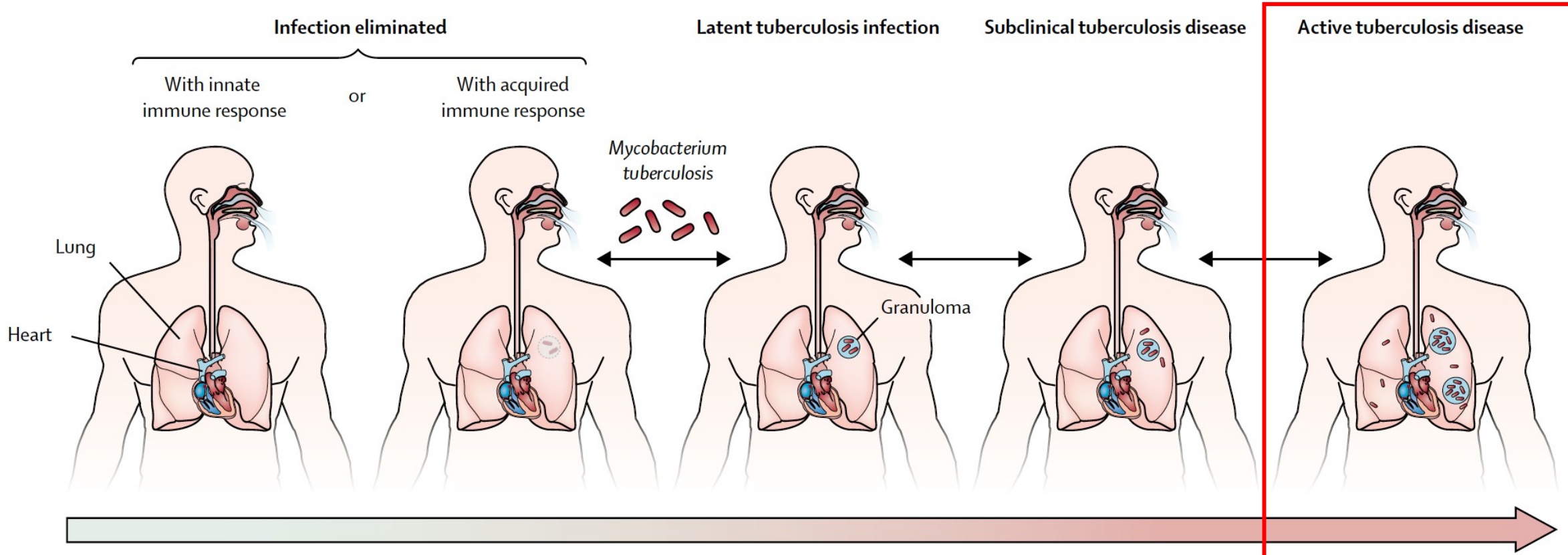
HIV/AIDS 的結核病預防

台大醫院內科部感染科

孫幸筠醫師

Outlines

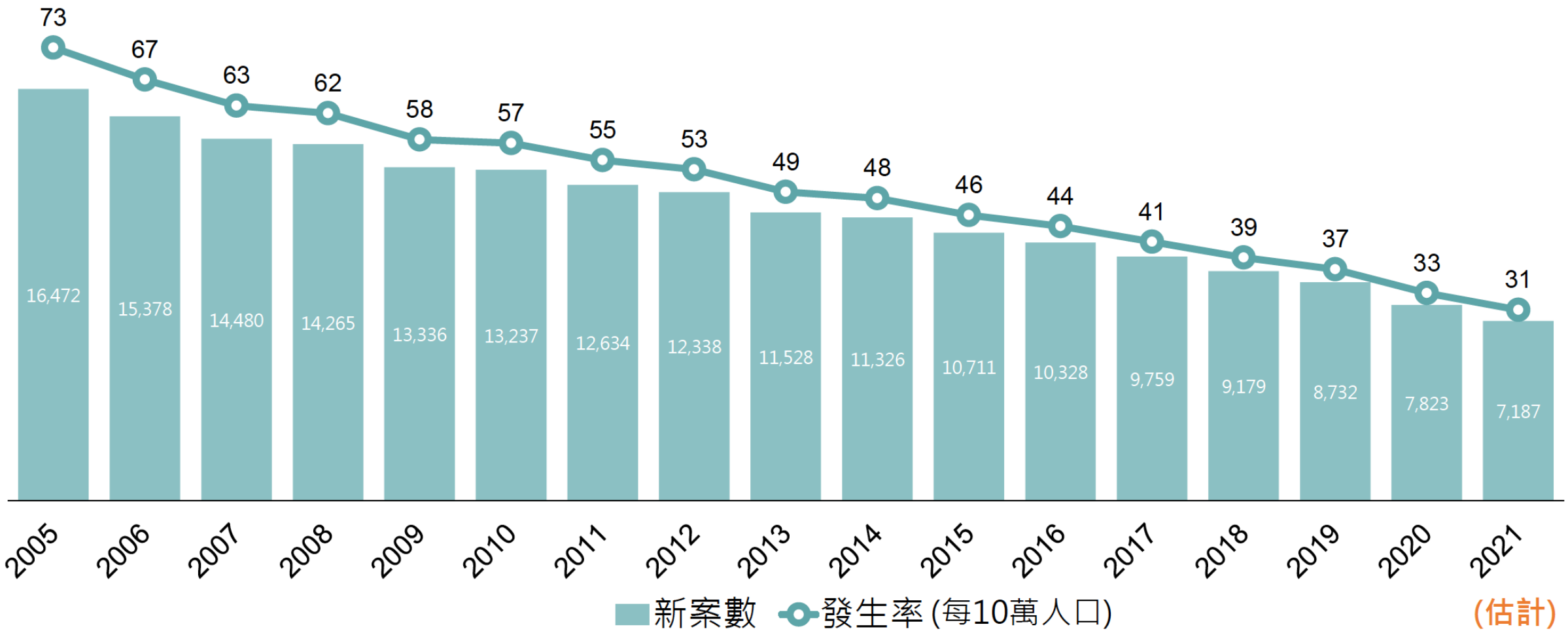
- Latent tuberculosis infection (LTBI) in people living with HIV (PLWH)
- Benefits of treatment for LTBI and early antiretroviral therapy (ART) in PLWH
- Regimens of LTBI
- Challenges of LTBI in PLWH
  - Drug-drug interactions between LTBI regimens and ART



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

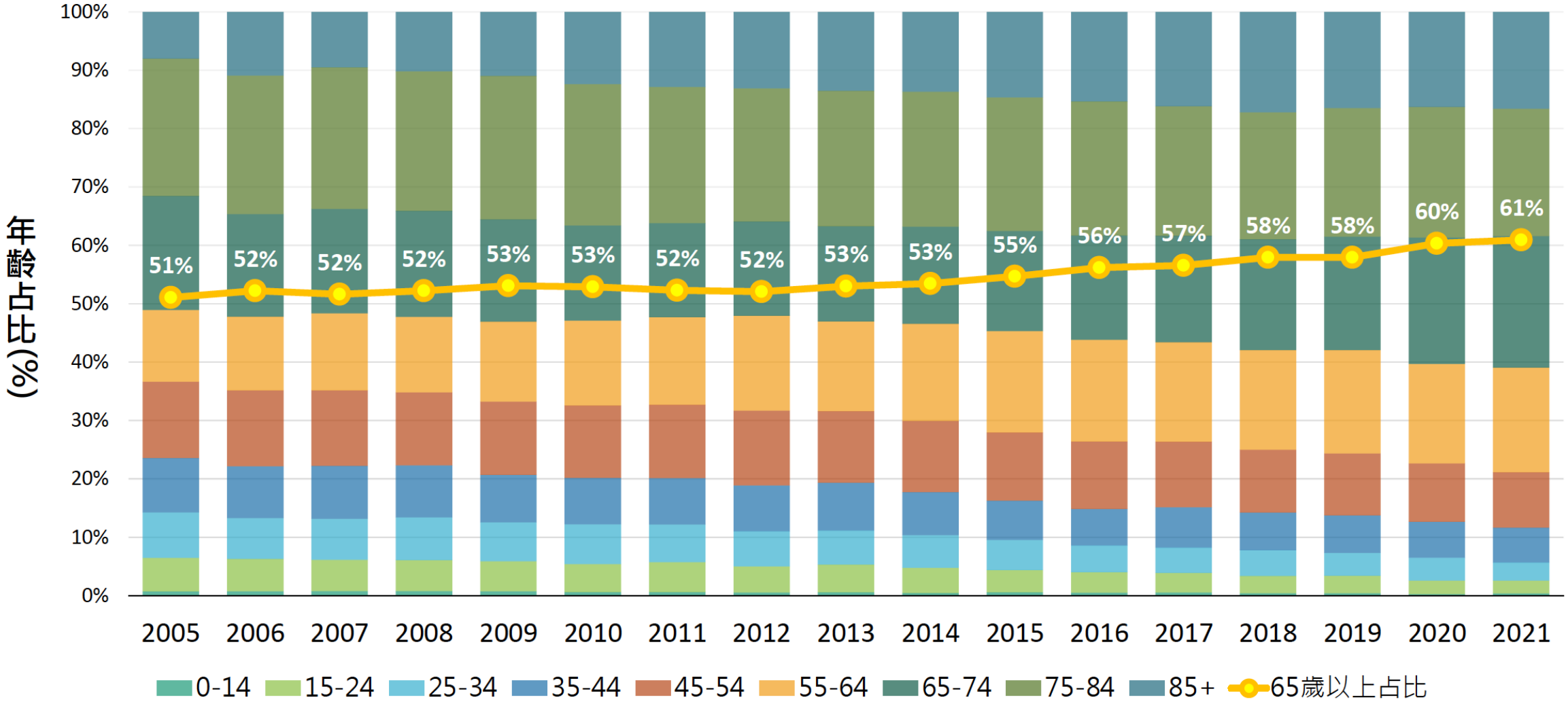
Furin J, et al. Lancet 2019

全國結核病發生率



資料來源：台灣 CDC

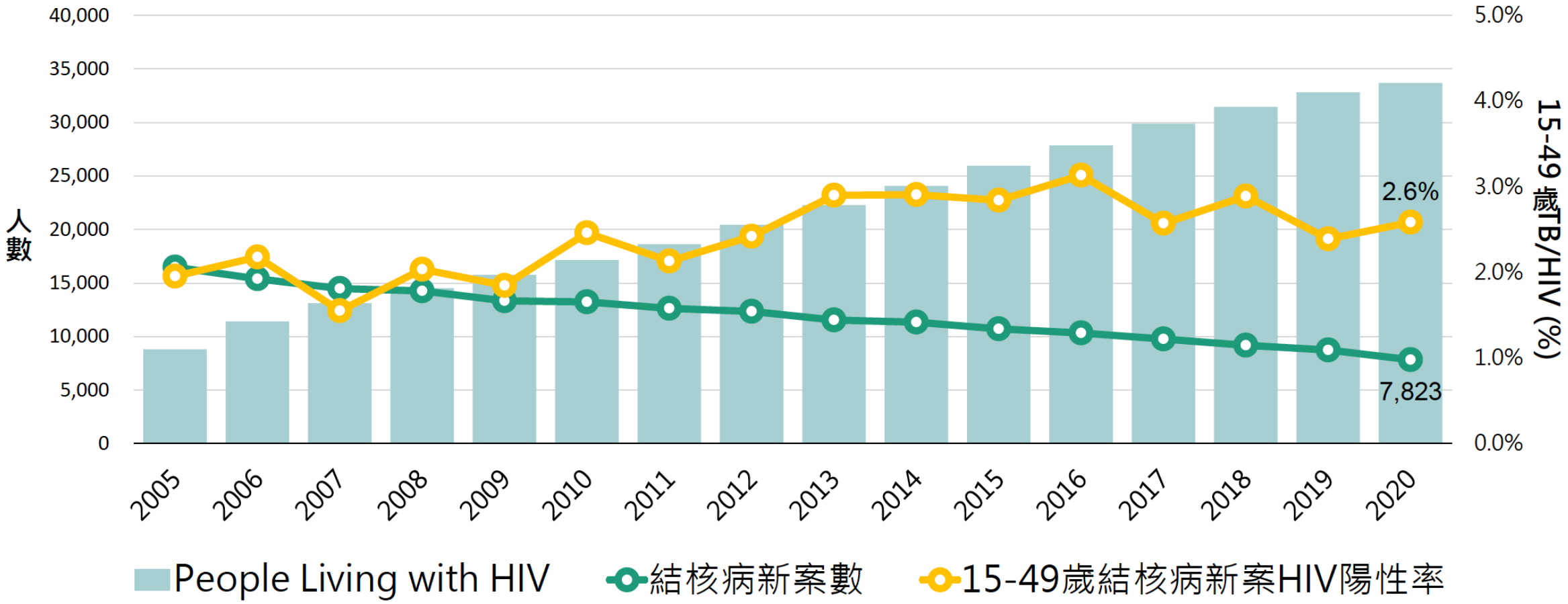
結核病新案之年齡分佈(2005-2021)



65歲以上個案占所有個案大於60%

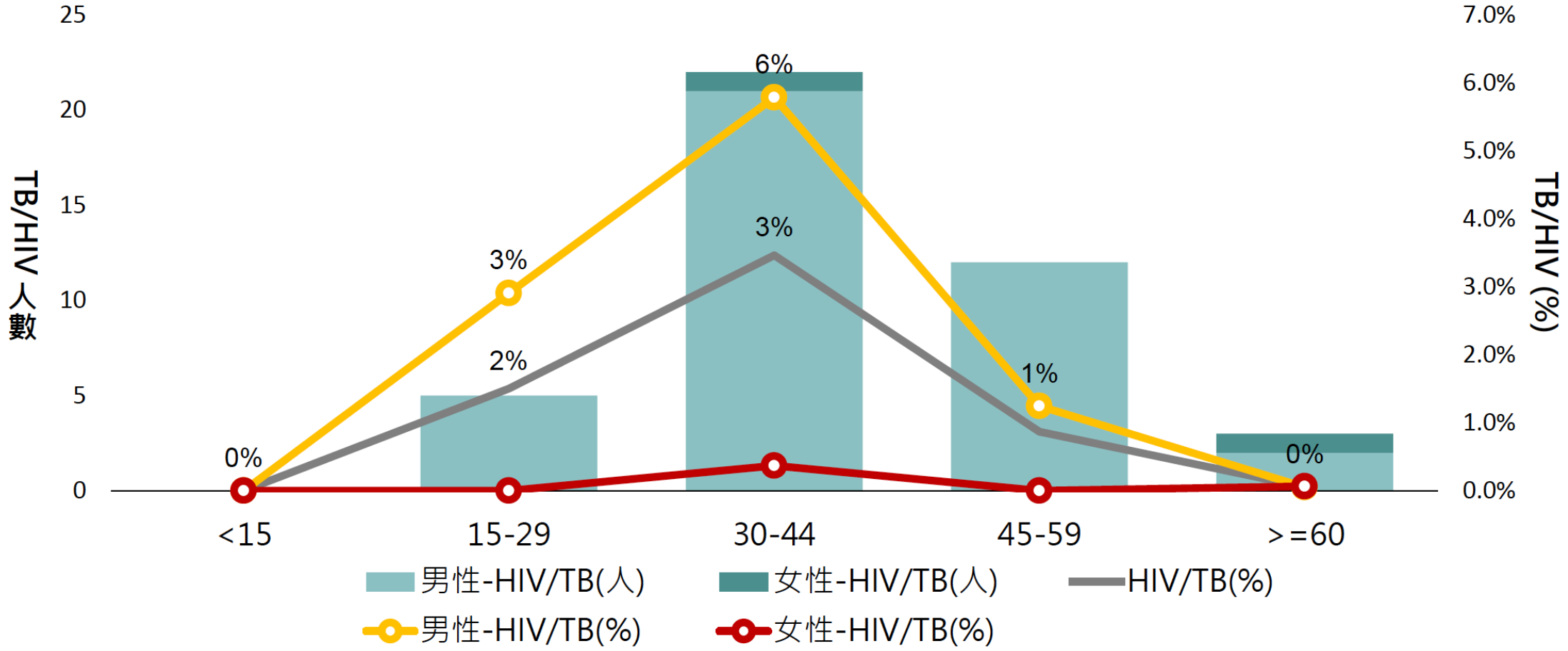
資料來源：台灣 CDC

新診斷結核病個案之HIV盛行率趨勢



資料來源：台灣 CDC

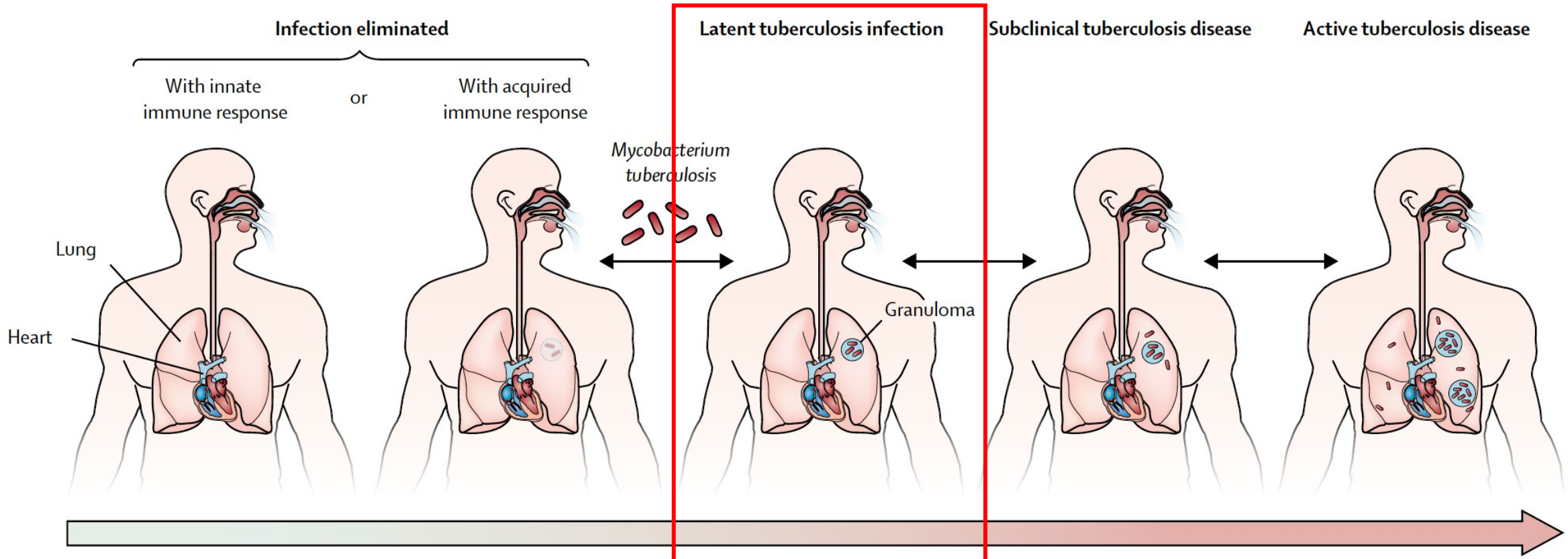
結核病各年齡層新案之HIV感染比率



2020年TB新案中HIV個案數42人(HIV/TB比率：0.5%，男性0.7%，女性0.1%)

15-49歲TB新案中HIV個案數33人(HIV/TB比率：2.6%，男性4.3%，女性0.2%)

資料來源：台灣 CDC



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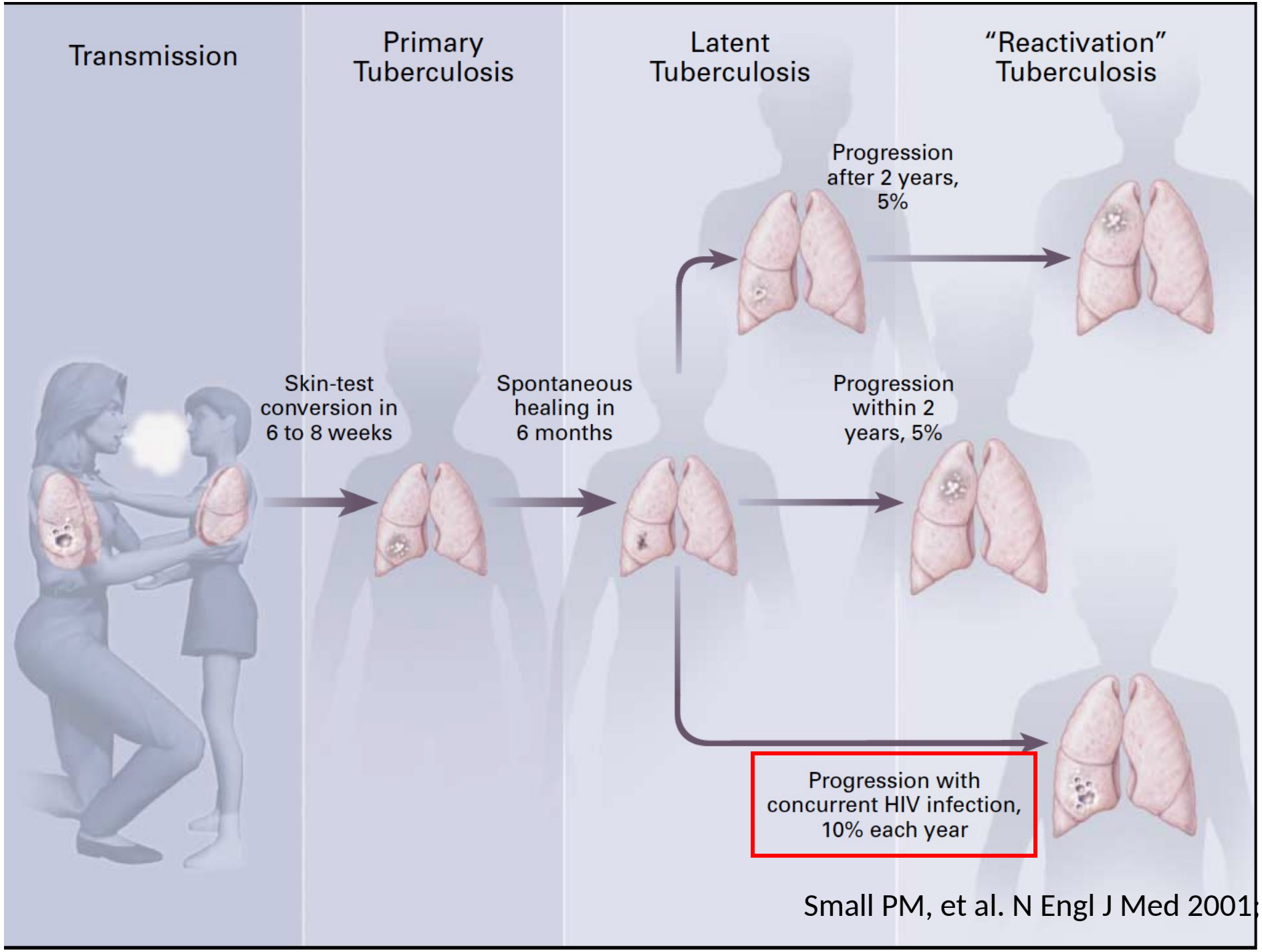
Furin J, et al. Lancet 2019



Small PM, et al. N Engl J Med 2001; 345: 189-200

造成結核菌從感染進而發病的危險因子

Conditions That Increase The Risk of Developing Active TB

Condition	Relative Risk	Annual Risk of Developing Active TB (%)	Cumulative Lifetime Risk (%)†
AIDS	90-170	8-17	100
HIV infection	40-113	4-11.3	100
Transplantation	20-74	2-7.4	100
Pulmonary silicosis	30	3	100
Chronic renal failure/hemodialysis	10-25	1-2.5	50-100
Recent infection within 2 years	15	1.5	75
Carcinoma of head and neck	16	1.6	80
Fibronodular disease on chest radiograph	6-19	0.6-1.9	30-95
Diabetes mellitus	2-3.6	0.2-0.36	10-18
Granuloma on chest radiograph	2	0.2	10
No known risk factor	1	0.1	5

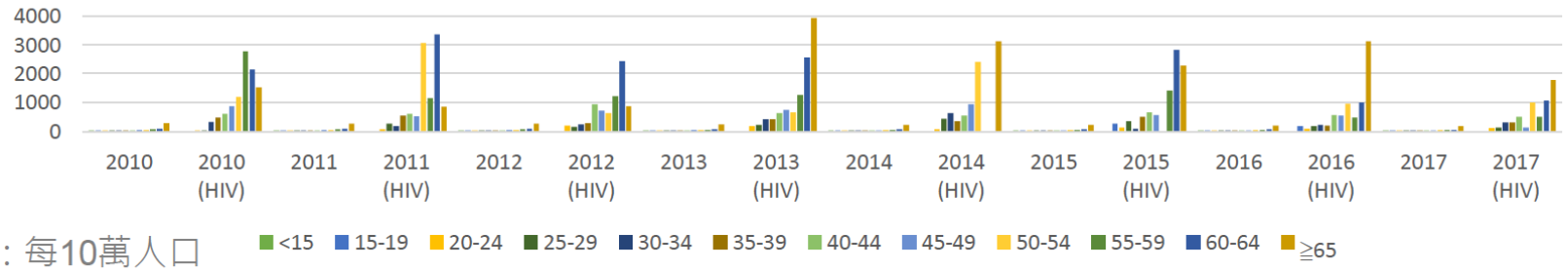
†Estimates for young adults

The Canadian Journal of CME / May 2001

我國HIV感染者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	725.3	31.9	939.8	27	572.5	26.4	552.5	24.2	141.6
50-54	50.9	1197.6	47.9	3067.5	47.8	27	4	3.6	42.4	41.8	3	0.0	36.9	963.9	35.4	1005.0
55-59	66.2	2777.8	61.9	1149.4	58.1	1219	53.3	1250.0	3	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

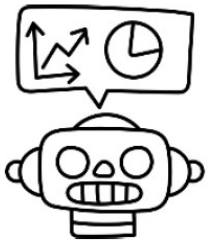


單位：每10萬人口

國外文獻指出，HIV感染者如果同時為潛伏結核感染者，進展為結核病人的機率是非HIV感染者的**50~170倍**

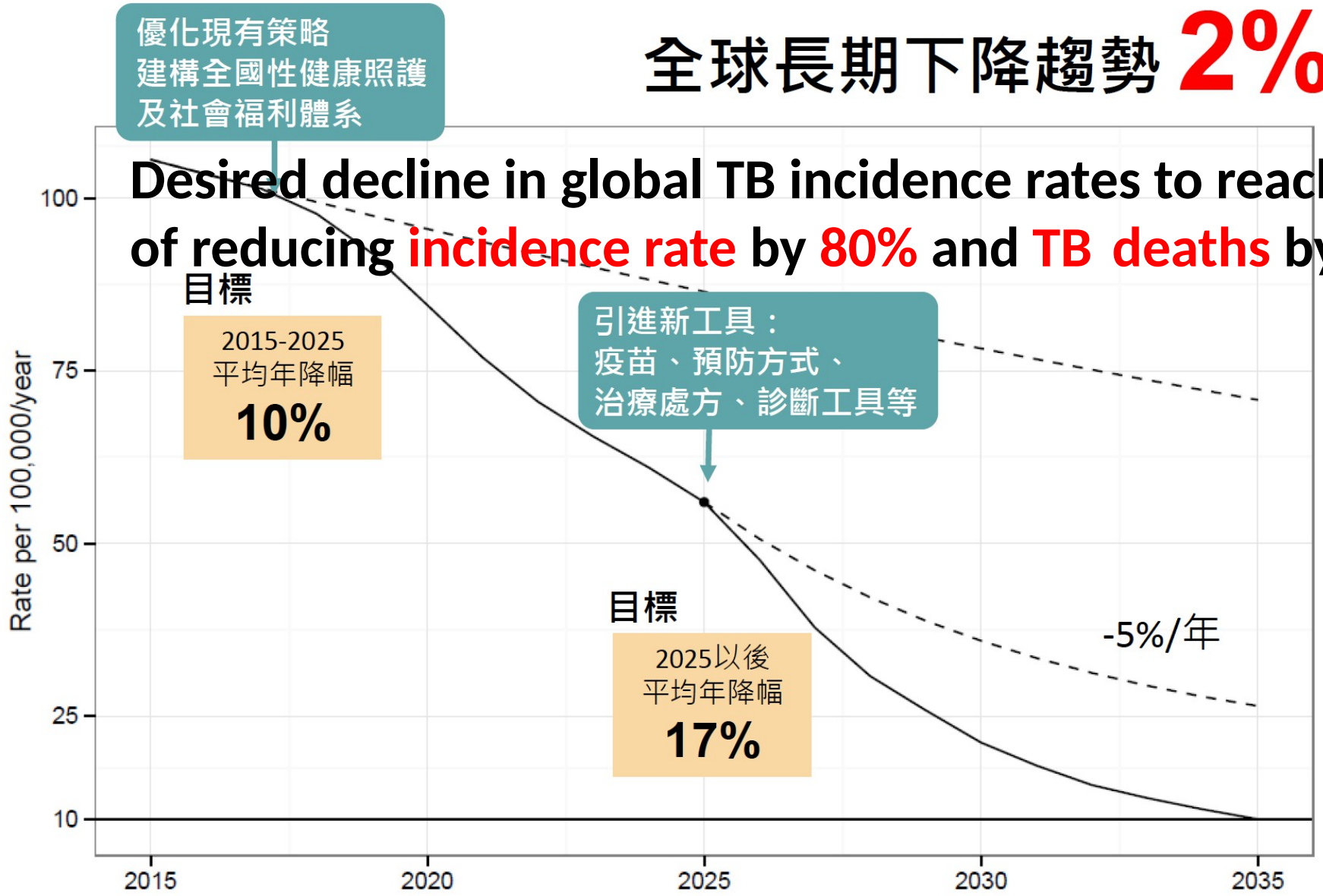
資料來源：台灣 CDC

全球消除結核目標與趨勢

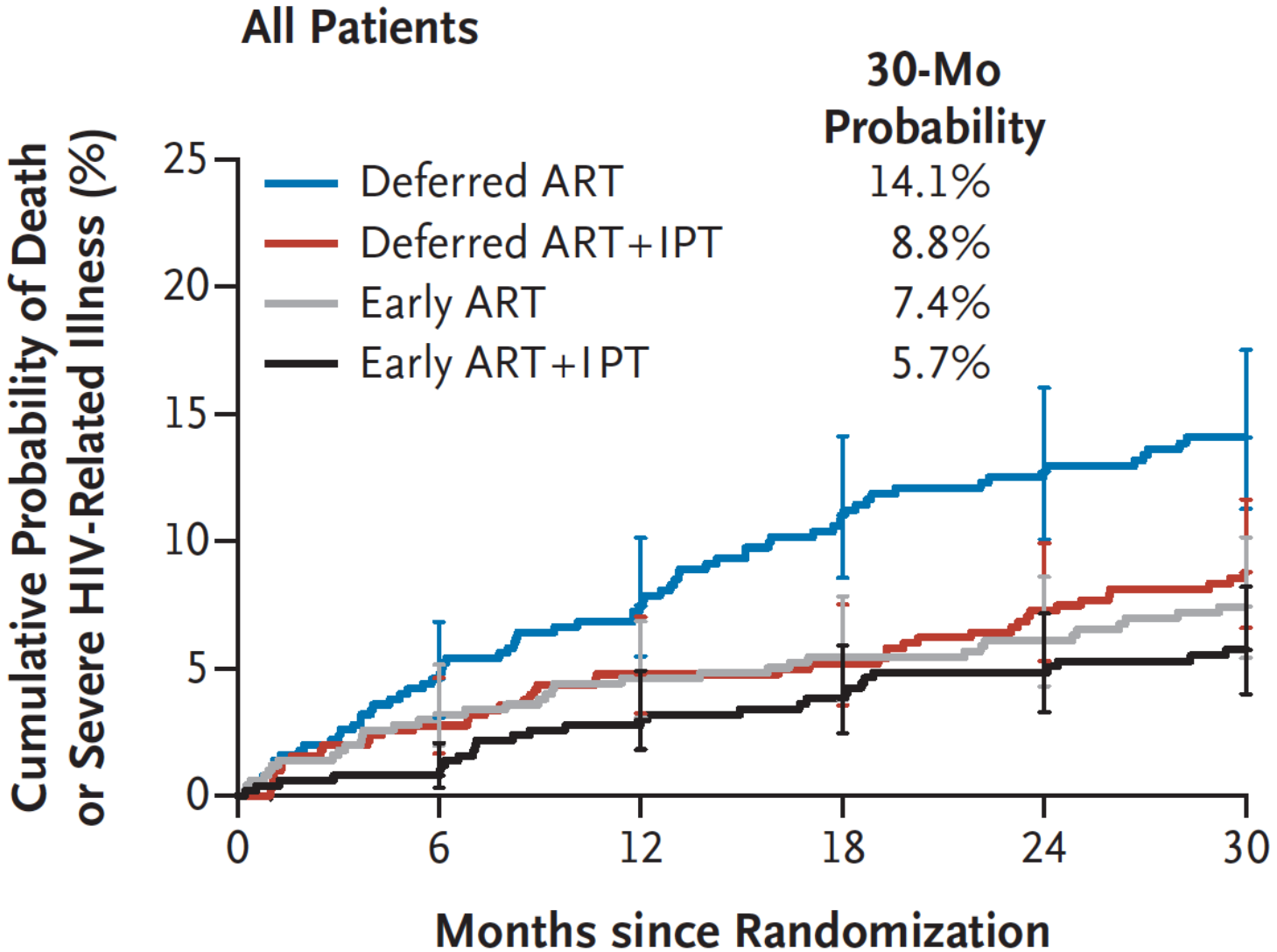


全球長期下降趨勢 **2%**

Desired decline in global TB incidence rates to reach 2030 goals of reducing incidence rate by 80% and TB deaths by 90% (WHO)



資料來源：台灣 CDC



No. at Risk

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418

TEMPRANO Study, N Engl J Med 2015

Benefits of treatment for LTBI in PLWH

- Treatment of TBI reduces the risk of progression to active TB disease
  - treatment of TBI in individuals with HIV
    - reduces **active TB disease** by 62 percent and **mortality** by 26 percent

- Treatment of TBI reduces **TB transmission**

潛伏結核感染治療處方一覽表

處方	處方藥品		療程頻率	劑量			常見副作用	使用限制(不適用對象)	都治 DOPT	推薦順序 (接觸者除指標抗藥或使用限制外)
				每日最大劑量	兒童	成人				
3HP[a]	複方	Isoniazid (INH)300mg+Rifapentine (RPT)300mg	12個劑量 (3個月) 每週服用	900 mg	體重50kg以上 固定劑量3顆		皮疹、類流感症狀、過敏反應、(少數)肝毒性	• 指標個案INH或RMP抗藥之接觸者 • 孕婦[c]	必須	推薦推薦
	單方	Isoniazid (INH)	12個劑量 (3個月) 每週服用	900 mg	• 2-11 歲 25mg/kg • 12 歲(含)以上15mg/kg		皮疹、類流感症狀、過敏反應、(少數)肝毒性	• 指標個案INH或RMP抗藥之接觸者 • 孕婦 • <2歲兒童	必須	推薦處方
		Rifapentine (RPT)		900 mg	• 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					
3HR[b]	Isoniazid (INH)		90天 (3個月) 每日服用	300 mg	10 (7-15)mg/kg	5 mg/kg	過敏反應、(少數)肝毒性	指標個案INH或RMP抗藥之接觸者	必須	推薦處方
	Rifampin (RMP)			600 mg	15 (10-20)mg/kg	10 mg/kg				
4R	Rifampin (RMP)		120天 (4個月) 每日服用	600 mg	15 (10-20) mg/kg	10 mg/kg	皮疹、腸胃不適/腸胃障礙、(少數)肝毒性	指標個案RMP抗藥之接觸者	必須	推薦處方
9H	Isoniazid (INH)		270天 (9個月) 每日服用	300 mg	10 (7-15) mg/kg	5 mg/kg	皮疹、周邊神經病變、肝毒性	指標個案INH抗藥之接觸者	建議	替代處方
1HP[a]	Isoniazid (INH)		28天 (1個月) 每日服用	300mg	300 mg		皮疹 肝毒性	• 指標個案INH或RMP抗藥之接觸者 • <13歲兒童	必須	限疾管署專案計畫使用
	Rifapentine (RPT)			600mg	• <35 kg：300 mg • 35-45 kg：450mg • >45 kg：600 mg					

a：3HP及1HP處方使用之INH300mg及HP複方為專案進口藥品，須請個案簽立藥品使用同意書
b：3HR可依體重使用INH+RMP之二合一劑型
c：目前尚未有足夠之孕婦臨床安全性相關試驗數據
參考資料：WHO operational handbook on tuberculosis (Module 1 – Prevention): Tuberculosis preventive treatment . World Health Organization. 2020及本署結核病診治診引

INH300mg藥品使用同意書

HP複方藥品使用同意書

資料來源：台灣 CDC

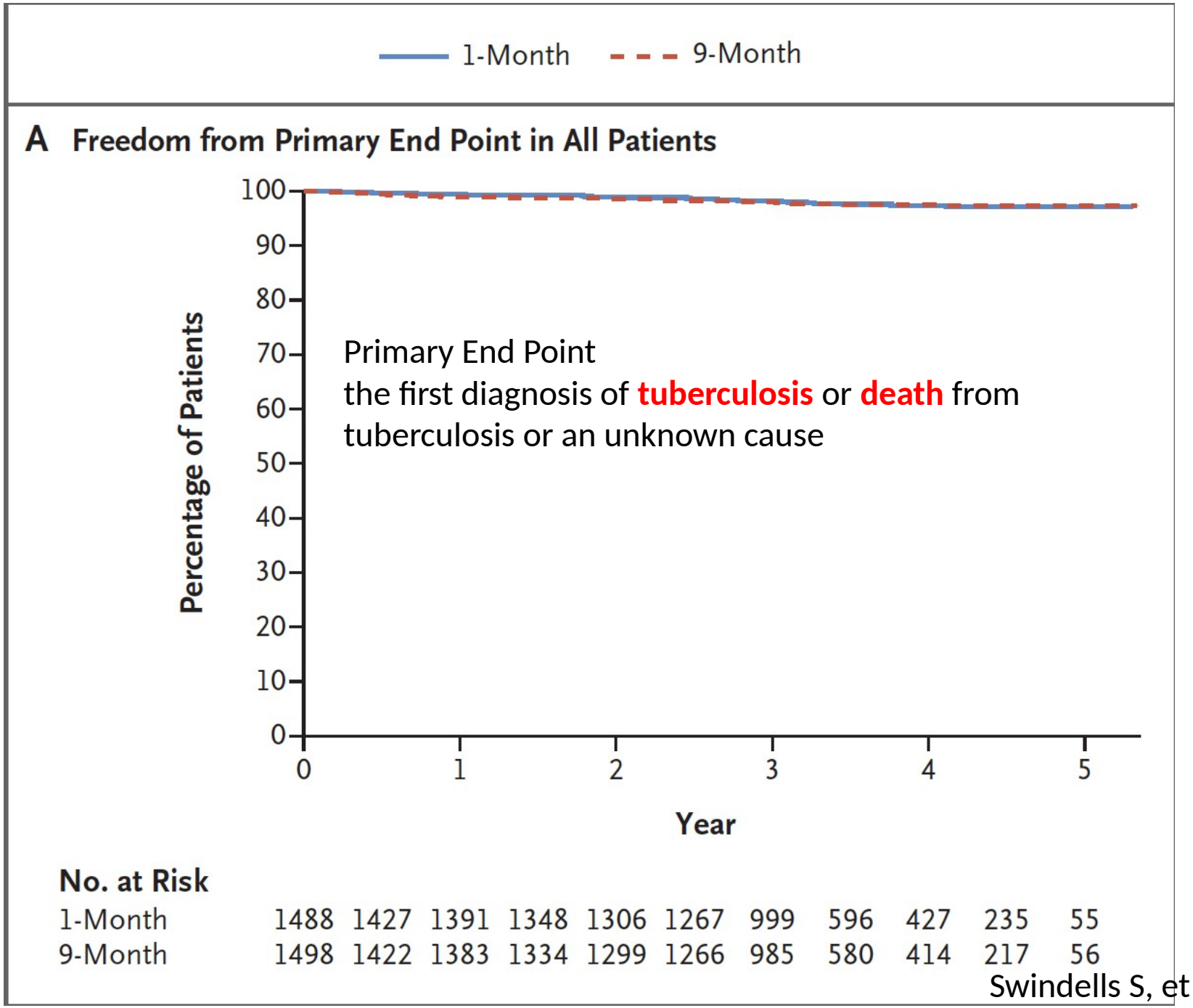
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2019 VOL. 380 NO. 11

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*

Swindells S, et al. N Engl J Med 2019



Swindells S, et al. N Engl J Med 2019

LTBI治療處方轉換建議表

已服用3HP劑次 每週服用(總療程12週)	轉換為3HR處方 每天服用(總療程90天)	轉換為4R處方 每天服用(總療程120天)	轉換為9H處方 每天服用(總療程270天)
已服用1劑次	餘83天	餘110天	餘248天
2	75	100	225
3	68	90	203
4	60	80	180
5	53	70	158
6	45	60	135
7	38	50	113
8	30	40	90
9	23	30	68
10	15	20	45
11	8	10	23

備註:

- 1個月以30天計算；4R需服用滿120天、9H需服用滿270天、3HR需服用滿90天
- 各處方間得相互轉換；除指標個案對原治療處方抗藥外，轉換後處方須按已服用比例，接續服用滿該處方的療程，並儘可能不要短少
- 接觸者於LTBI治療期間或已完成LTBI治療後，發現指標個案藥敏具抗藥性，建議依指標個案藥敏情形重新治療，以確保治療效果；倘無法重新以有效處方治療，則建議仍完成該療程，惟目前無證據確認其保護效果

MDR-TB Preventive therapy (ongoing…)

- **PHOENIx** (Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (A5300B/I2003B/)
  - a Phase III, open-label, multicenter trial
  - to compare the efficacy and safety of
    - **26 weeks of delamanid (DLM)** versus **26 weeks of isoniazid (INH)**
  - for preventing confirmed or probable active TB among high-risk household contacts (HHCs) of adults (index case) with multidrug-resistant tuberculosis (MDR-TB)

https://actgnetwork.org/2019/06/30/phoenix-mdr-tb-study-prepares-to-open/

MDR-TB Preventive therapy (ongoing…)

- **the VQUIN MDR trial**
  - A double-blind **placebo**-controlled parallel group randomised controlled trial
  - aims to evaluate the efficacy of the antibiotic **levofloxacin** in preventing the development of active TB among latently infected contacts of index patients with MDR-TB

BMJ Open 2020, 10(1):e033945

HIV感染者LTBI檢驗及治療專案

2016-2017
- 本署委託研究計畫(義大.桃療)

2017-2018
- 縣市自提計畫

2019-2020
- 本署委請26家指定醫院

2021年
- 併入愛滋品質提升計畫計42家醫院參與

2022年
- 尚未IGRA檢驗人數超過50人之醫院必執行計畫

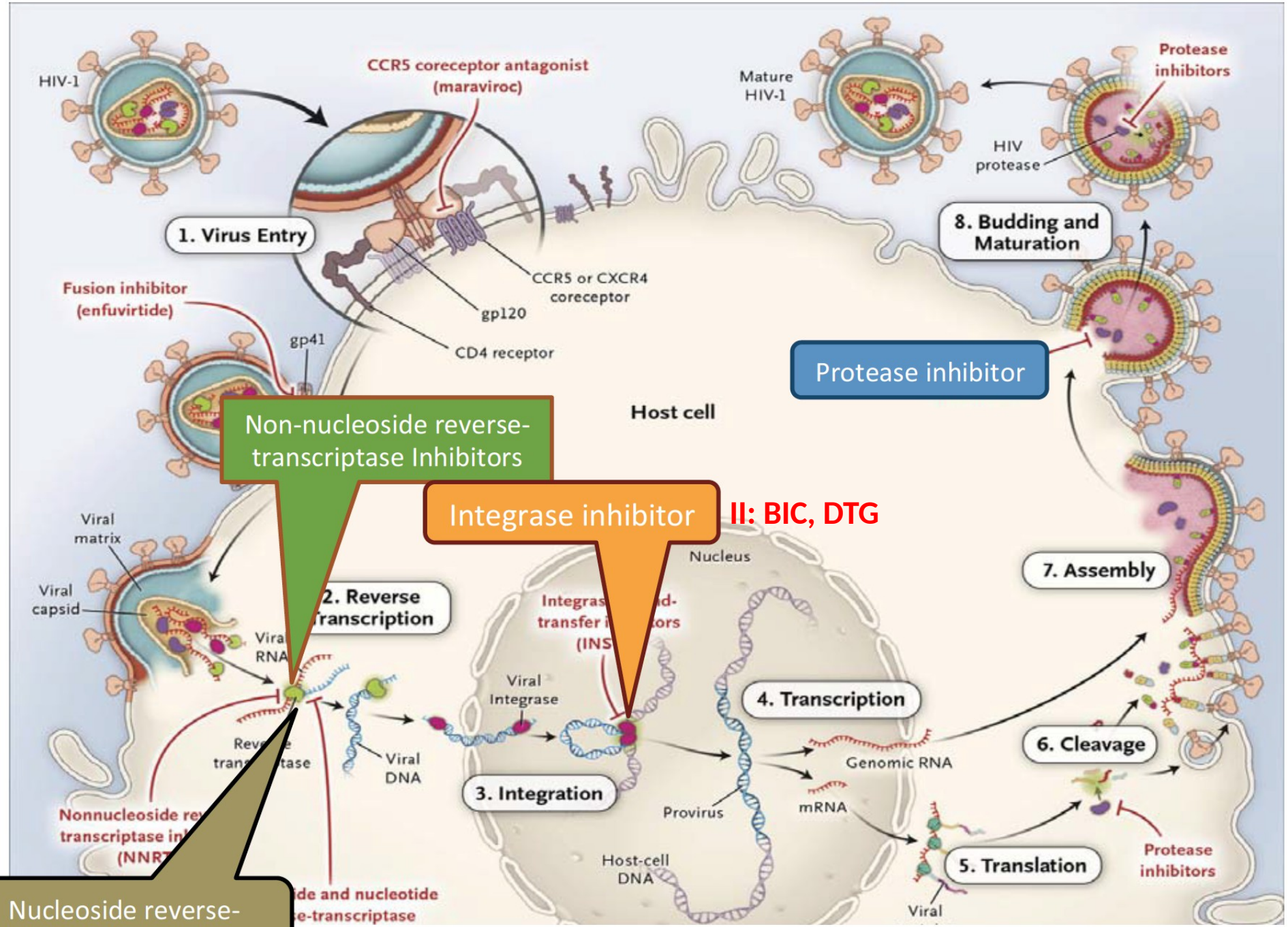
2019-2021年執行情形

主動發現結核病5人

檢驗	檢驗陽性	加入治療	完成治療*
15,290人	844人 (5.5%)	609人 (72%)	455人 (83%)

*僅計追蹤治療期滿者

資料來源：台灣 CDC



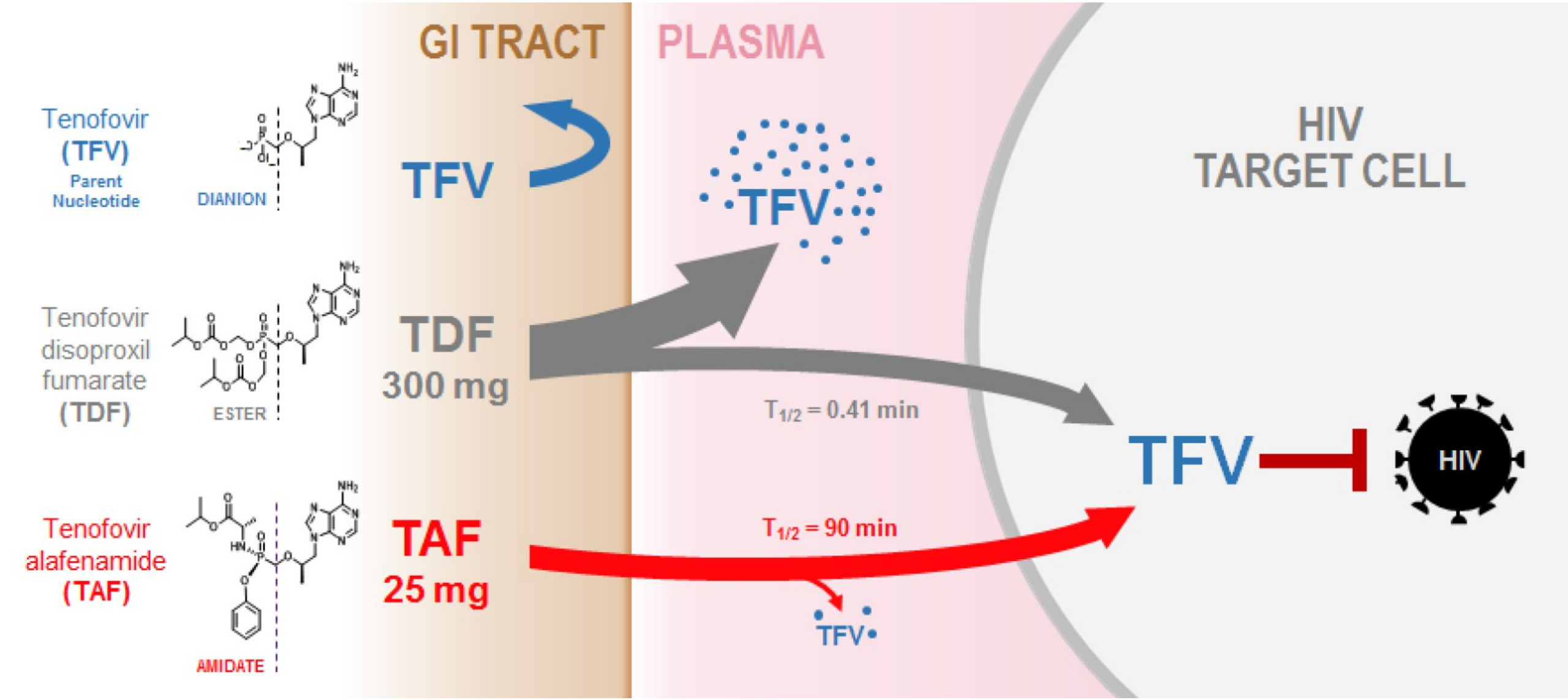
Gandhi M and Gandhi RT. N Engl J Med 2014;371:248-59.

抗人類免疫缺乏病毒藥品處方使用規範 第一線推薦處方(一天一顆)

109.12

類別	2NRTI/NNRTI			2NRTI/II		NRTI/II
商品名	Atripla 亞翠佩	Delstrigo 達滋克	Odefsey 安以斯	Biktarvy 吉他韋	Triumeq 三恩美	Dovato 洛瓦梭
外觀	 20 x 10.4 mm	 21.6 x 11.3 mm	 15 x 7 mm	 15 x 8 mm	 22 x 11 mm	 18.5 x 9.5 mm
成分	EFV 600 mg/ FTC 200 mg/ TDF 300 mg	DOR 100 mg/ 3TC 300 mg/ TDF 300 mg	RPV 25 mg/ FTC 200 mg/ TAF 25 mg	BIC 50 mg/ FTC 200 mg/ TAF 25 mg	DTG 50 mg/ 3TC 300 mg/ ABC 600 mg	DTG 50 mg/ 3TC 300 mg
服用方式	空腹 (睡前)	空腹或隨餐	隨餐	空腹或隨餐	空腹或隨餐	空腹或隨餐
切半或磨碎	不可	不可	不可	不可	可	可
病毒量限制 (copies/mL)	無	無	< 100,000	無	無	< 500,000
CD4限制 (cells/μL)	無	無	>200	無	無	無[a]
腎功能限制 (mL/min/1.73m²)	eGFR≧ 50	eGFR≧ 50	eGFR≧ 30	eGFR≧ 30	eGFR≧ 50	eGFR≧ 50
肝硬化限制	Child A/ B：可用 Child C ：無資料	Child A/ B：可用 Child C ：無資料	Child A/ B：可用 Child C ：無資料	Child A/ B：可用 Child C ：無資料	不建議	Child A/ B：可用 Child C ：無資料
潛在副作用	皮疹、肝炎、神經精神症狀、腎功能損傷、骨密度降低...等	噁心、腎功能損傷、骨密度降低...等	噁心、頭暈、做夢 (發生率均較Atripla低) ...等	腹瀉、噁心、體重增加...等	頭痛、失眠、體重增加...等	頭痛、失眠、體重增加...等

2NRTI/II		NRTI/II
Biktarvy 吉他韋	**Triumeq 三恩美**	**Dovato 洛瓦梭**
 15 x 8 mm	 22 x 11 mm	 18.5 x 9.5 mm
BIC 50 mg/ FTC 200 mg/ TAF 25 mg	DTG 50 mg/ 3TC 300 mg/ ABC 600 mg	DTG 50 mg/ 3TC 300 mg


GI TRACT
PLASMA
HIV
TARGET CELL
Tenofovir
(TFV)
Parent
Nucleotide
DIANION
TFV
TFV
Tenofovir
disoproxil
fumarate
(TDF)
ESTER
TDF
300 mg
T1/2 = 0.41 min
TFV
HIV
Tenofovir
alafenamide
(TAF)
AMIDATE
TAF
25 mg
T1/2 = 90 min
TFV

Drug-drug interactions (藥物交互作用)

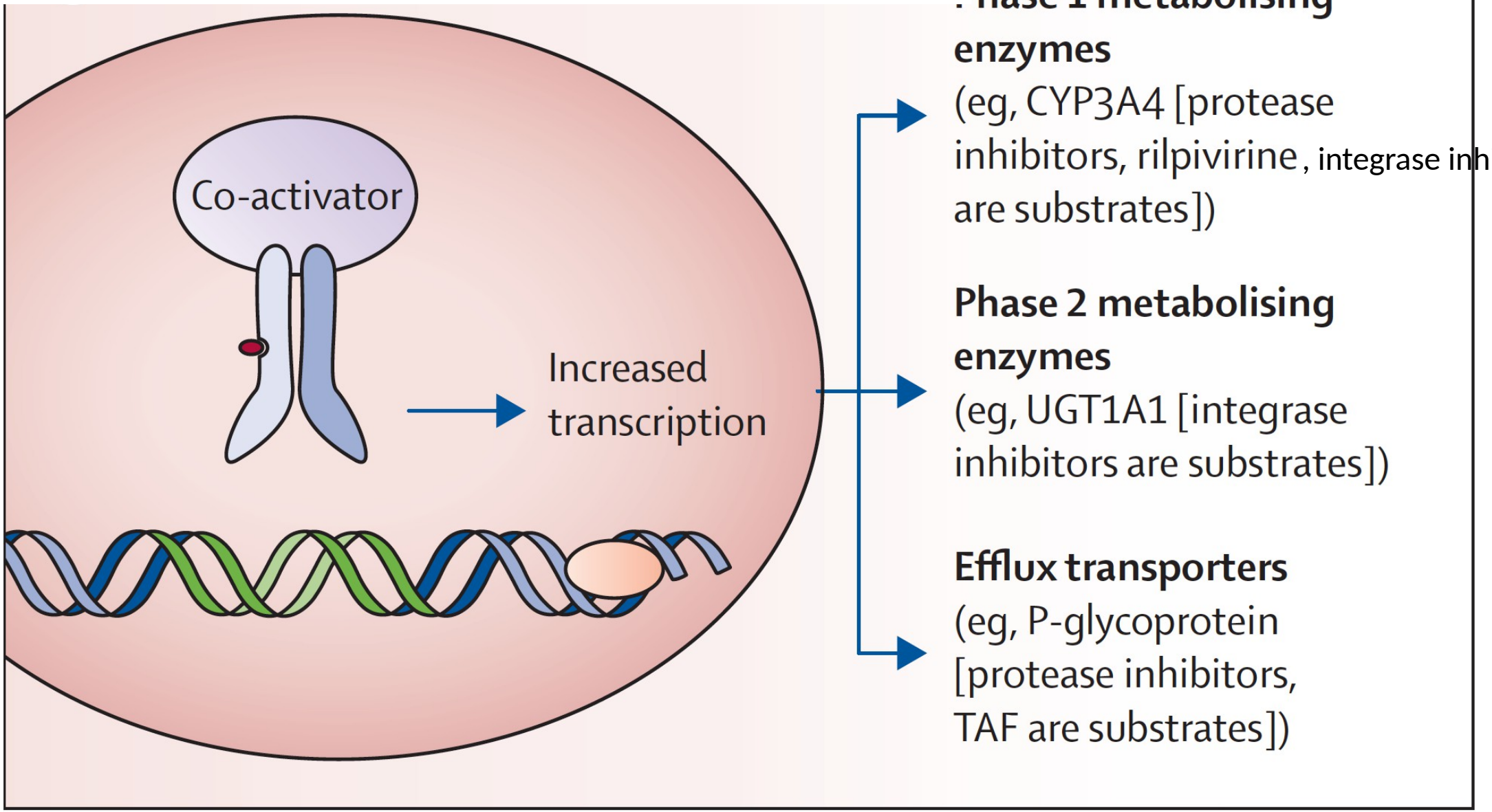


Figure 1: Mechanism of induction by rifampicin

Meintjes G, et al. Lancet HIV 2019

Table 1. Comparing features of rifampin versus rifapentine.

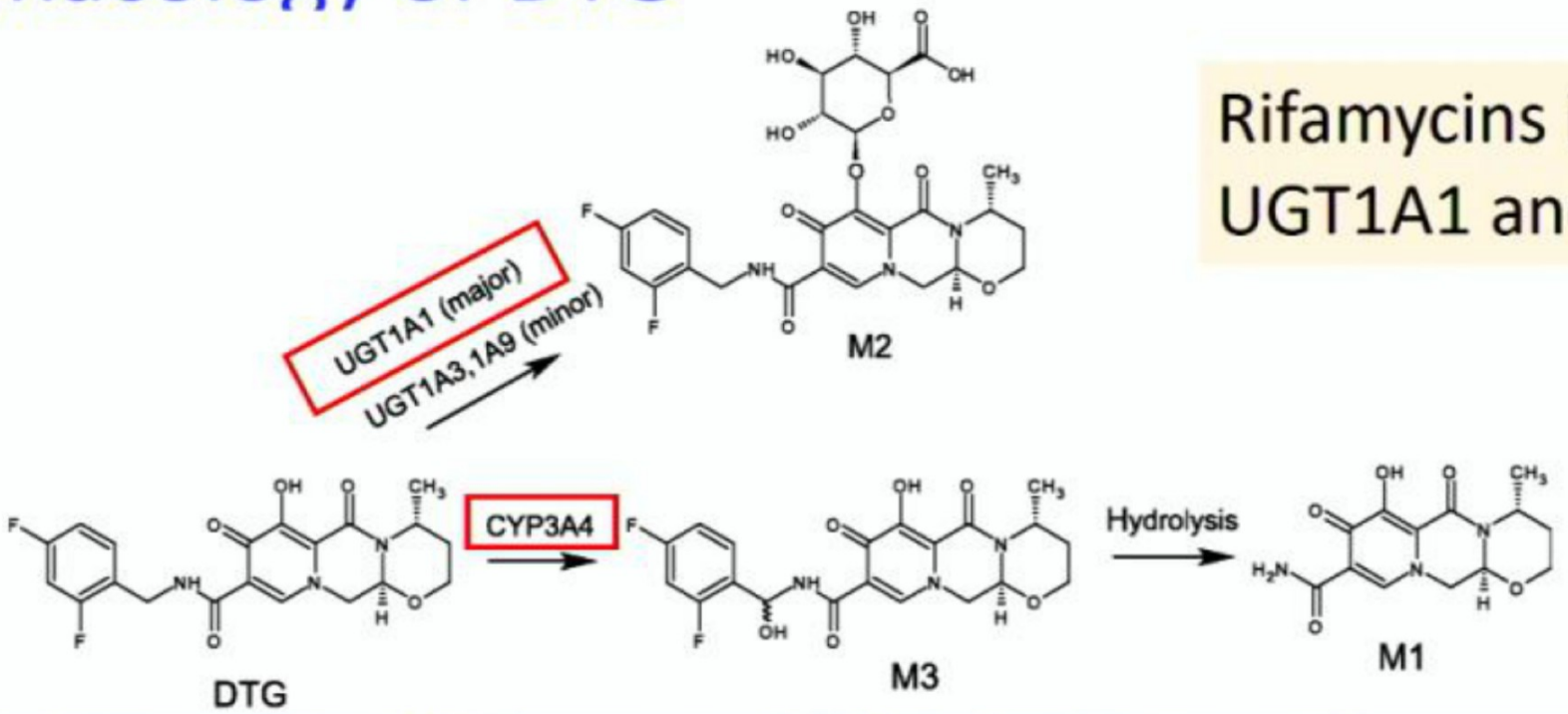
	Rifampin	Rifapentine
MIC	0.125–0.25 µg/mL	0.01–0.06 µg/mL
Half-life	2 h	15 h
Protein binding	80–85%	97–99%
Food requirement	No	Yes
Kinetic	Nonlinear (Michaelis–Menten)	Nonlinear (saturable absorption)
Hepatic enzyme induction	3-fold	4.5-fold
Flat vs. mg/kg dosing	mg/kg	Flat
Cavitary penetration	Good	Poor
Access	Global	Limited
Efficacy	Comparative efficacy at high doses is to be determined	

MIC: Minimum inhibitory concentration.

Alfarisi O, et al. Expert Rev Clin Pharmacol 2017

Rifampin induces both hepatic and intestinal **CYP (3A4/2C8/9) enzymes** and **P-glycoprotein transporters**.

Pharmacology of DTG



Rifamycins induce both UGT1A1 and CYP3A4

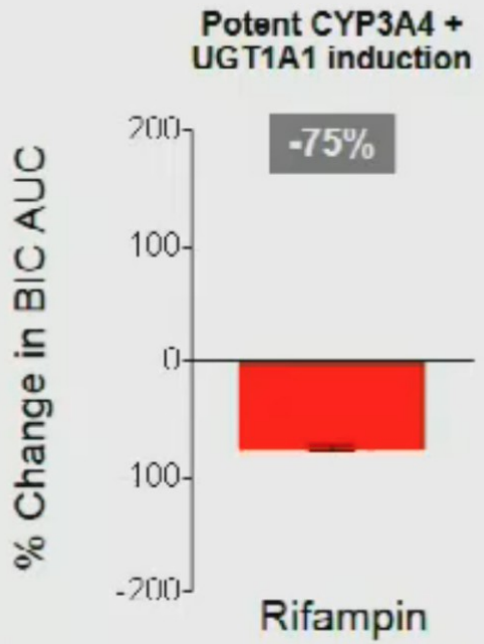
- How much DTG do we need? What is the target?
  - The protein-adjusted IC_{90} for DTG is 64 ng/mL
  - A 10 mg dose had similar 96-week virologic outcomes to a 50 mg dose, when given as part of combination therapy
  - Average trough concentration (C_T) with a 10 mg once daily dose is 300 ng/mL
  - Equivalent to the EC_{90} based on E_{max} model from PK/PD analysis of monotherapy study

SPRING-1 Van Lunzen Lancet ID 2012; Reese et al Drug Metab Disp (2013) 41: 353.

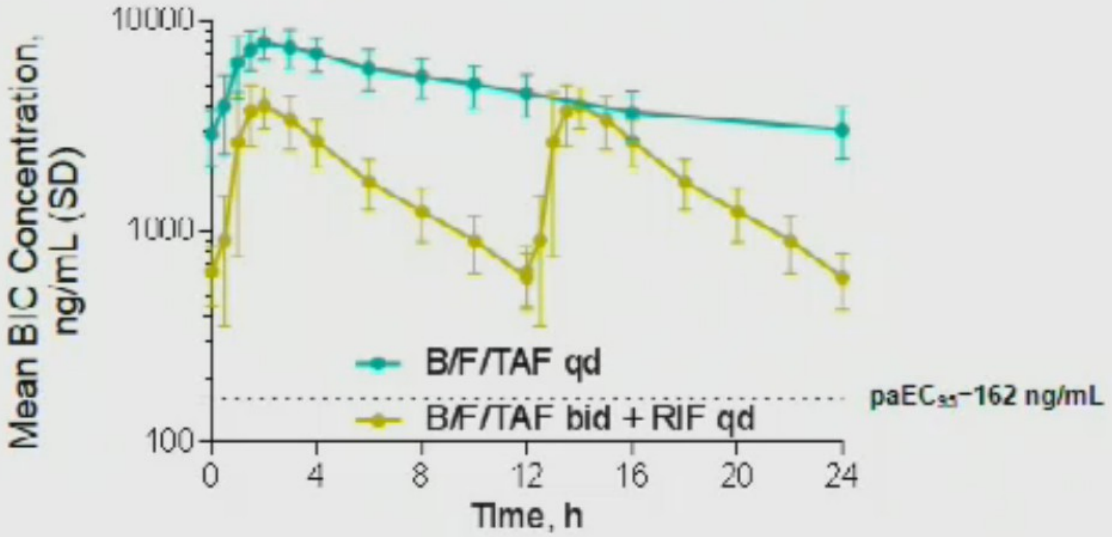
Introduction
Bictegravir (BIC)

- BIC is a substrate of drug metabolizing enzymes[1]

		BIC	RIF
Drug metabolizing enzymes	CYP3A	Substrate	Inducer
	UGT1A1	Substrate	Inducer



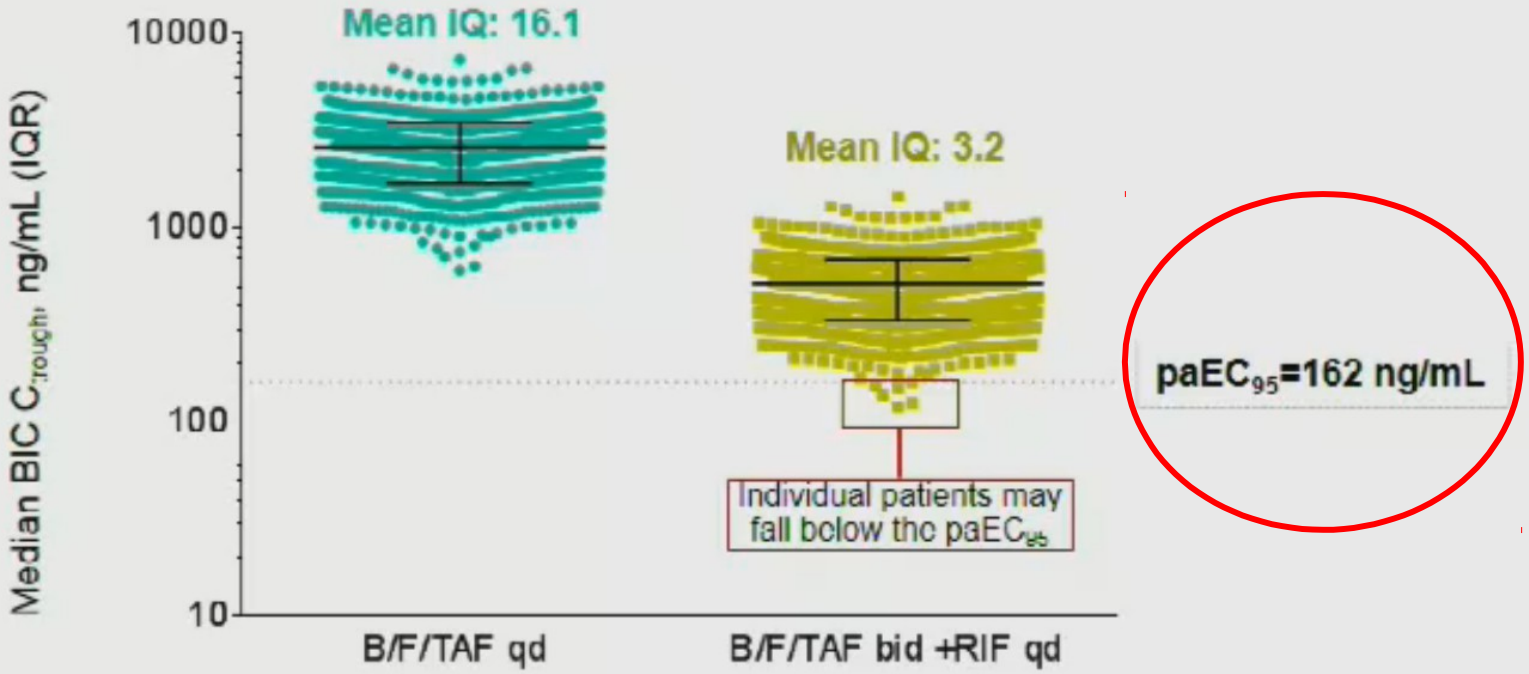
Results: Plasma BIC PK Following B/F/TAF qd vs B/F/TAF bid + RIF qd



BIC PK Mean (%CV)	B/F/TAF qd n=26 (ref)	B/F/TAF bid + RIF qd n=26 (test)	GLSM Ratio (90% CI)
AUC_{0-24}, ng•h/mL	115,000 (21)	45,600 (23)	39.5 (35.7, 43.7)
C_{max}, ng/mL	8530 (16)	4560 (19)	53.2 (49.1, 57.6)
C_{trough}, ng/mL	3070 (28)	608 (30)	19.7 (17.2, 22.7)

- Daily BIC exposure (AUC_{0-24}) is expected to be ~60% lower following administration of B/F/TAF bid + RIF qd vs B/F/TAF qd
- Following administration of B/F/TAF bid + RIF qd, mean BIC C_T was reduced by ~80% vs B/F/TAF qd

Results: BIC IQ in HIV-Infected Patients in Phase 3 (n=1193) B/F/TAF qd vs B/F/TAF bid + RIF qd



- Following administration of B/F/TAF in HIV-infected patients in Phase 3 studies (N=1193), mean IQ of BIC was 16.1[1]
  - After accounting for ~80% reduction in BIC C_{trough} following B/F/TAF bid + RIF qd vs B/F/TAF qd, individual patients may fall below the $paEC_{95}$

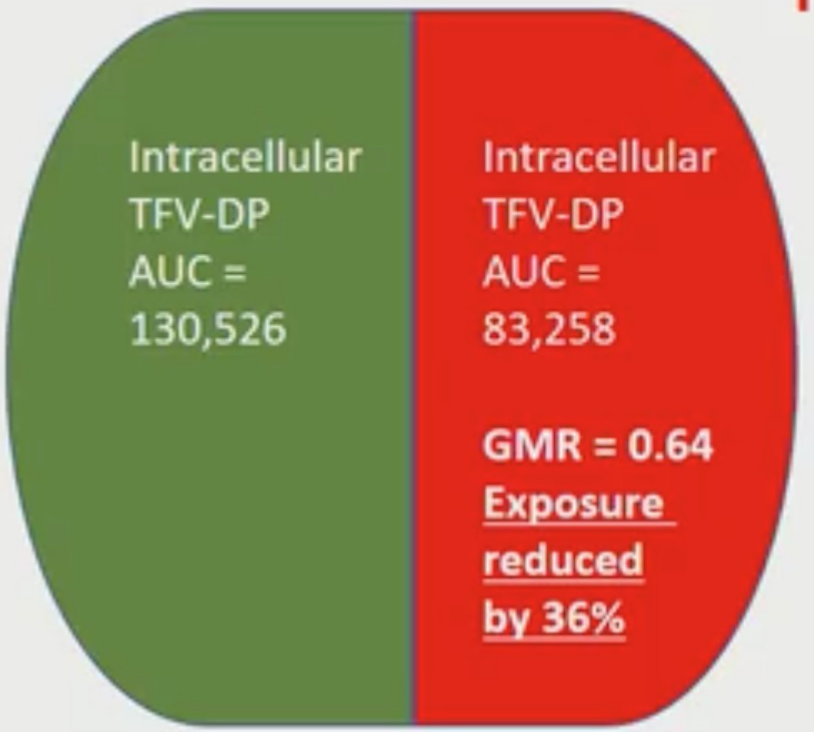
1. Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2018.

TAF versus TAF + rifampicin

RIFT trial
Healthy volunteers, n = 21

TAF 25mg

Plasma TAF AUC = 88



TAF 25mg + Rifampicin

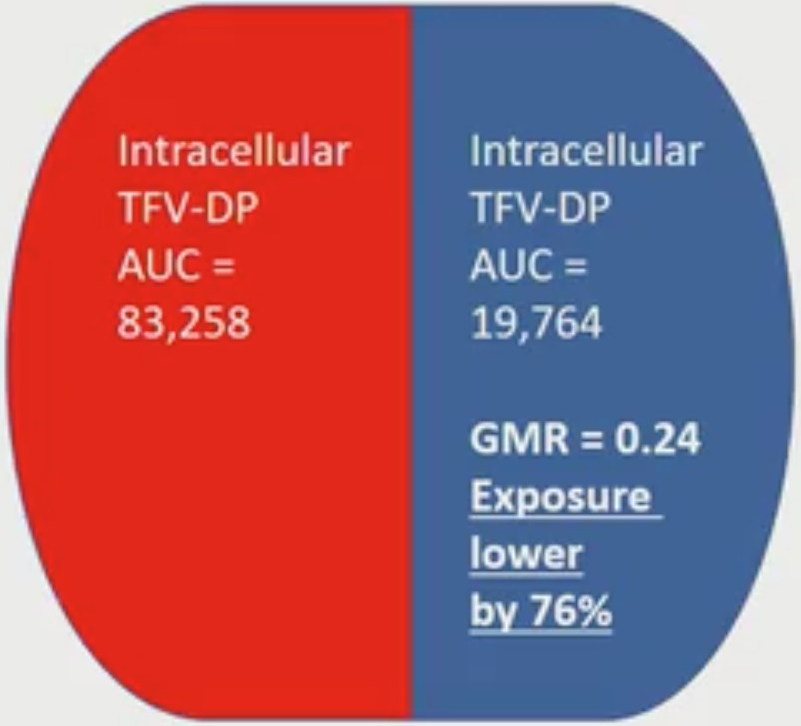
Plasma TAF AUC = 39
GMR = 0.45
55% reduction in exposure

GMR = Geometric mean ratio
Plasma AUC in ng*h/mL
Intracellular AUC in fmol*h/10^6

Cerrone, CROI 2018, Abstract 28LB

TAF + rifampicin versus TDF

TAF 25mg + Rifampicin



Tenofovir Disoproxil Fumarate 300mg

GMR = Geometric mean ratio
Intracellular AUC in fmol*h/10^6

➡ Evaluation in HIV-TB patients planned

Treatment of LTBI vs. ART

- 3HP
  - The DTG-based regimen
  - The BIC-based regimen
- 1HP
  - The DTG-based regimen
  - The BIC-based regimen

Clinical Infectious Diseases

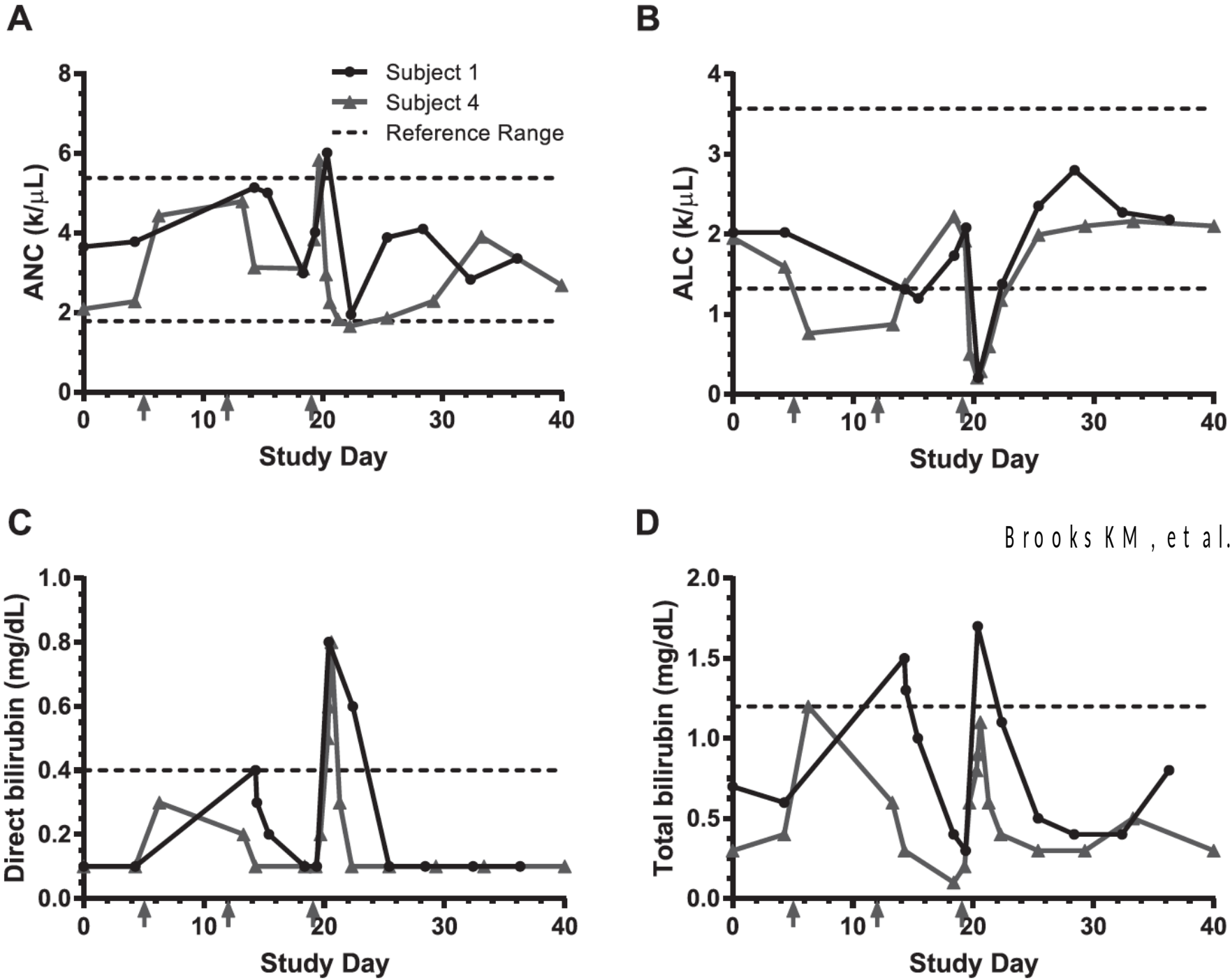
MAJOR ARTICLE

Cytokine-Mediated Systemic Adverse Drug Reactions in a Drug–Drug Interaction Study of Dolutegravir With Once-Weekly Isoniazid and Rifapentine

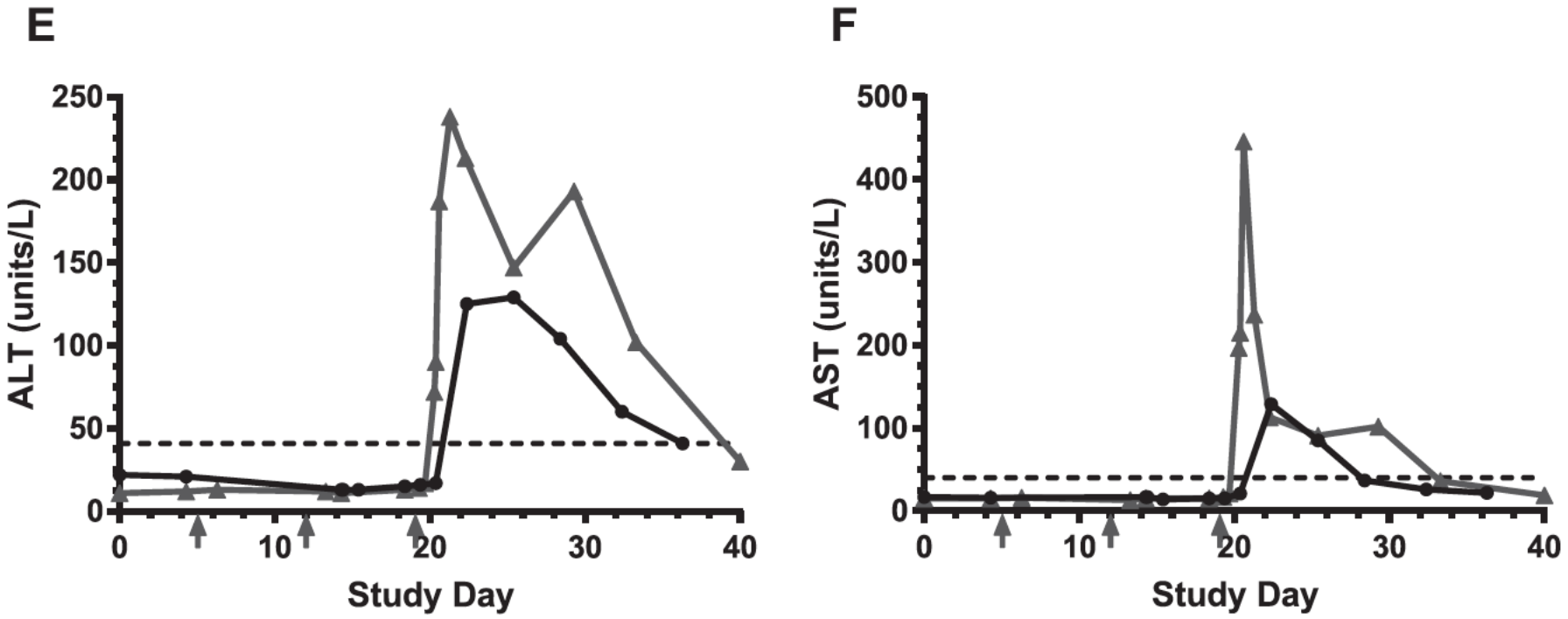
Kristina M. Brooks,[1,a] Jomy M. George,[1] Alice K. Pau,[2] Adam Rupert,[3] Carolina Mehaffy,[4] Prithwiraj De,[4] Karen M. Dobos,[4] Anela Kellogg,[5] Mary McLaughlin,[6] Maryellen McManus,[7] Raul M. Alfaro,[1] Colleen Hadigan,[6] Joseph A. Kovacs,[7] and Parag Kumar[1]

[1]Clinical Pharmacokinetics Research Unit, Pharmacy Department, Clinical Center, National Institutes of Health (NIH), and [2]Division of Clinical Research, National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, and [3]AIDS Monitoring Laboratory, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc, Frederick, Maryland; [4]Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins; and [5]Clinical Monitoring Research Program, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc, Frederick, and [6]Clinical Research Section, NIAID, and [7]Critical Care Medicine Department, Clinical Center, NIH, Bethesda, Maryland

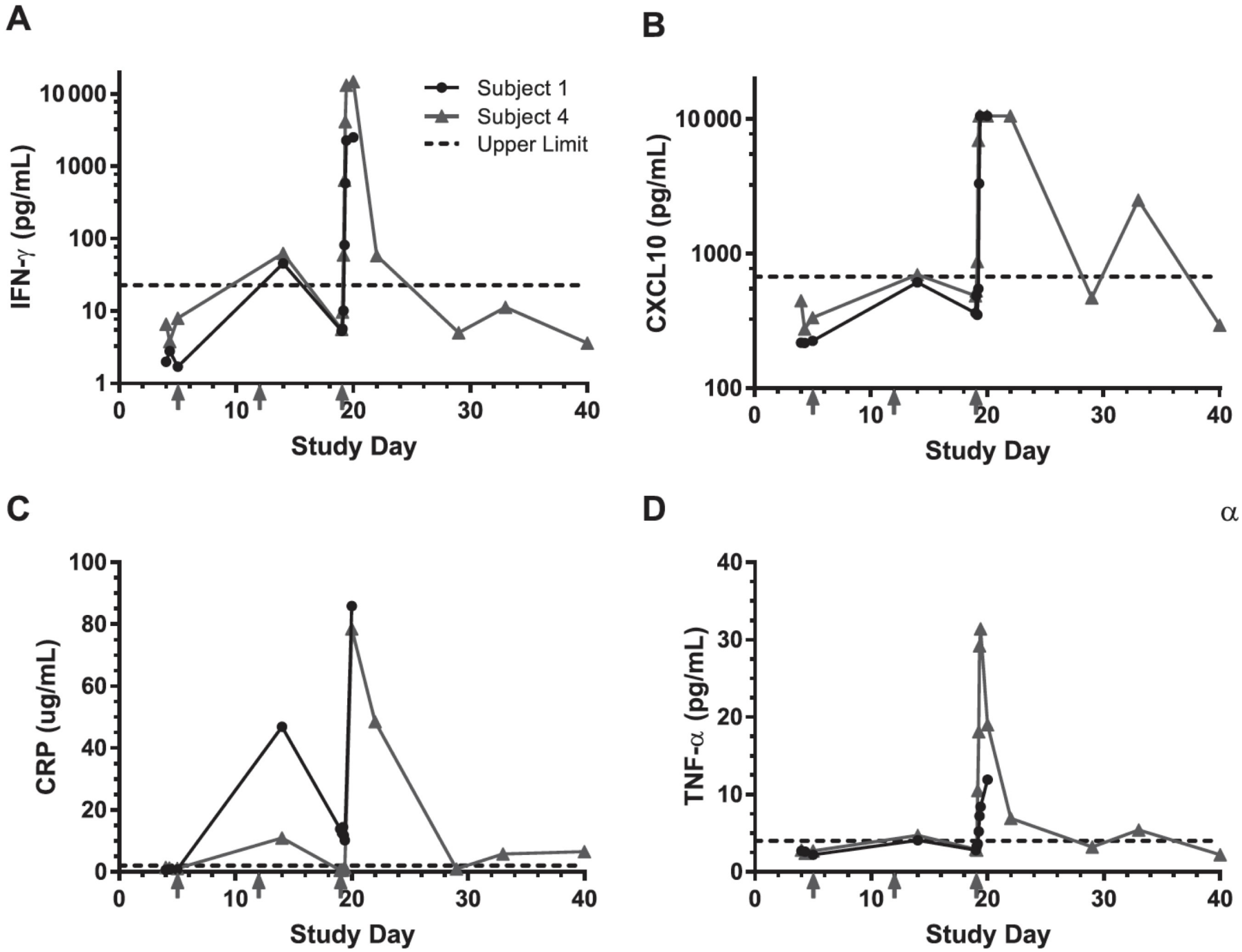
Brooks KM, et al. Clin Infect Dis 2018



Brooks KM, et al. Clin Infect Dis 2018



Brooks KM, et al. Clin Infect Dis 2018


A
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Subject 4
Upper Limit
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Study Day
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CXCL10 (pg/mL)
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1000
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20
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Study Day
C
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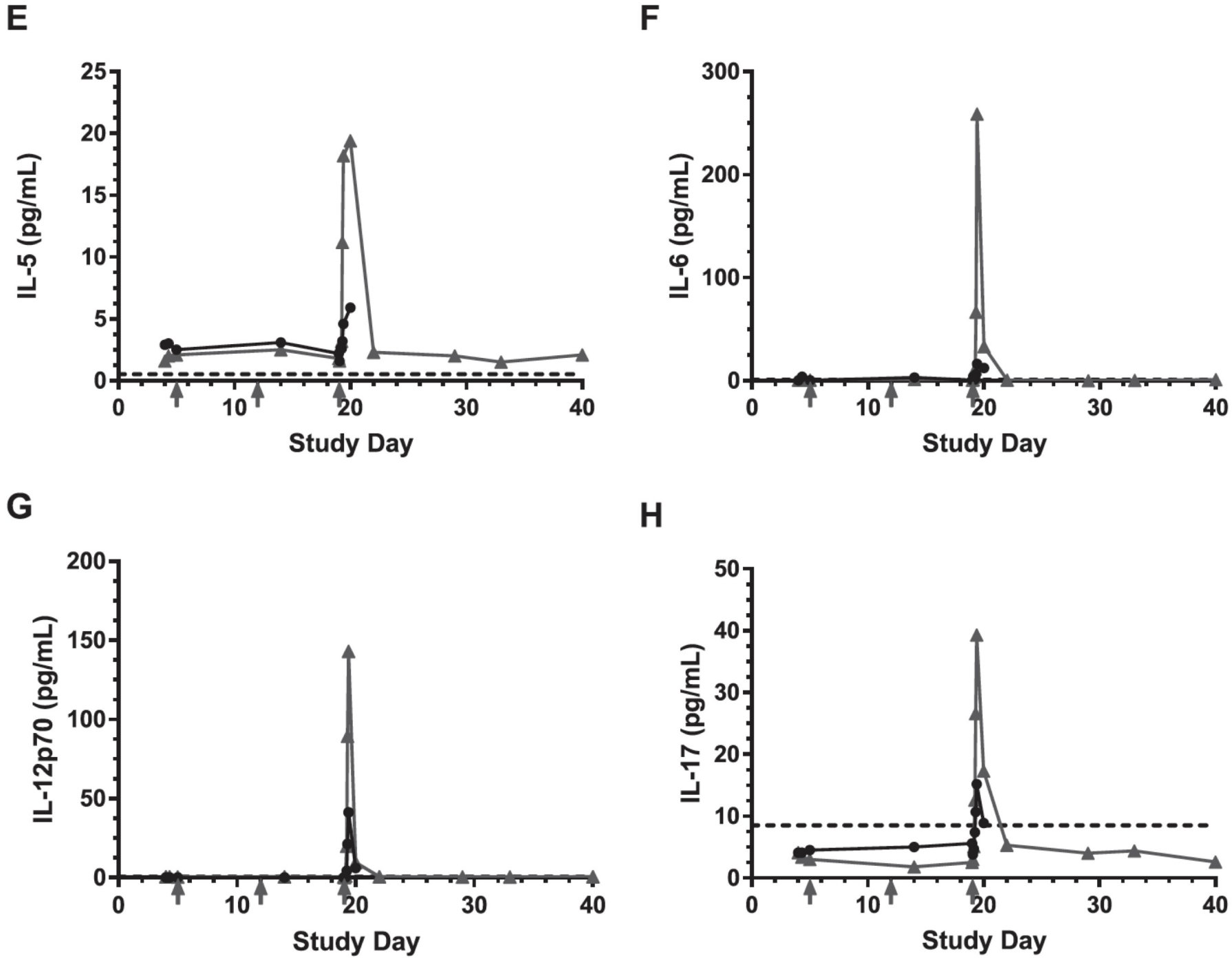
E
IL-5 (pg/mL)
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Study Day
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IL-6 (pg/mL)
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IL-12p70 (pg/mL)
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150
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Study Day
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30
40
Study Day

DTG-based regimen plus 3HP

Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial

*Kelly E Dooley, Radojkam Savic, Akshay Gupte, Mark A Marzinke, Nan Zhang, Vinodh A Edward, Lisa Wolf, Modulakgotla Sebe, Morongwe Likoti, Mark J Fyvie, Innocent Shibambo, Trevor Beattie, Richard E Chaisson, Gavin J Churchyard, the DOLPHIN Study Team**

Summary

Background Short-course preventive therapy with 12 doses of once-weekly rifapentine (900 mg) plus isoniazid (900 mg) could greatly improve tuberculosis control, especially in areas with high co-endemicity with HIV. However, a small previous trial of such therapy with dolutegravir in healthy, HIV-negative adults was halted early after two of the four patients developed serious adverse events. Because of the potential use of this therapy, and variable safety outcomes of tuberculosis drugs seen in patients with and without HIV, we aimed to characterise safety, pharmacokinetics, and virological suppression in adults who are HIV positive.

Methods DOLPHIN was a phase 1/2, single-arm trial done at The Aurum Institute (Tembisa Clinical Research Site, Tembisa, South Africa), with pharmacokinetic visits done at VxPharma (Pretoria, South Africa). Adults (≥18 years) with HIV infection and undetectable viral load (<40 copies per mL) after at least 8 weeks of efavirenz-based or

Lancet HIV 2020

Published Online
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https://doi.org/10.1016/S2352-3018(20)30032-1

See Online/Comment
https://doi.org/10.1016/S2352-3018(20)30074-6

*Members of the DOLPHIN Study Team are listed at the end of this Article

	Days after rifapentine plus isoniazid dose	Geometric mean (ng/mL)	Geometric mean 90% CI
Days 57 and 58 (n=60)	Not applicable	1003	900–1117
Day 59 (n=30)	1	1053	904–1226
Day 72 (n=30)	7	492	400–605
Day 73 (n=60)	1	657	584–739
Day 74 (n=60)	2	355	307–410
Day 78 (n=30)	6	388	327–460
Day 108 (n=60)	1	703	614–805
Day 109 (n=60)	2	394	344–452

Rifapentine plus isoniazid doses were given on days 58, 65, 72, 79, 86, 93, 100 107, 114, 121, 128, and 135. Values from study days 57 and 58 represent dolutegravir, taken alone. Subsequent dolutegravir doses were taken in the context of once-weekly rifapentine plus isoniazid. For n=30, Groups 1A (n=12) and 1B (n=18) have been combined. For n=60, all three groups have been combined.

Geometric mean ratio DTG/RPT/INH vs. DTG

Overall: 0.53 (90% CI 0.49-0.56)

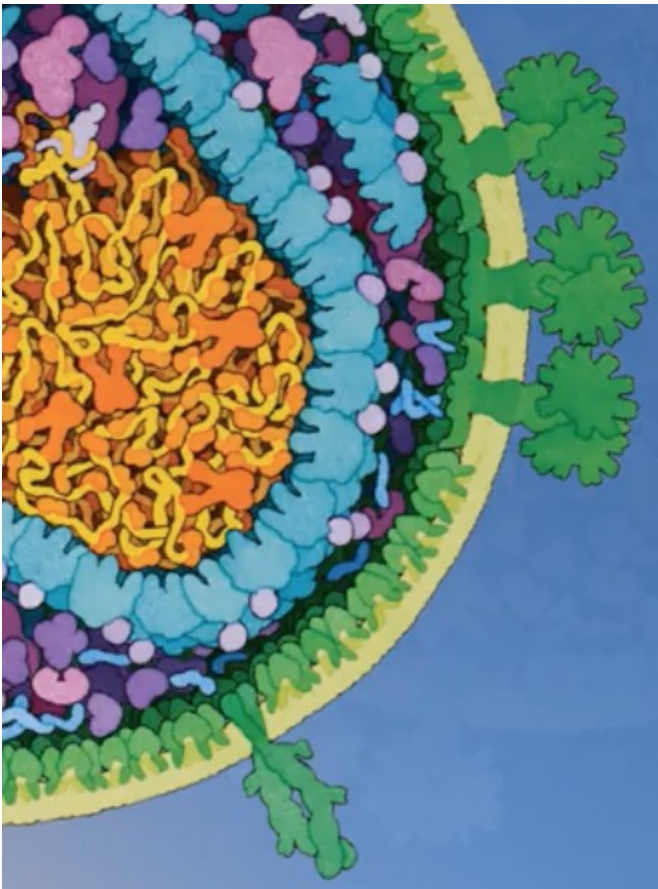
Day 1: 0.77 (0.71-0.84)

Day 2: 0.36 (0.32-0.40)

Day 5-6: 0.44 (0.40-0.48)

Dooley KE, et al. Lancet HIV 2020

BIC-based regimen plus 3HP



SCIENCE SPOTLIGHT™

DRUG INTERACTIONS WITH ONCE-DAILY B/F/TAF IN COMBINATION WITH ONCE-WEEKLY RIFAPENTINE

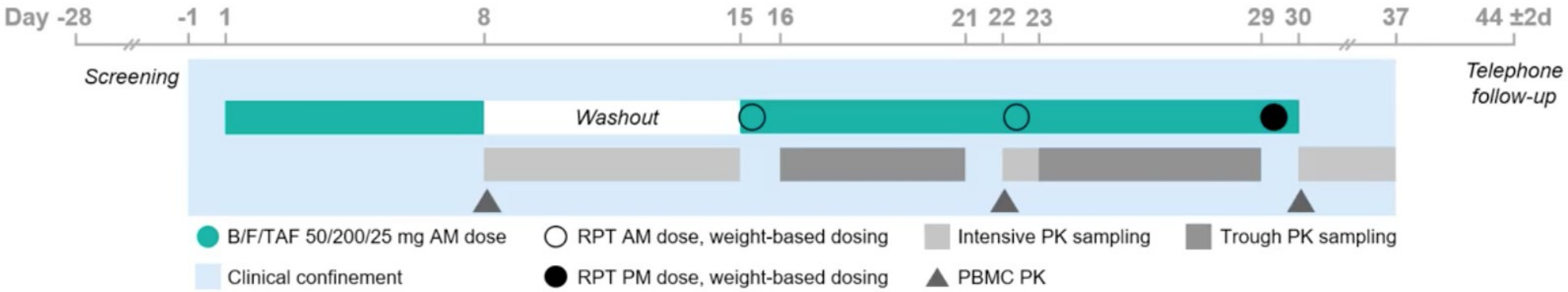
Priyanka Arora, PhD

Gilead Sciences, Inc
Foster City, CA, USA

Disclosure: Presenting author Priyanka Arora is an employee of Gilead Sciences, Inc and holds stock in the company

CROI 2021

Study Design

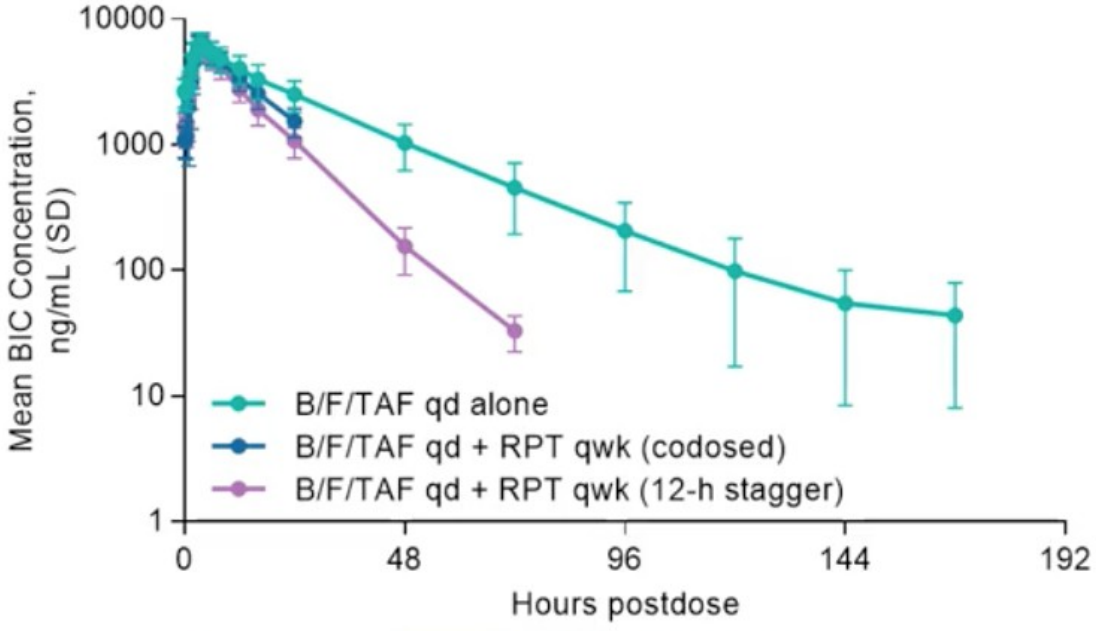


- A Phase 1, open-label, 3-period fixed sequence, multiple-dose, single-center study was conducted in 30 HIV-negative healthy volunteers
- An even distribution (1:1) of healthy male and nonpregnant, nonlactating female participants aged 18–45 y were enrolled in the study
- PK in plasma and PBMC was assessed at pre-specified timepoints
- PK parameters were estimated by noncompartmental methods using WinNonlin v8.2*
- Statistical analysis
  - GLSM ratios and corresponding 90% CIs were used for statistical comparisons of exposures
  - Test: B/F/TAF qd coadministered with RPT qwk or administered 12 h after RPT; reference: B/F/TAF qd alone

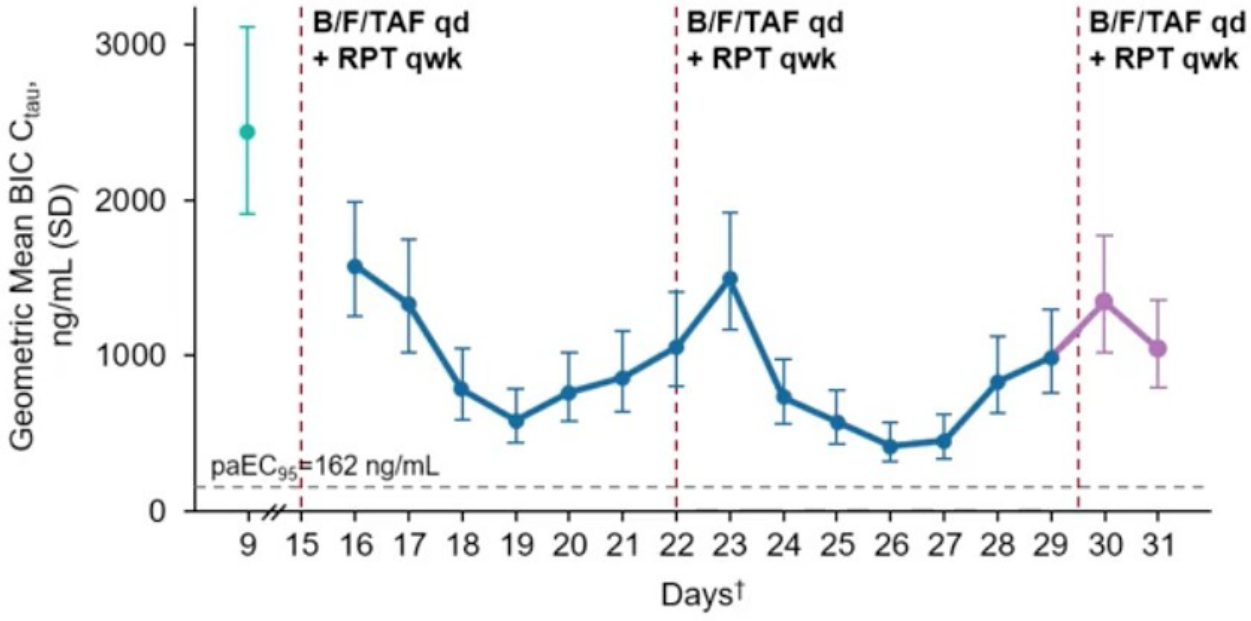
*Certara USA, Inc., Princeton, NJ. CI, confidence intervals; GLSM, geometric least-squares mean; qd, once daily; qwk, once weekly.

Results: BIC PK

BIC Plasma PK Following B/F/TAF qd Alone vs Coadministered With or Administered 12-h After RPT qwk



Trend of BIC C_{tau} Throughout Study Days Across Treatment Periods



PK Parameter Mean (%CV)	B/F/TAF qd n=29	B/F/TAF qd + RPT qwk codosed n=29	B/F/TAF qd + RPT qwk 12-h stagger n=28	%GLSM (90% CI)	
				Codosed vs alone	12-h stagger vs alone
C_{max}, ng/mL	6870 (16.3)	6880 (16.9)	6590 (16.6)	100 (95.5, 105)	96.0 (91.8, 100)
AUC_{tau}, h·ng/mL	96100 (23.3)	81400 (17.9)	70800 (18.3)	85.5 (81.3, 89.8)	74.1 (70.2, 78.3)
C_{tau}, ng/mL	2510 (28.1)	1520 (26.6)	1080 (27.2)	60.4 (56.3, 64.7)*	42.5 (39.1, 46.2)*
Median $T_{1/2}$, h (Q1, Q3)	20.7 (18.5, 22.3)	10.3 (9.71, 11.2)	8.82 (8.07, 9.23)		

Key findings:

- BIC C_{tau} reduced by as low as 83% by Day 4 post RPT dosing (nadir)
- BIC C_{tau} never recovered back to steady state concentrations between RPT doses
- 12-hr staggered (vs coadministration) of RPT qwk resulted in more pronounced decline in BIC C_{tau}

*Outside no-effect drug-drug interaction boundaries; †Relative to date of first study drug administration (Day 1). AUC_{tau}, area under plasma concentration-time curve over dosing interval; C_{max}, maximal concentration; C_{tau}, trough concentration; CV, coefficient of variation; $paEC_{95}$, protein-adjusted 95% effective concentration; SD, standard deviation.

DTG-based regimen plus 1HP

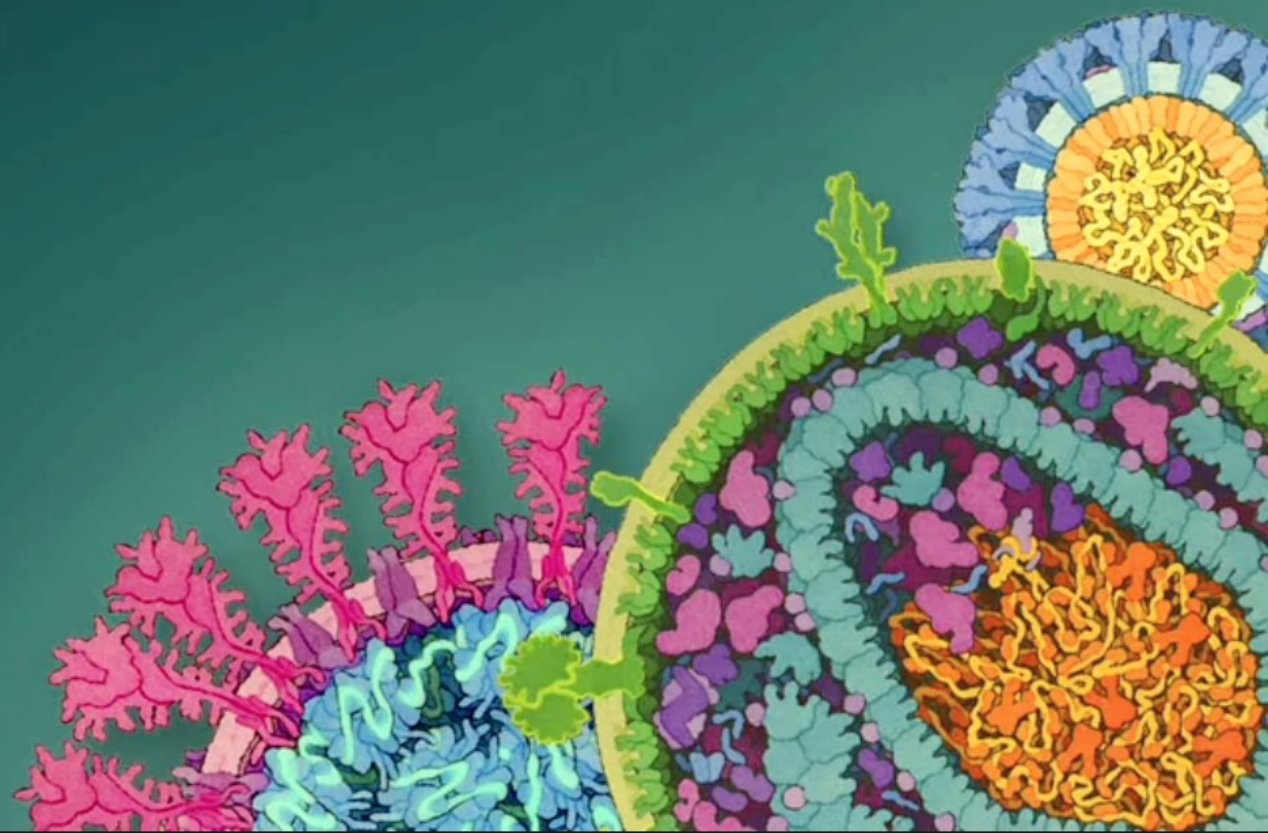
CROI 2022

Dolutegravir Pharmacokinetics In People with HIV Receiving Daily 1HP for Latent TB Treatment (ACTG A5372)

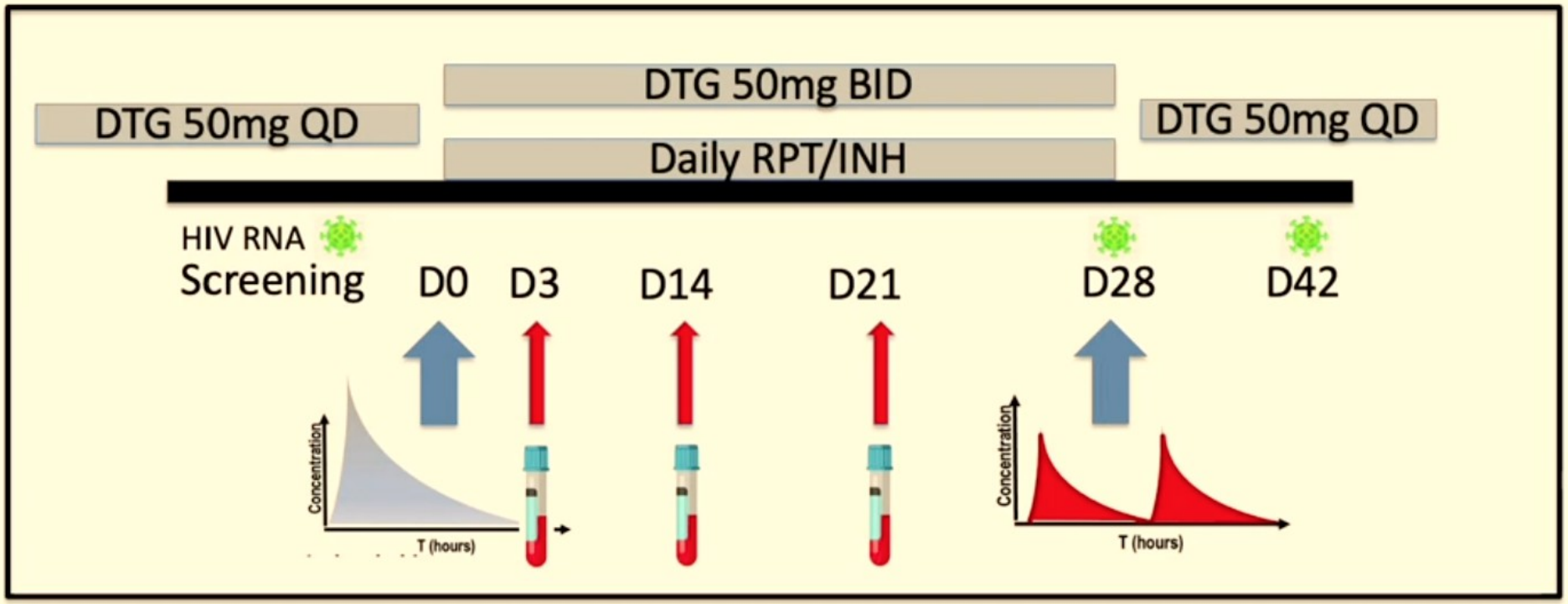
Anthony Podany

University of Nebraska Medical Center

Disclosure: None



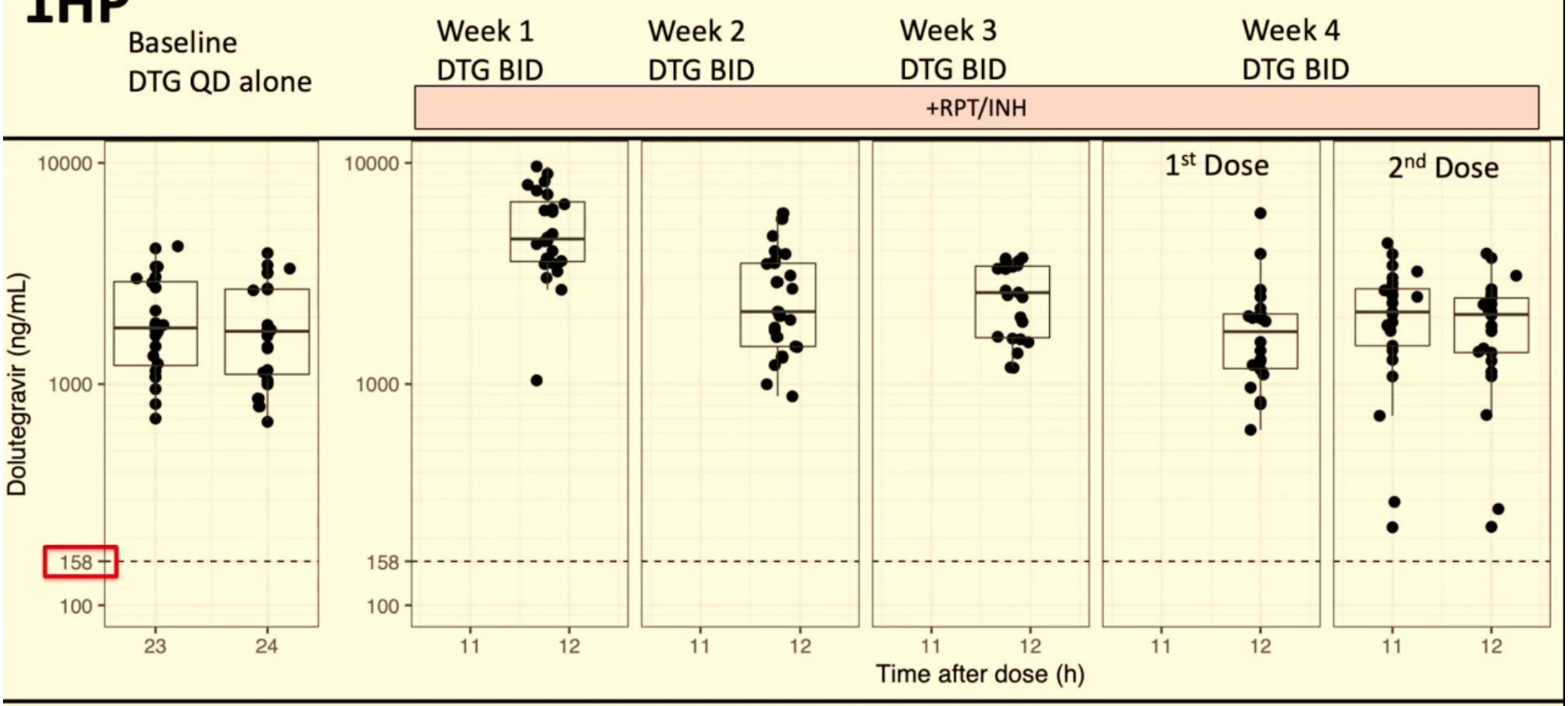
ACTG 5372 Methods



DTG Sampling & Analysis

- Intensive PK: Day 0 and 28: pre-dose, 1,2,4,8,12,13,14,23,24 hours
- Sparse PK (trough only): Days 3, 14 and 21
- DTG concentrations analyzed by validated LC/MS/MS method

Dolutegravir Trough Concentrations Before and During 1HP



Conclusion

- DTG trough concentrations with 50mg twice daily dosing during 1HP were higher, not lower, than those with standard dose DTG once daily alone
- A decrease in DTG trough concentrations from day 3 to day 28 is suggestive of a time dependent induction of DTG metabolism from RPT
- All DTG trough concentrations were above the DTG target of 158ng/mL
- Combination of DTG and 1HP was well tolerated and no participants experienced hypersensitivity
- These interim PK, virologic suppression, and safety data provide evidence for twice daily DTG in combination with the 1HP regimen
- A5372 has the potential to investigate once daily DTG in combination with 1HP pending full analysis of arm 1 data

BIC-based regimen plus 1HP

Liou B-H et al. *Journal of the International AIDS Society* 2021, **24**:e25844
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25844/full | https://doi.org/10.1002/jia2.25844

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Short-course daily isoniazid and rifapentine for latent tuberculosis infection in people living with HIV who received coformulated bictegravir/emtricitabine/tenofovir alafenamide

Bo-Huang Liou[1], Chih-Ning Cheng[2], Ya-Ting Lin[2], Yu-Jou Lin[3], Yu-Chung Chuang[4], Kuan-Yin Lin[4], Wen-Chun Liu[4], Shu-Wen Lin[2,3,5], Ching-Hua Kuo[2], Hsin-Yun Sun[4,§] and Chien-Ching Hung[4,6]

[§]**Corresponding author**. Hsin-Yun Sun, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, 7 Chung-Shan South Road, Taipei 100, Taiwan. (hysun@ntu.edu.tw)

The preliminary data of the present study were presented as an oral abstract (abstract no. 132) at the *Conference on Retroviruses and Opportunistic Infections* (CROI) 2021.

Liou BH, et al. JIAS 2021

Methods

- Inclusion criteria
  - PLWH who are 20 years of age or older seeking HIV care at the National Taiwan University Hospital (NTUH) and receiving Biktarvy with viral suppression (<200 copies/ml) for 6 months or longer who test positive for interferon gamma release assay (IGRA)

- Exclusion criteria
  - PLWH with active TB or suspicion of active TB
  - PLWH with a history of having received treatment for LTBI or active TB

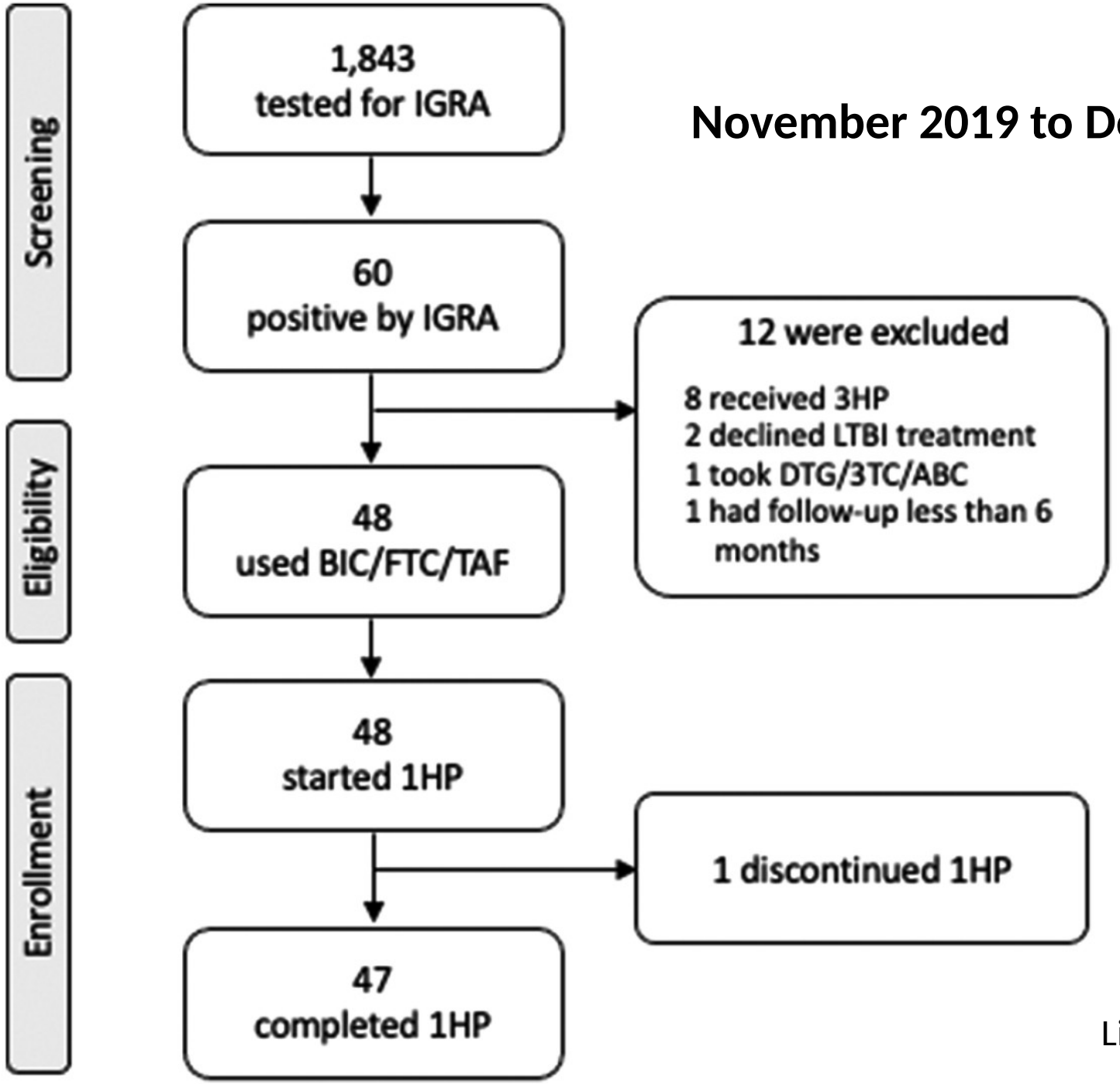
Liou BH, et al. JIAS 2021

General 1HP study

	D1 1st dose	D15 15th dose	D29	Week8 (D56) (治療完成後 28 天 , month 3 and 6)
Isoniazid (INH)	3hrs after 1HP	3hrs after 1HP		
Rifapentine (RPT)		24hrs after 1HP	24hrs after 1HP	
Bictegravir (BIC)	Before 1HP	24hrs after 1HP	24hrs after 1HP	
LFTs	v	v	v	
PVL	v	v	v	v
Cytokines	v	v	v	

Abbreviation: LFTs, liver function tests; PVL, plasma HIV RNA loads;

Liou BH, et al. JIAS 2021



November 2019 to December 2020

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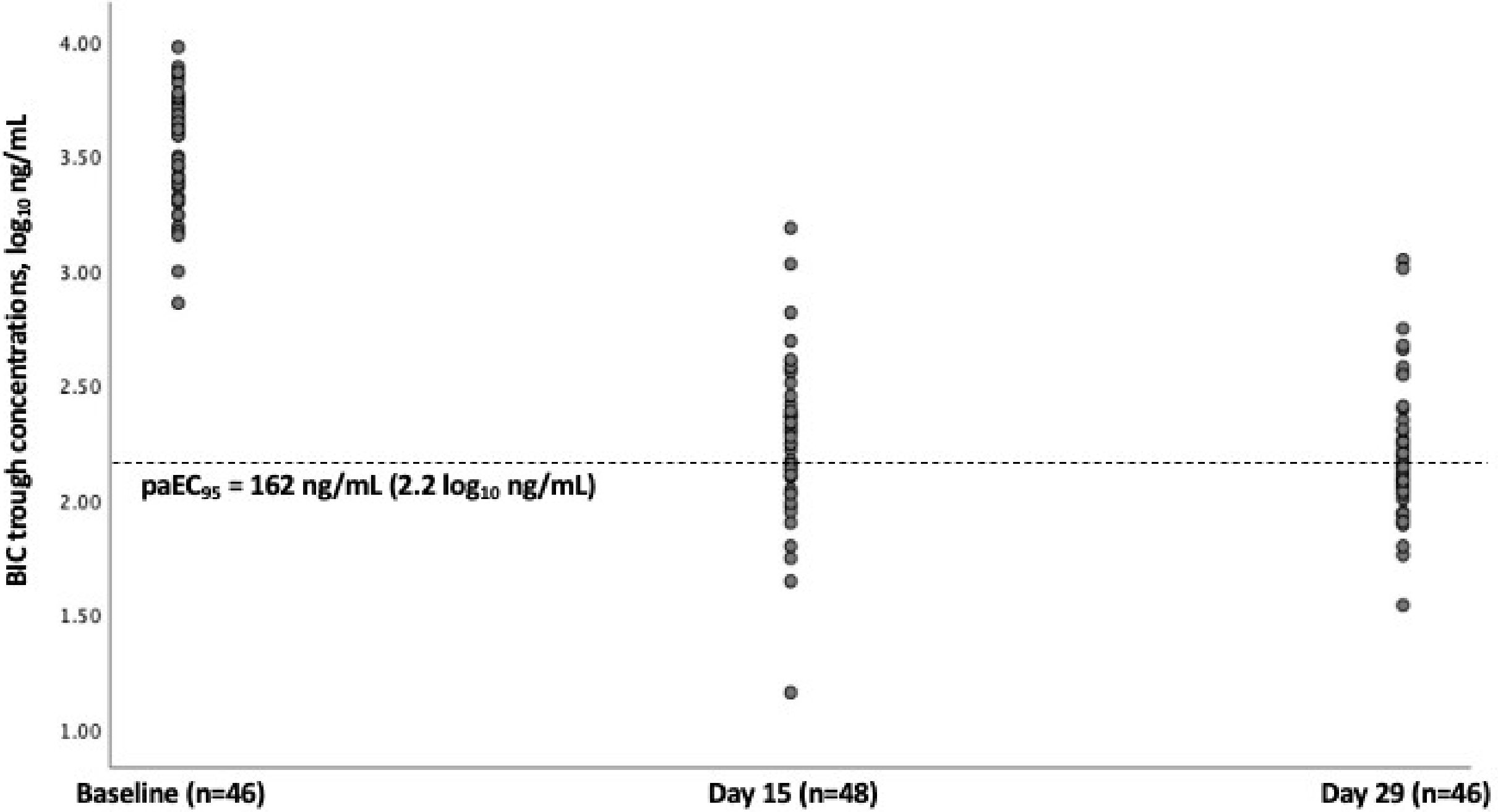

Liou BH, et al. JIAS 2021

Day 15 of 1HP	
PVL <200 copies/ml, n/N (%)	44/48 (91.7)
PVL <50 copies/ml	35/48 (72.9)
AST, median (IQR), U/L	21.0 (18.0–27.0)
ALT, median (IQR), U/L	17.5 (12.3–25.0)
Total bilirubin, median (IQR), mg/dl	0.8 (0.7–1.0)
Day 29 of 1HP	
PVL <200 copies/ml, n/N (%)	46/46[a] (100.0)
PVL <50 copies/ml	43/46[a] (93.5)
AST, median (IQR), U/L	21.0 (18.0–26.0)
ALT, median (IQR), U/L	19.0 (13.0–27.0)
Total bilirubin, median (IQR), mg/dl	0.8 (0.7–0.9)
Month 3 after 1HP discontinuation	
PVL <200 copies/ml, n/N (%)	44/44[b] (100.0)
PVL <50 copies/ml	43/44[b] (97.7)
Month 6 after 1HP discontinuation	
PVL <200 copies/ml, n/N (%)	46/46[c] (100.0)
PVL <50 copies/ml	46/46[c] (100.0)

Summary

- The risk of progression to active TB disease is high (10% per year) in PLWH with LTBI.
- Treatment for LTBI and early ART could decrease the risk of progression to active TB disease in PLWH with LTBI.
- Regimen of LBTI treatment for PLWH with LTBI
  - BIC-based regimen plus 1HP
  - DTG-based regimen (DTG 50 mg BID) plus 1HP
  - DTG-based regimen plus 3HP

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  - 洪健清，羅一鈞，莊祐中，林冠吟，劉旺達
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  - 巫沛瑩，張喜雁，陳伶雅，廖敏玲，張君瑜，施鐘卿
- NTUH HIV assistance
  - 劉玟君，蘇意青，陳怡婷，陳雅雯
- NTUH pharmacy team
  - 郭錦鏵，林淑文，林亞葶

Thank you!