HIV-TB合併感染病人的抗結核藥物治療

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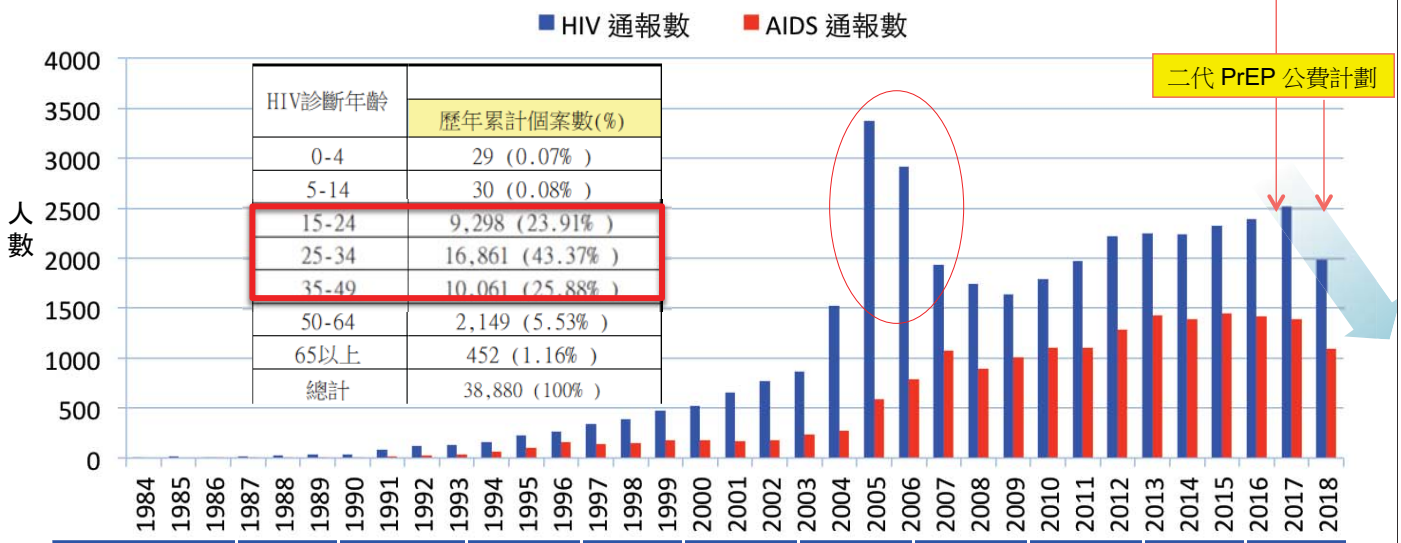
HIV infection vs TB

特徵	愛滋病毒感染	結核病
台灣每年新診斷數	1992 (2018)	7092 (2017)
主要傳染途徑	性行為、共用針器	呼吸道飛沫
感染發病者組成	年輕、男性	年長、免疫系統缺損
社會和醫療環境的汙名與歧視	很高	高
懷疑引發檢測的閾值	高	低
篩檢工具的敏感度特異性	非常高 (Combo)	不高 (TST, IGRA)
確認診斷工具的敏感度	非常高 (viral load)	高?
藥物治療原則	三合一	四合一後二合一
可以合併的治療藥物種類	多	有限
台灣現有每日單顆藥物	四種可以選擇	?
督治或都治計畫	無	有
治療時間	終身	六到十二個月
治癒率	0%	很高
影響平均存活餘命	延遲診斷影響存活	延遲診斷影響存活
藥物預防	預防感染 (PrEP, PEP)	預防發病(IPT)

積極治療與推展**PrEP**逐漸發揮防疫效果
近 10 年 台灣HIV 通報人數首次「負成長」

“全面治療、用藥升級”政策
加強篩檢、居家篩檢
PrEP 公費前驅計劃

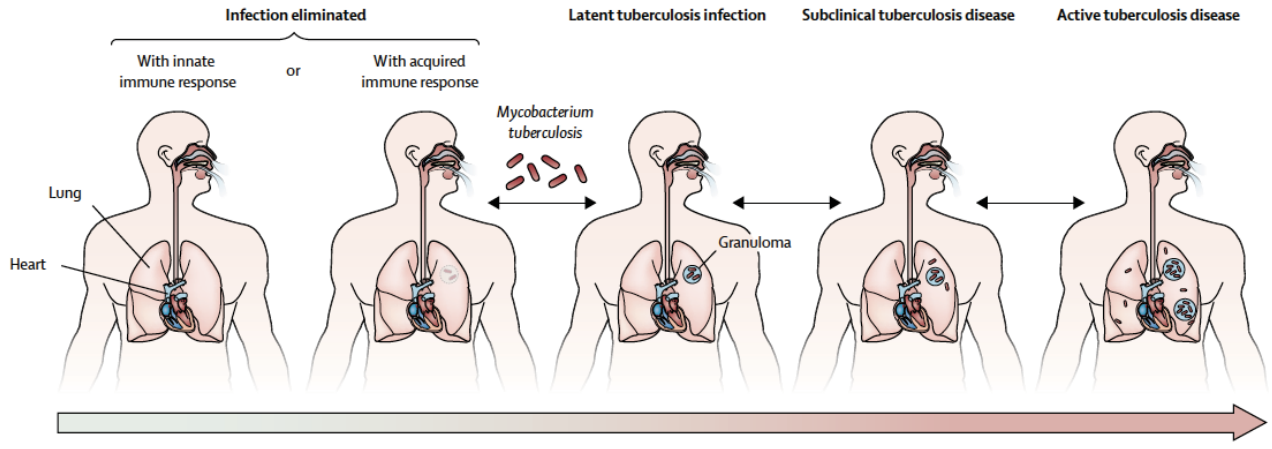
二代 PrEP 公費計劃



HIV診斷年齡	歷年累計個案數(%)
0-4	29 (0.07%)
5-14	30 (0.08%)
15-24	9,298 (23.91%)
25-34	16,861 (43.37%)
35-49	10,061 (25.88%)
50-64	2,149 (5.53%)
65以上	452 (1.16%)
總計	38,880 (100%)

診斷年份	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
HIV 通報數	1641	1793	1968	2220	2243	2234	2326	2394	2512	1993
AIDS 通報數	1009	1104	1100	1289	1431	1387	1443	1413	1390	1091

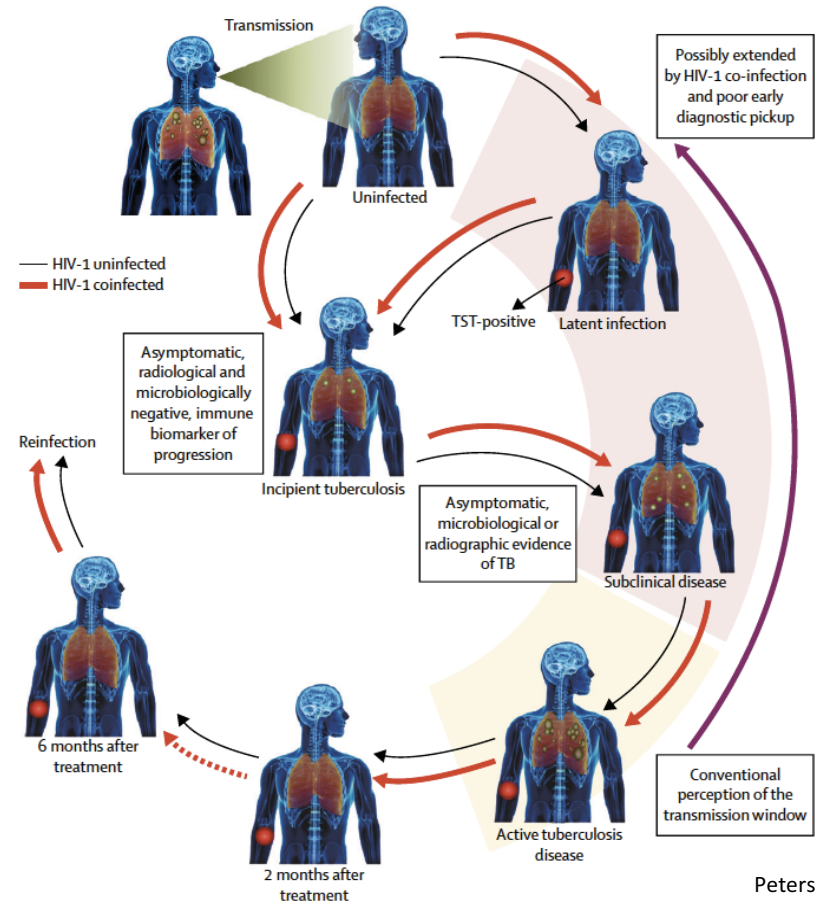
Spectrum of tuberculosis infection and disease



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

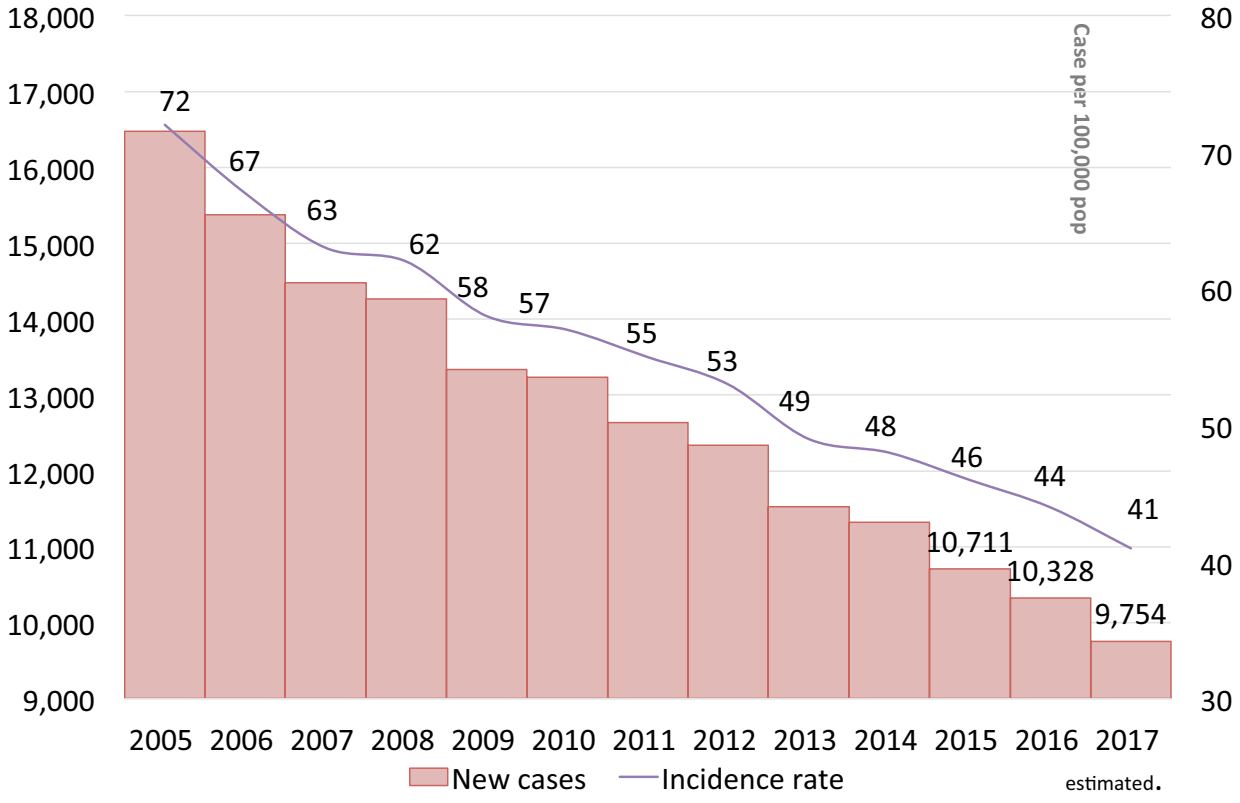
Furin J et al. Lancet 2019;393:1642-56.

Effects of HIV-1 infection on the progression of tuberculosis and the transmission window



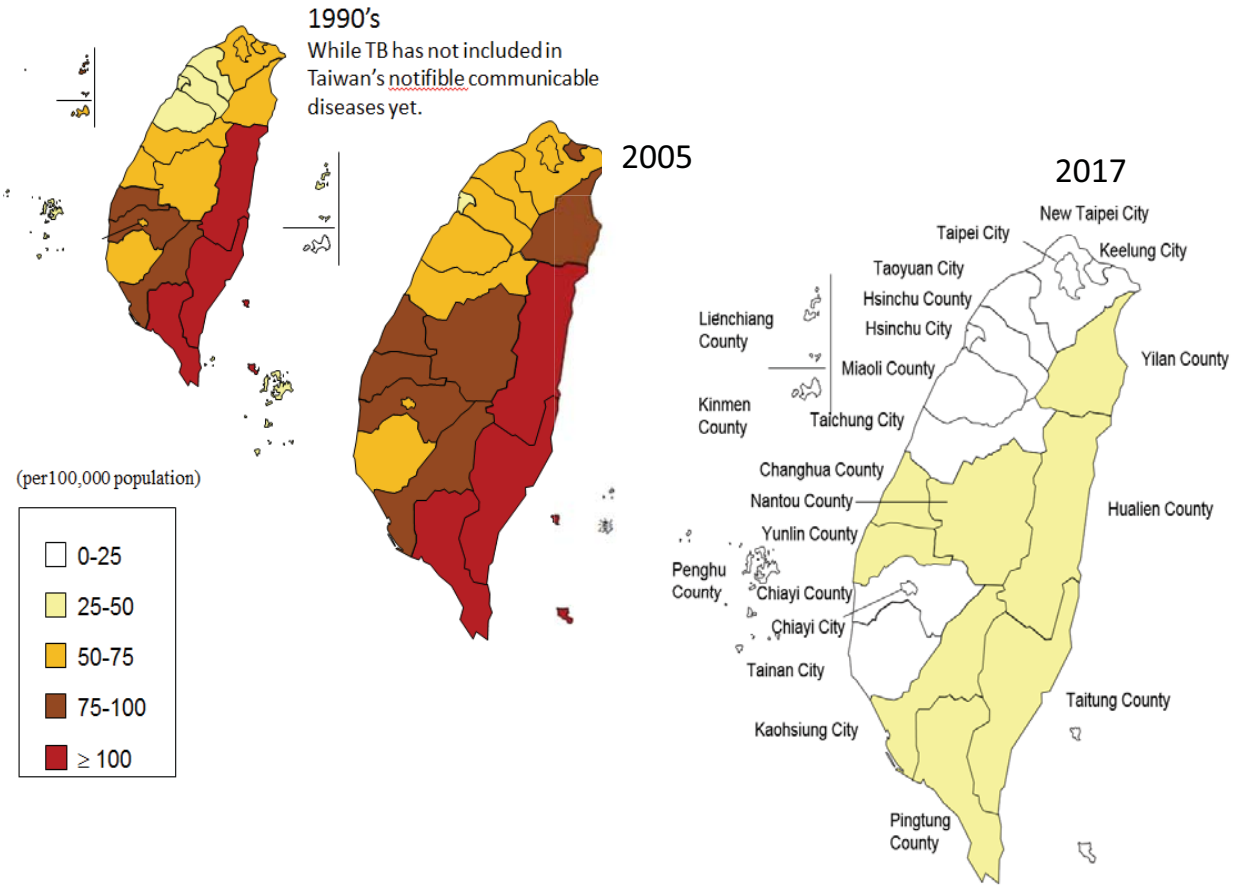
Peters JS, et al. Lancet Infect Dis 2019

TB incidence in Taiwan

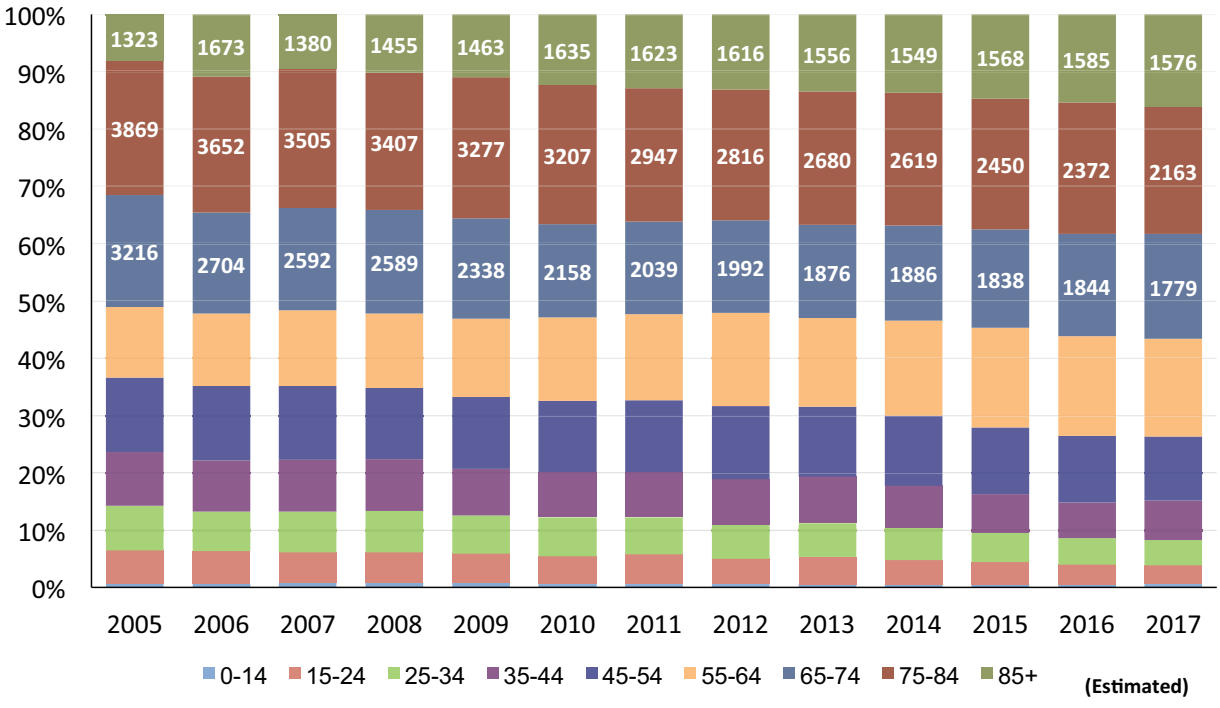


Courtesy of Dr. Chan PC, Taiwan CDC

TB incidence rate by county, 1990-2017



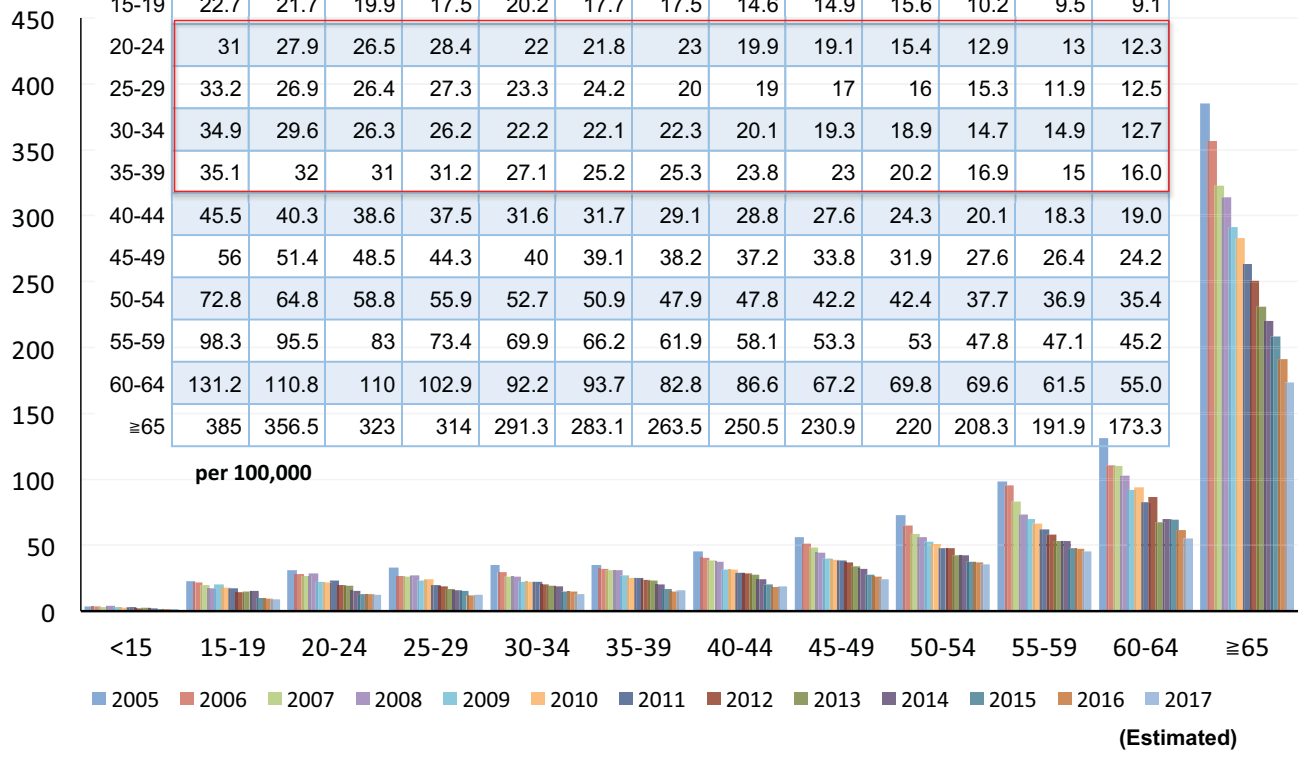
TB cases by age in Taiwan, 2005-2017



More than 50% of all TB cases were 65 years and older

Age-specific TB incidence 2005-2017

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
<15	3.5	3.5	3.3	4	3.2	2.6	3.3	2.2	2.7	2.2	1.5	1.6	1.7
15-19	22.7	21.7	19.9	17.5	20.2	17.7	17.5	14.6	14.9	15.6	10.2	9.5	9.1
20-24	31	27.9	26.5	28.4	22	21.8	23	19.9	19.1	15.4	12.9	13	12.3
25-29	33.2	26.9	26.4	27.3	23.3	24.2	20	19	17	16	15.3	11.9	12.5
30-34	34.9	29.6	26.3	26.2	22.2	22.1	22.3	20.1	19.3	18.9	14.7	14.9	12.7
35-39	35.1	32	31	31.2	27.1	25.2	25.3	23.8	23	20.2	16.9	15	16.0
40-44	45.5	40.3	38.6	37.5	31.6	31.7	29.1	28.8	27.6	24.3	20.1	18.3	19.0
45-49	56	51.4	48.5	44.3	40	39.1	38.2	37.2	33.8	31.9	27.6	26.4	24.2
50-54	72.8	64.8	58.8	55.9	52.7	50.9	47.9	47.8	42.2	42.4	37.7	36.9	35.4
55-59	98.3	95.5	83	73.4	69.9	66.2	61.9	58.1	53.3	53	47.8	47.1	45.2
60-64	131.2	110.8	110	102.9	92.2	93.7	82.8	86.6	67.2	69.8	69.6	61.5	55.0
≧65	385	356.5	323	314	291.3	283.1	263.5	250.5	230.9	220	208.3	191.9	173.3



HIV testing among TB patients in Taiwan

The coverage of this testing subsequently increased to 94%

2017

2016

Coverage of HIV testing exceeded 90%

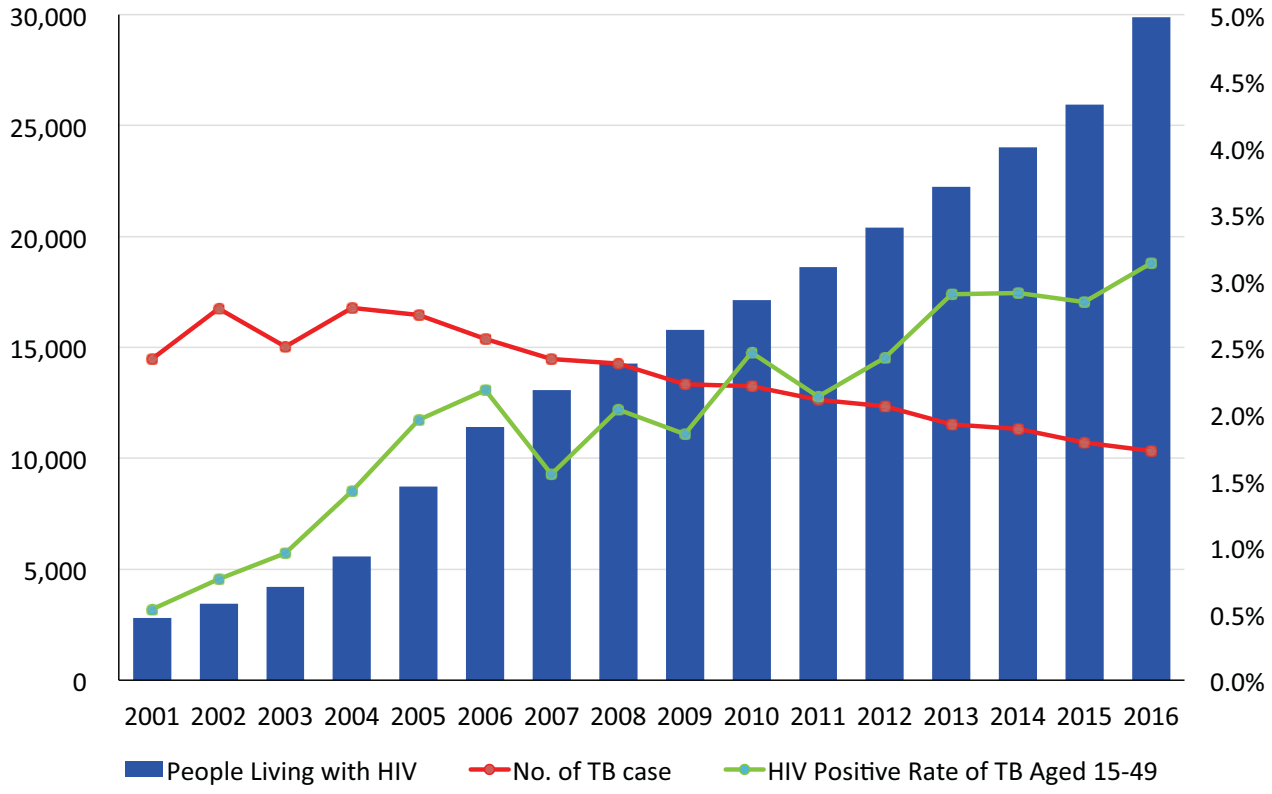
2015

TB-HIV co-infection patients aged between 15-49 represented 3.1% of all TB patients

Taiwan implemented HIV testing among TB patients aged between 15-49

2013

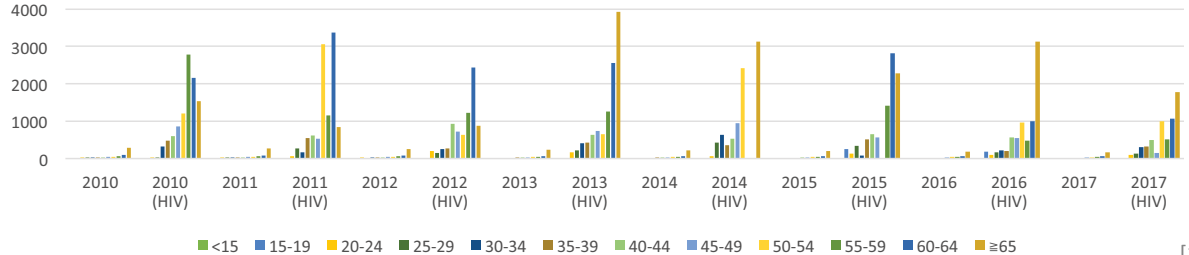
Trend of HIV prevalence of new TB cases in Taiwan, 2001-2016



HIV結核病發生率與總人口發生率

	2010	2010 (HIV)	2011	2011 (HIV)	2012	2012 (HIV)	2013	2013 (HIV)	2014	2014 (HIV)	2015	2015 (HIV)	2016	2016 (HIV)	2017	2017 (HIV)
<15	2.6	0.0	3.3	0	2.2	0	2.7	0	2.2	0	1.5	0	1.7	0	1.7	0.0
15-19	17.7	0.0	17.5	0	14.6	0	14.9	0	15.6	0	10.2	253.2	9.5	181.8	9.1	0.0
20-24	21.8	32.9	23	66.0	19.9	198.3	19.1	165.7	15.4	66.4	12.9	133.7	13	98.57	12.3	98.9
25-29	24.2	30.0	20	271.2	19	151.3	17	212.6	16	427.4	15.3	337.6	11.9	174.1	12.5	131.3
30-34	22.1	326.3	22.3	163.9	20.1	248.2	19.3	416.3	18.9	631.0	14.7	84.9	14.9	214.7	12.7	309.1
35-39	25.2	473.0	25.3	549.1	23.8	278.9	23	422.8	20.2	358.2	16.9	509.5	15	206.4	16	314.6
40-44	31.7	603.6	29.1	609.1	28.8	926.9	27.6	628.3	24.3	533.0	20.1	652.9	18.3	561.3	19	490.2
45-49	39.1	860.6	38.2	527.2	37.2	718.1	33.8	735.3	31.9	939.8	27.6	572.5	26.4	552.5	24.2	141.6
50-54	50.9	1197.6	47.9	3067.5	47.8	627.0	42.2	653.6	42.4	2413.8	37.7	0.0	36.9	963.9	35.4	1005.0
55-59	66.2	2777.8	61.9	1149.4	58.1	1219.5	53.3	1250.0	53	0.0	47.8	1418.4	47.1	485.4	45.2	507.6
60-64	93.7	2150.5	82.8	3370.8	86.6	2439.0	67.2	2564.1	69.8	0.0	69.6	2816.9	61.5	1000	55	1063.8
≧65	283.1	1526.7	263.5	840.3	251	869.6	230.9	3921.6	220	3125.0	208	2272.7	191.3	3125	173.3	1769.9

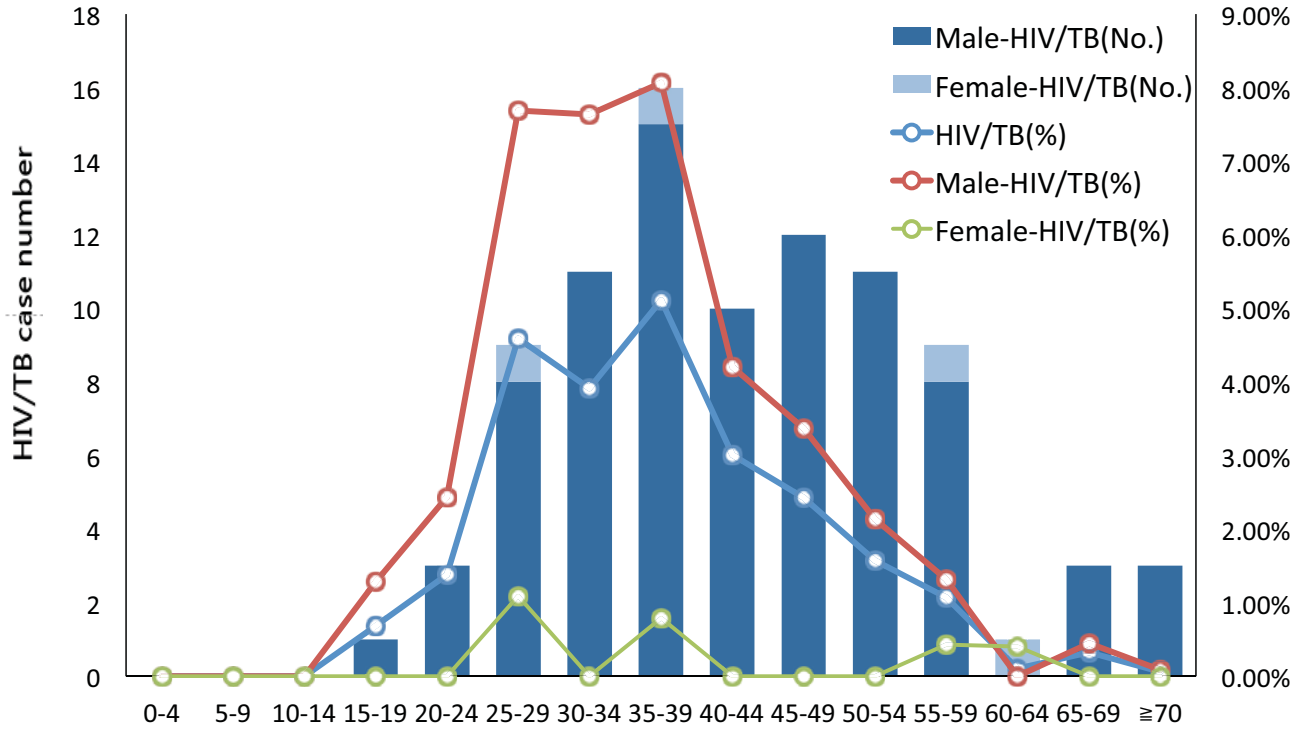
20倍-30倍



單位：每10萬人口

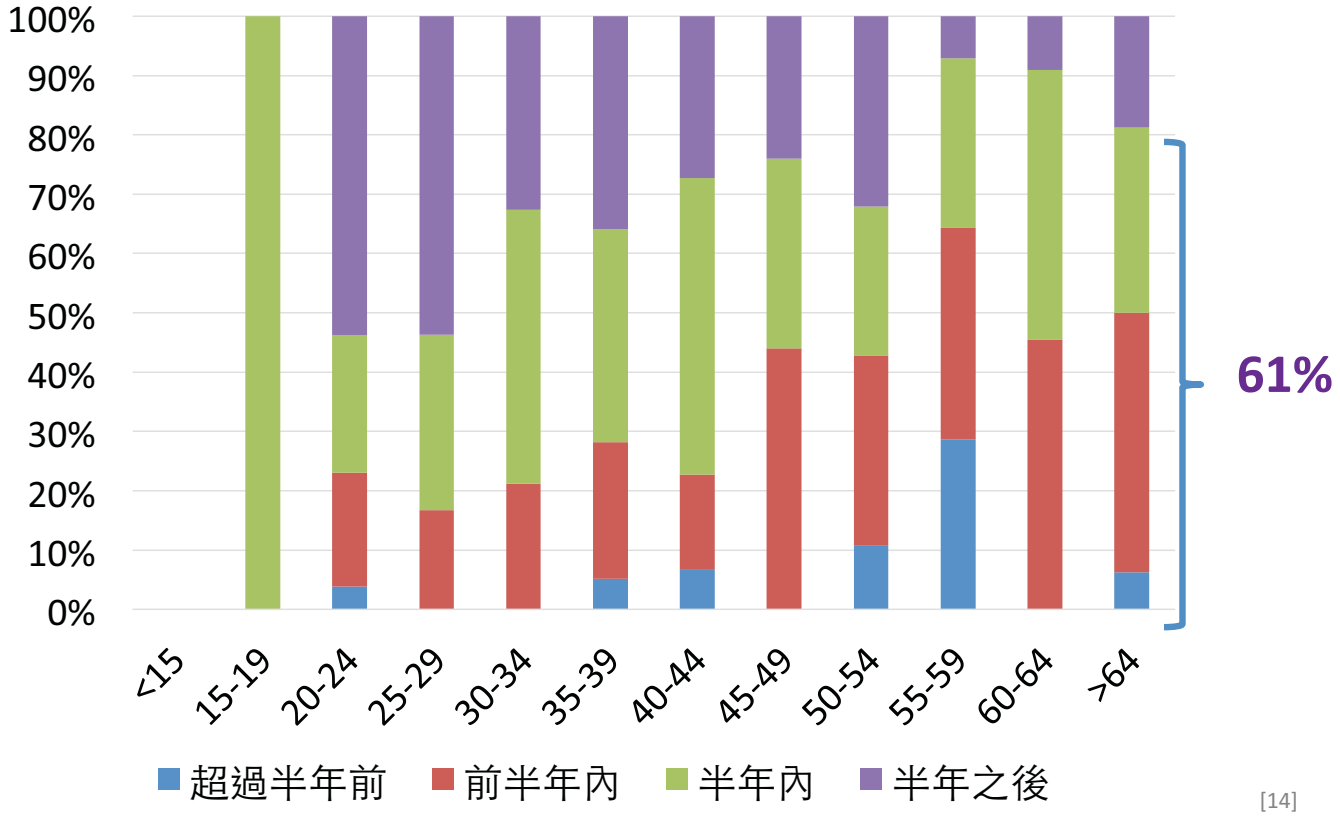
[12]

TB cases and percentage with HIV coinfection by age group, 2015

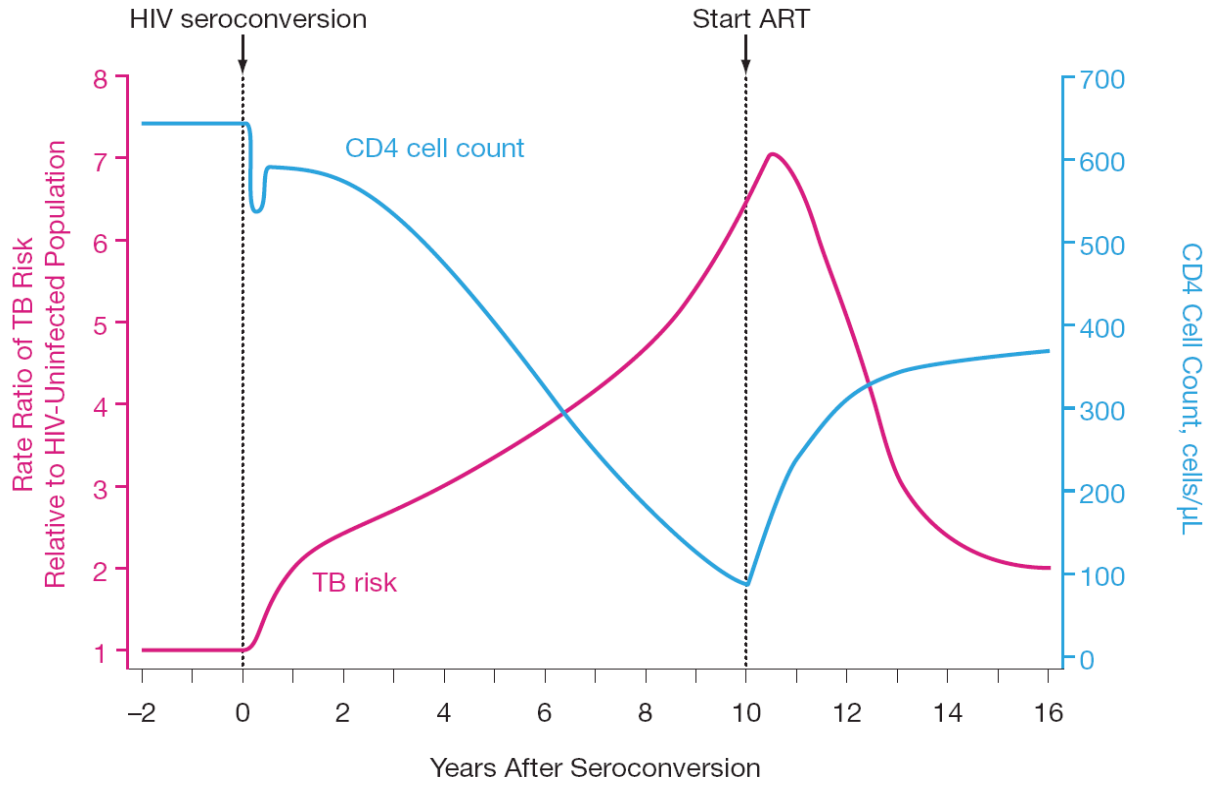


No. of new HIV/TB cases in 2016: 89 (HIV/TB, 0.9%; male, 1.2%; female, 0.1%)
No. of new HIV/TB cases in 15-49 y/o:62 (HIV/TB, 3.1%; male, 4.9%; female, 0.3%)

HIV個案TB診斷與HIV診斷的時間關係

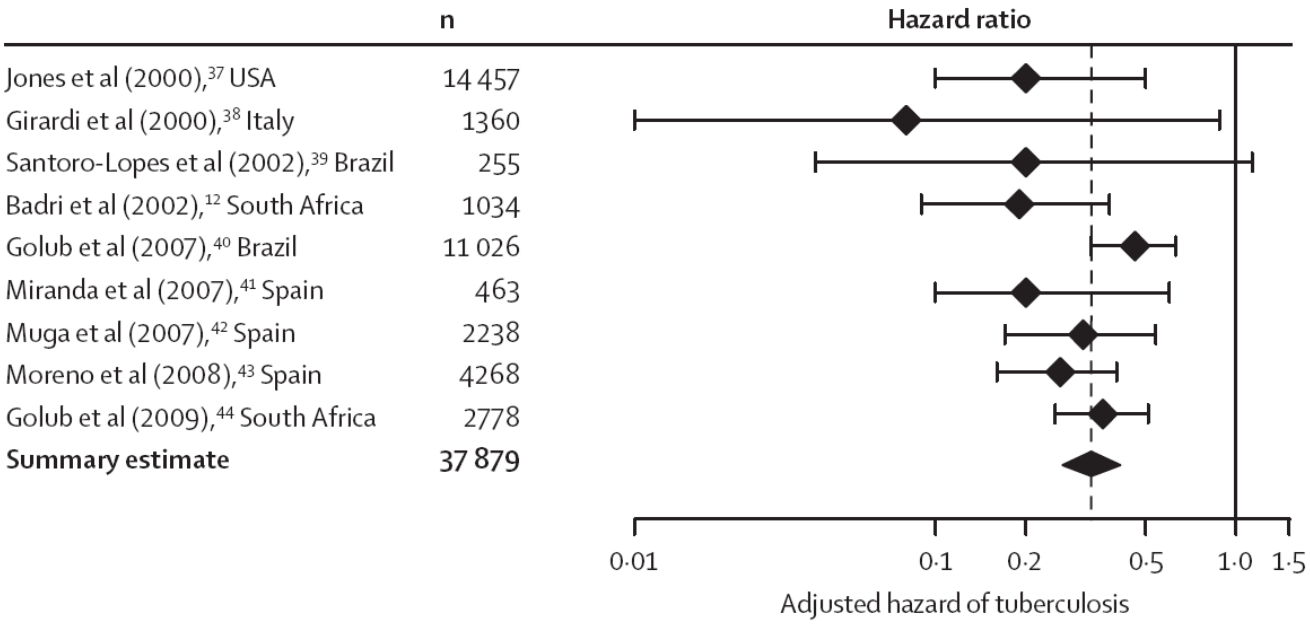


Impact of HIV on risk of TB



JAMA 2008;300:423-30.

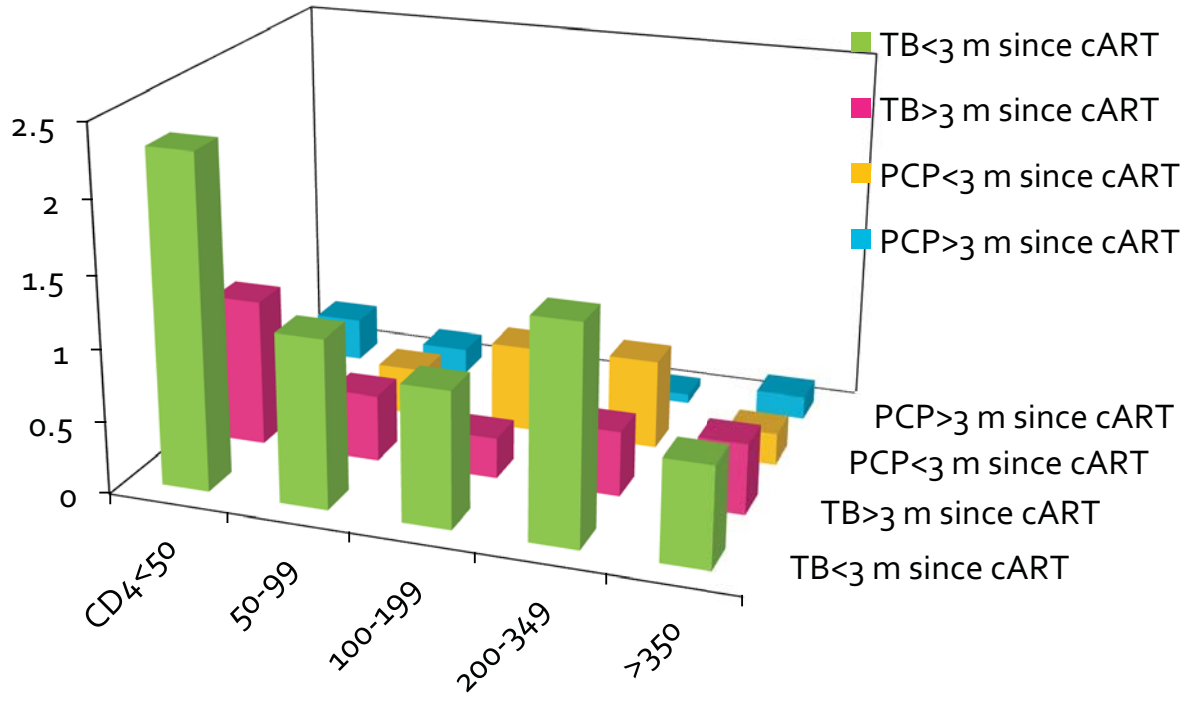
Combination antiretroviral therapy (CART) prevents TB in HIV-infected patients



Lancet Infect Dis 2010;10:489-98.

Decrease of TB incidence by antiretroviral therapy among HIV-positive patients in high-income countries

HIV-CAUSAL Collaboration. *Clin Infect Dis* 2012;54:1364-72.



常見的問題

- 抗結核藥物用於愛滋病人，和用於一般人有差別嗎？
  - 藥物組合種類
  - 治療時間
  - 治療成效
  - 副作用
  - 治療時間
  - 復發機會

Role of rifamycins in tuberculosis treatment

- Rifamycins are an essential part of successful tuberculosis treatment.
  - Despite complexity of drug interactions between rifamycins and antiretrovirals
  - Higher rates of treatment failure and relapse with anti-TB regimens without RIF or with RIF only used for the first two months.

- International multicentre randomised trial.
- 8-month regimens of EMB and INH vs 6-momth standard regimen

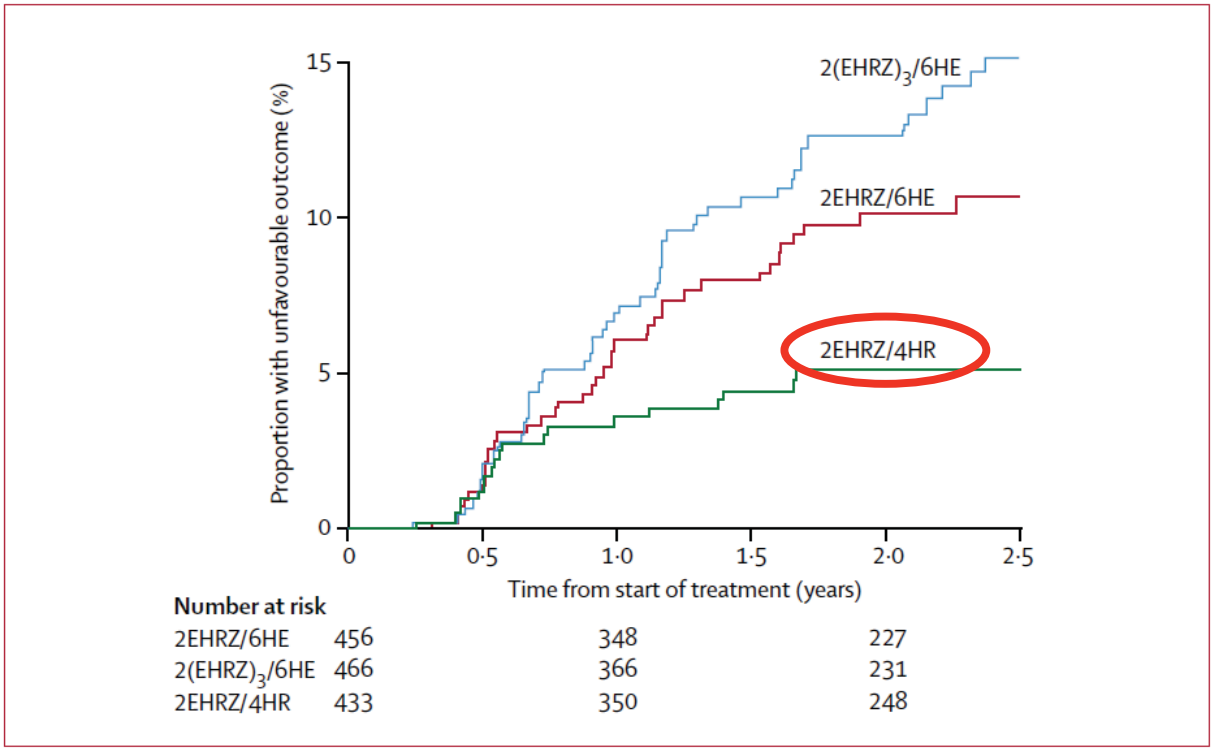
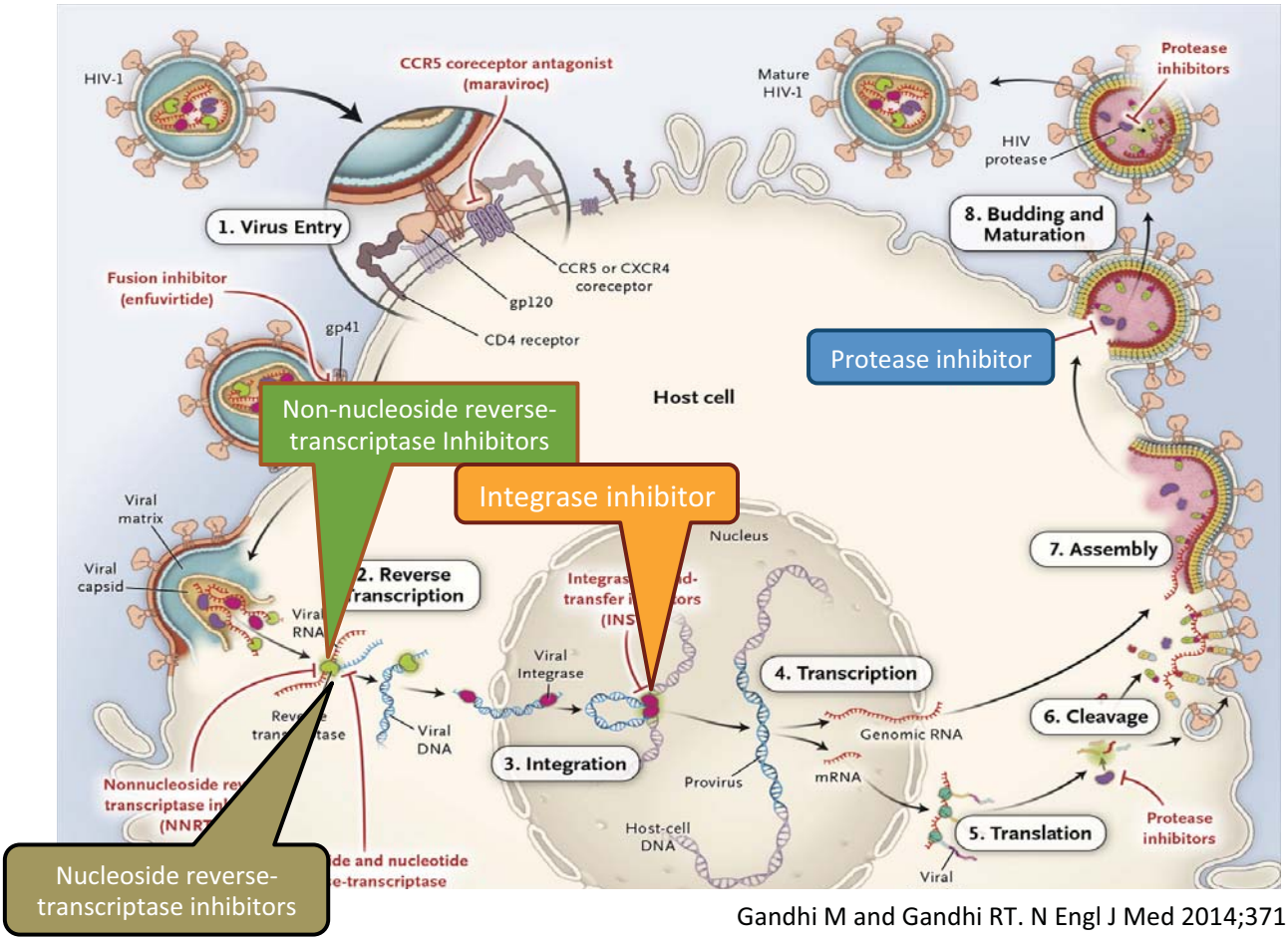


Figure 2: Time to unfavourable outcome by regimen

Lancet 2004;364:1244-51.

愛滋病毒複製與治療的標的

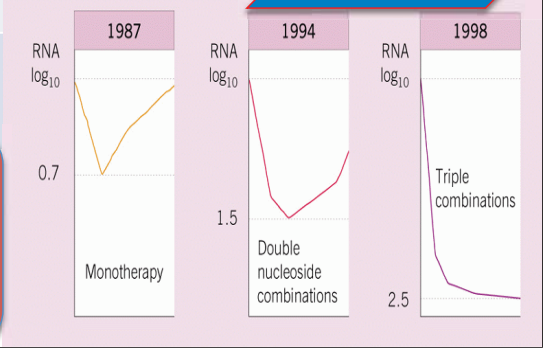


Gandhi M and Gandhi RT. N Engl J Med 2014;371:248-59.

抗愛滋病毒藥物種類

NRTIs	nNRTIs	Protease inhibitor (PI)	Integrase strand transfer inhibitor (InSTI)
Zidovudine (AZT)	**Efavirenz**	Saquinavir	**Raltegraivr**
Didanosine (ddI)	**Nevirapine**	**Ritonavir**	**Elvitegravir/cobicistat**
Deoxycitadine (ddC)	**Rilpivirine**	Indinavir	**Dolutegraivr**
Lamivudine (3TC)	**Etravirine**	Nelfinavir	**Bictegravir**
Emtricitabine (FTC)		**Lopinavir/ritonavir**	
Abacavir (ABC)		**Atazanavir**	
Tenofovir disoproxil fumarate (TDF)		**Darunavir**	
Tenofovir alafenamide (TAF)			

1996: Triple combination therapy



Triple therapy (2 NRTIs + 3rd agent) is the current standard of care in all international guidelines (DHHS, IAS-USA, EACS, WHO)

Predicting drug interactions involving tuberculosis treatment

	Metabolism	RIF as an inducer
NNRTIs		
EFV	CYP2B6 exclusively	RIF ↑ 9-fold CYP2B6 activity
NVP	CYP3A4, (some by CYP2B6)	RIF ↑ 55-fold CYP3A4 activity
PIs LPV ATV DRV RTV	CYP3A4 Phase II metabolizing enzyme Drug efflux pump p-glycoprotein	Potent inducer

Predicting drug interactions involving tuberculosis treatment

	Metabolism	RIF as an inducer
InSTI RAL DTG EVG	UGT1A1	Inducer

Combined regimens for HIV/TB	PK effect of the rifamycin on ART	Tolerability/ toxicity	Antiviral activity when used with rifamycin	Recommendation
EFV-based ART rifampin	Well-characterized. Modest ↓ in EFV con. In some p't	Low rates of discontinuation	Excellent	**Preferred** (Avoid EFV during the 1st trimester of pregnancy)

Potency
Simplicity
Proven clinical efficacy

Adopted from US CDC,
Managing Drug Interactions in the Treatments of HIV-related Tuberculosis

RIF and Protease inhibitors

- Not recommended
- RIF is potent inducers of
  - CYP3A4
  - Phase II metabolizing enzymes (UDP-glucuronyltranferases and sulfotransferases)
  - Transmembrane efflux pump P-glycoprotein.
  - All been implicated in PI disposition.
- PIs are reduced by as much as 90 to 95%
- Rifabutin, rather than RIF, is recommended when PIs used

Rifabutin (RBT) and NNRTIs

- EFV: co-administration **not recommended**
  - RBT C_{max} ↓29%, AUC ↓37%
- NVP: RBT may be an option with concomitant administration
  - NVP ↓16%
- RPV: **not recommended**
  - RPV AUC_{24} ↓46%, C_{max} ↓35%, C_{min} ↓49% in healthy volunteer
- ETR: no dose adjustment
  - ETR ↓37%, RBT ↓17%
  - No clinical experience

Rifabutin and Protease inhibitors

- Rifabutin: a moderate inducer of CYP3A4
  - As an inducer, 40% as potent as RIF
  - PIs level decreased when co-administration with RBT
- PIs: inhibitors of CYP3A4
  - Rifabutin (RBT) and its partially active desacetyl-rifabutin (d-RBT) are cleared by CYP3A4.
  - RBT and d-RBT plasma concentration can be increased by PIs

RIF with intergrase inhibitors

- UGT1A1 is an enzyme involved in RAL elimination.
  - Allelic variants of UGT1A1 genes can affect RAL PK
    - UGT1A1 *28 genotype is associated with decreased enzyme activity
    - UGT1A1 loss-of-function variants are more prevalent in African American then in white individuals
- RIF induces UGT1A1.
  - Potentially lowering RAL exposure.

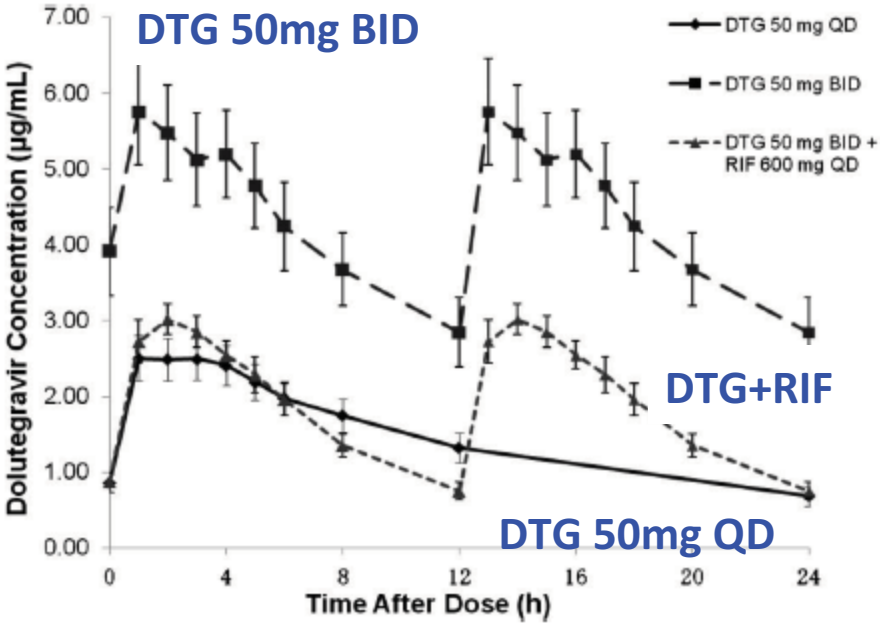
RIF with Intergrase inhibitors

- RIF + RAL in healthy volunteers
  - *Antimicrob Agents Chemother 2009;53:2852-6.*
  - RAL 400mg twice daily, RAL trough con. ↓ 61%.
  - RAL 800mg twice daily, RAL trough con.↓53%

RIF or RBT and DTG in healthy volunteer

- DTG+RIF vs DTG 50 mg twice daily
- GMR for AUC_{0-24} 0.46
- GMR for trough 0.28

- DTG+RIF vs DTG 50 mg daily
- GMR for AUC_{0-24} **1.33**
- GMR for trough **1.22**

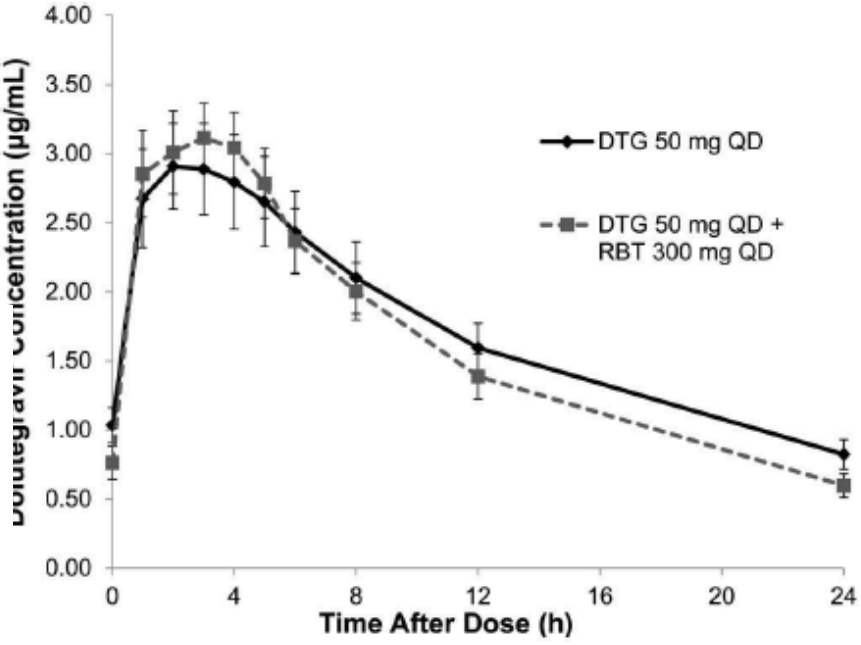


JAIDS 2013;62: 21-27

RIF or RBT and DTG in healthy volunteer

- DTG+RBT vs DTG 50 mg daily
- GMR for AUC_{0-24} 0.95
- GMR for trough 0.70

DTG trough concentration ↓ by 30%, unlikely to be clinical significantly



JAIDS 2013;62: 21-27

Starting ART in HIV-infected patients with TB

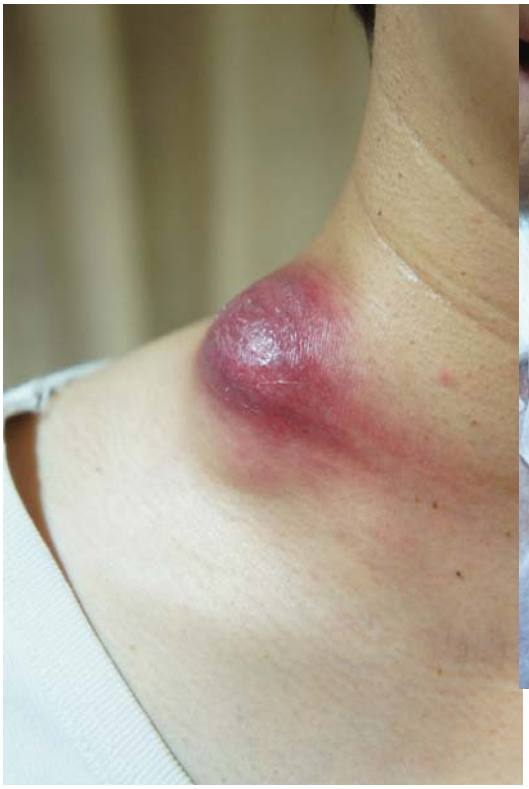
Tuberculosis	CD4 count (cells/mm^3)	Timing of ART after starting TB treatment
Mild/moderate/severe	<50	Within 2 weeks (AI)
Mild/moderate	50–500	Beyond 2–4 weeks, within 8–12 weeks (AI)
	≥500	Beyond 2–4 weeks, within 8–12 weeks (BIII)
Severe	50–200	Within 2–4 weeks (BI)
	≥200	Within 2–4 weeks (BIII)
MDR/XDR-TB	NA	Within 2–4 weeks after confirmation of drug resistance (BIII)

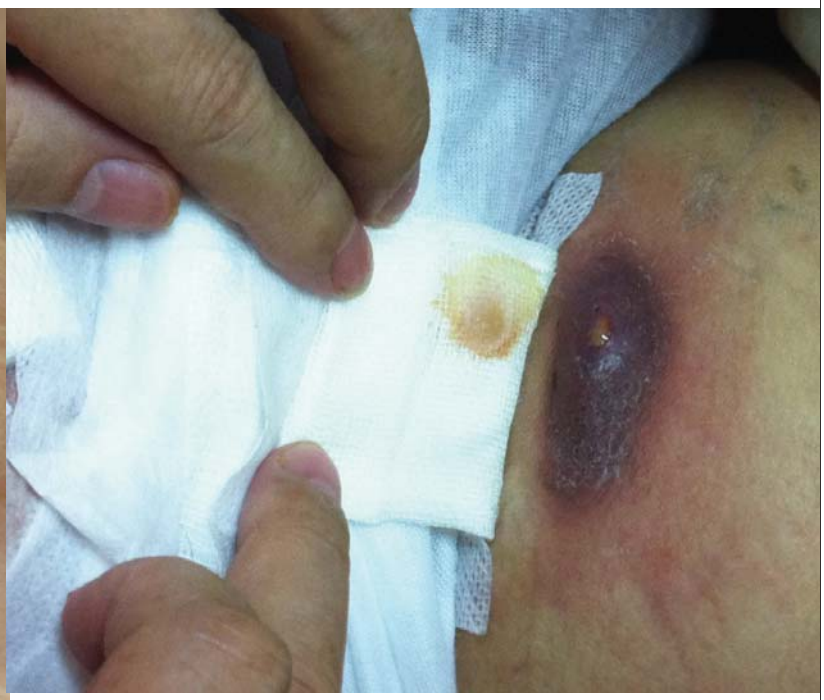
Severe: low Karnofsky score, BMI, hemoglobin, and albumin; or organ system dysfunction

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Accessed October 2014. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf.

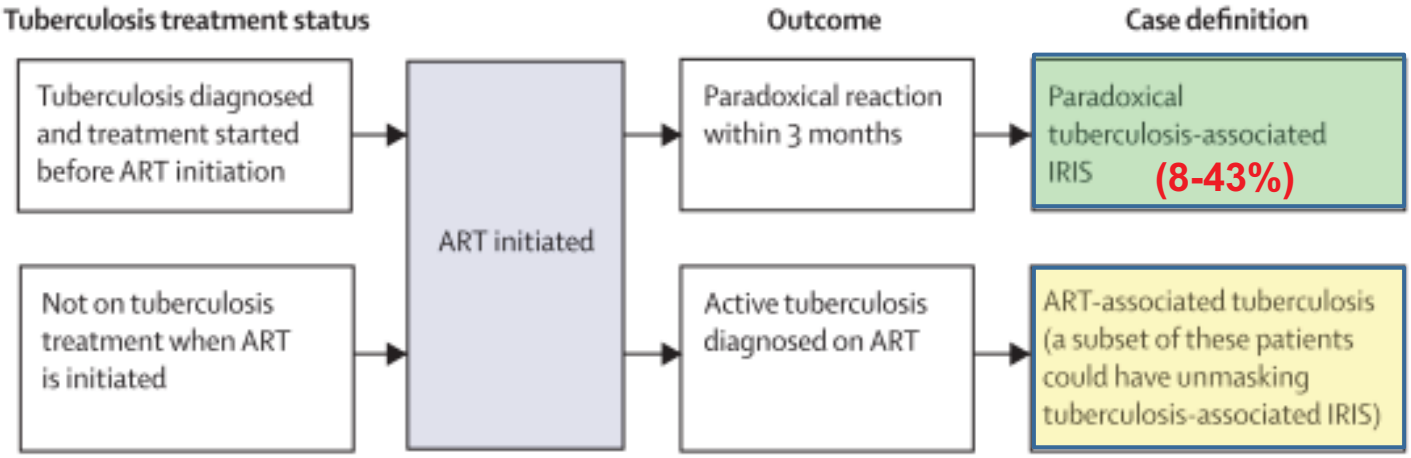
The optimal strategy in TB meningitis is less clear.
MDR: multidrug-resistant, XDR: extensively drug-resistant

Tuberculosis-related IRIS





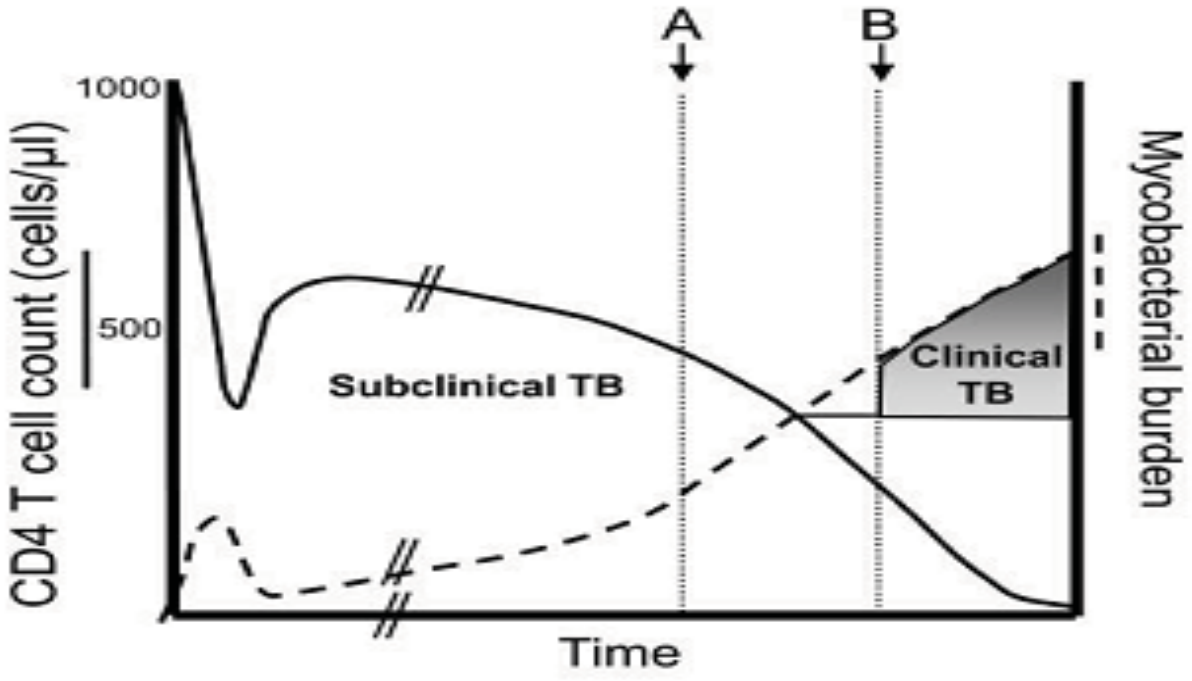
TB-IRIS
paradoxical *vs* **unmasking**



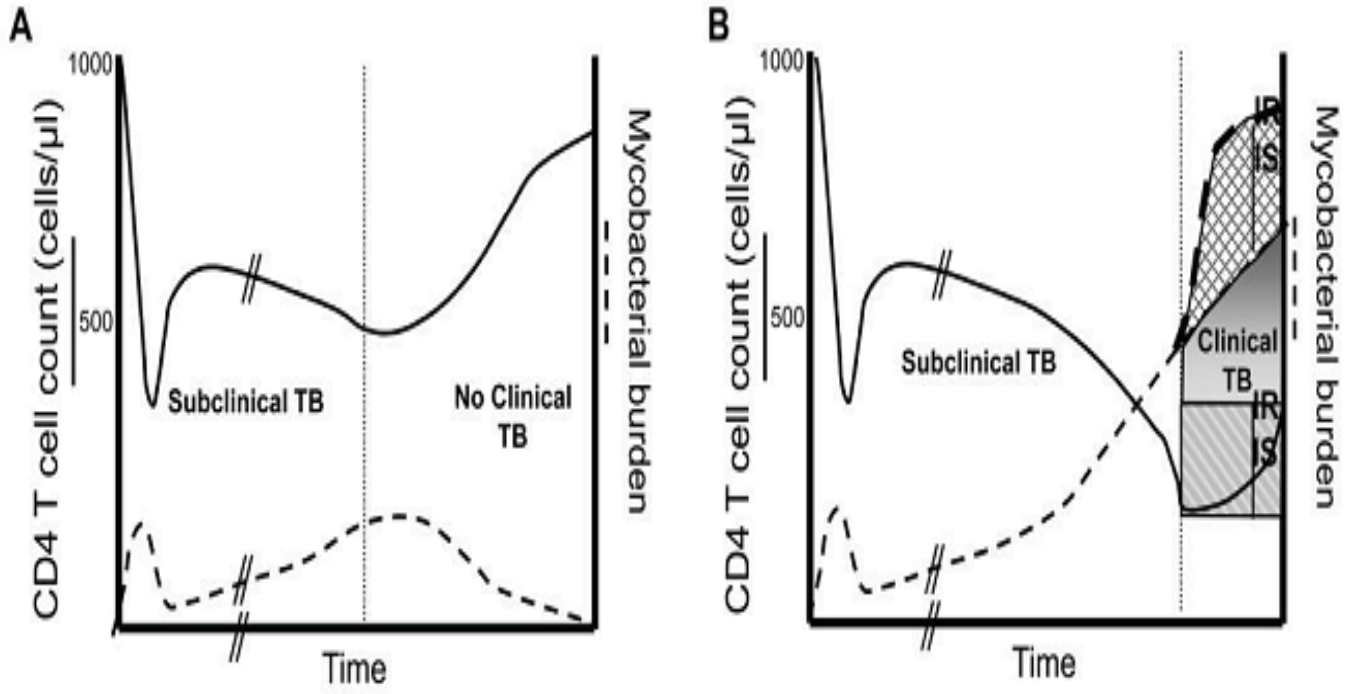
Meintjes G et al. Lancet Infect Dis 2008;8:516-23.

Unmasked TB and TB-IRIS: a disease spectrum after initiation of antiretroviral therapy

Manabe YC, et al. J Infect Dis 2009;199:437-44.



Relationship between CD4 cell counts and mycobacterial burden

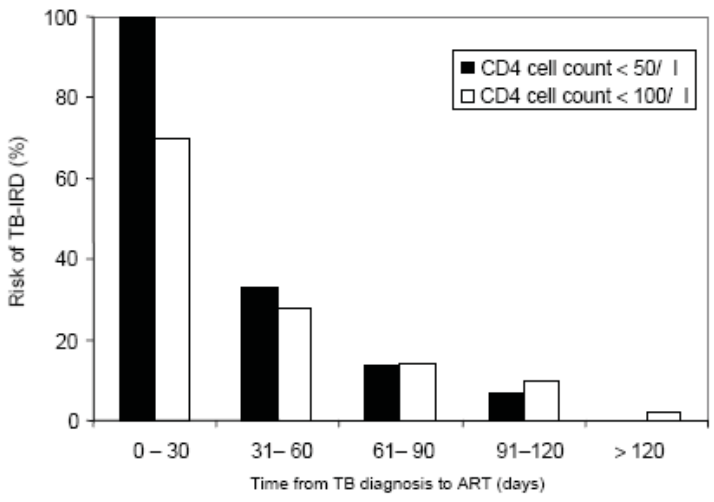


Manabe YC, et al. J Infect Dis 2009;199:437-44.

TB-associated IRIS:

incidence, risk factors, and impact on an ART service in SA

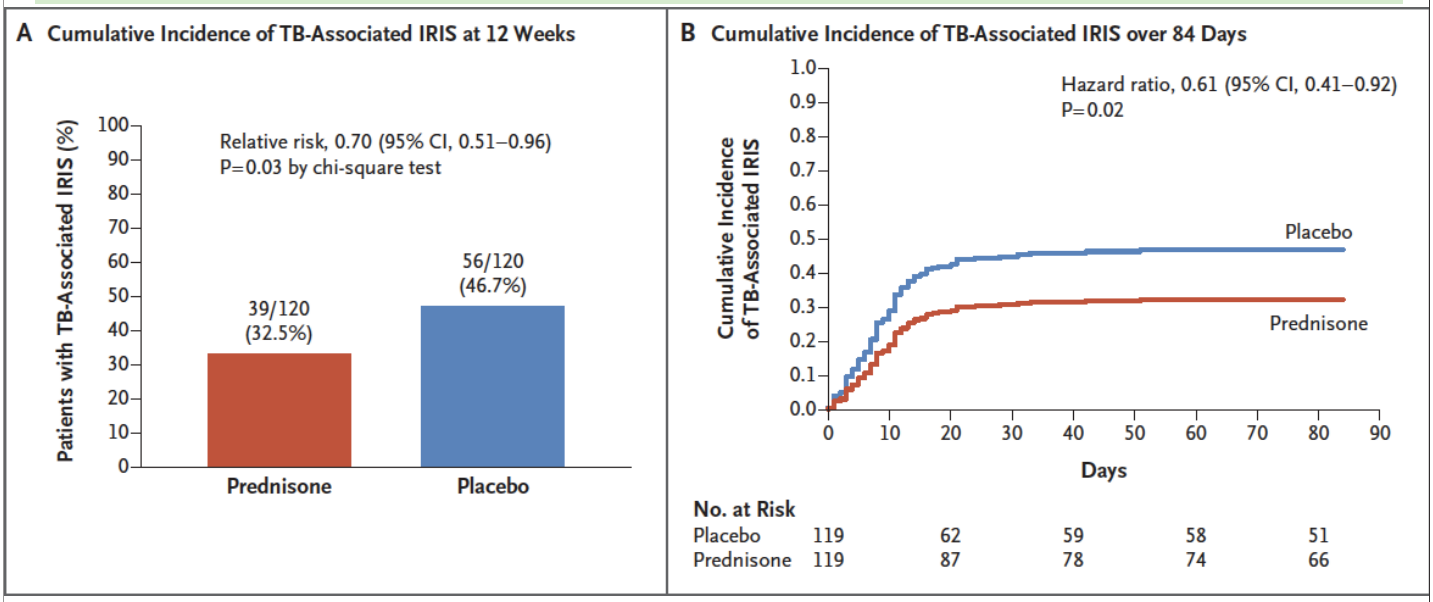
Lawn SD, et al. *AIDS* 2007;21:335-41.



- Retrospective study
- 12% (19/160) IRIS
  - Median time, 2 wk (1.5-3.5)
- Multivariate analysis
  - Low baseline CD4
  - Shorter interval between anti-TB and ART
    - IRIS (+), 40 days vs. IRIS (-), 107 days

Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS

240 HIV-infected patients who were initiating ART, had started TB treatment within 30 days before initiating ART, and had a CD4 count ≤100 cells/mm^3. Patients received either prednisone (at a dose of 40 mg per day for 14 days, then 20 mg per day for 14 days) or placebo. The primary end point was the development of tuberculosis-associated IRIS within 12 weeks after initiating ART.

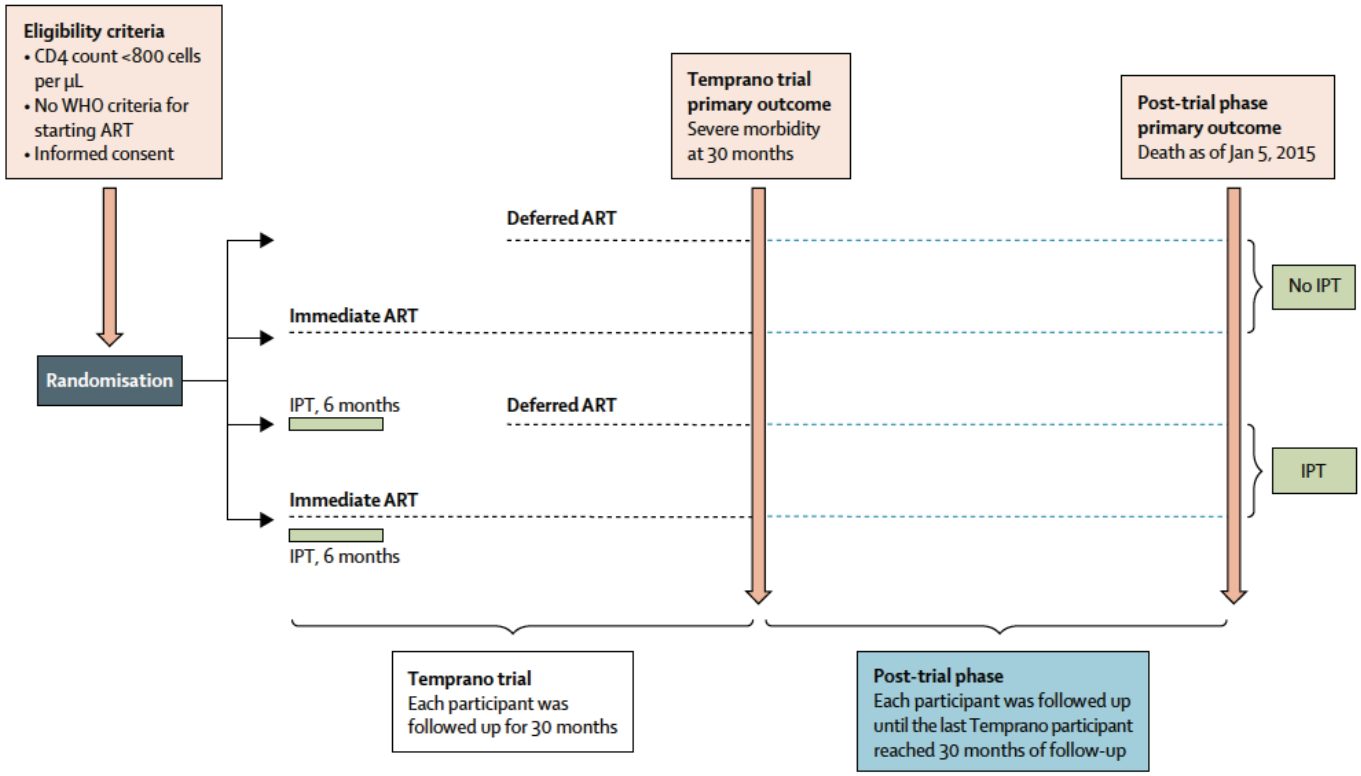


Meintjes G, et al. N Engl J Med 2018;379:1915-25.

WHO: Systematic testing and treatment of LTBI

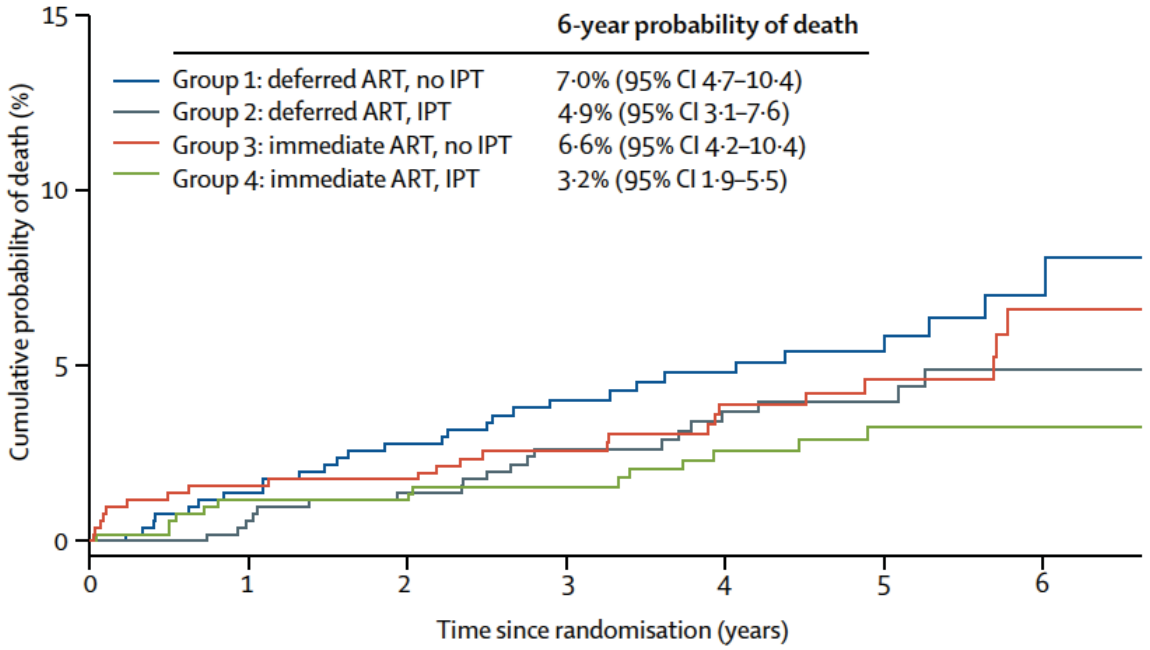
Strong recommendation	Conditional recommendation	Not recommended
• PLWHIV • TB contact • TNF-alpha • Dialysis • transplantation	• Prisoners • HCW • HBC Immigrants • Homeless • Illicit drug users	• DM • Alcohol use • Smokers • underweight

Study design in Temprano and post-trial phase



Badje, A, et al. Lancet Glob Health 2017;5:1080-89.

Lowest mortality in patients assigned to early ART and IPT

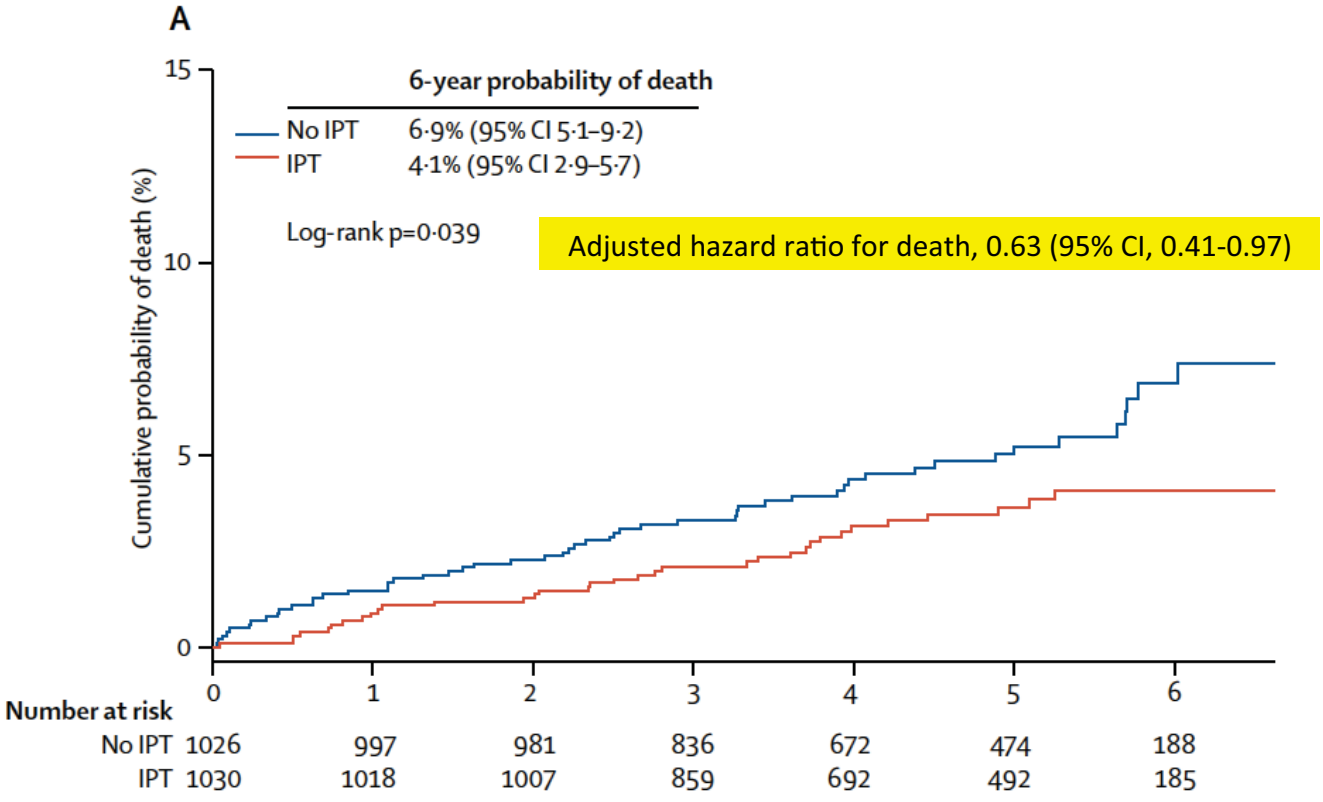


Number at risk

Group 1	511	497	485	414	334	226	89
Group 2	512	508	502	429	336	247	91
Group 3	515	500	496	422	338	248	99
Group 4	518	510	505	430	356	245	94

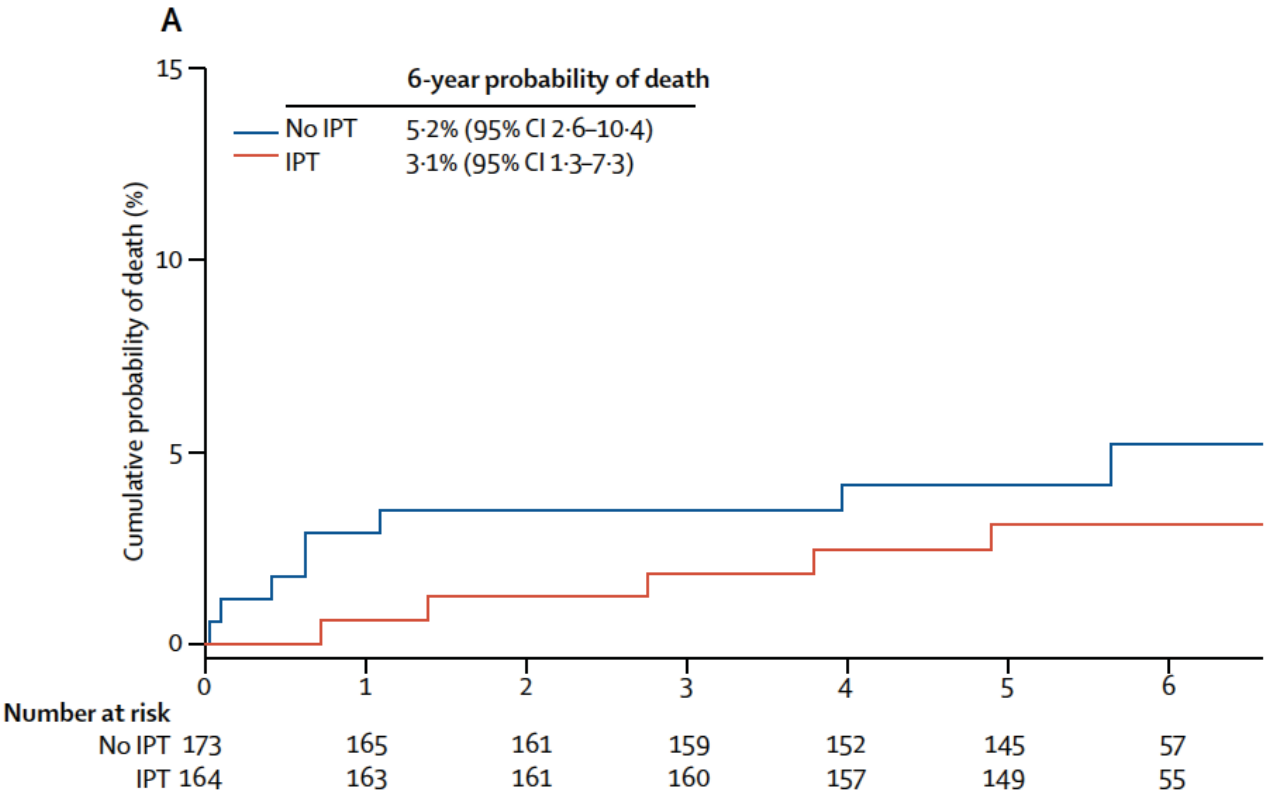
Badje, A, et al. Lancet Glob Health 2017;5:1080-89.

Lower mortality in patients assigned to 6-month IPT

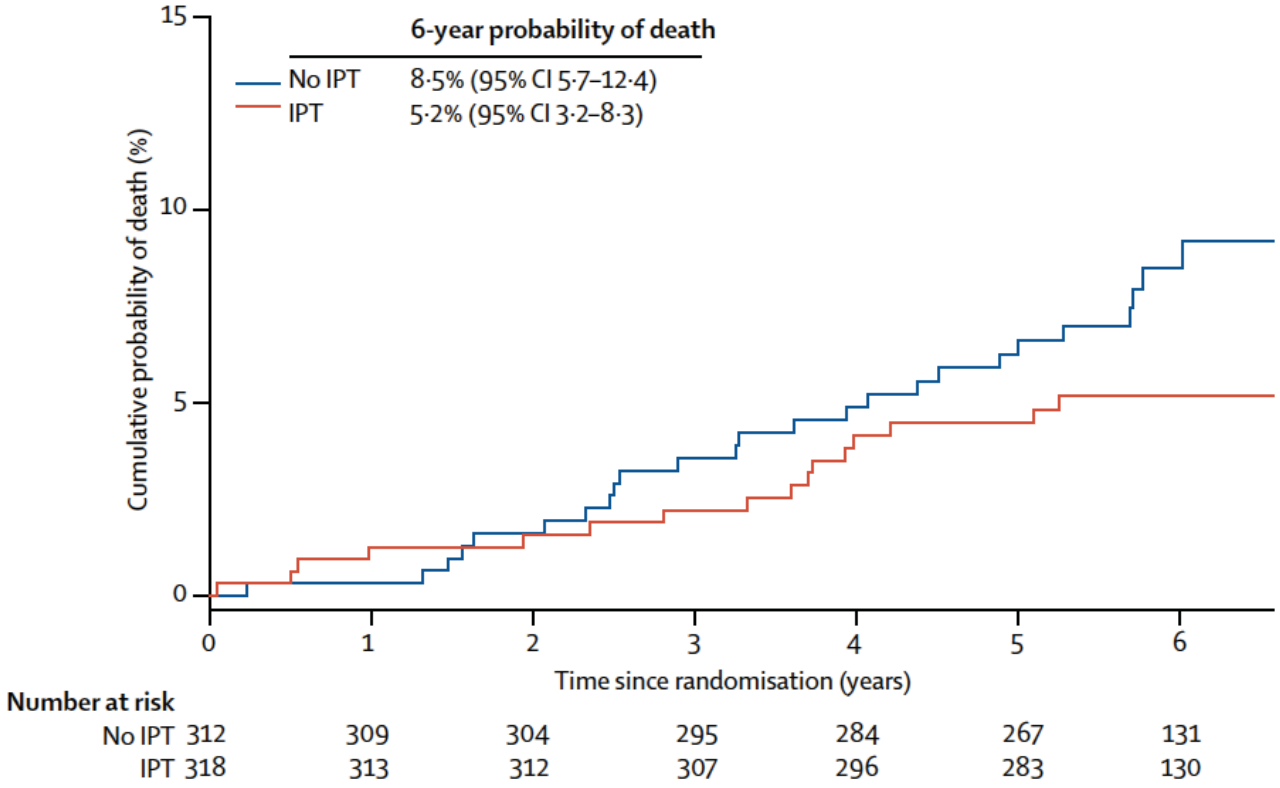


Badje, A, et al. Lancet Glob Health 2017;5:1080-89.

Lower mortality in patients testing positive by IGRA



Lower mortality in patients testing negative by IGRA



台灣感染者(含IDU)LTBI專案計畫

HIV(含IDU)接受IGRA檢驗: 1172

IGRA (+): 343 29%

開始LTBI: 184

完成治療: 125、
持續治療: 16

年齡	接受檢驗	IGRA陽性	陽性率
<20歲	76	4	5%
30-39歲	320	67	21%
40-49歲	478	144	30%
50-59歲	249	104	42%
>60歲	49	24	49%

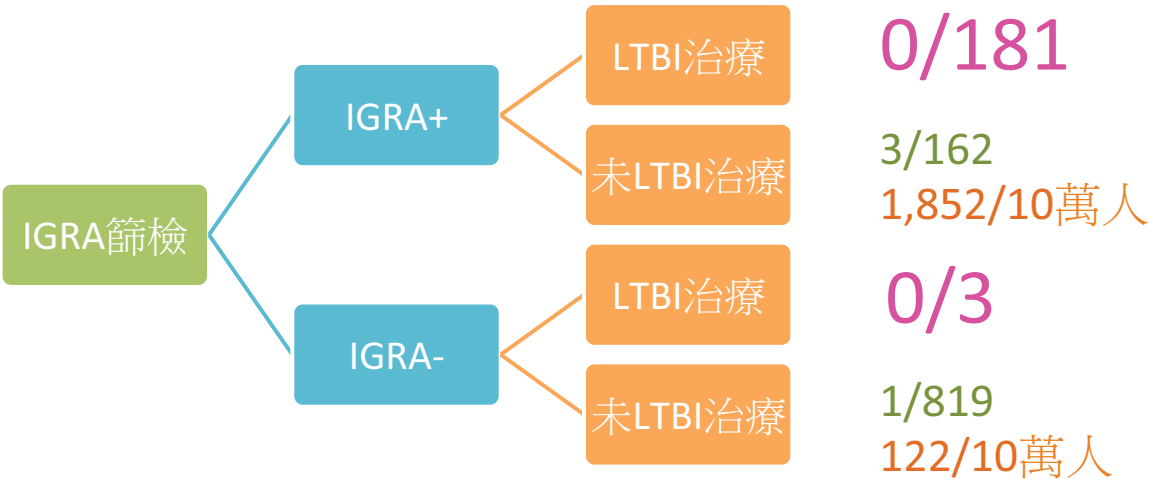
P<0.001

追蹤至2019/1/31

[46]

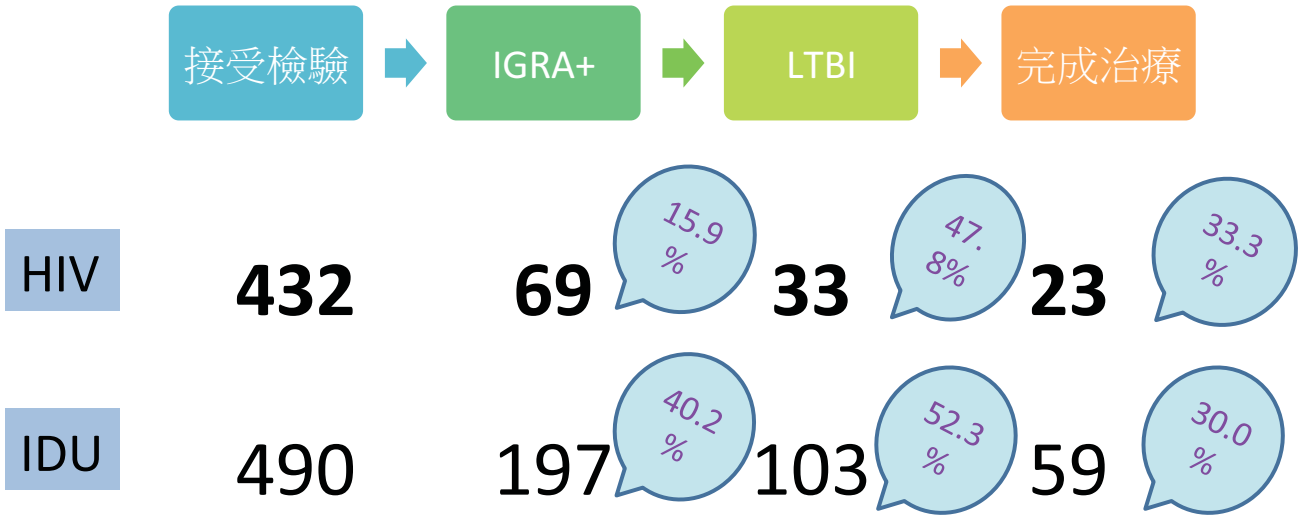
台灣感染者(含IDU)LTBI專案計畫

發病/觀察個案



追蹤至2019/1/31

HIV/IDU LTBI專案



致 謝

- 疾管署 詹佩君醫師提供疫情資料