Preventive therapy
or
Treatment of latent TB

- Early evidence of efficacy: trials
- Adverse effects and adherence
- Population efficacy of screening and treatment
- Issues

Contents

Controlled Chemoprophylaxis Trials in Tuberculosis A General Review

S.H. FEREBEE

Research Section, Tuberculosis Program-NCDC, Bethesda, MD, USA

Table I. Characteristics of selected controlled trials of isoniazid prophylaxis

Trial	Sites	Number	Randomization unit	Admission period
United States Public Health Service Program				
Primary tuberculosis [10, 21]	Pediatric clinics 29 Continental US 1 Puerto Rico 1 Canada 1 Mexico	2,750	Individual	Jan. 1955–Dec. 1957
Contacts of known active cases [22]	Health department 5 Continental US	2,814	Household	Oct. 1956–April 1957
Contacts of new active cases [8]	Health departments 37 Continental US 19 Puerto Rico 1 Mexico	25,033	Household	Jan. 1957–Dec. 1959
Mental institutions [11]	33 hospitals 4 schools	27,924	Ward or building	Oct. 1957–May 1960
Alaskan villagers [4, 5]	30 villages Bethel area	6,275	Household	Dec. 1957–Oct. 1959
Inactive lesions [8]	Health departments 25 Continental US 1 Puerto Rico 1 Mexico	4,575	Individual	Sept. 1960–Oct. 1964
Danish Tuberculosis Index				
Greenland villagers [12, 14]	76 Western Greenland villages	8,081	Village	July 1956–Nov. 1967
Tuberculosis Chemotherapy and BCG Centre, Nairobi, Kenya				
Contacts of new active cases [7]	Rural area of northern Kenya	775	Household	1959–1961
Tunis Ministry of Health				
Community [25]	Suburb of Tunis City	15,910	City blocks	Mar. 1958–Aug. 1959
Yodogawa Christian Hospital, Osaka, Japan				
Contacts of known active cases [2]	Hospital clinic	2,238	Household	June 1958–
Royal Netherlands Navy				
Tuberculin converters [29]	Marine training camp	261	Individual	May 1960–
Quezon Institute, Manila, Republic of the Philippines				
Household contacts [6]	Hospital clinic	293	Household	July 1961–Dec. 1962
Hudson River Hospital, New York State				
Inactive lesions [16, 17]	Mental hospital	513	Individual	April 1958–Feb. 1964

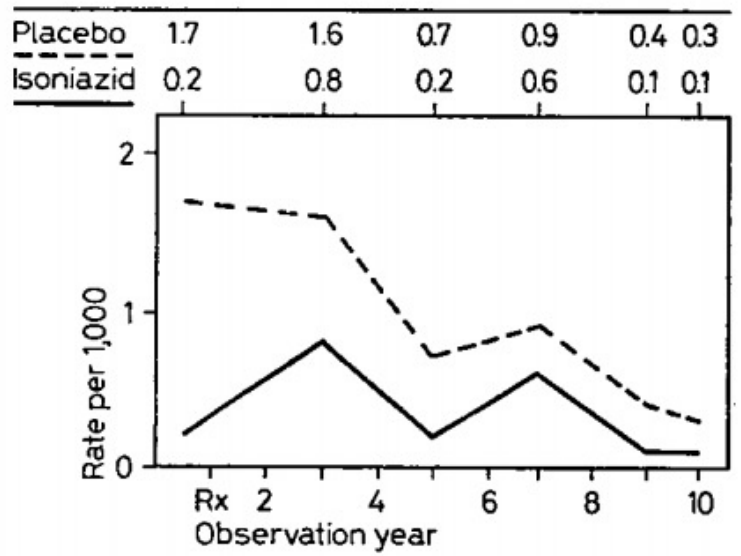


Fig. 6

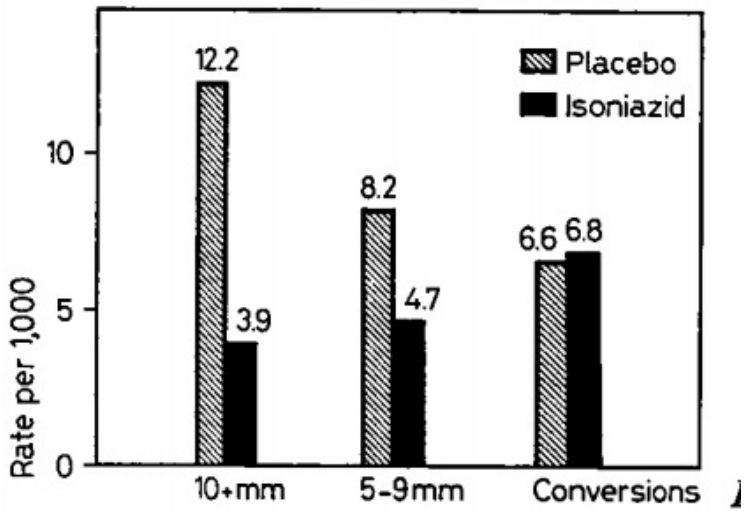


Fig. 6. Annual rate of new cases of pulmonary and extrapulmonary tuberculosis in USPHS trial in mental institutions, averaged for two-year periods after treatment.
Fig. 7. Ten-year morbidity from pulmonary and extrapulmonary tuberculosis among initial tuberculin reactors or converters during treatment in USPHS trial in mental institutions.

Table XXVII. Tuberculosis morbidity rates per 1,000 participants during treatment year and during total period of post-treatment observation

Trial	Population		Rate per 1,000				% change	
			During Rx		Post Rx		During	Post
	Placebo	Isoniazid	Placebo	Isoniazid	Placebo	Isoniazid	Rx	Rx
Primary	1,356	1,394	22.9	1.4	7.4	2.2	–93.8	– 70.3
Contacts								
USPHS	13,945	13,902	6.2	1.4	16.1	8.6	–77.4	– 46.6
Japan	1,096	1,142	10.0	7.0	–	–	–30.0	–
Kenya	376	399	74.5	15.0	10.6	7.5	–79.9	– 29.2
Manila	194	133	30.9	22.6	124.0	134.0	–26.9	+ 8.1
Netherlands	128	133	70.3	7.5	23.4	0.0	–89.3	–100.0
Mental institutions								
USPHS	12,326	12,884	1.7	0.2	7.4	3.4	–88.2	– 54.1
Inactive lesions								
USPHS								
Untreated	1,000	992	18.0	9.1	45.0	16.1	–49.4	– 64.2
Treated	1,060	1,061	12.3	10.4	20.8	17.0	–15.4	– 18.3
Hudson River	266	247	75.2	36.4	109.0	68.8	–51.6	– 36.9
Communities								
Alaska	3,017	3,047	15.2	5.3	30.8	13.8	–65.1	– 55.2
Greenland	3,907	4,174	18.7	12.7	64.0	44.3	–32.1	– 30.8
Tunisia	8,141	7,769	3.1[1]	2.3[1]	–	–	–25.8	–

[1]Positive bacteriology.

How long to treat with INH?

Bulletin of the World Health Organization, **60**: (4): 555 – 564 (1982)

Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial

INTERNATIONAL UNION AGAINST TUBERCULOSIS COMMITTEE ON PROPHYLAXIS[1]

Table 4. Efficacy of various durations of isoniazid therapy compared with placebo: all assigned participants

Regimen	No. of participants entering regimen	Cumulative no. of cases	5-Year incidence[a]	Percentage reduction	Relative risk
Placebo	6990	97[b]	14.3	0	4.0
12-I	6956	76	11.3	21	3.1
24-I	6965	34[b]	5.0	65	1.4
52-I	6919	24[c]	3.6	75	1.0

Table 3. Risk of hepatitis by quarter (per 1000 persons)

Weeks	Risk by quarter			Cumulative risk			Risk reduction (cases prevented per 1000 persons)
	Placebo (P)	Isoniazid (I)	Excess (I-P)	Placebo (P)	Isoniazid (I)	Excess (I-P)	
1 – 12	0.7	3.2	2.5	0.7	3.2	2.5	2.7
13 – 24	0.5	1.6	1.1	1.2	4.8	3.6	1.6
25 – 36	0.0	0.8	0.8	1.2	5.6	4.4	0.8
37 – 52	0.0	0.8	0.8	1.2	6.4	5.2	standard

Table 6. Efficacy of various durations of isoniazid therapy compared with placebo for "completer-compliers"

Regimen	No. of participants	No. of cases	Incidence[a]	Percentage reduction	Relative risk
Placebo	5616	83	15.0	0	13.6
12-I	6039	61	10.4	31	9.4
24-I	5437	25	4.7	69	4.3
52-I	4543	5	1.1	93	1.0

[a] Culture-positive tuberculosis per 1000 persons at risk.

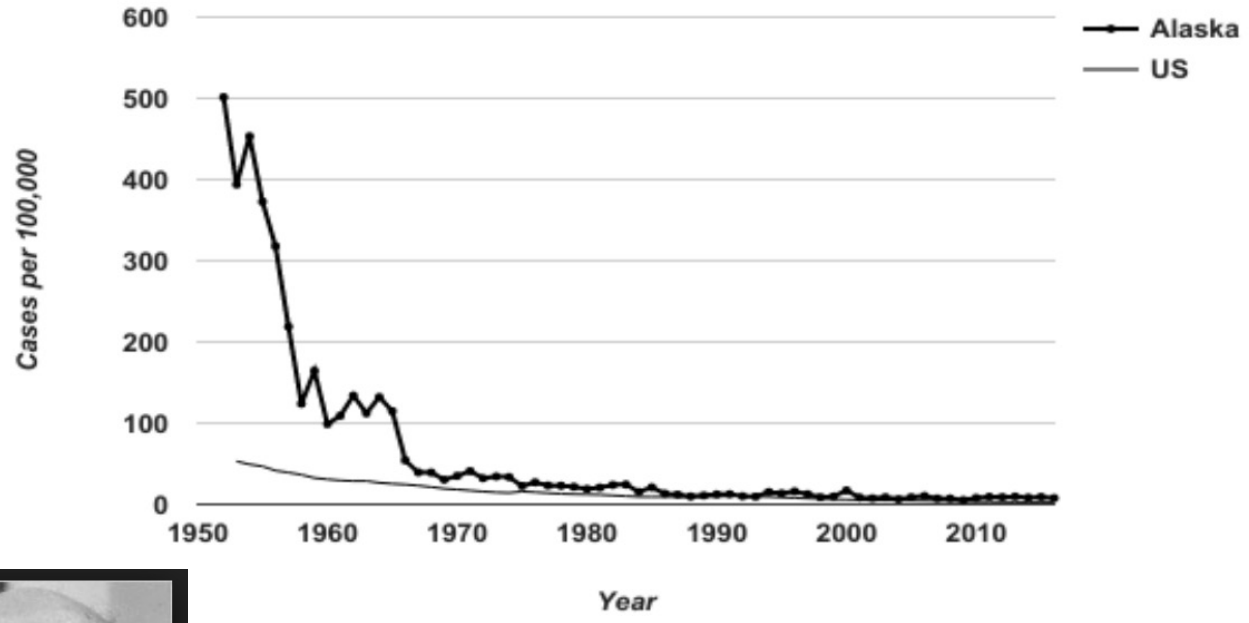
TABLE 1

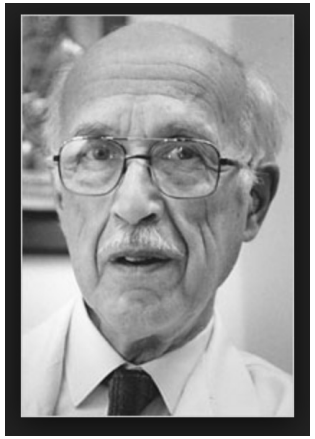
TUBERCULOSIS CASES AND CASE RATES FOR THE PERIOD FROM 1964 THROUGH 1977 AMONG PARTICIPANTS IN 2 ISONIAZID PROPHYLAXIS PROGRAMS, BY MEDICATION ASSIGNED IN THE FIRST PROGRAM AND BY PERCENTAGE OF ANNUAL DOSE OF MEDICATION TAKEN IN EACH PROGRAM

Annual Dose of Isoniazid Taken in Second Program (%)	Placebo in First Program			Isoniazid in First Program			Significance of Difference between Placebo and Isoniazid Rates
	Population	Cases (*no.*)	Cases (%)	Population	Cases (*no.*)	Cases (%)	
Took < 40 per cent of annual dose in first program							
0–39	208	8	3.85	191	4	2.09	P > 0.05
40–69	82	1	1.22	103	1	0.97	P > 0.05
70+	97	3	3.09	88	2	2.27	P > 0.05
Total	387	12	3.10	382	7	1.83	P > 0.05
Took 40 to 69 per cent of annual dose in first program							
0–39	210	5	2.38	210	3	1.43	P > 0.05
40–69	140	4	2.86	160	0	—	P > 0.05
70+	131	4	3.05	136	1	0.74	P > 0.05
Total	481	13	2.70	506	4	0.79	P < 0.05
Took 70 per cent or more of annual dose in first program							
0–39	513	28	5.46	572	10	1.75	P < 0.01
40–69	420	10	2.38	425	4	0.94	P > 0.05
70+	617	4	0.65	636	8	1.26	P > 0.05
Total	1,550	42	2.71	1,633	22	1.35	P < 0.01
Total for each medication group in first program							
0–39	931	41	4.40	973	17	1.75	P < 0.01
40–69	642	15	2.34	688	5	0.73	P < 0.05
70+	845	11	1.30	860	11	1.28	P > 0.05
Total	2,418	67	2.77	2,521	33	1.31	P < 0.001

TB rates decline in context of mass screening and treatment of latent TB treatment

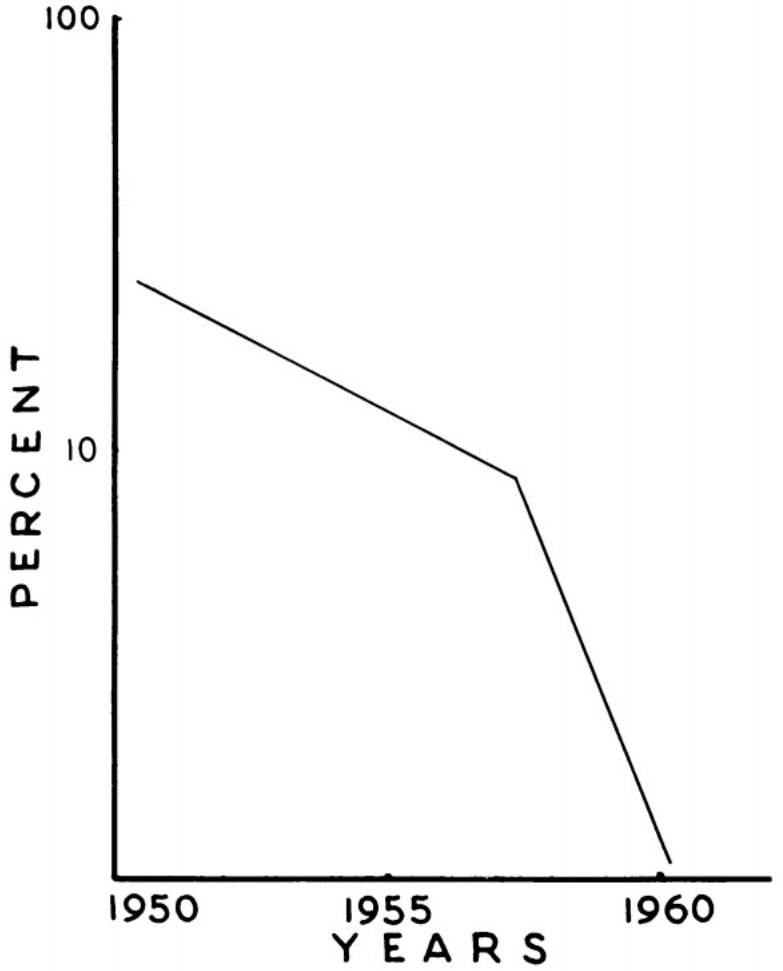
Figure 1. Alaska and the United States TB Incidence Rates, 1952–2016





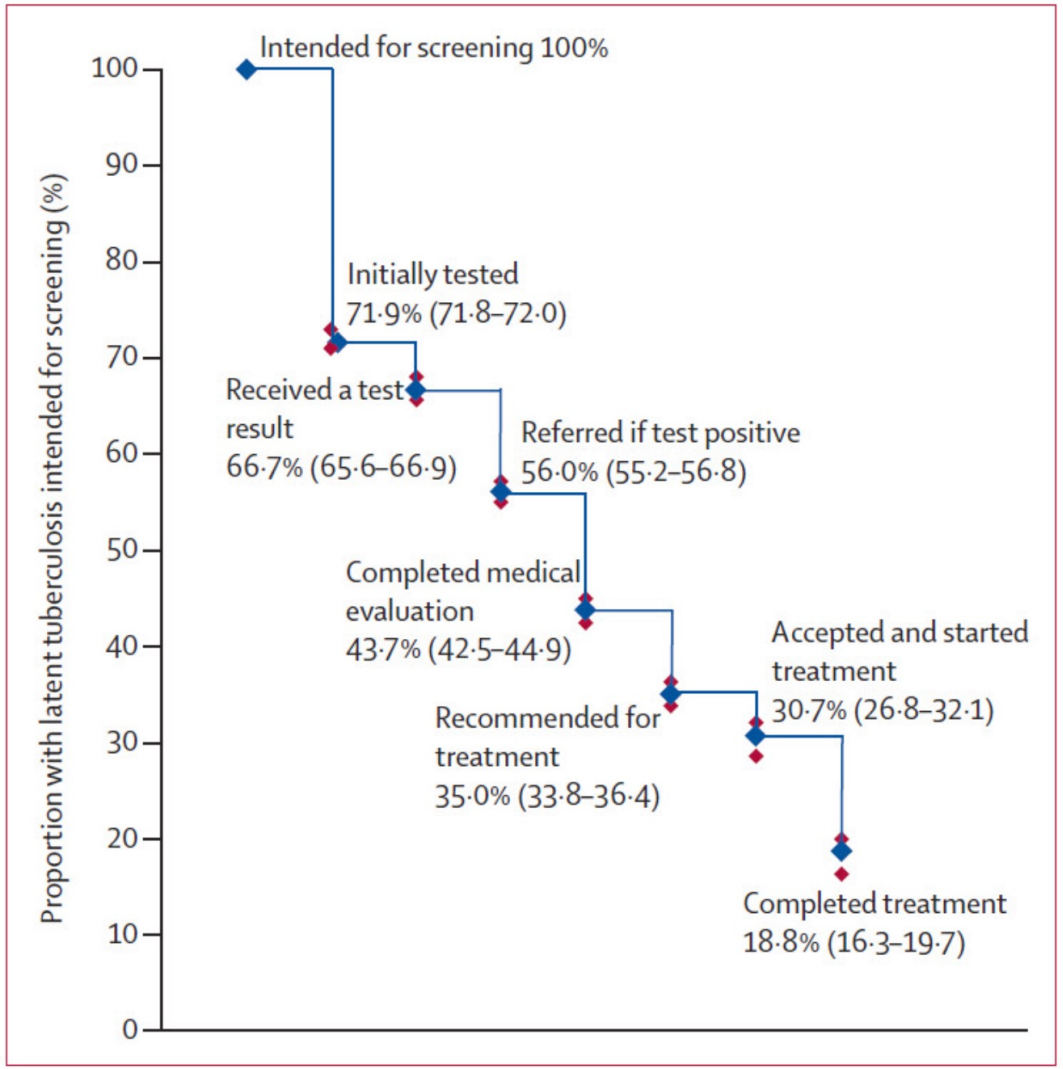
George Comstock

Figure 3. Average rate of decline in tuberculosis infection rates among Eskimo children 0–3 years of age in two periods: 1949–57 and 1957–60



Vol. 76, No. 1, January 1961

So what is the issue?



Source: Alsdurf H et al. Lancet Infect Dis 2016

Adherence

- Adherence ranges between 2—80%
- Causes of poor adherence
  - SES, homelessness, stigma, fear of side effects, lack of HCP support

Table 2 Adherence to antituberculosis treatment and preventive chemotherapy, and outcome according to preventive chemotherapy adherence

	Adherence (%)			
	Not given	Very poor	Poor	Reasonable
Treatment regimen				
TB treatment (n=38)	0	1 (3)	3 (8)	34 (89)
Preventive chemotherapy 6H (n=236)	56 (24)	130 (55)	14 (6)	36 (15)
Outcome				
Preventive chemotherapy group TB within 6/12	2/56 (4)	4/130 (3)	0	0

Very poor: received <2 months of therapy.

Poor: received 2–4 months of therapy.

Reasonable: received >4 months of therapy.

Hepatotoxicity

- 3 deaths in 1972 in PHS in PHS study in Baltimore = 55/100k
- In Union study in Eastern Europe = 14/100k with 5 X increase in hepatitis
- CDC study in US from 1970-1992: 60 deaths = 4.2/100k (7/100k in people completing treatment)
- Risk factors
  - Female
  - Black or Hispanic
  - <35 years old

Isoniazid-Related Fatal Hepatitis

PETER S. MILLARD, MD, PhD, *Bangor, Maine;*
TIMOTHY C. WILCOSKY, PhD, *and* SUSAN J. READE-CHRISTOPHER, PhD, *Research Triangle Park, North Carolina;*
and DAVID J. WEBER, MD, MPH, *Chapel Hill, North Carolina*

TABLE 1.—*Age and Sex of Probable and Possible Cases of Fatal Isoniazid Hepatitis, 1970 to 1992*

Sex	Age, yr	Probable Cases, No.	Possible Cases, No.	Total Cases, No. (%)
Female	0-14	1	1	2 (4)
	15-34	10	2	12 (24)
	35-64	16	14	30 (60)
	65+	5	1	6 (12)
	Total female	32	18	50 (100)
Male	0-14	2	0	2 (17)
	15-34	1	2	3 (25)
	35-64	4	2	6 (50)
	65+	0	1	1 (8)
	Total male	7	5	12 (100)

TABLE 2.—*Race-Ethnicity of Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Race-Ethnicity	Probable Cases, No.	Possible Cases, No.	Total Cases, No. (%)
White, non–Hispanic	7	5	12 (19)
Black, non–Hispanic	16	15	31 (50)
Hispanic	16	2	18 (29)
Asian	0	1	1 (2)
Total	39	23	62 (100)

TABLE 4.—*Appropriateness of Isoniazid Preventive Therapy Among Combined Probable and Possible Cases of Fatal Isoniazid Hepatitis*

Treatment Period	Appropriate Therapy, No.	Inappropriate Therapy, No.	Insufficient Data, No.
1970	1	0	0
1971-1973	3	0	15*
1974-1983	20	5	4
1984-1986	5	0	1
1987-1990	8	0	0

*In 13 cases, participants were from Maryland in the 1971-1973 US Public Health Service study, and data were not available concerning indications for isoniazid prophylaxis.

March 17, 1999

Hepatotoxicity Associated With Isoniazid Preventive Therapy

A 7-Year Survey From a Public Health Tuberculosis Clinic

Charles M. Nolan, MD; Stefan V. Goldberg, MD; Susan E. Buskin, PhD

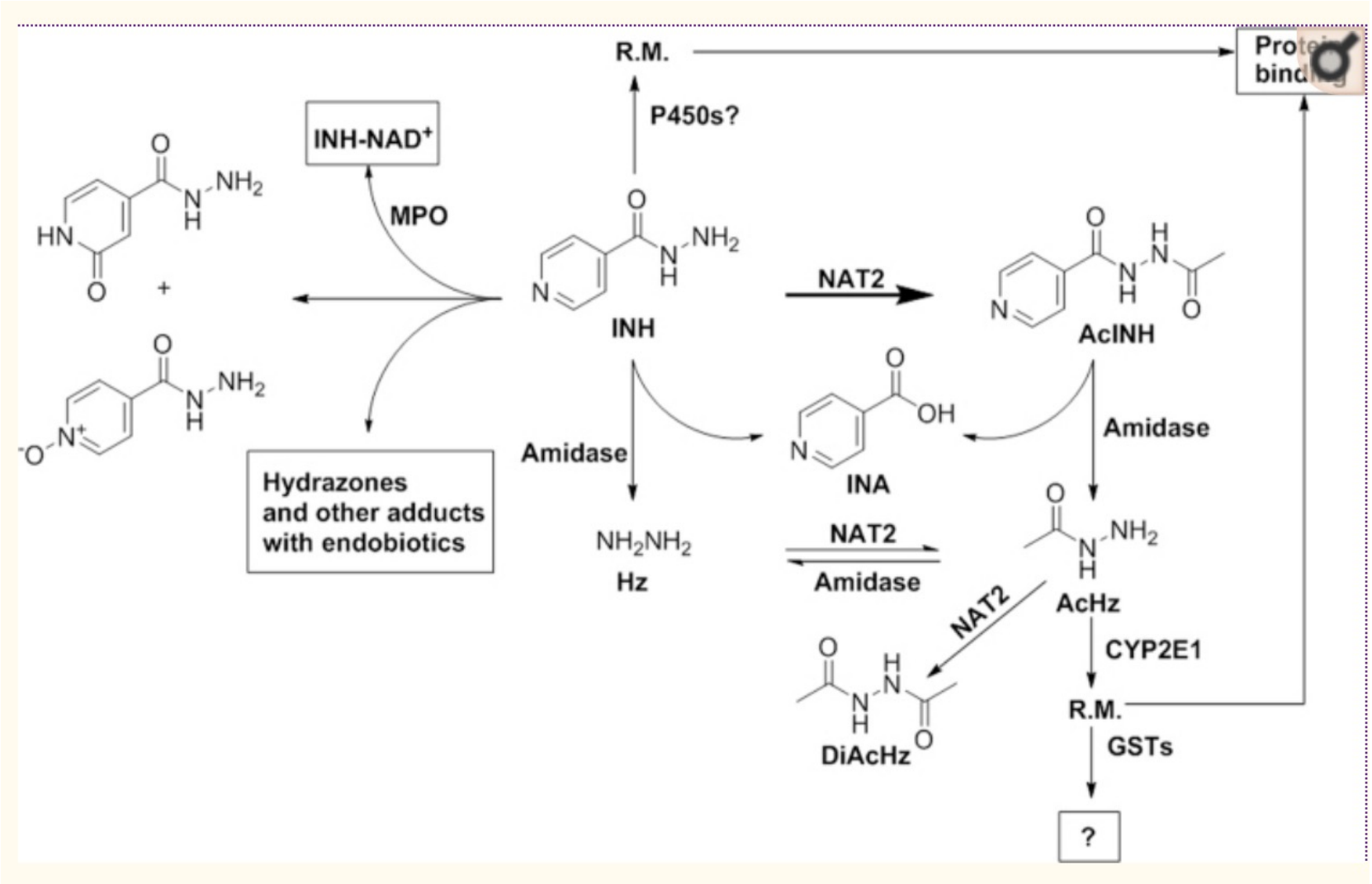
JAMA. 1999;281(11):1014-1018. doi:10.1001/jama.281.11.1014

Table 2. Rate of Hepatotoxicity in Persons Receiving Isoniazid Preventive Therapy and Treatment for Active Tuberculosis, 1989-1995

	Cases of Hepatotoxicity, No.	Rate of Hepatotoxicity, %	
		Persons Starting Therapy	Persons Completing Therapy*
Isoniazid preventive therapy (n = 11 141)†	11	0.10‡	0.15‡
Treatment for active tuberculosis (n = 1427)†	15	1.05‡	1.25‡

*Denominators for rate determinations: 11 141 × 0.64 and 1427 × 0.84 (see "Methods" section).
†Number of persons starting therapy.
‡$P<.001$.

Acetylator status: unclear associations



INH and alcohol

- Alcohol
  - Potentiates liver injury with INH uses
  - Evokes and “intolerance” response similar to but by a different mechanism than disulfiram.

Target populations

- HHCs
- HIV infected patients
- Other high risk groups: homeless, imprisoned, RA patients on T-cell suppressing drugs, DM?

- Policy issue: do people need to be TST/IGRA positive to be started?

Risk of TB in HHCs

- Ranges from 1-5% per year after exposure depending on age and previous infection status.
- In our study, IPT reduced risk by 70% in all age groups.
- Most often recommended for <5s, in some cases <15 or 19.

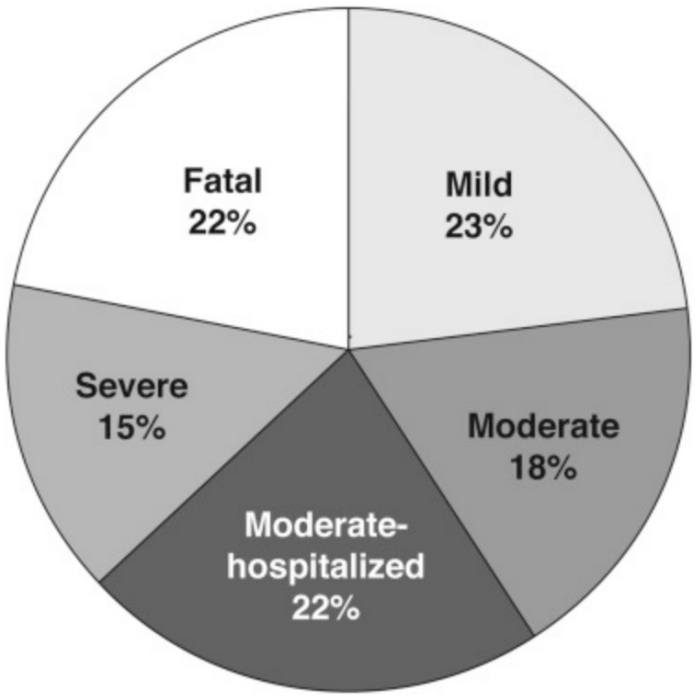
Why not treat all infected people?

- Impractical if 1/3 world infected
- As risk declines, trade-off with hepatotoxicity less favorable.
- Frequent false positives with TST (BCG, atypicals)
- Cost of IGRA, monitoring of treatment, etc.

But many cases are under-reported.

Drug induced liver injury network reports 60 cases between 20014 and 2013, of whom 13 died or had liver transplant. Only one case had been counted by CDC. Many had not been stopped following existing ATS guidelines.

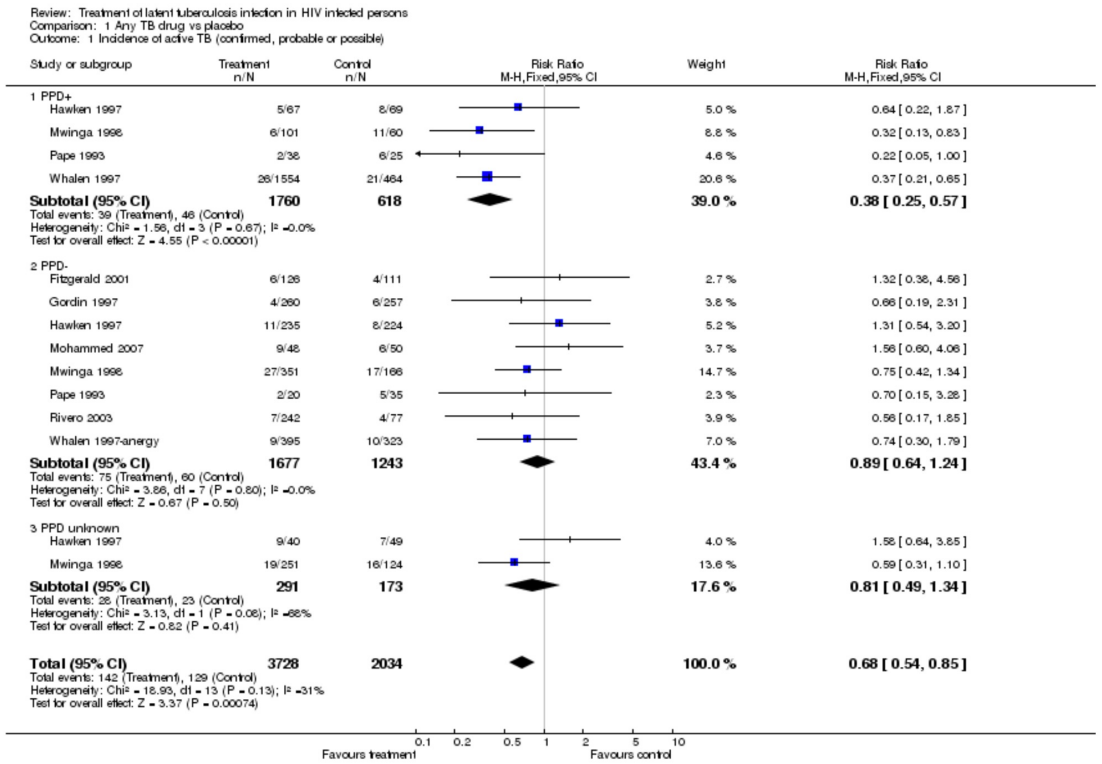
Female pattern persist but not racial pattern.



Under-reporting and Poor Adherence to Monitoring Guidelines for Severe Cases of Isoniazid Hepatotoxicity

Paul H. Hayashi, MD, MPH,[1] Robert J. Fontana, MD,[2] Naga P. Chalasani, MD,[3] Andrew A. Stolz, MD,[4] Jay A. Talwalker, MD,[5] Victor J. Navarro, MD,[6] William M. Lee, MD,[7] Timothy J. Davern, MD,[8] David E. Kleiner, MD, PhD,[9] Jiezhun Gu, PhD,[10] and Jay H. Hoofnagle, MD[11], for the U.S. DILIN Investigators

HIV: Cochrane review



Conclusions

12 trials reviewed including 8578 people

In all comers, RR of TB = .68

(so efficacy .32)

In TST+, RR = .38

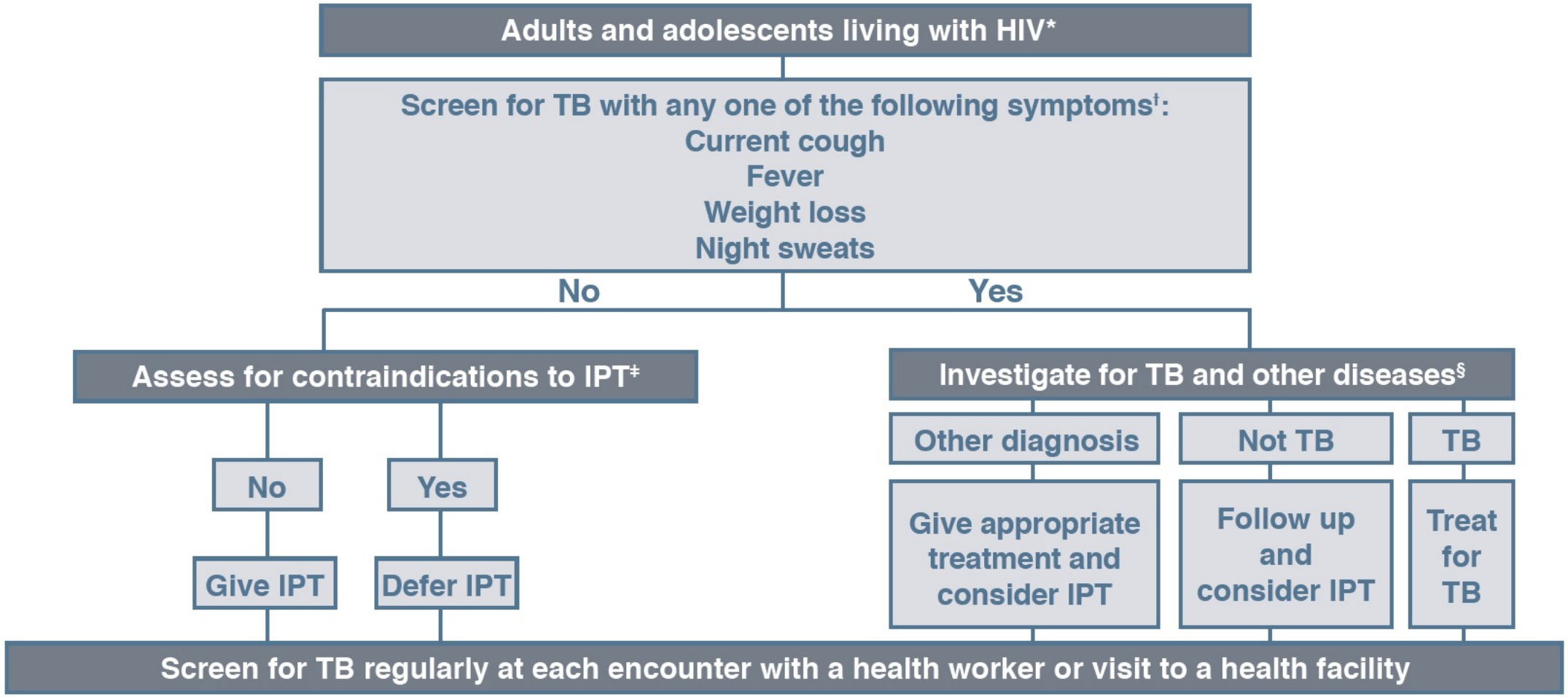
In TST – RR = .89

Mortality benefit in TST+ and -

Possible issues

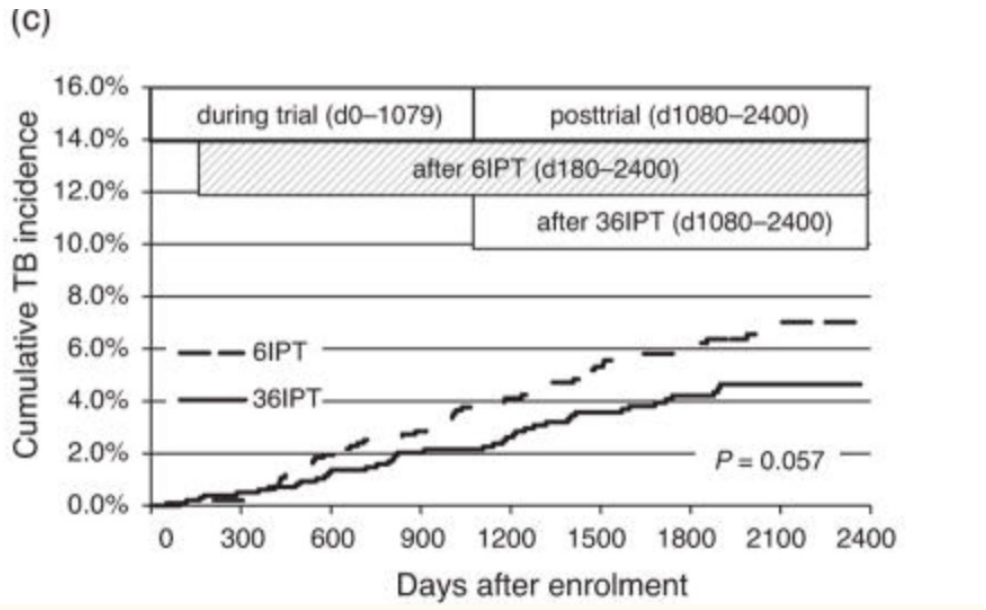
- TST unreliable in HIV
- Active TB difficult to diagnose in HIV so at risk for treating TB with one drug. Algorithms involve screening for active TB.
- Interactions with HIV drugs or other meds.
- Duration of treatment
- Population impact

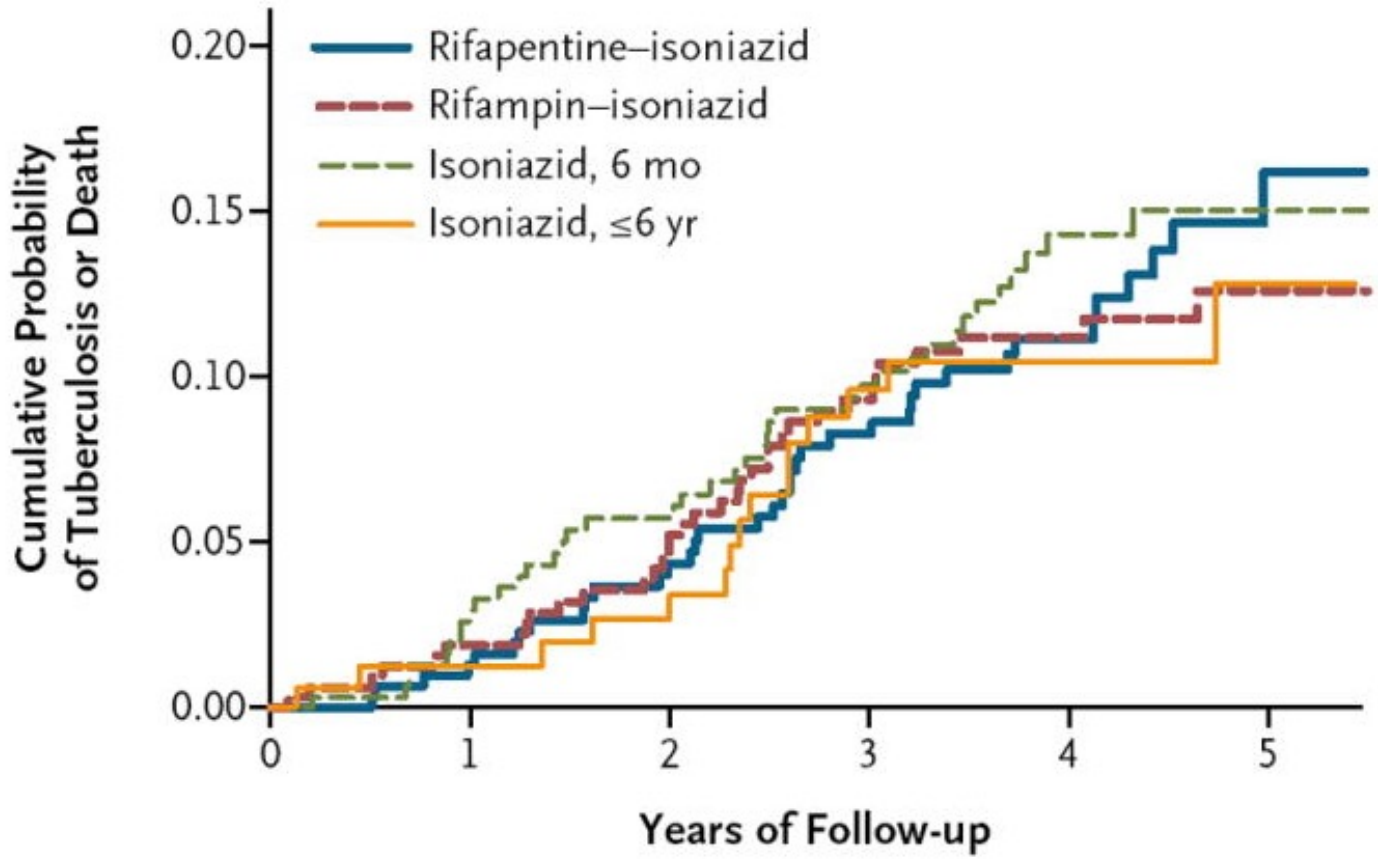
2.2.7 Figure 1. Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



Duration: Botswana experience

- 6 months IPT benefit lost 6-19 months after therapy
- 3 years IPT reduced TB incidence by 43% in all compared to 6 months.
  - 74% efficacy in TST positive vis a vis TB
  - 68% efficacy in mortality in TST positives
- Post-trial benefits

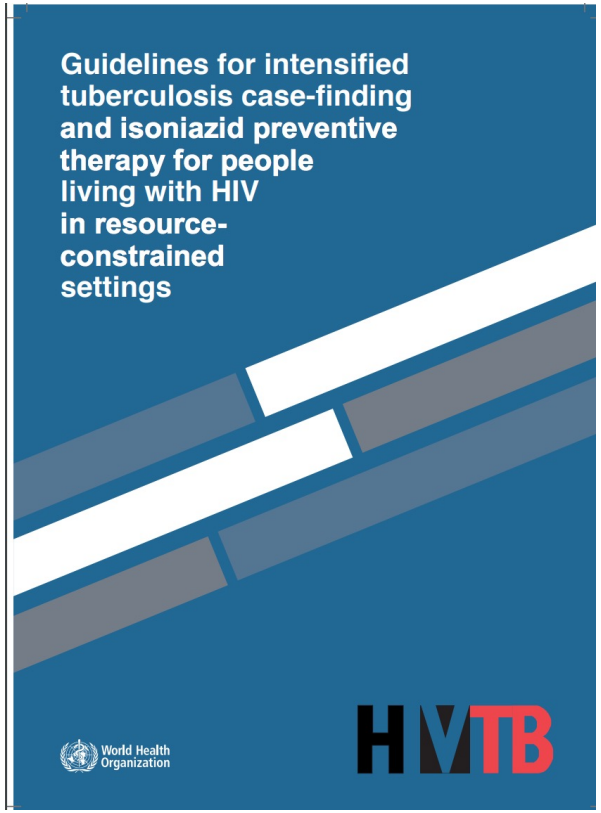




No. at Risk

Rifapentine–isoniazid	326	299	275	249	160	52
Rifampin–isoniazid	327	301	284	252	162	56
Isoniazid, 6 mo	327	289	260	238	145	49
Isoniazid, ≤6 yr	164	144	131	109	73	26

Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11–20.



Key recommendations

1. Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT.

   Strong recommendation, moderate quality of evidence[1]

2. Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.

   Strong recommendation, moderate quality of evidence

3. Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least six months of IPT as part of a comprehensive package of HIV care. IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

   Strong recommendation, high quality of evidence

4. Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT.[2] IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

   Conditional recommendation, moderate quality of evidence[3]

5. TST is not a requirement for initiating IPT in people living with HIV.

   Strong recommendation, moderate quality of evidence

6. People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.

   Strong recommendation, high quality of evidence

7 Providing IPT to people living with HIV does not increase the risk of developing isoniazid (INH)-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

Strong recommendation, moderate quality of evidence

8 Children living with HIV who do not have poor weight gain,[4] fever or current cough are unlikely to have active TB.

Strong recommendation, low quality of evidence

9 Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.

Strong recommendation, low quality of evidence

10 Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.

Strong recommendation, moderate quality of evidence

11 In children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.

Strong recommendation, low quality of evidence

12 All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.

Conditional recommendation, low quality of evidence

Resistance

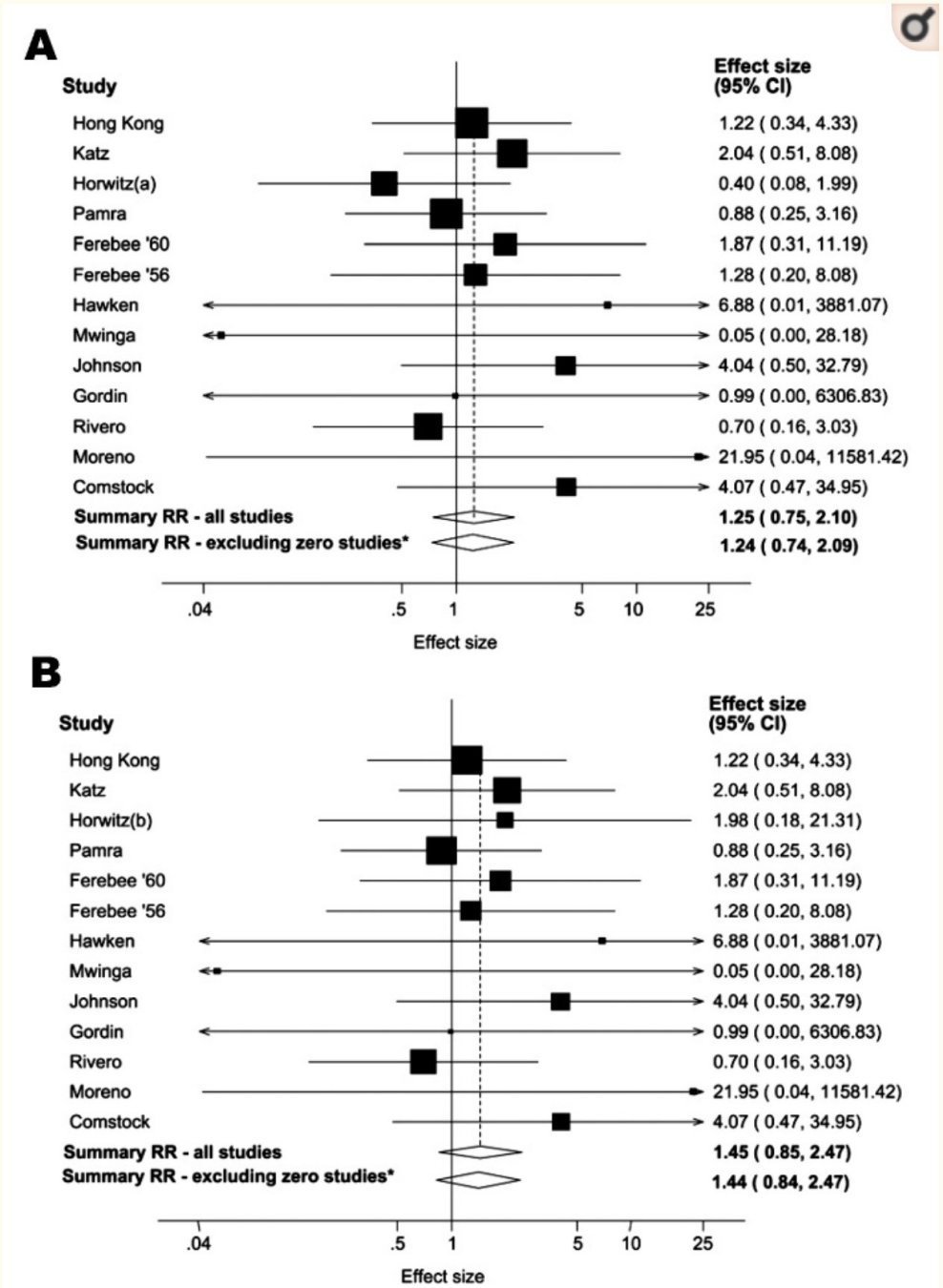
- Does widespread use of single drug increase INH resistance?

Emerg Infect Dis. 2006 May; 12(5): 744–751.
doi: 10.3201/eid1205.050681
PMCID: PMC3374455
PMID: 16704830

Isoniazid Preventive Therapy and Risk for Resistant Tuberculosis

Maria Elvira Balcells,[*,1] Sara L. Thomas,[*] Peter Godfrey-Faussett,[*] and Alison D. Grant[*]

- Depends on one's definition of resistance. Neither Definition A or B is currently used.



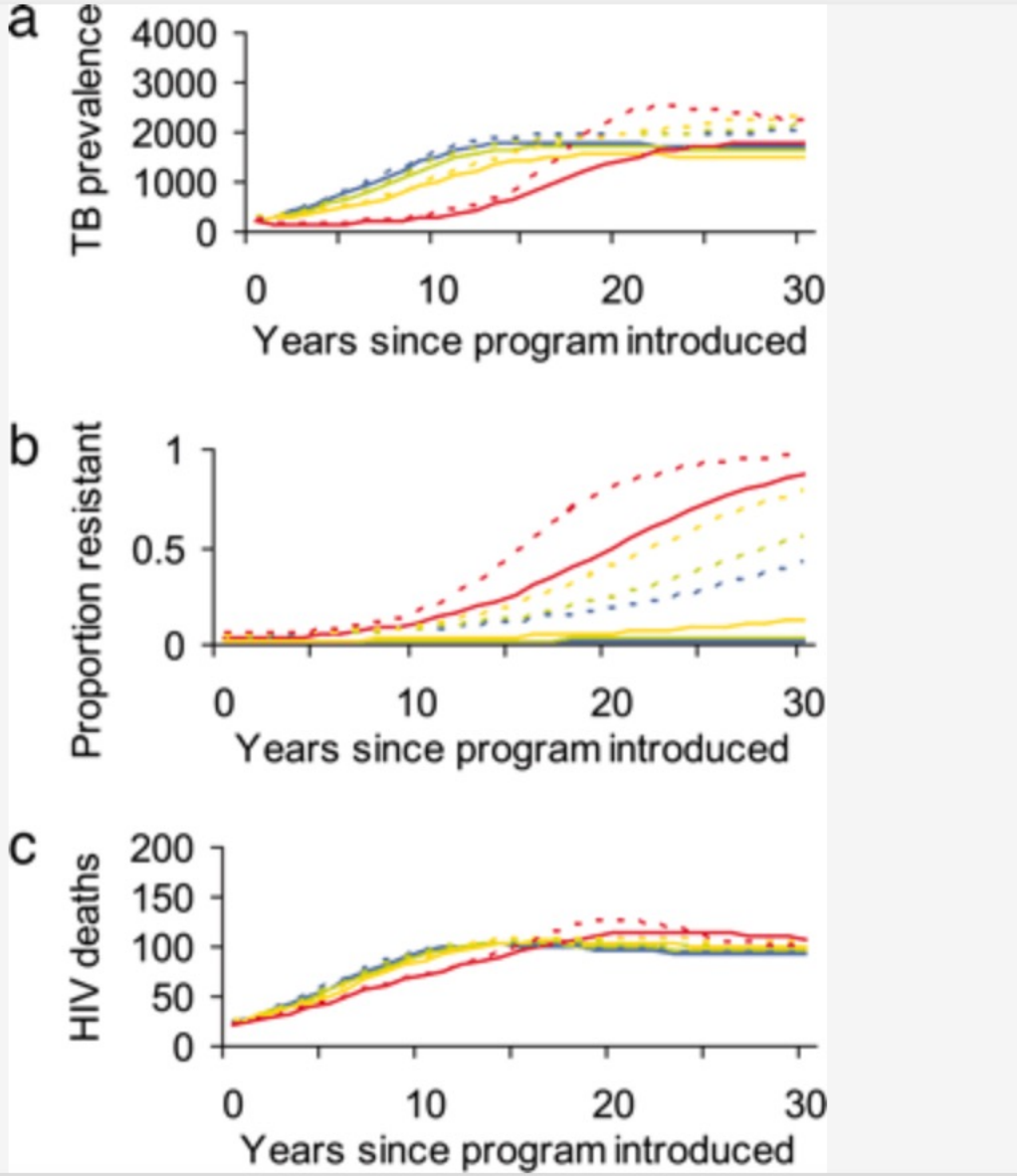
Beneficial and perverse effects of isoniazid preventive therapy for latent tuberculosis infection in HIV–tuberculosis coinfected populations

Ted Cohen, Marc Lipsitch, Rochelle P. Walensky, and Megan Murray

PNAS May 2, 2006 103 (18) 7042-7047; https://doi.org/10.1073/pnas.0600349103

Table 1.
Baseline epidemiologic measures and 5-year impact of IPT

Outcome	Baseline*	Five-year projections under varying IPT coverage			
		0%	33%	66%	99%
TB prevalence per 100,000 people	252	779	675	496	190
Proportion of population with latent infection, %	34.5	37.4	34.1	28.6	19.8
Proportion of TB that is drug-resistant, %	4.0	4.9	5.3	6.4	12.7
Prevalence of drug-resistant TB per 100,000 people	10	38	36	32	24
Proportion of population HIV-infected, %	16.3	33.5	34.4	36.1	39.6
Percent reduction in cumulative HIV deaths (years 0–5) attributable to IPT, %	—	Reference †	3.5	9.6	21.2



New regimens

ORIGINAL ARTICLE

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

Dick Menzies, M.D., Menonli Adjobimey, M.D., M.P.H., Rovina Ruslami, M.D., Ph.D., Anete Trajman, M.D., Ph.D., Oumou Sow, M.D., Heejin Kim, M.D., Joseph Obeng Baah, M.D., Guy B. Marks, Ph.D., F.R.A.C.P., Richard Long, M.D., Vernon Hoeppner, M.D., Kevin Elwood, M.D., Hamdan Al-Jahdali, M.D., Martin Gninafon, M.D., Lika Apriani, M.D., Raspati C. Koesoemadinata, M.D., Afranio Kritski, M.D., Ph.D., Valeria Rolla, M.D., Ph.D., Boubacar Bah, M.D., Alioune Camara, M.D., Ph.D., Isaac Boakye, B.Sc., Victoria J. Cook, M.D., Hazel Goldberg, M.B., B.S., Chantal Valiquette, C.N.A., Karen Hornby, M.Sc., Marie-Josée Dion, B.Sc., Pei-Zhi Li, M.Sc., Philip C. Hill, M.D., M.P.H., Kevin Schwartzman, M.D., M.P.H., and Andrea Benedetti, Ph.D.

ORIGINAL ARTICLE

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., et al., for the TB Trials Consortium PREVENT TB Study Team*

Current promising regimens

- 4R
  - Non-inferior
  - Less toxicity than 6-9 months INH
- 3HP
  - Non-inferior
  - Weekly dosing
  - Well tolerated in non-HIV
  - May interact with dolutegravir
  - High cost (45$ for rifapentine)
- 1HP
  - Non-inferior
  - Not yet published but presented at CROI
  - Daily use for one month often preferable

Less promising regimens

- Adding FLQ
  - Study in liver transplant patients that compared INH to FLQ stopped due to high rates tenosynovitis in FLQ recipients.
  - Two additional studies in MDR exposed people (Vietnam V-Quin) and South Africa TB-CHAMP) pending
- Adding PZA
  - Unacceptable toxicity

Will shorter regimens improve adherence?

Regimen and manner of administration	9H, SAT	57 (8.5)	30 (52.6)	27 (47.4)	Ref
	9H, ESAT	17 (2.5)	13 (76.5)	4 (23.5)	2.9 (0.9–10.1)
	9H, DOPT	178 (26.7)	158 (88.8)	20 (11.2)	7.1 (3.5–14.3)
	4R, SAT	79 (11.8)	66 (83.5)	13 (16.5)	4.6 (2.1–10.1)
	4R, ESAT	18 (2.7)	16 (88.9)	2 (11.1)	7.2 (1.5–34.2)
	4R, DOPT	35 (5.2)	34 (97.1)	1 (2.9)	30.6 (3.9–239)
	3HP	283 (42.4)	274 (96.8)	9 (3.2)	27.4 (11.8–63.7)

SAT = self admin
ESAT = enhanced self admin
DOPT = directly observed

Big picture issues

- Why does IPT/ LTBI treatment have so little population benefit?
  - Children and HIV infected least likely to transmit TB
- Trade-off for mass screening and treatment
  - Should we screen for TB infection or treat all?
  - Are risks unacceptable in people at low risk of TB progression?
  - Will we increase drug resistance over time?

Route forward

- Who to target?
- Adverse events in low risk people
- MDA?
- What regimens
  - Can new drugs be included?
- Duration of treatment
- Policies based on levels of TB burden