Clinical trials for treatment of latent TB infection: the current state of affairs

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Conflict of interest disclosure

UpToDate: textbook chapters on TB, TB/HIV

<u>Grant funding</u>

National Institutes of Health

Centers for Disease Control and Prevention

CRDF Global

Outline

Latent *M. tuberculosis* Infection

- Epidemiology
- Pathogenesis
  - Transcriptomic signatures
  - Spectrum: latent *M. tuberculosis* infection to TB disease
- Treatment of latent *M. tuberculosis* infection
  - Nitrosamines
  - Pregnancy
  - Regimens
    - Short-course, ultra short-course
  - Strategies
    - HIV-positive
      - Antiretroviral therapy + isoniazid
      - Extended duration / continuous isoniazid
      - Repeated courses of short-course treatment
- Treatment based on transcriptomic signature
    - HIV-negative

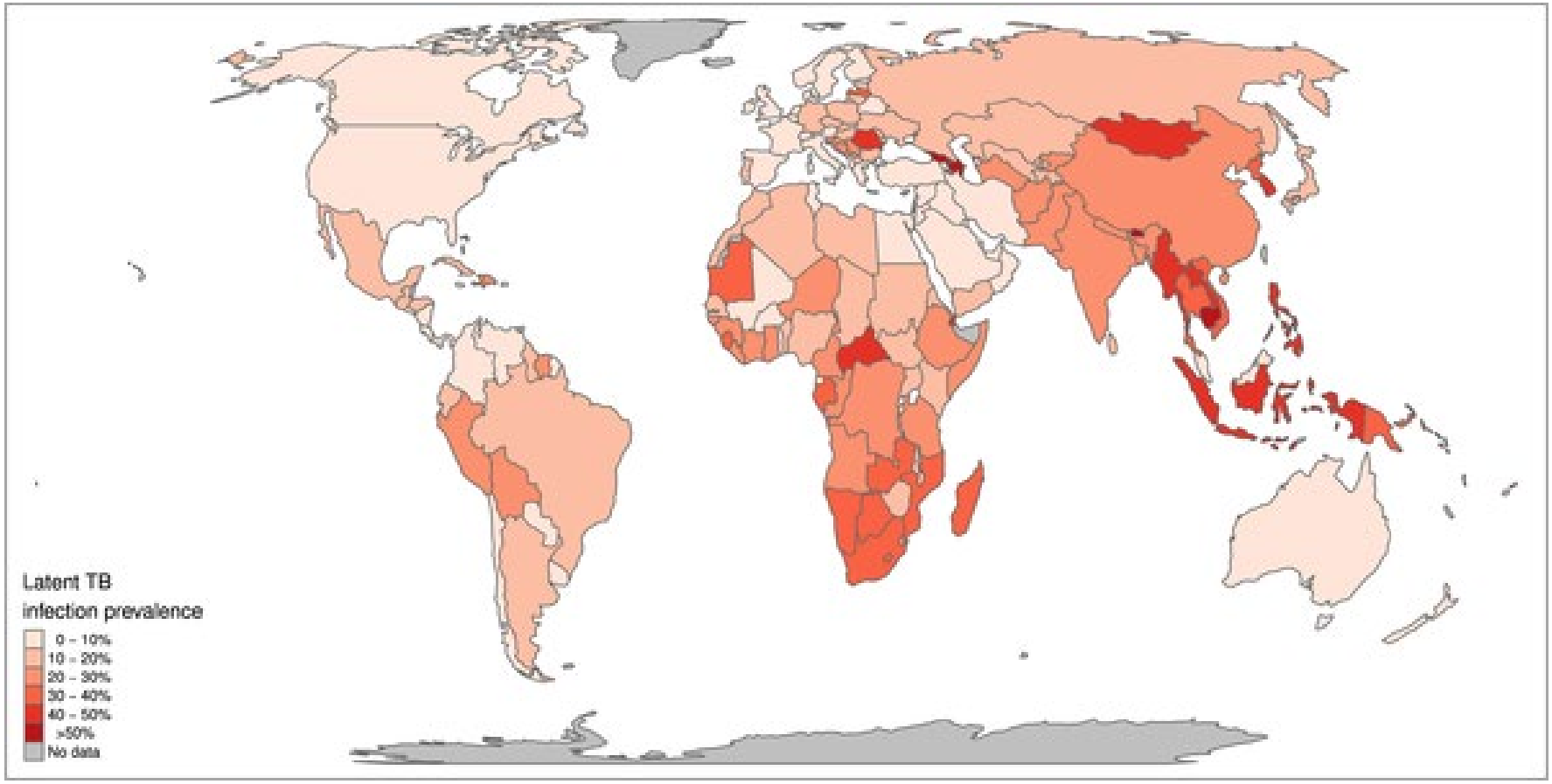
Prevalence of latent *M. tuberculosis* infection in the world

One-quarter of the global population is infected with *M. tuberculosis*

- Global population February 2021: 7.8 billion
- Approximately 2 billion people infected
  - Raviglione M. JAMA 1995;273:220. Dye C et al. JAMA 1999;282:677. Houben R PLoS Med 2016.
- Prevalence of *M. tuberculosis* infection varies by location
  - High TB incidence setting: (Kampala, Uganda): 49% (95% CI: 44-55)
    - Kizza FN. BMC Infect Dis 2015:165
  - Low TB incidence setting (United States): ~5%
    - Miramontes R. PLoS ONE 2015:10 (11):e0140881
    - Mancuso JD. Am J Respir Crit Care Med 2016 Feb 11.
    - Ghassemieh BJ. Am J Respir Crit Care Med 2016 Feb 18.

Global map of prevalence of latent TB infection

From this reservoir of ~2 billion infected persons, 100-200 million TB cases could develop



Houben RMGJ, Dodd PJ (2016) The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLOS Medicine 13(10): e1002152. https://doi.org/10.1371/journal.pmed.1002152
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002152

PLOS | MEDICINE

Approximately 5-10% of persons with *M. tuberculosis* infection will develop TB

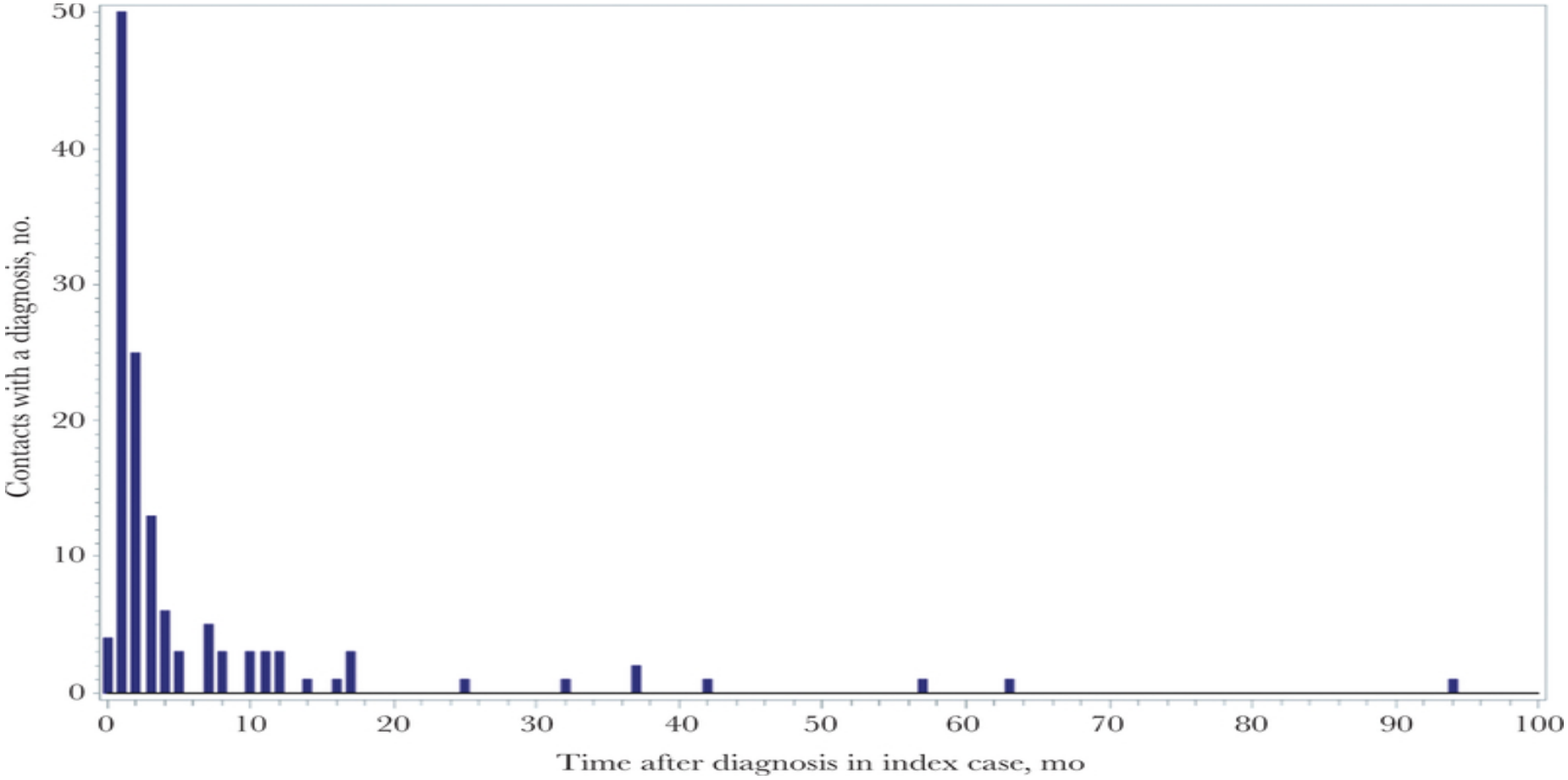
- Europe and Brazil: 1960s – 1990s
  - The TB rate among close contacts and recent converters who did not receive treatment is 5-8% over two years

    Sutherland I. Adv Tuberc Res 1976;19:1-63.
    Sutherland I. TSRU Progress Report 1968.
    Kritski AL. AJRCCM 1996;153:331-5.
- Amsterdam: 2002-2011
  - Among 372 infected contacts who did not receive treatment, 10 developed TB over 5 years (2.4%; 95% CI: 1.2-4.7)

    Sloot R. AJRCCM 2014;190:1044-52.
- Meta-analysis of 203 studies
  - Prevalence of TB in contacts:
    - Low/middle income: 3.1%
    - High income: 1.4%
    - TB incidence highest in the first year after infection

    Fox GJ. Eur Respir J 2013;41:140-56.

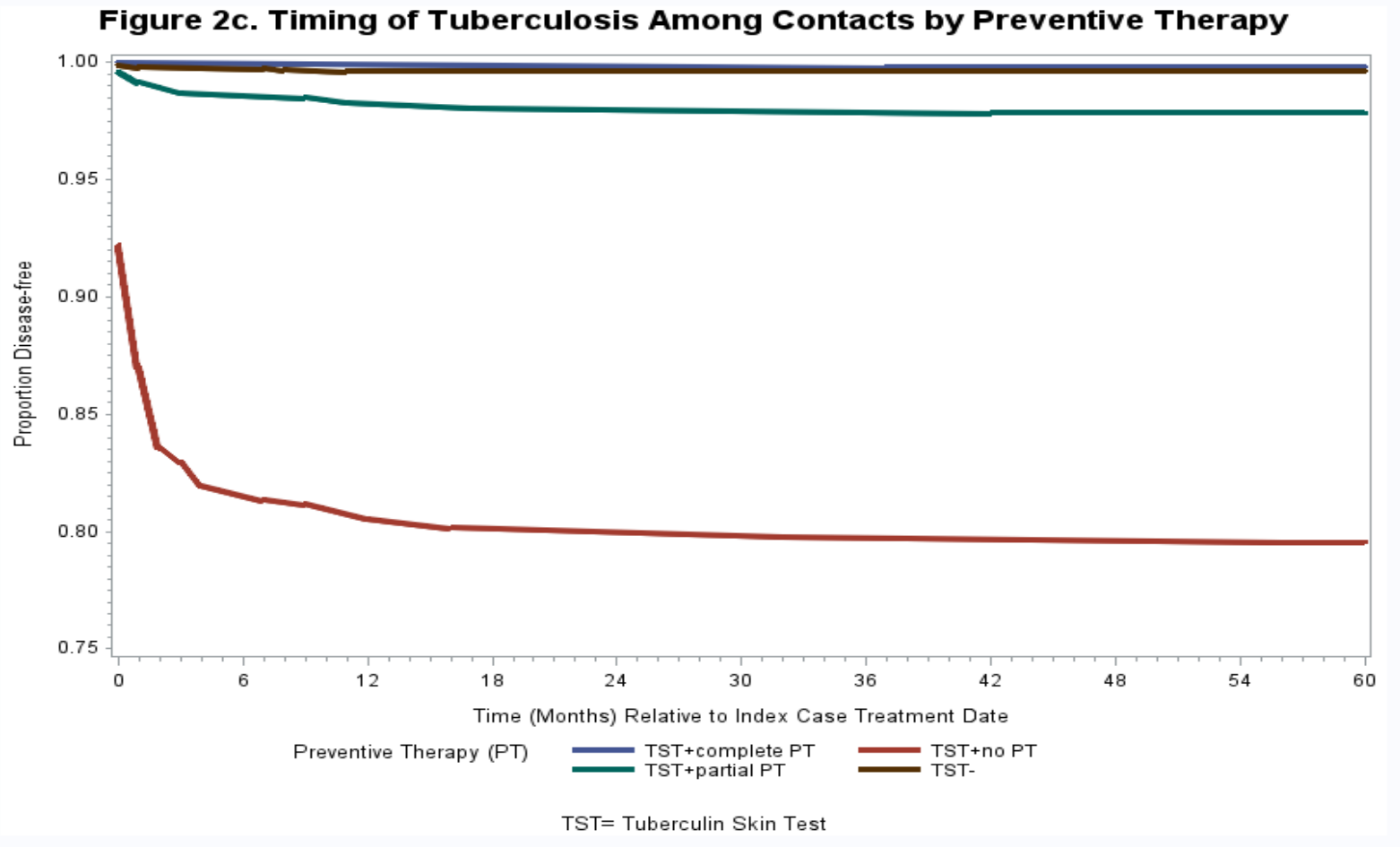
Timing of TB among 131 contacts, by interval from index case TB treatment initiation to contact TB treatment initiation



- 9 health departments in U.S. and Canada; TB diagnosed in 158 / 4,490 (4%) contacts
- TB diagnosed in the contact before the index case: 27
- Of TB cases in contacts, 128 (81%) diagnosed by month 6; 145 (92%) by month 12

Reichler MR. J Infect Dis 2018;218:1000-8.

TB risk among the 499 contacts with a positive tuberculin skin test



Cumulative TB risk among TST+ contacts who were not treated for latent *M. tuberculosis* infection: 20.4%

Reichler MR. J Infect Dis 2018;218:1000-8.

A prognostic PCR test for incident TB

- South Africans age 12-18 years infected with M. tb. Followed q 6 months for 2 years for development of TB
  - A signature of TB risk was derived from whole blood RNA sequencing
    - TB cases (n=46) vs. those who did not progress (n=107)
    - 16-gene signature (COR: correlate of risk)
    - In the 12 months prior to TB diagnosis:
      - Sensitivity 66%
      - Specificity 81%
  - This signature also predicted TB in other cohorts of South African and Gambian adults
    - In the 12 months prior to TB diagnosis
      - Sensitivity 54%
      - Specificity 83%

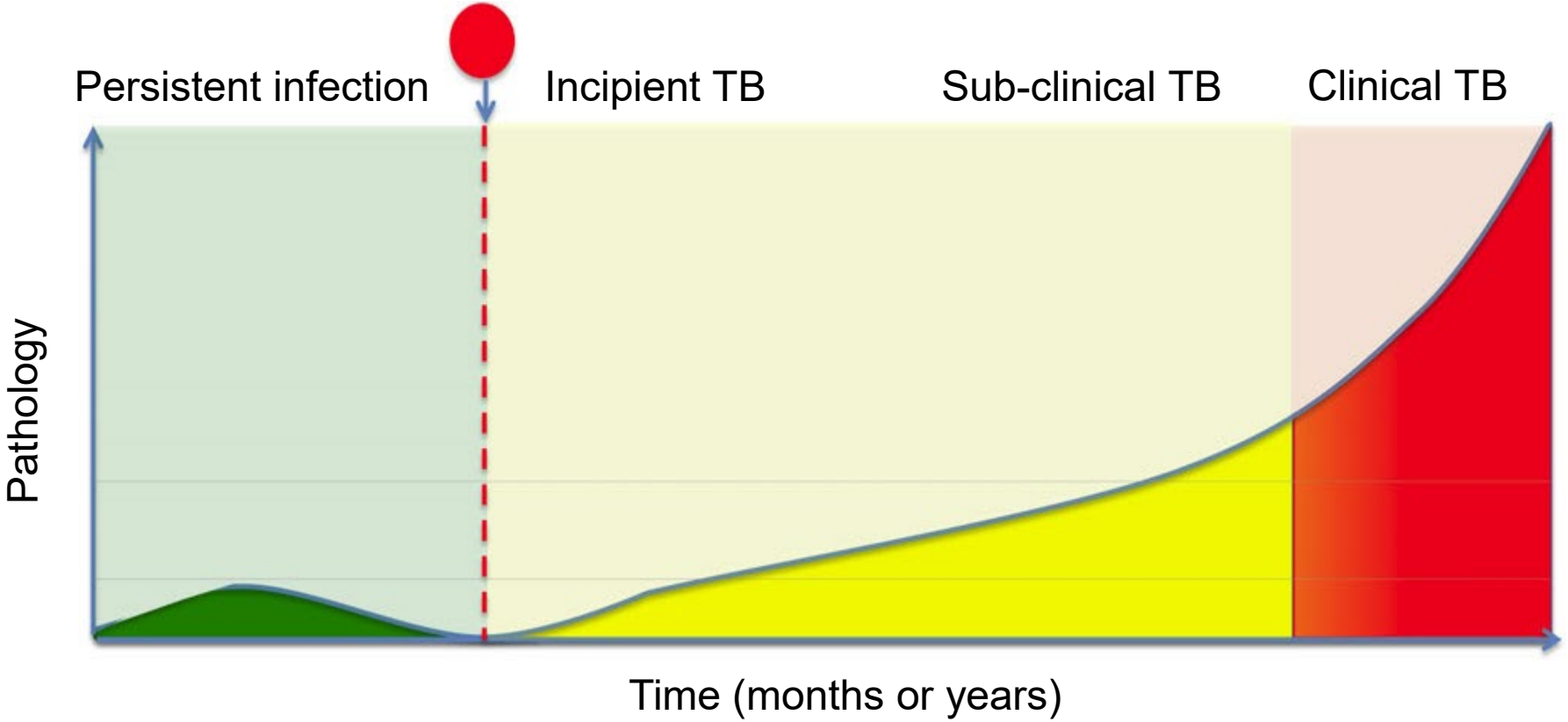
Zak DE. Lancet 2016;387:2312-22.

A prognostic PCR test for incident TB

Days prior to TB diagnosis	Sensitivity	95% Confidence Interval
1-180 (< 6 months)	71%	67 - 75
181-360 (6 – 12 months)	63%	59 - 66
361-540 (12 – 18 months)	48%	43 - 53
541-720 (18 – 24 months)	29%	23 – 36
>720 (> 24 months)	5%	2 - 13

Zak DE. Lancet 2016;387:2312-22.

The spectrum of *M. tuberculosis* infection and TB disease



Adapted from Esmail H. Phil Trans R Soc B 2014;369: 20130437

Additional RNA signatures of TB disease diagnosis and progression

- ***RISK11:*** a sub-set of the 16-gene COR signature: equivalent prognostic, diagnostic performance
  - Darboe F. Tuberculosis 2018;108:124-6.
- ***RISK6:*** developed as prognostic signature, but with excellent diagnostic and treatment response performance in South African and Gambian patients.
  - Penn-Nicholson A et al. Sci Rep 2020 May 25;10(1):8629.
- ***RESPONSE_5:*** this a 5-gene signature was designed for monitoring TB treatment response, including rapid resolution after treatment initiation as an early indicator for successful treatment.
  - Thompson EG. Tuberculosis 2017;197:48-58.
- ***DIAG4 TB:*** this 4-gene signature was developed as a diagnostic test for TB from Indian participants, and validated on Ugandan and Gambian cohorts.
  - Maertzdorf J. EMBO Mol Med 2016;8:86-95.
- ***RISK_4 GC6:*** this 4-gene signature was developed as a "pan-African" prognostic test in a household contact study performed in South Africa, The Gambia and Ethiopia.
  - Suliman et al., AJRCCM 2018 April 6.
- ***DIAG3 TB:*** this 3-gene signature was developed as a diagnostic test on previously published data from a 3 cohorts from South Africa, Malawi, UK, USA and France, and validated on 7 cohorts from around the globe.
  - Sweeney TE. Lancet Respir Med 2016;4:e29.
- ***2_Bacterial vs Viral*** is a 2-gene signature designed to discriminate between febrile children with bacterial or viral infection. Since many TB biomarkers measure a type I interferon response, which is typically an anti-viral response, this distinction may be important to reduce false positives caused by acute viral infection.
  - Herberg JA. JAMA 2016;316:835-45.

Performance of transcriptomic signatures

Systematic review and meta-analysis

- **HIV-negative adults and adolescents**
- **Studies with independent validation cohort**
- **Meta-analysis performed for signatures validated in ≥ 3 comparable cohorts**
- **TB diagnosis: 18 studies of 24 signatures**
  - **3 signatures were validated in clinically relevant cohorts, and differentiated TB from other diseases**
    - **Berry393 (2010), Kaforou27 (2013), Zak16 (2016)**
      - **Pooled sensitivity: 84%, 87%, 90%**
      - **Pooled specificity: 79%, 88%, 74%**
- **TB progression: 4 studies of 5 signatures**
  - **1 signature (within 6 months of TB diagnosis) met minimal target product profile: PPV > 5.8%, 75% sens, 75% spec**
    - **Sweeny3 (2016)**

Mulenga H. PLoS ONE 2020 Aug 21;15(8):e0237574

Treatment of *M. tuberculosis* infection is highly efficacious in preventing TB

But:

- Most persons who start isoniazid for treatment of *M. tuberculosis* infection do not complete it

- The longer the treatment duration, the lower the completion rate
    - Horsburgh CR. Chest 2010.
    - Stuurman AL. BMC Infect Dis 2016.

Treatment of *M. tuberculosis* Infection

Current Regimens—United States

Regimen	Efficacy	Effectiveness	Comments
3 months INH + rifapentine once-weekly	90% (estimated)	90% (estimated)	≥82% completion Lower rates when self-administered than DOT
4 months rifampin daily	---	50-90% (estimated)	Limited data in HIV+ persons
3 months INH + rifampin daily	---	41-59%	Concern re: hepatoxicity
6-9 months INH daily	90%	25-88% (median:60%)	6 and 12 months well-studied; 30-60% completion

Treatment of *M. tuberculosis* infection

- CDC/National TB Controllers Association
  - 3-4 month rifamycin-based regimens are preferred over 6-9 months of INH (alternative)
    - Given similar efficacy yet better safety and higher treatment completion rates with shorter regimens, the 3-4 month regimens could have higher effectiveness than 6-9INH
- World Health Organization
  - Regardless of HIV status or local TB burden
    - Recommended: 6-9INH, 3HP, 3HR
    - Alternatives: 4R, 1HP
  - If HIV+ in settings of high M.tb transmission, 36 months of INH regardless of LTBI status, antiretroviral therapy, CD4 count

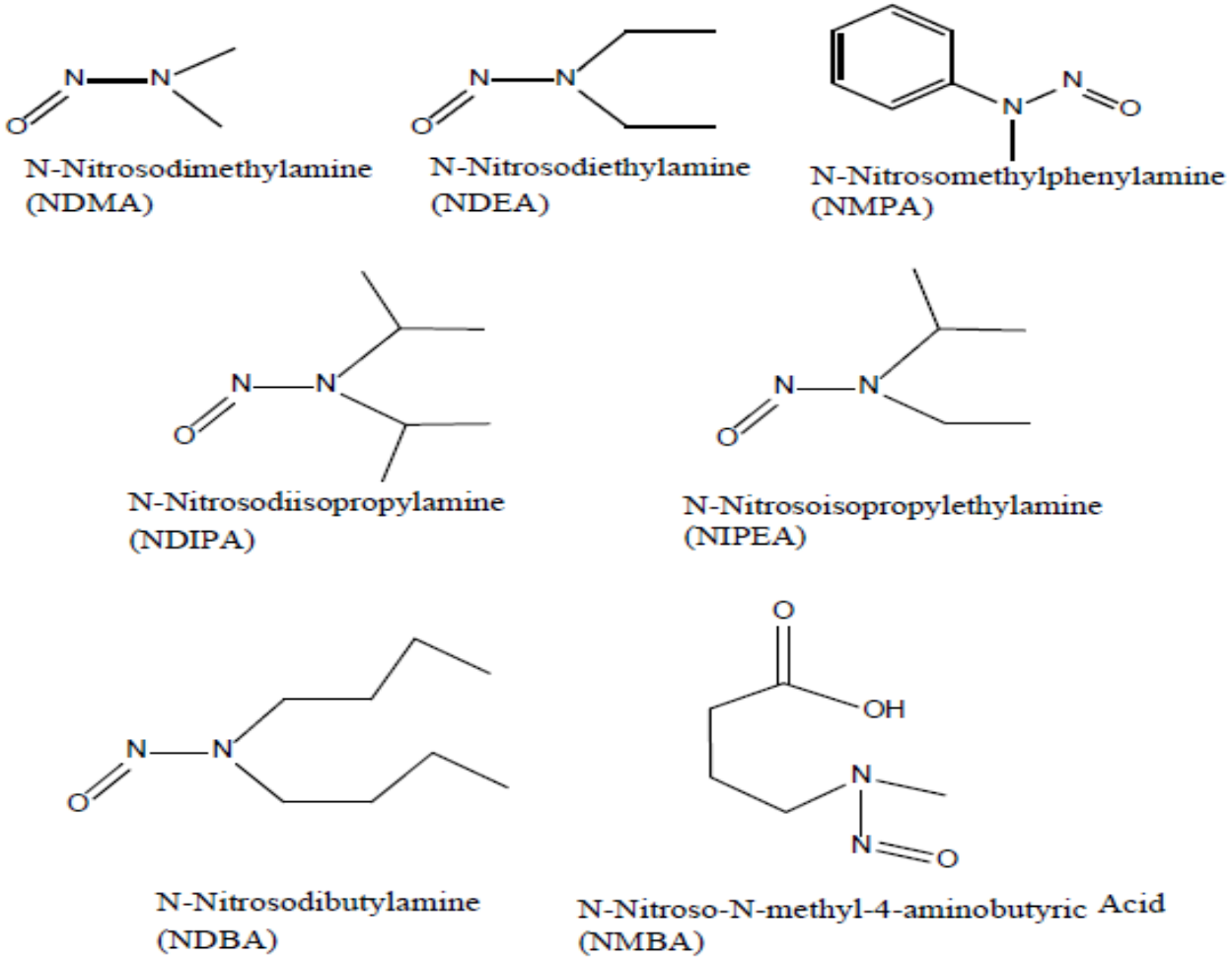
- Sterling TR et al. CDC and NTCA Guidelines. MMWR Recomm Rep 2020; 69:1-11.
- WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Geneva: World Health Organization; 2020.

Nitrosamines

- August 2020: FDA became aware of nitrosamine impurities in some samples of rifampin and rifapentine
  - Rifampin: 1-methyl-4-nitrosopiperazine (MNP)
    - Acceptable limit: 0.16 parts per million (ppm)
      - Temporary limit: 5 ppm
  - Rifapentine:1-cyclopentyl-4-nitrosopiperazine (CPNP)
    - Acceptable limit: 0.1 ppm
      - Temporary limit: 14 ppm
- October 2020:
  - FDA revised the temporary limit of CPNP to 20 ppm
- January 2021
  - FDA confirmed the above guidance, and provided levels in currently available formulations

Control of nitrosamine impurities in human drugs. Guidance for industry. U.S. Food and Drug Administration. September 2020.

Figure 2. Chemical Structures of Seven Potential Nitrosamine Impurities in APIs and Drug Products



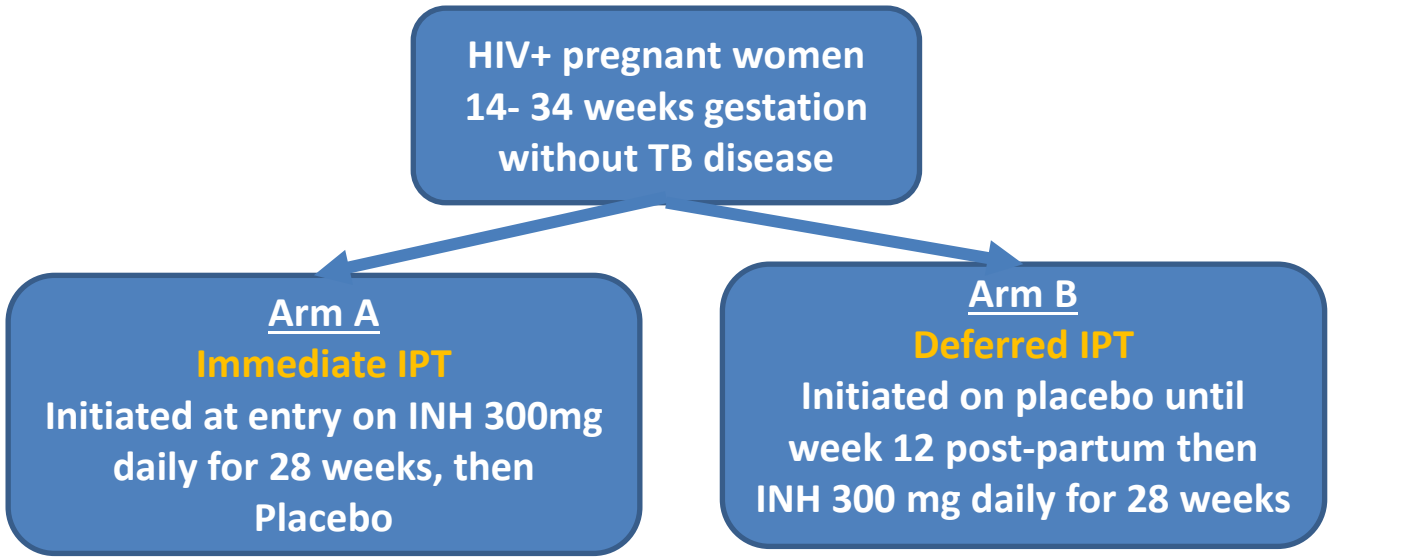
Control of nitrosamine impurities in human drugs. Guidance for industry. U.S. Food and Drug Administration. September 2020.

Nitrosamines

- Nitrosamines are present in water, meat, dairy, fruits, vegetables
  - Also in angiotensin II receptor blockers, ranitidine, nizatidine, and metformin
- Some nitrosamines have been classified as possible human carcinogens, based on rodent carcinogenicity studies
  - FDA: possible increased cancer risk (> 1:100,000) after 70 years of exposure
- MNP and CPNP are nitrosamines, but there are no data evaluating their carcinogenic potential
- FDA (August 2020): TB is a deadly disease; the risk of not taking rifampin or rifapentine outweighs any potential risk from MNP or CPNP
- CDC (September 2020): continue rifampin and rifapentine for TB treatment and prevention, per existing guidelines

TB APPRISE: TB Ante vs. Postpartum Prevention with INH in HIV Seropositive Mothers and their Exposed Infants

- **Study Design**: **Phase IV multicenter, randomized, double-blind, placebo-controlled, non-inferiority trial**
- **Population**: HIV-positive pregnant women ≥ 14 - ≤ 34 weeks gestation who live in a **high TB burden area**, defined as TB prevalence ≥ 60/100,000 population



Study drugs (INH vs. placebo), open label pyridoxine (vitamin B_6) and open label prenatal multivitamin terminated at 40 weeks post-partum

End of follow-up: 48 weeks post-partum

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Primary Endpoint Analysis

Primary endpoint = First maternal treatment-related Grade ≥ 3 adverse event or permanent drug discontinuation due to toxicity

Outcomes	Arm A Immediate	Arm B Deferred	IR/100 PY	IRD (upper limit of 95% CI)
Primary endpoint: Intent-to-treat	**72/477 (15%)**	**73/479 (15%)**	**15.0 vs 14.9**	**0.1 (4.98)**
Primary endpoint: Per protocol	**64/376 (17%)**	**69/388 (18%)**	**16.0 vs 16.7**	**-0.7 (4.9)**

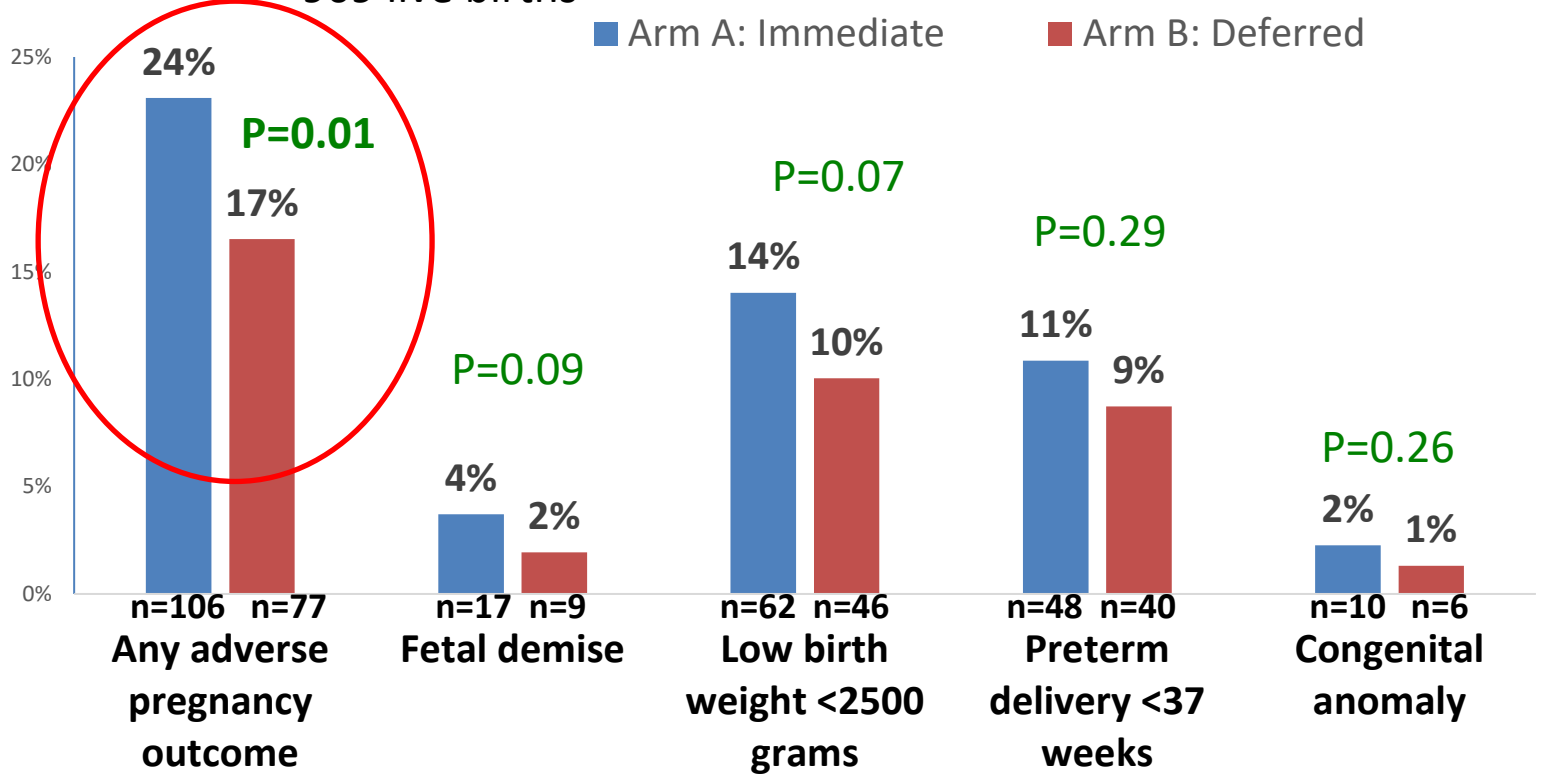
Non-inferiority margin for the primary endpoint: 5/100 PY

Gupta A et al. N Engl J Med 2019 Oct 3;381(14):1333-1346

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Secondary Outcomes: Adverse Pregnancy Outcomes

- 926 deliveries (460 in immediate arm vs 466 in deferred arm)
  - 915 singletons, 11 twins for total of 937 fetuses/infants
  - 26 stillbirths (fetal demise)
  - 2 abortions (1 spontaneous, 1 induced)
  - 909 live births



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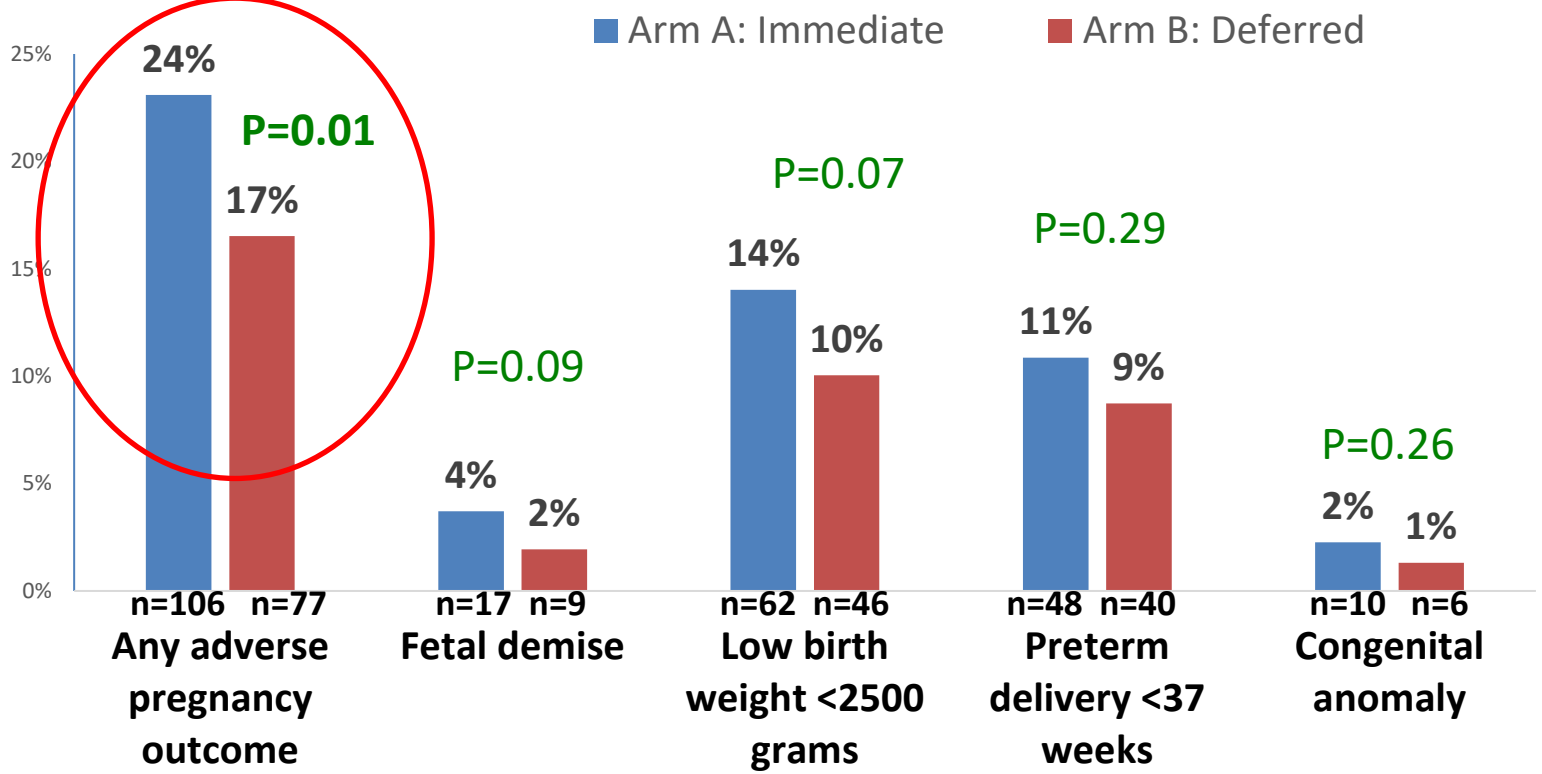


Gupta A et al. N Engl J Med 2019 Oct 3;381(14):1333-1346

Secondary analysis 925 mother-infant pairs: **adjusted odds of adverse pregnancy outcome--**immediate INH: 1.63 (95% CI: 1.15, 2.31). Theron G. CID 2020.

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Safety of INH in HIV+ pregnant women
Observational studies

- Soweto, South Africa; 2011-2014. Tshepiso study
  - Adverse pregnancy outcome:
    - fetal demise, prematurity, low birth weight, congenital anomaly
  - 151 women with known pregnancy outcomes
    - 69 (46%) reported initiation of INH during pregnancy
      - 11 (16%) had an adverse pregnancy outcome
    - 82 (54%) did not initiate INH during pregnancy
      - 23 (28%) had an adverse pregnancy outcome
  - Adjusted odds of an adverse pregnancy outcome:
    - 2.5 (95% CI 1.0, 6.5; P = 0.48) in INH unexposed women
    - Controlling for maternal age, CD4, viral load, ART regimen, BMI, anemia
      - Salazar-Austin N. Clin Infect Dis 2020;71(6):1419-26.
- Western Cape, South Africa. Public sector electronic health data
  - 43,917 pregnant women; 17% received INH
  - Poor pregnancy outcome: miscarriage, stillbirth, low birth weight, neonatal death
  - Adjusted odds ratio of poor pregnancy outcome if received INH: 0.83 (95%CI: 0.78, 0.87)
    - Kalk E. Clin Infect Dis 2020;71(8):e351-8.

3 months of weekly INH + rifapentine
Recent Updates

- The regimen is rolling out in high TB burden settings
  - IMPAACT4TB (UNITAID): in persons with HIV and children < 5 years old
  - Project countries: Brazil, Cambodia, Ethiopia, Ghana, India, Indonesia, Kenya, Malawi, Mozambique, South Africa, Tanzania and Zimbabwe
    - G Churchyard, R Chaisson
- Pregnancy did not ↑ RPT clearance, but HIV did; appears safe (n=50)
    - Mathad JS. CROI March 11, 2020; 144LB. Union October 2020; Hibma JE AJRCCM 2020 Sep
- Can be given with dolutegravir without dose adjustments
    - Dooley KE et al. DOLPHIN Study. Lancet HIV 2020 Jun 7 (6):e401-9. DOLPHIN TOO to start soon.
- Possible flu syndrome
  - Risk 4-19%. Risk factors: race (white; Asian), female sex, ↑ age, ↓ BMI, NAT2 genotype
    - Sterling TR. CID 2015; Jo KW. Respir Med 2019; Huang HL. CID 2020 Nov; Ruan QL. Clin Microbiol Infect 2020; Feng JY. IJID 2020; Lee MR. J Clin Med 2019
- Lower hepatotoxicity risk than with 9INH
    - Bliven-Sizemore E. IJTLD 2015; Sun Tuberculosis 2018.
- Completion rate lower when self-administered vs. directly-observed
  - 74-76% vs. 87%
    - Belknap B. Ann Intern Med 2017
- Safe and effective in several patient populations
  - Health departments, clinics, high school contacts, jails, homeless, renal transplant candidates. Higher completion rates than in trials.
    - Bargman MMWR 2014, Stennis CID 2016, Juarez-Reyes OFID 2016, Yamin OFID 2016, Lines G JHCPU. Simkins J Transpl 2016. Sandul CID 2017. Moro Ann Am Thorac Soc 2018. Schmit CID 2020

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

- Population: HIV-positive persons ≥ 13 years old in high TB incidence settings
  - ≥ 60 / 100,000 population
- Intervention: daily INH + rifapentine for 1 month
- Comparator arm: daily INH for 9 months
- Antiretroviral therapy: efavirenz or nevirapine-based
- Follow-up: 3 years after last participant enrolled
- Primary endpoint: TB (confirmed or probable), TB death, death due to unknown cause
- Non-inferiority design:
  - Expected TB rate in 9H arm: 2.0 per 100 person-years
  - Non-inferiority margin: 1.25 per 100 person-years

Swindells S. N Engl J Med 2019 Mar 14;380:1001-1011.

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

Characteristic	9H N=1504	1HP N=1496
Median age (years)	35	35
Male sex	692 (46%)	694 (46%)
Median BMI	23.5	23.6
Median CD4	469	473
ART at entry	749 (50%)	747 (49%)
TST-positive	21%	21%

Swindells S. N Engl J Med 2019 Mar 14;380:1001-1011.

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

Endpoint	9H N=1504	1HP N=1496	IRR (95% CI)
Primary endpoint All-comers	33/4896 p-y 0.67 / 100 p-y	32/4926 p-y 0.65 / 100 p-y	0.023 (-0.30, 0.35)
Primary endpoint CD4 ≤ 250	1.275 / 100 p-y	1.931 / 100 p-y	-0.656 (-2.06, 0.75)
Active TB, confirmed	14	18	
Active TB, probable	10	11	
Death due to TB	2	0	
Death-unknown cause	7	3	

Swindells S. N Engl J Med 2019 Mar 14;380:1001-1011.

4 weeks of daily INH + rifapentine

Brief Rifapentine-INH Efficacy for TB Prevention (BRIEF-TB)
AIDS Clinical Trials Group 5279

Endpoint	9H N=1498	1HP N=1488
Grade ≥ 3 adverse event	274 (18%)	250 (17%)
Treatment completion (self-report)	90%	97%
Premature drug discontinuation	2%	1%

Swindells S. N Engl J Med 2019 Mar 14;380:1001-1011.

Additional study of 1HP

- Ultra Curto
  - 1HP vs. 3HP in HIV-negative adults in Brazil
    - TST- or IGRA-positive close contacts or convertors
  - Sample size: 250 per arm
  - Primary outcomes:
    - Treatment completion, safety, cost-effectiveness
  - Status: funded. Awaiting rifapentine

NCT04703075. Update from R. Chaisson 22 Feb 2021

ASTERoiD

Assessment of the Safety, Tolerability and Effectiveness of Rifapentine given Daily for LTBI

Six weeks of daily rifapentine vs. a comparator arm of 12-16 week rifamycin-based treatment of latent *M. tuberculosis* infection: assessment of safety, tolerability and effectiveness

TB Trials Consortium: Study 37
Sterling TR, Belknap R, Robinson A, Boyd R

Enrollment started August 2019; on hold since March 2020
Enrolled to date: 92 participants
Target: 1,120 for safety; 3,400 for effectiveness

2R2

Higher dose rifampin for 2 months

- Rifampin 10 mg/kg daily for 4 months
- Rifampin 20 mg/kg daily for 2 months
- Rifampin 30 mg/kg daily for 2 months

- Phase 2b; Canada, Vietnam, Indonesia
- >= 10 years old with latent TB infection

- Randomized 1:1:1
- Target enrollment: 1,359 (453 per arm)
- Enrollment to date slow due to COVID-19
- Current enrollment: 178
- 1st interim safety analysis: when 150 participants have completed 4 months of follow-up

NCT03988933. Update from R Menzies 22 Feb 2021

Strategies to optimize TB prevention

- INH plus antiretroviral therapy in HIV+ persons
- Prolonged INH in HIV+ persons in high TB burden settings
- Periodic preventive therapy in HIV+ persons living in high TB burden settings
- Preventive therapy among persons with the Correlate of Risk (COR) transcriptomic signature

INH + ART to prevent TB in HIV+

Randomized, double-blind placebo-controlled trial

- **Khayelitsha, South Africa**
- **Randomly assigned 12 months of INH (n=662) vs. placebo (n=667) to persons on ART**
- **Primary endpoint: time to incident TB**

	INH	Placebo	HR	95% CI
TB per 100 p-y	**2.3**	**3.6**	**0.63**	**0.41,0.94**

- **The beneficial effect of INH was not limited to those who were TST+ or IGRA+**
- **Without a more predictive test, authors suggest that INH should be recommended to all patients receiving ART in moderate or high TB incidence areas, regardless of TST or IGRA status.**

Rangaka MZ. Lancet 2014;384:682-90.

Empiric TB therapy vs. isoniazid in HIV+ adults starting ART

REMEMBER study

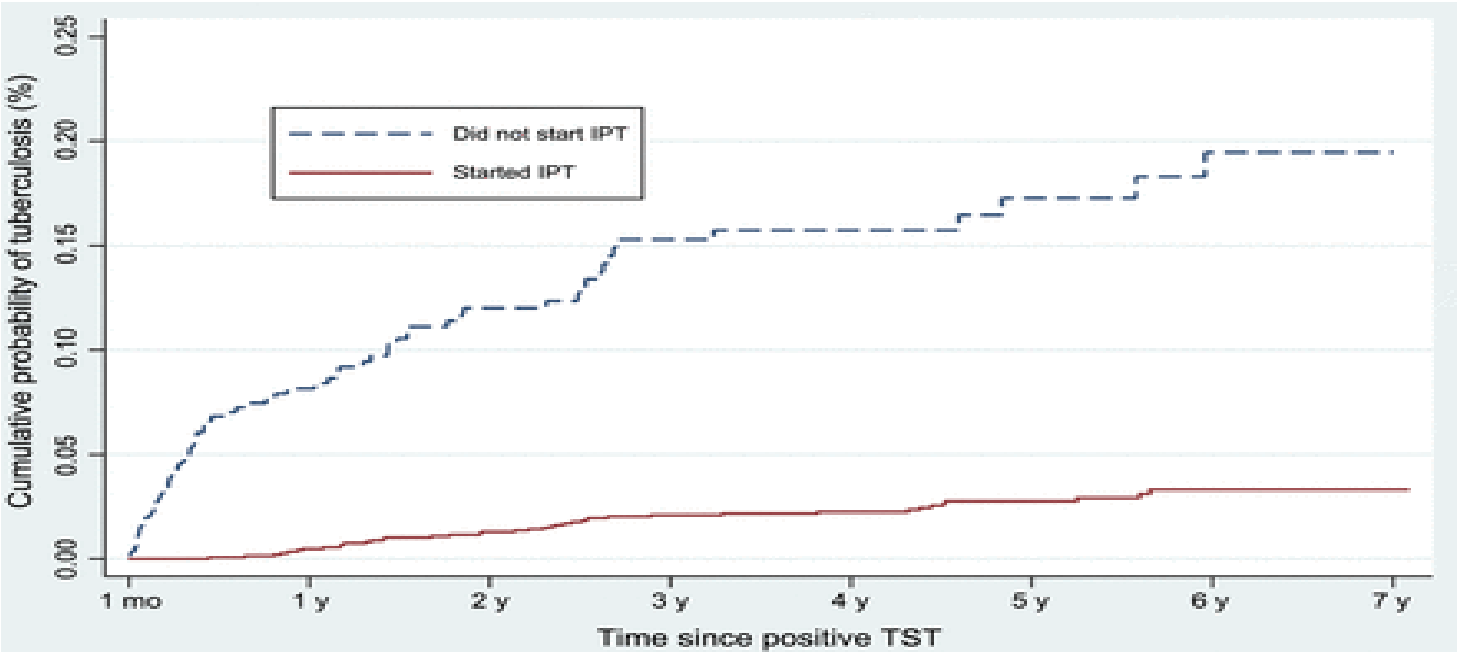
- **CD4 < 50**
- **Malawi, South Africa, Haiti, Kenya, Zambia, India, Brazil, Zimbabwe, Peru, Uganda**
- **Persons with confirmed or suspected TB excluded**
- **Primary endpoint: survival (death or unknown status) at 24 weeks**
  - **ART + anti-TB therapy (n = 424) 5% (3.5, 7.8)**
  - **ART + INH (n = 426) 5% (3.4, 7.8)**
- **Grade 3-4 lab abnormalities**
  - **ART + anti-TB therapy: 23%**
  - **ART + INH 23%**

Hosseinipour MC. Lancet 2016;387:1198-1209.

Protective effect of INH through 7 years

Rio de Janeiro, Brazil

- **1,954 TST+/HIV+ persons**
  - **1,601 (82%) initiated INH**
    - **1,330 (83%) completed 6 months of INH**



Golub J. Clin Infect Dis 2015;60:639-45.

INH for 6 months vs. 36 months
in HIV+ persons

- Botswana
- Randomized double-blind placebo-controlled trial
- Tuberculin skin test-positive or -negative
- All patients received 6 months INH
  - INH vs. placebo for next 30 months
- Antiretroviral therapy provided if CD4 < 200
- INH dose: 300 mg + 25 mg B6

Samandari T. Lancet 2011;377:1588-98.

INH for 6 months vs. 36 months

	6H	36H	Hazard ratio	P-value
TB per 100 p-y (**All**)				
ITT (n=989 / 1,006)	1.26	0.72	0.57	0.047
PP (n=665 / 653)	1.18	0.51	0.43	0.045
TB per 100 p-y (**TST+**)				
ITT	2.22	0.57	0.26	0.019
PP	1.81	0.00	0.00	0.007

ITT: intention to treat **PP: per protocol**

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ITT	2.22	0.57	0.26	0.019
PP	1.81	0.00	0.00	0.007

TST-negative: HR = 0.75 P = 0.40

ITT: intention to treat **PP: per protocol**

Samandari T. Lancet 2011;377:1588-98.

TB Incidence after 36 months of INH
Botswana

- Post-trial observational analysis for durability of protection
  - 36 months vs. 6 months of INH

	Trial period	95% CI	Post-trial	95% CI
All participants	0.57	0.33, 0.99	0.82	0.46, 1.49
TST + participants	0.26	0.08, 0.80	0.40	0.15, 1.08

- In multivariable analysis, ART ↓ risk of death but not TB in post-trial period

Samandari T. Lancet 2011;377:1588-98.
Samandari T. AIDS 2015;29:351-9.

WHIP3TB

3HP vs. Periodic 3HP vs. 6H in HIV-positive individuals

- **High TB burden settings; 38% IGRA-positive**
  - Study sites: South Africa, Ethiopia, Mozambique
- **3HP: mostly self-administered**
- **Part A: single round of 3HP vs. 6 months INH:**
  - Primary endpoint: self-reported treatment completion
- **Part B: 3HP given once per year x 2 years vs. 3HP given only once**
  - Primary endpoint: confirmed TB (culture, Xpert, smear) or clinical TB

Churchyard G. CROI March 11, 2020. 143LB.

WHIP3TB

3HP vs. Periodic 3HP vs. 6H in HIV-positive individuals

Part A

Treatment completion:

3HP (n = 3,610): 90%
6H (n = 404): 51%

Outcome	Time period (months)	3HP Events/p-y Rate/100 p-y	6H Events/p-y Rate/100 p-y	HR (3HP vs. 6H) 95% CI	P-value
TB incidence	0-12	55/3808 1.44	4/372 1.07	1.06 (0.38 – 2.95)	0.91
Mortality incidence	0-12	16/3838 0.42	1/430 0.23	1.79 (0.24 – 13.5)	0.57

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WHIP3TB

3HP vs. Periodic 3HP vs. 6H in HIV-positive individuals

Part B

Outcome	Time period (mos)	p3HP Events/p-y Rate/100 p-y	3HP Events/p-y Rate/100 p-y	HR p3HP vs. 3HP (95% CI)	P-value
TB incidence	0-24	37/3141 1.18	39/3149 1.24	0.95 (0.61-1.49)	0.83
TB incidence	12-24	14/1463 0.96	14/1471 0.95	1.01 (0.48-2.12)	0.98
TB incidence, IGRA+	0-24	19/1142 1.66	18/1113 1.62	0.99 (0.52-1.89)	0.98
RIF-resistant TB incidence	0-24	4/3141 0.13	4/3149 0.13	1.00 (0.25-4.01)	>0.99
Mortality incidence	0-24	29/3238 0.90	19/3239 0.59	1.55 (0.87-2.76)	0.14

Churchyard G. CROI March 11, 2020. 143LB.

WHIP3TB

3HP vs. Periodic 3HP vs. 6H in HIV-positive individuals

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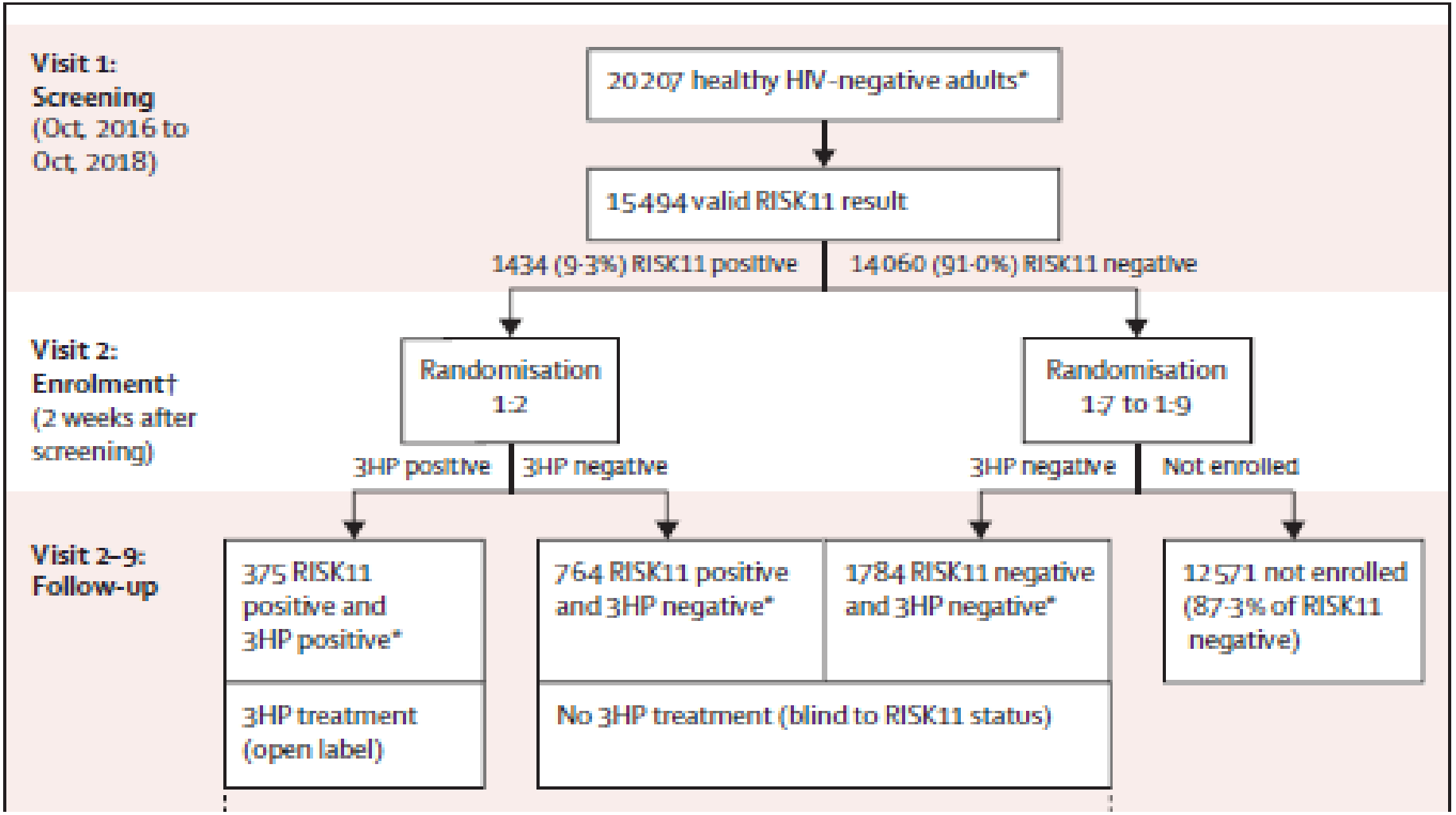
Churchyard G. CROI March 11, 2020. 143LB.

Correlate of Risk Targeted Intervention Study (CORTIS)

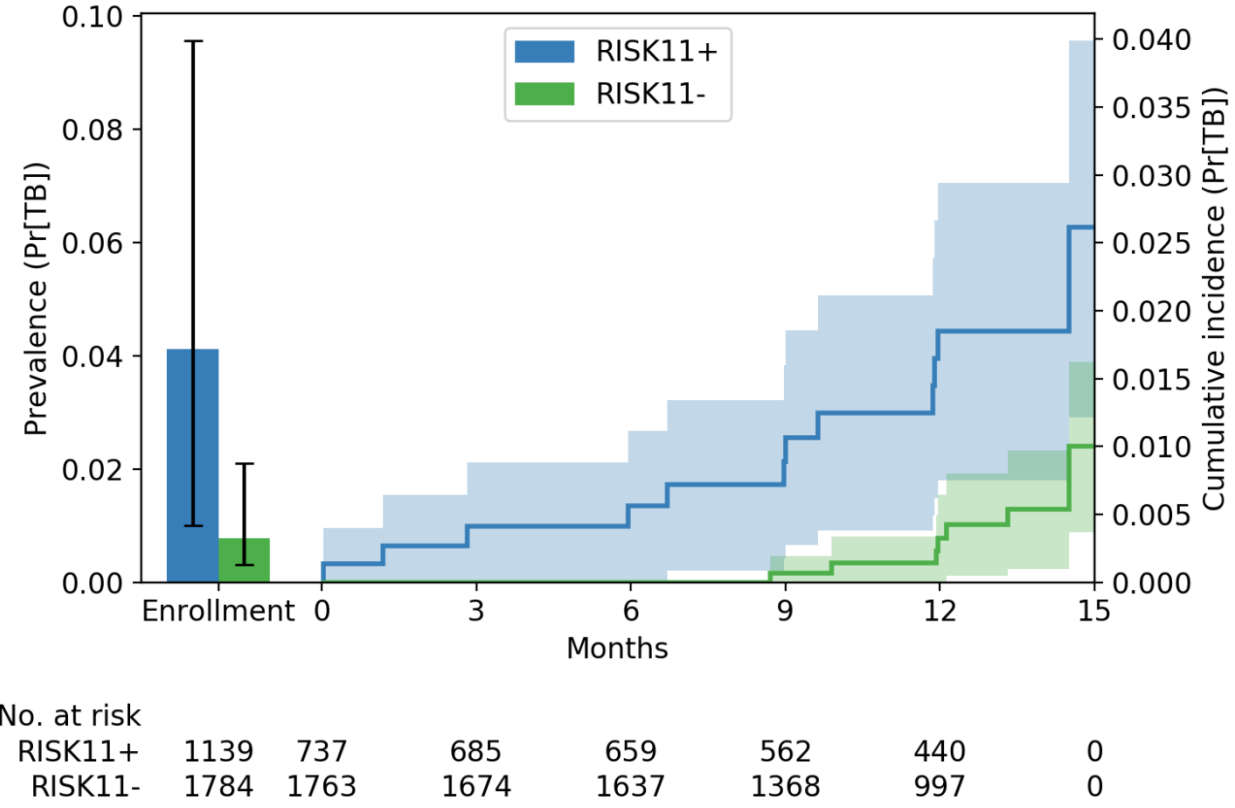
A Randomized, Partially-blinded, Clinical Trial of Isoniazid and Rifapentine (3HP) Therapy to Prevent Pulmonary Tuberculosis in High-risk Individuals Identified by a Transcriptomic Correlate of Risk (COR)



Scriba TJ et al. Lancet Infect Dis. Jan 25, 2021

RISK11 Status: Prevalent and Incident TB Cases

Among persons who did not receive 3HP



No. at risk							
RISK11+	1139	737	685	659	562	440	0
RISK11-	1784	1763	1674	1637	1368	997	0

TB Prevalence
61 cases

RISK11+	(47/1,139)	4.1%
RISK11-	(14/1,784)	0.8%

TB incidence
24 cases

RISK11+	(14/737)	2.6/100 py
RISK11-	(10/1,763)	1.0/100 py

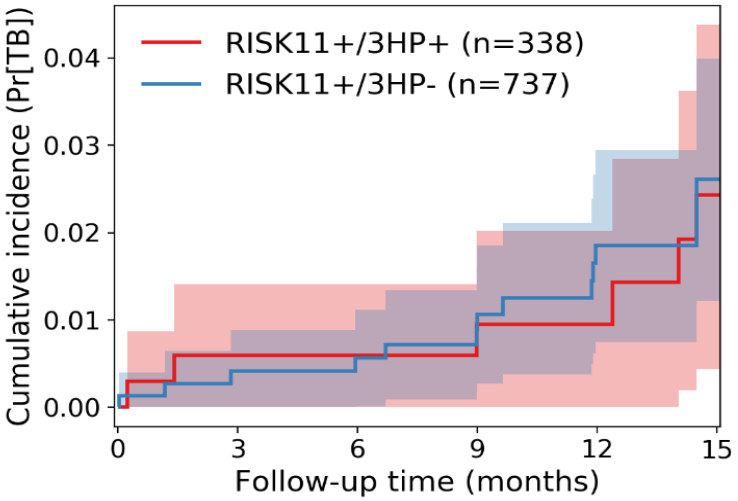
No incident TB cases in RISK11- participants until 9 months

Scriba TJ et al. Lancet Infect Dis. Jan 25, 2021

Effectiveness and Efficacy of 3HP in RISK11+ persons

Cumulative incidence (RISK11+)					
Cohort	**3HP+**	**3HP-**	**TE (%)**	**95% CI***	**P-value**
MITT	0.024 (6/338)	0.026 (14/737)	7.0	-145 – 64.7	0.88

Effectiveness of 3HP (MITT; 15 months)



Scriba TJ et al. Lancet Infect Dis. Jan 25, 2021

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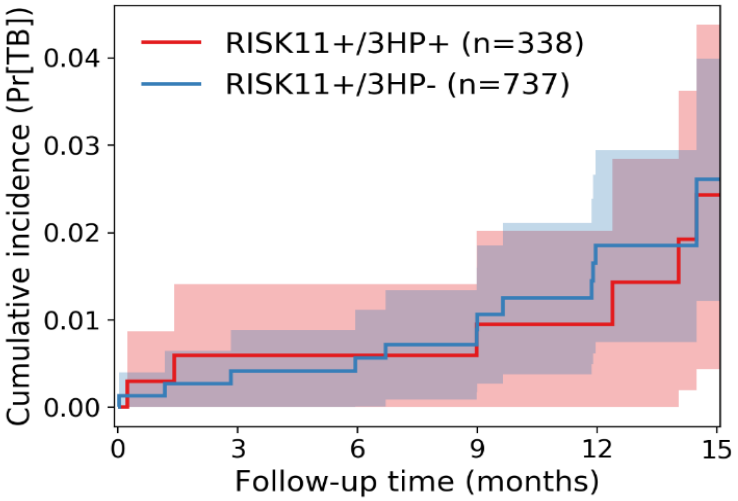
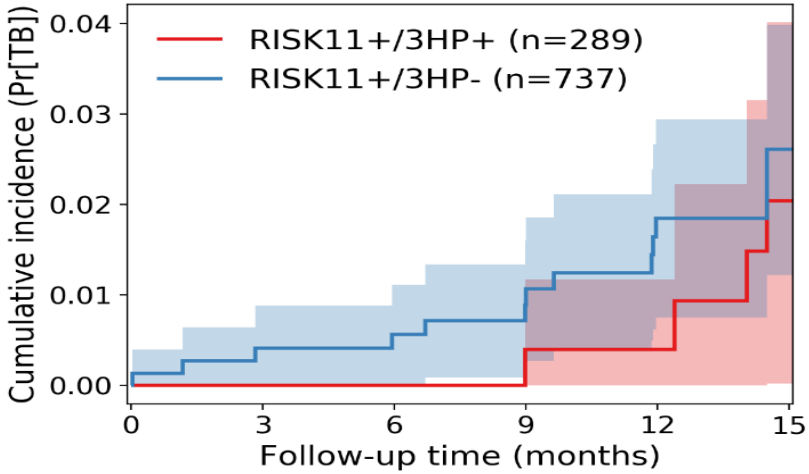
Cumulative incidence (RISK11+)					
Cohort	**3HP+**	**3HP-**	**TE (%)**	**95% CI**	**P-value**
MITT per protocol	0.020 (4/289)	0.026 (14/737)	22.0	-137 – 74.4	0.66

Effectiveness of 3HP (MITT; 15 months)



Efficacy of 3HP (per protocol; 15 months)



No incident TB cases in participants fully adherent to 3HP until 9 months

Scriba TJ et al. Lancet Infect Dis. Jan 25, 2021

CORTIS

Impressions

- RISK11 identified HIV-negative adults in TB-endemic communities (but no other TB risk factors) in South Africa at increased risk of:
  - Prevalent TB
  - Incident TB
- The positive predictive value was relatively low (~5%; ~95% of RISK11+ persons did not have prevalent or incident TB)
- 3HP did not decrease the incidence of TB in RISK11+ persons
  - Related to the low positive predictive value of the test?
    - The positive predictive value of TST or IGRA for TB is also low, but it identifies persons in whom treatment of latent TB infection decreases TB incidence
  - Due to incipient TB? Because of Mtb reinfection?
    - 3HP was effective among HIV+/TST+ persons in Soweto, South Africa
      - Martinson N. N Engl J Med 2011

Conclusions

- Our understanding of “latency” is evolving, including appreciation of “incipient” TB
  - The treatment of latent TB infection may be different from treatment of persons with a positive transcriptomic signature score
    - Need greater detail re: transcriptomic signatures
- Clinical trial and operational data support use of 3-4 month rifamycin-based treatment of latent *M. tuberculosis* infection
  - Higher treatment completion rates and better tolerability compared to 6-9 months of isoniazid
- Ultra-short course regimens hold great promise

Conclusions

- Need to follow emerging data on the safety of treatment of latent TB infection in pregnancy
- Antiretroviral therapy and treatment of latent *M. tuberculosis* infection independently decrease TB risk in HIV-positive persons
- The optimal approach to confer long-term protection against developing TB among HIV+ persons in high TB incidence settings is unclear

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    - P30AI110527 (CFAR)
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