The treatment of Latent TB Infection in PLWHIV

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Disclosures

	Jinell White
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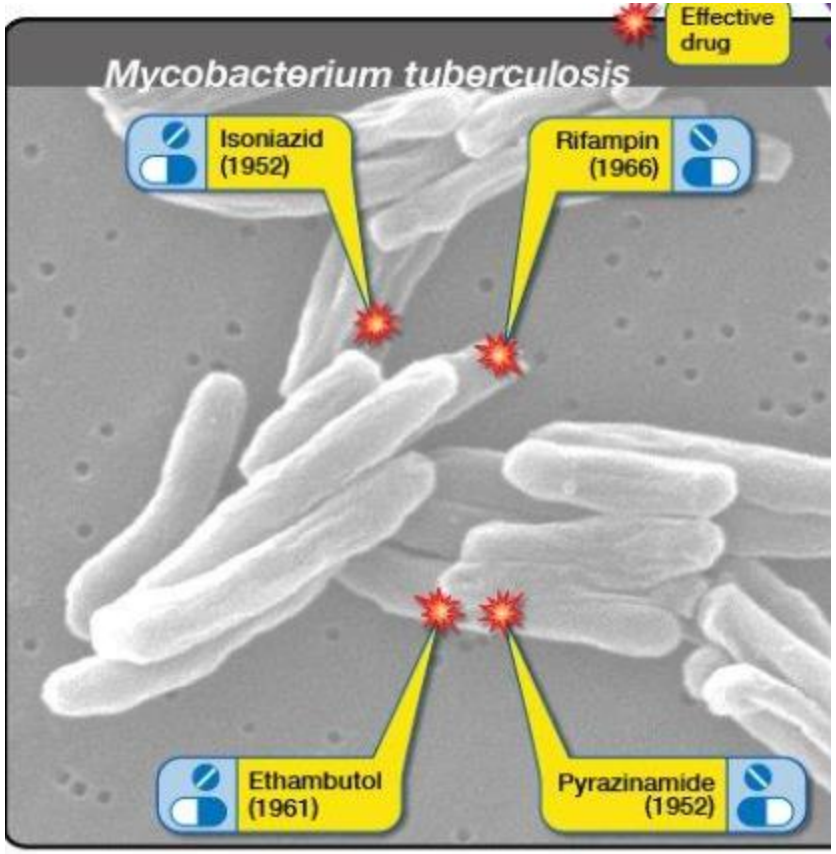
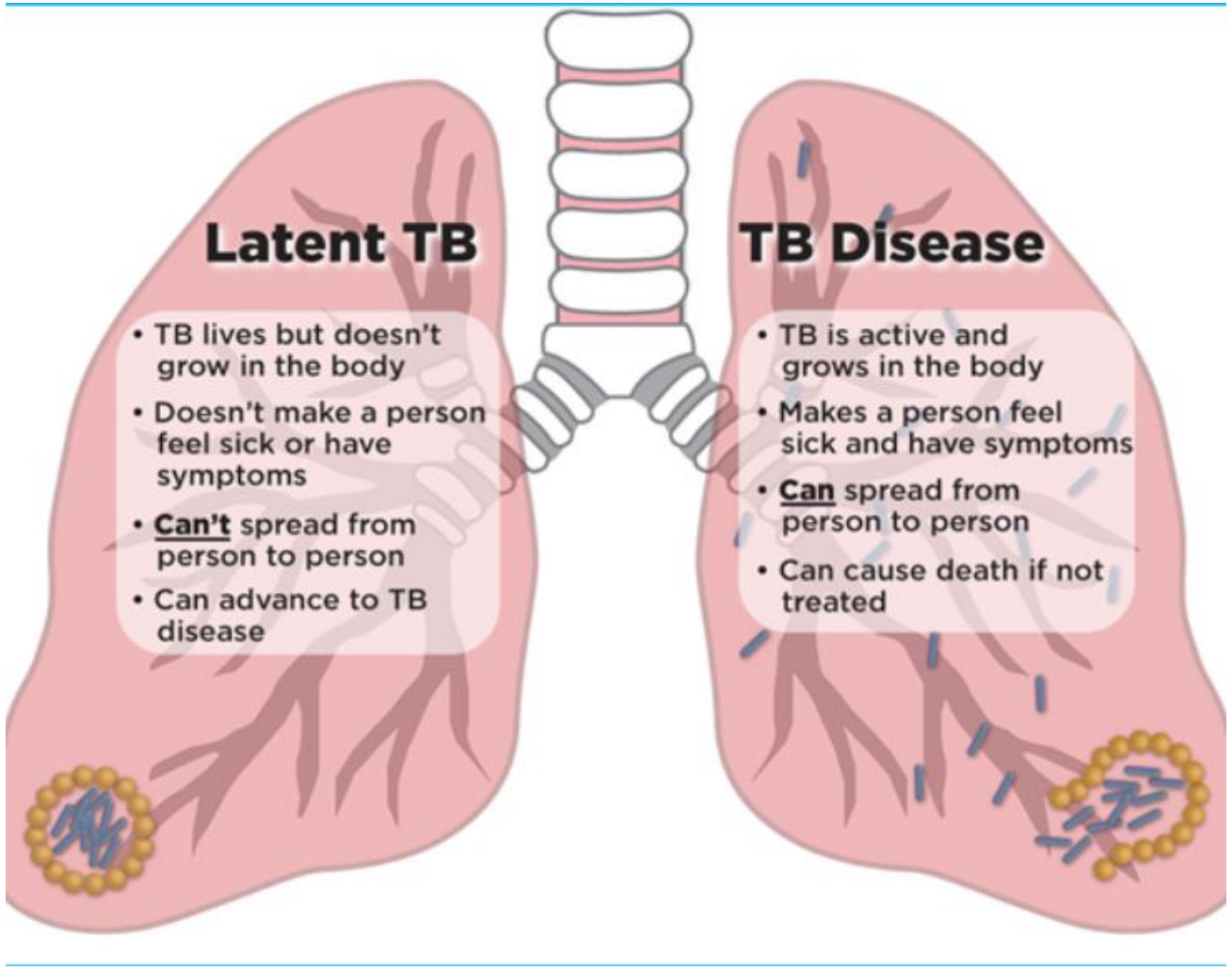
This presentation may content data on products that is outside the local product monograph

PRESENTATION OVERVIEW

1. Tuberculosis disease vs Tuberculosis infection
2. Tuberculosis Preventative Treatment (TPT)
3. Dolutegravir and Rifampin – DDIs in both TB disease and TB infection
4. Rifampin vs Rifapentine
5. Fun Facts –Rifapentine
6. Dolutegravir and Rifapentine –DDIs, 3HP and 1HP
7. Bictegravir and Rifampin – DDIs
8. Bictegravir and Rifapentine –DDIs
9. Research in Tuberculosis infection update
10. Cost of TPT treatments and ART

Mycobacterium Tuberculosis

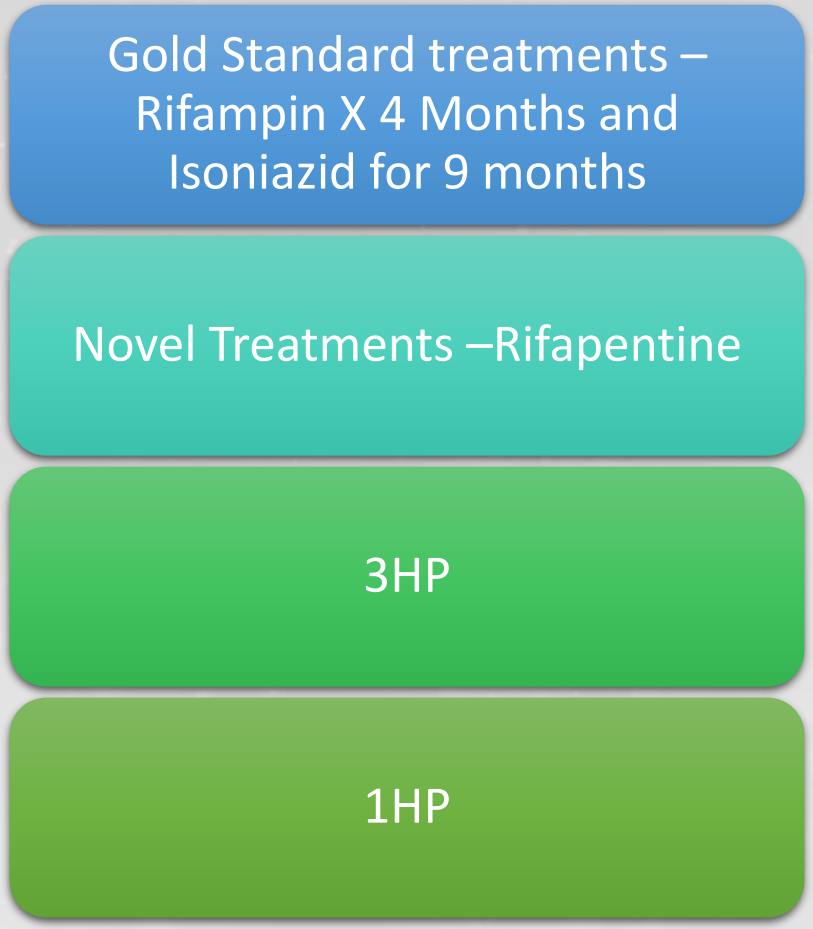




WHO KEY FACTS about Tuberculosis (TB)

- TB occurs in every part of the world. In 2022, the largest number of new TB cases occurred in WHO's South-East Asian Region (46%), followed by the African Region (23%) and the Western Pacific (18%). Around 87% of new TB cases occurred in the 30 high TB burden countries, with more than two-thirds of the global total in Bangladesh, China, Democratic Republic of the Congo, India, Indonesia, Nigeria, Pakistan and the Philippines.
- TB treatment has saved 75 million lives between 2000 and 2022
- People living with HIV are 16 to 27 (uncertainty interval with various studies) times more likely to fall ill with TB disease than people without HIV.
- **A total of 1.3 million people died from TB in 2023 (including 214 000 people with HIV). Tuberculosis (TB) is the infectious disease with the highest mortality rate in the world, excluding the peak years of the COVID-19 pandemic.**

Tuberculosis Preventative Treatment (TPT) in HIV



Comparison of TPT for Tuberculosis infection

ISONIAZID	RIFAMPIN	1HP	3HP
Isoniazid 300mg QD	Rifampin 10mg/kg Max. 900mg QD	Isoniazid 300mg QD	Isoniazid 900mg X 1 weekly
Pyridoxine 25mg QD		Pyridoxine 25mg QD	Pyridoxine 50mg X 1 weekly
		Rifapentine 600mg QD	Rifapentine 900mg x 1 weekly (> 50kg)
2 Pills QD	2-3 Capsules QD	6 Pills QD	11 Pills qweekly
6-9 months	4 months	30 days	12 weeks

DOLUTEGRAVIR AND RIFAMPIN (PK study)

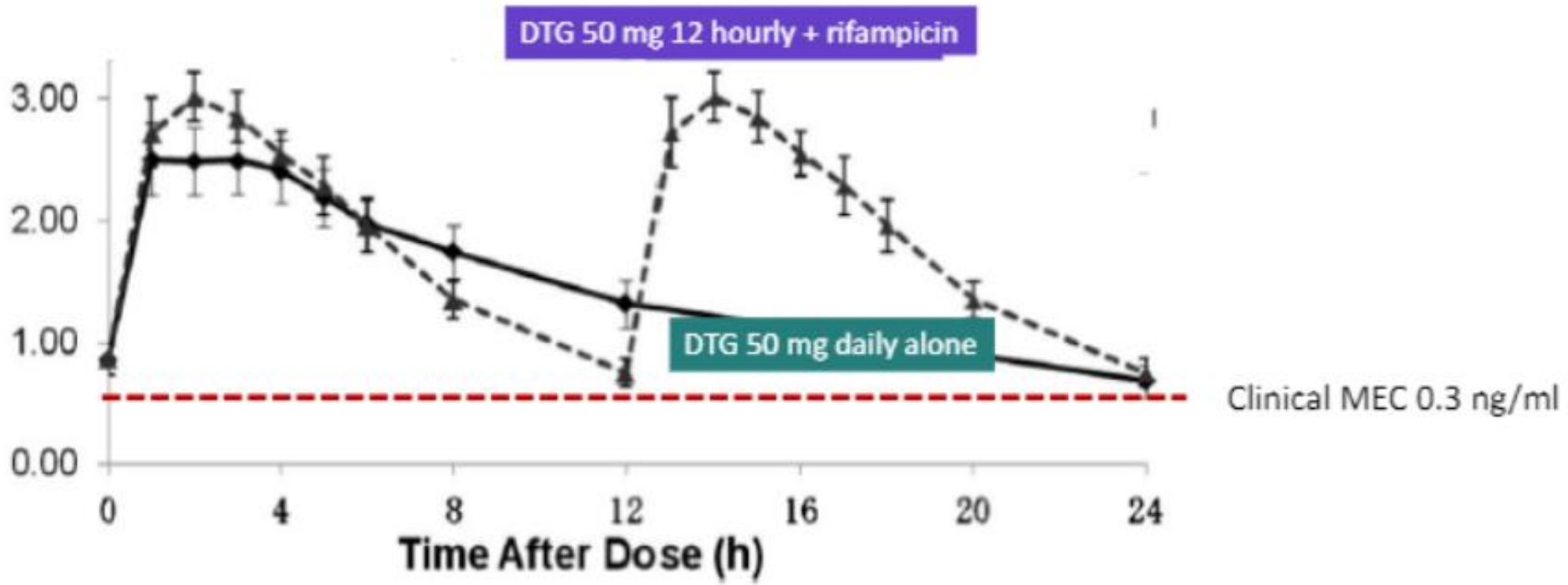
- Dolutegravir 50 mg BID plus rifampin 600 mg daily:

- In open-label, single center PK drug interaction study, healthy volunteers received dolutegravir 50 mg once daily for 7 days (period 1), then dolutegravir 50 mg twice daily for 7 days (period 2), then DTG 50 mg twice daily together with rifampin 600 mg once daily (period 3) for 14 days. Dolutegravir 50 mg BID plus rifampin achieved mean AUC 33% ↑ and Ctau 22% ↑ versus DTG 50 mg daily alone. There were no discontinuations for adverse events (AEs) and no Grade 3 or higher AEs.

Dooley K, Sayre P, Purdy E, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acq Immune Def Syndr 2013;62(1):21-27.

Safety, Tolerability, and Pharmacokinetics of the HIV Integrase Inhibitor Dolutegravir Given Twice Daily With Rifampicin

Dooley 2013 JAIDS, Phase 1 Safety and PK study in healthy volunteers



Virologic suppression & good clinical outcomes in INSPIRING trial: supports clinical recommendations

Dooley 2019, CID

SAfety and EFficacy in high-dose RIFampicin (SAEFRIF trial)

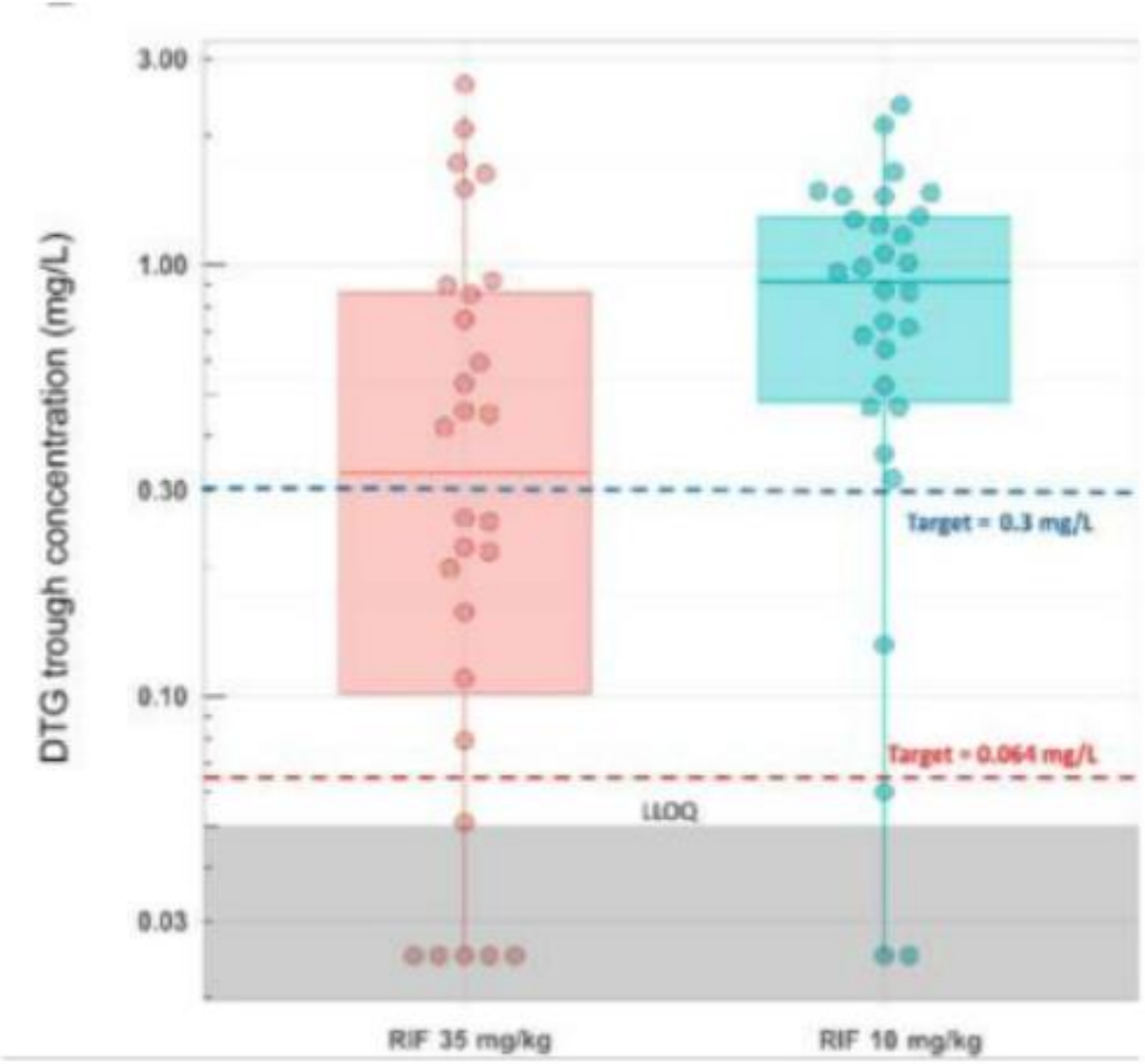
Sekaggya-Wiltshire CID 2023

Study Design (N=128, Ugandan)

- New diagnosis of TB, on ART or ART naïve
- Randomised 1:1 to $R_{10}HEZ$ or $R_{35}HEZ$
- If ART naïve, randomised 1:1 to DTG (50mg BID or EFV; if on ART, continue current regimen
- PK analysis after 6 weeks TB treatment

Results:

- Reduced DTG with high dose rifampicin
- All participants maintained viral suppression
- Regimen well tolerated



DOLUTEGRAVIR AND RIFAMPIN

Standard-dose versus double-dose dolutegravir in HIV-associated tuberculosis in South Africa (RADIANT-TB): a phase 2, non-comparative, randomised controlled trial

Griesel R, Zhao Y, Simmons B, Omar Z, Wiesner L, Keene CM, Hill AM, Meintjes G, Maartens G. Standard-dose versus double-dose dolutegravir in HIV-associated tuberculosis in South Africa (RADIANT-TB): a phase 2, non-comparative, randomised controlled trial. Lancet HIV. 2023 Jul;10(7):e433-e441. doi: 10.1016/S2352-3018(23)00081-4. Epub 2023 May 22. PMID: 37230101; PMCID: PMC10322729.

RADIANT -TB

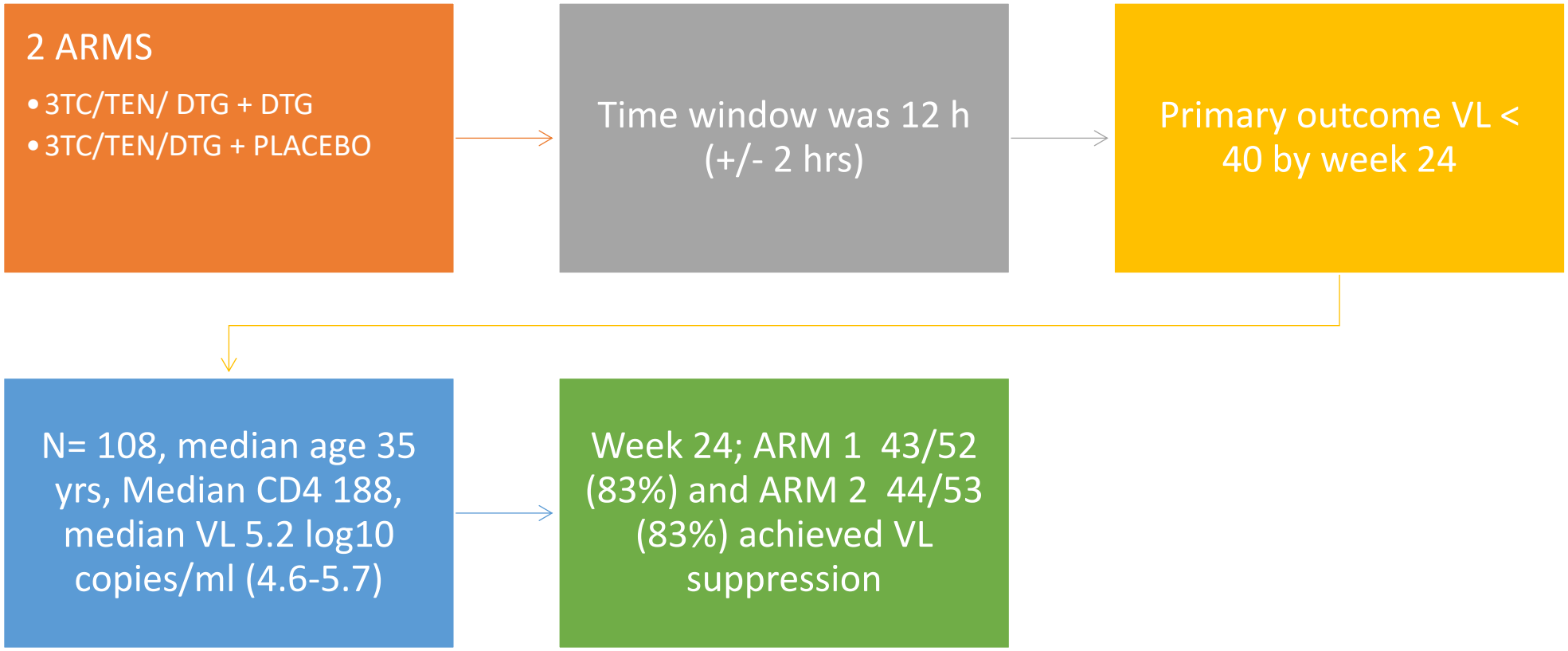
- Phase 2b double blind non comparative, placebo-controlled trial
- Cape town, Africa
- Adults (> 18)
- VL > 1000 c/ml, tx naïve or tx interrupted
- CD4 > 100
- On Rifampin based therapy for < 3 months (active TB treatment)
- Active TB treatment; Standard RIPE (Rifampin, Isoniazid, Pyrazinamide, Ethambutol) X 2 months, then 4 months of RIF/INH

Baseline characteristics of participants by study arm

	Supplemental dolutegravir arm (n=53)	Placebo arm (n=55)	Total (n=108)
Demographics			
Age, years	33 (28–38)	37 (33–44)	35 (31–40)
Sex			
Female	19 (36%)	19 (35%)	38 (35%)
Male	34 (64%)	36 (65%)	70 (65%)
Weight, kg	56 (51–62)	55 (51–62)	56 (51–62)
BMI, kg/m^2	20·0 (18·7–22·3)	20·2 (18·3–22·8)	20·1 (18·5–22·6)
HIV characteristics			
HIV-1 RNA log_{10}(log_{10} copies per mL)	5·1 (4·6–5·6)	5·2 (4·6–5·7)	5·2 (4·6–5·7)
≤100 000 copies per mL, n (%)	21 (40%)	21 (38%)	42 (39%)
>100 000 copies per mL, n (%)	32 (60%)	34 (62%)	66 (61%)
CD4 count (cells per μL)	197 (145–260)	183 (145–316)	188 (145–316)
≤200	27 (51%)	30 (55%)	57 (53%)
>200	26 (49%)	25 (45%)	51 (47%)

Baseline ART status, n (%)			
ART naive	44 (83%)	44 (80%)	88 (81%)
First-line ART interrupted	9 (17%)	11 (20%)	20 (19%)
On ART <6 months before interruption	8 (15%)	5 (9%)	13 (12%)
On ART ≥6 months before interruption	1 (2%)	6 (11%)	7 (6%)
Tuberculosis characteristics			
Diagnosis			
Microbiological or histological (or both)	38 (72%)	39 (71%)	77 (71%)
Clinical or radiological (or both)	15 (28%)	16 (29%)	31 (29%)
Site			
Pulmonary	40 (75%)	37 (67%)	77 (71%)
Extrapulmonary	10 (19%)	13 (24%)	23 (21%)
Disseminated	3 (6%)	5 (9%)	8 (7%)
Weeks on tuberculosis treatment at enrolment	8·0 (7·0–8·9)	8·0 (6·0–8·3)	8·0 (6·6–8·6)

RADIANT -TB


2 ARMS
• 3TC/TEN/ DTG + DTG
• 3TC/TEN/DTG + PLACEBO
Time window was 12 h (+/- 2 hrs)
Primary outcome VL < 40 by week 24
N= 108, median age 35 yrs, Median CD4 188, median VL 5.2 log10 copies/ml (4.6-5.7)
Week 24; ARM 1 43/52 (83%) and ARM 2 44/53 (83%) achieved VL suppression

RADIANT – TB

No treatment-emergent dolutegravir resistance mutations were detected up to week 48 in the 19 participants with study-defined virological failure.

Interpretation: Our findings suggest that twice-daily dolutegravir might be unnecessary in people with HIV-associated tuberculosis.

My morning run along the Promenade des Anglais

NICE, FRANCE

RIFAMPIN VS RIFAPENTINE

Rifampin

1966

Used in both Active and Latent TB

Strong Inducer

PK

- Absorption: Oral: Well absorbed; food may delay or slightly reduce peak.
- Bioavailability, oral: Rapidly absorbed
- Distribution: Highly lipophilic; crosses blood-brain barrier well.
- Protein binding: 80%.
- Metabolism; 25-desacetyl-rifampin (major); Active, inducer of CYP3A4, CYPC8/9, glucuronosyltransferases (UGT1A) and p-glycoprotein
- T1/2 Adults: ~2 to 3 hours (steady-state)

Time to peak, serum:

- Infants and Children 6 months to <5 years: Oral: 1 hour.
- Adults: Oral: ~2 hours

Rifapentine

1998

Used in both Active and Latent TB

Moderate Inducer

PK

- Absorption: High-fat meals increase AUC and C_{max} by 40% to 50%
- Crushing the tablet results in 26% lower exposure than whole tablets.
- Bioavailability: 70%
- Distribution: Highly lipophilic; crosses blood-brain barrier well.
- > lipophilic than Rifampin
- Protein binding: 98%, primarily to albumin; 25-desacetyl rifapentine: ~93%
- Metabolism: Hepatic; 25-desacetyl rifapentine (major): Active, inducer of CYP3A4, CYP2C8/9
- T1/2: Adults: ~17 hours; 25-desacetyl rifapentine: ~24 hours
- Time to peak, serum: 3 - 10 hours

Time for Canada to align with global innovations in treatment for tuberculosis

Adam R. Houston and Elizabeth Rea

CMAJ July 31, 2023 195 (29) E985-E986; DOI: https://doi.org/10.1503/cmaj.230246

RIFAPENTINE FUN FACTS

Rifapentine is a stronger inducer of cytochrome P-450 oxidative enzymes as well as the P-glycoprotein transport system than Rifampin when given daily

Listed as a drug for an "Urgent Public Need" *rifapentine is being imported in bulk via the Access to Drugs in Exceptional Circumstances mechanism*

The indication for use in Canada is strictly for Latent Tuberculosis

Rifapentine is increasingly used in other countries for active TB as well as LTBI, as it constitutes part of the breakthrough 4-month treatment regimen now recognized by the World Health Organization. However, in Canada, the Exceptional Circumstances mechanism restricts the use of rifapentine for indications other than LTBI.

3HP (SINGLES) – PRODUCT OVERVIEW

INH: 900mg + RPT: 900mg

IMPAACT4TB
PREVENTING TB TO END TB

FORMULATION

RIFAPENTINE (RPT/P)

150mg

- ✔ Single Tablet
- ✔ Antimycobacterial
- ✔ Shelf Life: 36 months
- ✔ Manufacturer: Sanofi

ISONIAZID (INH/H)

300mg

- ✔ Single Tablet
- ✔ Prophylaxis
- ✔ Shelf Life: 48 months
- ✔ Manufacturer: Differs by country

PACKAGING

RIFAPENTINE

Packaging: Blister packs of 8 tablets.
One box = 24 tablets.

Patient course:
1 Month: 24 Tablets (1x box)
Full Course: 72 Tablets (3x boxes)

ISONIAZID

Packaging: Loose or in bulk depending on the manufacturer

Patient course:
1 Month: 12 Tablets
Full Course: 36 Tablets

DOSAGE

CHILD PATIENTS 2 – 14 YEARS

SINGLES

WEIGHT BAND	10 – 15 KG	16 – 23 KG	24 – 30 KG	>31 KG
INH (300mg)	3	5	6	7
RPT (150MG)	2	3	4	5

ADULT PATIENTS >14 YEARS

SINGLES

INH(300mg) - 3

RPT(150mg) - 6

Add Pyridoxine 25mg weekly in PLHIV (increase to 50mg if symptoms of peripheral neuropathy)

PREVENT TB (3HP – 12 dose regimen vs 9H)

The use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing tuberculosis and had a higher treatment-completion rate.

Efficacy similar 0.19% (3HP) vs 0.43% (9H) developed TB disease (followed for 33 months)

Adherence was better **83% (3HP) vs 69% (9H)**

N= 3986 (3HP) DOT

N=3745 (9H) Self admin

Adverse Events

- - More hepatotoxicity in 9H group (2.7% vs 0.4%)
- - **Systemic drug reaction** with 3HP (Flu like or rash – 3.5% manageable, 0.3% severe) vs 0.4% INH
- -Occurs at the 3rd or 4th dose, and onset of 4 hours afterwards
- -Symptoms resolve within 24hrs; recommend to pre-hydrate before next dose
- -Severe reactions; syncope/hypotension **– STOP!**
- -mild to moderate reactions, close monitoring and can continue to treatment completion

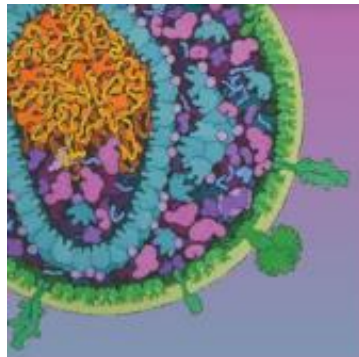
Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, Hackman J, Hamilton CD, Menzies D, Kerrigan A, Weis SE, Weiner M, Wing D, Conde MB, Bozeman L, Horsburgh CR Jr, Chaisson RE; TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155-66. doi: 10.1056/NEJMoa1104875. PMID: 22150035.

Known as the DOLPHIN TRIAL presented at CROI 2019

HIV patients - VL < 40, Adults > 18 years, N=60 patients (70% women and ALL black African) Median age was 40 years, CD4 cell count was 683, all had VL < 40 before the start of LTBI

8 weeks of Efavirenz based regimen vs 8 weeks of Dolutegravir based regimen
EFA group then switched to Dolutegravir at initiation of 3HP

Conclusion - **12 doses of once-weekly rifapentine-isoniazid can be given for tuberculosis prophylaxis to patients with HIV taking dolutegravir-based antiretroviral therapy, without dose adjustments**



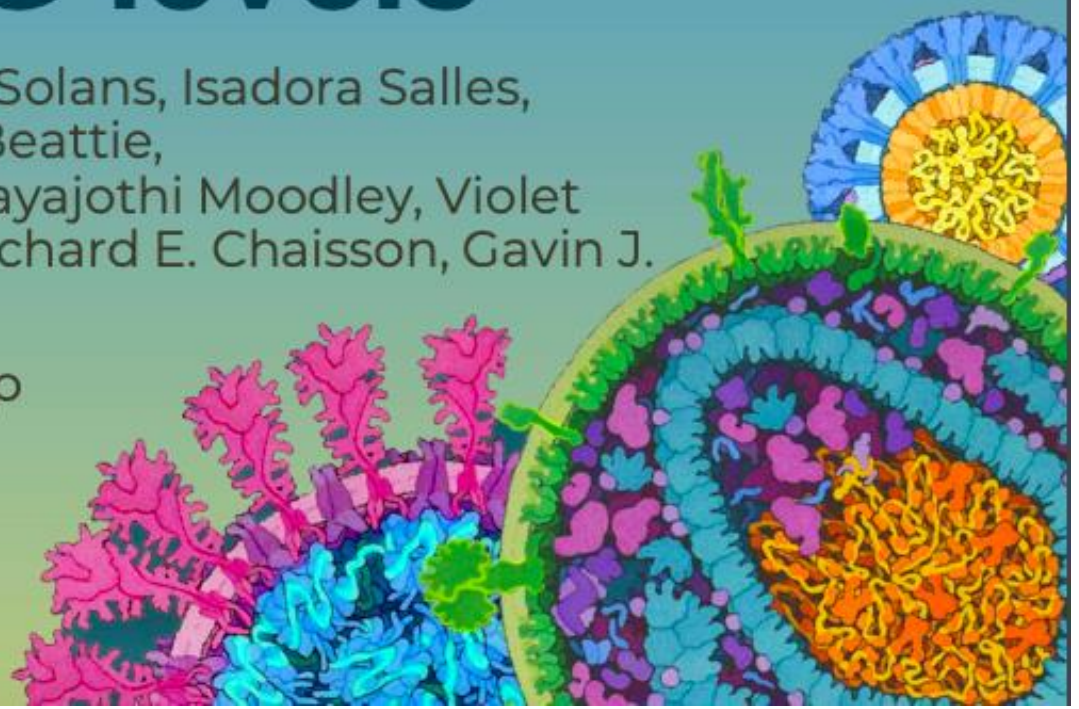
Simultaneous initiation in ART-naïve PWH of DTG-based ART & 3HP maintains efficacious DTG levels

Ethel D. Weld, MD, PhD, Belén Perez Solans, Isadora Salles, Bareng A.S. Nonyane, M Sebe, Trevor Beattie, Manasa Mapendere , Tanya Nielson , Jayajothi Moodley, Violet Chihota, Rada Savic, Kelly E. Dooley, Richard E. Chaisson, Gavin J. Churchyard

UNITAID IMPAACT4TB Research Group

DOLPHIN-TOO Study

Roland Wiehraun/AFP/Getty Images

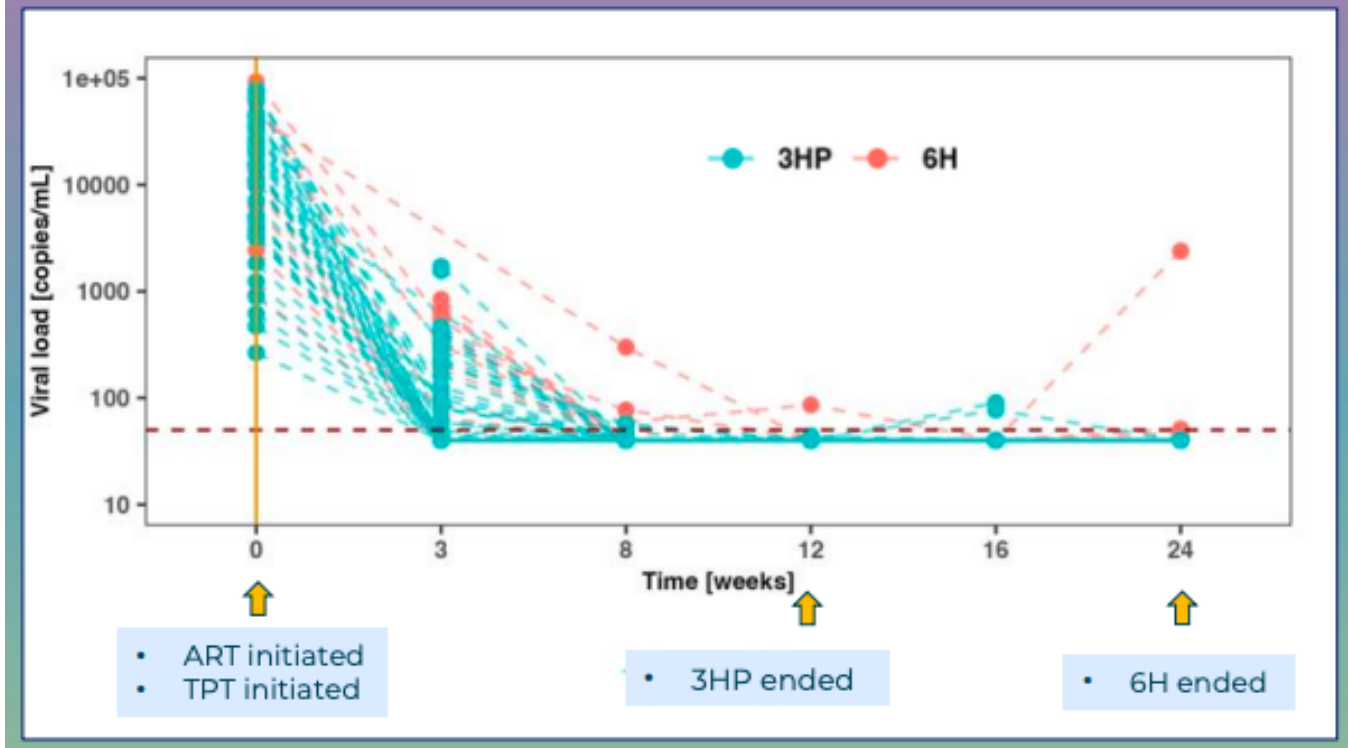


Pharmacokinetic Sampling Scheme

	Day 0	Day 1 (Week 0)	Day 14	Day 17 (Week 3)	Day 49	Day 52 (Week 8)	Week 12	Week 16	Week 24
INH dose (6H group)		Begins →	→	→	→	→	→	→	Ends
HP dose (3HP group)		X Begins →	X (3rd HP)	→	X (8th HP)	→	Ends		
DTG/TDF/ 3TC daily	Begins →	→	→	→	→	→	→	→	Cont.
DTG trough (both groups)		**X** *Pre-TPT*		**X** *72 hrs after 3rd dose HP*		**X** *72 hrs after 8th dose HP*			
HIV Viral load	X			X			X	X	X

Participant Characteristics	Overall n=75	6H n=25	3HP n=50
Age (years)			
median (IQR)	35 (27-41)	35 (29-39)	34 (27-42)
Female sex n (%)	37 (49%)	14 (56%)	23 (46%)
BMI (kg/m^2)			
median (IQR)	23.7 (22-28.6)	23.8 (22-28.6)	23.4(22.1-28.3)
<18.5, n (%)	2 (3%)	0	2 (4%)
QGIT +ve n (%)	17 (23%)	3 (12%)	14 (28%)
missing, n(%)	9 (12%)	4 (16%)	5 (10%)
Baseline HIV VL (copies/mL), median (IQR)	27056 (7088-111620)	63863 (11381-220005)	21949.5 (5101-72620)
200-10,000, n(%)	21 (28%)	6 (24%)	15 (30%)
10,001-50,000, n(%)	26 (35%)	5 (20%)	21 (42%)
50,001-100,000, n(%)	13 (17%)	7 (28%)	6 (12%)
100,000-1 million, n(%)	15 (20%)	7 (28%)	8 (16%)
Baseline CD4+ (cells/mm3), median (range)	283 (3-1020)	283 (21-1070)	285.5 (3-804)
>200	54 (72%)	15 (60%)	39 (78%)
100-200	15 (20%)	7 (28%)	8 (16%)
<100	4 (5%)	2 (4%)	2 (8%)
<50	2 (3%)	1 (2%)	1 (4%)

HIV Viral Load over Time



For those with missing HIV VL data*:

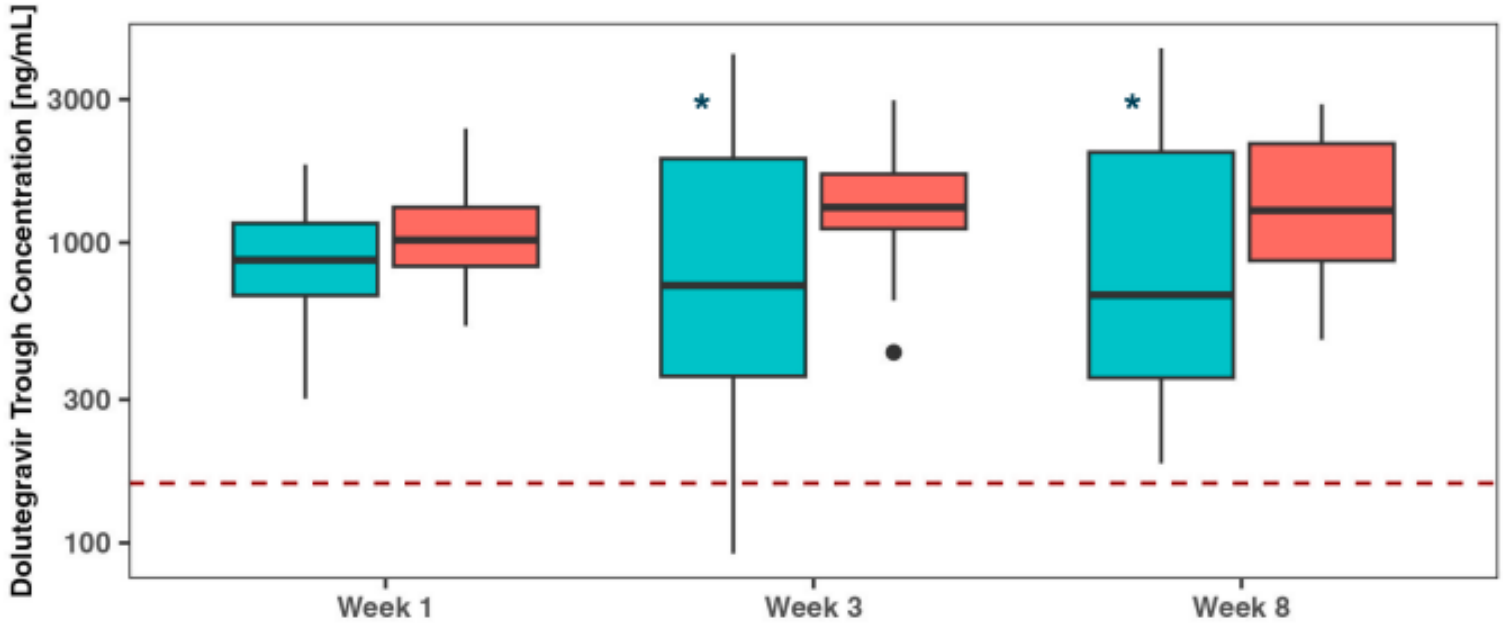
CARRY-FORWARD ANALYSIS OF MOST RECENT HIV VIRAL LOAD

Participants with Virologic Suppression (HIV-1 RNA < 50 c/mL)	Overall n=75	6H Group n=25	3HP Group n=50
Week 12			
Number	73/75	24/25	49/50
Proportion [95% C.I.]	0.97 [0.91-1.0]	0.96 [0.80-1.0]	0.99 [0.89-1.0]
Week 16			
Number	72/75	25/25	47/50
Proportion [95% C.I.]	0.96 [0.89-0.99]	1.0 [0.86-1.0]	0.94 [0.83-0.99]
Week 24			
Number	71/75	23/25	48/50
Proportion [95% C.I.]	0.95 [0.87-0.99]	0.92 [0.74-0.99]	0.96 [0.86-1.0]

- Median HIV VL decline from study initiation to week 12 (end of 3HP):
  - **3HP group:** 4.3 (3.7-4.9) $\log_{10}$
  - **6H group:** 4.8 (4.1-5.3) $\log_{10}$

*Carrying forward the LAST/**most recent viral load** that we have for these participants, and **assuming it is the same at the subsequent timepoint** (e.g., if < 50 c/mL at week 16, we assume also <50 c/mL at week 24

Dolutegravir Trough over Time



3HP 6H

Nonlinear mixed-effects modeling showed a **72% induction effect** of rifapentine on DTG clearance, from 0.954 L/hr to 1.64 L/hr

← 158 ng/mL (5^{th} %ile C_{min} w/ 10 mg daily DTG in SPRING-1 Trial[1])

* Wilcoxon rank sum p-value <0.01

DTG troughs (ng/mL)	3HP (N=50)			6H (N=25)		
Sampling Time	Day 1	Day 21	Day 56	Day 1	Day 21	Day 56
n (# samples)	50	49	44	25	23	24
Median (5^{th}, 95^{th} %ile)	875 (411, 1580)	720 (219, 3325)	669 (208, 2593)	1020 (546, 2292)	1310 (642, 2915)	1344 (595, 2615)
Below 300 (#)	-	5	8	-	-	-
Below 158 (#)	-	2	-	-	-	-
Below 64 (PA-IC_{90}) (#)	-	-	-	-	-	-
%Target attainment (<158)	100%	96%	100%	100%	100%	100%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ORIGINAL ARTICLE

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

Authors: Susan Swindells, M.B., B.S., Ritesh Ramchandani, Ph.D., Amita Gupta, M.D., Constance A. Benson, M.D., Jorge Leon-Cruz, M.S., Noluthando Mwelase, M.B., Ch.B., Marc A. Jean Juste, M.D., +18, for the BRIEF TB/A5279 Study Team* Author Info & Affiliations

Published March 13, 2019 | N Engl J Med 2019;380:1001-1011 | DOI: 10.1056/NEJMoa1806808 | VOL. 380 NO. 11

ALSO CALLED " The BRIEF - TB TRIAL

A 1-month regimen of rifapentine plus isoniazid was noninferior to 9 months of isoniazid alone for preventing tuberculosis in HIV-infected patients. The percentage of patients who completed treatment was significantly higher in the 1-month group. (Funded by the National Institute of Allergy and Infectious Diseases; BRIEF TB/A5279 ClinicalTrials.gov number, NCT01404312.).

BRIEF - TB (1HP vs 9H)

N= 3000 patients

A total of 1614 patients (54%) were women; the median CD4+ count was 470 cells per cubic millimeter

50% of patients were on antiretroviral therapy at entry, and 77% of these patients had an undetectable HIV viral load (HIV RNA, <40 copies per milliliter).

97% areas with a high prevalence of tuberculosis (≥60 cases per 100,000 population)

692 (23%) had a positive tuberculin skin test, a positive result on the interferon-γ release assay, or both.

patient-reported adherence to treatment was 90% or more in each group; treatment was completed in 97% of the patients in the 1-month group and in 90% of those in the 9-month group (P<0.001).

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	1-Month Group (N=1496)	9-Month Group (N=1504)	All Patients (N=3000)
Continent of residence — no. (%)			
Africa	772 (52)	781 (52)	1553 (52)
Asia	121 (8)	124 (8)	245 (8)
South America	360 (24)	355 (24)	715 (24)
North America	243 (16)	244 (16)	487 (16)
Median age (IQR) — yr	35 (28–43)	35 (28–43)	35 (28–43)
Sex — no. (%)			
Male	694 (46)	692 (46)	1386 (46)
Female	802 (54)	812 (54)	1614 (54)
Race or ethnic group — no. (%)†			
Black non-Hispanic	992 (66)	991 (66)	1983 (66)
White non-Hispanic	16 (1)	12 (1)	28 (1)
Asian or Pacific Islander	122 (8)	128 (9)	250 (8)
Hispanic	361 (24)	369 (25)	730 (24)
Unknown	5 (<1)	4 (<1)	9 (<1)
Median body-mass index (IQR)‡	23.6 (20.9–27.1)	23.5 (20.8–26.9)	23.5 (20.9–27.1)
CD4+ count			
Median (IQR) — no. of cells/mm^3	473 (349–636)	469 (341–634)	470 (346–635)
Patients — no. (%)			
>250 cells/mm^3	1299 (87)	1302 (87)	2601 (87)
100 to ≤250 cells/mm^3	160 (11)	165 (11)	325 (11)
<100 cells/mm^3	37 (2)	37 (2)	74 (2)
Receipt of antiretroviral therapy at entry — no. (%)			
Efavirenz-based regimen	650 (43)	649 (43)	1299 (43)
Nevirapine-based regimen	97 (6)	100 (7)	197 (7)
Other	3 (<1)	6 (<1)	9 (<1)
None	746 (50)	749 (50)	1495 (50)
Viral load in patients receiving antiretroviral therapy — no./total no.(%)			
Undetectable — <40 copies/ml	569/750 (76)	586/755 (78)	1155/1505 (77)
Detectable — ≥40 copies/ml	154/750 (21)	143/755 (19)	297/1505 (20)
Unavailable	27/750 (4)	26/755 (3)	53/1505 (4)
Previous diagnosis of tuberculosis — no. (%)	82 (5)	89 (6)	171 (6)
Tuberculin skin test — no. (%)			
Positive	311 (21)	324 (22)	635 (21)
Negative	1033 (69)	1021 (68)	2054 (68)
Not done	152 (10)	159 (11)	311 (10)
IGRA for tuberculosis — no. (%)§			
Positive	36 (2)	37 (2)	73 (2)
Negative	1 (<1)	2 (<1)	3 (<1)
Not done	1459 (98)	1465 (97)	2924 (97)

One Month of Rifapentine + Isoniazid to Prevent HIV-Related Tuberculosis

RANDOMIZED, OPEN-LABEL, MULTICENTER, PHASE 3 NONINFERIORITY TRIAL

3000

HIV-infected persons at high risk for TB

	Rifapentine + isoniazid (1 mo)	Isoniazid alone (9 mo)
	(N=1488)	(N=1496)
Incidence of TB or death per 100 person-yr	0.65	0.627
	Difference, −0.02; 95% CI, −0.35–0.30; noninferiority shown	
Serious adverse events	83 Patients (6%)	108 Patients (7%)
	P=0.07	

The NEW ENGLAND JOURNAL of MEDICINE

Swindells et al. 2019

MEDICATION	MORNING	AFTER DINNER
DOLUTEGRAVIR (YELLOW TABLET)		
Tenofovir/Emtricitabine (BLUE TABLET)		
Rifapentine (Red Tablet)		
Isoniazid (White tablet)		
Pyridoxine (SMALL white tablet)		

Individuals with LTBI serve as an important reservoir of future active tuberculosis (TB) disease.1 Studies have estimated that in low incidence settings such as Canada, 80% to 85% of active TB cases could be attributable to reactivation of LTBI.2-4 For this reason, the identification and treatment of individuals with LTBI is an important strategy for preventing and eliminating TB

1. World Health Organization. Framework towards tuberculosis elimination in low-incidence countries. Geneva, Switzerland: World Health Organization; 2014. Available from: who.int/tb/publications/elimination_framework/en/ 2. France AM, Grant J, Kammerer JS, Navin TR. A field-validated approach using surveillance and genotyping data to estimate tuberculosis attributable to recent transmission in the United States. Am J Epidemiol. 2015;182(9):799-807. 3. Ricks PM, Cain KP, Oeltmann JE, Kammerer JS, Moonan PK. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005-2009. PLoS One. 2011;6(11):e27405. 4. Shea KM, Kammerer JS, Winston CA, Navin TR, Horsburgh CR, Jr. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. Am J Epidemiol. 2014;179(2):216-25

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new

Preferred Drugs for Treatment of Latent TB Infection

3HP

Rifapentine (weight-based dosing) orally (PO) once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks is one of two preferred regimens for the treatment of LTBI **(AI).**[54]

Alternative Drugs for Treatment of Latent TB Infection

1HP

Isoniazid 300 mg PO daily plus rifapentine (weight-based dosing to a maximum of 600 mg) PO daily plus pyridoxine 25 mg to 50 mg PO daily for 4 weeks (1HP) is an alternative therapy for the treatment of LTBI in people with HIV treated with efavirenz **(BI).**

JOURNAL ARTICLE

US Guidelines Fall Short on Short-Course Tuberculosis-Preventive Therapy

Sonya Krishnan, Richard E Chaisson ✉ Author Notes

Clinical Infectious Diseases, Volume 78, Issue 3, 15 March 2024, Pages 514–517,
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Abstract

The provision of tuberculosis-preventive therapy (TPT) to vulnerable populations is critical for global control. Shorter-course TPT regimens are highly effective and improve completion rates. Despite incorporation of 1 month of rifapentine and isoniazid into global guidelines, current US TPT guidelines do not include this as a recommended regimen, but should.

1.4 TB preventive treatment options

TPTs for an infection with *M. tuberculosis* strains presumed to be drug-susceptible can be broadly categorized into two types: monotherapy with isoniazid for at least 6 months (IPT) and treatment with regimens containing a rifamycin (rifampicin or rifapentine). IPT has been the most widely used form of TPT, but the shorter duration of rifamycin regimens presents a clear advantage, making these regimens increasingly preferred. TPT for MDR/RR-TB requires a different approach, primarily with levofloxacin. The recommendations for these treatment options and the conditions under which they apply are discussed below.

19. The following TB preventive treatment options are recommended regardless of HIV status: 6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid, or a 3-month regimen of daily isoniazid plus rifampicin. *(Strong recommendation, moderate-to-high certainty of the estimates of effect).*
20. The following alternative TB preventive treatment options may be used regardless of HIV status: a 1-month regimen of daily rifapentine plus isoniazid or 4 months of daily rifampicin. *(Conditional recommendation, low to moderate certainty of the estimates of effect).*

TPT with isoniazid or rifamycins

A strong recommendation for TPT alternatives to 6 months of daily isoniazid monotherapy (6H), based on evidence of moderate to high certainty, has featured in previous WHO guidance *(17,37,77)*. These consist of 3 months of weekly isoniazid plus rifapentine (3HP) and 3 months of daily isoniazid plus rifampicin (3HR). In the 2020 guidelines, the GDG made conditional recommendations for two regimens: daily rifapentine plus isoniazid for 1 month (1HP) and daily rifampicin monotherapy for 4 months (4R) in all settings, based on low to moderate certainty of the estimates of effect. In the current second edition, the recommendation from 2020 has been divided: **recommendation 19** for regimens that are strongly recommended and **recommendation 20** for alternative regimen options. Recommended TPT options are applicable in all settings, regardless of TB burden.

Rifampin Drug Interactions – Bictegravir (contraindicated)

- Combination is contraindicated due to decreased bictegravir concentrations.[1] [2]
- In the presence of rifampin 600 mg daily, plasma exposures of single dose bictegravir 75 mg were significantly reduced (AUC decreased 75%, Cmax decreased 28%).[1]
- Bictegravir 50mg/emtricitabine 200mg/tenofovir alafenamide 25mg **BID** + rifampin 600mg daily was compared to standard once daily administration in 26 patients. Rifampin reduced bictegravir Cmax and AUC by 47% and 61% respectively. **Bictegravir trough concentration was approximately 80% lower in BID+ Rifampin arm compared to once daily without rifampin**. All subjects were able to maintain levels above protein adjusted 95% effective concentrations. BID administration of bictegravir/emtricitabine/tenofovir alafenamide failed to mitigate the interaction between rifampin and bictegravir. [3]

- 1: Gilead Sciences, Inc. Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) Product Monograph. Foster City, CA. May 2023.
- 2: Gilead Sciences Canada, Inc. Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) Product Monograph. Mississauga, ON. April 14, 2023.
- 3: Custodio JM, West SK, Collins S et al. Pharmacokinetics of bictegravir administered twice daily in combination with rifampin. [abstract 34]. Conference on Retroviruses and Opportunistic Infections (CROI), March 4-8, 2018, Boston, MA.

Efficacy, Safety, and PK of BIC/FTC/TAF in Adults With HIV and Tuberculosis on Rifampicin at Week 24

- Abstract 211, open-label, non-comparative, phase-2b randomised controlled trial in ART-naïve or non-naïve adults with HIV (CD4+ >50 cells/µL) and TB, taking a rifampicin-based TB regimen (for ≤ 8 weeks). Participants were randomised 2:1 to the BIC arm [bictegravir/emtricitabine (FTC)/tenofovir alafenamide (TAF)] or a standard of care DTG arm [tenofovir, lamivudine, dolutegravir (TLD)], with BIC/FTC/TAF or DTG **dosed twice daily**, until 2 weeks post-TB treatment and once daily thereafter, until 48 weeks.
- N = 80 Biktarvy vs N= 42 DTG/3TC/TEN, CD4 172 vs 139, median VL at baseline 75, 649 vs 73, 735 copies/ml
- Trough concentrations for twice daily BIC during TB treatment and once daily BIC after TB treatment were 0.397 (73.4%) mg/L and 2.29 (45.1%) mg/L. HIV-1-RNA at week 24 was <50 copies/mL in 71/72 (97%) and 36/37 (97%) of participants in the BIC and DTG arms, respectively, in the per-protocol analysis.

Primary Endpoint: Viral Suppression at Week 24

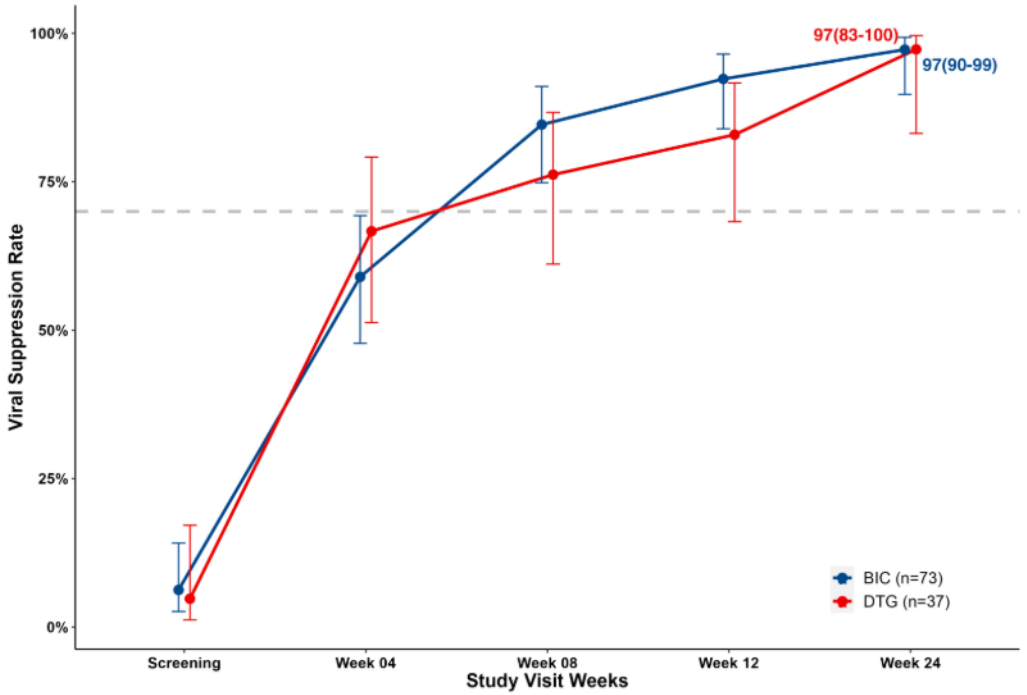

Figure 1: Viral Suppression rate (per protocol analysis) over study visits by Arm with two-sided 95% Confidence Interval

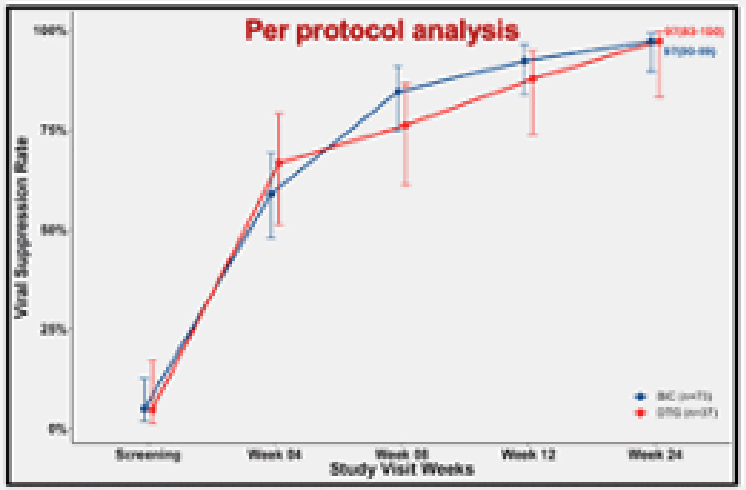

Figure 2: Viral Suppression Rate (per protocol analysis) over study visits by Arm with two-sided 95% Confidence Interval

- **Median CD4+ cell count** (Q1, Q3) cells/mm^3 at Week 24
  - BIC: 259 (213, 505)
  - DTG: 231 (170, 311)
- **Median change in CD4+ cell count** (Q1, Q3) cells/mm^3 at Week 24
  - BIC: 96 (35, 137)
  - DTG: 69 (27, 122)

Viral suppression rates were high and similar in participants receiving BIC/FTC/TAF vs DTG/3TC/TDF

CROI 2024

** two relocations; **hemoptysis*

Summary of Adverse Events

n (%)	BIC (n=80)	DTG (n=42)
Any AE	80 (100)	42 (100)
Most frequently occurring AEs in either group		
Increased Amylase	44 (55)	23 (55)
Arthralgia	31 (39)	18 (43)
Peripheral neuropathy	21 (26)	21 (50)
Hyperglycaemia	28 (35)	14 (33)
Proteinuria	26 (33)	13 (31)
Anaemia	23 (29)	14 (33)
Decreased creatinine clearance	22 (28)	13 (31)
Any serious AE (SAE)	**9 (11)**	**3 (7)**
Any Grade 3 and 4 AEs		
Grade 3	30 (38)	15 (36)
Grade 4	6 (8)	6 (14)
Grade 3 and 4 Liver Chemistry Abnormalities		
Grade 3	3 (4)	3 (7)
Grade 4	1 (1)	0 (0)

NO AE's leading to treatment discontinuations, withdrawals or drug switches

Rifapentine drug interactions and Bictegravir

Significant decreased concentrations of bictegravir occurs with concurrent use of rifapentine.

Daily Rifapentine as 1HP with BIKTARVY, in 48 PLWH with LTBI receiving BIC/FTC/TAF along with the one-month regimen of daily rifapentine 600mg plus isoniazid 300mg (1HP).

BIC trough concentration above 162 ng/mL (the protein-adjusted 95% effective concentration) before 1HP initiation was 100%, and dropped to 56.2% (27/48) and 37% (17/46) on day 15 and 29, respectively. VL < 50 copies/mL 97.9%, before concurrent use of 1HP, the proportions of patients with VL ≥50 copies/ml were 27.1% on day 15 and 6.5% on day 29 . The decreased BIC trough concentration on days 15 and 29 appeared to result in an increased rate of on-treatment virologic blips.

100% had viral load re-supresssion during and 3-6 months after completion of 1HP.

Ref: Liou BH, Cheng CN, Lin YT, Lin YJ, Chuang YC, Lin KY, Liu WC, Lin SW, Kuo CH, Sun HY, Hung CC. Short-course daily isoniazid and rifapentine for latent tuberculosis infection in people living with HIV who received coformulated bictegravir/emtricitabine/tenofovir alafenamide. J Int AIDS Soc. 2021 Nov;24(11):e25844. doi: 10.1002/jia2.25844. PMID: 34822220; PMCID: PMC8614225.

TPT Research is ongoing!

Asteroid Trial

Sstarlet Trial

What is ASTEROID?

Assessment of the Safety, Tolerability, and Effectiveness of Rifapentine Given Daily for LTBI (ASTERoiD) – TBTC 37

To compare the safety and effectiveness of 6 weeks of daily rifapentine to “local comparator” (daily rifampin for 4 months)

2 arms

Open label

Random Allocation

SSTARLET

SHORTER AND SAFER

TREATMENT REGIMENS FOR LATENT TB

INCLUSION CRITERIA MUST MEET ALL 3 CRITERIA
ADULTS OR CHILDREN ≥ 5 YEARS OLD
TB PREVENTIVE TREATMENT RECOMMENDED
EVIDENCE OF TB INFECTION MEANING: TST ≥ 5MM OR POSITIVE QFT
EXCLUSION CRITERIA
ACTIVE TB DISEASE (CURRENT CONFIRMED OR CLINICAL)
THE PATIENT HAS ALREADY STARTED TREATMENT FOR TB INFECTION (DEFINED AS AT LEAST 7 DAYS OF TREATMENT WITHIN THE LAST 90 DAYS)
ALREADY ADEQUATELY TREATED FOR TB INFECTION OR TB DISEASE (DOCUMENTED HISTORY OF COMPLETION OF TREATMENT)
CLOSE OR CASUAL CONTACT OF A PATIENT KNOWN TO HAVE TB THAT IS RESISTANT TO RIFAMPIN
ALLERGY TO RIFAMPIN
FEMALES WHO ARE CURRENTLY PREGNANT OR BREASTFEEDING
TREATMENT ARMS
STANDARD TREATMENT: RIFAMPIN 10MG/KG/DAY FOR 4 MONTHS
RIFAMPIN 20MG/KG/DAY FOR 2 MONTHS
LEVOFLOXACIN1 15MG/KG/DAY + RIFAPENTINE 10MG/KG/DAY FOR 1 MONTH

Costs of Latent TB treatment

LTBI REGIMEN	DURATION	COST	ARVs additional cost	TOTAL COST
1HP	30 days	184.50	TEN/FTC/DTG + DTG	doubled
3HP	12 weeks	123.24	TEN/FTC/DTG	----------
Rifampin 600mg QD	4 months	165.60	TEN/FTC/DTG + DTG	quadrupled
Isoniazid 300mg/B6 25mg QD	9 months	191.70	TEN/FTC/DTG	----------

World **AIDS** Day, Dec.1

TB is the leading cause of death in people with HIV/AIDS

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