TB and HIV in 2022: An Update

Kelly Dooley, MD, PhD

VCCC and AETC Symposium
November 4th, 2022
Nashville, TN

VANDERBILT UNIVERSITY MEDICAL CENTER

Vanderbilt Tuberculosis Center (VTC)

SNTC Southeastern National Tuberculosis Center

https://sntc.medicine.ufl.edu/home/index#/

CFAR TB / HIV CENTERS FOR AIDS RESEARCH COINFECTION WORKING GROUP

Let’s start with some Epidemiology

Tennessee TB Cases and Rates* by Region and County – 2020

3/25/2021

Region / County	Cases	Rate
Metropolitan Regions		
Memphis/Shelby	36	3.8
Jackson/Madison	3	3.1
Nashville/Davidson	29	4.2
Chattanooga/Hamilton	7	1.9
Knoxville/Knox	4	0.9
Sullivan County	0	0.0
West Tennessee Region 1	**0.2**	
Benton County	0	0.0
Carroll County	0	0.0
Chester County	0	0.0
Crockett County	0	0.0
Decatur County	0	0.0
Dyer County	0	0.0
Fayette County	0	0.0
Gibson County	0	0.0
Hardeman County	0	0.0
Hardin County	0	0.0
Haywood County	0	0.0
Henderson County	0	0.0
Henry County	0	0.0
Lake County	0	0.0
Lauderdale County	0	0.0
McNairy County	1	3.9
Obion County	0	0.0
Tipton County	0	0.0
Weakley County	0	0.0
Mid-Cumberland Region 19	**1.5**	
Cheatham County	0	0.0
Dickson County	0	0.0
Houston County	0	0.0
Humphreys County	0	0.0
Montgomery County	2	1.0
Robertson County	1	1.4
Rutherford County	8	2.5
Stewart County	0	0.0
Sumner County	2	1.1
Trousdale County	0	0.0
Williamson County	5	2.2
Wilson County	1	0.7

Region / County	Cases	Rate
South Central Region 4	**1.0**	
Bedford County	1	2.0
Coffee County	1	1.8
Giles County	1	3.4
Hickman County	0	0.0
Lawrence County ★	0	0.0
Lewis County	0	0.0
Lincoln County	0	0.0
Marshall County	0	0.0
Maury County	0	0.0
Moore County	1	15.6
Perry County	0	0.0
Wayne County	0	0.0
Upper Cumberland Region 3	**0.8**	
Cannon County	0	0.0
Clay County	0	0.0
Cumberland County	1	1.7
DeKalb County	0	0.0
Fentress County	0	0.0
Jackson County	0	0.0
Macon County	0	0.0
Overton County	0	0.0
Pickett County	0	0.0
Putnam County	1	1.3
Smith County	0	0.0
Van Buren County	0	0.0
Warren County	1	2.4
White County	0	0.0
Southeast Region 1	**0.3**	
Bledsoe County	0	0.0
Bradley County	1	0.9
Franklin County	0	0.0
Grundy County	0	0.0
McMinn County	0	0.0
Marion County	0	0.0
Meigs County	0	0.0
Polk County	0	0.0
Rhea County	0	0.0
Sequatchie County	0	0.0

Region / County	Cases	Rate
East Tennessee Region 2	**0.3**	
Anderson County	0	0.0
Blount County	0	0.0
Campbell County	0	0.0
Claiborne County	0	0.0
Cocke County	0	0.0
Grainger County	0	0.0
Hamblen County	1	1.5
Jefferson County	1	1.9
Loudon County	0	0.0
Monroe County	0	0.0
Morgan County	0	0.0
Roane County	0	0.0
Scott County	0	0.0
Sevier County	0	0.0
Union County	0	0.0
Northeast Region 4	**1.1**	
Carter County	0	0.0
Greene County	2	2.9
Hancock County	0	0.0
Hawkins County	0	0.0
Johnson County	0	0.0
Unicoi County	0	0.0
Washington County	2	1.6

https://sntc.medicine.ufl.edu/home/index#/

2020 Total	Cases	Rate
Tennessee	113	1.7
United States	7,163	2.2

*Rate = number of TB cases per 100,000 population
Pop. Source: United States Census Bureau - American FactFinder – 11/2019

Tuberculosis Elimination Program
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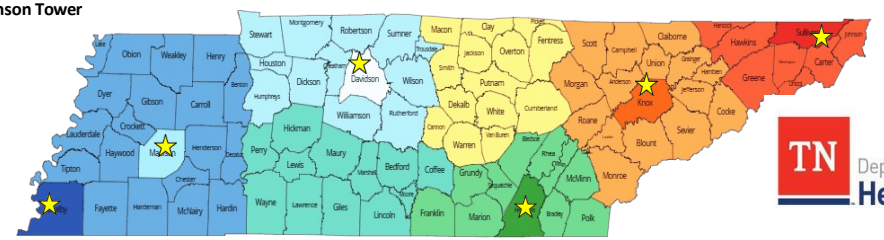
Fax: 615-253-1370

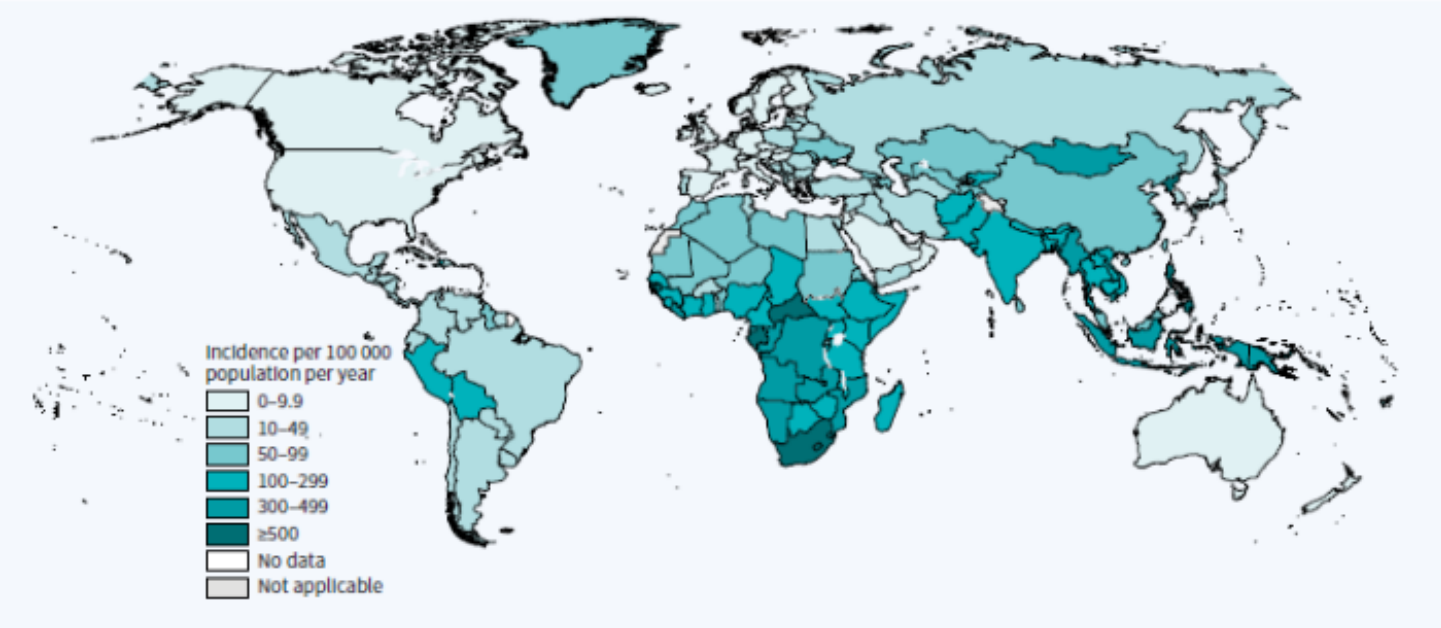


TN Department of Health


TB ANYWHERE IS EVERYWHERE
The image
The dandelion is a plant which propagates itself by airborne means. In the same way, social action can spread and take root, carried on the winds of our efforts and the global determination to overcome this disease.
ge also represents the vulnerability of
here the disease, located anywhere,
d everywhere.
reventable and curable.
BAL PLAN TO STOP TB.
WORLD TB DAY
REUTERS

State-of-the-state: Global burden of TB disease

FIG. 14
Estimated TB incidence rates, 2021



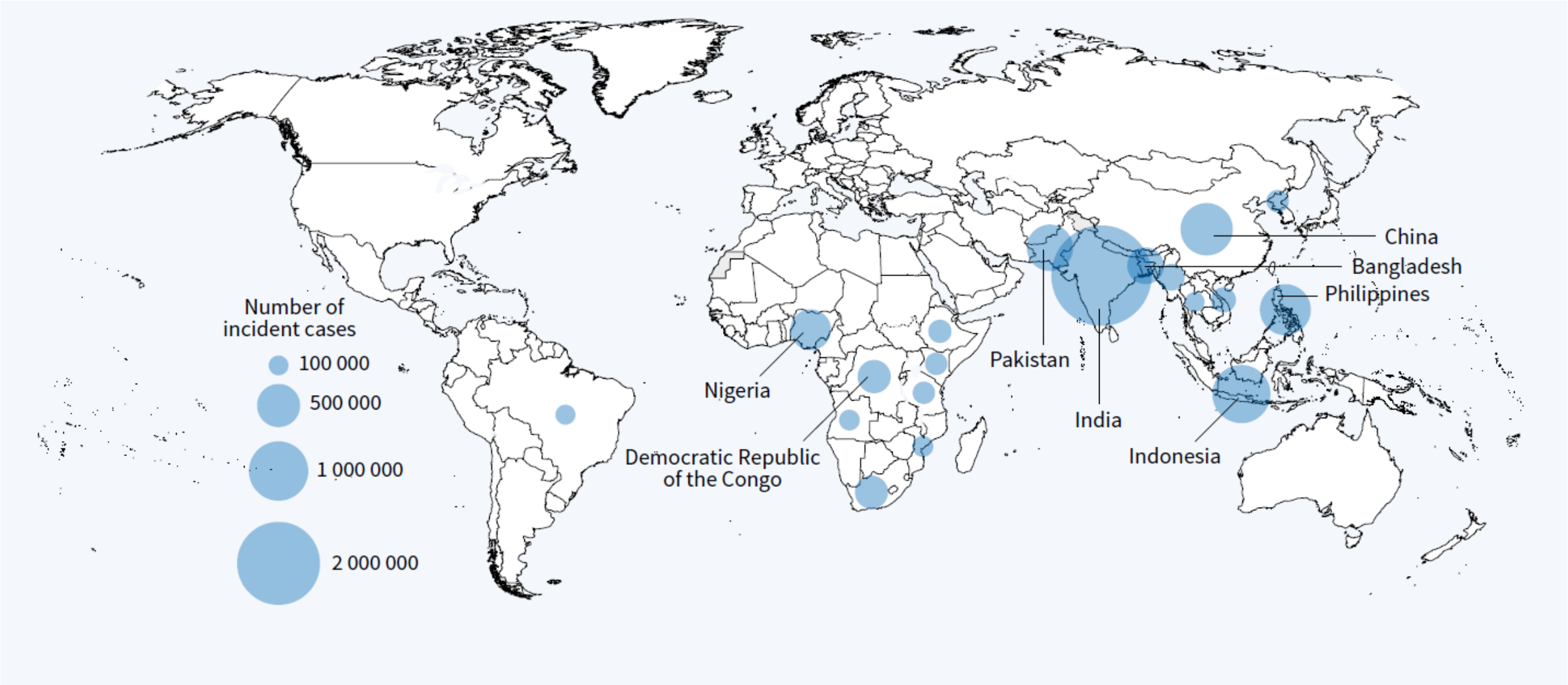
In 2014, TB surpassed HIV as the **#1 infectious disease killer worldwide** (now it is #2)

In 2021, 10.6M cases
A top 15 global cause of death

In 2021 & 2022, for the first time in a decade, TB mortality increased

WHO Global Tuberculosis Report 2022

Global burden of TB disease, in absolute numbers



WHO. Global TB Report, 2022.

THE COVID-19 PANDEMIC HAS REVERSED YEARS OF PROGRESS MADE IN THE FIGHT TO END TUBERCULOSIS

World Health Organization

END TB

IN 2021

TB deaths and disease increased
reversing years of decline between 2005 and 2019

Fewer people were diagnosed and treated
or provided with TB preventive treatment

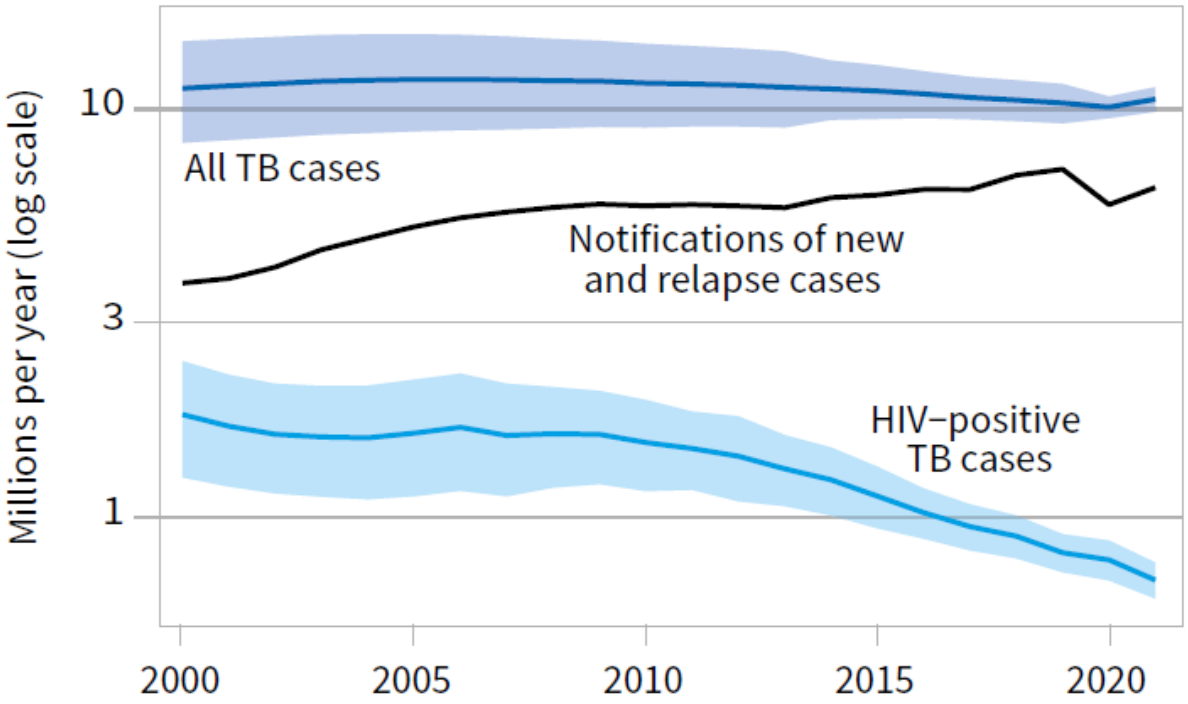
Fewer resources
for essential TB services and TB R&D

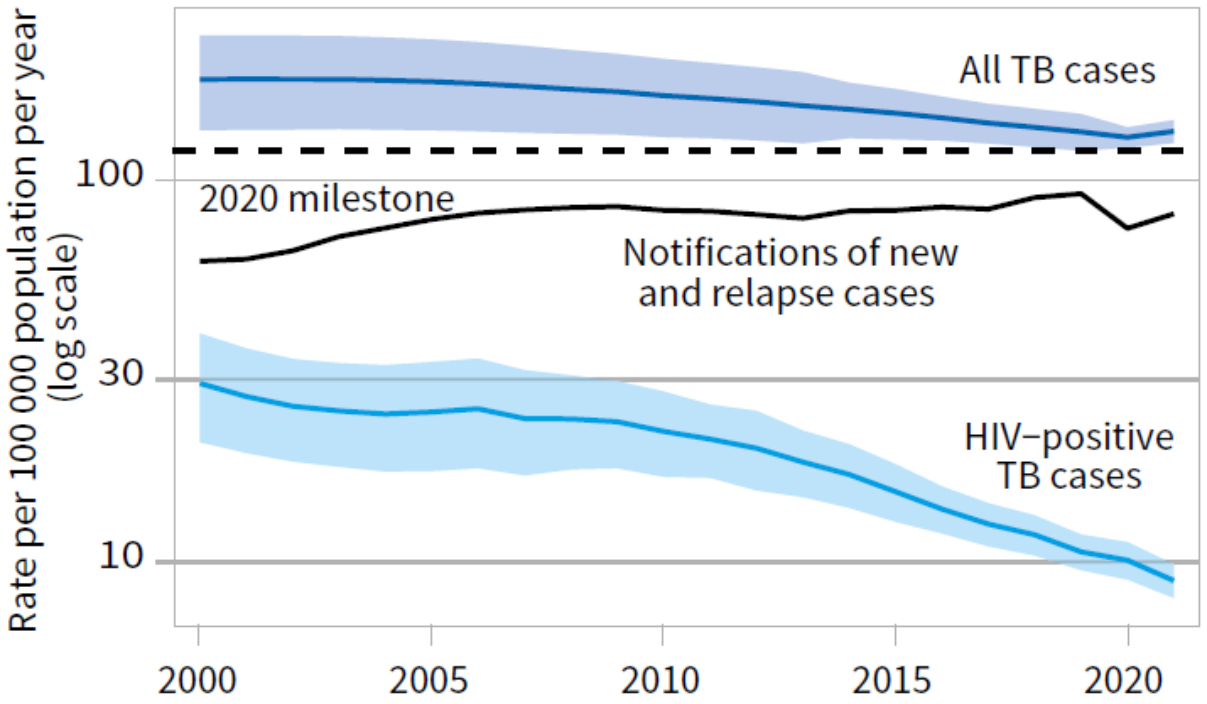
Actions to mitigate and reverse the impact of the COVID-19 pandemic on access to essential TB services are urgently needed

https://www.who.int/multi-media/details/global-tuberculosis-report-2022-infographic-9

Global trends in the estimated number of incident TB cases (left) and the incidence rate (right), 2000–2021

The horizontal dashed line shows the first milestone of the End TB Strategy, which was a 20% reduction in the TB incidence rate between 2015 and 2020. Shaded areas represent 95% uncertainty intervals.

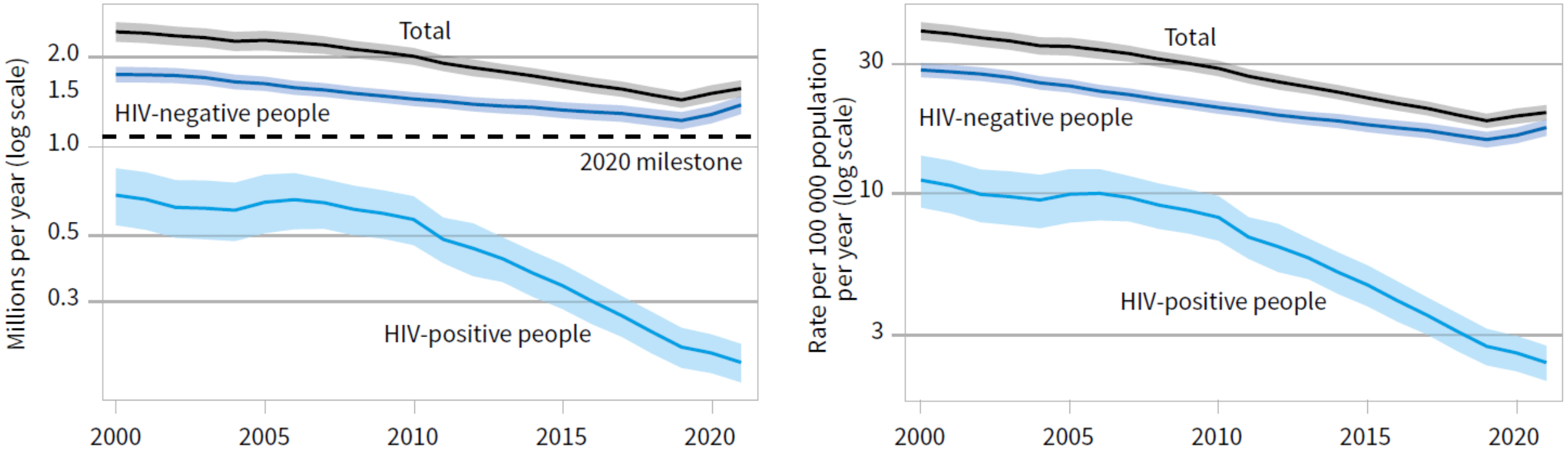




WHO. Global TB Report, 2022.

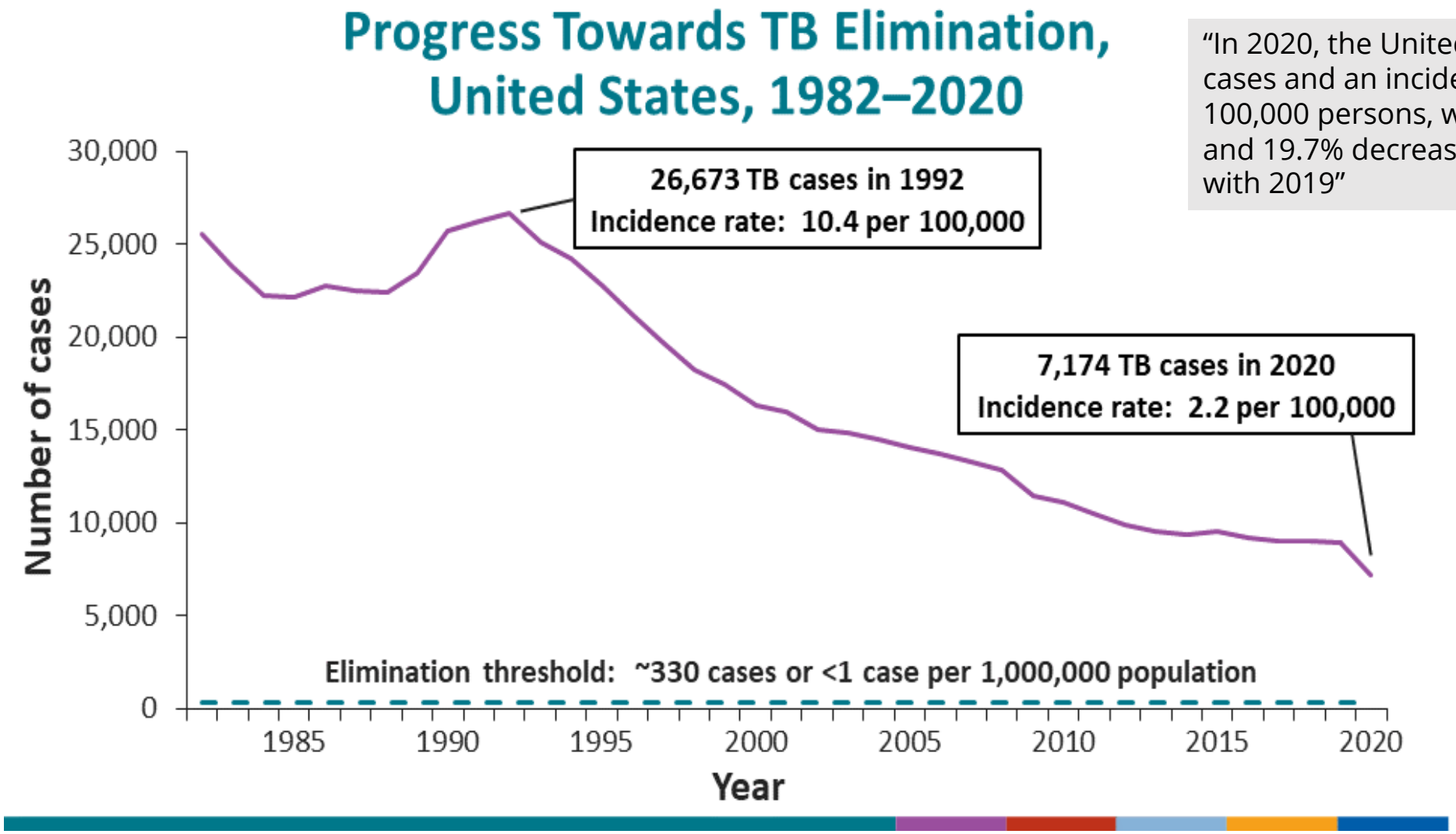
Global trends in the estimated number of TB deaths (left) and the mortality rate (right), 2000–2021

The horizontal dashed line shows the 2020 milestone of the End TB Strategy, which was a 35% reduction in the total number of TB deaths between 2015 and 2020. Shaded areas represent 95% uncertainty intervals.



WHO. Global TB Report, 2022.

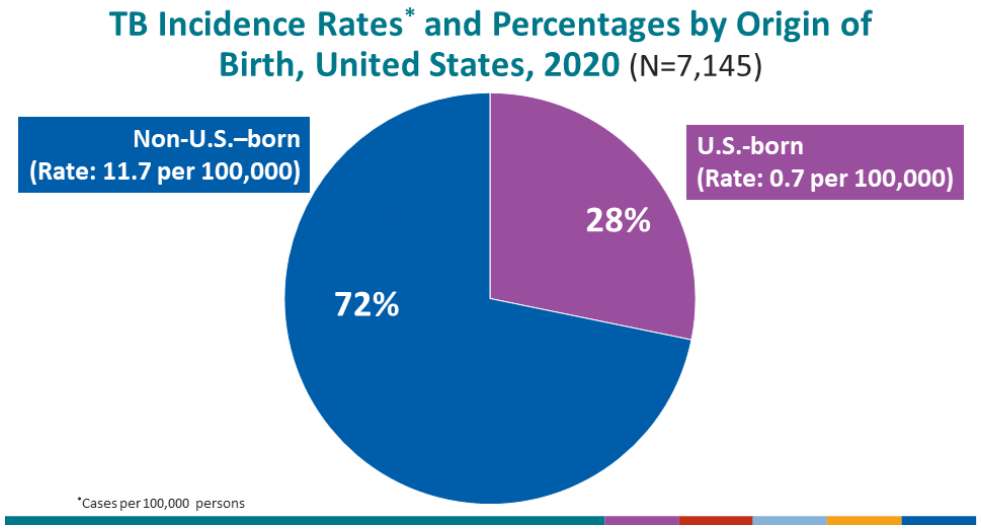
How about in the US?

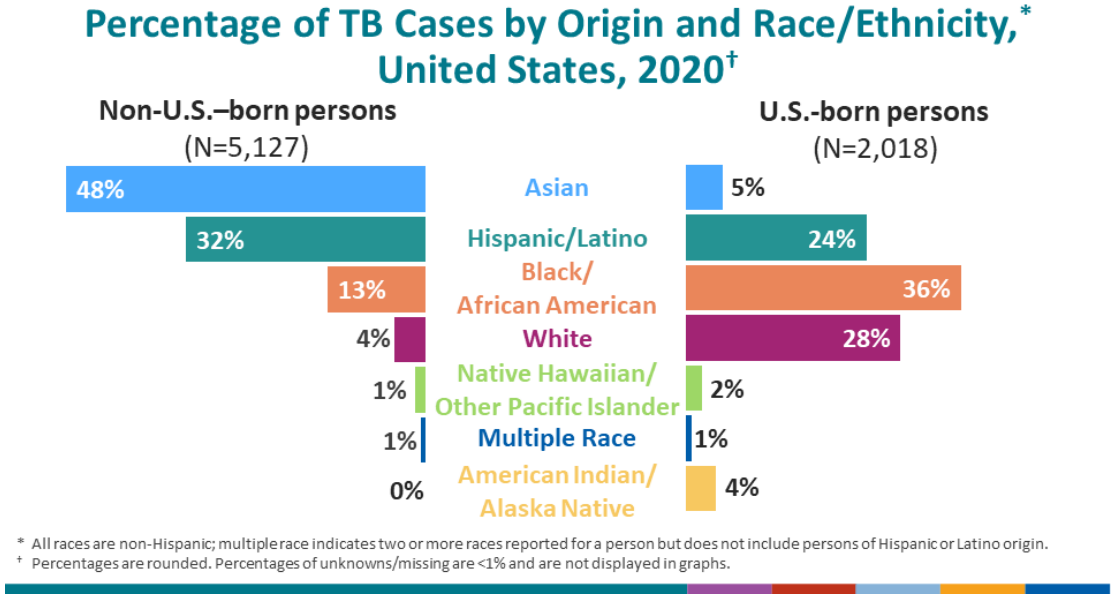


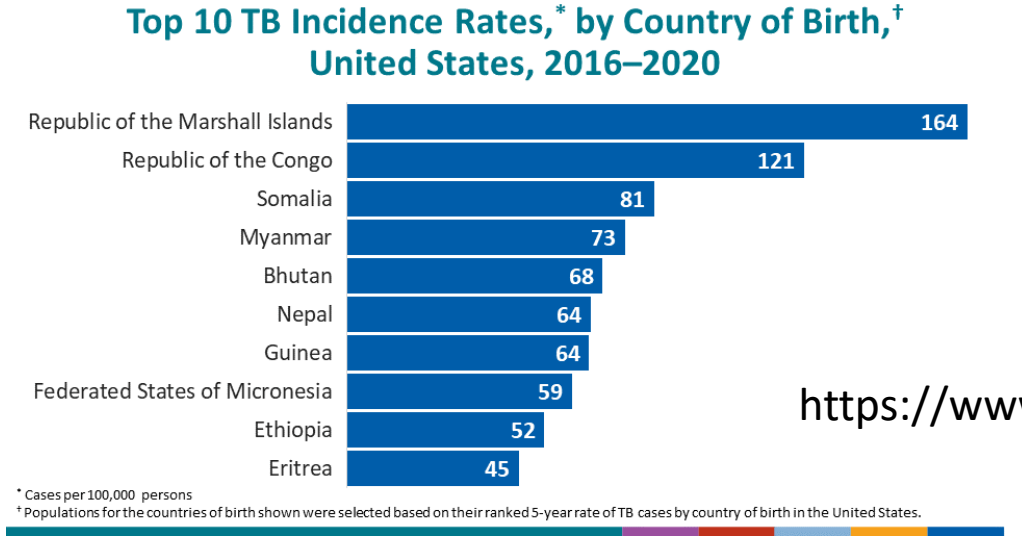
"In 2020, the United States reported 7,174 TB cases and an incidence rate of 2.2 cases per 100,000 persons, which represents a 19.4% and 19.7% decrease, respectively, compared with 2019"

https://www.cdc.gov/tb/statistics/reports/2020/national_data.htm

TB National Statistics







https://www.cdc.gov/tb/statistics/reports/2020/

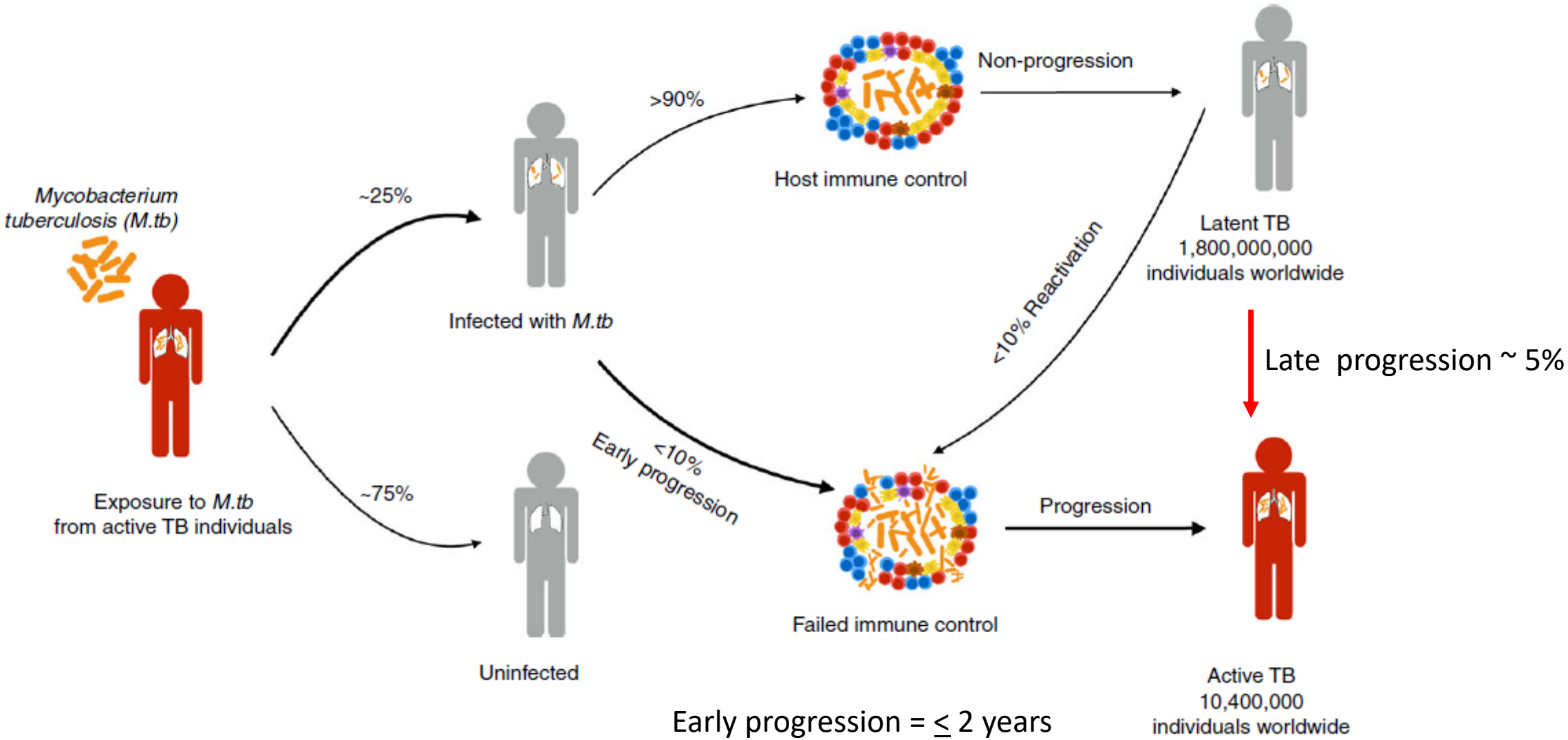
TB and PWH

Let's back up-- TB: The Basics

- TB is caused by *Mycobacterium tuberculosis-complex*
  - *M. bovis* and *M. africanum* infrequent causes
- Humans are the only important reservoir
  - Cattle, badgers, water buffalo, lions, elephants rare sources
- TB infection (aka LTBI) is asymptomatic and non-infectious
- Active TB disease is infectious through aerosols/droplet nuclei
- Host immune responses are effective in controlling the organism in the vast majority of infections

Slide, adapted, from Dick Chaisson

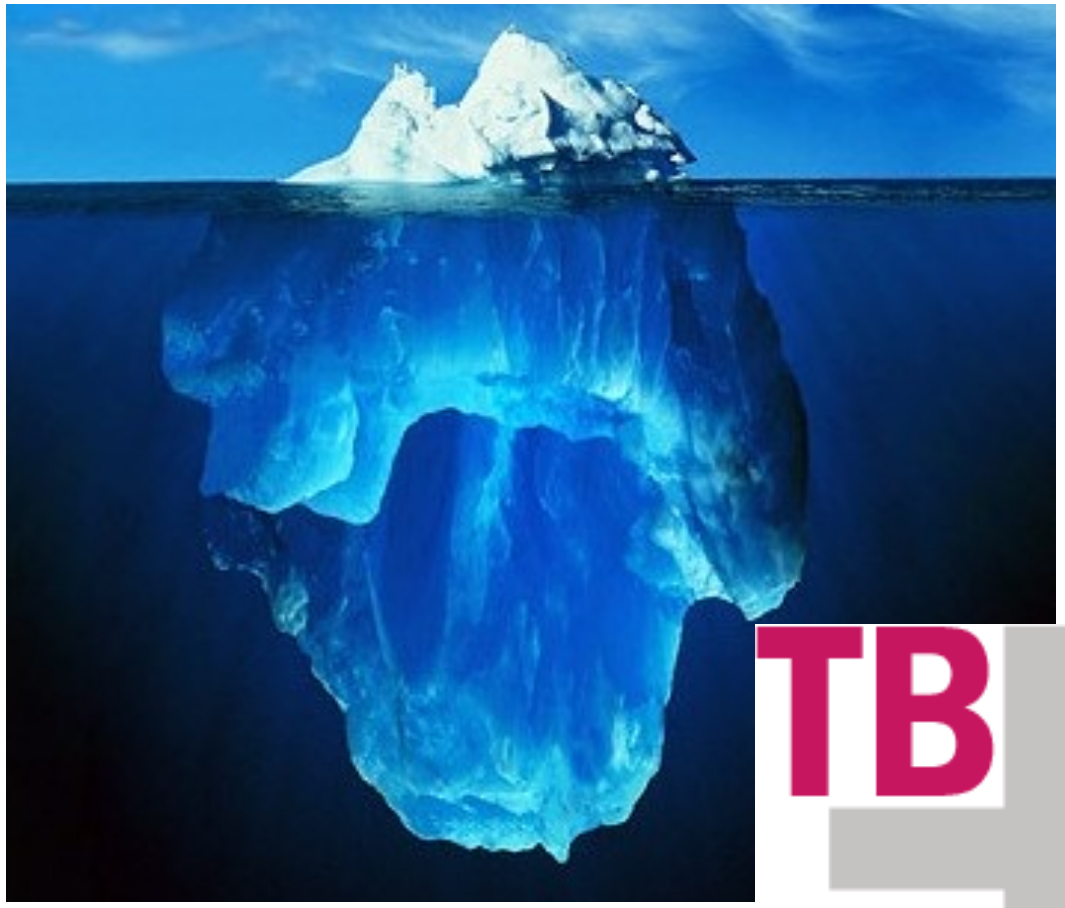
Risk of Infection and Progression to Disease

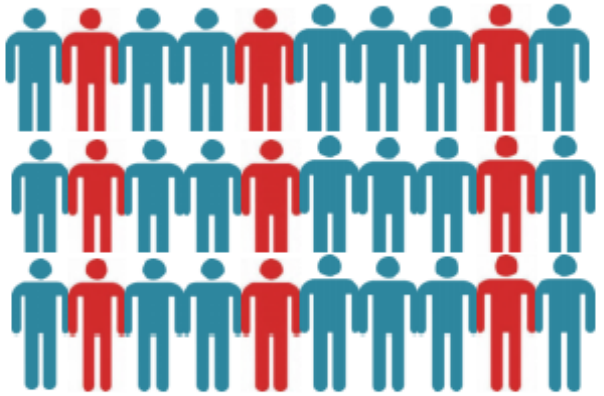


Early progression = ≤ 2 years

Luo (2019) Nat Comm PMID 31434886

Latent TB infection (LTBI)

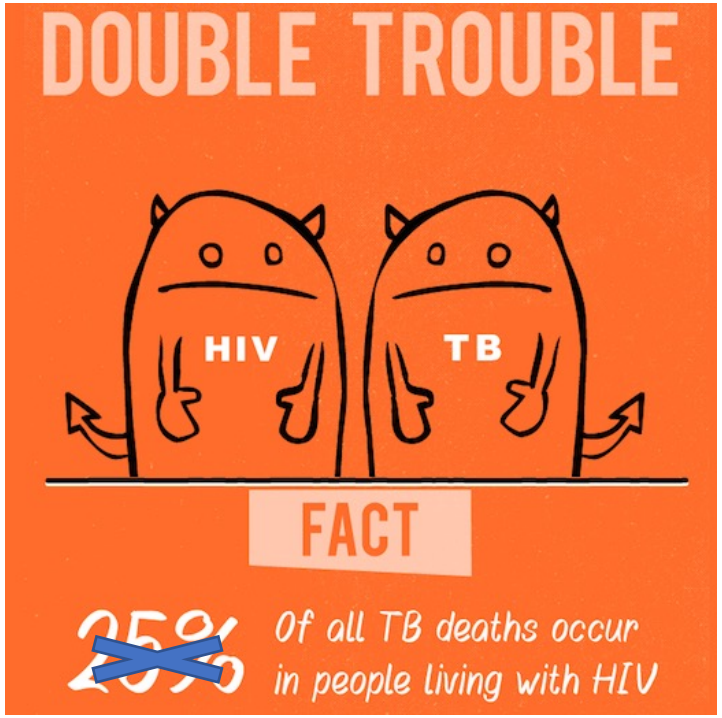




2-3 billion

persons with LTBI globally

About 1 in 4 persons



12%

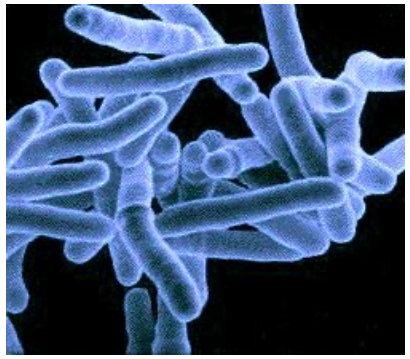
Houben and Dodd. PLoS Med 2016;13(10):e1002152

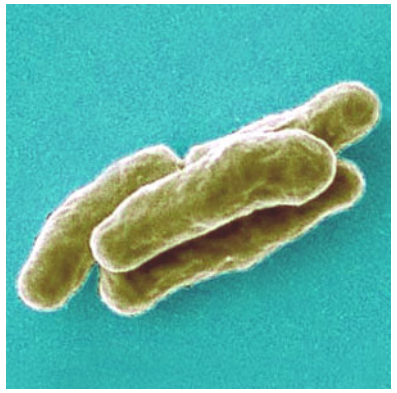
http://www.who.int/tb/challenges/ltbi_factsheet_25nov15.pdf?ua=1;
http://www.results.org.au/living-with-hiv-dying-of-tb/; https://msdh.ms.gov/msdhsite/_static/14,0,150,728.html

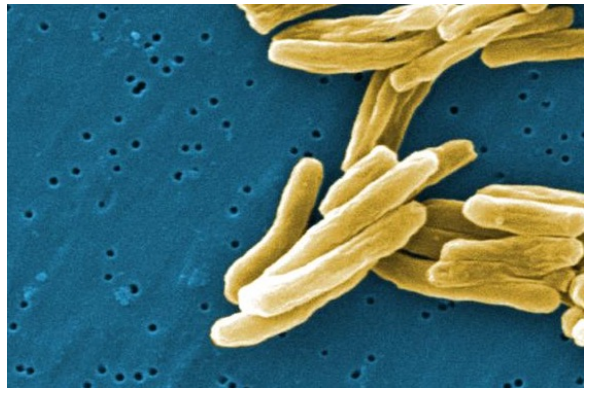
HIV and Tuberculosis Epidemiology

Global Burden of Tuberculosis, 2021

	Total Population	PWH
Incidence	10.6	710,000 (6.7%)
Deaths	1.59 million	187,000 (12%)







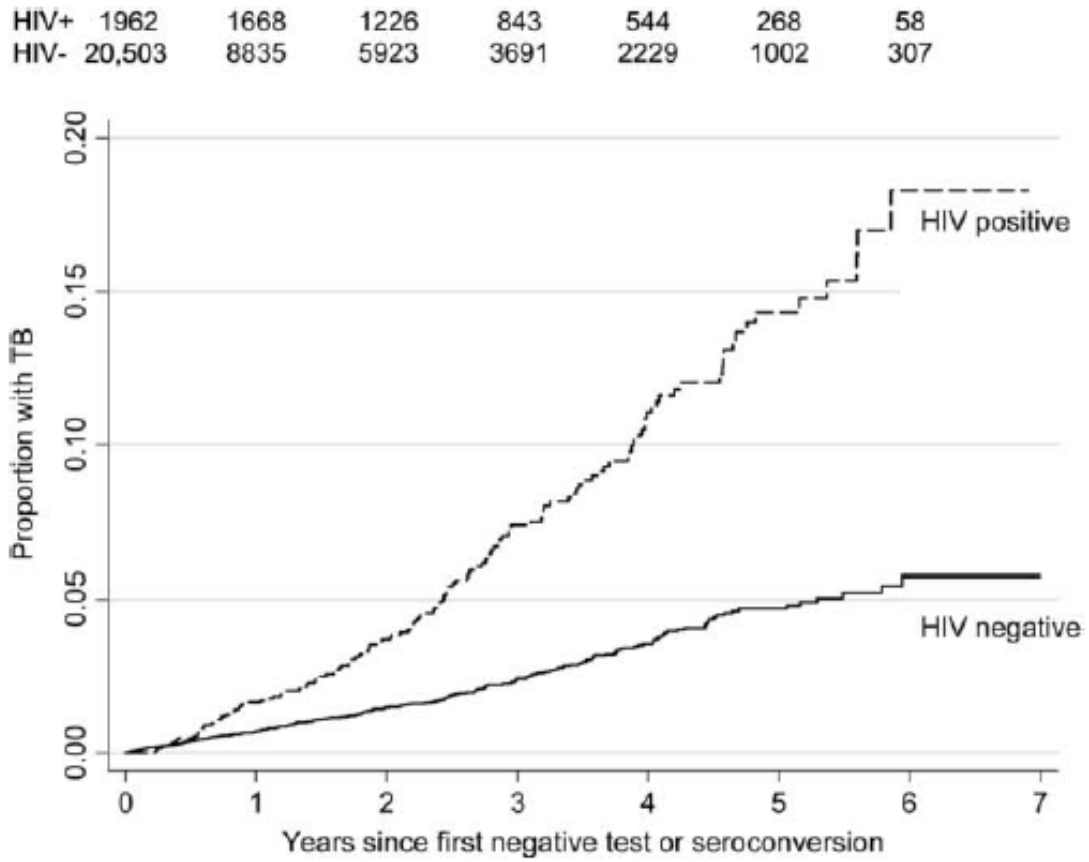
<u>Co-treatment challenges</u>:

- Drug interactions
- Disease interactions
- Overlapping toxicities
- Pill burden
- Immune reconstitution inflammatory syndrome (IRIS)
- Treatment coordination

WHO 2022 Global Tuberculosis Report

Impact of HIV on TB disease incidence

- TB incidence doubles in first year following HIV seroconversion, then increases as CD4 declines
- Both low CD4 counts and high HIV viral loads associated with risk of TB
- Early natural history of *M. tuberculosis* infection profoundly altered by HIV infection → ~40% progression to active disease in 3 months
- Can be prevented (by ART, by TPT)



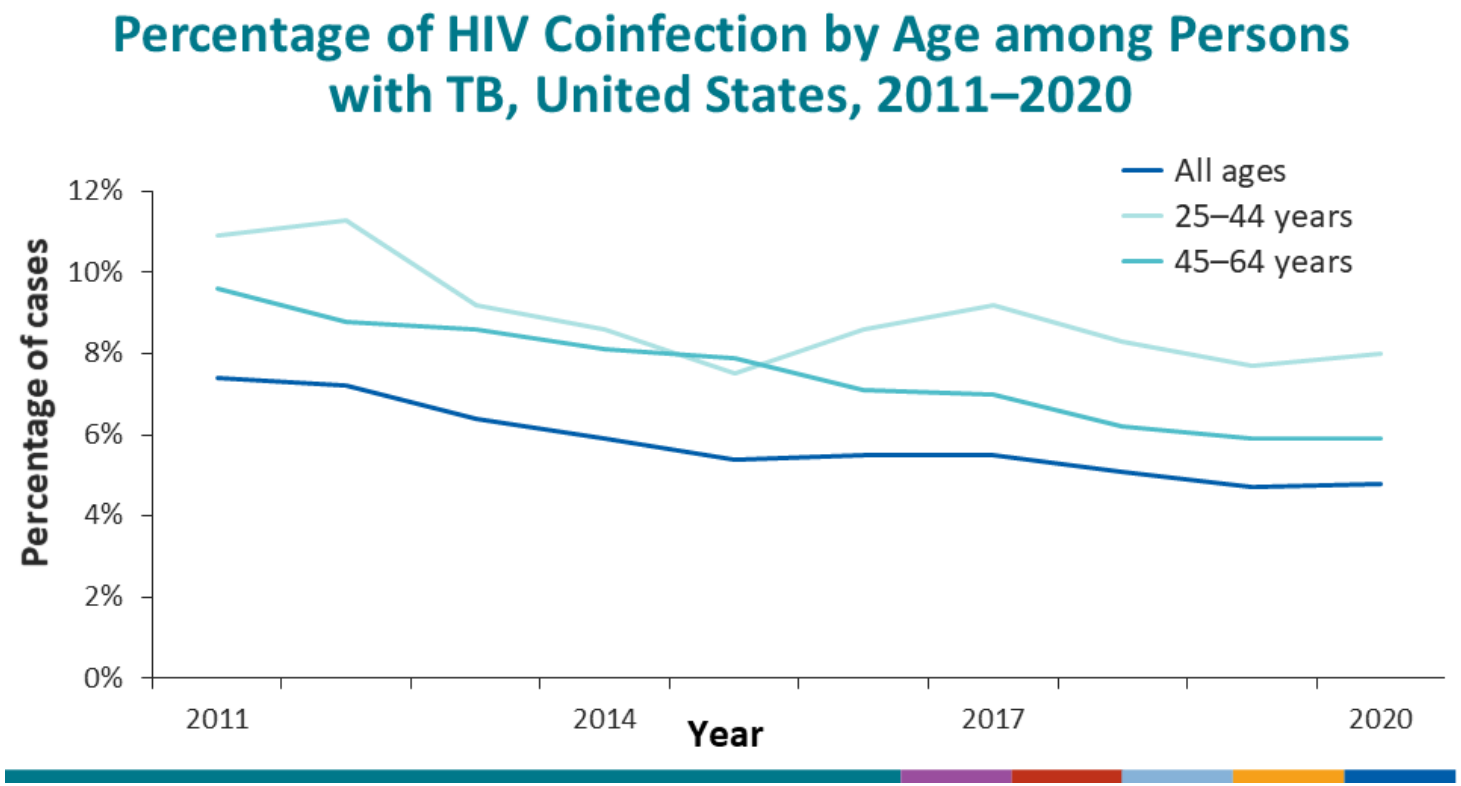
Sonnenberg et al., J Infect Dis 2005;191:150; Lawn et al. AIDS; Day et al., J Infect Dis 190:1677; Daley et al. N Engl J Med 1992;326:321

Effect of TB on HIV

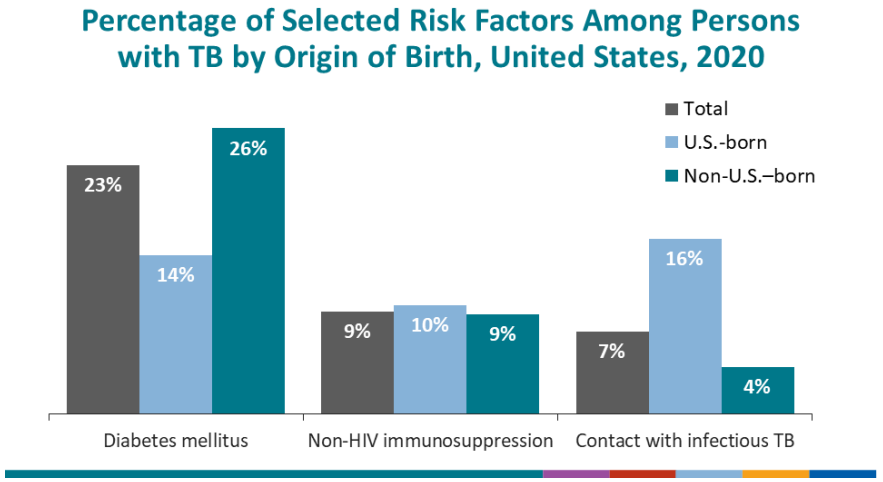
- TB increases the risk of progression to AIDS or death
- Multiple theories as to why this may happen: increased HIV viremia in those with TB disease, increased CD4 activation

Slide via Connie Haley, from L. Beth Gadkowski
University of Florida, SNTC

HIV-TB in the United States

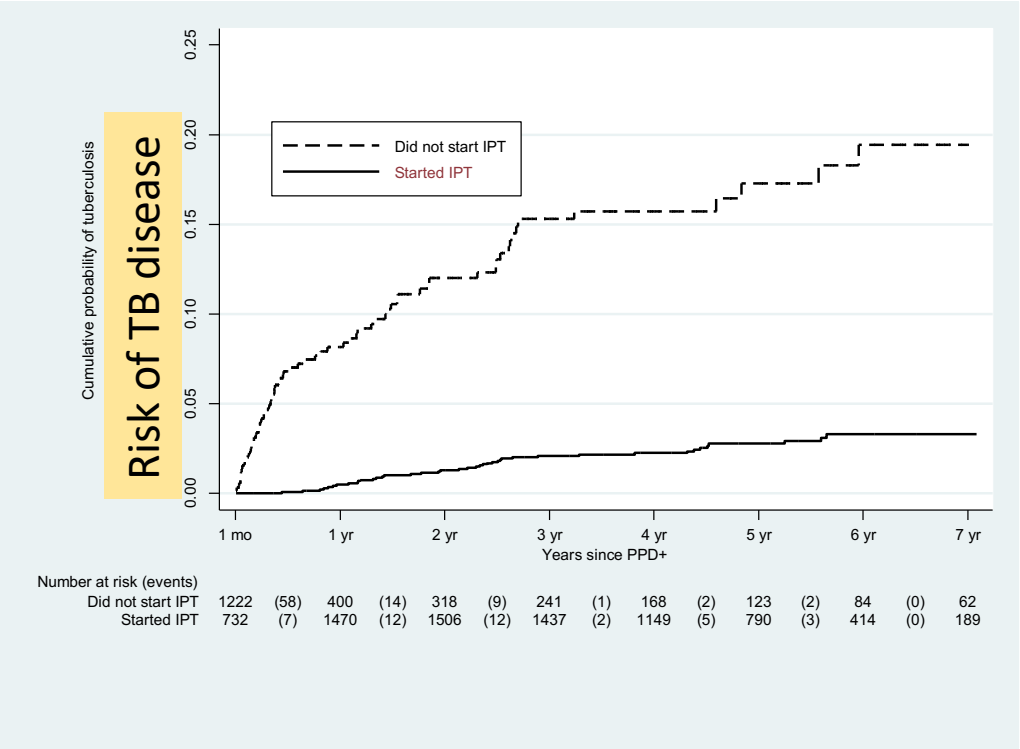


Other risk factors for TB



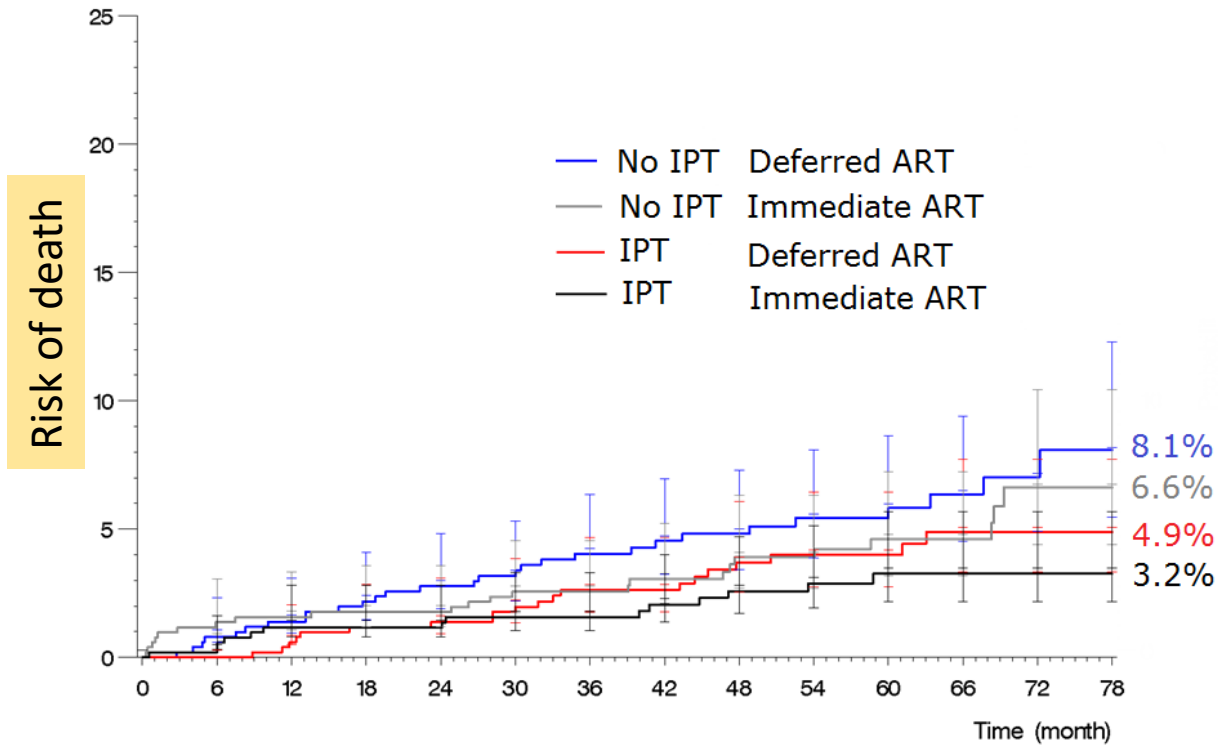
https://www.cdc.gov/tb/statistics/reports/2020/

TB Preventative Therapy (TPT) and ART both work independently to reduce risk of TB disease in PWH



IPT for 6 months
HIV+, TST+ , Rio de Janeiro

Golub et al CID 2015



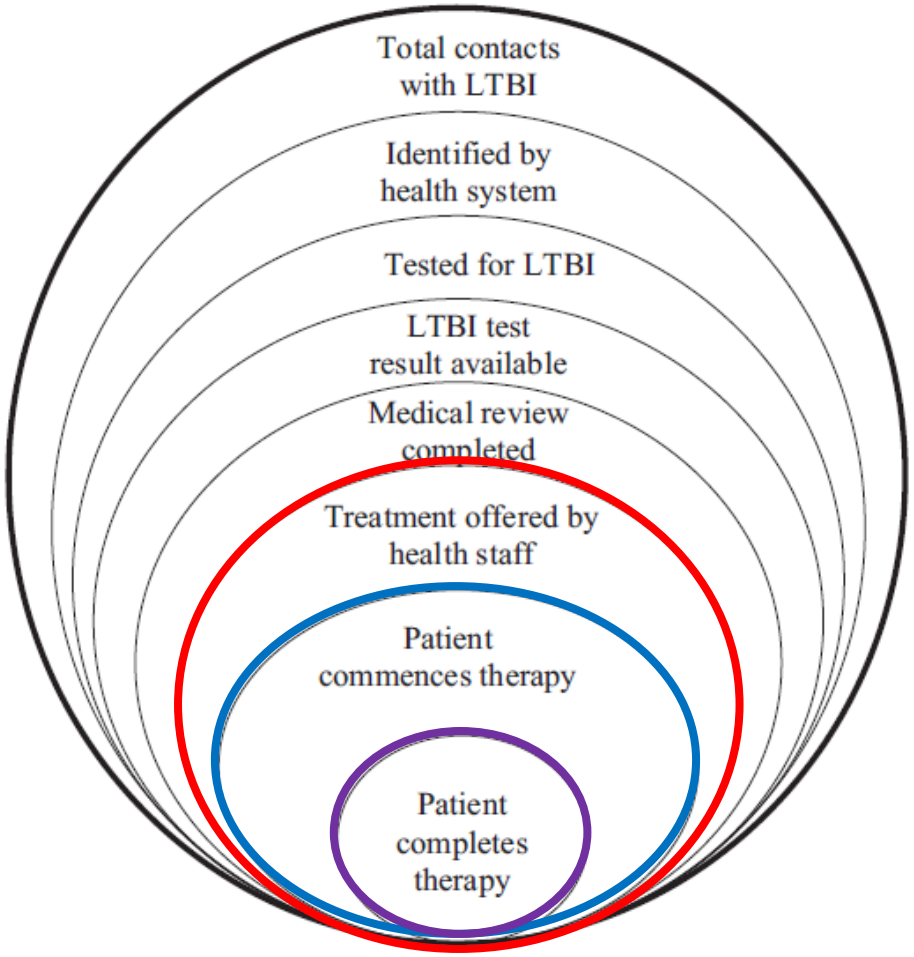
Temprano ANRS Study

IPT for 6 months
HIV+, TST not done, Côte d'Ivoire

Badje et al., Lancet Global Health, 2017

TB prevention in PWH

Prevention: Not prescribed, not taken
Simplify treatment



Fox et al 2017 IJID

Completion rates varied from 6% to 94%

"… and were inversely proportional to the duration of treatment"

WHO 2018 Guidelines on the management of latent tuberculosis infection

Preventing TB disease:
Latent TB infection (LTBI) Treatment Options

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	**ISONIAZID[†] AND RIFAPENTINE[††] (3HP)** 	3 months	Once weekly	12	**Adults and children aged ≥12 yrs** INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 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 maximum
					Children aged 2–11 yrs INH[†]: 25 mg/kg; 900 mg maximum RPT[††]: See above
	RIFAMPIN[§] (4R) 	4 months	Daily	120	**Adults:** 10 mg/kg; 600 mg maximum
					Children: 15–20 mg/kg; 600 mg maximum
	ISONIAZID[†] AND RIFAMPIN[§] (3HR) 	3 months	Daily	90	**Adults** INH[†]: 5 mg/kg; 300 mg maximum RIF[§]: 10 mg/kg; 600 mg maximum
					Children INH[†]: 10-20 mg/kg[#]; 300 mg maximum RIF[§]: 15-20 mg/kg; 600 mg maximum
Alternative	**ISONIAZID[†] (6H/9H)**	6 months	Daily	180	**Adults** Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
			Twice weekly[¶]	52	
		9 months	Daily	270	**Children** Daily: 10-20 mg/kg[#]; 300 mg maximum Twice weekly: 20–40 mg/kg[#]; 900 mg maximum
			Twice weekly[¶]	76	

Note: **1HP** (daily rifapentine plus isoniazid for 28 days) is now an alternative regimen for PWHIV

from Maunank Shah

Prevention for People with HIV

Treating LTBI to Prevent TB Disease in People with HIV

Indications

- Positive screening test[a] for LTBI, no evidence of active TB disease, and no prior history of treatment for active disease or latent TB infection **(AI)**
- Close contact with a person with infectious TB, regardless of screening test result **(AII)**

Preferred Therapy

- Rifapentine (see weight-based dosing below) PO once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks **(AI).** Note: Rifapentine is recommended only for virally-suppressed patients receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen **(AI).**
  - Rifapentine Weekly Dose (maximum 900 mg)
    - *Weighing 32.1–49.9 kg*: 750 mg
    - *Weighing ≥50.0 kg*: 900 mg

3HP

- Isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25–50 mg PO daily **(AI)** for 3 months. See Table 3 for the list of ARV drugs not recommended for use with rifampin and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc).

3HR

Alternative Therapies

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6–9 months **(AII)** *or*

9H

- Rifampin 600 mg PO daily for 4 months **(BI)** See Table 3 for the list of ARV drugs not recommended for use with rifampin and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc) *or*

4R

- Isoniazid 300 mg PO daily plus rifapentine PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks **(BI)** Note: Rifapentine is recommended only for patients receiving an efavirenz-based ARV regimen **(AI).**
  - Rifapentine Daily Dose (maximum 600 mg)
    - *Weighing <35 kg*: 300 mg
    - *Weighing 35–45 kg*: 450 mg
    - *Weighing >45 kg*: 600 mg

1HP

New (Feb 2022) OI Guidelines, US NIH/CDC/IDSA

3HP- Once-weekly rifapentine + INH (900/900mg) x 12 doses

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

See also:
Schechter et al Am J Respir Crit Care Med 2006
Martinson et al NEJM 2011

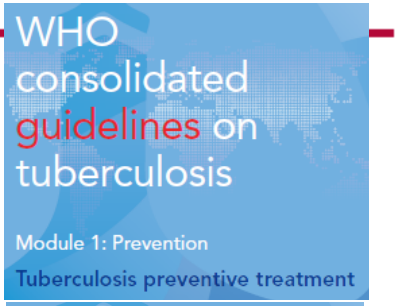
Subgroup with HIV

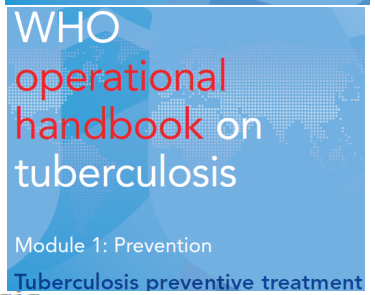
	3HP	9H
Efficacy	0.39/p-y	1.25/p-y
Treatment completion	89%	64%
Drug d/c from hepatotoxicity	1%	4%

Sterling et al AIDS 2016

3HP is more likely to be completed, more efficacious, less likely to cause liver toxicity than 9H in PLWH…

LTBI: 3HP plus dolutegravir-- TB prophylactic therapy in patients with HIV taking DTG: DOLPHIN





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, Radojka M 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**

Interpretation Our results suggest 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. Further exploration of the pharmacokinetics, safety, and efficacy in children and pharmacodynamics in individuals naive to antiretroviral therapy is needed.

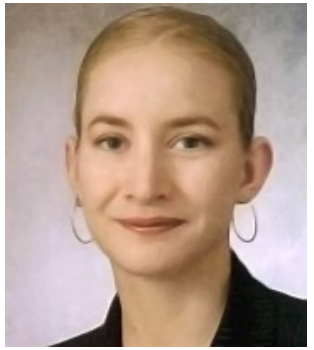
Coming soon: 3HP + DTG in pregnant women (stage set by 3HP study by Mathad et al), 3HP + DTG in children, HIV treatment-naïve adults (enrolling)

Lancet HIV (2020) PMID 32240629
Funder: UNITAID (Churchyard/Chaisson)
(Mathad et al is CID (2021) PMID 34323955)

THE AURUM INSTITUTE

Jyoti Mathad

Nicole Salazar-Austin



Ethel Weld

1HP- Once-daily rifapentine + INH x 28 days

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

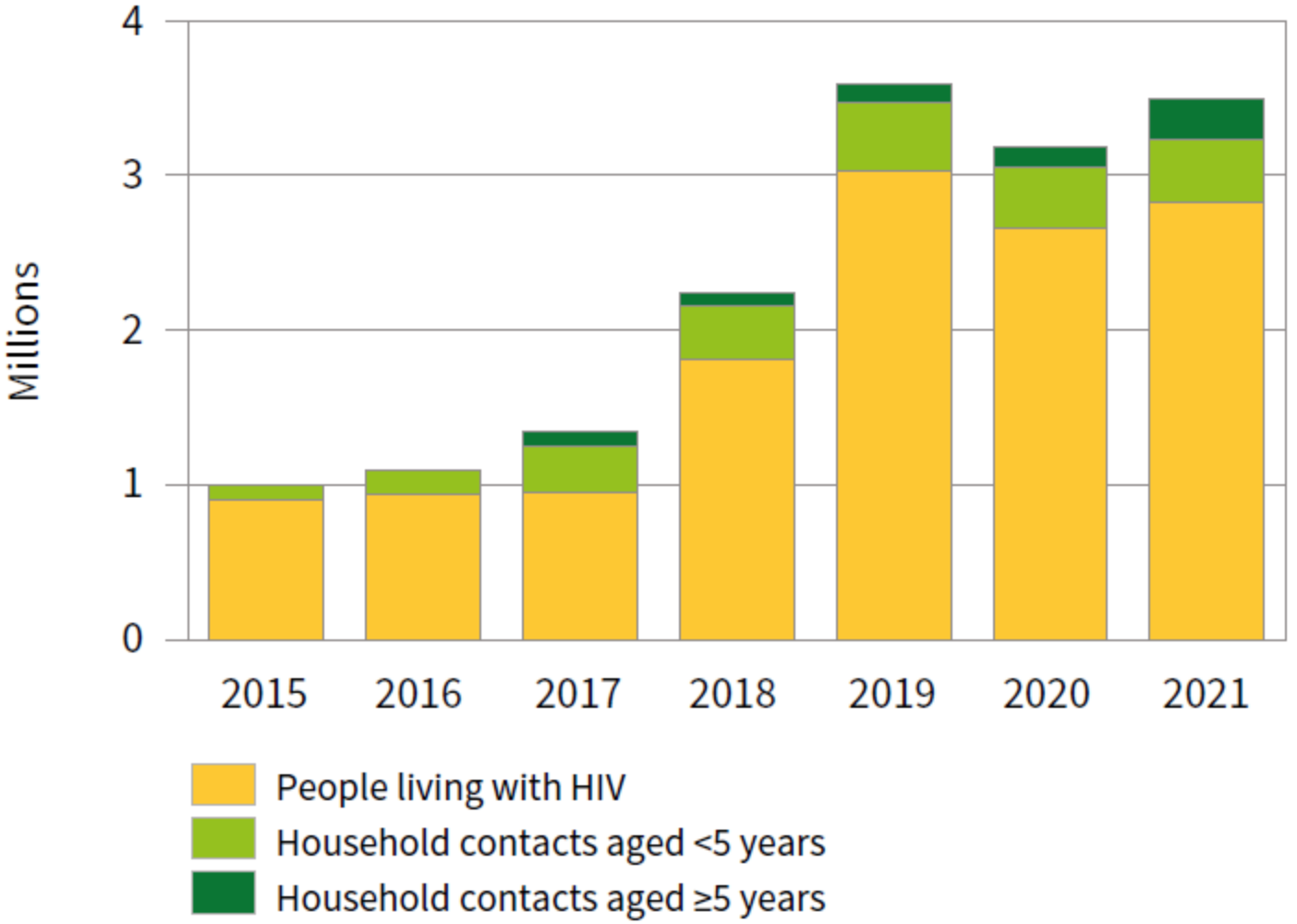
S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

CONCLUSIONS

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.)

ACTG A5372 will help us understand how to dose DTG with 1HP

The global number of people provided with TB preventive treatment, 2015–2021



WHO. Global TB Report, 2022.

Pulmonary TB: Treatment Innovations

Drug-Sensitive TB:
The Role of Individual Drugs in "Short Course" Therapy

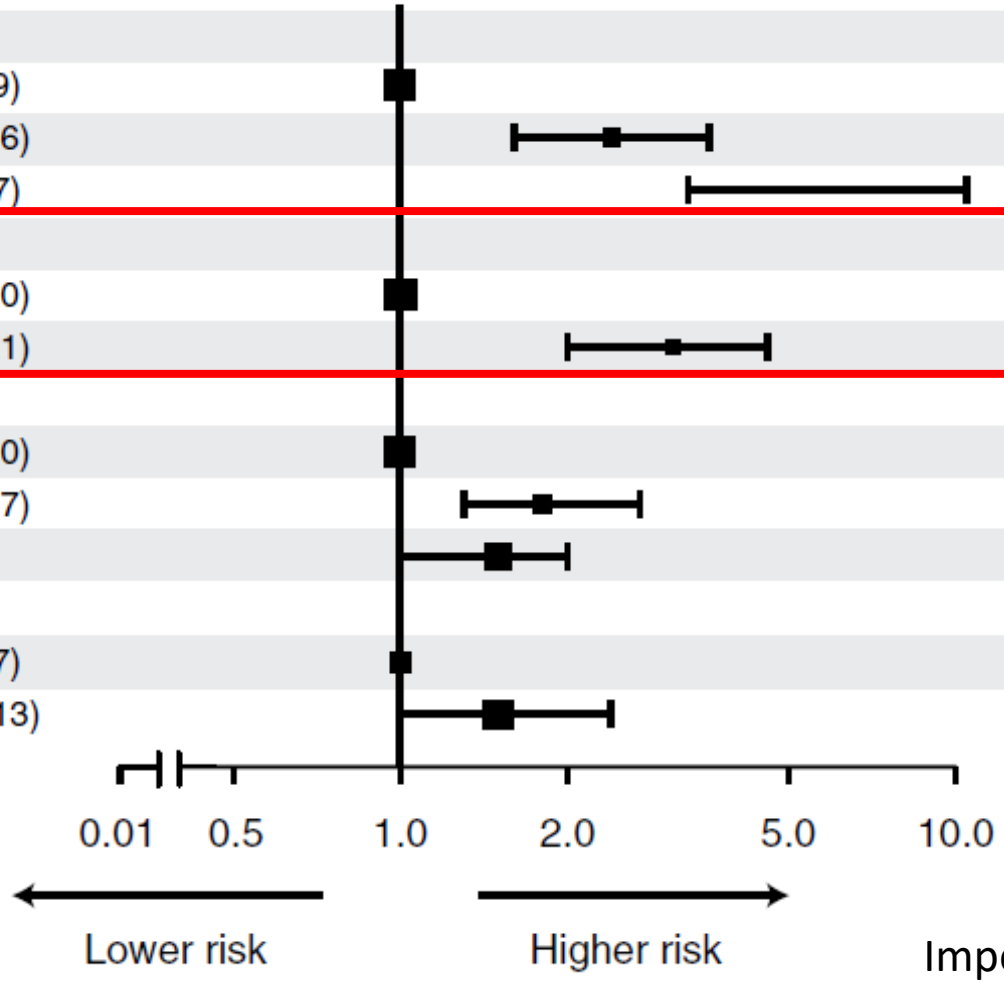
INH:	Early **bactericidal** activity, rapid reduction in organism burden
Rifampin:	Unique **sterilizing** activity against "persisters", key contributor to cure without relapse
Pyrazinamide:	Sterilizing activity in **acidic environments** over the first 2 months, allowing for shortening of treatment
Ethambutol:	**Prevents resistance** to other antibiotics

Each drug has a role. Together, they comprise an effective regimen

Standard treatment: long duration and imperfect efficacy

Baseline characteristics, on-treatment culture status and adherence

Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
Adherence		
100%	85/913 (9)	Reference
>90 and <100%	37/230 (16)	2.4 (1.6–3.6)
≤90%	16/43 (37)	5.9 (3.3–10.5)
HIV status		
Negative	98/999 (10)	Reference
Positive	40/187 (21)	3.1 (2.0–4.6)
Month 2 culture status		
Negative	93/922 (10)	Reference
Positive	45/264 (17)	1.8 (1.3–2.7)
BMI (per 5 kg m^{-2} decrease)	[d]	1.5 (1.0–2.0)
Sex		
Female	30/347 (7)	Reference
Male	108/839 (13)	1.5 (1.0–2.4)



Imperial (2018) Nature Medicine

A Four-Month Regimen for Drug-Sensitive TB: TBTC31/ACTG A5349

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

**ACTG A5406 will evaluate HPZM with dolutegravir-based ART in PWH

Rifapentine plus moxifloxacin (2PHZM/2PHM) regimen achieves non-inferiority for efficacy in all analyses
Rifapentine regimen (2PHZE/2PH) does NOT ach[illegible]NY analysis

World Health Organization
GLOBAL TB PROGRAMME
NewsFlash

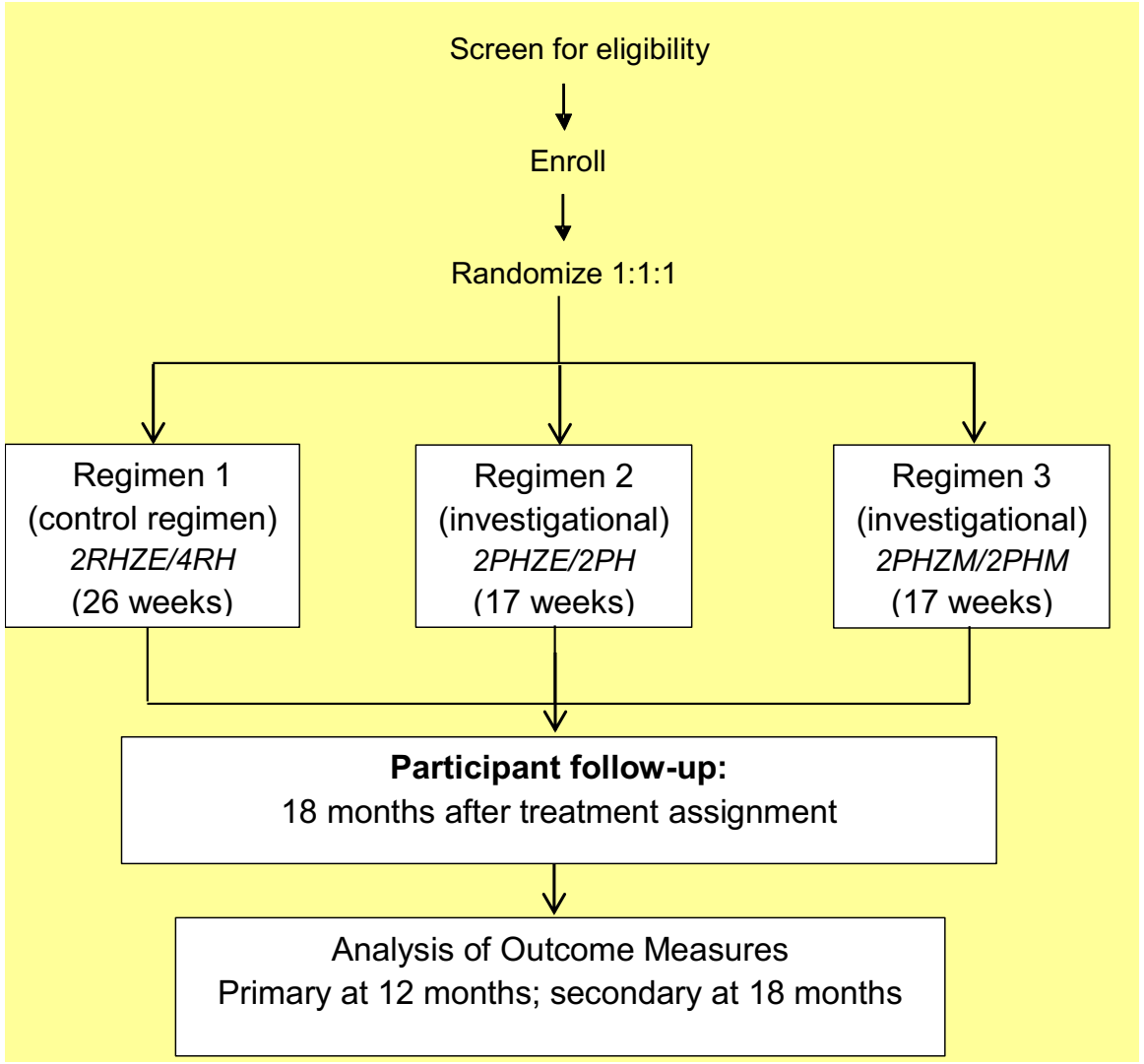
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 71 / No. 8
February 25, 2022

Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

Wendy Cart, PhD[1]; Ekaterina Kurbatova, MD[2]; Angela Starks, PhD[3]; Neela Goswami, MD[2]; Leonora Allen, MPH[1]; Carla Winston, PhD[2]

Dorman *et al.* NEJM (2021) 384: 1705, PMID 33951360

Drug-Sensitive TB-A 4-month regimen! TBTC Study 31



Key

P=rifapentine
R=rifampin

M=moxifloxacin
E=ethambutol

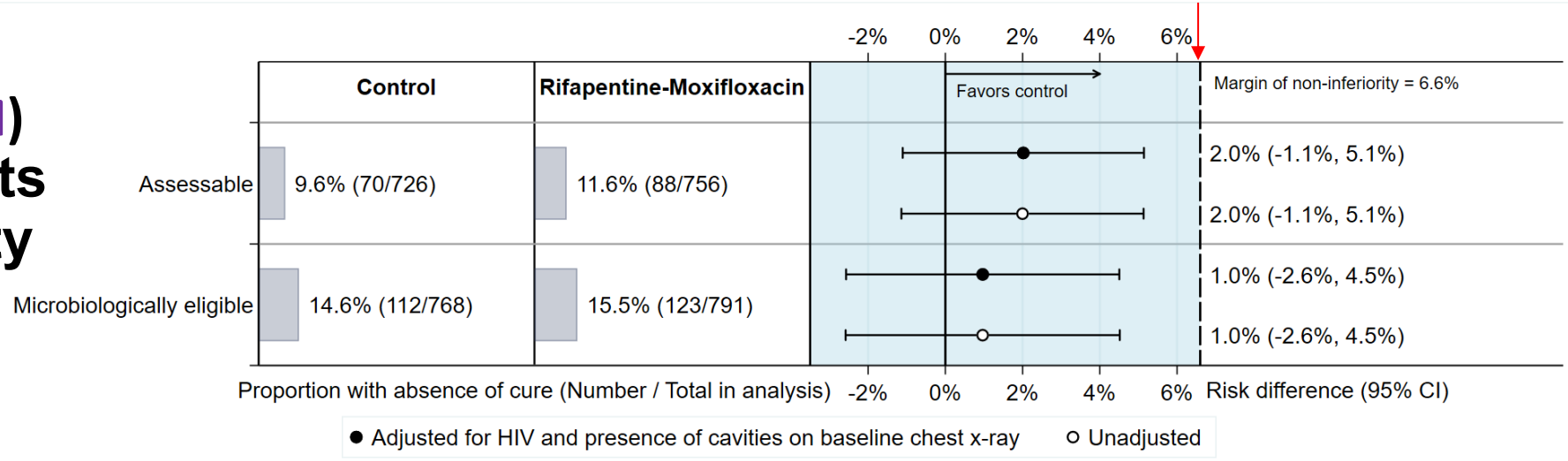
H=isoniazid
Z=pyrazinamide

34 clinical research sites, 13 countries, 4 continents

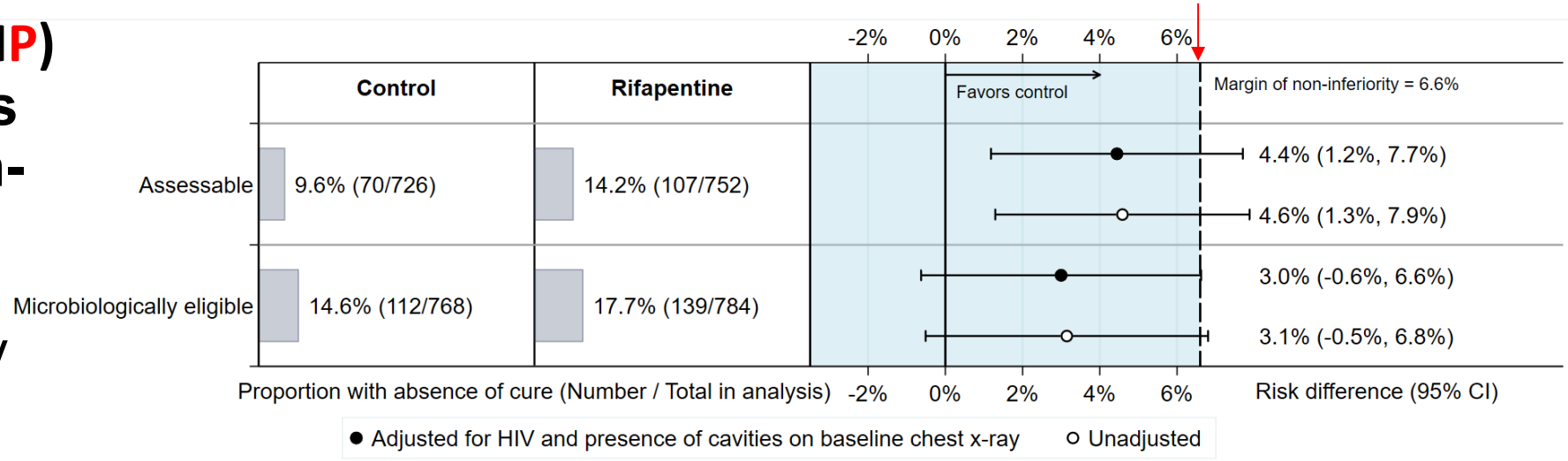
S31/A5349 slides courtesy of Susan Dorman et al

Primary Efficacy Results

RPT-MOX (2HPZM/2HPM) regimen meets non-inferiority criteria for efficacy in <u>all</u> analyses



RPT (2HPZE/2HP) regimen does not meet non-inferiority criteria for efficacy in any analysis

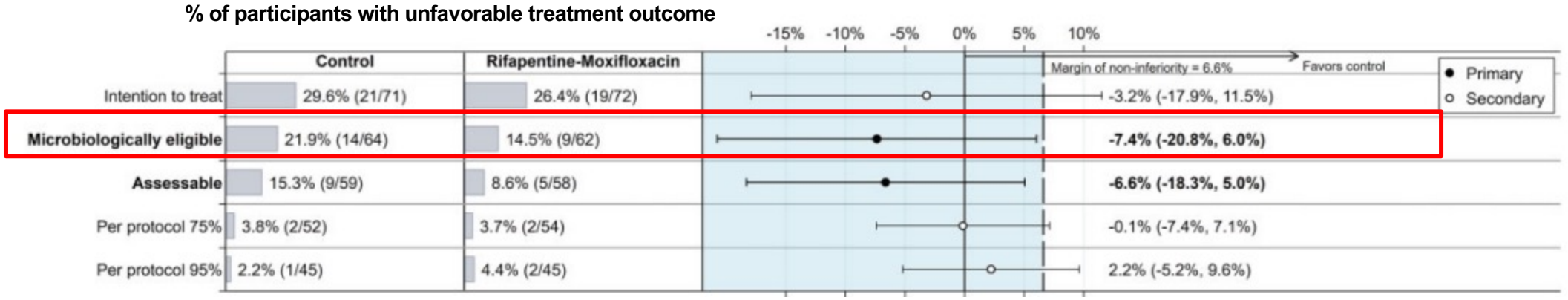


Clinical Infectious Diseases

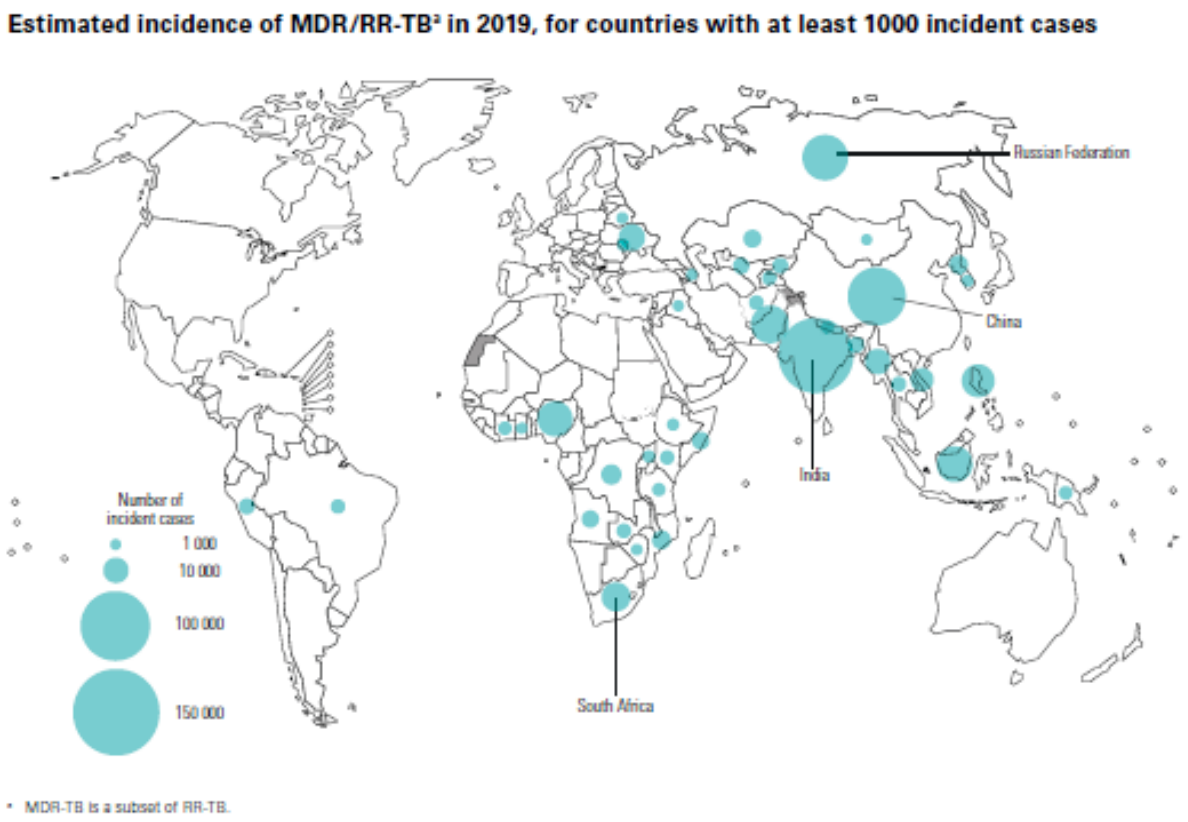
MAJOR ARTICLE

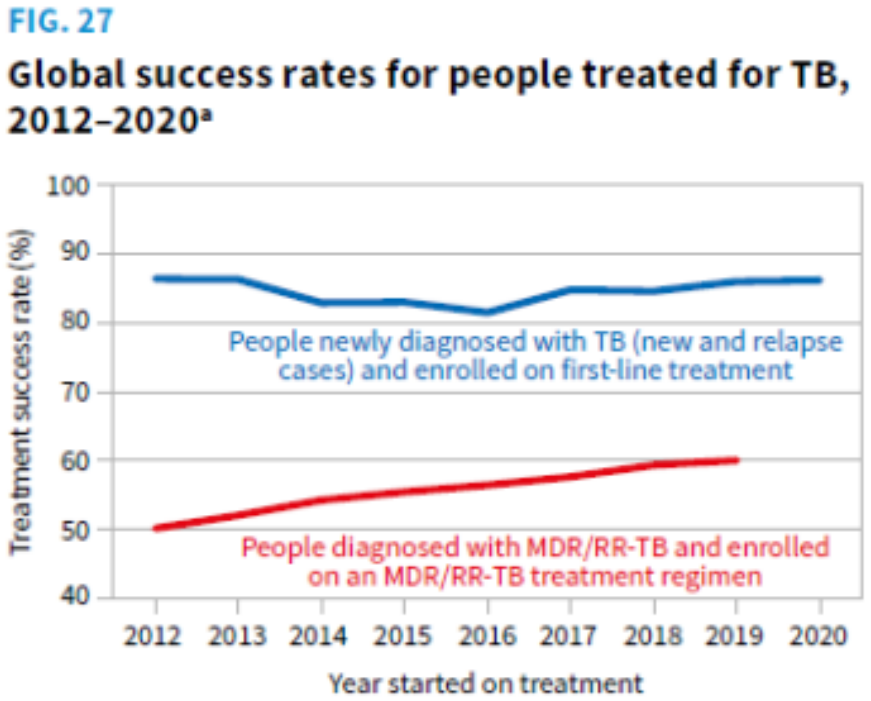
Rifapentine With and Without Moxifloxacin for Pulmonary Tuberculosis in People With HIV (S31/A5349)

April C. Pettit,[1,a] Patrick PJ Phillips,[2,a] Ekaterina Kurbatova,[3] Andrew Vernon,[3] Payam Nahid,[2] Rodney Dawson,[4] Kelly E. Dooley,[5] Ian Sanne,[6] Ziyaad Waja,[7] Lerato Mohapi,[7] Anthony T. Podany,[8] Wadzanai Samaneka,[9] Rada M. Savic,[2] John L. Johnson,[10,11] Grace Muzanyi,[11] Umesh G. Lalloo,[12] Kia Bryant,[3] Erin Sizemore,[3] Nigel Scott,[3] Susan E. Dorman,[13] Richard E. Chaisson,[5] and Susan Swindells,[14] for the Tuberculosis Trials Consortium (TBTC) Study 31/AIDS Clinical Trials Group (ACTG) A5349 study team



MDR-TB Treatment

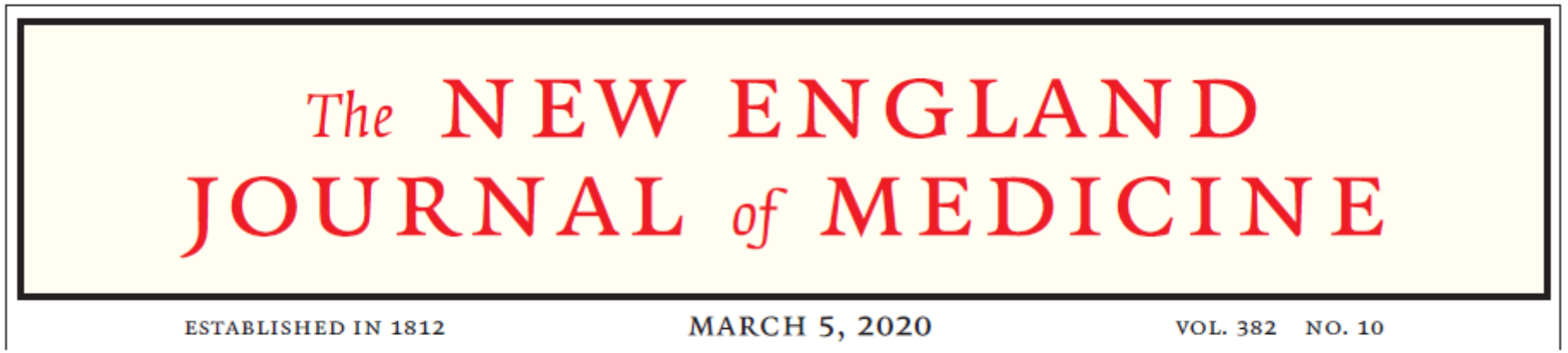




Multidrug-resistant TB:
Mycobacterium tuberculosis **resistant to isoniazid and rifampin**: ~500,000 incident cases in 2020

WHO Global Report 2022

MDR/XDR-TB: BPaL, the NixTB trial


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

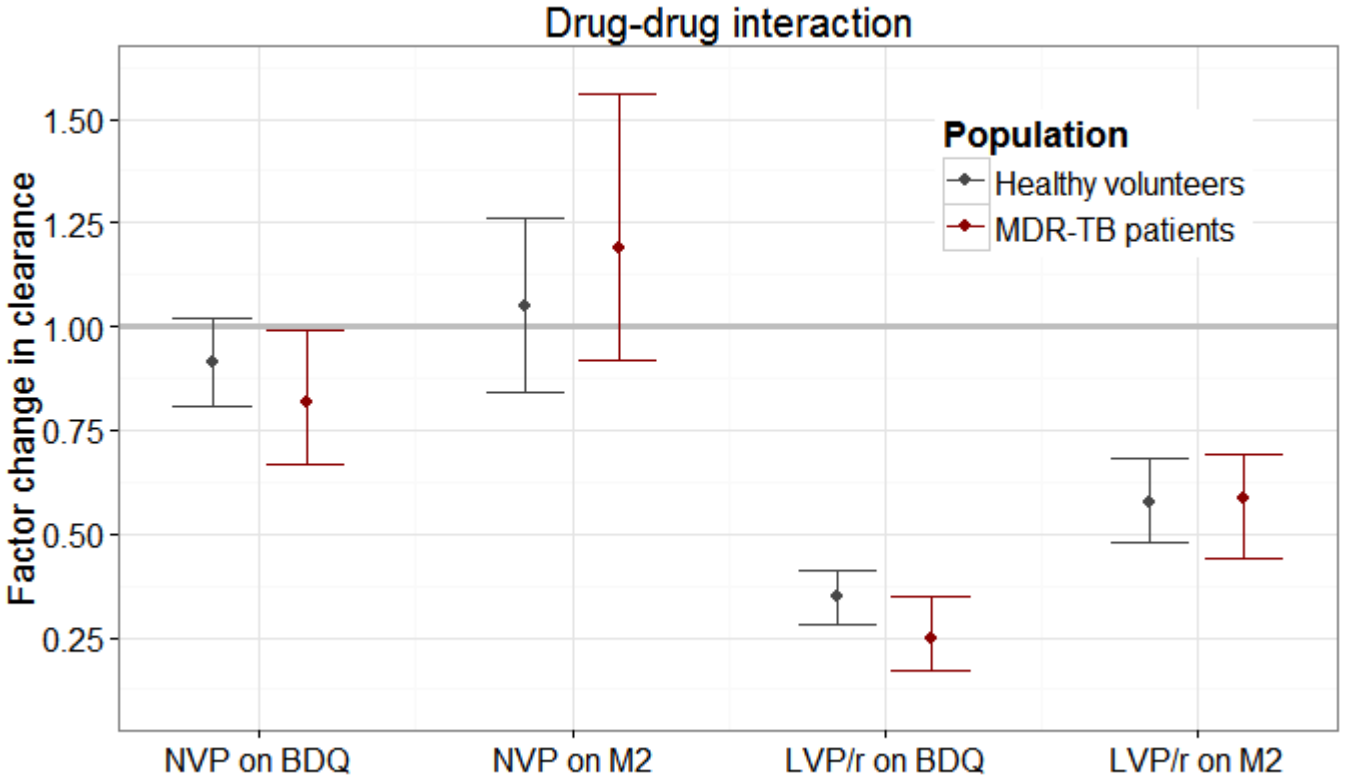
Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Summary points:

- Single-arm study of 109 patients in South Africa with XDR-TB or treatment-intolerant MDR-TB
- 6-month regimen of **bedaquiline, pretomanid, linezolid** (BPaL) with 90% treatment success
- Peripheral neuropathy in 81%, myelosuppression in 48%, mostly manageable and reversible

→ Registration of pretomanid, as BPaL

Bedaquiline: Drug interactions with ART



NEVIRAPINE

No significant effect on BDQ

DOLUTEGRAVIR

Unlikely to have significant effect on BDQ

LOPINAVIR/RITONAVIR

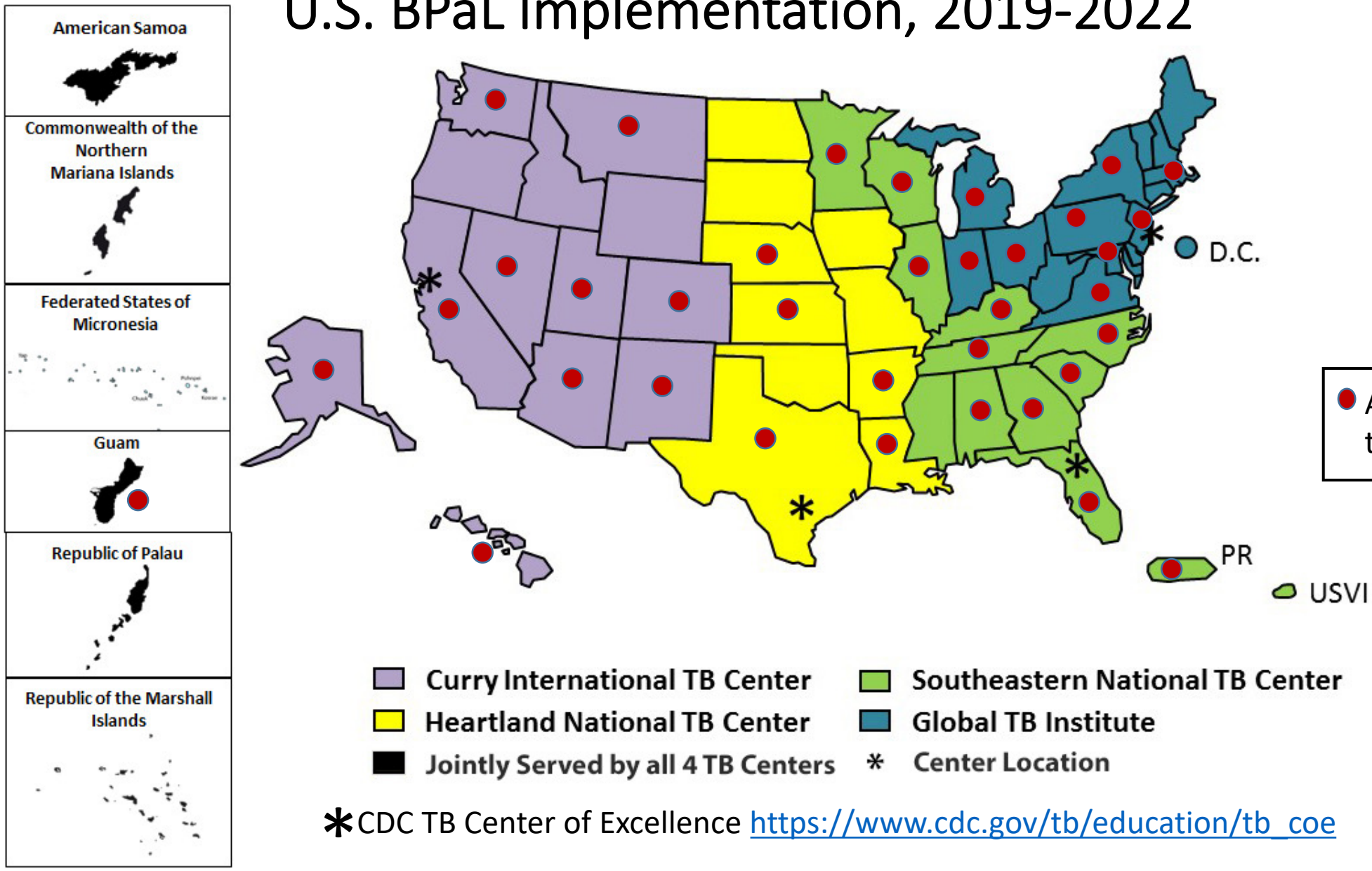
2-3 fold increase in BDQ exposures

EFAVIRENZ

50% reduction in BDQ exposures

Brill IJAA 2017; Svensson AAC 2014; Svensson AAC 2013

U.S. BPaL Implementation, 2019-2022



*CDC TB Center of Excellence https://www.cdc.gov/tb/education/tb_coe

Conclusions from the U.S Experience with BPaL

- BPaL is well tolerated, has less impact on patients' daily activities
  - Few discontinued BPaL for toxicity
  - Few treatment interruptions for toxicity—shorter total treatment duration
- No patients needed 1200mg QD; only a few needed 900mg
- Almost half of patients changed to LZD 3 times per week
- One has relapsed after treatment
- Time to culture conversion appears shorter than prior MDR regimens
- Positive feedback from TB staff and providers
- Too many patients with drug resistance have delayed diagnosis
- **Collaboration enables increased access to diagnostics & treatment**

SNTC
From Connie Haley

A Couple of Other Tidbits

Is there a best test for LTBI in PWH?

- 1510 US-born PWH evaluated for LTBI with TST, T-SPOT, QFT
- Median self-reported CD4 count: 532 cells/mm3
- Overall estimated LTBI prevalence: 4.7%
- IGRA more sensitive than TST

Table 3. Diagnostic Test Characteristics for US-Born PLWH Estimated Directly From Latent Class Analysis Using Standard US Cutoffs at 4.7% Estimated LTBI Prevalence

	Sensitivity (95% CrI)	Specificity (95% CrI)	PPV (95% CrI)	NPV (95% CrI)
TST (≥5 mm)	54.2% (45.2–64.3)	96.8% (95.7–97.7)	45.4% (33.3–58.4)	97.7% (96.4–98.7)
QFT (≥0.35 IU/mL)	72.2% (58.7–85.4)	96.5% (95.3–97.6)	50.7% (37.1–65.6)	98.6% (97.4–99.4)
TSPOT (≥8 spots)	51.9% (39.3–66.7)	99.7% (99.3–99.9)	90.0% (77.1–98.1)	97.6% (96.1–98.8)

Abbreviations: CrI, credible interval; LTBI, latent tuberculosis infection; NPV, negative predictive value; PLWH, people living with human immunodeficiency virus; PPV, positive predictive value; QFT, QuantiFERON Gold In-Tube; TSPOT, T-SPOT.TB; TST, tuberculin skin test.

Slide from L. Beth Gadkowski, via Connie Haley

Pettit et al. CID 2021:73 (1 October)

2022 Global New TB Drug Pipeline[1] Updated 10/21/2022

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Macrolides
Mycobacterial Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13, F-ATP synthase
Oxazolidinones

MK-7762, -3854
MPL-447*
JSF-3285*
CPZEN-45*
NTB-3119*
MBX-4888A (1810)*
FNDR-10045*, FNDR-20364*
TZY-5-84

GSK-839*
OTB-658

BVL-GSK098*
GSK-286*
TBAJ-876
TBAJ-587
TBI-223
Macozinone* (PBTZ-169)

Sanfetrinem
Delpazolid
Sutezolid
Sudapyridine (WX-081)
BTZ-043*
TBA-7371*
OPC-167832*
GSK-656* (070)
Telacebec*
Pyrifazimine (TBI-166)
SPR720*
SQ-109*

Results Reported / Expected in 2022

TB Practecal
ZeNix
Simplici TB (4-month regimen)
Truncate TB (2-month regimens)
STREAM 2

Bedaquiline*
Delamanid*
Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since May 2022

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: October 2022

DIVERSITY OF THE TB VACCINE PIPELINE: 14 TB VACCINE CANDIDATES IN CLINICAL TRIAL

SUBUNITS

VIRAL VECTORED

Ad Ag85A	ChAdOx MVA 85A	TB/Flu04L
M. tuberculosis	*M. tuberculosis*	*M. tuberculosis*
Adenovirus	Chimpanzee Adenovirus +MVA	Influenza virus
Ag85A	Ag85A	ESAT-6 Ag85A

ADJUVANTED

M72/ASO1E	H56:IC31	GamTBVac	ID93/GLASE
M. tuberculosis	*M. tuberculosis*	*M. tuberculosis*	*M. tuberculosis*
AS01E 3-O-desacyl-4'-MPL and saponin QS-21	IC31® antibacterial peptide and a synthetic oligonucleotide	DEAE-dextran core and CpG oligonucleotide	GLA-SE Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (SE)
Rv0125 Rv1196	ESAT-6 Rv2660 Ag85B	ESAT-6 CFP-10 Ag85A	Rv3620 Rv3619 Rv2608 Rv1813

WHOLE CELL MYCOBACTERIA

INACTIVATED

M. vaccae™	MIP	DAR-901	RUTI
M. vaccae	*M. indicus pranii*	*M. vaccae* *M. obuense*	*M. tuberculosis* (fragments)
			↓ O_2 ↓ pH
?	?	?	?

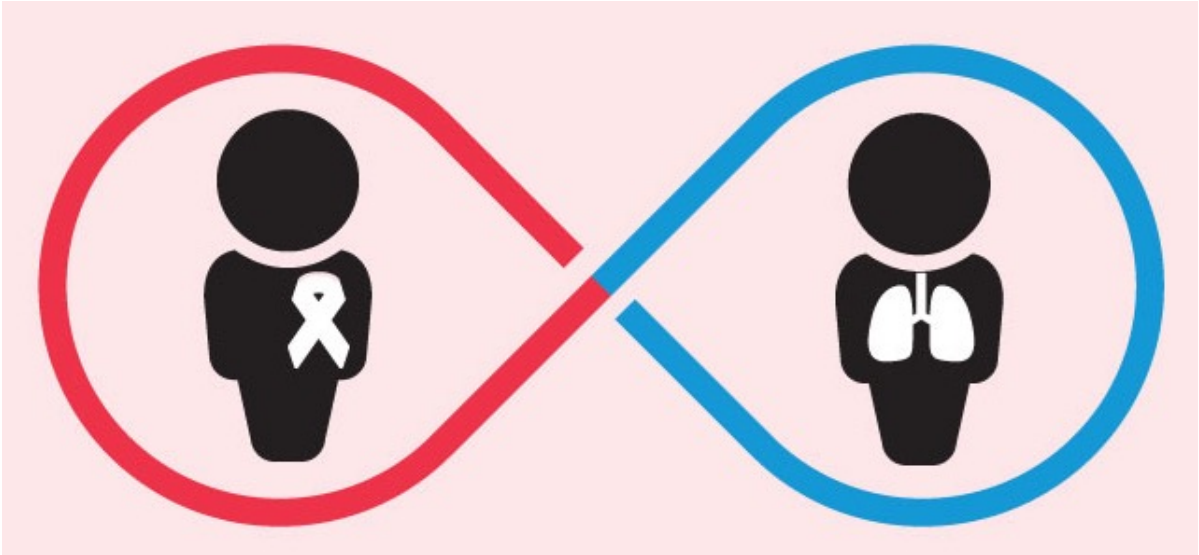
LIVE ATTENUATED

BCG revaccination	VPM1002	MTBVAC
M. bovis	*M. bovis*	*M. tuberculosis*
Epitopes in RD regions absent	Epitopes in RD regions absent	ALL

epitope content

Adapted from Martín *et al.* Appl. Sci. 2020

High impact strategies to treat and prevent HIV and TB are needed



Universal antiretroviral therapy

TB preventive therapy

https://www.who.int/tb/cHILD3.jpg

Summary

- TB incidence and TB-related mortality are rising, we need to be vigilant and keep our focus in the context of competing infectious disease threats
- There has been significant progress in treatments for TB: We now have a 1-month treatment for latent TB, a 4-month treatment for drug-sensitive TB, and a 6-month treatment for MDR-TB!
- There are several safe, effective regimens for co-treatment of HIV and (L)TB(I)
- PWH constitute an ever-smaller proportion of those with TB disease and with TB-related death, owing to global provision of ART and increasing provision of TPT
- More to come (new drugs, new formulations, vaccines in development)…

Acknowledgments

- Johns Hopkins University
  - Center for TB Research
  - Division of Clinical Pharmacology
  - JHU Clinical Research Site (CRS)
  - Center for NTM and Bronchiectasis

- Clinical Trials Networks
  - Tuberculosis Trials Consortium/CDC
  - AIDS Clinical Trials Group
  - IMPAACT Network

- Vanderbilt University Medical Center
  - New colleagues
  - Warm and generous welcome
  - Outstanding administrative team
  - Vanderbilt Tuberculosis Center!

- Partners
  - TB Alliance, Sanofi, ViiV, Janssen, Otsuka, Pfizer, Gilead
  - UCSF
  - Uppsala
  - NIRT, BJGMC, UNC/Malawi Project
  - Stellenbosch, DTTC, UCT, UCTLI, CAPRISA, Aurum

- Funding
  - R01FD004794 (FDA)
  - R01HD074944 (NICHD)
  - R01FD005724 (FDA)
  - R01AI152142 (NIAID)
  - K24AI150349 (NIAID)
  - TBTC/CDC, ACTG/DAIDS
  - UNITAID

- Connie Haley

- **Thanks to VCCC and AETC for the invitation**

Thank you.

WHO. Roadmap for Childhood Tuberculosis: Towards Zero Deaths