
THE UNIVERSITY of ADELAIDE
PREVENTING TB IN PEOPLE WITH HIV:
NO MORE EXCUSES
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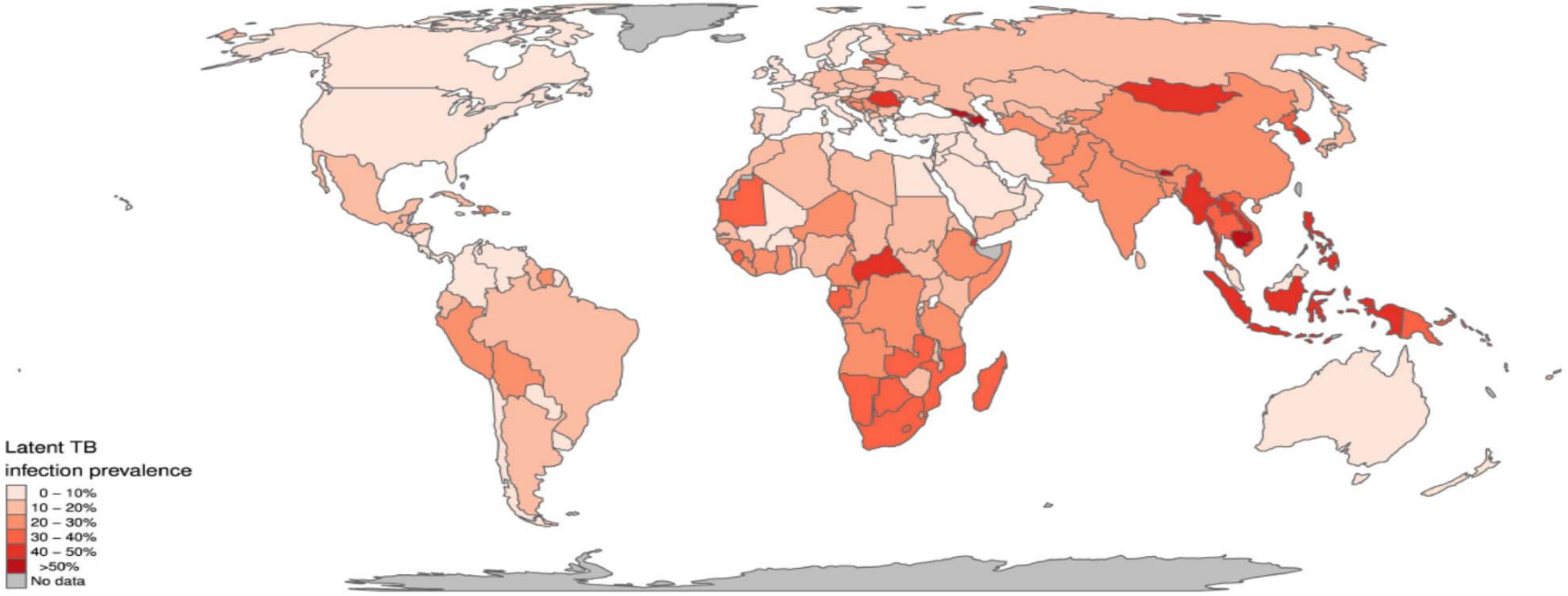
20-1-2018
seek LIGHT

Estimated prevalence of latent tuberculosis infection by country (estimated global prevalence 23%)

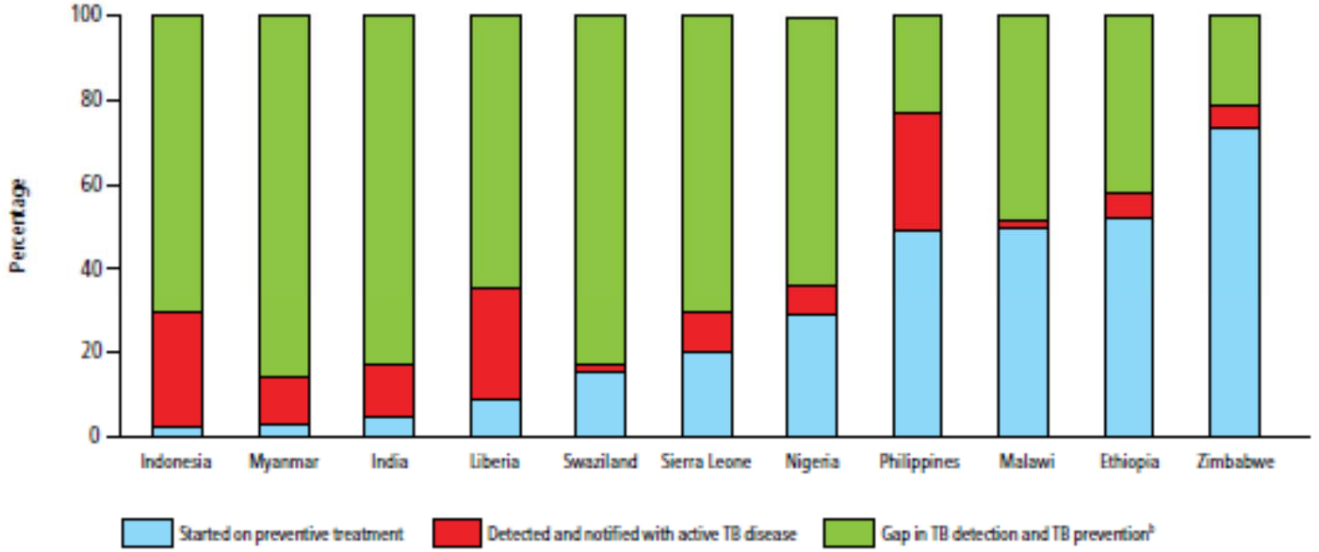


Houben and Dodd. PLoS Med 2016;13(10):e1002152

Global TB Report WHO 2017

FIG. 5.3

Gaps in TB preventive treatment for people who were newly enrolled in HIV care in 2016, selected countries[a]

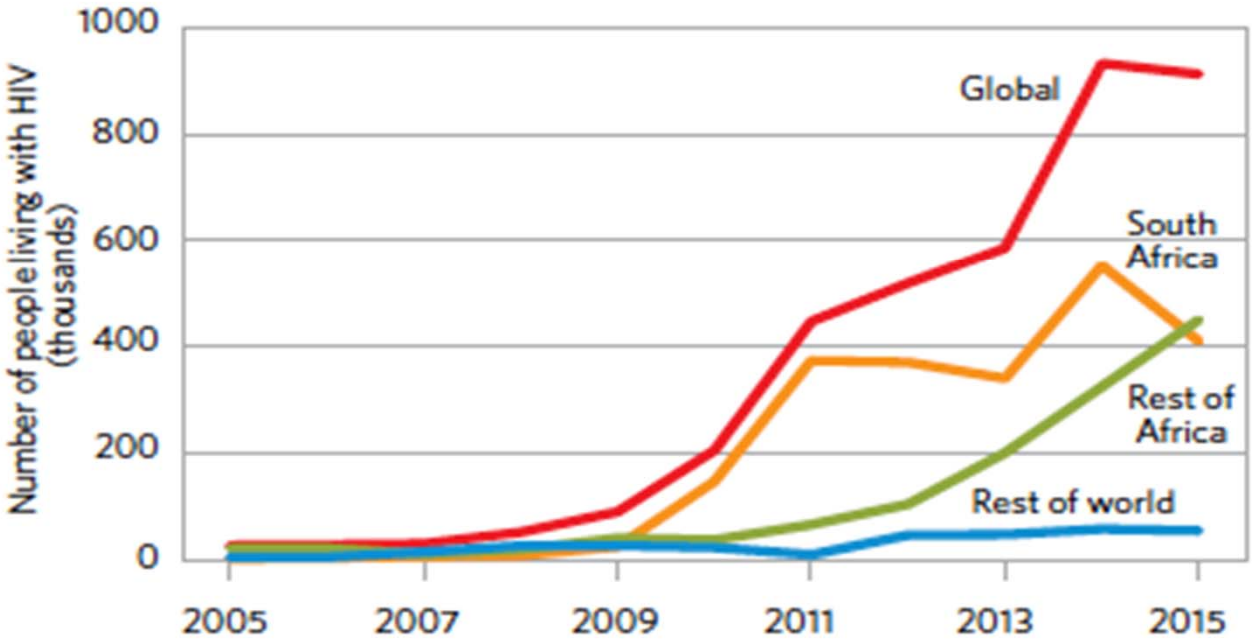


[a] The selected countries are high TB or TB/HIV burden countries that reported on all three of the following: the number of people newly enrolled in HIV care; the number of TB cases detected among people newly enrolled on HIV care; and the number of people newly enrolled on HIV care who were started on TB preventive treatment. In high TB burden countries, testing for LTBI is not a requirement for initiation of TB preventive treatment, such that all those without active TB disease are eligible for TB preventive treatment.

[b] The gap represents people living with HIV who should have undergone complete evaluation for TB disease or TB preventive treatment.

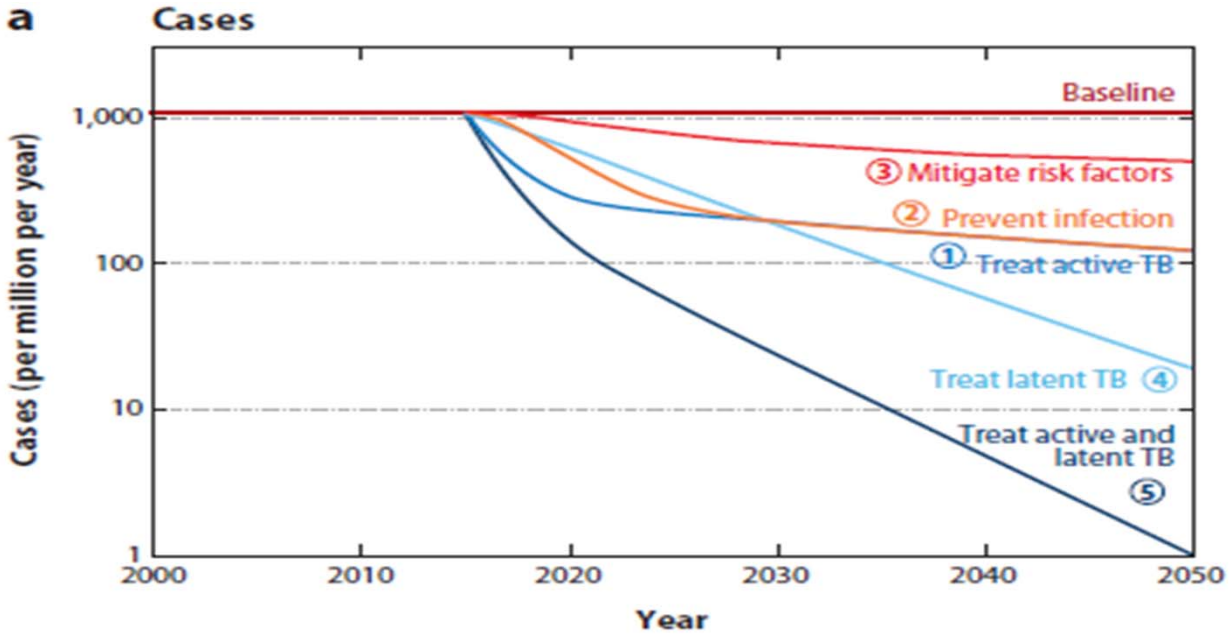
Poor Global Uptake of IPT for PLHIV

Provision of TB preventive treatment to people living with HIV, 2005–2015[a]



WHO. Global TB Report, 2016

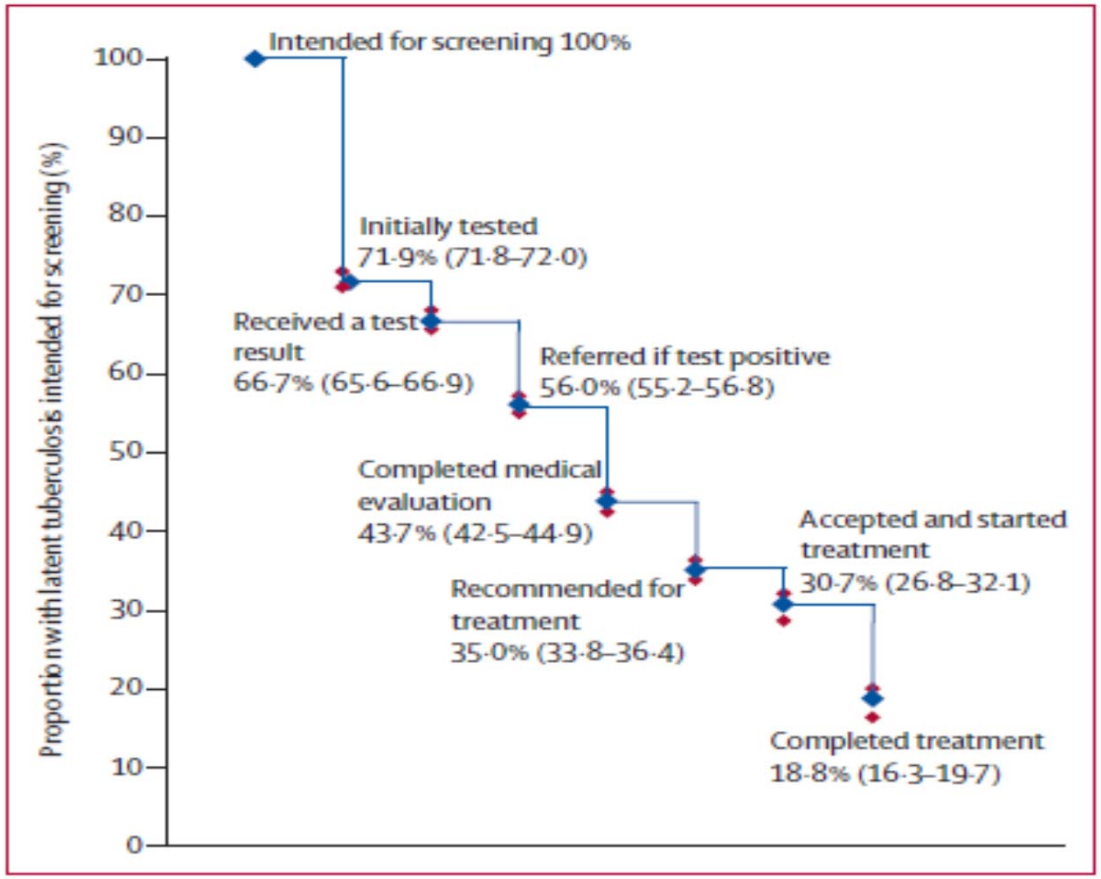
Modeled approaches to reaching TB elimination



IPT is a necessary component if we are to eliminate TB

Dye, et al., Ann Rev Publ Health 2013

Cascade of Care for Latent LTBI Treatment

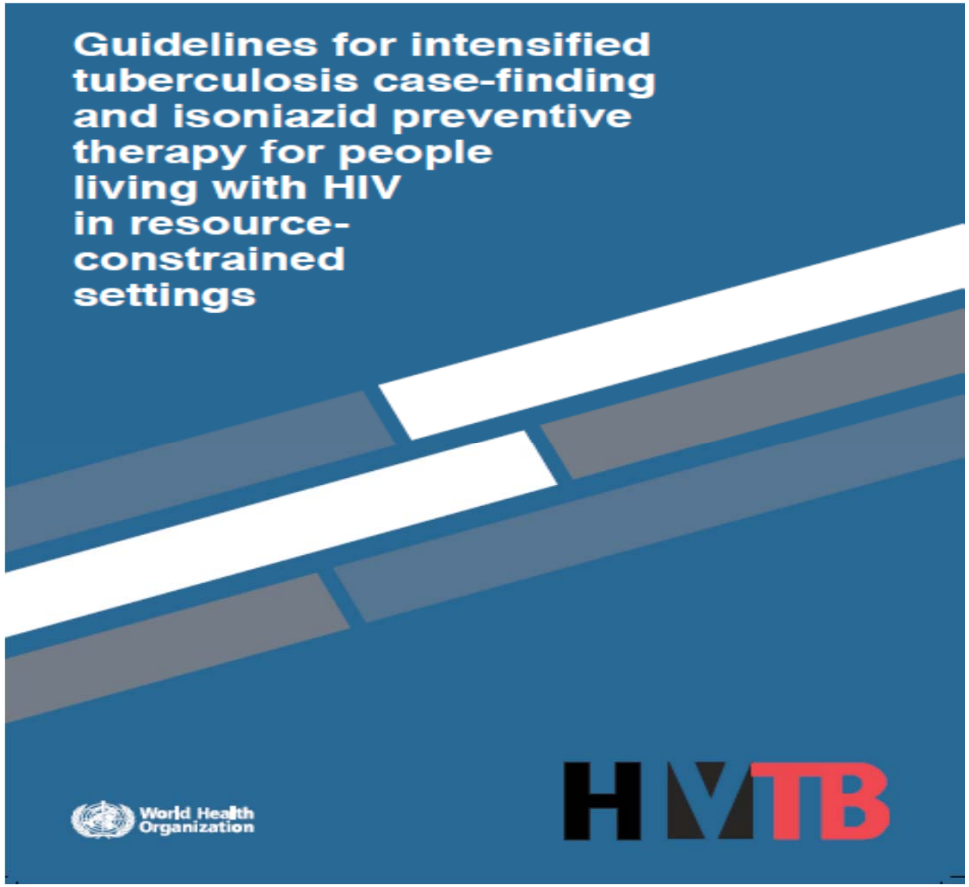


31% start PT

18.8% complete PT

Alsdurf et al., Lancet ID 2016

IPT in PLHIV: NO MORE EXCUSES



WHO 2011

IPT in PLHIV: NO MORE EXCUSES

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]

WHO 2011

IPT in PLHIV: NO MORE EXCUSES

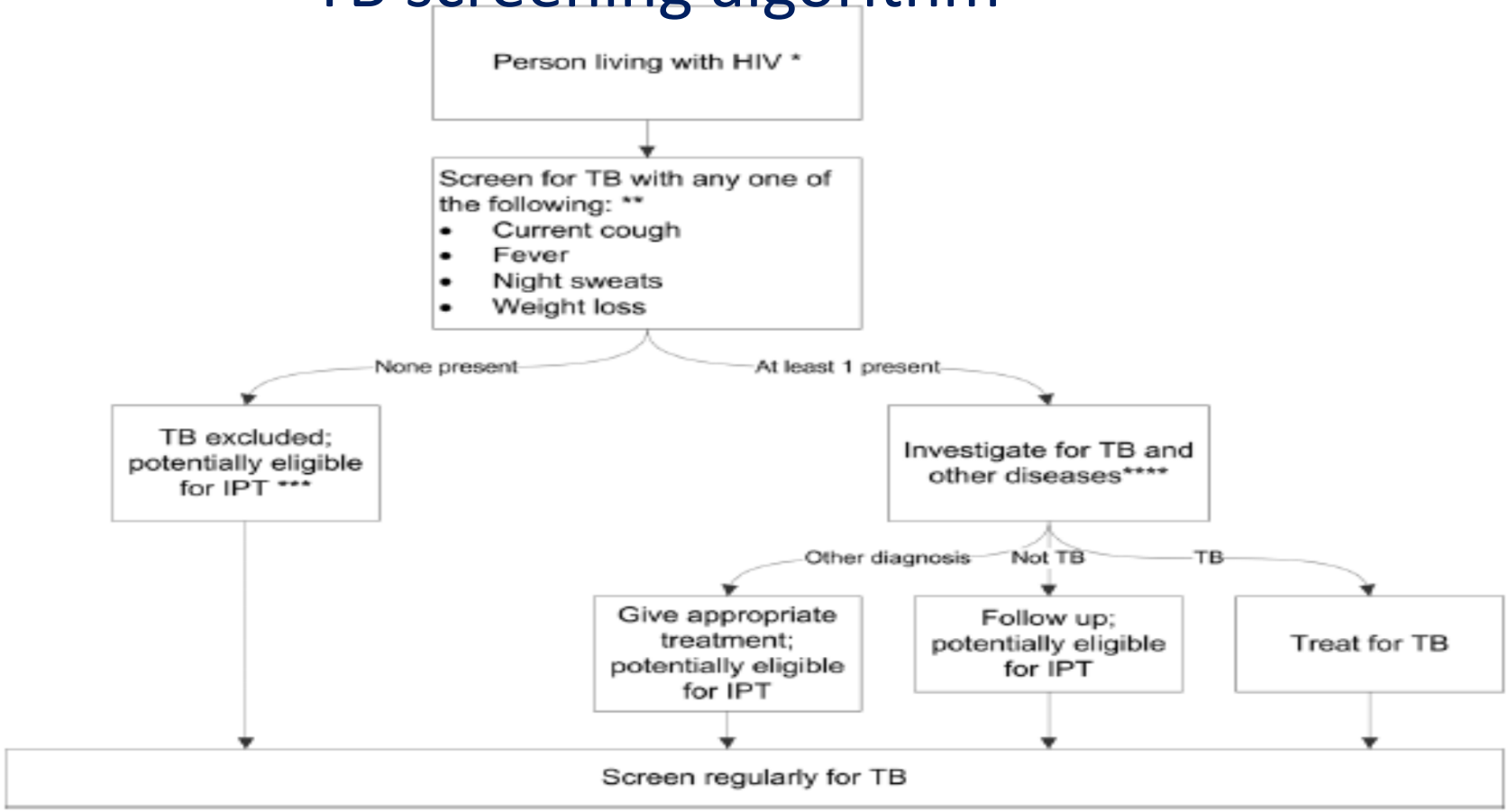
	5% TB Prevalence			10% TB Prevalence		
	NPV	(95% CI)	NNS	NPV	(95% CI)	NNS
All study participants	97.7	(97.4-98.0)	12	95.3	(94.6-95.9)	6
Clinical setting	98.3	(97.5-98.8)	15	96.4	(94.8-97.5)	8
Community setting	97.3	(96.9-97,7)	11	94.5	(93.7-95.2)	5
SE Asia	98	(95.9-99.0)	16	95.9	(91.6-98.0)	8
s-S Africa	97.4	(97.1-97.8)	10	94.8	(94.0-95.4)	5
CD4+ count ≥200	96.9	(95.1-98.0)	16	93.6	(90.2-95.9)	8
CD4+ count <200	98.9	(97.5-95.5)	16	97.8	(94.8-99.1)	8

NPV and NNS using rule 'CFSW' in a hypothetical population of PLHIV

Getahun G et al. PLoS Med 2011

IPT in PLHIV: NO MORE EXCUSES

TB screening algorithm



Getahun G et al. PLoS Med 2011

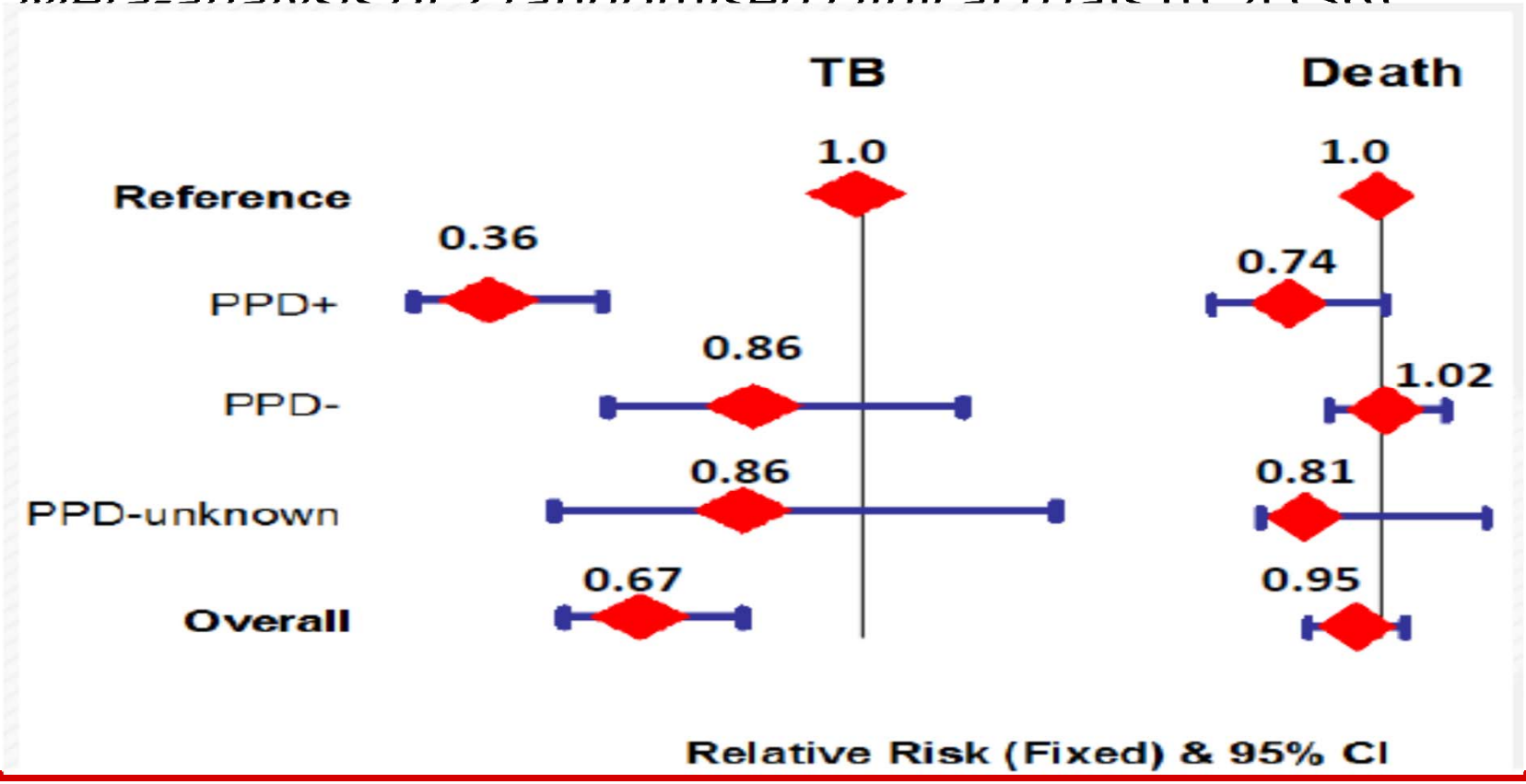
IPT in PLHIV: NO MORE EXCUSES

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

Effect of IPT on TB in PLHIV:

Meta-analysis of 7 randomised clinical trials (n=4136)



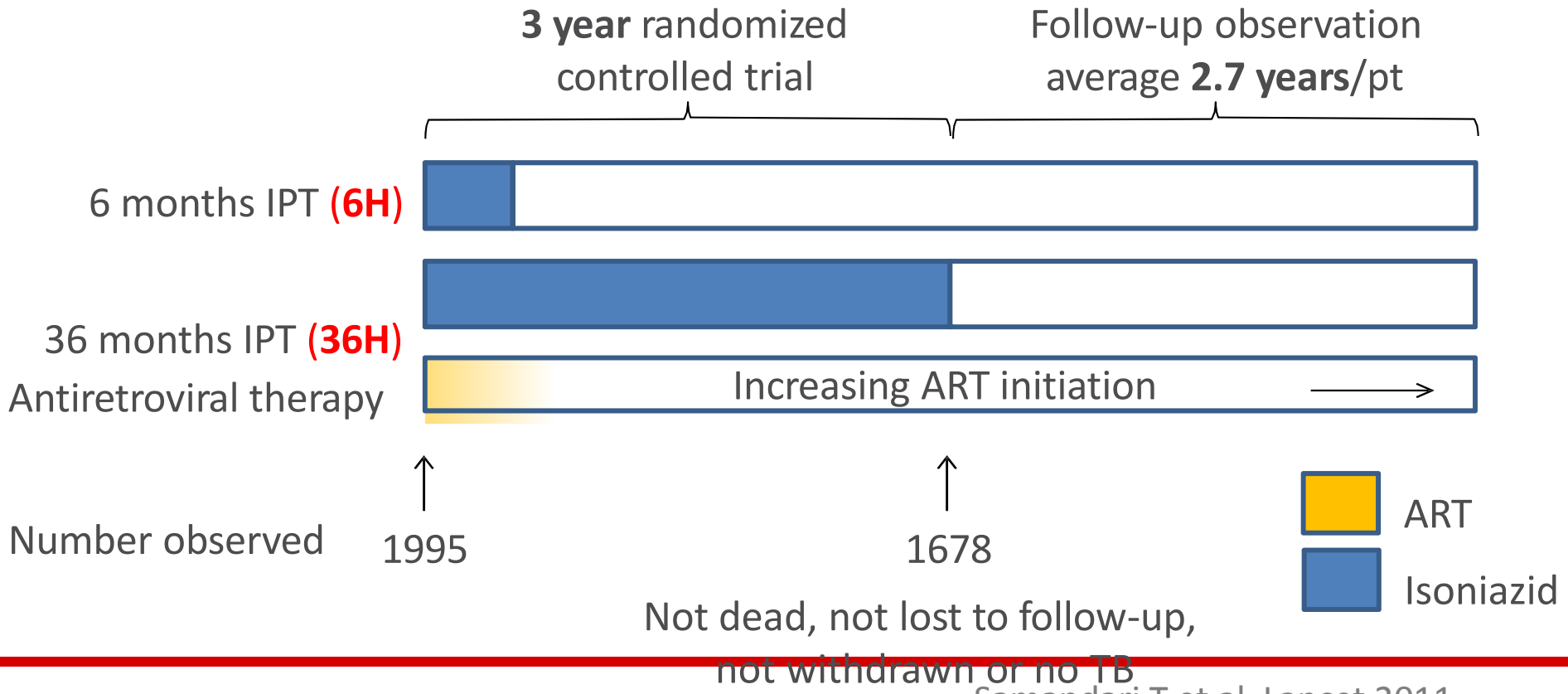
Akolo, Cochrane Collaboration 2010

IPT in PLHIV: NO MORE EXCUSES

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.

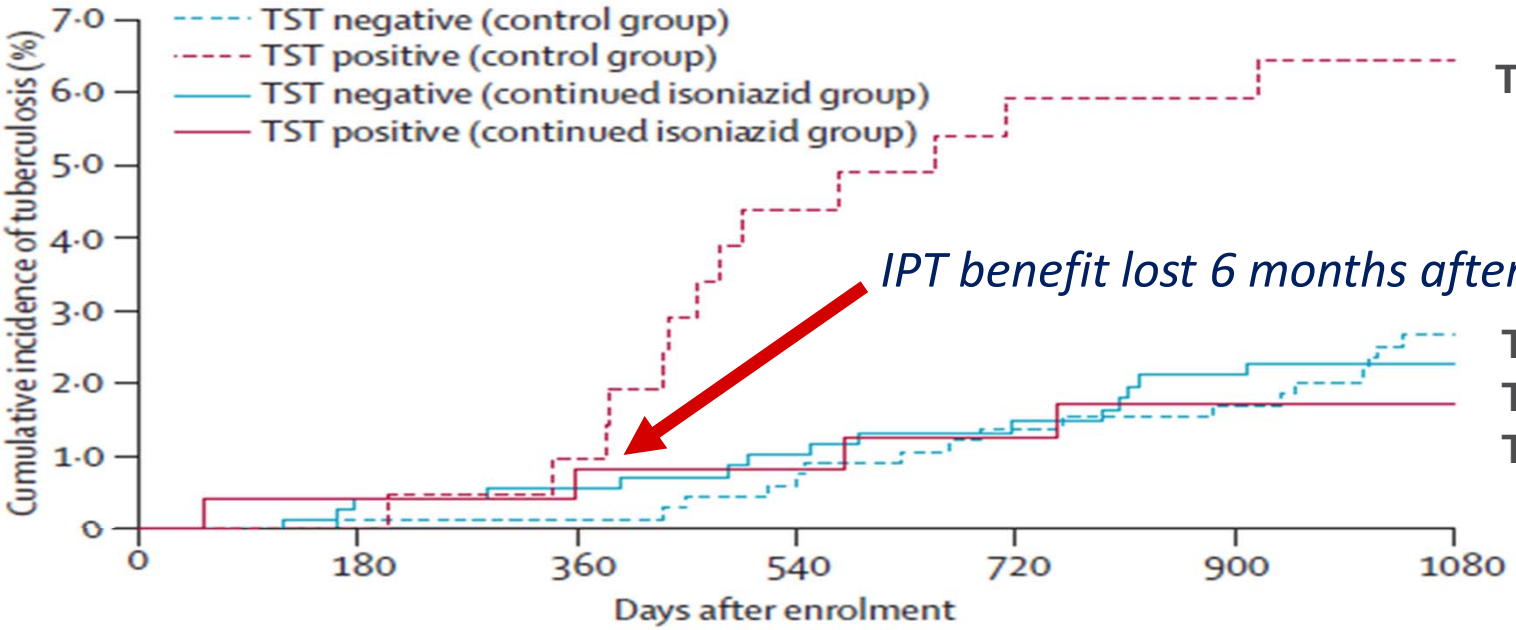
Conditional recommendation, moderate quality of evidence[3]

IPT randomised trial and ART for PLHIV
~6 year observation



Samandari T et al. Lancet 2011

6 vs 36 months IPT in Botswana: a randomised, double-blind, placebo-controlled trial



TST+ HR: 0.26 (0.09–0.80)

TST- HR: 0.75 (0.38–1.46)

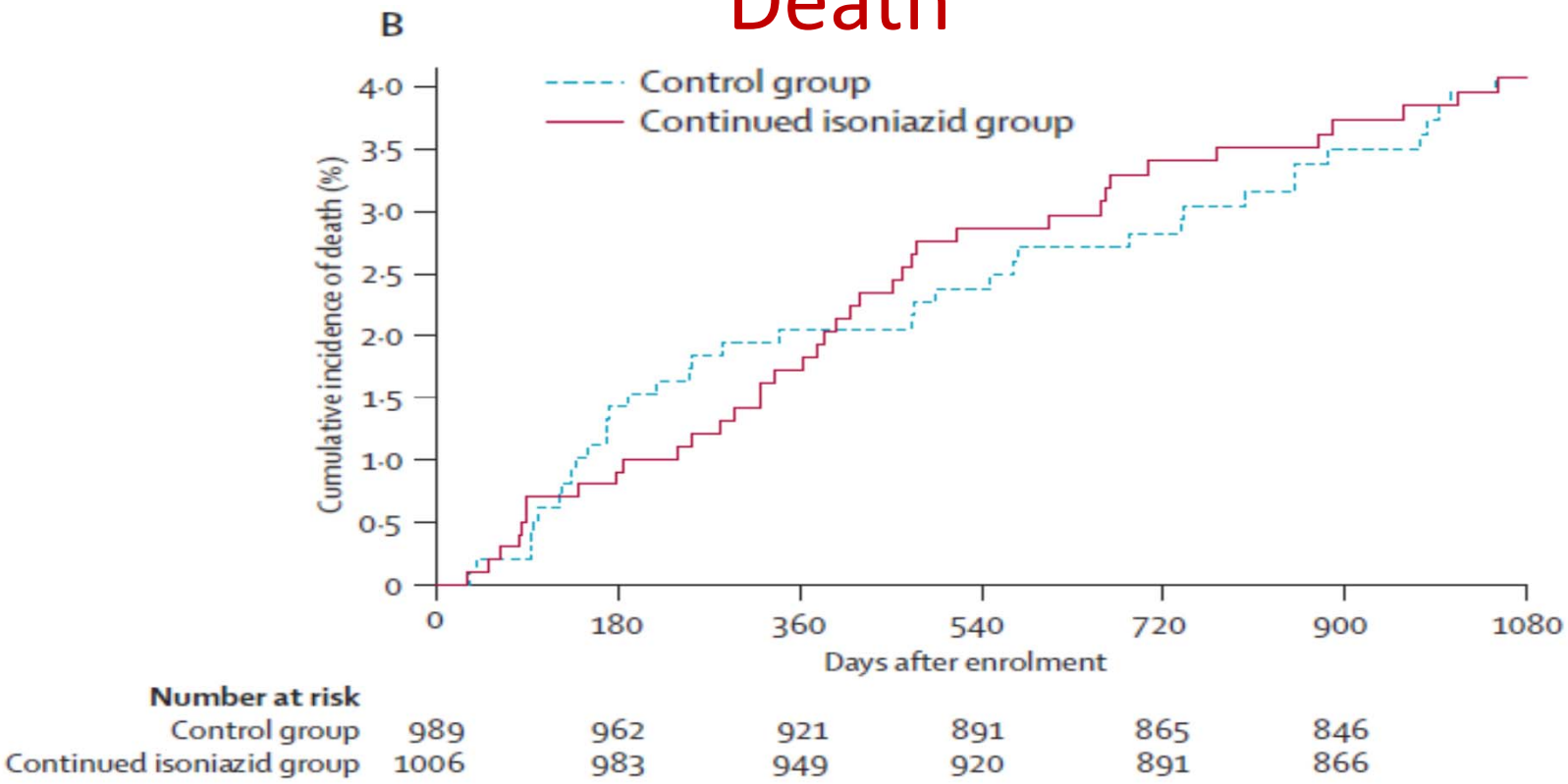
Severe AEs >6 months

1% placebo, 1.3% INH

Samandari T et al. Lancet 2011

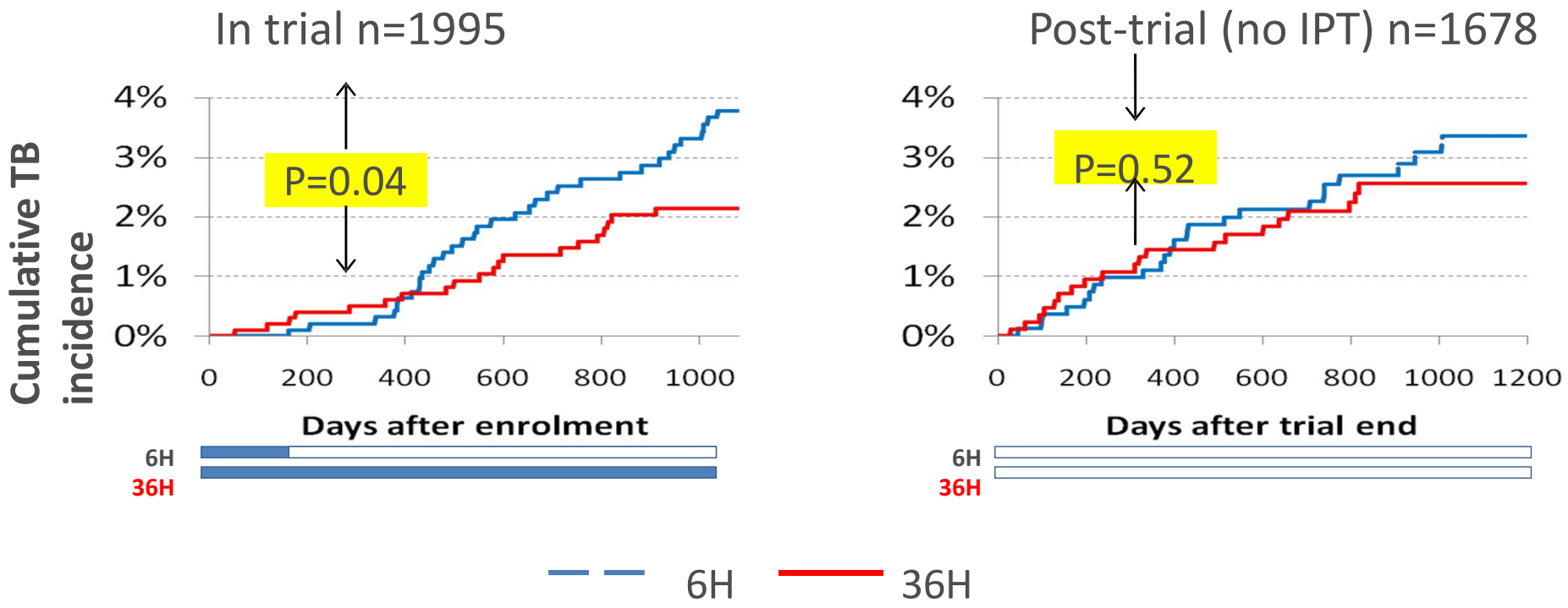
6 vs 36 months IPT in Botswana: a randomised, double-blind, placebo-controlled trial

Death



Samandari T et al. Lancet 2011

Cumulative TB incidence in the in-trial & post-trial period by study arm for all participants



Samandari T et al., Lancet 2011

TEMPRANO

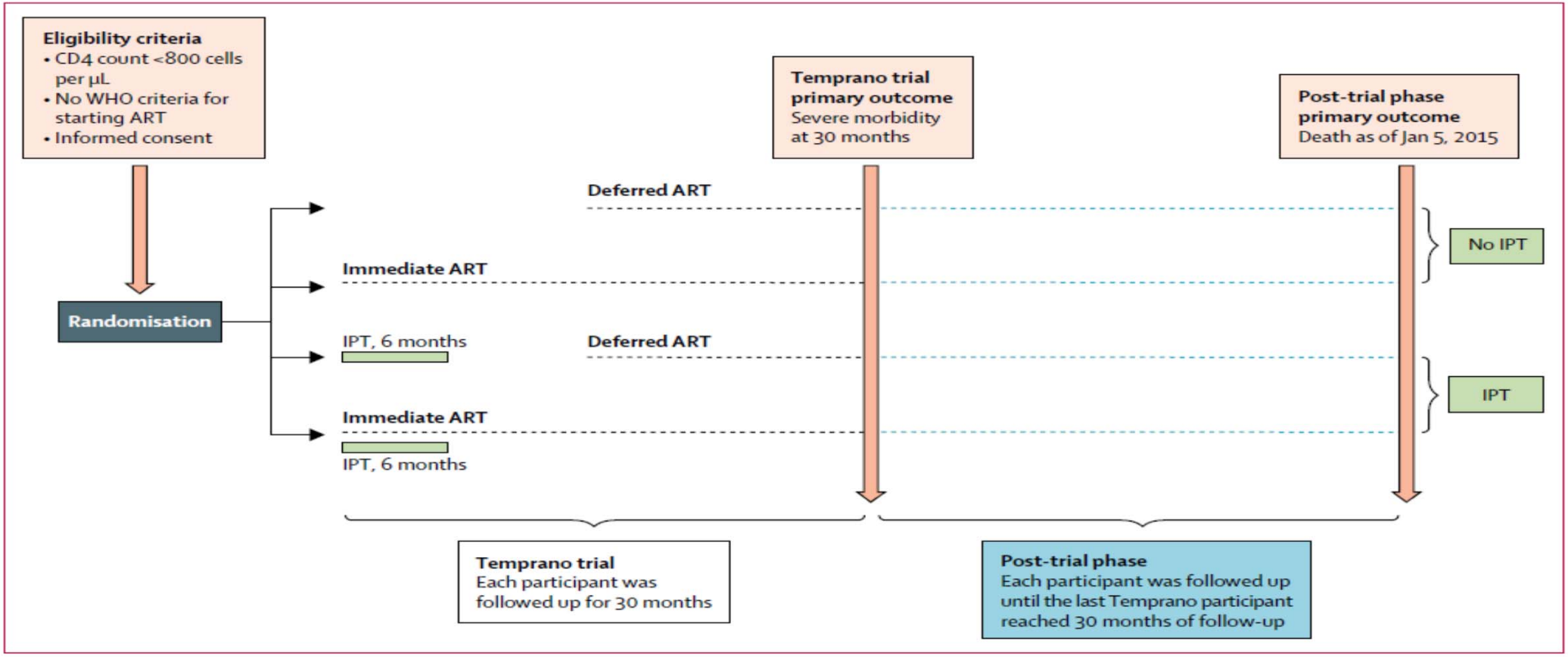
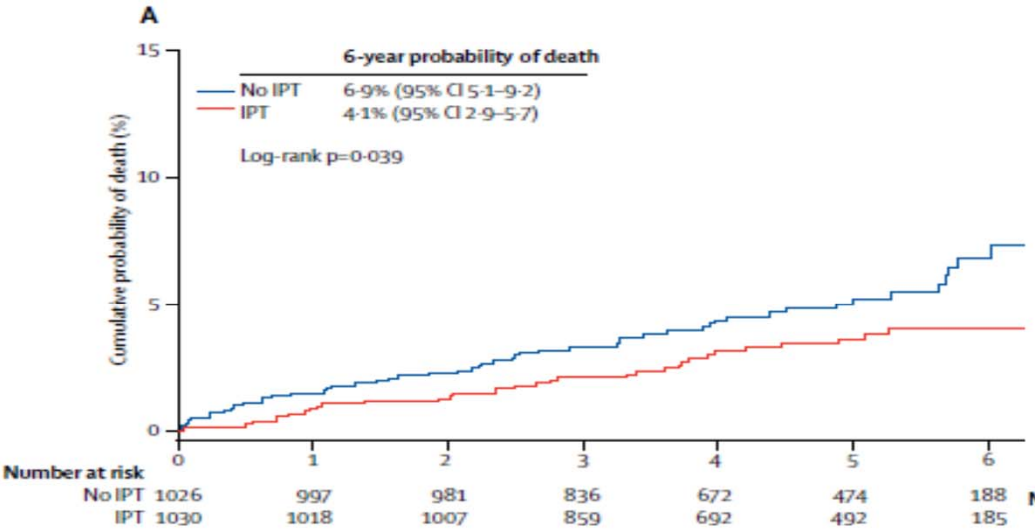


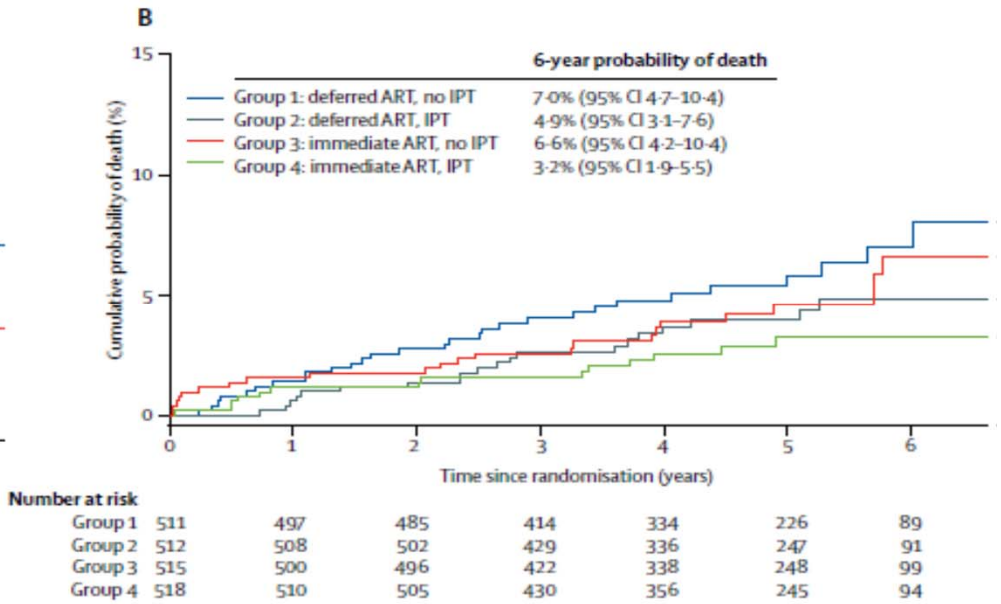
Figure 1: Study design of the Temprano trial and post-trial phase
ART=antiretroviral therapy. IPT=isoniazid preventive therapy.

NEJM 2015; Lancet GH 2017

TEMPRANO

IPT reduced risk of death by 37% independent of ART





Badje et al, Lancet GH 2017

IPT in PLHIV: NO MORE EXCUSES

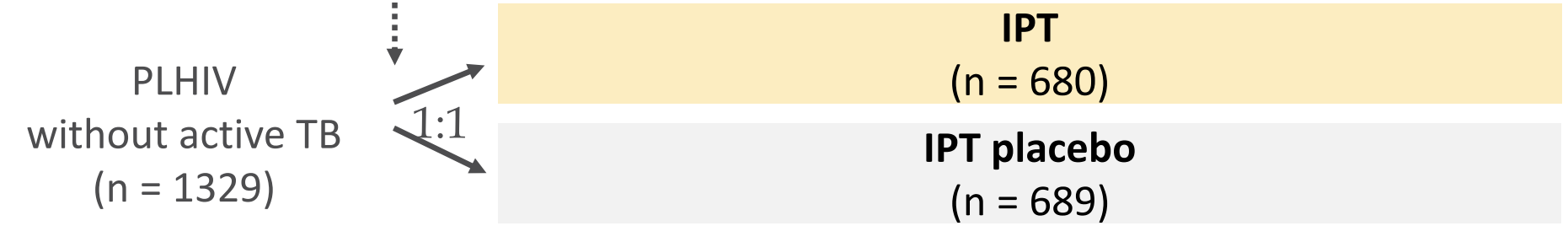
5 TST is not a requirement for initiating IPT in people living with HIV.

Strong recommendation, moderate quality of evidence

IPT plus ART to prevent TB in South Africa

A double-blind, placebo controlled RCT

Stratified by antiretroviral therapy status at baseline (i.e. ART at initiation versus maintenance of ART)

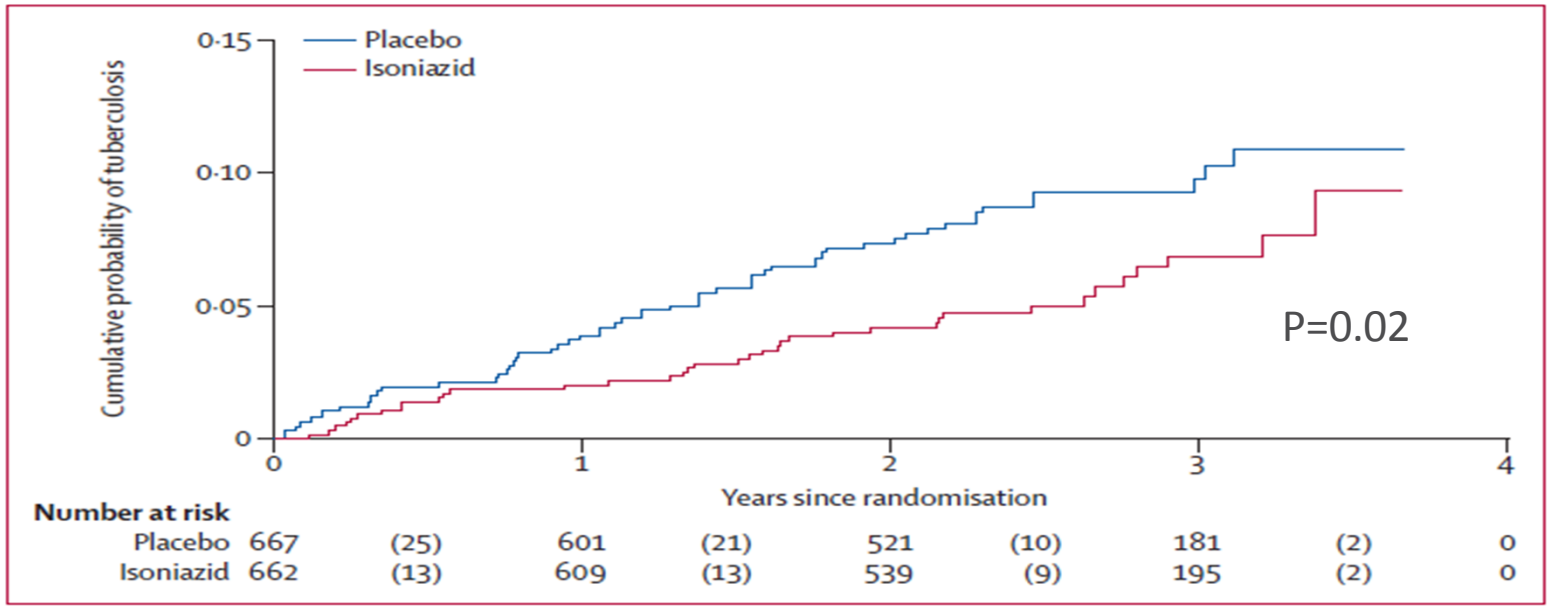


Primary endpoint: time to TB (definite, probably, possible)

Rangaka M et al. Lancet 2014

IPT plus ART to prevent TB in South Africa

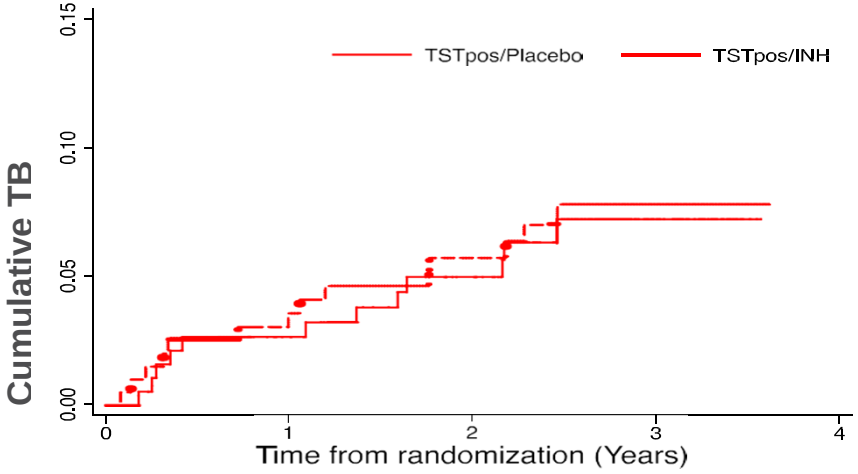
Time to TB



Hazard ratio 0.63 (95% CI 0.41-0.94)

Rangaka M et al. Lancet 2014

Effect modification by TST status at baseline

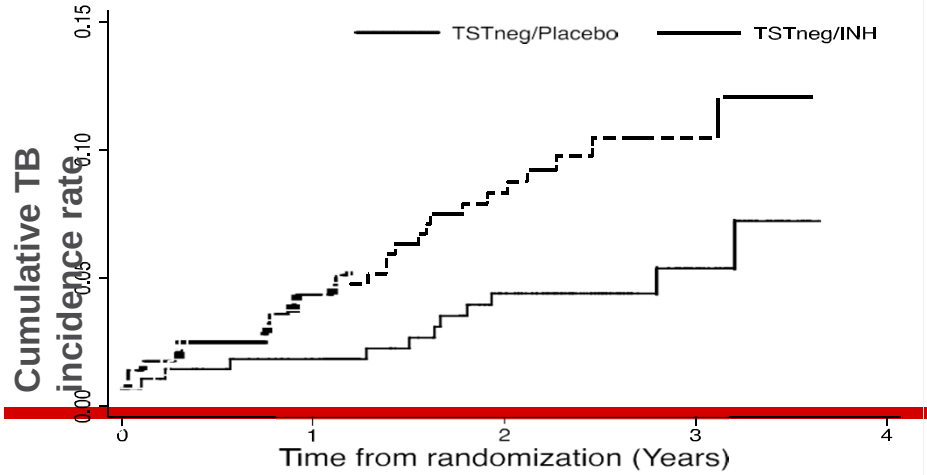


TST pos/Placebo: 2.8/100PY

TST pos/INH: 2.6/100PY

HRu=0.92 (0.43-1.97)

Logrank P=0.83



TST neg/Placebo: 4.1/100PY

TST neg/INH: 1.7/100PY

HRu=0.41 (0.20-0.83)*

Logrank P=0.06

Nyangaka M et al. Lancet 2014

IPT ART risk:benefit

Number needed to treat to prevent 1 case TB = 25

Number needed to harm (stop study drug due to toxicity) = 100

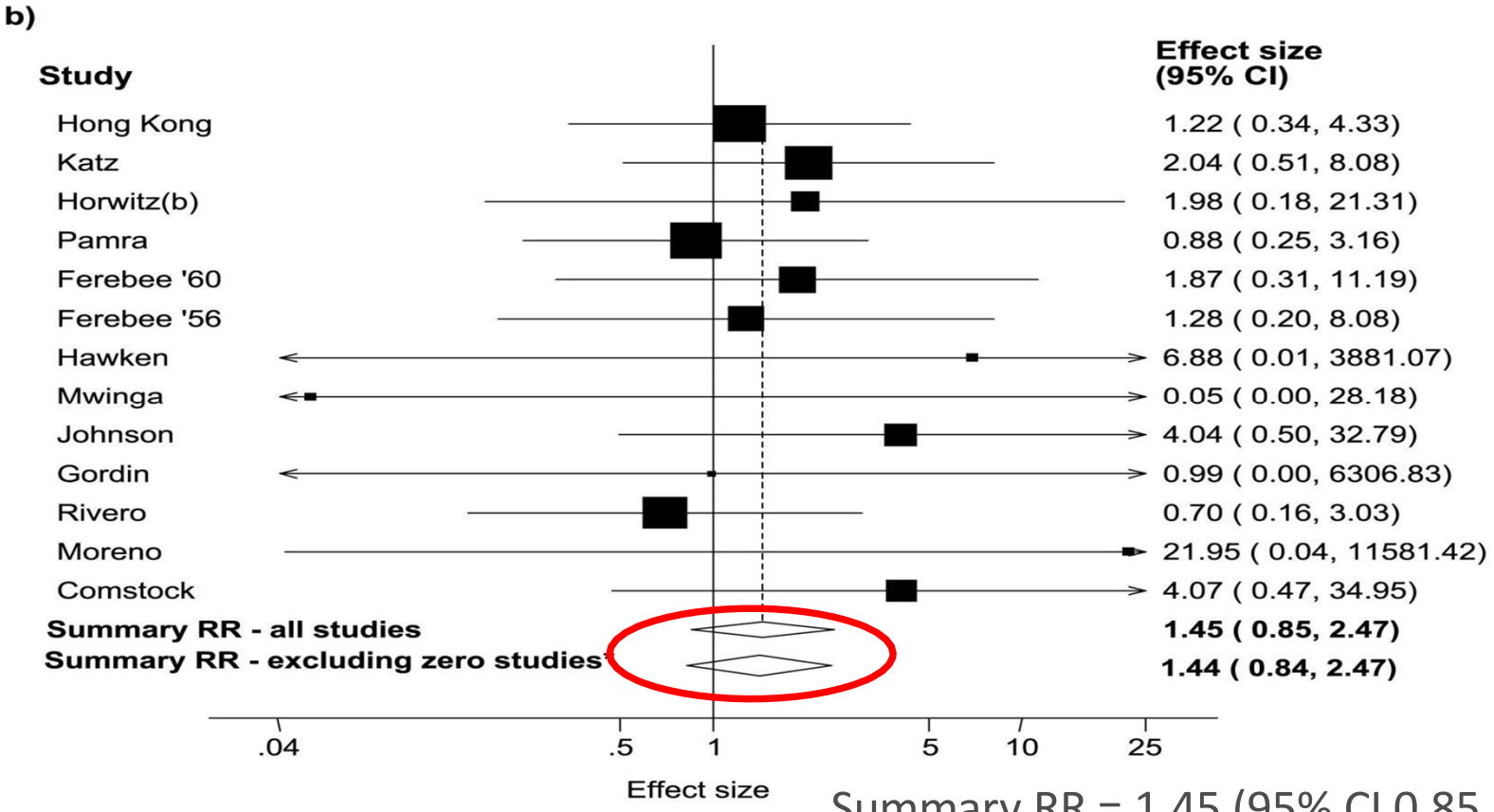
Rangaka M et al. Lancet 2014

IPT in PLHIV: NO MORE EXCUSES

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

Evidence suggests that IPT does not promote isoniazid resistance



Summary RR = 1.45 (95% CI 0.85, 2.47)

Balcells M, et al. Emerg Infect Dis 2006;12:744-51

IPT does not increase TB resistance

- **Most resistance arises from suboptimal treatment of active disease; preventing active disease should reduce resistance**
- **First line TB treatment is effective for INH-resistant TB**
  - Nolan IJTLD 2002;6:952; Mitchison et al. Am Rev Respir Dis 1986;133(3):423-30
- Risk of increased resistance, if any, is small:
  - Summary RR = 1.45 (95% CI 0.85, 2.47)
- There is still a need for surveillance of resistance

IPT: hepatotoxicity is rare

South Africa, cohort, routine, pre-ART

- 1/777 stopped INH with asymptomatic raised AST Grant JAMA 2005;293:2719-2725

South Africa, placebo RCT, all on ART

- IHN discontinued for Grade 3-4 ALT rise in 19/662 (2.9%) INH recipients
- INH discontinued for Grade 3-4 ALT rise in 10/667 (1.5%) receiving INH placebo Rangaka M et al Lancet 2014
  - Risk ratio 1.9, 95% CI 0.9-4.09

IPT systems issues

- **IPT is feasible**
  - 270,500 started on IPT in South Africa in one year (April 2013 –March 2014)
- **IPT is cost effective**
  - Cost to prevent TB case in mines ($353); less than treating a TB case ($1,736) Kumaranayake, IAS 2004
  - Cost to prevent TB case in PHC clinics ($486-$962); less then the cost of treating TB ($823-$1362)

    Hausler, Bulletin WHO 2006;84(7):528-36

Isoniazid preventive therapy (IPT) in PLHIV is a priority

- IPT works
- IPT is safe
- IPT does not increase risk of TB resistance
- IPT is feasible and cost effective
- IPT will help eliminate TB
- IPT is policy

Acknowledgments

Richard Chaisson
Anton Pozniak

TB Control and elimination

FIND TB

Undiagnosed TB is common

3-4 million missed cases per year

TREAT TB

Early treatment saves lives

Treatment reduces transmission

Prevent TB

Isoniazid preventive therapy (IPT) works

IPT can reduce TB rates in patients on ART

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IPT in PLHIV: NO MORE EXCUSES

Rule	Sensitivity (95% CI)		Specificity (95% CI)		LRN (95% CI)	
CFSW	78.9	(58.3–90.9)	49.6	(29.2–70.1)	0.426	(0.349–0.520)
HFSW	75.7	(53.9–89.2)[a]	52.7	(31.8–72.7)	0.461	(0.391–0.544)
CFW	74.0	(51.7–88.3)[a]	53.8	(32.8–73.6)	0.483	(0.416–0.561)
CSW	73.4	(51.0–88.0)	53.8	(32.8–73.5)	0.494	(0.428–0.570)
CFS	73.1	(50.6–87.9)	61.1	(39.7–79.0)	0.440	(0.382–0.506)
HFW	70.6	(47.5–86.4)	57.5	(36.2–76.4)	0.511	(0.454–0.576)
FSW	69.2	(45.9–85.6)	55.7	(34.5–75.0)	0.554	(0.497–0.617)
HSW	68.1	(44.6–85.0)	58.7	(37.3–77.2)	0.544	(0.492–0.602)
CW	65.3	(41.6–83.3)	60.3	(38.8–78.4)	0.576	(0.530–0.625)
CF	65.0	(41.3–83.1)	68.6	(47.7–83.9)	0.510	(0.470–0.553)
HFS	63.7	(39.9–82.3)	66.3	(45.2–82.4)	0.548	(0.509–0.589)
FW	63.1	(39.3–81.9)	61.4	(40.0–79.1)	0.601	(0.560–0.644)
SW	61.0	(37.2–80.5)	61.9	(40.5–79.5)	0.630	(0.594–0.669)
CS	59.7	(35.9–79.6)	69.4	(48.7–84.4)	0.581	(0.551–0.613)
HW	56.8	(33.3–77.6)	66.8	(45.7–82.8)	0.647	(0.620–0.675)
FS	56.3	(32.8–77.3)	70.1	(49.6–84.9)	0.623	(0.598–0.649)
HF	52.0	(29.2–74.1)	75.0	(55.6–87.7)	0.640	(0.620–0.660)
W	49.3	(27.0–71.9)	71.1	(50.8–85.5)	0.712	(0.693–0.733)
F	42.8	(22.2–66.3)	79.8	(62.4–90.4)	0.716	(0.695–0.738)
HS	38.9	(19.5–62.6)	78.1	(59.9–89.5)	0.782	(0.753–0.813)
C	38.5	(19.2–62.2)	81.8	(65.3–91.5)	0.753	(0.724–0.783)
S	31.4	(14.8–54.6)	82.2	(65.9–91.7)	0.835	(0.780–0.893)
H	5.9	(2.3–14.5)	94.4	(87.6–97.6)	0.996	(0.735–1.351)

Diagnostic performance of 23 candidate *1-of-n* rules