

# Kick TB Out.....

## Using Isoniazid Prophylactic Therapy

# IPT

Training slides provided by  
Wits Reproductive Health and HIV  
Institute





# The Case for IPT

What is the evidence that IPT works?  
Do we need to be concerned about  
drug resistance?



# Risk of TB

- *HIV negative persons*
  - 1 in 10 **lifetime** risk of developing TB
- *HIV positive*
  - 1 in 10 **annual** risk of developing TB
  - 20-37 times higher risk than HIV negative persons
  - Higher risk if skin test positive (ie latent TB infection)
- *HIV + on ART*
  - Risk much lower but still higher than that of general population

# INH prophylactic therapy

- Recommended by WHO for HIV-infected persons since 1998
- Introduced in SA guidelines in 2004
- Reduces the risk of TB in HIV positive persons by **33% overall** (ie TST positive and TST negative persons)
  - In persons with latent TB (TST positive), IPT has been shown to reduce the risk of TB by **64%\***
  - Antiretroviral therapy reduces risk of TB by +/- **67%\***

\*Lawn et al. Antiretrovirals and isoniazid preventative therapy in the prevention of HIV-associated Tuberculosis in settings with limited health-care resources. Lancet 2010;10:489-498.

# Understanding the studies that have shown the effectiveness of IPT

- The study design
  - Placebo controlled, randomised trials
  - Amongst HIV+ adults, one group got INH, one group got placebo. Neither group knew which drug they were getting
  - After two years or so, the number of cases of TB were measured in each group
- The relative risk or the ODDS ratio (OR)
  - The risk of INH recipients getting TB compared with placebo recipients
  - $OR = 1$  Identical risk
  - $OR < 1$  INH recipients are protected
  - $OR > 1$  INH recipients are more at risk

# Efficacy of primary IPT

IPT given to persons who have never had TB

All studies done in Africa, in HIV+ persons not on ART

PPD+	TB incidence	Death
Author / year	Relative Risk	Relative Risk
Hawken 1997	0.64	0.34
Mwinga 1998	0.42	2.02
Pape 1993	0.22	0.28
Whalen 1997	0.29	0.78
<b>Sub Total</b>	<b>0.36</b>	<b>0.74</b>

# Efficacy of IPT (primary prevention)

TB incidence amongst  
IPT recipients

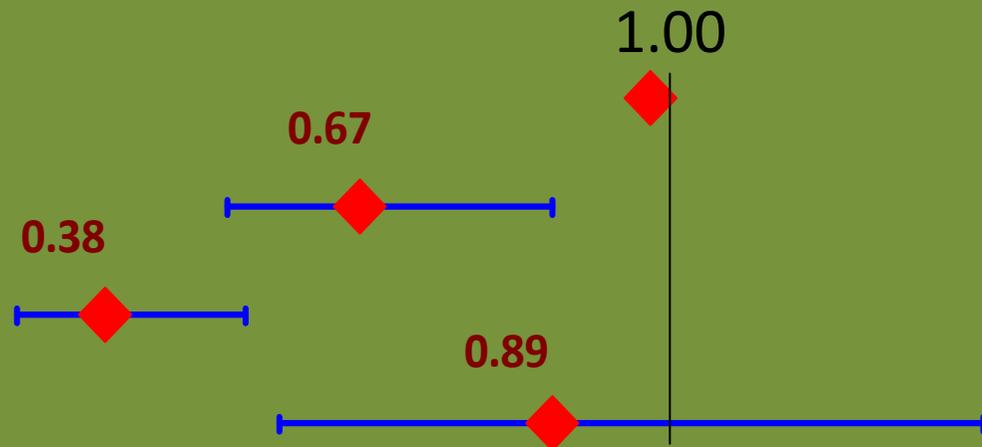
(RR & 95% CI)

Placebo

Overall

TST+\*

TST-



Relative risk



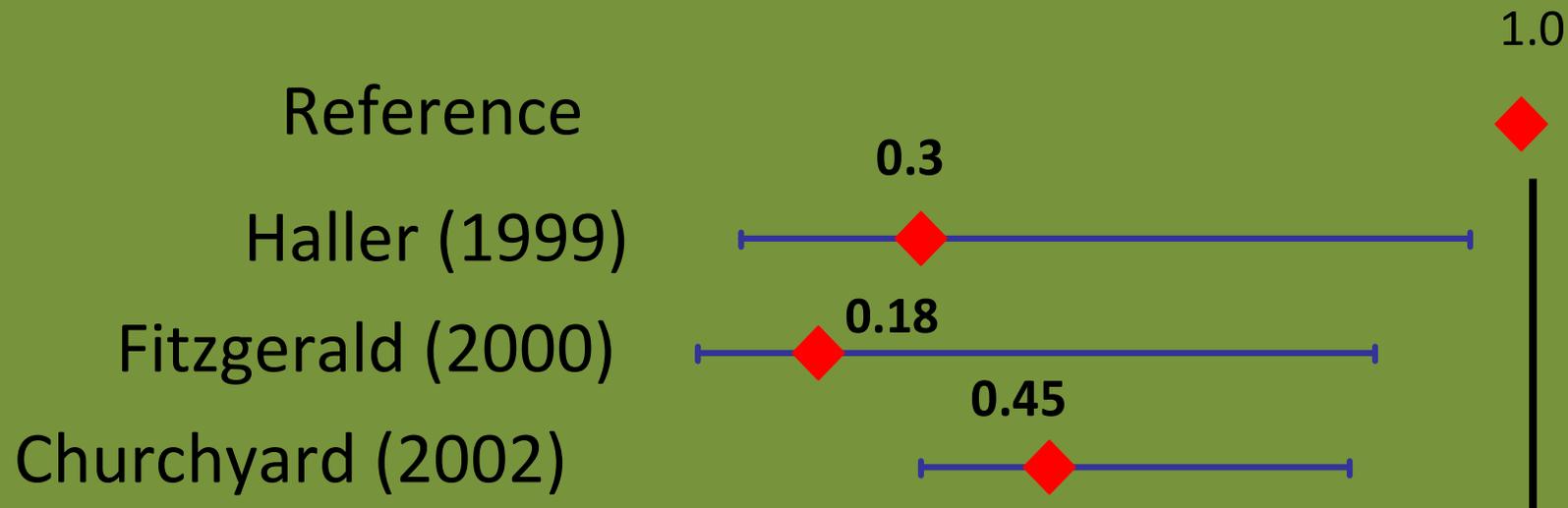
95% confidence interval for  
relative risk

(Akolo C. Cochrane infectious disease group. 2009)

\*4 trials; 2378 participants

# Efficacy of secondary IPT among HIV+ individuals

(Incidence Rate Ratios & 95% CIs)



# Duration of protective effect of IPT

- Studies revealed that the protective effect of IPT lasts 18-24 months only
  - Some patients who received IPT will still develop TB
  - Most likely this is because of early re-infection after killing of latent TB infection
  - Infection control is important.
- More recent studies demonstrate that IPT is best if given continuously or for at least 36 months!!

# Retrospective studies amongst IPT and ART recipients - Brazil

A retrospective study done in Brazil, where INH and ART were implemented as part of routine primary health care services showed a decreased incidence of TB as follows

	Incidence rate of TB (per 100 person-years)
Naïve	7.1
IPT only	5.2
HAART only	4.6
IPT & HAART	1.1

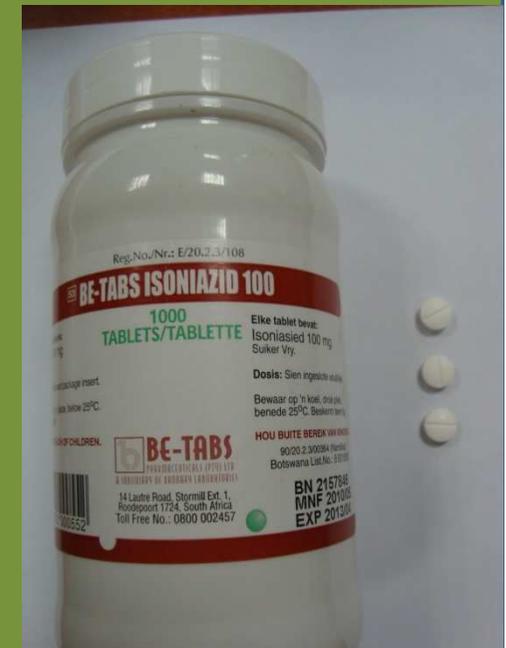
# Retrospective studies amongst IPT and ART recipients - JHB

A retrospective study done in here in Johannesburg, looking at incidence of TB amongst IPT recipients and non-recipients, from routine services, none of whom were on ART showed the following

Duration of IPT received	Incidence rate of TB per 100 person-years) (95% CI)
Eligible for IPT but did not receive	3.8 (1.7-8.5)
Received 1-5 months of IPT (ie not adherent)	2.7 (0.88-8.4)
Received 6 or more months of IPT (ie completed course)	1.9 (0.7-5.2)

# Two major concerns re IPT

- Drug resistance – theoretical, not supported by research\*
- IPT and ART



\*Lawn et al. Antiretrovirals and isoniazid preventative therapy in the prevention of HIV-associated Tuberculosis in settings with limited health-care resources. Lancet 2010;10:489-498.

# IPT and drug resistance

- Uninfected



- Latent TB



INH kills latent (dormant TB)  
•Therefore TB disease cannot occur  
•Resistance to TB drugs (INH) cannot develop because the numbers of bacteria are VERY low in latent TB infection

- TB disease



Treatment of TB disease requires 4 drugs because  
•Large numbers of TB bacilli mean that resistance can develop

# IPT and drug resistance

- Uninfected



- Latent TB



- TB disease



**DANGER**



If, in selecting a patient for IPT, we *miss active TB disease*, we may give IPT to someone who actually has TB disease

Then we run the risk of causing that person's TB to become resistant to INH

# IPT and drug resistance

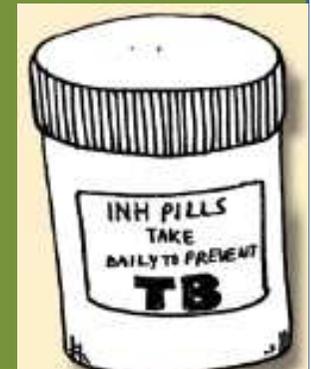
- So, screening for TB is **CRITICALLY IMPORTANT** in selecting patients for INH prophylaxis
  - If we miss patients with active TB, we run the risk of treating TB with one drug (INH), and causing resistance
- How do we screen for TB disease?
  - Symptoms **ONLY** (cough, fever, night sweats, LOW)
  - If the patient is not well, they are **NOT SUITABLE** candidates for IPT

# IPT and drug resistance

- INH prophylaxis is an intervention for the WELL HIV+ person, only
  - Just like CPT!
  - IPT is prevention for well persons

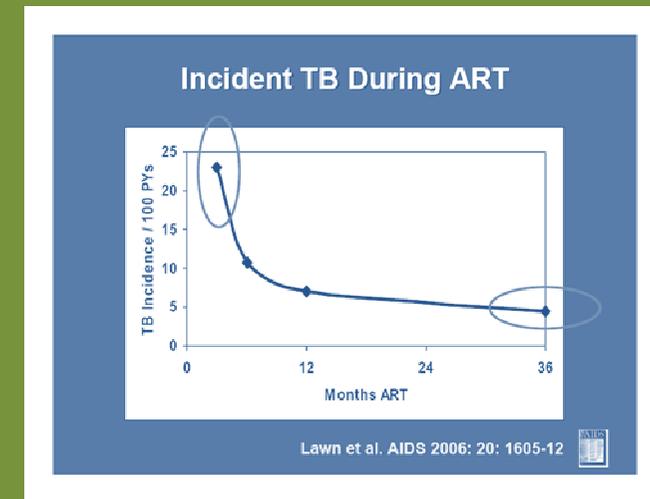
# IPT & Drug Resistance

- Meta-analysis of studies looking for drug resistance amongst persons who have received IPT concluded that the provision of IPT is **not** associated with the development of resistance
- Regular screening for TB whilst on IPT will identify patients who develop TB as soon as possible therefore reducing the chance that someone with TB is treated with mono-therapy



# TB and ART

- If a person is eligible for both ART and IPT (ie HIV+, well, CD4<200cells/mm<sup>3</sup>), ART is ALWAYS the priority.
- Start ART (refer for ART) first.
- What about IPT then?
  - The risk of TB is highest in the first 3-6 months after initiating ART
  - We don't want to treat TB disease with INH alone.
  - Therefore, once ART started, IPT can be commenced after 3-6 months



**AFTER excluding active TB!**

# Additional concerns re IPT

- Side effects
  - Peripheral neuropathy, hepatitis
  - Prior counselling is important re management
- Availability and accessibility of IPT
  - Important that stock outs don't occur
- Lack of knowledge amongst HCW and patients leads to poor delivery, uptake and adherence

# Conclusion

- IPT is an effective intervention to reduce the incidence of TB in HIV positive persons
- Drug resistance is a theoretical risk
- IPT and ART in combination provided added benefit
- IPT may reduce TB mortality in those on ART

# ISONIAZID PREVENTIVE THERAPY (IPT) FOR HIV INFECTED INDIVIDUALS: SA National Guidelines



# **1. IPT is considered BEST PRACTICE for PLWA**

## **SA National Guidelines on IPT**

- Revised in 2010
- Part of the ART guidelines as approved by the National Health Council
- Based on evidence based research results
- Recommended duration-6 months but can go up to 9 months
- Adult dose: 300mg daily given with Pyridoxine 25 mg daily

## 2. Who can get IPT?

- HIV positive patients, adults and children
  - Including pregnant women, persons recently having completed TB treatment, persons on ART already
  - Any CD4 count – regardless of stage of HIV
- TB contacts, especially <5 years, regardless of HIV status

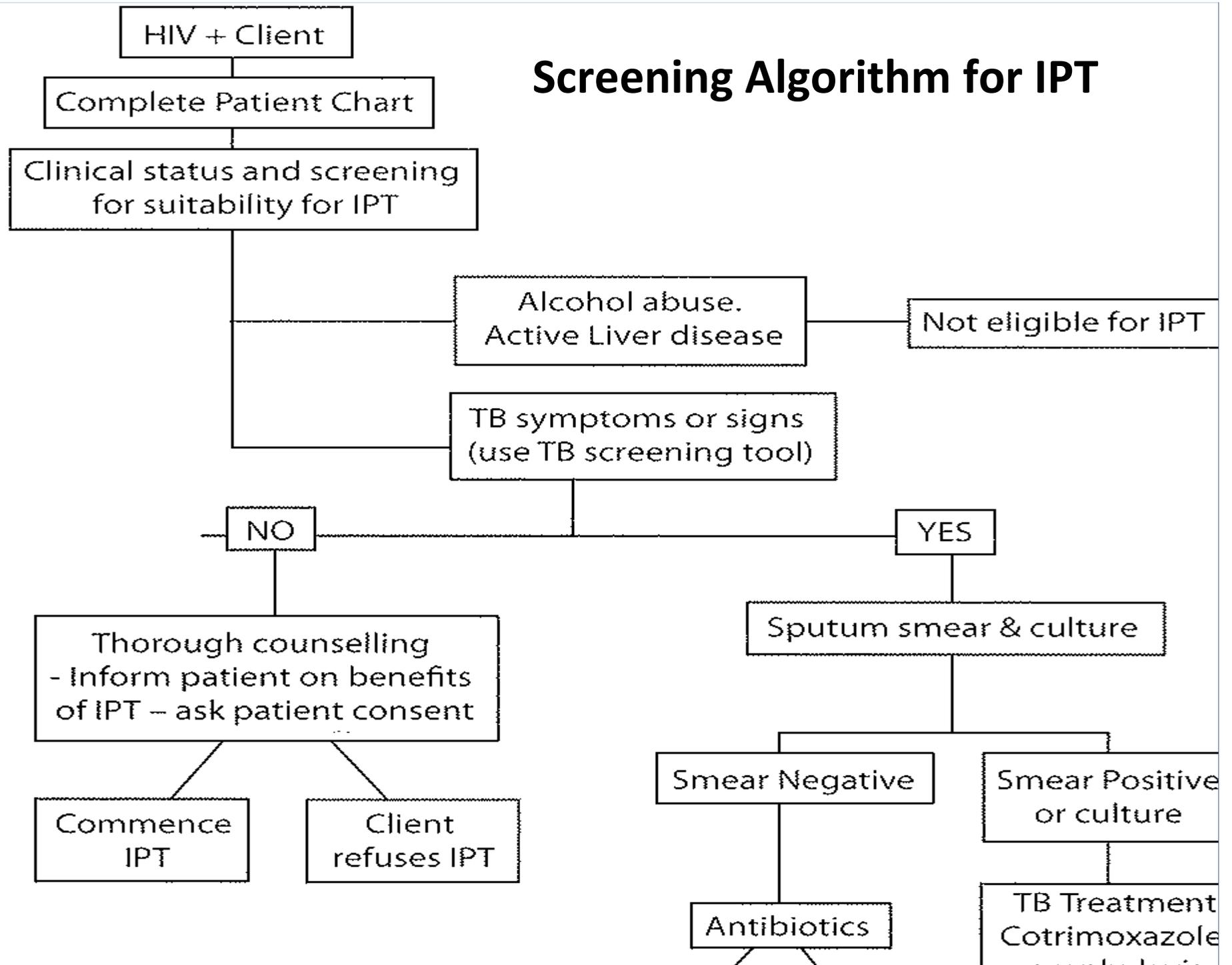
# IPT and ART

- High CD4 – IPT
- Low CD4 – ART
- If patient on IPT is ready for ART, do not delay ART
- Patient on ART
  - ART protective to an extent
  - Still at risk for TB
  - Risk for IRIS
  - IPT well tolerated (Caution d4T and NVP)
  - But **EXCLUDE ACTIVE TB FIRST!**

### 3. Exclude active TB disease in all potential IPT recipients

- TB symptom screen: ask the following
  - Cough > 24 hours
  - Fever
  - Drenching night sweats
  - Loss of weight
- No CXR or sputum screen required to exclude IPT if the patient is well
- If patient is symptomatic
  - Investigate for TB– smear, CXR and culture as necessary
  - Do NOT give IPT under any circumstances, even if smear comes back negative (smear is a terrible test!)
  - If TB cannot be proven, re-evaluate patient after 3 months.
    - If well at that stage, IPT can be given

# Screening Algorithm for IPT



## 4. Who is not eligible for IPT?

- Persons with active TB disease on treatment
- Persons with unexplained symptoms, possibly due to TB
  - Can re-evaluate after 3 months, if still well.
- Alcoholic liver disease
- Hepatic disease

# 5. Monitor and evaluate

- Always record in patients record
  - Use BANC card for ANC, or patient handheld record, and clinic card
  - Document that symptoms of TB not observed
- Use facility monitoring tools
  - GDH 1.1 (standard headcount tool)
  - If in ANC, use Ante-natal register
- If facility has WRHI register – use it to monitor completion and adherence
- Consider continuity of care esp in ANC
  - Explain to clients that they need a minimum of 6 months, and they will need to obtain this from post natal or HIV wellness clinics after delivery.
  - Be sure that your facility has arranged for referral for moms to receive IPT with the above clinics

# 5. Monitor and evaluate

- What to do if persons are not adherent?
  - Remember, IPT is prophylaxis NOT treatment
  - Interrupting IPT is not as serious as interrupting TB treatment
  - The goal is to give the person their 6 months of IPT within 9 months
    - It can be some allowances made for interruptions
  - Always counsel patients as to benefit of IPT before initiation – understanding leads to adherence
  - Counsel interrupters to establish reasons and commitment to adherence.
    - If persons are not committed, don't push the matter. Allow them to refuse to take.