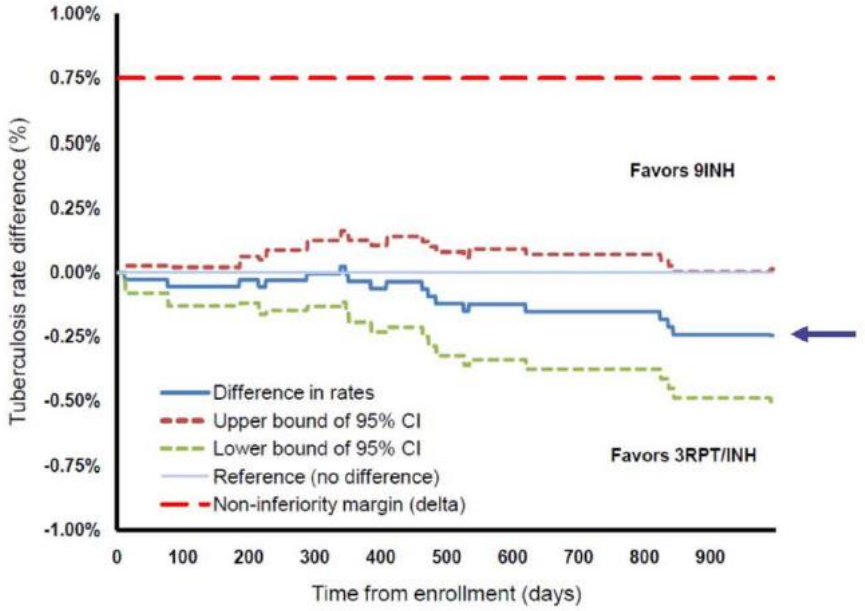
年齡較輕，但**自述有飲酒習慣偏高且靜脈毒癮者，收容人及慢性肝病皆有收案**

TBTC S26 – The Prevent TB Study

-Primary endpoint : TB rates by Mo33 – mITT

短程處方3HP累積結核發生率比傳統9H低, 統計無顯著差異





Non-inferiority demonstrated as 97.5% upper-bound of diff = 0.08% (<0.75%= NI margin)

此項臨床試驗證實，短程處方3HP的療效是不輸給傳統9H的

Sterling TR. N Engl J Med 2011;365:2155-66.

Tolerability in mITT Population

Outcome	9H傳統治療 (N=3,745)	**3HP短程處方** (N=3,986)	P-value
Treatment completion	2,585 (69.0%)	**3,362(84.3%)** 勝	< 0.0001
Permanent drug discontinue - any reason	1,160 (31.0%)	**624(15.7%)** 勝	< 0.0001
Permanent drug discontinue - due to an adverse event	135 (3.6%)	188(4.7%)	0.004
Death	39 (1.0%)	31 (0.8%)	0.22

使用3HP短程處方，**治療時間短，完治率大幅提高**

Courtesy of M. Elsa Villarino

Hepatotoxicity

among persons receiving ≥ 1 dose
during treatment or within 60 days of the last dose

Toxicity	9H傳統治療 N=3,759	**3HP短程處方** N=4,040	P-value
All hepatotoxicity	113 (3.0)	**24 (0.6)** 勝	<0.0001
Related to drug	103 (2.7)	**18 (0.4)** 勝	<0.0001
Not related	10 (0.3)	6 (0.2)	0.319

使用3HP短程處方，與藥物相關之肝炎比例明顯較低

Courtesy of M. Elsa Villarino

Possible Drug Hypersensitivity

臨床試驗定義

- 在PREVENT trial 中，預期會有RMP 類的過敏反應，其定義如下
- A broad definition of was used (以下任一)

  a) hypotension, urticaria, angioedema, acute bronchospasm, or conjunctivitis that occurred in relation to study drug; or

  b) > 4 of the following (one of which had to be > grade 2) that occurred in relation to study drug:

  - weakness, fatigue, nausea, vomiting, headache, fever, aches, sweats, dizziness, shortness of breath, flushing, or chills.

Reported Adverse Events

Among persons receiving ≥ 1 dose
During treatment or within 60 days of the last dose
Accounting for attribution to study drug

HS: hypersensitivity reaction

Toxicity	9H N=3,759	**3HP** N=4,040	P-value
Related to drug	206 (5.5)	**332 (8.2)**	<0.001
Rash only	21 (0.6)	31 (0.8)	0.26
Possible HS	17 (0.5)	**152 (3.8)**	<0.001
Other	65 (1.7)	**131 (3.2)**	<0.001
Not related	410 (10.9)	226 (5.6)	<0.001

注意

使用短程處方較傳統9H多的是**過敏反應和其他副作用**

兒童的臨床試驗

Original Investigation

Treatment for Preventing Tuberculosis in Children and Adolescents

A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

M. Elsa Villarino, MD, MPH; Nigel A. Scott, MS; Stephen E. Weis, DO; Marc Weiner, MD; Marcus B. Conde, MD; Brenda Jones, MD; Sharon Nachman, MD; Ricardo Oliveira, MD; Ruth N. Moro, MD, MPH; Nong Shang, PhD; Stefan V. Goldberg, MD; Timothy R. Sterling, MD; for the International Maternal Pediatric and Adolescents AIDS Clinical Trials Group (IMPAACT) and the Tuberculosis Trials Consortium (TBTC)

IMPORTANCE Three months of a once-weekly combination of rifapentine and isoniazid for treatment of latent tuberculosis infection is safe and effective for persons 12 years or older. Published data for children are limited.

OBJECTIVES To compare treatment safety and assess noninferiority treatment effectiveness of combination therapy with rifapentine and isoniazid vs 9 months of isoniazid treatment for latent tuberculosis infection in children.

DESIGN, SETTING, AND PARTICIPANTS A pediatric cohort nested within a randomized, open-label clinical trial conducted from June 11, 2001, through December 17, 2010, with follow-up through September 5, 2013, in 29 study sites in the United States, Canada, Brazil, Hong Kong (China), and Spain. Participants were children (aged 2-17 years) who were eligible for treatment of latent tuberculosis infection.

INTERVENTIONS Twelve once-weekly doses of the combination drugs, given with supervision by a health care professional, for 3 months vs 270 daily doses of isoniazid, without supervision by a health care professional, for 9 months.

MAIN OUTCOMES AND MEASURES We compared rates of treatment discontinuation because of adverse events (AEs), toxicity grades 1 to 4, and deaths from any cause. The equivalence margin for the comparison of AE-related discontinuation rates was 5%. Tuberculosis disease diagnosed within 33 months of enrollment was the main end point for testing effectiveness. The noninferiority margin was 0.75%.

RESULTS Of 1058 children enrolled, 905 were eligible for evaluation of effectiveness. Of 471 in the combination-therapy group, 415 (88.1%) completed treatment vs 351 of 434 (80.9%) in the isoniazid-only group ($P = .003$). The 95% CI for the difference in rates of discontinuation attributed to an AE was −2.6 to 0.1, which was within the equivalence range. In the safety population, 3 of 539 participants (0.6%) who took the combination drugs had a grade 3 AE vs 1 of 493 (0.2%) who received isoniazid only. Neither arm had any hepatotoxicity, grade 4 AEs, or treatment-attributed death. None of the 471 in the combination-therapy group developed tuberculosis vs 3 of 434 (cumulative rate, 0.74%) in the isoniazid-only group, for a difference of −0.74% and an upper bound of the 95% CI of the difference of +0.32%, which met the noninferiority criterion.

CONCLUSIONS AND RELEVANCE Treatment with the combination of rifapentine and isoniazid was as effective as isoniazid-only treatment for the prevention of tuberculosis in children aged 2 to 17 years. The combination-therapy group had a higher treatment completion rate than did the isoniazid-only group and was safe.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00023452

JAMA Pediatr. doi:10.1001/jamapediatrics.2014.3158
Published online January 12, 2015.

Editorial

Supplemental content at jamapediatrics.com

- A pediatric cohort nested within an open-label RCT conducted from June 11, 2001, through December 17, 2010, with follow-up through September 5, 2013
- in 29 study sites in the United States, Canada, Brazil, Hong Kong (China), and Spain.
- Participants were children (aged 2-17 years) who were eligible for treatment of LTBI

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A list of the International Maternal Pediatric and Adolescents AIDS Clinical Trials Group (IMPAACT) and the Tuberculosis Trials Consortium (TBTC) members is included in eAppendix 1 in the Supplement.

Corresponding Author: Ruth N. Moro, MD, MPH, Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Building 12, Mail Stop E-10, Atlanta, GA (rmoro@cdc.gov).

M. Elsa Villarino et al. *JAMA Pediatr.* 2015;169(3):247-255

Tolerability and Effectiveness in Children

TBTC S26 + IMPAACT

- Study 26 amended to enroll 352 additional children; 1,058 total & 908 for efficacy evaluation
- No hepatotoxicity, grade 4 events, or deaths

Endpoint	3HP N=471 勝	9H N=434	P-value
Treatment completion	88%	81%	0.003
D/C—adverse drug reaction	1.7%	0.5%	0.11
TB	0 (0%)	3 (0.78%)	Upper bound of difference: 0.44%

使用3HP短程處方，**治療時間短，完治率大幅提高;** 相較於成人，因為沒有肝炎，副作用沒有統計顯著的差別。

Discontinuation 3HP Due to AEs in Children

- 3HP 共8位
  - 3 influenza-like AEs (grade 2)
  - 3 cutaneous (all with pruritic rash [2 were grade 2], 1 with oral blisters and fever [grade 3])
  - 2 gastrointestinal reactions (1 was grade 1 and 1 was grade 2)
- 9H只有2位
  - 1 cutaneous AE (grade 2) and 1 gastrointestinal reaction (grade 3)

結論是: 9H 對兒童來說已經很安全，3HP對兒童來說，是一個縮短療程的alternative選擇。

兒童注意事項

- INH 的劑量:
  - 15 mg/kg for children ≥12 years old
  - **25 mg/kg for those 2-11 years**
  - the maximum weekly dose was 900 mg
- RPT 的劑量:
  - Not adjusted for age, 請參照a dose-per-weight band table
- 無法吞藥粒的兒童建議磨碎後，與液體或半固體食物服用，建議**巧克力布丁之類**的澱粉類布丁，不建議水果口味 (果凍類)。

Blake MJ et al. Pharmacokinetics of rifapentine in children. *Pediatr Infect Dis J*. 2006;25(5):405-409.
Peloquin CA et al. Stability of antituberculosis drugs mixed in food. Clin Infect Dis. 2007;45(4):521.

3HP短程處方建議劑量

Drug	Duration	Dose (≧2 year-old)	Frequency	Total doses
Isoniazid (INH) **300mg 3#**	3 months	**≥12 years old: 15 mg/kg rounded up to the nearest 50 or 100 mg;** **2-11 years old: 25 mg/kg** **900 mg maximum**	Once weekly	12
Rifapentine (RPT) **150mg 6#**	3 months	**10.0–14.0 kg 300 mg** 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg **≥50.0 kg 900 mg** maximum	Once weekly	12

US CDC Latent Tuberculosis Infection: A Guide for Primary Health Care Providers (http://www.cdc.gov/tb/publications/ltbi/)
Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection (https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w)

對於新藥

我們用較謹慎地態度來監測”非肝炎”的其他副作用

MONITOR AND SURVEILLANCE OF ADVERSE EVENTS

MAJOR ARTICLE

Flu-like and Other Systemic Drug Reactions Among Persons Receiving Weekly Rifapentine Plus Isoniazid or Daily Isoniazid for Treatment of Latent Tuberculosis Infection in the PREVENT Tuberculosis Study

Timothy R. Sterling,[1,a] Ruth N. Moro,[2,3,a] Andrey S. Borisov,[2] Elizabeth Phillips,[1,4] Gillian Shepherd,[5] Newton Franklin Adkinson,[6] Stephen Weis,[7] Christine Ho,[2] and Margarita Elsa Villarino[2]; for the Tuberculosis Trials Consortium

[1]Vanderbilt University School of Medicine, Nashville, Tennessee; [2]Centers for Disease Control and Prevention, and [3]CDC Foundation, Research Collaboration, Atlanta, Georgia; [4]Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Australia; [5]New York-Presbyterian Hospital/Weill Cornell Medical Center, New York; [6]Johns Hopkins University School of Medicine, Baltimore, Maryland; and [7]University of North Texas Health Science Center at Ft. Worth

Background. Weekly rifapentine plus isoniazid for 3 months (3HP) is as effective as daily isoniazid for 9 months (9H) for latent tuberculosis infection in high-risk persons, but there have been reports of possible flu-like syndrome.

Methods. We identified clinically significant systemic drug reactions (SDR) and evaluated risk factors in patients who did not complete treatment in the PREVENT Tuberculosis study.

Results. Among 7552 persons who received ≥1 dose of study drug, 153 had a SDR: 138/3893 (3.5%) with 3HP vs 15/3659 (0.4%) with 9H ($P < .001$). In the 3HP arm, 87 (63%) had flu-like syndrome and 23 (17%) had cutaneous reactions; 13/3893 (0.3%) had severe reactions (6 were hypotensive) and 6 reported syncope. Symptoms occurred after a median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours. There were no deaths. In multivariate logistic regression analysis, factors independently associated with SDR included receipt of 3HP (adjusted odds ratio [aOR] 9.4; 95% confidence interval [CI], 5.5, 16.2), white non-Hispanic race/ethnicity (aOR 3.3; 95% CI, 2.3, 4.7), female sex (aOR 2.0; 95% CI, 1.4, 2.9), age ≥35 years (aOR 2.0; 95% CI, 1.4, 2.9), and lower body mass index (body mass index [BMI]; $P = .009$). In a separate multivariate analysis among persons who received 3HP, severe SDR were associated with white non-Hispanic race/ethnicity (aOR 5.4; 95% CI, 1.8, 16.3), and receipt of concomitant non-study medications (aOR 5.9; 95% CI, 1.3, 27.1).

Conclusions. SDR were more common with 3HP, and mostly flu-like. Persons of white race, female sex, older age, and lower BMI were at increased risk. Severe reactions were rare and associated with 3HP, concomitant medication, and white race. The underlying mechanism is unclear.

Clinical Trials Registration. NCT00023452.

Clin Infect Dis. 2015;61(4):527-35.

因為hypersensitivity 是RPT在PREVENT Trial 中較重要的副作用，接下來我們看看在PREVENT Trial 與 NYC 的衛生局經驗，了解發生的狀況和嚴重度。

全身性藥物反應

Systemic Drug Reaction

Clinical Infectious Diseases

MAJOR ARTICLE

Treatment for Tuberculosis Infection With 3 Months of Isoniazid and Rifapentine in New York City Health Department Clinics

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New York City Department of Health and Mental Hygiene, Bureau of Tuberculosis Control, Long Island City, New York

Background. Completion of treatment for tuberculosis infection (TBI) with 9 months of self-administered daily isoniazid (9H) has historically been low (<50%) among New York City (NYC) Health Department tuberculosis clinic patients. Treatment of TBI with 3 months of once-weekly isoniazid and rifapentine (3HP) administered under directly observed therapy (DOT) might increase treatment acceptance and completion.

Methods. The study population included patients diagnosed with TBI at 2 NYC Health Department tuberculosis clinics from January 2013 through November 2013. Treatment acceptance and completion with 3HP were compared with historical estimates. Treatment outcomes, side effects, and reasons for refusing 3HP were described.

Results. Among 631 patients eligible for TBI treatment, 503 (80%) were offered 3HP; 302 (60%) accepted, 92 (18%) chose other treatment, and 109 (22%) refused treatment. The most common reason for refusing 3HP was the clinic-based DOT requirement. Forty (13%) patients treated with 3HP experienced side effects—9 were restarted on 3HP, 18 switched treatment regimens, and 13 discontinued. Although treatment acceptance did not differ from historical estimates (78% vs 79%, $P = .75$), treatment completion increased significantly (65% vs 34%, $P < .01$).

Conclusions. Implementation of 3HP in 2 NYC Health Department tuberculosis clinics increased TBI treatment completion by 31 percentage points compared with historical estimates. More flexible DOT options may improve acceptance of 3HP. Wider use of 3HP may substantially improve TBI treatment completion in NYC and advance progress toward tuberculosis elimination.

Keywords. latent tuberculosis infection; 3-month treatment; directly observed therapy; public health.

Clin Infect Dis. 2016; 62 (1): 53-59

Systemic Drug Reaction in the PREVENT Tuberculosis Study

- 3.5%的3HP (n=3893) 接受者有systemic drug reaction (SDR)
- Symptoms occurred after a median of 3 doses, and 4 hours after the dose; median time to resolution was 24 hours.
  - 4/3893 (0.1 %) admission
  - 13/3893 (0.3%)有severe reactions
    - 8: Grade 4 toxicity (including 1 syncope)
    - 6: hypotensive
    - 6: syncope (no admission, 有一個有loss consciousness)
  - No death reported

Clin Infect Dis. 2015;61(4):527-35.

Table 2. Characterization of the 153 Systemic Drug Reactions According to Syndrome

	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
Gastrointestinal[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

注意

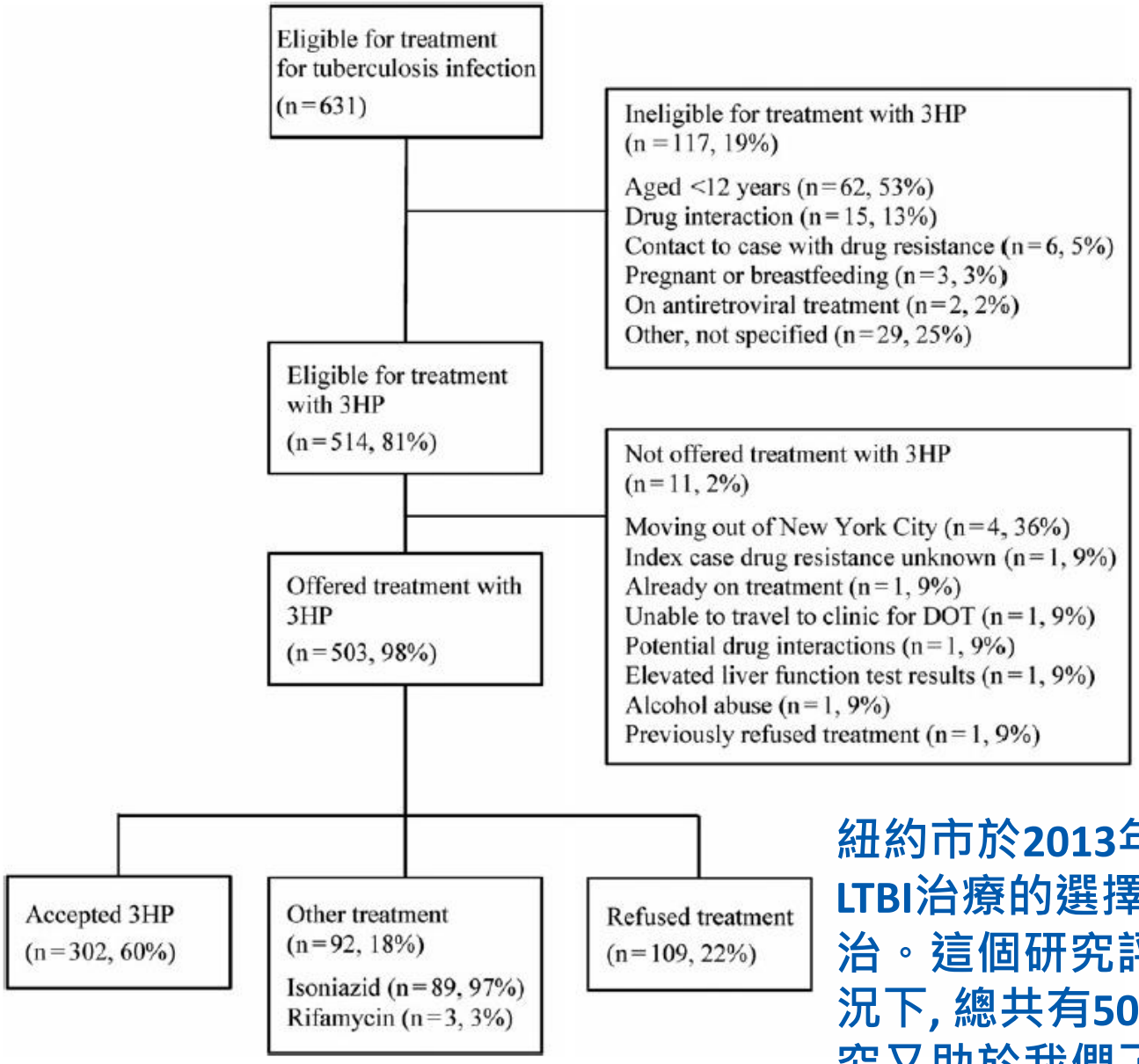
3HP的系統性藥物反應最常見的還是Flu-like syndrome (2.2%), 嚴重的類流感反應, 佔服藥總人數的0.15%

Clin Infect Dis. 2015 Aug 15;61(4):527-35.

Frequency of signs and symptoms in 153 cases of systemic drug reactions (SDR), stratified by arm

Signs and symptoms	SDR (n=153)		3HP (n=138)		9H (n=15)	
	Number	%	Number	%	Number	%
Fatigue	107	70	99	72	8	53
Headache	104	68	97	70	7	47
Nausea	99	65	94	68	5	33
Weakness	94	61	91	66	3	20
Chills	87	57	82	59	5	33
Myalgia (muscle pain)	82	54	79	57	3	20
Fever	81	53	77	56	4	27
Dizziness	63	41	58	42	5	33
Joint pain	54	35	51	37	3	20
Rash	46	30	36	26	10	67
Abdominal Pain	47	31	45	33	2	13
Flushing	43	28	41	30	2	13
Conjunctivitis (red eyes)	43	28	42	30	1	7
Vomiting	42	27	40	29	2	13
Itching	37	24	28	20	9	60
Sweats	35	23	34	25	1	7
Shortness of breath	27	18	25	18	2	13
Eye pain	27	18	25	18	2	13
Palpitations						
Diarrhea						
Anorexia						
Body aches						
Angioedema						
Hypotension	6	4	6	4	0	0
Tachycardia	7	5	7	5	0	0
Urticaria (hives)	7	5	5	4	2	13
Syncope[a]	6	4	6	4	0	0
Chest pain	5	3	5	4	0	0
Bone pain	2	1	2	1	0	0
Bronchospasm	1	1	1	1	0	0

Fever: 3HP 有2% , 9H有 0.1%; 3HP 最常被抱怨的是 疲倦, 頭痛, 噁心, 無力; 9H最常被抱怨的是疹子, 癢, 疲倦



THE END TB STRATEGY

紐約市於2013年 1月開始提供3HP當作LTBI治療的選擇, 但必須衛生所進行都治。這個研究評估在非臨床試驗的情況下, 總共有503人被提供3HP, 這個研究又助於我們了解病人的想法

Natalie L. Stennis et al. Clin Infect Dis. 2016; 62 (1): 53-59

Side Effects Experienced by New York City Health Department Tuberculosis Clinic Patients Treated With 3HP

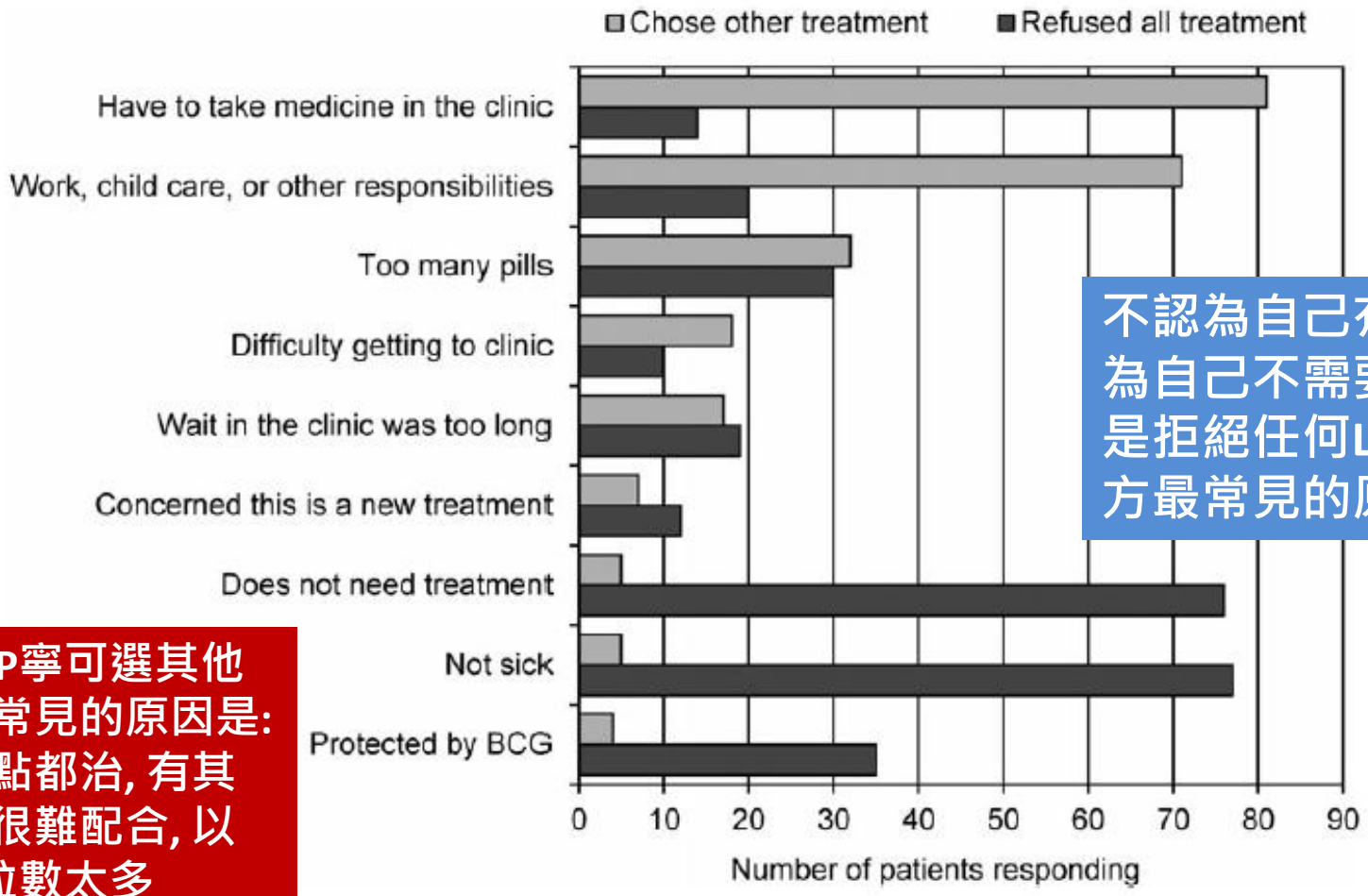
Side Effect	Did Not Complete Treatment With 3HP, n (%)	Completed Treatment With 3HP,[a] n (%)
Total	32	8
Nausea	8 (25)	2 (25)
Rash/itching	8 (25)	2 (25)
Abdominal pain	7 (22)	2 (25)
Fatigue	7 (22)	2 (25)
Dizziness	6 (19)	2 (25)
Headache	5 (16)	2 (25)
Fever	5 (16)	1 (13)
Elevated liver function test results	5 (16)	0 (0)
Vomiting	4 (13)	1 (13)
Dark urine	2 (6)	1 (13)
Muscle pain	2 (6)	1 (13)
Loss of appetite	2 (6)	1 (13)

注意

有32人沒有辦法完成治療 (10.6%), 主要的副作用: 包括噁心, 癢疹, 肚子痛和疲倦. 沒有特別觀察到syncope 的副作用, 類流感沒有特別被整理出來，但發燒的有5位, 約1.7%.

Clin Infect Dis. 2016; 62 (1): 53-59

紐約病人拒絕 3HP 治療的理由 (多選)



不認為自己有病/認為自己不需要治療，是拒絕任何LTBI處方最常見的原因

不選擇3HP寧可選其他處方，最常見的原因是: 必須要到點都治, 有其他事要做很難配合, 以及3HP顆粒數太多

Natalie L. Stennis et al. Clin Infect Dis. 2016; 62 (1): 53-59

The Treatment Completion Rate and Side Effects of 9H and 3HP Regimens Population (courtesy of 部立彰化醫院黃伊文主任)

	9H (n=590)		**3HP (n=101)**		
	n	%	**n**	**%**	p value
Results of treatment					
勝 completed	515	87.29%	**98**	**97.03%**	p<0.001
discontinued	75	12.71%	**3**	**2.97%**	
Reason of discontinued					
勝 side effects	28	4.75%	**3**	**2.97% ***	p<0.001
reject	44	7.46%	**0**	**0 %**	
death	1	0.17%	**0**	**0 %**	
TB	2	0.34%	**0**	**0 %**	

- 3HP completion rate was significantly higher than 9H
- Low discontinue rate in 3HP

部立彰化醫院之3HP先驅計畫

Hepatotoxicity and Discontinue (courtesy of 台大醫院王振源教授)

	3HP N=104	9H N=90	***p*-value**
勝 **Hepatotoxicity**	**1 (0.9%)**	4 (4.3%)	0.184
AST/ALT >10 ULN	0	1	
AST/ALT 5~10 ULN	1	3	
T-Bil >3 mg/dL	0	0	
Discontinuation	**11 (9.6%)**	18 (20.0%)	0.066
注意 Not supervised	0	11	
Due to AE	**9 (8.6%)**	(4.4%)	
Tx not necessary	2	2	
Family against	0	1	

研究何種潛伏結核感染的治療較為安全且可達成 - 台灣的多中心隨機分派研究
MOHW103-CDC-C-114-112301

Any AE During the treatment (courtesy of 台大醫院王振源教授)

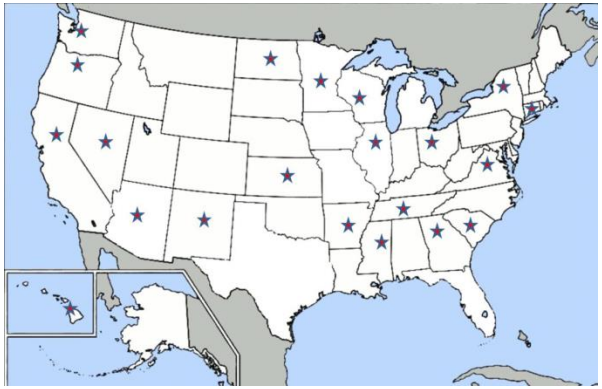
	3HP (n=104)	9H (n=90)	*p*-value
Any AE	**48 (46.2%)**	26 (28.9%)	**0.014**
Flu-like symptoms	22 (21.2%)	16 (17.8%)	0.555
Malaise	22 (21.2%)	13 (14.4%)	0.226
Fever/Flush	**20 (19.2%)**	4 (4.4%)	0.002
GI upset	14 (13.5%)	8 (8.9%)	0.316
Cutaneous AE	6 (5.8%)	3 (3.3%)	0.508
Blur vision	1 (1.0%)	1 (1.1%)	>0.999
Irregular menstruation	1 (1.0%)	0 (0.0%)	>0.999

注意

研究何種潛伏結核感染的治療較為安全且可達成 - 台灣的多中心隨機分派研究
MOHW103-CDC-C-114-112301

Post Marketing Surveillance by US CDC

- Vigilance for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia
- No further alarm signal was detected for syncope (hypotensive in nature and suspect associated with concomitant medications
- HTN / CNS depressive drugs
- 在上市後監視發現安全性無顧慮



Curtsey of Christine S. Ho, 18th Annual Conference of the Union-NAR, 2014
46th IUATLD world conference, 2015

使用「速克伏」需要做哪些監測

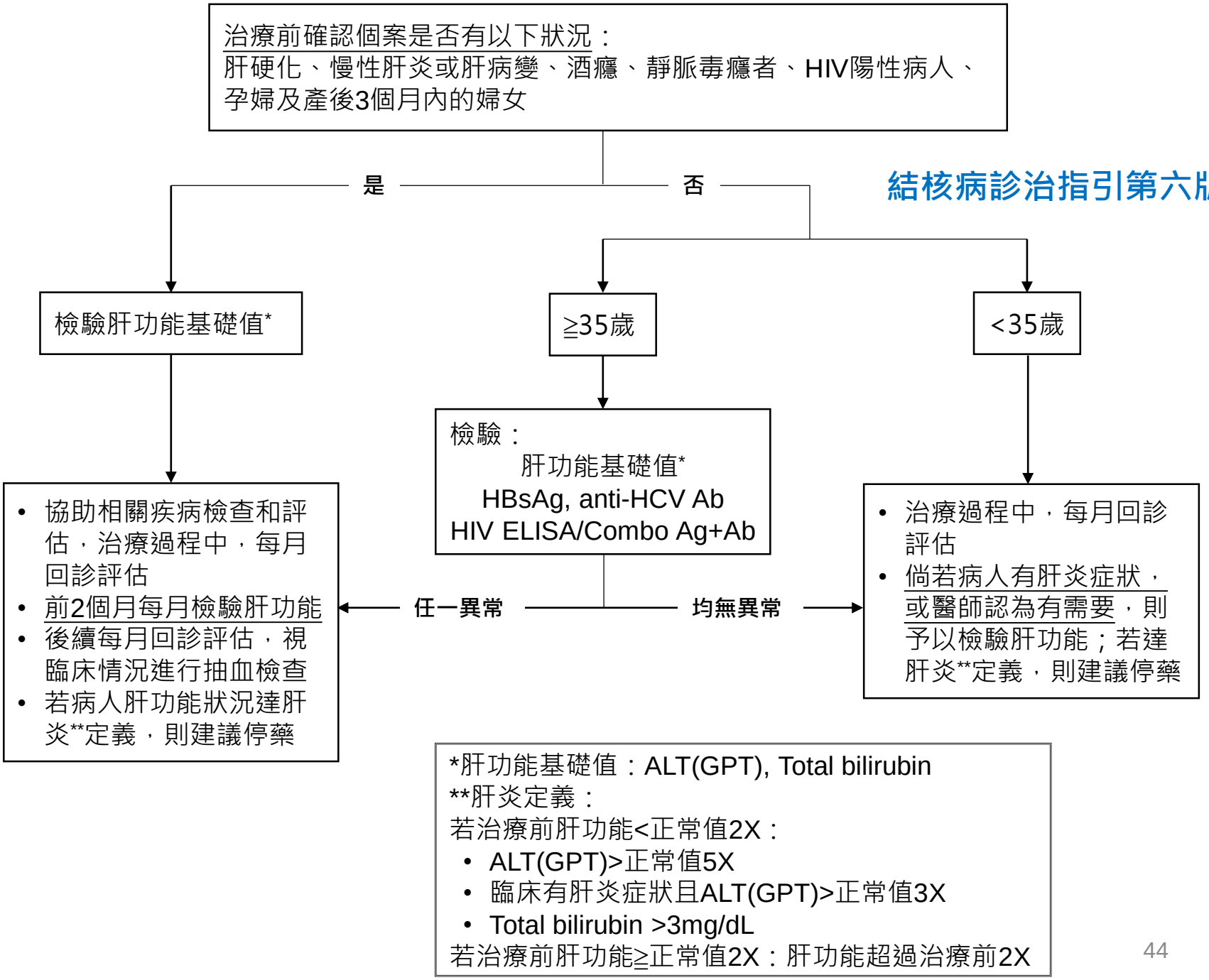
- 「速克伏」短程治療處方(3HP)較9H更少發生藥物性肝炎，肝功能檢查(ALT, total bilirubin) **原則上比照9H處方的肝炎監測建議**。
- 與9H不同的地方是，**在肝病或者有其他醫療的考慮(貧血或血小板相關的疾病) 時，需要抽驗CBC/DC的基礎值，再決定追蹤的頻率**。
- 治療期間**仍然要每月回診**

停藥的標準

- **全身性過敏反應 (立刻)**
- 肝炎的原則如9H
- 其餘非過敏反應的副作用，視臨床需要給予支持療法，**停藥與否視個別病人是否能耐受，及臨床嚴重度而決定。**

建議處置原則

- 若遇到發燒的flu-like syndrome，經驗上可先確認**病人是否在服藥後幾小時發生，一天內即緩解**, 那表示藥物相關的機會最大; 若非上述之典型症狀，鑑別診斷是否有其他發燒的疾病，例如流感、泌尿道感染等，再依各疾病對症治療。
- **預先讓病人知道可能的flu-like syndrome**，開立解熱鎮痛劑(例如普拿疼)，讓病人碰到發燒先觀察反應，而不是跑急診。部分病人噁心嘔吐厲害，可使用服藥前止吐劑，來**緩解服藥當下的不適**。
- **若遇到肝炎，依9H停藥標準處理，原則上不再re-challenge同樣的處方**
- 其他的副作用，可考慮re-challenge，若失敗亦可考慮轉換成9H。


治療前確認個案是否有以下狀況：
肝硬化、慢性肝炎或肝病變、酒癮、靜脈毒癮者、HIV陽性病人、孕婦及產後3個月內的婦女
是
否
結核病診治指引第六版
檢驗肝功能基礎值*
≧35歲
<35歲
檢驗：
肝功能基礎值*
HBsAg, anti-HCV Ab
HIV ELISA/Combo Ag+Ab
• 協助相關疾病檢查和評估，治療過程中，每月回診評估
• 前2個月每月檢驗肝功能
• 後續每月回診評估，視臨床情況進行抽血檢查
• 若病人肝功能狀況達肝炎**定義，則建議停藥
任一異常
均無異常
• 治療過程中，每月回診評估
• 倘若病人有肝炎症狀，或醫師認為有需要，則予以檢驗肝功能；若達肝炎**定義，則建議停藥
*肝功能基礎值：ALT(GPT), Total bilirubin
**肝炎定義：
若治療前肝功能<正常值2X：
• ALT(GPT)>正常值5X
• 臨床有肝炎症狀且ALT(GPT)>正常值3X
• Total bilirubin >3mg/dL
若治療前肝功能≧正常值2X：肝功能超過治療前2X

使用「速克伏」短程治療處方應注意什麼 I

- **因RPT 為專案進口，故使用速克伏前，須簽署同意書。**
- 使用「速克伏」者**均應加入DOPT。醫師處方後，請病人與公共衛生聯繫，討論每次服藥時間，以利病人預先規劃其個人行程。**
- 已知紫質症 (porphyria)的病人， RMP使用會使疾病本身惡化，故避免開立 RPT。
- RPT抑制荷爾蒙避孕藥的效用, 請提醒病人**改用其他非荷爾蒙避孕法，例如保險套等。**

使用「速克伏」短程治療處方應注意什麼 II

- RPT會活化CYP450之3A4 與 2C8/9，經由CYP450代謝的藥物與RPT合併使用的話, **可能導致這些藥物的血中濃度降低, 療效減低**。
- RPT誘導的酶活性在首次投予後4天發生,酶活性在停止使用RPT之後14天恢復。
- 比較重要會因交互作用而被降低濃度的藥物，例如: coumadin, methadone, phenytoin 等。對於Azole類抗黴菌藥物，中樞神經抑制藥物或三環抗憂鬱劑，及免疫抑制劑也常有交互作用。**需知會處方之臨床醫師，以利病人其他疾病的控制和生活品質**。
- **使用抗愛滋病毒藥物之HIV感染者，其藥物交互作用為可接受之程度，建議於醫師評估下可安心使用。**

可能與RPT有藥物交互作用的藥單

藥物分類	**Examples of Drugs Within Class**
Antiarrhythmics	Disopyramide, mexiletine, quinidine, tocainide
Antibiotics	Chloramphenicol, clarithromycin, dapsone, doxycycline; Fluoroquinolones (such as ciprofloxacin)
Oral Anticoagulants	Warfarin
Anticonvulsants	Phenytoin
Antimalarials	Quinine
Azole Antifungals	Fluconazole, itraconazole, ketoconazole
Antipsychotics	Haloperidol
Barbiturates	Phenobarbital
Benzodiazepines	Diazepam
Beta-Blockers	Propanolol
Calcium Channel Blockers	Diltiazem, nifedipine, verapamil
Cardiac Glycoside Preparations	Digoxin
Corticosteroids	Prednisone
Fibrates	Clofibrate
Oral Hypoglycemics	Sulfonylureas (e.g., glyburide, glipizide)
Hormonal Contraceptives/ Progestins	Ethinyl estradiol, levonorgestrel
Immunosuppressants	Cyclosporine, tacrolimus
Methylxanthines	Theophylline
Narcotic analgesics	Methadone
Phophodiesterase-5 (PDE-5) Inhibitors	Sildenafil
Thyroid preparations	Levothyroxine
Tricyclic antidepressants	Amitriptyline, nortriptyline

病人臨時無法於約定日服藥，可以提前或延後嗎？

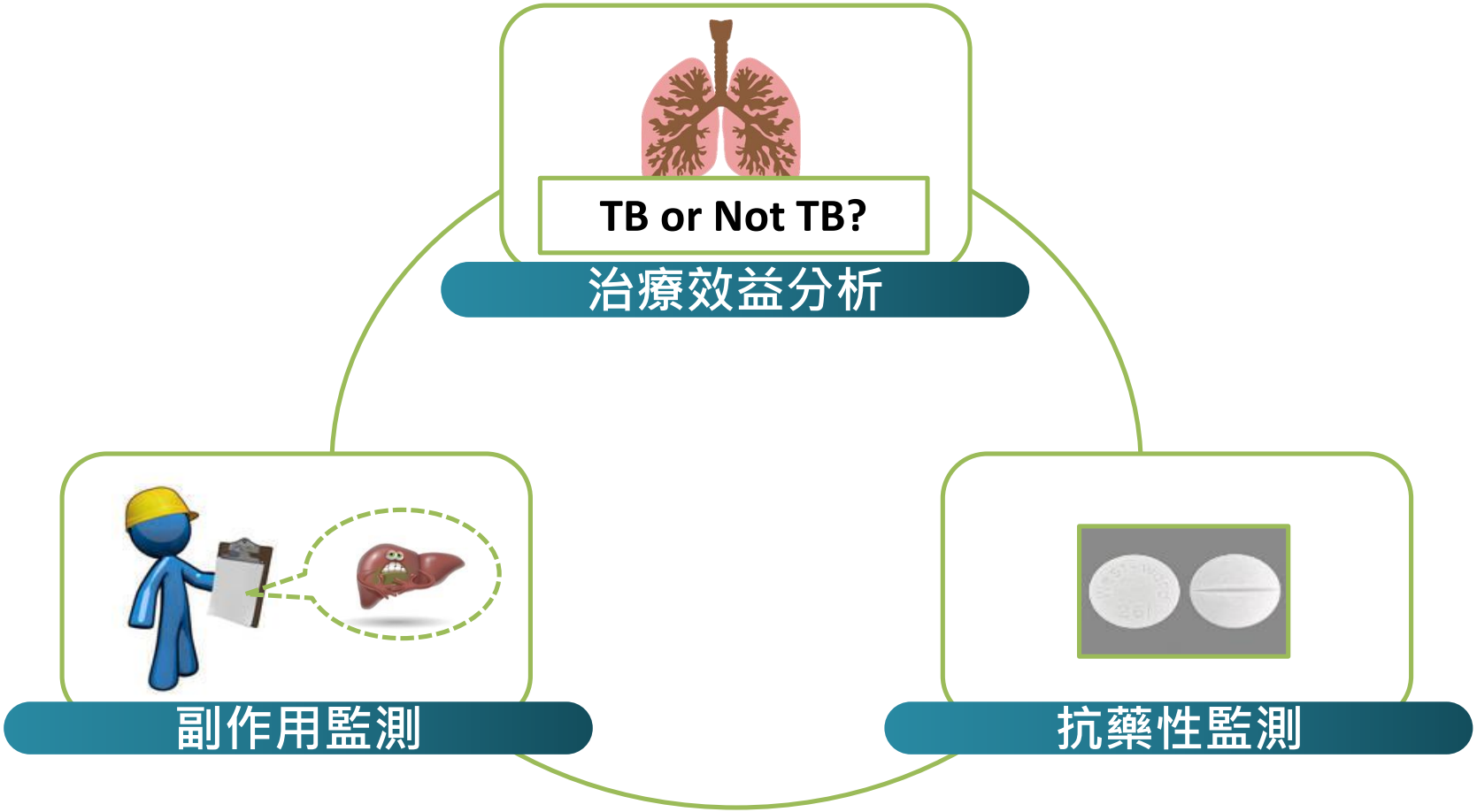
- 考慮「速克伏」短程治療處方藥物半衰期，及配合實務上都治計畫可能面臨爽約之情形，爽約後的第二天，儘快目視服藥，總之越快越好。
- 依據美國CDC的建議，若欲提早或延後，兩個劑量間，**間隔須大於72小時**，並於下個劑量回到原來的每七天服藥週期，**28天內不超過5個劑量來給予為原則**。

Sterling TR. N Engl J Med 2011;365:2155-66. (supplementary protocol)

轉換藥物後使用時間的建議

- **以下為專家意見**
- 原則上3HP 與 9H 如果病人無法耐受副作用，可嘗試互換
- 若服用3HP後碰到無法忍耐的副作用，或者有具體實驗值不宜繼續時，服用過4 doses 3HP + 6H可完成治療

計畫成效評估與監測



副作用的經驗分享

- 成立諮詢醫師專線，可透過1922反映，本署防疫醫師會主動與您聯繫，協助解決相關問題。
- 建立合作醫師電子郵件群組，定期發送相關訊息
- 計畫初期，定期舉辦電話會議，邀請專家們列席，讓醫師及個管師自由參加提問討論
- 鼓勵臨床醫師向全國不良反應通報中心通報 **https://adr.fda.gov.tw/Manager/WebLogin.aspx**

若發生嚴重不良反應

- 產生嚴重副作用: **住院或者死亡**
- 請依一般藥害救濟申請程序辦理。
- 倘服用速克伏至少一劑後，產生嚴重副作用(住院或者死亡)，請透過1922進線，通報嚴重不良反應給疾病管制署。
- 本署將派員儘速至醫院陪同診治醫師了解嚴重不良反應，是否與藥物安全性有關。

Choosing a Regimen for Treatment of LTBI

Factors to Consider

- Likelihood of completion
- Appropriate for age, exposure, other issues
  - <2, 2 years +
  - Co-morbidities, pregnancy, drug interactions
  - Social concerns: homelessness, drug and alcohol use, mental health issues, etc.
  - Drug resistance

Choosing a Regimen for Treatment of LTBI

Factors to Consider

- Efficacy
- Patient preference
- Possible side effects
- Cost
  - Drug (s)
  - Directly observed therapy (DOT) costs, if any
  - Staff time
  - Monitoring
- DOT access / availability

Choosing a regimen for LTBI contacts

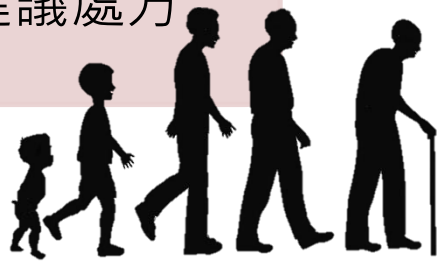
Quiz

- HIV + pregnant woman
- **Homeless, alcohol-using man**
- 8 month-old girl, contact of her mother
- **An 11 y/o boy, failed INH after 2 months of self administration, living in a remote village**

3HP短程處方不同年齡層使用建議

2歲(含)以上

- 9H及3HP為INH susceptible (9H)及INH & RMP susceptible (3HP)的建議處方



未滿2歲

- 不建議3HP，只有9H為INH susceptible的建議處方

US CDC Latent Tuberculosis Infection: A Guide for Primary Health Care Providers
http://www.cdc.gov/tb/publications/ltbi

Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis* Infection
https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w

不適用3HP處方者

Ineligible Patients

孕婦 (或準備懷孕的婦女 **Pregnant and those expecting to become pregnant during treatment**	指標個案為INH或RMP抗藥 **Source case is INH or RMP resistant**	未滿2歲之兒童 **< 2 years of age**

正在使用coumadin, methadone, phenytoin等藥物者，須考慮藥物交互作用可能產生之影響。

歡迎成為短程處方LTBI治療合作醫師！

- **2016 年我們徵求願意一起使用3HP短程處方12劑的LTBI治療合作醫師**
  - 療效確定，不輸給 9H
  - 較高的完成率 84% vs. 69%
  - 較低的肝毒性 0.6% vs. 3%
- **在台灣應該會有同樣的結果**
  - 在4R vs. 6H 的收容人治療方案已經注意到
- **由公共衛生都治團隊 (DOPT) 100%與您一起照顧潛伏結核感染的病人！**

Chan PC, et al. Int J Tuberc Lung Dis. 2012;16(5):633-8.
Sterling TR, et al. N Engl J Med 2011;365:2155-66.
Clin Infect Dis. 2015;61(4):527-35.

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Case presentation of severe systemic drug reaction

- A 37-year-old female developed anaphylaxis **6 hours after receiving the fourth dose.**
- Signs and symptoms associated with this reaction included pruritic rash, blood pressure of 85/45 mmHg, dizziness, weakness, fatigue, nausea, subjective fever, flushing, muscle pain, and headache.
- The **event did not require hospitalization** and the patient **completely recovered within 48 hours.**

Clin Infect Dis. 2015;61(4):527-35.

Case presentations of thrombocytopenia, anemia, or leukopenia that were reported in relation to study drug

- Laboratory values at enrollment and during treatment of were evaluated, looking for values of hemoglobin < 10.0 g/dL, platelets < 100,000/mm^3, and white blood cell count (WBC) < 3x10^3/mm^3.
- Study participants **did not undergo routine** laboratory monitoring**, nor were lab values a study exclusion criterion**.
- Study investigators had the option of performing laboratory testing if the study participant **developed clinical evidence of anemia or thrombocytopenia.**

Clin Infect Dis. 2015;61(4):527-35.

Thrombocytopenia

- A 21 year old female developed a systemic drug reaction / serious adverse event (SAE) **after the third dose of 3HP.**
- platelet count of 8,000 /mm^3 The next day the platelet count was 191,000 / mm^3**, suggesting that the initial result may have been lab error.**
- **No manifestations of bleeding** were reported.
- She was HIV-seronegative and there was no history of hepatitis B, hepatitis C, alcohol abuse, or cirrhosis. The WBC was 1.99x10^3 /mm^3. She was receiving no concomitant medications. Clin Infect Dis. 2015;61(4):527-35.

Anemia

- a HIV-seronegative 39 year old was reported to develop a systemic drug reaction **after receiving four 3HP doses.**
- There was no report of jaundice or dark urine; the hemoglobin was 8.7 mg/dl.

Clin Infect Dis. 2015;61(4):527-35.

Leukopenia with fever

- a 21 year old developed a systemic drug reaction / serious adverse event (SAE) **after the third 3HP dose**.
- The event **started 4 hours after study drug ingestion.** Signs and symptoms included conjunctivitis, rash, pruritus, and facial erythema. Also fatigue, headache, fever (102.1°F), myalgias, arthralgias, flushing, chills, palpitations, and shortness of breath.
- She was found to **have elevated ALT/AST, thrombocytopenia, and a WBC of 1.3x10^3/mm^3**. She reported no concomitant medications.
- The event **resolved within 48 hours.**

Clin Infect Dis. 2015;61(4):527-35.

發燒

- 20歲女性, 抱怨服第二次3HP後自覺發燒
- 確實超過38°C, 但除了Flu-like illness之外並沒有嚴重不適感, 服退燒藥。
- 會診抽血沒有sepsis 的跡象，也沒有臨床其他感染的情況
- 再服藥依然微燒, 並不需要退燒藥, 自退
- 完成12 doses 3HP

MOHW103-CDC-C-114-112301

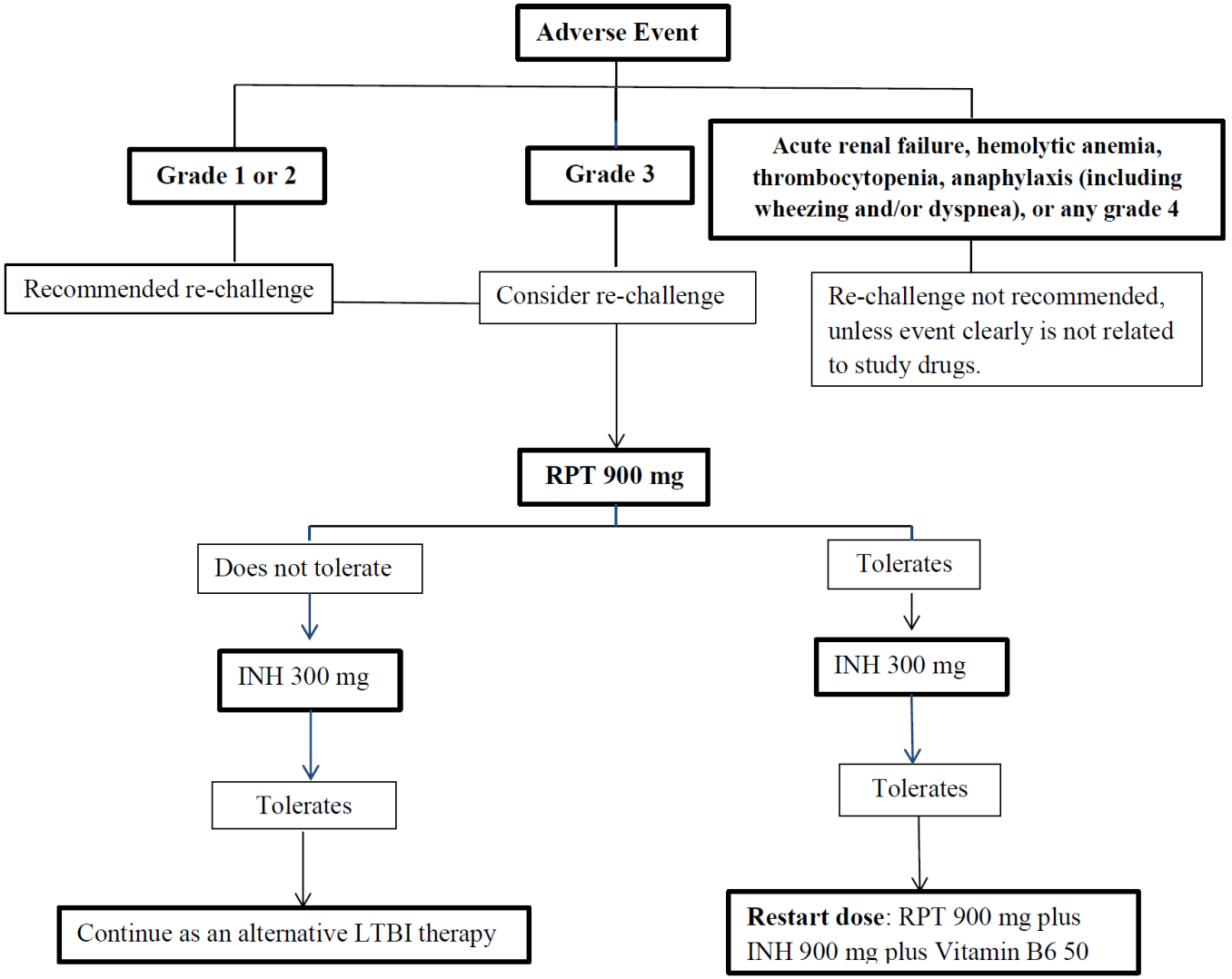
基礎值直接型黃疸

- 23歲男性，無特殊病史
- 個案肝功能正常，但基礎值黃疸異常(1.3mg/dL)
- 服藥中每月抽血並無肝功能異常，發現為直接型黃疸,臨床無黃疸症狀
- 無特殊用藥史
- 完成12 doses 3HP

MOHW103-CDC-C-114-112301

Flow chart for LTBI study regimen 3HP re-challenge

(re-challenge doses given at least 24 hours apart)



Modified by supp of Clin Infect Dis. 2015;61(4):527-35.

Guidelines for drug re-challenge

- Do not re-challenge if patient does not want to re-challenge
- Never re-challenge if grade 4 toxicity and no other likely cause of the toxicity
- Consider re-challenge if grade 3 toxicity
- Recommend re-challenge if grade 1-2 toxicity (though not mandated)
- For serious manifestations of presumed rifamycin-associated hypersensitivity reactions (acute renal failure, hemolytic anemia, thrombocytopenia, anaphylaxis—including wheezing and/or dyspnea), the patient should not be re-challenged with rifamycin.

Supp of Clin Infect Dis. 2015;61(4):527-35.

Modified Naranjo adverse drug reaction probability scale

	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?[a]	+1	0	0	0 (Do not know)
2. Did the adverse event appear ≤ **24 hours** after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve **or resolve** when the drug was discontinued?	+1	0	0	
4. Did the adverse reaction **re**appear when the **study** drug**(s)** was/**were** readministered **(as a re-challenge or as a full dose)**?[b]	**+2**	**-1**	**0**	+2, -1, or 0
5. Are there alternative causes (other than the drug), **such as concomitant drugs and other diseases**, that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo **(vitamin B6)** was given?[c]	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?[a]	+1	0	0	0 (Do not know)
8. Was the **adverse** reaction more severe **with a re-challenge or full dose**?[d]	**+1**	**0**	**0**	+1 or 0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?[a]	+1	0	0	0 (no)
10. Was the adverse event confirmed by any objective evidence?[e]	+1	0	0	
			Total Score	

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

Total Score	*ADR Probability Classification*
≥9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Supp of Clin Infect Dis. 2015;61(4):527-35.

Doses of Rifapentine mg/kg

Weight Range (kg)	Dose (mg)	Dose (mg/kg)
10.0-14.0	300	21.4 - 30.0
14.1-25.0	450	18.0 - 31.9
25.1-32.0	600	18.8 - 23.9
32.1-50.0	750	15.0 - 23.4
>50.0	900	≤18.0

The PREVENT TB Study (TBTC 26)

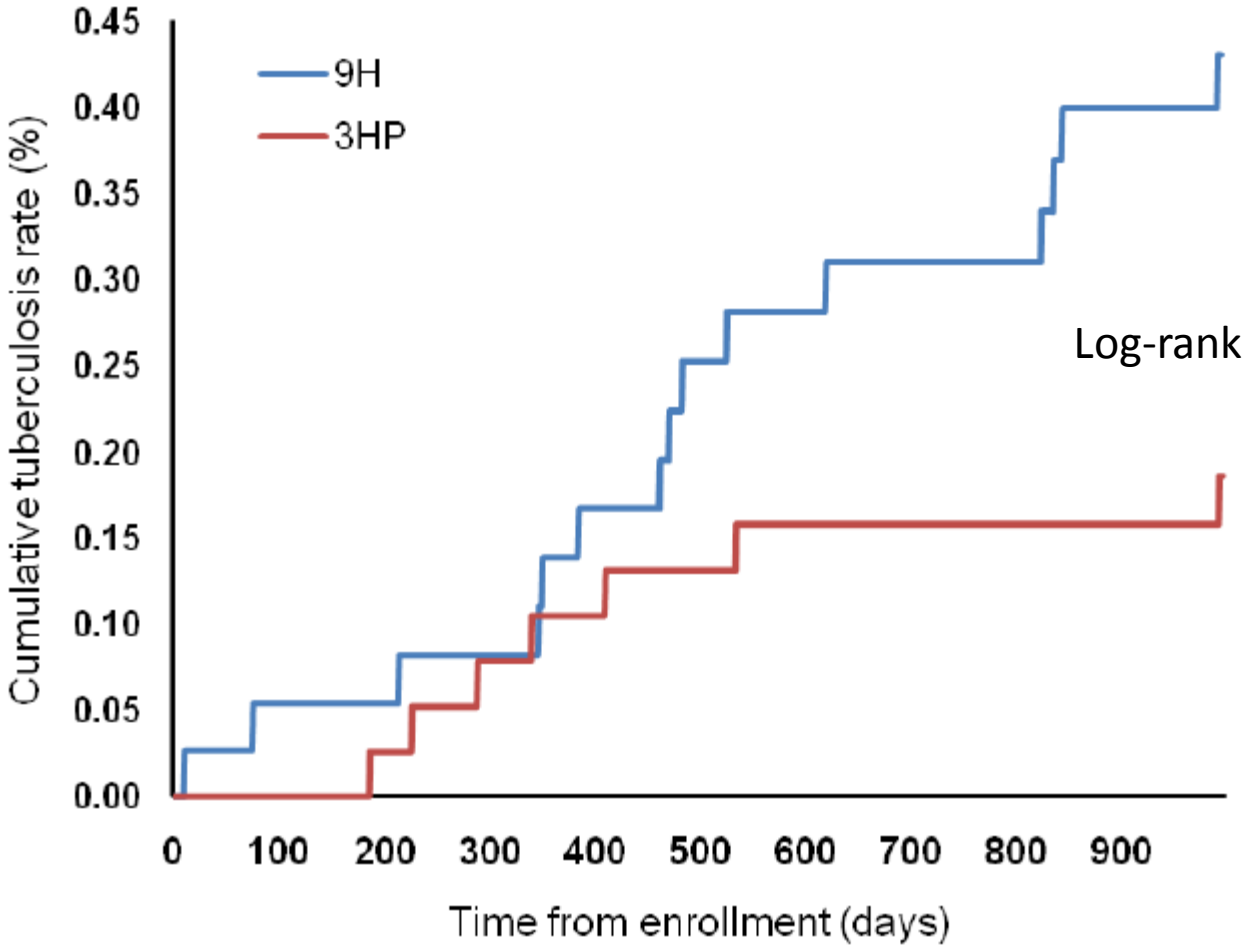
Summary

- 8,053 persons, ≧2 y/o, enrolled
  - United States, Canada, Brazil, Spain
  - June 2001-February 2008
  - 33 months of follow-up
  - Pre-defined non-inferiority margin: 0.75%
- 7,731 in modified intention-to-treat (MITT)
  - Enrolled in the study, and eligible
- Tuberculosis risk (cumulative)
  - 3HP: 7 / 3,986 (0.19%) -> DOPT
  - 9H: 15 / 3,745 (0.43%) -> self administration
  - Rate difference: -0.24%
  - Upper limit of 95% CI of difference: 0.01%

Sterling TR. N Engl J Med 2011;365:2155-66.

Cumulative Tuberculosis Event Rates

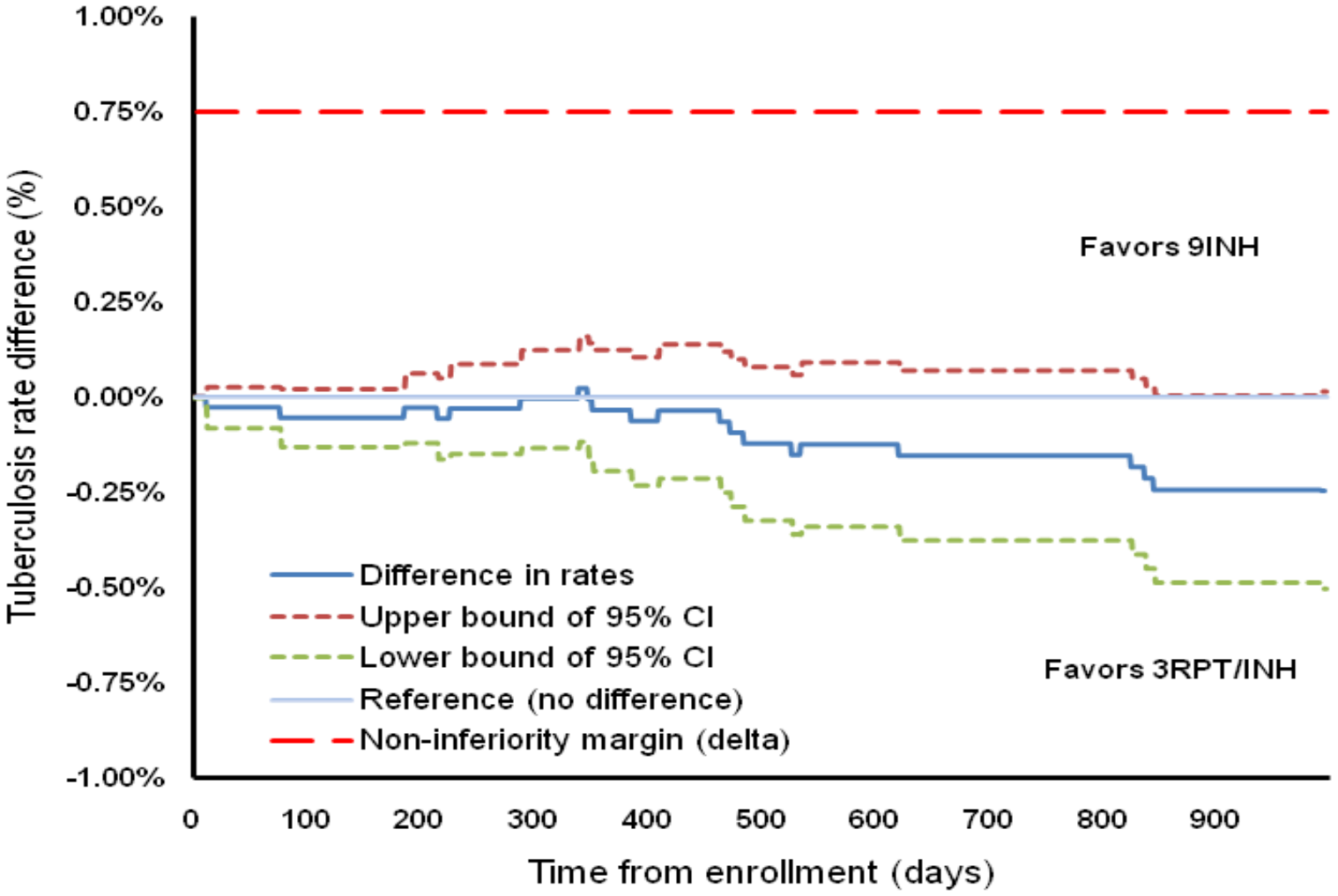
短程處方3HP累積結核發生率比傳統9H低, 統計無顯著差異



Log-rank P-value = 0.06

Difference in Rates of Tuberculosis MITT Analysis

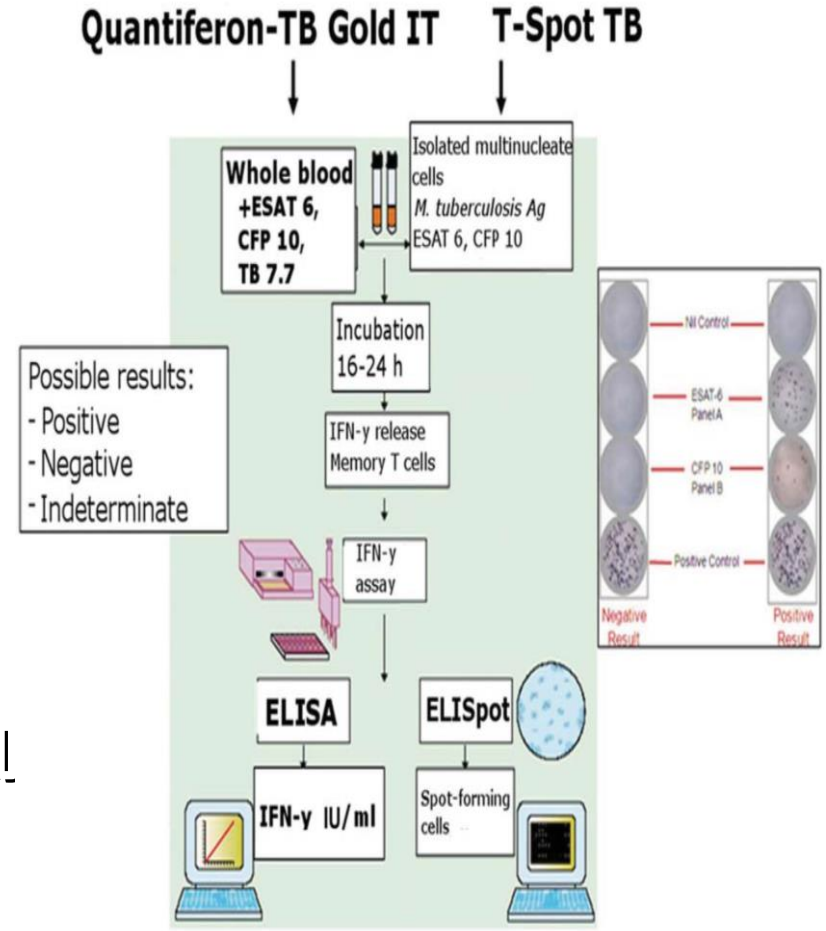
此項臨床試驗證實，短程處方3HP的療效是不輸給傳統9H的



Sterling TR. N Engl J Med 2011;365:2155-66.

Interferon-Gamma Release Assay (IGRA)

- 感染結核菌者，其T cell 與 *M. tuberculosis*之抗原反應會產生interferon-gamma
- 因此可以抽取病人血液中 T cell 與結核菌的特異性抗原（ESAT-6，CFP-10，TB7.7）於體外反應，觀察是否產生足夠的 interferon-gamma
- 減少了卡介苗的干擾提高特異性，且使用 T cell 體外測試的方式，病人不須再次就診以判讀結核菌素測驗結果
- 目前在台灣核准使用的有 QuantiFERON-TB 與 T-SPOT.TB



結果判讀

	QFT-GIT	T-SPOT
檢驗方法	Enzyme-linked immunosorbent assay	Enzyme-linked immunospot
結果		
不確定 (indeterminate)	mitogen < 0.5 IU/ml 或 Nil > 8.0	> 10 spots in Nil 或 < 20 (spot forming unit, SFU) mitogen
陽性	≥ 0.35 IU/ml且≥ 25% Nil 值*	>8 spots
陰性	< 0.35 IU/ml* ，或 ≥ 0.35 IU/ml且< 25% Nil值*	< 4 spots
臨界值		5, 6, or 7 spots

* TB抗原減Nil

不確定的ＱＦＴ結果，可能是採檢操作問題或與病人的免疫功能低下有關

1. 考慮重新採檢
2. 免疫低下則如同ＴＳＴ可能出現偽陰性。由臨床給予接觸者關於活動性結核病之衛教與後續追蹤