共病族群之潛伏結核感染治療

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Outlines

- LTBI treatment in HIV cases
- LTBI treatment in CKD
- LTBI treatment in biological agents receivers
- LTBI treatment in organ transplant

LTBI Treatment General Rule

- 完成治療才是有意義的治療
- Exclude active TB and review of current medications
  - anti-HIV, immunosuppressant, anti-coagulant, anti-convulsant, anti-fungal
  - Communicate with other physicians
- Evaluation of baseline liver/renal function
- Well-informed the possibilities of adverse reactions
- Prescribe prophylaxis medication if needed

Risk Factors for LTBI Reactivation

Risk factor	TB risk[a]	WHO's recommendation for screening and treatment for LTBI[41]	
		Country A[b]	Country B[c]
High-risk factors **High risk**			
HIV/AIDS	10–100	Required	Required
Close contacts	15	Required	Required for close contacts (<five years old)
Organ-transplantation recipients	20–70	Required	Not mentioned
Chronic renal failure requiring dialysis	6.9–52.5	Required	Not mentioned
TNF-alpha blockers	1.6–25.1	Required	Not mentioned
Silicosis	2.8	Required	Not mentioned
Moderate-risk factors **Moderate risk**			
Fibronodular disease on chest x-ray	6–19	Not mentioned	Not mentioned
Immigrants from high-TB-prevalence countries	2.9–5.3	Options to be considered	Not mentioned
Health-care workers	2.55	Options to be considered	Not mentioned
Prisoners, homeless persons, illicit drug users	–	Options to be considered	Not mentioned
Low-risk factors **Low risk**			
Diabetes mellitus	1.6–7.83	Not recommended	Not mentioned
Smoking	2–3.4	Not recommended	Not mentioned
Use of corticosteroids	2.8–7.7	Not recommended	Not mentioned
Underweight	2–3	Not recommended	Not mentioned

Ai JW, et al. Emer Micro Infec 2016

LTBI treatment in HIV cases

- 依世界衛生組織建議，愛滋病毒感染者不論 CD4 高低，有無使用抗愛滋病毒藥物治療，都應接受 LTBI 預防性治療
- Rifamycin類藥物 (Rifampin, Rifabutin, Rifapentine)與抗愛滋病毒藥物有明顯藥物交互作用
- 過往愛滋病毒感染者的 LTBI 治療選擇主要是 9H
- 目前使用的3HP處方雖然會與抗病毒藥物有交互作用，但研究顯示不影響抗病毒效果
- Tenofovir (TDF) /emtricitabine(FTC)/ efavirenz (EFV) (商 品 名 Atripla)即將停產

Antiretroviral agent	Rifampin	Rifabutin	Rifapentine
Non-nucleoside reverse transcription inhibitors （NNRTIs）			
Efavirenz (EFV) **EFV**	EFV 濃度↓26%，可維持正常劑量。Rifampi是使用 EFV 時首選的抗結核藥物。	Rifabutin ↓ 38%，併用會降低 rifabutin 濃度，建議 rifabutin 劑量為 450 mg QD。	EFV 600 mg 可維持正常劑量。
Etravirine (ETR)	可能大幅降低 ETR 濃度，不建議和 rifampin 併用。	ETR AUC↓37%，rifabutin 和 rifabutin 代謝物 AUC↓17%，可維持 rifabutin 劑量 300mg QD。若 ETR 合併使用 darunavir/ritonavir，不應選用 rifabutin 治療結核病。	可能大幅降低 ETR 濃度，不建議同時使用。
Rilpivirine (RPV)	RPV 濃度↓80% & AUC↓80%，兩者不能併用。	RPV 濃度↓31% & AUC↓42%，RPV 劑量應由 25 mg QD 調整至 50mg QD。	RPV 濃度↓，兩者不能併用。
Doravirine (DOR)	DOR AUC↓88%，兩者不能併用。	DOR AUC↓50%，建議 DOR 由 100 mg QD 增加劑量到 100 mg 每日兩次使用。Rifabutin 不需改變劑量	DOR 濃度↓，兩者不能併用。
Protease inhibitors （PIs）			
Atazanavir (ATV)	PI 濃度↓大約 75%；所有蛋白酶抑制劑都不建議和 rifampin 併用。	ATV 濃度沒有影響，但是會增加 rifabutin 濃度。建議 rifabutin 劑量由原來 300mg QD 減為 150 mg QD。	Rifapentine 對於 CYP3A4 induction 的效果雖然比 rifampin 差，但比 rifabutin 強。同時使用預計會下降 ATV 濃度，因此不建議。
Lopinavir/ritonavir （LPV/r）	PI 濃度↓大約 75%；所有蛋白酶抑制劑都不建議和 rifampin 併用。	併 LPV/r，和單用 rifabutin 300 mg 相比，rifabutinAUC↑473%。因此，rifabutin 劑量為 150 mg QD。	Rifapentine 對於 CYP3A4 induction 的效果雖然比 rifampin 差，但比 rifabutin 強。同時使用預計會下降 LPV/r 濃度，因此不建議。
Darunavir/cobicistat （DRV/c）	PI 濃度↓大約 75%；所有蛋白酶抑制劑都不建議和 rifampin 併用。	Rifabutin 濃度增加，DRV/c 濃度下降，不建議同時使用。	Rifapentine 對於 CYP3A4 induction 的效果雖然比 rifampin 差，但比 rifabutin 強。同時使用預計會下降 DRV/c 濃度，因此不建議。

HIV+TB共病—評估Atripla可替代藥品

對象	TB		LTBI	
藥品	Rifampin	Rifabutin	Rifapentine	Rifampin
替代方案	DTG/3TC+1#DTG ABC/3TC/DTG+1#DTG TDF/FTC+DTG(1#bid) TDF/FTC+RAL(2#bid)	**ABC/3TC/DTG** **DTG/3TC** TDF/FTC+DTG TDF/FTC+RAL	3HP-**ABC/3TC/DTG** 1HP-**TAF/FTC/BIC** (不會超過審查界限)	3HR或4R DTG/3TC+1#DTG ABC/3TC/DTG+1#DTG TDF/FTC+DTG(1#bid) TDF/FTC+RAL(2#bid)

台灣結核病診治指引 第七版

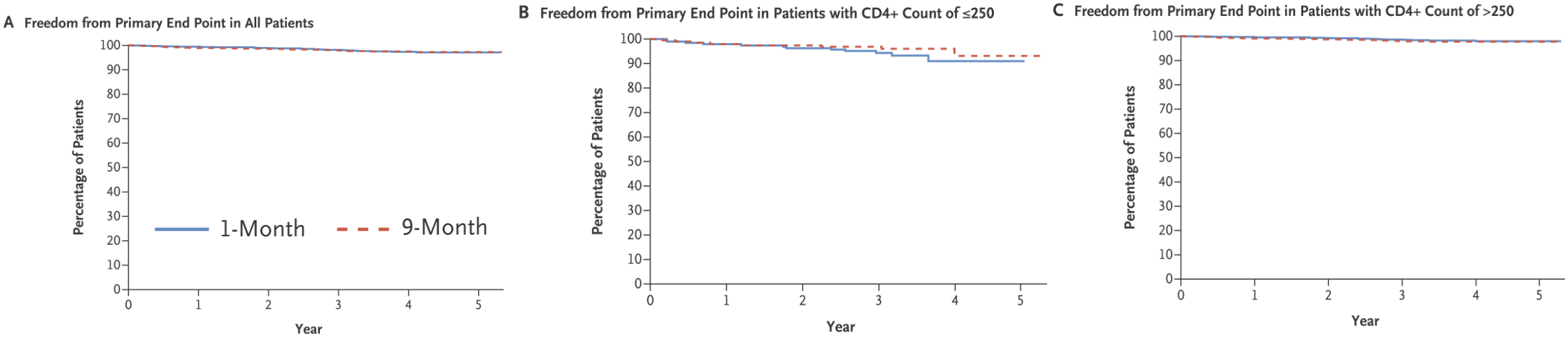
One Month of Rifapentine plus Isoniazid (1HP) to Prevent HIV-Related Tuberculosis

3000 HIV(+) patients

1M Daily rifapentine/INH (1HP) vs. Isoniazid (9M)

Daily max. dose: Rifapentine 600mg; INH 300mg

1st endpoint: diagnosis of ATB or death



Completion rate: 1HP: 97%, 9H: 90%

≥ Gr 3 ADR: 1HP 17% vs. 9H: 18%

No difference in ATB prevention

Seindells S, et al. NEJM 2019

How does CKD and the diagnosis of tuberculosis (TB) interact?

CJASN
Clinical Journal of American Society of Nephrology

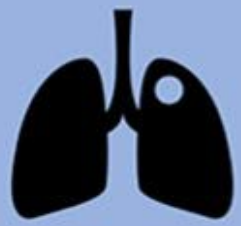
Methods and Cohort

17,000,000 Koreans with two health screens between 2012 and 2016

CKD assessed by albuminuria and GFR

No CKD: 408,873

3 years



122 per 100,000 patient years

1.0 Hazard ratio reference

matched for age, sex, low-income status, smoking history

New diagnosis of active TB

CKD: 408,873

eGFR<60, predialysis

3 years

138 per 100,000 patient years

1.2 Hazard ratio

adjusted	CKD 1	CKD 2	CKD 3	CKD 4,5
HR	1.8	1.2	NS	1.9

Conclusions Pre-dialysis CKD patients had an elevated risk of active-TB. Profoundly reduced eGFR or, conversely, stage 1 CKD with high eGFR were associated with higher risk of incident TB.

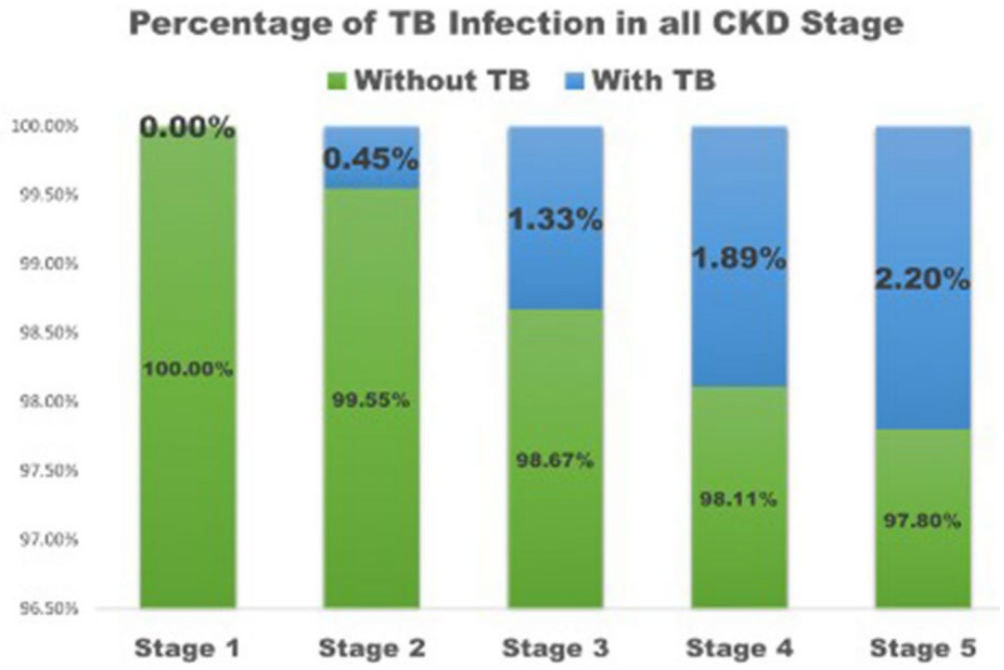
Sehoon Park, Soojin Lee, Yaerim Kim, Yeonhee Lee, et al. ***Association of CKD with Incident Tuberculosis.*** CJASN doi: 10.2215/14471218. **Visual Abstract by Joel Topf, MD, FACP**

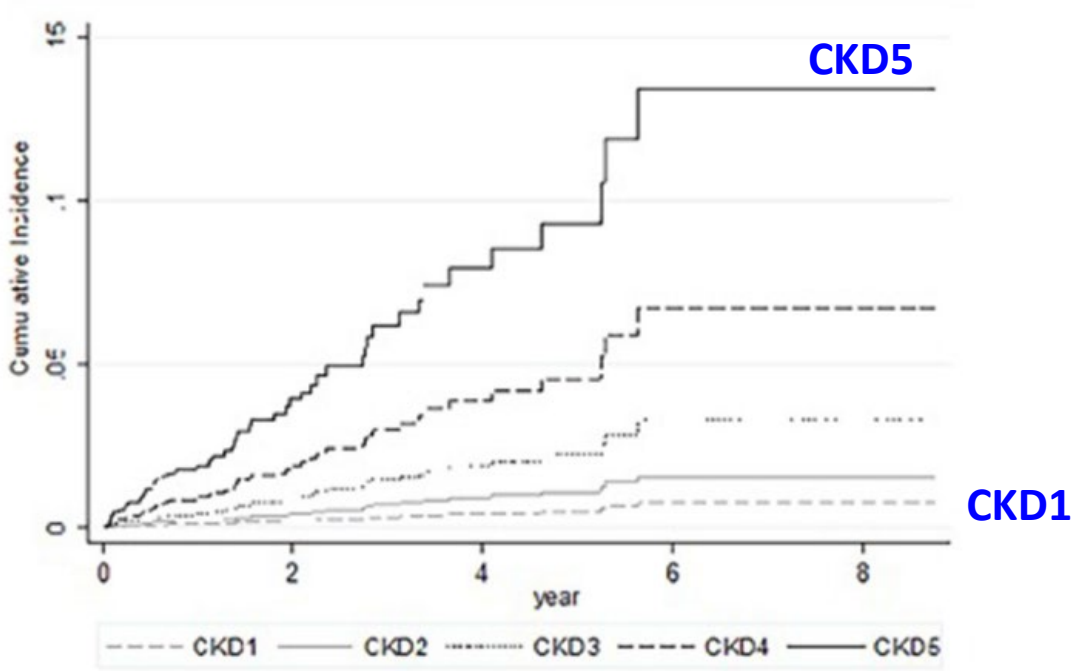
Park S, et al. CJASN 2019

The Risk of Tuberculosis Infection in Non-dialysis Chronic Kidney Disease Patients

7221 Non-HD CKD cases from single center, 2003 to 2014

Median follow up 1.4 years





aSHR 1.22 for ↓ 5ml/min/1.73m2 in eGFR

Li CH, et al. Front Med 2021

LTBI screening in CKD with HD

Society	Year	CKD	Dialysis
American Thoracic Society[37]	2000	—	TST for immune compromised. No specific recommendations for dialysis
American Transplant Society (donor)[38]	2012	—	—
American Transplant Society (recipient)[39]	2011	—	—
British Thoracic Society[29]	2010	CKD patients should receive a TB risk assessment and if appropriate an IGRA	All dialysis patients should receive a TB risk assessment and, if appropriate, an IGRA
Canadian Thoracic Society[40]	2014	—	TST or IGRA recommended for immune compromised. No specific recommendations for dialysis
Canadian Transplant Society[41]	2005	—	—
European Centre for Disease Prevention and Control[42]	2011	—	IGRA with concurrent TST for immune compromised. No specific recommendations for dialysis patients
National Institute for Health and Clinical Excellence[43]	2011	—	IGRA or IGRA and concurrent TST for immune compromised. No specific recommendations for dialysis
World Health Organization[36]	2015	—	Screen all dialysis patients with TST or IGRA
Taiwan CDC	**2022**	**--**	**Candidate of LTBI treatment**

* 縣市衛生局合作醫院可事前申請配合都治使用**短程處方**

Romanowski K, et al. Kidney Inter. 2016
台灣結核病診治指引 第七版

Safety and treatment completion of latent tuberculosis infection treatment in the elderly population

Feng JY, IJID 2020

Table 4

Multivariate analysis of clinical factors associated with SARs in older and younger LTBI patients.[a]

	Overall patients, N = 406		≥60 years old, n = 167		<60 years old, n = 239	
	aOR (95% CI)	p-Value	aOR (95% CI)	p-Value	aOR (95% CI)	p-Value
LTBI regimens						
9H	1.00	–	1.00	–	1.00	–
3HP	2.90 (1.14–7.40)	0.026	4.00 (0.73–22.04)	0.111	2.63 (0.79–8.80)	0.116
4R	0.94 (0.10–9.15)	0.957	–	–	1.35 (0.11–16.69)	0.818
Age (years)						
<35	1.00	–	–	–	1.00	–
35–59	3.46 (1.13–10.55)	0.029	–	–	3.58 (1.16–11.08)	0.027
60–79	3.05 (0.95–9.74)	0.060	1.00	–	–	–
≥80	3.75 (0.98–14.40)	0.054	1.18 (0.44–3.12)	0.747	–	–
Female	1.64 (0.92–2.93)	0.095	1.61 (0.68–3.79)	0.281	1.69 (0.74–3.87)	0.217
BMI < 23 kg/m^2	2.23 (1.26–3.96)	0.006	1.83 (0.77–4.32)	0.169	2.52 (1.13–5.62)	0.024
ESRD	3.96 (1.83–8.53)	<0.001	2.94 (1.06–8.16)	0.038	5.09 (1.54–16.90)	0.008
Immunosuppressant	0.76 (0.27–2.15)	0.603	0.74 (0.13–4.16)	0.729	0.72 (0.19–2.73)	0.626

Completion and Adverse Drug Events of Latent Tuberculosis Infection Treatment in Patients Receiving Dialysis

91 LTBI cases with HD from 4 centers in Taiwan

41 with 9H and 50 with 3HP

Variable	Value for group[a] 9H (*n* = 41)	3HP (*n* = 50)	*P* value[b]
ADE, no. (%)[d]	9H (*n* = 37)	3HP (*n* = 48)	
Hypersensitivity	4 (10.8)	14 (29.2)	0.040
Flu-like syndrome	3 (8.1)	7 (14.6)	0.502
Gastrointestinal symptoms	6 (16.2)	14 (29.2)	0.163
Reported maximal grade of ADE[d]	9H (*n* = 37)	3HP (*n* = 48)	0.001
Grade 1	12 (32.4)	17 (35.4)	
Grade 2	2 (5.4)	16 (33.3)	
Grade 3	3 (8.1)	5 (10.4)	
Grade 4	0	1 (2.1)	
Grade 2 or more	5 (13.5)	22 (45.8)	0.002

Outcome and variable	Adjusted OR	95% CI	*P* value
≥Grade 2 ADE			
3HP (vs 9H)	9.77	2.55–37.49	0.001
Age over 60			
Male			
Active smoking			
Diabetes mellitus	7.73	2.06–29.06	0.002
Peritoneal dialysis	7.21	1.45–35.98	0.016
Eosinophil count[b]			
<349/μl	Reference		
350–699/μl	1.54	0.20–11.69	0.675
≥700/μl	11.00	1.48–83.53	0.019

Completion rate: 9H 61%, 3HP 82%

Lin SY, Feng JY, et al. AAC 2021

Biological Agents and Tuberculosis

	Biologic	FDA-approved indications (as of 1 November 2016)[a]	RR of TB compared to that in the general population
Humira	Adalimumab	AS, JIA, RA, Ps, PsA, Crohn's, UC	29.3 (95% CI, 20.3–42.4) (3) based on SIR (standardized for age and sex)
Remicade	Infliximab	AS, RA, Ps, PsA, Crohn's, UC	18.6 (95% CI, 13.4–25.8) (3) based on SIR (standardized for age and sex)
Enbrel	Etanercept	AS, JIA, RA, Ps, PsA	1.8 (95% CI, 0.7–4.3) (3) based on SIR (standardized for age and sex) 3.5
Cimzia	Certolizumab pegol	AS, RA, PsA, Crohn's	No definite increase in RR in pooled data from RCTs (4)
Simponi	Golimumab	AS, RA, PsA, UC	No definite increase in RR in pooled data from RCTs (5)
Anti-CD20	Rituximab	Chronic lymphocytic leukemia, non-Hodgkin lymphomas, granulomatosis with polyangiitis, microscopic polyangiitis, RA	No definite increase in RR in pooled data from RCTs (6)
Anti-IL6	Tocilizumab	JIA, RA	No definite increase in RR in pooled data from RCTs (7)
	Vedolizumab	UC, Crohn's	No definite increase in RR from drug safety data (8)
Anti-IL12/23	Ustekinumab	Ps, PsA, Crohn's	No definite increase in RR from drug safety data (9) First choice in patients with PsA at high infection and TB risk (10)
	Abatacept	JIA, RA	No definite increase in RR in pooled data from RCTs (6)

Anti-TNF-a

anti-JAKs, anti-IL17: no documented risk for TB

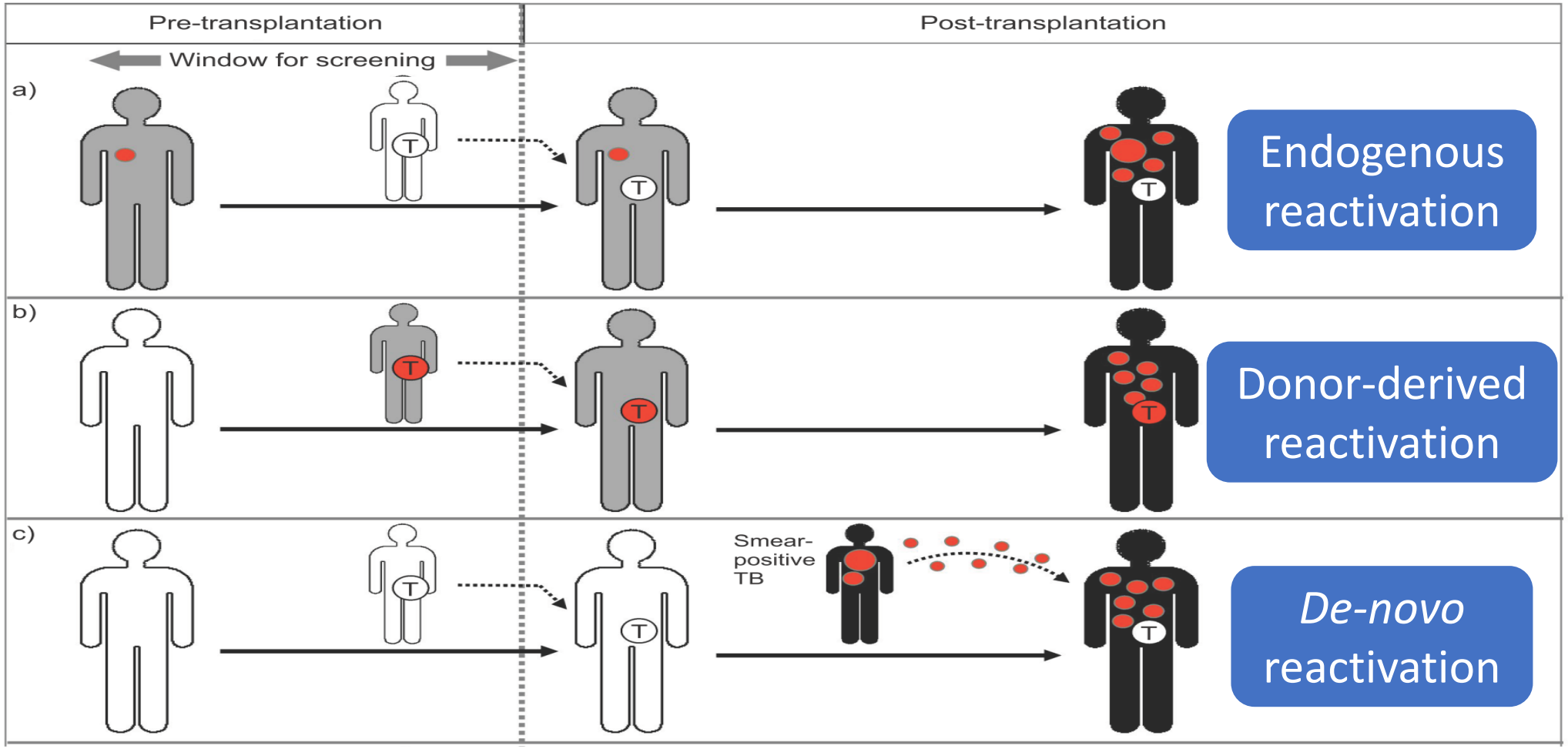
Dobler C, et al. Micro Spec 2016

When to Start Biologic Agents

Agency and/or country or region, year	LTBI treatment regimen (duration in months, medication)	Anti-TNF-α starting delay	Repeat testing
Centers for Disease Control and Prevention, United States, 2004 and 2010 (update) (54, 55)	9H	No definite recommendation, completion of LTBI treatment before anti-TNF-α therapy, if possible	Only in individuals at increased risk for TB infection
American College of Rheumatology, United States (56)	Not specified	1 mo	Annually in individuals with risk factor for future or ongoing TB exposure
Canada, 2013 (57)	9H	No recommendation	Only in individuals at increased risk for TB infection
British Thoracic Society, United Kingdom, 2005 (58)	6H 3RH	≥2 mo Delay until completed LTBI treatment if abnormal chest X ray, history of TB	Not specified
France, 2003 (59, 60)	2RZ 3RH 9H	≥3 wks	Not specified
Switzerland, 2007 (61)	9H 4R	1 mo	Not specified
TBNET International consensus, Europe (23)	9–12H 3RH	4 wks	Not specified
Taiwan CDC, 2022	**3HP*/3HR*/9H/4R***	**4 wks**	

* 限縣市衛生局合作醫院或事前申請加入衛生局專案計畫可配合都治使用**短程處方** Dobler C, et al. Micro Spec 2016

TB Infection/Reactivation in Transplant Settings



Both donor and recipient should be screened and treated

Bumbacea D et al. Eur Respir J **2012**; 40: 990-1013

Incidence and Risk Factors for Tuberculosis After Liver Transplantation in an Endemic Area: A Nationwide Population-Based Matched Cohort Study

3202 liver transplant cases in NHIRD, 2001~2011

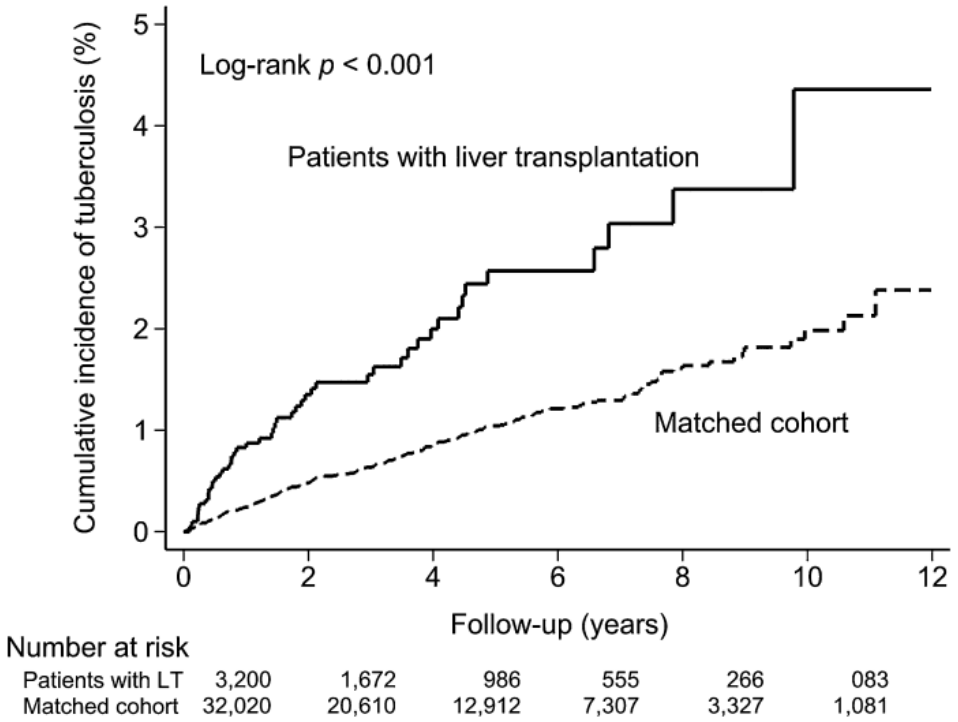


Table 2: Incidence of tuberculosis (TB) in patients with liver transplantation

	Patients with liver transplantation	Matched cohort		
	Per 10 000 person-years	Per 10 000 person-years	Adjusted[1] HR (95% CI)	p-value
Total	50.0	21.0	2.25 (1.65–3.05)	<0.001
Age				
≥50	69.9	25.2	2.64 (1.87–3.72)	<0.001
<50	22.1	15.0	1.34 (0.67–2.68)	0.412
Sex				
Male	53.3	25.4	1.97 (1.40–2.77)	<0.001
Female	40.5	8.1	4.83 (2.31–10.10)	<0.001

aHR for ATB: **2.25X**

aOR for mortality: **2.27X**

Chen CY, et al. American Journal of Transplantation 2015

Tuberculosis after Solid-Organ Transplant: Incidence, Risk Factors, and Clinical Characteristics in the RESITRA (Spanish Network of Infection in Transplantation) Cohort

Table 3. Frequency and incidence of tuberculosis (TB) in the RESITRA (Spanish Network of Infection in Transplantation) cohort.

Transplant type	Recipients with TB, proportion (%)	Incidence[a] (95% CI)	RR (95% CI)
Heart	1/404 (0.25)	255 (6.5–1421)	13.7 (1.9–97.3)
Kidney	7/2052 (0.34)	358 (144–728)	19.0 (9.0–39.7)
Liver	8/1507 (0.53)	541 (269–1065)	29.5 (14.8–58.9)
Kidney-pancreas	1/122 (0.82)	1204 (30.5–6710)	45.5 (6.5–320.4)
Lung	4/303 (1.32)	2072 (565–5306)	73.3 (27.7–194.1)
All	21/4388 (0.48)	512 (317–783)	26.6 (17.4–40.8)

Torre-Cisneros, et al. CID 2009:48

Prevention and management of tuberculosis in solid organ transplantation: a consensus statement of the Transplantation Society of Taiwan

Prevention of donor-derived tuberculosis

- Donors should be evaluated for active TB disease and LTBI.
- Organs from living or deceased donors with active TB disease should not be used due to a high risk of disseminated disease in the recipients.
- Treatment for LTBI prior to organ donation may be considered in living donors with LTBI, especially in recent IGRA converters or donors of the lung.
- A donor with untreated LTBI is not a contraindication for organ donation. Recipients who received organs from donors with untreated LTBI may benefit from treatment for LTBI post transplantation.

Diagnosis of LTBI in candidates and recipients

- Screening for LTBI is suggested when the transplant candidate is under preparation for solid organ transplantation.
- For a candidate with a negative IGRA result who has been waiting for transplant for a prolonged period of time, repeat screening for LTBI is recommended if the candidate has close contact with individuals with active TB.
- If testing for LTBI is not done at transplantation, testing for LTBI at **12** months after transplantation is suggested.
- If recipients had negative results of IGRA before transplantation, repeat testing for LTBI at **12** months after transplantation may be considered.

台灣移植醫學學會
Transplantation Society of Taiwan

台灣結核暨肺部疾病醫學會

Chiang CY, et al. Unpublished

Prevention and management of tuberculosis in solid organ transplantation: a consensus statement of the Transplantation Society of Taiwan

LTBI treatment in solid organ transplant candidates and recipients

- Transplant candidates with documented LTBI should be treated for LTBI before organ transplant if clinically feasible.
- If candidates cannot tolerate treatment for LTBI prior to transplantation, treatment should be initiated as soon as possible following transplantation.
- If treatment of LTBI cannot be completed before transplantation, it should be reinitiated as soon as the patient is clinically stable after transplantation. Reassessment of active TB is required before LTBI treatment is re-initiated after interruption.
- Recommended regimens for LTBI for candidates before transplant include 3HP, 3HR, 4R, and 9H. Due to drug-drug interaction, rifampin/rifapentine need to be used with caution in recipients under immunosuppressive therapy.

台灣移植醫學學會
Transplantation Society of Taiwan

台灣結核暨肺部疾病醫學會

Chiang CY, et al. Unpublished

正　本

檔　　號：
保存年限：

衛生福利部疾病管制署　函

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受文者：台灣結核暨肺部疾病醫學會

發文日期：中華民國111年11月30日
發文字號：疾管慢字第1110300817號
速別：普通件
密等及解密條件或保密期限：
附件：

主旨：有關潛伏結核感染(LTBI)之丙型干擾素釋放試驗（Interferon-gamma release assay，IGRA）檢驗結果為不確定性（indeterminate）處理方式，詳如說明，請轉知會員或LTBI合作院所配合辦理，請查照。

說明：

一、旨揭IGRA檢驗結果為不確定性（indeterminate）有二種情況，處理方式分別說明如下：

(一)Nil值>8(不論TB抗原及mitogen值高低)通常為人為操作不當(例如微量盤清洗不完全、試管(劑)保存不當、培養時間及溫度等問題)，建議重新抽血檢驗。

(二)Nil值≤8且mitogen-nil<0.5，可能是個人免疫力不佳，淋巴球不足導致無法產生足夠的IFN-γ，考量接觸者發病風險高，建議LTBI合作醫師排除結核病發病後，提供LTBI治療，以避免接觸者發病，如有疑義可以重新採檢。

Mitogen <0.5 之免疫不全族群合併不確定性IGRA，建議提供LTBI治療

二、分析國內近年IGRA檢驗結果不確定性（indeterminate）比率<2%，倘有出現不確定性比率偏高情形或團體檢驗出現異常情事，除向採檢及檢驗單位釐清處理，並請通知衛生單位，以提升LTBI診斷品質。

三、另，結核病接觸者除5歲以下幼童LTBI檢驗應於指標個案確診後馬上執行，以辦理預防性治療(window prophylaxis)，5歲(含)以上接觸者應於與指標個案終止有效暴露滿8週後辦理，以避免偽陰性結果；另LTBI檢驗結果陽性者應於排除結核病發病後，儘速開始LTBI治療，考慮到治療期程越短，越有利於完成治療，請優先使用短程處方，避免發病。

四、相關資訊可至本署網站(https://www.cdc.gov.tw/)傳染病與防疫專題/傳染病介紹 /第三類法定傳染病/結核病/Q&A/「接觸者檢查及潛伏結核感染評估與治療」項下查閱。

PS: 可能實驗室/抽血檢驗問題，或無共病/接觸史之健康者可重新採檢

The Take Away…

- Population with high risk for TB reactivation
  - HIV/AIDS, organ transplant, ESRD with dialysis, TNF-a blocker user
- Despite possibilities of DDI, 3HP is still recommended in HIV/AIDS with LTBI
- Dialysis patients are candidate for LTBI screen and treatment
  - High risk of adverse reaction: hypersensitivity and GI upset
- TNF-a blocker is the only biologic agent with documented risk of TB reactivation
  - In cases with LTBI, TNF-a blocker should be started after at least 1M of LTBI treatment
- Both donor and recipient of organ transplant should be screened and treated for LTBI
  - Treatment before transplantation if feasible
- 立場堅定、耐心溝通、保持彈性、完成治療

LTBI screen in organ transplants- AST 2019

Summary Recommendations

- All transplant candidates should undergo screening for TB with careful epidemiologic history, exam, TST or IGRA testing, and CXR or Chest CT (strong, moderate).
- Transplant candidates with positive TST or IGRA should be considered for latent TB therapy once active TB is ruled out (strong, moderate).
- IGRA may have advantages over TST in transplant, especially in those who received prior BCG vaccine, or have end-stage renal disease or advanced liver disease (strong, low).
- Those with high epidemiologic risk (including close or prolonged contact with a case of active TB) and/or chest radiographic evidence of prior TB without adequate treatment should be considered for latent TB therapy even with an indeterminate or negative TST or IGRA test (strong, low).
- Those who have received an organ from a donor who is TST-positive, had recent exposure to active TB, or had radiographic evidence of untreated TB should be considered for latent TB therapy (strong, low)
- All living donors should undergo screening for TB and should be evaluated for a need for therapy (strong, low).
- Active TB in the donor is a contraindication to organ donation, and active TB in a transplant candidate needs to be treated prior to transplant (strong, moderate).

Subramanan AK, et al. Clinical Transplantation 2019