TB preventive therapy : Thailand guideline update

Anchalee Avihingsanon, MD, PhD

24 Aug 2023

Advanced HIV Disease

Adults, adolescents and children ≥ 5 years of age with CD4 count < 200 cells/mm$_3$ or at WHO clinical stage 3 or 4.
All children < 5 years of age with HIV infection

- Newly enrolled clients (baseline CD4) and every 6 months for patients on unstable ART
- Re-enrollment after interruption in treatment
- ARV treatment failure

WHO Stage 3

Most typical/common syndromes:

- Severe weight loss (> 10% of body weight)
- Chronic diarrhea for > 1 month
- Persistent fever for > 1 month
- Recurrent oral candidiasis
- Pulmonary tuberculosis
- Severe bacterial infections
- Unexplained anemia, neutropenia, or thrombocytopenia

WHO Stage 4

Most typical/common syndromes:

- Extrapulmonary tuberculosis
- Pneumocystis jiroveci Pneumonia (PCP)
- Esophageal candidiasis
- CNS Toxoplasmosis
- Cryptococcal meningitis
- Penicilliosis
- Persistent herpes simples over 1 month
- CMV retinitis

Diagnosis and prophylaxis package of care for individuals with AHD[1,2]

MANAGEMENT

TB screening using 4 symptoms — CXR

- (+) → Transfer for TB diagnosis and treatment
- (−) → TB preventive therapy

Assessing symptoms of meningitis (fever, headache,vomitting, stiff neck…)

- (+) → Transfer for diagnosis and treatment
- (−) → Not on ARV treatment and CD4 < 100 cells/mm³: Conduct CrAg/blood analysis → CrAg (+): Cryptococcosis preventive treatment

Diagnosis and treatment for other opportunistic infections

Advanced HIV hospitalized patients has poor outcome
20% died in hospital
19% of people successfully discharged from hospital are re-admtted in a year
14% died within a year of discharge

Preventive treatment with co-trimoxazole

ARV Treatment

- **Not on ARV treatment or having experienced interruption in treatment:** Immediately start ARV treatment (same day, or as soon as possible)
  Delay for patients with TB or Cryptococcal meningitis
- **On ARV Tteatment:** Routine viral load testing to monitor response to ART = early diagnosis of treatment failure in order to change ARV regimens in a timely and appropriate manner

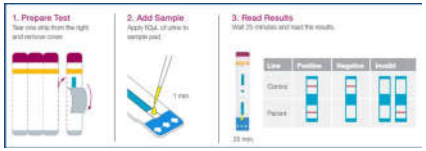
Support patients in treatment adherence and continuation

CRP > 5 mg/L : sensitivity40-94%, specificity 49-96%

Urine LF-LAM* for TB diagnosis in patients with symptoms and signs of TB

≤ 100 cells/mm³ (Outpatient)
≤ 200 cells/mm³ (Inpatient)
or at any CD4 cell count value if seriously ill

LAM=lipoarabinomannan : Sen 56%, Spec 90% if CD4< 100
Sen 49%, Spec 90% if CD4 < 200
Sen 54%, Spec 90% if inpatient



ART: 65% reduction in TB[3,4] , ART + TPT additional 35% reduction in TB in high TB transmission areas[5,6]

TPT effective 29- 85%

TPT reduced mortality 35-50% [7]

1. https://www.fhi360.org/sites/default/files/media/documents/resource-epic-vietnam-hiv-management-toolkit.pdf; 2.WHO providing care to PLHIV who are seriously ill policy brief 27 Mar 2023; 3. Lancet HIV. 2020;7(6):e401-e409; 4.Suthar, PLOS Medicine , 2012;5. Golub JE AIDS 200923(5):631;6. Rangaka MX Lancet 2014:384 (9944):682-90;7 4. Badje A Lancet Glob Heal 2017; 5:e1080–9

Recommendations in the 2020 WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment (regardless of HIV status)

สูตรยาTPT

regimen	duration	comments
Strong recommendation, moderate to high certainty in the estimates of effect		
INH 300 mg daily + pyridoxine 25-50 mg	6-9 months	• 9 months preferable • No drug interaction • Lower completion rate
INH 15 mg /kg, (max900) plus weight based Rifapentine (max900 mg) weekly + B6 25-50 mg Wt based RPT dose 32.1-49.9kg: 750 mg, ≥ 50 kg: 900 mg	12 weeks	• PREVENT study: as effective as 9H • Higher completion rate(82% versus 69%), Lower rates of hepatotoxicity (0.4% versus 2.7%) • effective and better tolerate in PWH with CD4 > 350 c/ml • RPT drug interaction
isoniazid 300 mg plus rifampicin 600 mg +B6 25-50 mg	3 months	• Limited data in PWH • RIF drug interaction
Conditional recommendation, low to moderate certainty in the estimates of effect		
INH 300 mg plus wt based RPT (max 600 mg) daily +B6 Wt based RPT dose <35 kg: 300 mg, 35-45 kg: 450 mg, > 45 kg:600 mg	4 weeks (1 month)	• BRIEF trial: as effective as 9 H • Co-administer with EFV/NVP
Rifampin 600 mg PO daily	4 months	• Limited data in PWH • Low ADR

ผลข้างเคียงของrifapentine (RPT) : Hypersensitivity Reaction อันตรายควรจะหยุด RPT

- ปัจจัยเสี่ยง
  - white non-Hispanic ethnicity
  - female sex
  - age ≥35 years
  - low body-mass index

- ระยะเวลาเฉลี่ยที่เกิด; 3 doses, 4 hr หลังกินยา
- อาการ : Flu-like symptoms (fever, chills, fatigue, malaise, headache, myalgia, and arthralgia, cutaneous reactions) fever is the most common presentation

Clinical Infectious Diseases 2015;61(4):527–35

systemic drug reaction : 3 HP (3.8%)vs. 9 H (0%);
Grade 3 : 2.3% (3HP) vs 0% (9H)
Cutaneous reaction: 10.6% (3HP) vs 6.9%(9H)
Hypersomnia : 6.8% (3HP) vs 3.8% (9H)

	1HP (N=629)	3HP (N=628)
CD4 median < 200 cells/mm3 200-350	353 (228-539 18% 31%	353 (235-537) 20% 29%
Hypersensitivity reaction	0.3%	0.5%
Asymtomatic hepatis	1.9% (HBV, HCV =40%)	2% (HBV, HCV =50%)

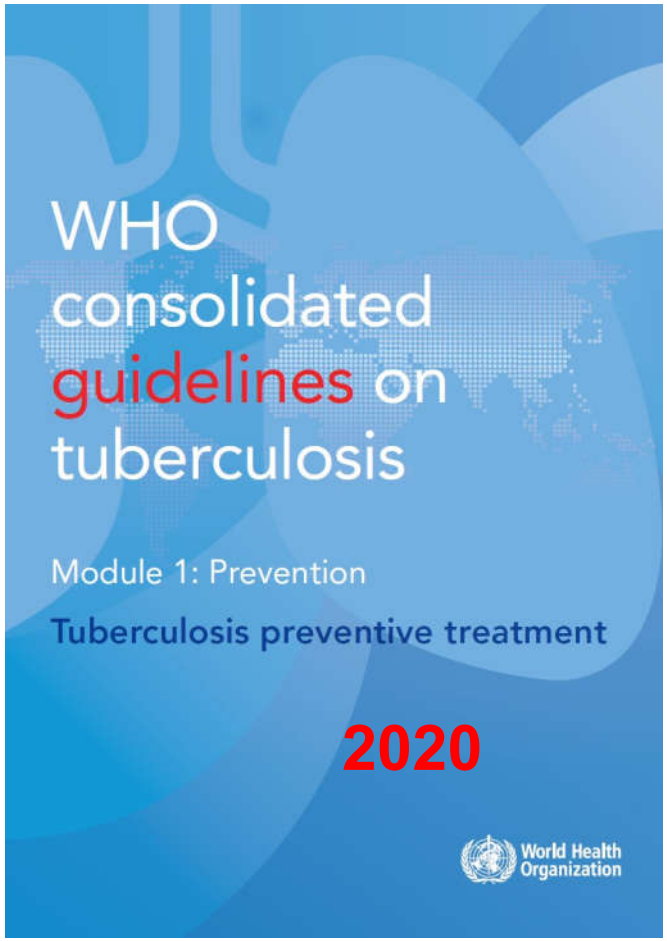
Hepatotoxicity (Transient Asymptomatic Hyperbilirubinemia, hepatitis) เกิดประมาณร้อยละ 0.4 ในคนที่รับประทาน RPT

Cutaneous reaction เช่น คัน (+/-ผื่น) อาจเกิดขึ้นในคนที่รับประทาน RPT โดยทั่วไปจะหายเอง

อาการทางเดินอาหาร เช่น คลื่นไส้ อาเจียน ปวดท้อง เกิดได้แต่น้อยมาก ที่จะเป็นมากจนต้องหยุดยา

การที่สารคัดหลั่งในร่างกายเช่น ปัสสาวะ น้ำลาย เหงื่อ น้ำตา เปลี่ยนสี เป็นสีส้ม-แดง (Orange-red Discoloration) เป็นภาวะปกติที่พบได้ ไม่ต้องหยุดยา ผลกระทบนี้จะไม่เป็นอันตรายและจะหายไปเมื่อหยุดยา

TPT: WHO guideline 2020



Treated without tested

People living with HIV ***(Strong)***

Children < 5 contacts of pulmonary ***(Strong)***

Appropriate clinical evaluation according to national guideline

•Children ≥ 5 years, adolescent → household

(Conditional recommendation)

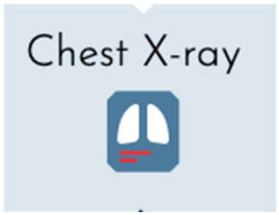
Tested and Treated

(Strong recommendation)

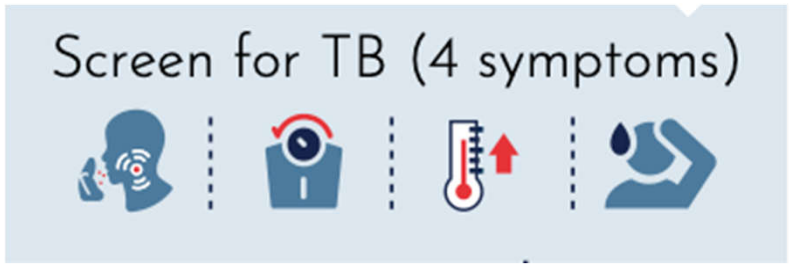
- Silicosis
- Anti-TNF treatment
- Dialysis
- Transplantation

Updated Guidelines for screening and treatment of latent TB in adults with HIV 2023

All adults with HIV, including pregnant women, should be screened for active TB before and during treatment at every check-up



Pregnant women: CXR at GA >14 wk. with radiation protection on the abdomen



1. Fever of unknown cause within the past 1 month
2. Weight loss of at least 5% within 1 month
3. Unexplained cough (e.g., hemoptysis/cough > 2 weeks)
4. Unusually excessive sweating at night > 3 weeks within 1 month

Scenario 1: No symptoms, no history of tuberculosis exposure. Not in prison and normal CXR results
(No S/S + no contact TB + normal CXR)

Newly diagnosed PLHIV on ARV ≤12 months

TPT

- After tolerate to ARV/cotrimoxazole
- Pregnant woman: start after 1st trimester; rifapentine is not recommended

PLHIV on ART>12 m, no history of prior TPT

-CD4< 200*
-HIV treatment failure or unsuppressed HIV VL>1000 c/ml
-ARV discontinuation > 90 days
-ESRD on long term dialysis

Prescribe TPT, considering that the benefit of TPT outweigh risks of developing active TB in this group

CD4≥ 200*

IGRA or skin test

- Pos → TPT
- Neg → TB screening at every visit
- Not done → at the discretion of the physician

- Rifapentine and rifampicin can not be used with boosted PIs, TAF
- 3 HP can be used with EFV, RAL, DTG without dose adjustment
- 1 HP and 3 HR with DTG, DTG should be adjusted to 50 mg BID

ART: 65% reduction in TB[1,2] , ART + TPT additional 35% reduction in TB in high TB transmission areas[3,4]

*cells/mm3

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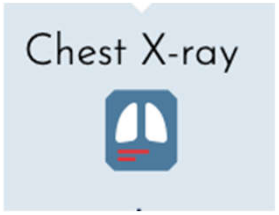
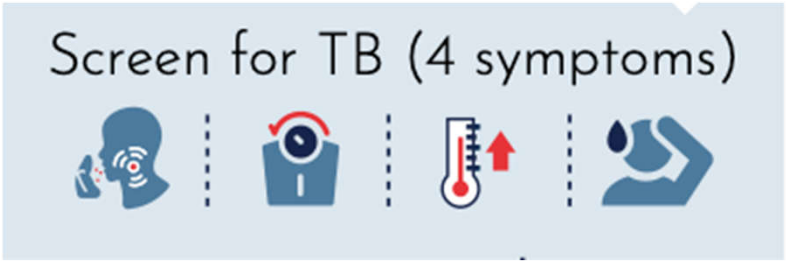


Close contact with 1) pulmonary tuberculosis or Laryngeal tuberculosis within the past year (recent TB exposure).
If yes, obtain information regarding the drug-resistant TB status of the close contact cases
2) prison

Pregnant women: CXR at GA >14 wk. with radiation protection on the abdomen



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Scenario 2: History of exposure to tuberculosis or asymptomatic inmate and normal CXR results. (Contact TB or in prison + no S/S & normal CXR)

TPT (Tuberculosis preventive therapy)

Index case	*Choice of TPT medicines*
No drug resistance detected/ Unknown drug resistance status	Preferred regimen: 1HP or 3HP 1. 1 HP= INH 300 mg + rifapentine daily x 4 wk. (Rifapentine : BW < 35 kg = 300 mg / 35-45 kg = 450 mg / > 45 kg = 600 mg) 2. 3HP = INH 15 mg/kg (max 900 mg) + rifapentine weekly x 12 wk. (Rifapentine : BW > 25-32 kg = 600 mg / > 32.1-49.9 kg = 750 mg / ≥ 50 kg = 900 mg)
	Alternative regimen: 9H; INH 300 mg OD x 9 m
	*If receiving DTG-based regimen, 1HP: add 1 DTG tablet in addition to the current DTG-based regimen 3HP: use normal dose DTG * Give pyridoxine 25-50 mg OD with all regimens
Resistant to INH	Rifampicin 10 mg/kg (max 600 mg) OD x 4 months
MDR-TB	In the absence of strong evidence, it is advised to follow up (f/u every 6 months for 2 yrs)

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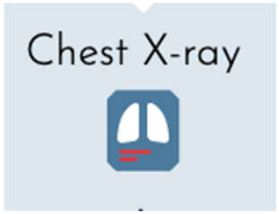

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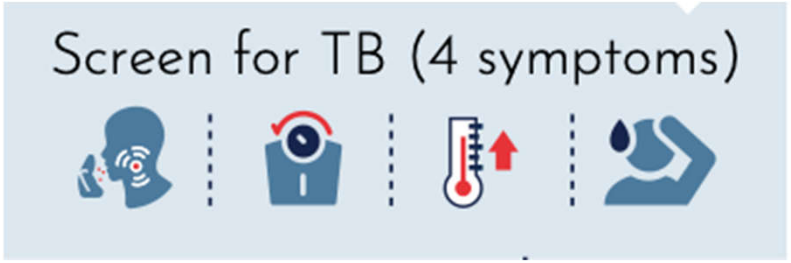

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Scenario 3: Present with signs and symptoms suggesting suspicion of tuberculosis or abnormal CXR results.
(S/S of TB or Abnormal CXR)

- Collect quality Sputum AFB testing at least twice (1st visit and the next morning's first phlegm sample)
- Perform TB culture, Drug Susceptibility Test (DST) & Molecular Method (e.g., Xpert MTB/RIF, Line probe assay (LPA), PCR for MTB), urine LF LAM

Positive

TB disease

Anti-TB drugs

- DOT (Directly observed Rx)
- VOT (Video observed Rx)

Negative, but CXR abnormal/possible TB

- Perform diagnostic tests on extra-pulmonary organs cause)
- Consider repeating with molecular biology tests if needed using specimens for tuberculosis testing, including AFB, Xpert and culture. such as CSF (meningitis), bone marrow aspiration (pancytopenia), needle aspiration or tissue biopsy (cases involving LN, liver, spleen), hemoculture for TB, urine LF LAM

TB disease

Anti-TB drugs

Other lung disease

Treatment for the disease & consider TPT

Patients who are taking anti-HIV drugs should promptly initiate anti-TB treatment without discontinuing their anti-HIV medication

Rifamycins/TB drug interaction potential

- Induce of
  - Cytochrome P450 (CYP3A4),
  - UDP-glucuronosyltransferases (UGT1A1)
  - P-glycoprotein to reduce GI absorption

DTG: UGT1A1, 3A4 (minor), p-gp
Bic : UGT1A1, 3A4 , p-gp
CAB : UGT1A1, p-gp
RAL: UGT1A1

⇩ ARV (eg INSTI, TAF, NNRTIs, Pis, contraceptives, statins, macrolides, methadone

Inducer: ทำให้ระดับยาที่ใช้ร่วมมีระดับต่ำลง

Table 1. Summary of pharmacokinetic and pharmacodynamic parameters of rifamycins.

Drug	C_{max} (mg/mL)	T1/2 (hours)	Protein Binding %	CYP450 Enzyme induction	MIC* mg/mL
Rifampicin	8–24	3–4	80	+++	0.125–0.25
Rifapentine	8–30	13–15	>95	++	0.01–0.05
Rifabutin	0.3–0.9	25–62	85	+	0.03–0.06

CYP450: cytochrome P450, T1/2: half-life, C_{max}: maximum concentration
*Minimum Inhibitory Concentration for susceptible strains of Mycobacteria.

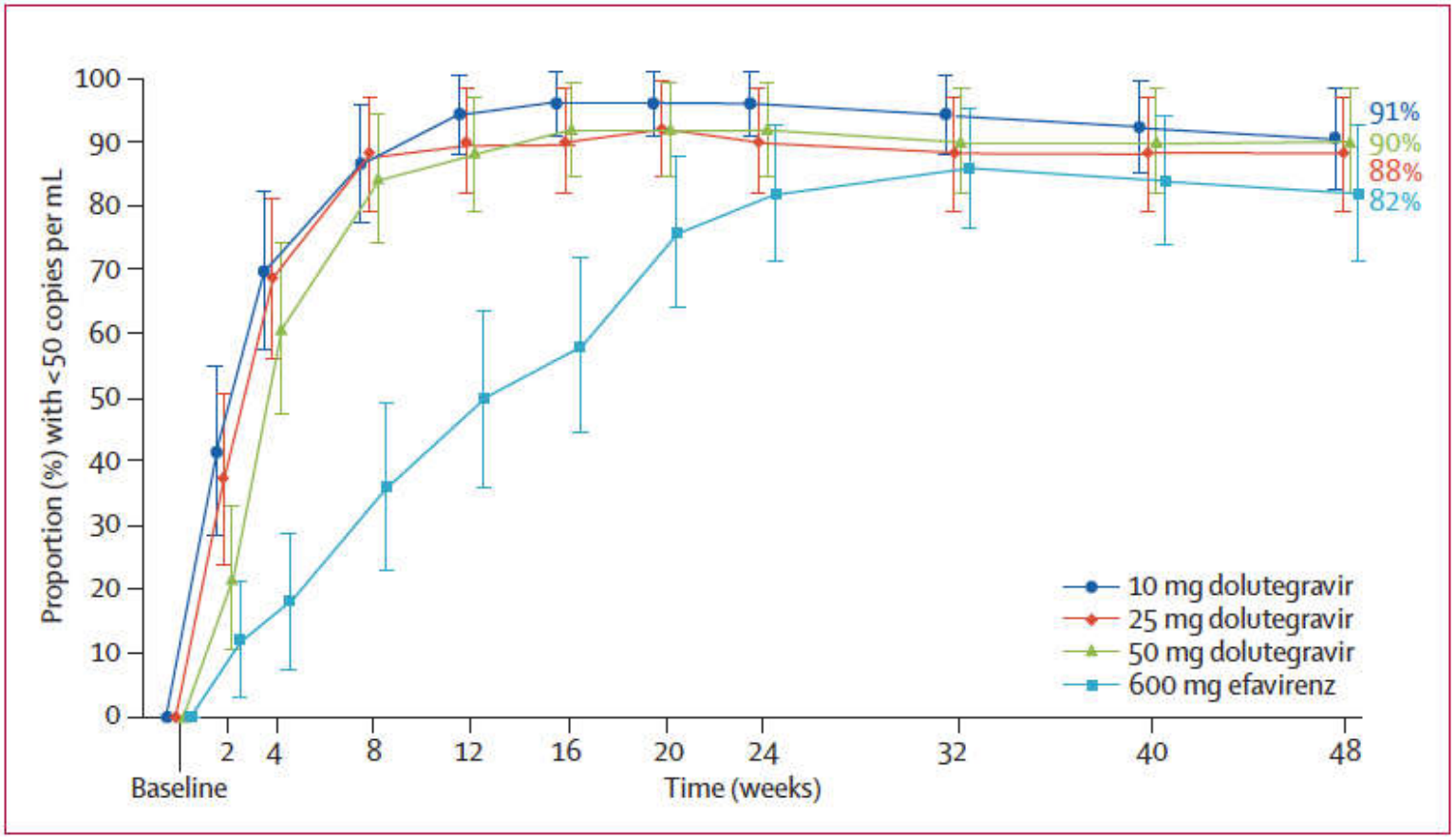
Rifampin reduces plasma exposure to TAF, NNRTI, INSTIs, PIs, fostemsavir and maraviroc

Potency of CYP3A inducers
Rifampin > Rifapentine > Rifabutin

Rifapentine (RPT) : longer t1/2 than RIF and increased potency
Induction potency 85% of rifampin with daily RPT dosing, less with weekly

Sekaggya-Wiltshire et al 2019 Expert Opinion Drug Metabolism & Tox; 15, 8 p.615-618-341

SPRING 1 trial : efficacy of DTG 10 mg= DTG 50 mg



SPRING-1 trial

Lancet Infect Dis 2012; 12: 111–18

Similar efficacy and safety of Integrase inhibitors versus efavirenz ART for TB/HIV co-infection: a meta-analysis of RCT (3 RCT, N= 672 TB/HIV)[1]

[2] Dolutegravir-based regimen safe and effective for HIV/TB (N=1225) taking rifampicin : programmatic experience from Bosawana 2016-2018

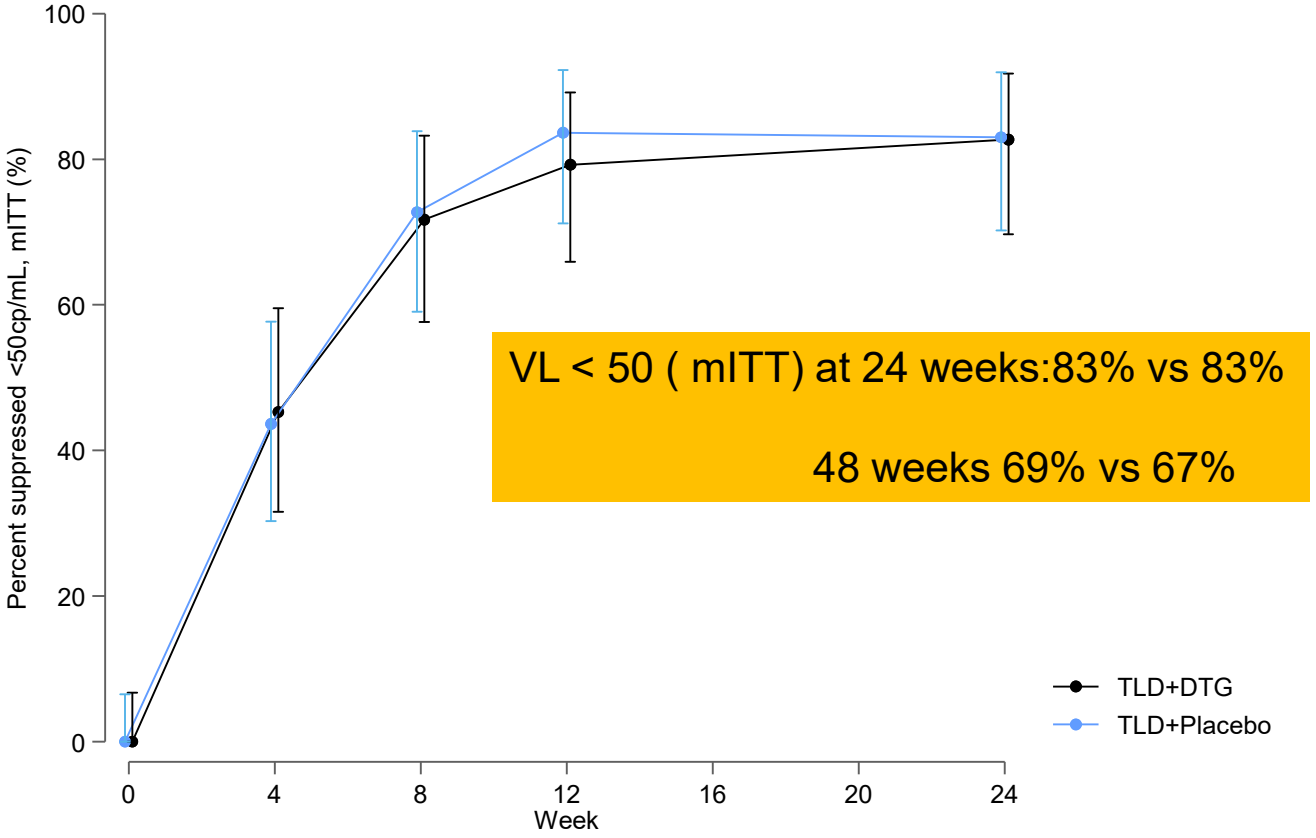
	TB treatment success(n=1225)	HIV VL suppression (<400c/ml) (n=797)
No DTG	429/486 (88.3%)	288/307 (93.8%)
DTG 50 mg OD	298/322 (92.6%)	204/214 (95.3%)
DTG 50 mg BID	352/390 (90.3%)	241/254 (94.9%)
Missing dosage	22/27 (81.5%)	21/22 (95.4%)

- DTG with RIF N=739
  - 52.8% DTG 50 mg BID
  - 43.6% DTG 50 mg OD
- DTG had slightly better TB treatment outcome than those without DTG

1 Shu Y et al. AIDS Research and Therapy 2021:25 (18); 2. Modongo C JAIDS October 1, 2019

RADIANT-TB : DTG 50 mg QD vs DTG 50 mg BID in HIV/TB on RIF based anti TB

- Phase IIb RCT, South Africa
- HIV-TB (n =
- 108)
- RIF + TLD + DTG 50 mg vs placebo
- No emergent DTG resistance
- No safety concerns



Griesel R et al Lancet HIV May 23, 2023

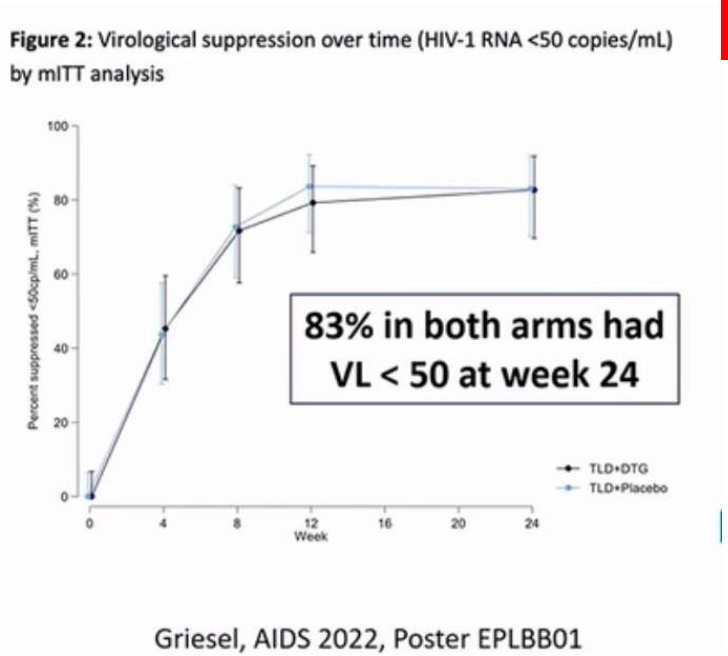
RADIANT-TB trial: Dolutegravir with rifampicin : South Africa

- DTG 50 mg daily (TLD) vs 50 mg twice daily

(TLD in the morning and DTG 50 mg in the evening) with RIF based TB

- Phase2 non comparative RCT
- N=108, ARV naïve, CD4> 100

Food increased DTG concentration 30-60 %



Griesel, AIDS 2022, Poster EPLBB01

DTG-RIF trial: Dolutegravir with rifampicin : Thailand

- DTG 50 mg daily (TLD) vs 50 mg twice daily

(TLD in the morning and DTG 50 mg in the evening) with RIF based TB

- Phase2 non comparative RCT
- N=40, ARV naïve, any CD4

- Median baseline CD4 was 194 (IQR 46-238) cells/μL. Median baseline HIV-1 RNA was 4.9 (IQR 3.6-5.6) log10copies/mL; 43% had HIV-1 RNA >100,000 copies/mL.
- 70% and 95% of study and control arm participants had DTG Ctrough>64 ng/mL.
- **At week 48, 90% of** the participants in the study arm (18/20) and control arm (18/20) had HIV-1 RNA <40 copies/mL using ITT analysis.
- Premature study discontinuation occurred in 3 cases (1 in study arm: RIF-induced cholestasis; 2 in control arm: rash and non-TB).

Avihingsanon A AIDS 2022 Montreal : PESAB09

PK of Dolutegravir with 3HP: (the DOLPHIN trial)

60 African PLHIV with HIV RNA < 50 c/ml เปลี่ยนจาก EFV เป็น DTG

70% female, BMI : 28·9 kg/m^2 (24·0-32·9)

3HP + DTG 50 mg OD

Study Day	Week on 3HP	N	Day Post HP Dose	Geometric mean	Troughs, 5th and 95th %	Regimen
57/58		60	0	1003	500 -2080	DTG alone
59	Week 1	30	1	1053	412 - 1834	DTG+3HP
72	Week 2	30	7	492	200-1063	DTG+3HP
73	Week 3	60	1	657	295-1502	DTG+3HP
74	Week 3	60	2	355	134-933	DTG+3HP
78	Week 3	30	6	388	140 - 794	DTG+3HP
108	Week 8	60	1	703	289 - 1603	DTG+3HP
109	Week 8	60	2	394	121 - 1079	DTG+3HP

*HP doses were given on Days 58, 65, 72, 79, 86, 93, 100, 107

	Change in AUC (n=60)
Delta AUC week 1	+16% (75)
Delta AUC week 3	-29% (23)
Delta AUC week 8	-29% (27)

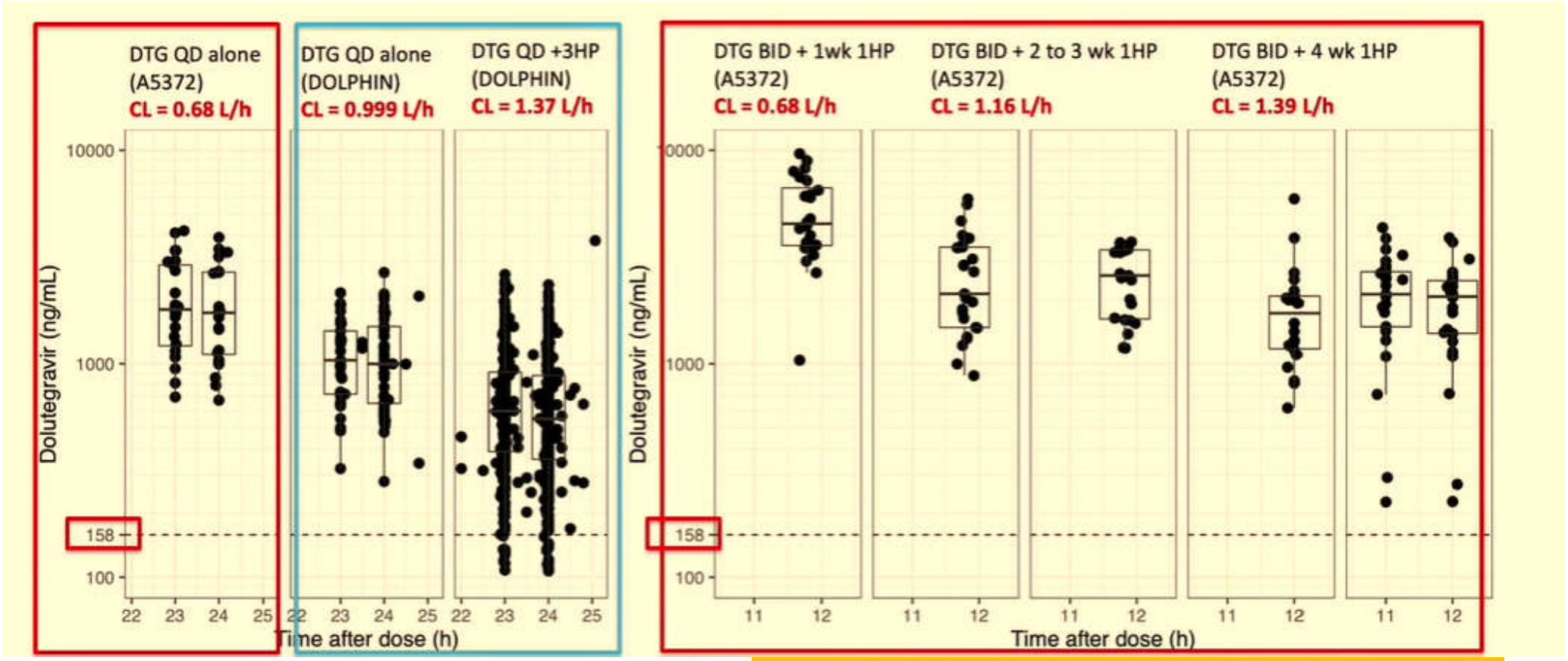
Viral load < 40 copies/mL at Baseline and Week 9 in all participants

RPT/INH increased DTG clearance by 36%, resulting in a 26% decrease in DTG AUC

Geometric mean troughs were above IC90 at all time points

Dooley, et al., Lancet HIV 2020 Mar 30;S2352-3018(20)30032-1

เปรียบเทียบระดับยาโดลูทิกราเวียร์ในโครงการA5372 (1HP+ DTG 50mgBID) และโครงการ DOPHIN (3HP+DTG 50 mg OD



N=25, ผู้ชาย 56%, อายุเฉลี่ย 41 ปี เอเชีย 32%

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.

Bictegravir/TAF/FTC 1 tab+ 1 HP

48 PLWH, 56.3% and 37.0% on days 15 and 29,respectively had BIC concentration above IC90. PVL<200 copies/ml was 91.7% on day 15, 97.8% on day 29 and 100% at both months

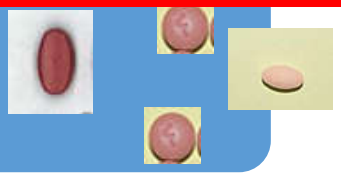
Short-course rifapentine-based regimen for LTBI among PLWH who received InSTI-based ART
Kuan-Yin Lin IAS 2023
1 HP (N=205; B/F/TAF 69%), 3HP (N=274; DTG 78%) : only incarceration was associated with PVL> 200 copies/ml

Guideline of TPT among PLHIV in Thailand: 2023

Prefer A

All PLWH receive ART ≤ 12 months. " Treat without Test"

INH 300 mg+ RPT 450-600mg dailyx4 weeks (+B6)



BW<35 kg, RPT 300mg
BW 35-45 kg, RPT 450 mg
BW > 45 kg, RPT 600 mg

Completion rate 97% (1HP) vs 90% (9H), p<0.001 (BRIEF study)[1]

RPT + INH
300 mg/300 mg
Film-coated

1 HP:
EFV: no dose adjustment
DTG 50 mg BID
Avoid boosted PI, NVP, RPV

Prefer B

INH 15 mg/Kg (max 900)

INH 900 mg+ RPT 900 mg weekly x12 weeks (+B6)

BW ≥ 50 kg, RPT 900mg
BW 32-49.9 kg, RPT 750 mg
BW > 60 kg, INH 900 mg

3HP
EFV, DTG : no dose adjustment
Avoid boosted PI, RPV, NVP

Completion rates 82% (3HP) vs 69% (9H)

Alternative

INH 300 mg +B6 dailyx9 months

ผลข้างเคียงสำคัญ
: Elevated ALT : 1HP 2%, 3HP 0.4%, 9H 2.7-5%, Rifam 0%
Hypersensitivity reaction : 3HP
systemic drug reaction : 3 HP (3.8%)vs. 9 H (0%)
Cutaneous reaction: 10.6% (3HP) vs 6.9%(9H)
Hypersomnia : 6.8% (3HP) vs 3.8% (9H)

	1HP (N=629)	3HP (N=628)
CD4 median < 200 cells/mm3 200-350	353 (228-539 18% 31%	353 (235-537) 20% 29%
Hypersensitivity reaction	0.3%	0.5%
Asymtomatic hepatis	1.9% (HBV, HCV =40%)	2% (HBV, HCV =50%)
TLD, VL < 50 copies/ml, N(%) 24 weeks 1 yr 2 yr 3 yr	 92.1% 92.2% 95% 98.4%	 92.6% 95.2% 94.7% 96.8%

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