Is IPT a Priority for South Africa?

Robin Wood
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Four questions that need to be addressed

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2. Is the research transferable to the potential recipients of the intervention?
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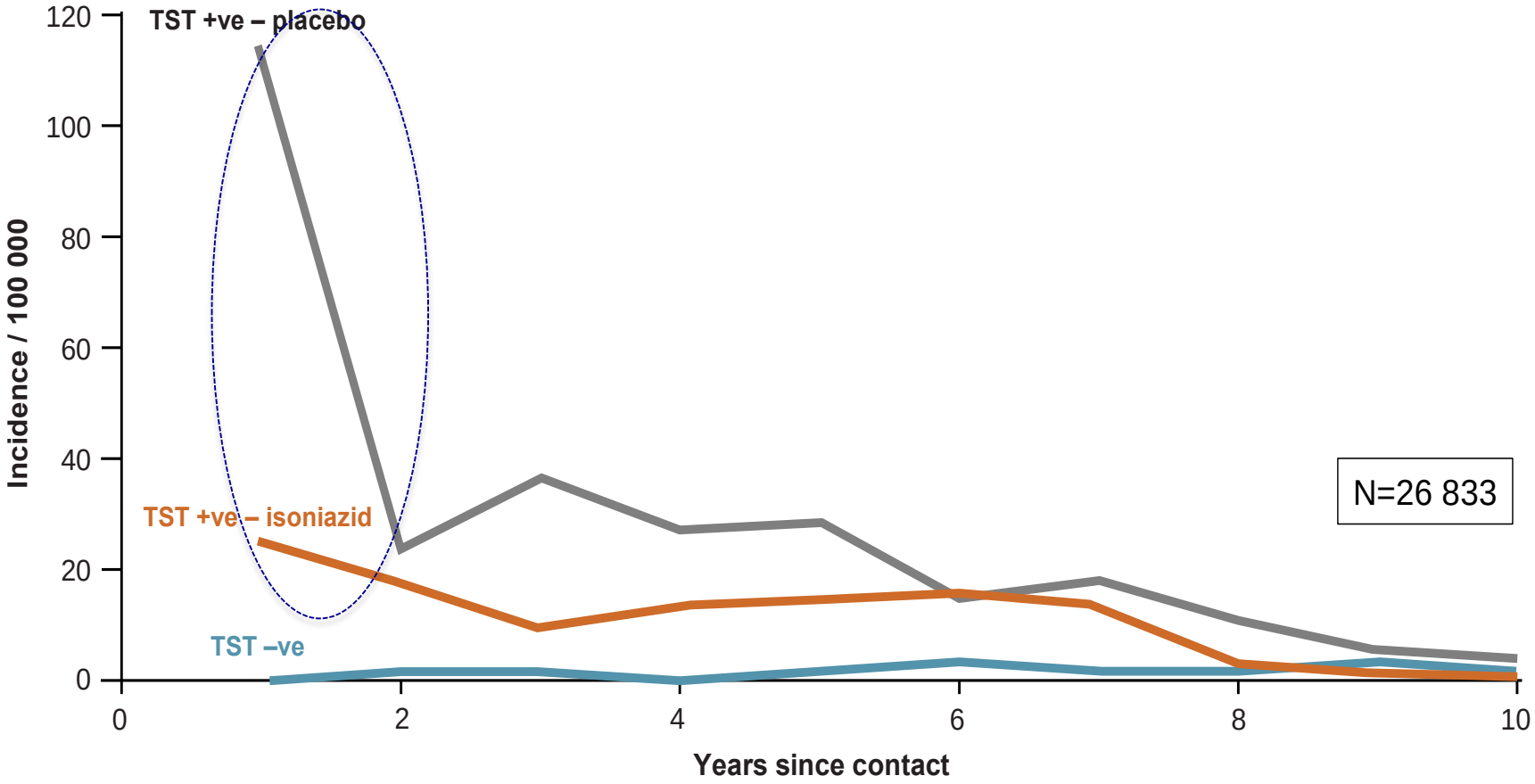
4. Are there potential harms of the intervention?

L Rychetnic *et al.* Criteria for evaluating evidence on public health interventions *J. Epidemiol Community Health* 2002

INH preventive therapy



H. Esmail, C. E. Barry, 3rd, D. B. Young and R. J. Wilkinson. The ongoing challenge of latent tuberculosis Phil. Trans. R. Soc. 12 May 2014

Ferebee SH. 1970 Controlled chemoprophylaxis trials in tuberculosis: a general review. Bibl. Tuberc. 26, 28–106.

Interventions for Tuberculosis Control and Elimination

2002

Hans L Rieder

International Union Against Tuberculosis and Lung Disease

68, boulevard Saint Michel, 75006 Paris, France

The publication of this guide was made possible thanks to the support of the United States Centers for Disease Control and Prevention, the British Columbia Lung Association, the French Ministry of Foreign Affairs, and the Norwegian Royal Ministry of Foreign Affairs.

Indications and recommendations for the use of prophylactic treatment

Prophylactic treatment is, for all practical purposes, rarely indicated. Even if the evidence is scant, however, it makes sense to provide it to a new-born child with a potentially infectious parent, especially the mother. This is recommended in industrialized countries, but should most likely be a universal indication.

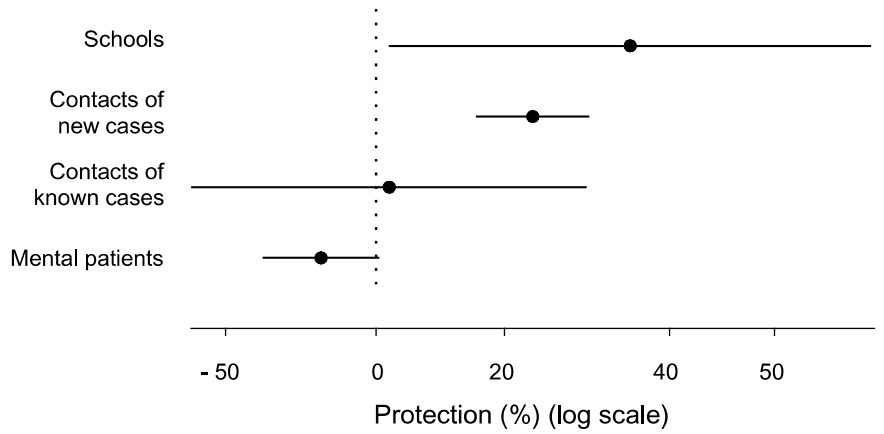


Figure 53. Protection from prophylactic treatment in the prevention of acquisition of tuberculous infection in four clinical trials conducted by the US Public Health Service.[641]

The South African Antiretroviral Treatment Guidelines 2013

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

7.2 INH Prophylaxis

a. All people living with HIV should be screened for active TB and eligibility for ART.
b. Those who are eligible should be started on ART.
c. TB preventive therapy is an effective intervention for HIV infected individuals.
d. All people living with HIV, in whom active TB has been reasonably excluded, should be started on IPT (as soon as practically possible after initiation of ART in those who are eligible for ART).
e. In patients with no TB signs or symptoms, TB prophylaxis with Isoniazid Preventive Therapy (IPT) should be started, unless alcohol abuse, adherence or side-effects are a concern, 5mg/kg to a maximum dose of 300mg daily, with pyridoxine 25mg/day. **A TST (Mantoux) test is required.**
f. Pregnancy is not a contraindication to INH prophylaxis.
g. If no TST is done IPT should be continued for 6 months as per existing guidelines but all effort should be made to perform TST as soon as possible after starting IPT.

Summary Recommendations		
	Pre-ART(CD4>350)	**On ART**
TST not done*	IPT for 6 months	IPT for 6 months
TST negative	IPT for 6 months	IPT for 12 months
TST positive	IPT for at least 36 months	IPT for at least 36 months

Unclear of what INH does?

- Prophylaxis before and after known TB exposure
- Sterilization of LTBI recently or distantly acquired
- Treatment of childhood active TB
- Treatment of pauci/multi bacillary adult disease

Unclear who will benefit?

- Anergic patients are **not** a group without prior TB exposure
- INH before and after ART seems to act differently – Pre-ART studies are less relevant now in today's ART "universal access".

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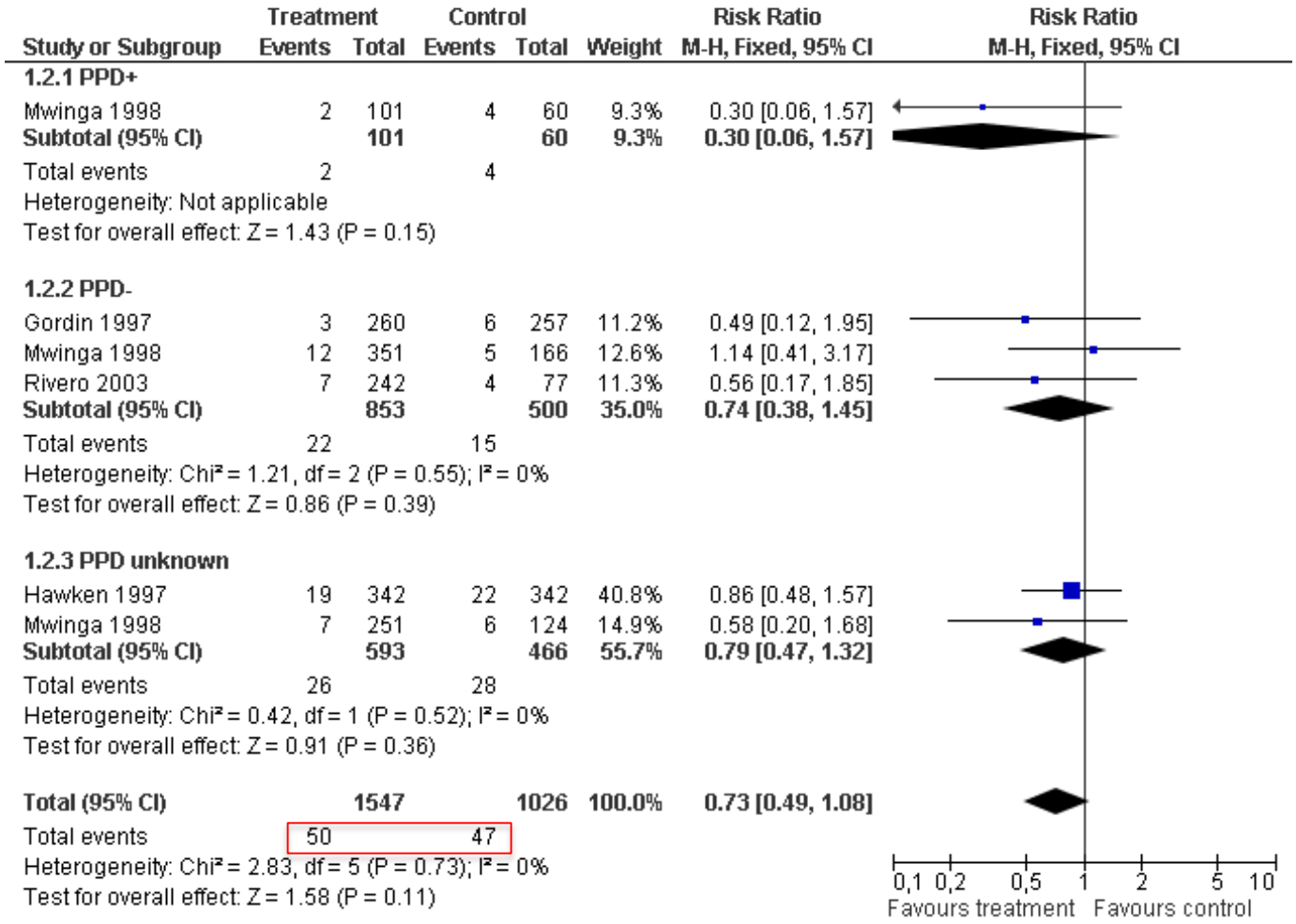
South African IPT Randomised Controlled Studies

	Study Population	Mean age	Baseline ART	Baseline TB prev %	TB incidence per 100 pys	
					IPT	Placebo
Zar *et. al*.	263, HIV+ hospital symptomatic	25 m	9%	N/A	7.2‡	23.4
Madhi *et. al.*	548, HIV+ hospital outpatients	4 m	32%	N/A	8.2	9.4
	804, HIV- exposed outpatients	4 m	N/A	N/A	6.9	7.7
Gray *et. al.*	167, HIV+ hospital & outpatients	35 m	100%	7%	1.5§§	2.9
Mohammed *et. al.*	118, HIV+ symptomatic, TST-ve	38 y	0	9.3	18	11.6
	20 HIV+ symptomatic, TST+ve	36 y	0	N/A	6.8	N/A
Rangaka *et. al.*	1,580, HIV+ ART clinic attenders	34 y	72%	16.2	2.3**	3.6
Churchyard *et. al.*	78,744, mining workforce	41 y	2.7%	6.9††	3.02	2.95

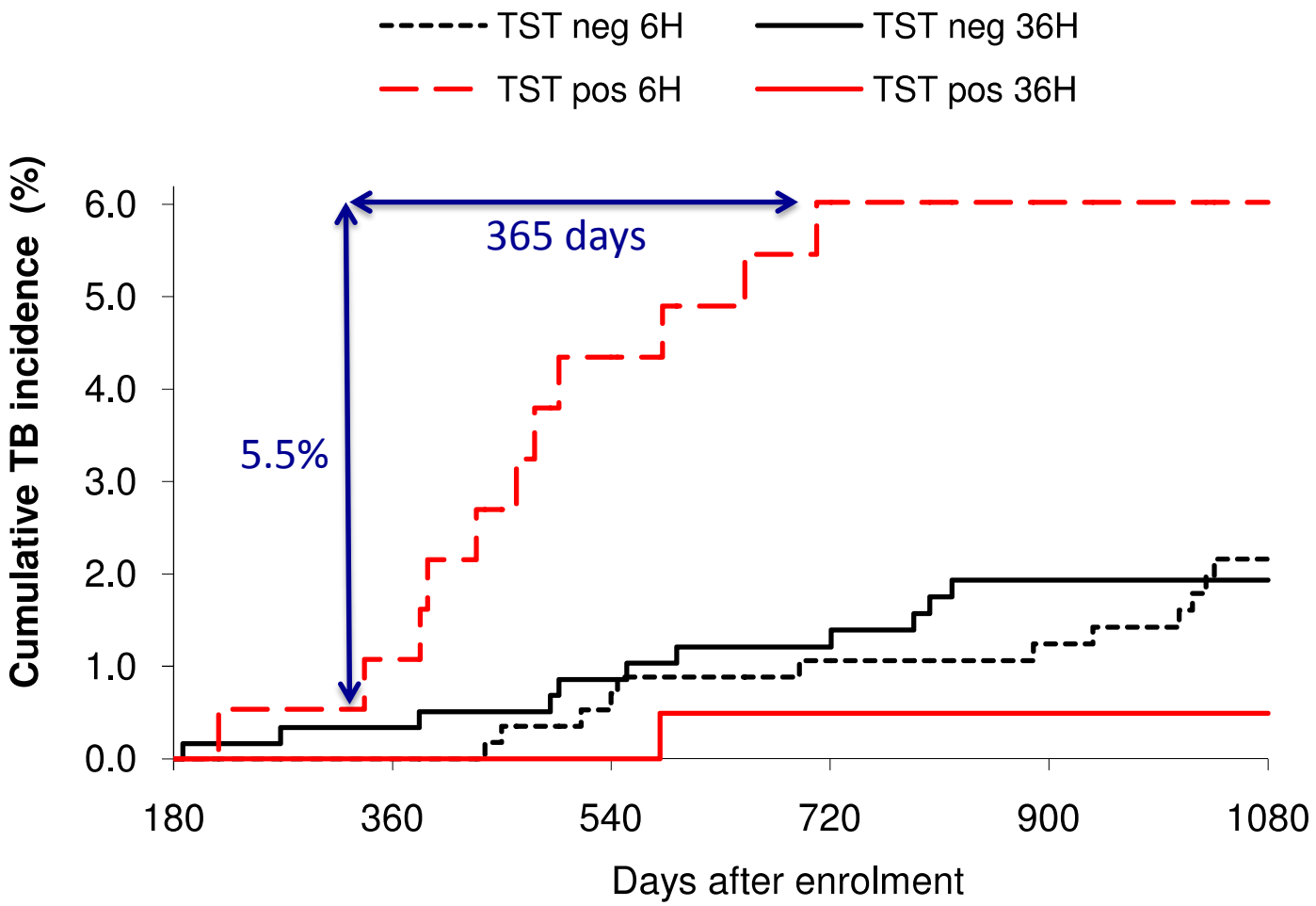
Study variability & trial design differences?

- 4 out of 6 SA RCTs showed no significant IPT benefit
- Much fewer TB clinical events with ART use
- Much lower TB incidence in those studies with MTB culture at screen
- Thibela, 7% more TB found in IPT arm at screening than standard of care screening in control arm
- Rangaka study 250 TB cases diagnosed at baseline (39 post randomisation) far exceeded the 21 cases (58 versus 37) “prevented by IPT”

Incidence of Confirmed TB in Cochrane Review 2011



Cumulative rates of tuberculosis among HIV-infected participants commencing masked medication after 180 days of open-label isoniazid, Botswana 2004-2009



Samandari *et al. Lancet* 2011

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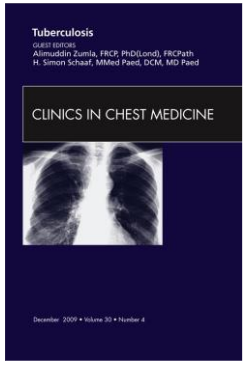

Antiretroviral Therapy for Control of the HIV-associated Tuberculosis Epidemic in Resource-Limited Settings

Stephen D. Lawn, MD[a,b,*], Katharina Kranzer, MD[a,b], Robin Wood, FCP MMed[a]

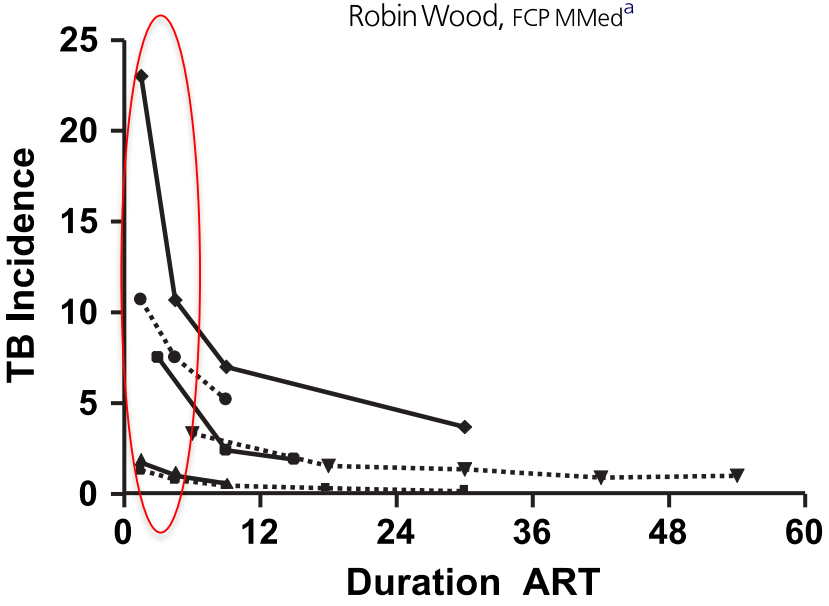

Fig. 3. TB incidence rates during ART. The graph shows data from studies included in (see Table 2) in which changing TB incidence rates were calculated accord ing to increasing duration of ART. The two lowest curves present data from studies conducted in high- income countries.15,18 The remaining four studies are from South Africa (diamonds13 and inverted trian- gles14), a range of resource-limited countries (circles15), and Uganda (squares16).

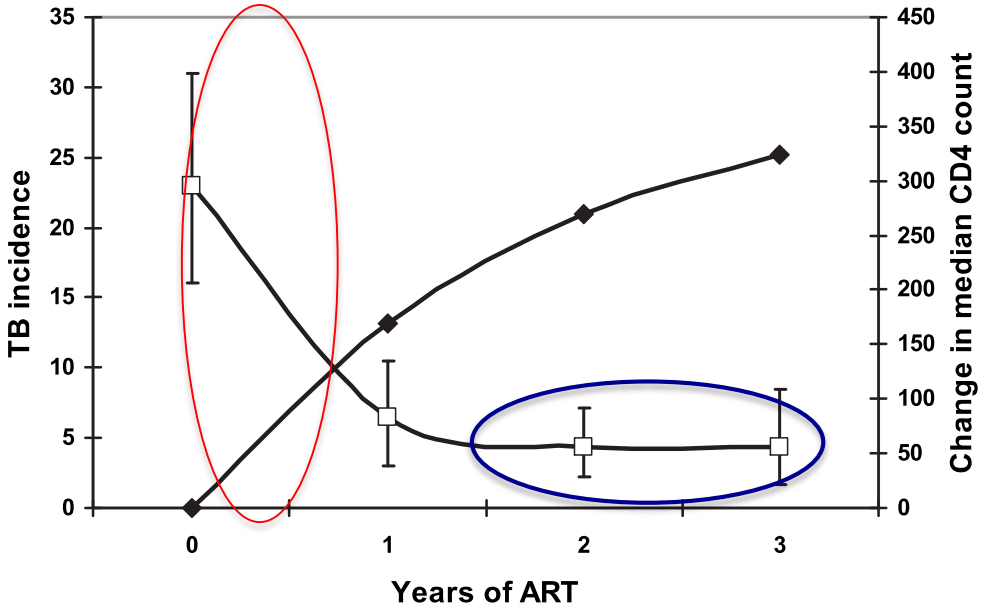

Fig. 4. Decreasing TB incidence rates (cases/100 person-years, white squares) and rising median CD4 cell counts (cells/mL, black diamonds) during the first 3 years of ART. These data are from a community-based ART cohort in a township in Cape Town, South Africa. (Data from Refs.13,19,56).

Tuberculosis during the first year of antiretroviral therapy in a South African cohort using an intensive pretreatment screening strategy

Stephen D. Lawn[a,b], Katharina Kranzer[a,b], David J. Edwards[a], Matthew McNally[c], Linda-Gail Bekker[a] and Robin Wood[a]

Objective: To determine the baseline prevalence of tuberculosis (TB) in a cohort using a strategy of intensive pretreatment screening for TB and the subsequent incidence rate and temporal distribution of cases during the first year of antiretroviral therapy (ART).

Design: Prospective observational community-based ART cohort in South Africa.

Methods: Adults enrolling for ART and who did not have a current TB diagnosis were intensively screened for TB at baseline using culture of two sputum samples, chest radiography and investigations for extrapulmonary disease as required. Patients who developed symptoms consistent with incident TB during ART were similarly investigated.

Results: Two hundred forty-one patients had a median CD4 cell count of 125 cells/μl (interquartile range 70–186) and 200 (83%) started ART. TB was diagnosed in 87 (36%) patients, with 82% of pulmonary cases being culture-proven. Most TB cases (87%) were prevalent disease detectable at baseline, whereas just 11 (13%) were incident cases that presented during the first year of ART. The incidence rate during 0–4 months of ART was similar to the rate during months 5–12 of ART [10.9 (95% confidence interval [CI] 4.6–23.3) cases per 100 person-years versus 8.1 (95% CI 3.6–18.0) cases per 100 person-years].

Conclusion: Systematic culture-based screening detected a very high burden of prevalent TB present at baseline. This intensified screening strategy was associated with an approximately two-fold lower incidence rate in the first 4 months of ART than previously observed in this cohort. This suggests that many incident cases of symptomatic TB presenting during early ART can be detected as prevalent disease prior to ART initiation using sensitive diagnostic tests.

AIDS 2010, 24:1323–1328

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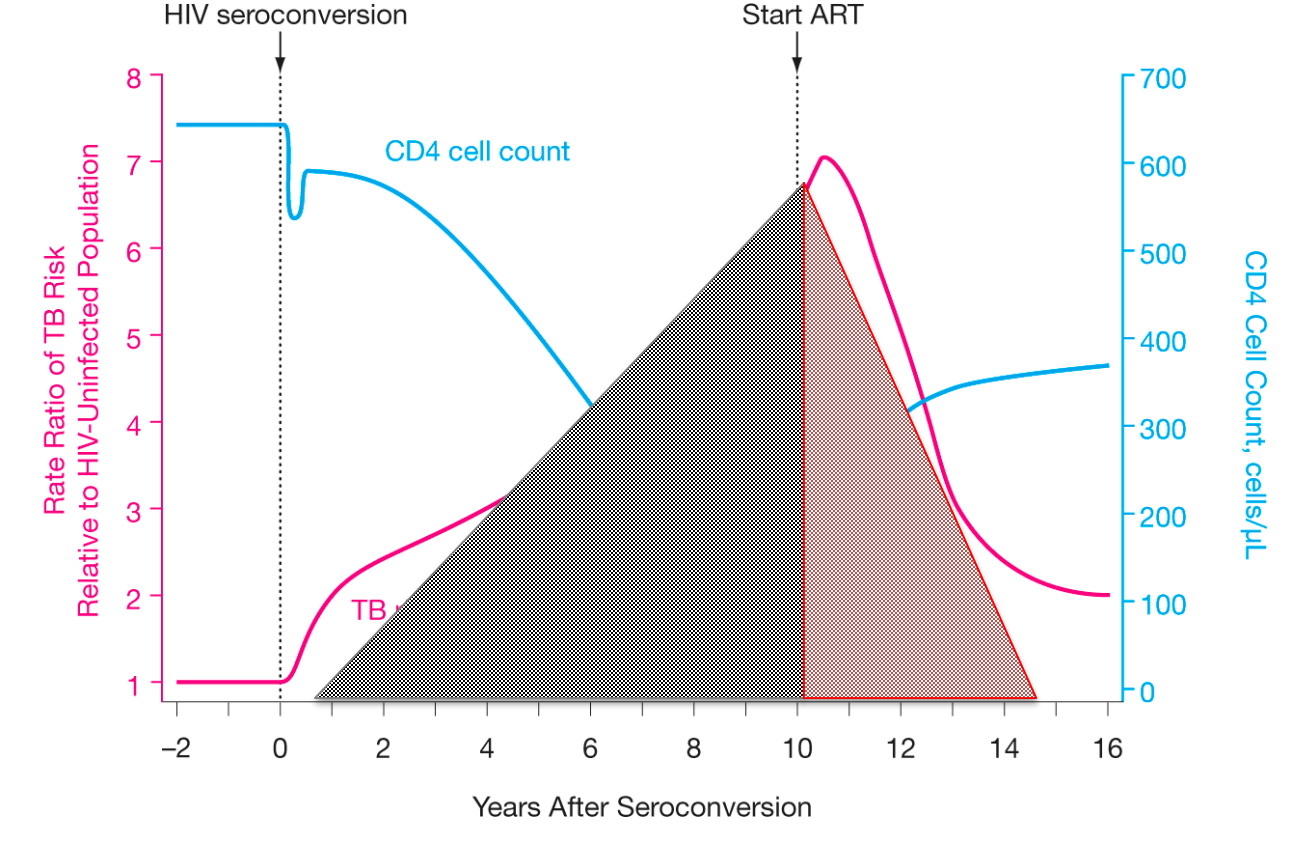
Opportunities and Challenges for HIV Care in Overlapping HIV and TB Epidemics

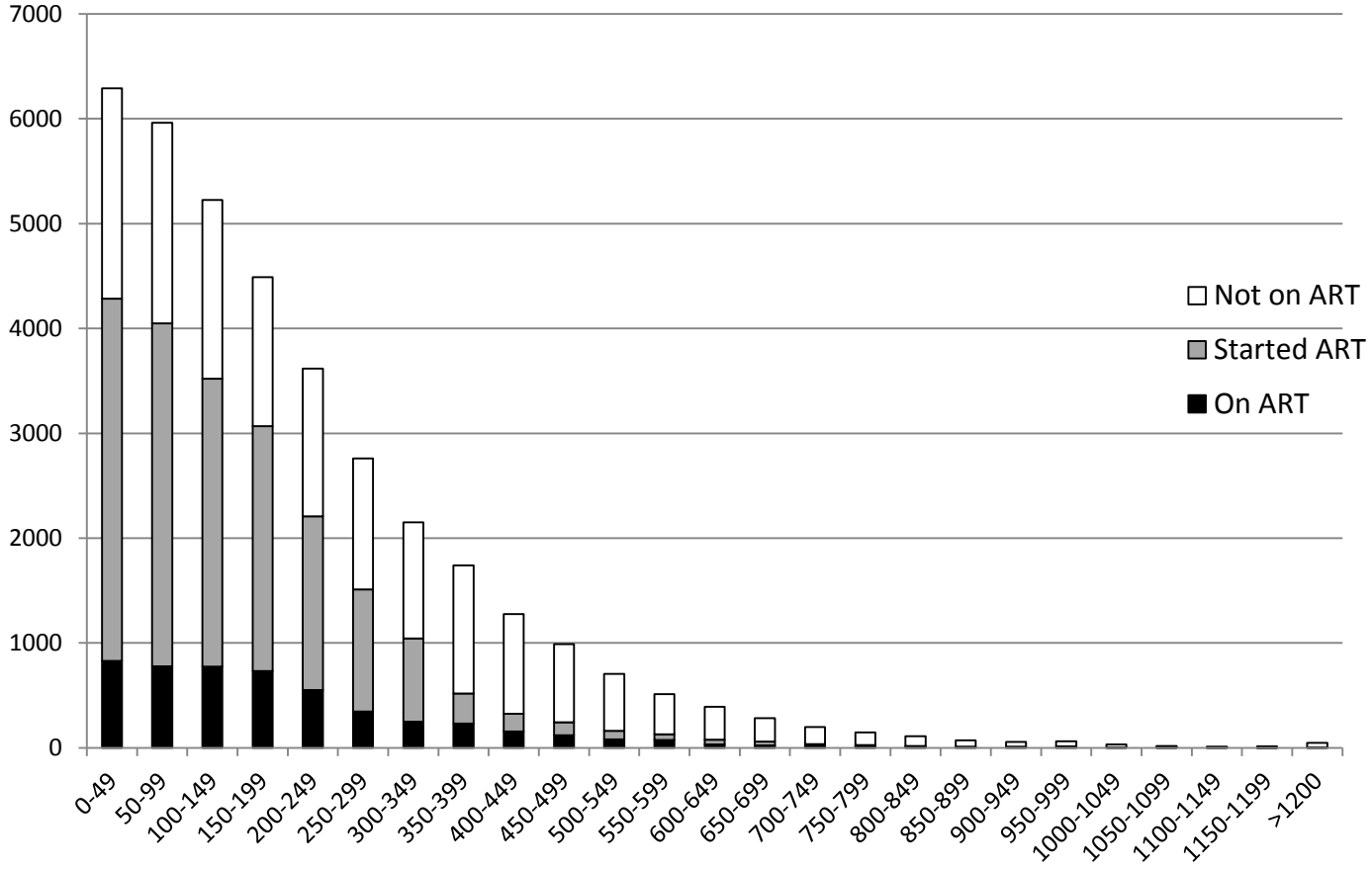
Diane V. Havlir, MD; Haileyesus Getahun, MD, PhD, MPH; Ian Sanne, MBBCH, FCP(SA); Paul Nunn, MD, FRCP

JAMA. 2008;300(4):423-430. doi:10.1001/jama.300.4.423.



Impact of ART on TB Case Fatality Stratified by CD4 Count for HIV-Positive TB Patients in Cape Town, South Africa (2009–2011)

Richard Kaplan, MD, Judy Caldwell, RN, RM, BCur,† Keren Middelkoop, MBChB, PhD,*‡ Linda-Gail Bekker, MBChB, FCP, PhD,*‡ and Robin Wood, MMed, FCP, DSc*‡*



CD4 count distribution by ART uptake for HIV+ve patients with baseline CD4 counts over the 3 year period (n=37,162)

JAIDS 2014

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Ability of preventive therapy to cure latent *Mycobacterium tuberculosis* infection in HIV-infected individuals in high-burden settings

Rein M. G. J. Houben[a,b,1,2], Tom Sumner[a,b,2], Alison D. Grant[b,c], and Richard G. White[a,b]

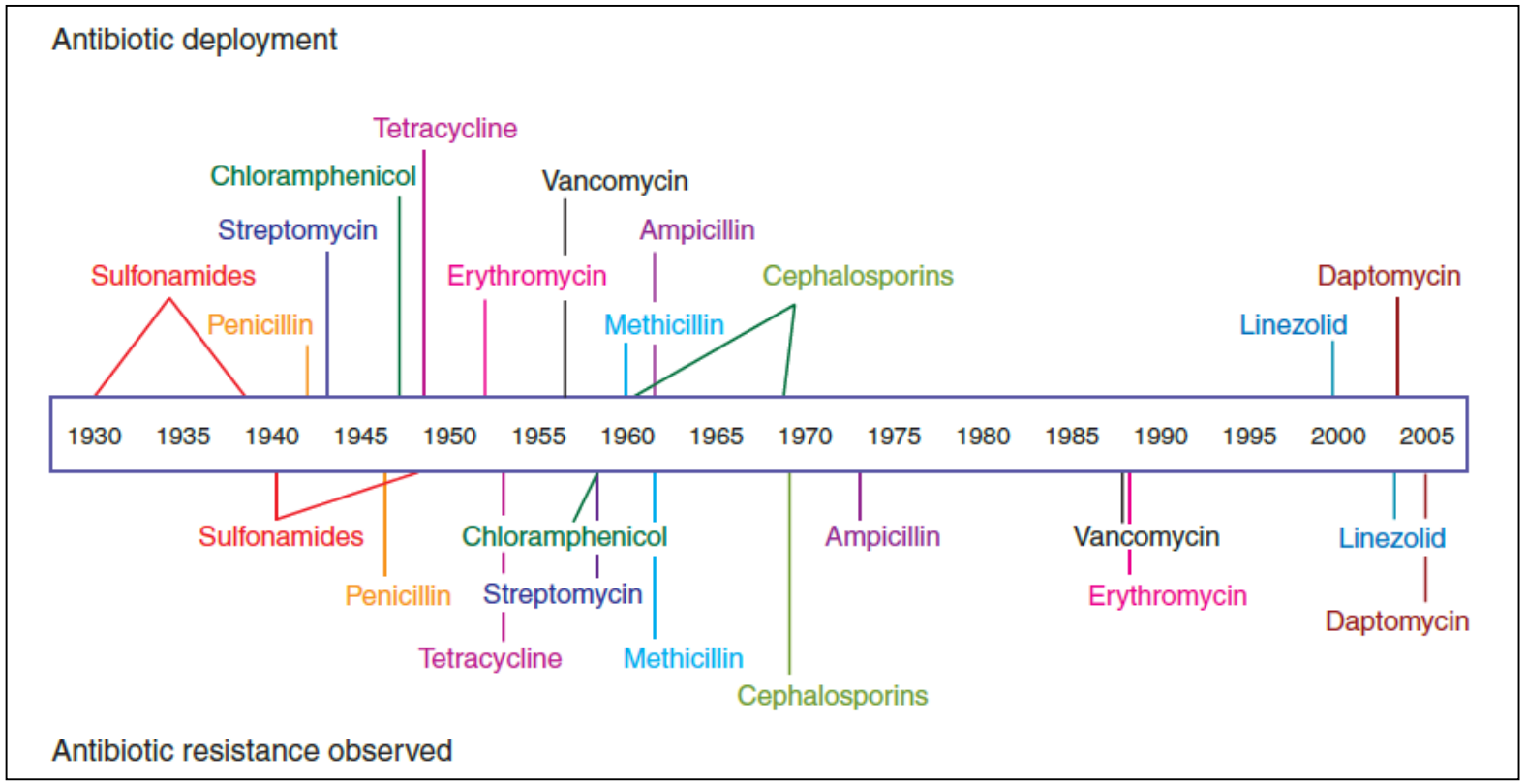
[a]TB Modelling Group, Department of Infectious Disease Epidemiology, [b]TB Centre, and [c]Department of Clinical Research, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom

Significance:

Using mathematical modeling, fitted to trial data, we show **IPT does not cure Mycobacterium tuberculosis infection in the majority of HIV-infected individuals.** These results contrast with long-held beliefs about the working mechanism of IPT, but explain the empirical results. These results are important for determining appropriate clinical guidelines for IPT use in varying epidemiological settings.

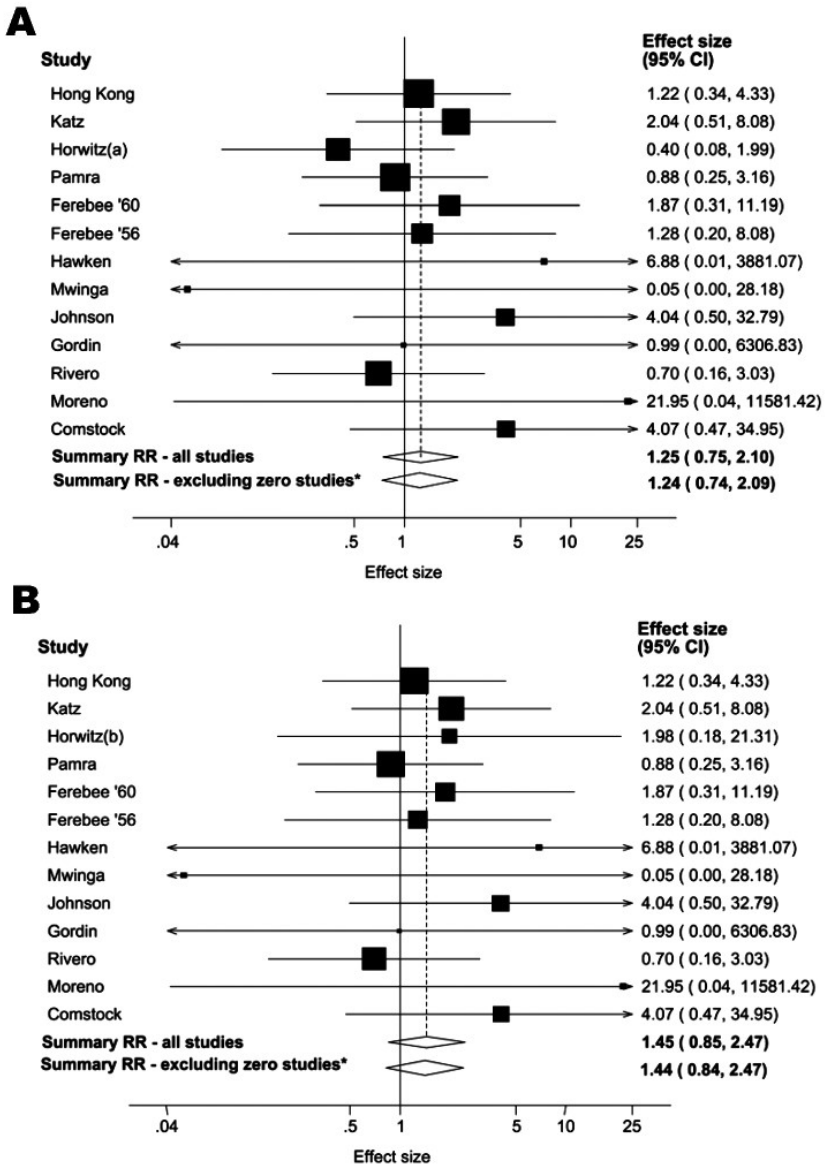
2014 *PNAS*

A return to the Pre-antibiotic era?



Clatworthy *et al*. 2010*; Nat Chem Biol* 3:541-548

Isoniazid preventive therapy and risk for resistant tuberculosis (13 studies HIV+ & HIV-)



These are relative risks
NB. SA RCTs reported 12%, 23% & 24% INH resistance

How will INH resistance develop if 6,5 million HIV+ individuals in South Africa receive IPT in the public sector?

Balcells ME *et al*, *Emerg Infect Dis*. 2006 May;12(5):744-51.

Science Translational Medicine AAAS

Community-Wide Isoniazid Preventive Therapy Drives Drug-Resistant Tuberculosis: A Model-Based Analysis

Harriet L. Mills *et al.*

Sci Transl Med **5**, 180ra49 (2013);
DOI: 10.1126/scitranslmed.3005260

A Deeper Look at Drug Resistance

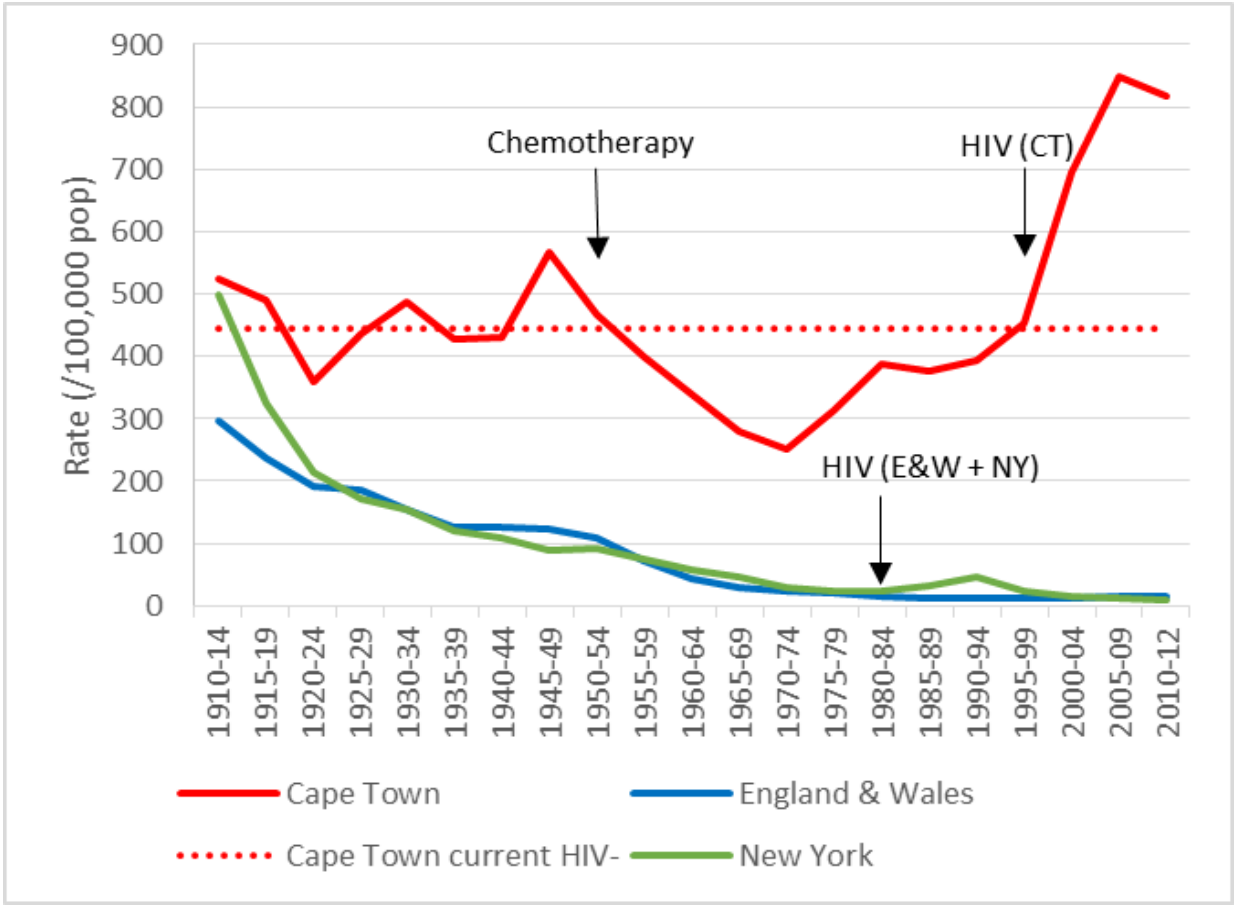
Although some things may seem obvious at first glance, looking in more depth may paint a different picture. In some complex situations, asking questions in different ways may lead to very different answers. One example is the use of isoniazid preventive therapy (IPT) for tuberculosis (TB) in HIV-prevalent communities. Because HIV-infected individuals are much more likely to develop TB than immunocompetent people, the World Health Organization has recommended the use of IPT in HIV-infected individuals that are symptom-free for TB co-infection. The use of IPT has raised the specter of drug resistance; however, to date, studies have not observed an increase in drug-resistant TB in individuals on IPT. Now, Mills *et al.* use mathematical modeling to show that even if IPT does not increase drug resistance in infected individuals, **community-wide IPT can drive increases in drug resistance at the population level.**

They found that community-wide IPT increases selective suppression of drug-sensitive infection, thus indirectly conferring an advantage to drug-resistant strains. **These data should be considered when determining policy for preventive therapy.**

Conclusions: INH preventive therapy-will it contribute to TB control in RSA?

- Total lack of any effect in a large community study
- Modest impact in 1 of adult studies
- Active intensive screening pre-IPT more productive!
- Rebound TB on stopping IPT (even after 36 months)
  - lack of cure
  - removal of protection
- Risk of resistance, especially when screening relaxes
- Spending resources on IPT with little or no benefit will divert us from meeting the ART gap
- And thinking about transmission interruption……

TB notification rates Cape Town, England & Wales and New York 1910-2012



The current (2009-2012) HIV-negative rate in Cape Town was 445 per 100,000 population, the HIV-positive rate was 6338 per 100,000 population .

Transforming the Fight Against Tuberculosis: Targeting Catalysts of Transmission

David W. Dowdy,[1] Andrew S. Azman,[1] Emily A. Kendall,[2] and Barun Mathema[3]

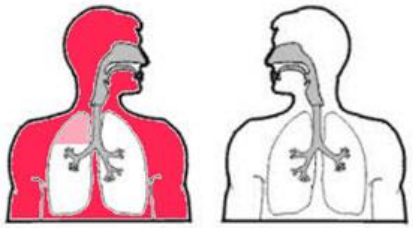
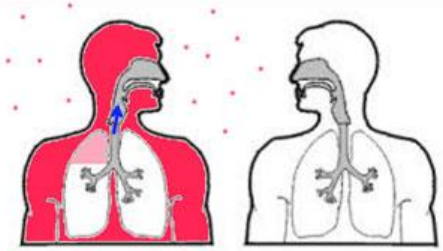
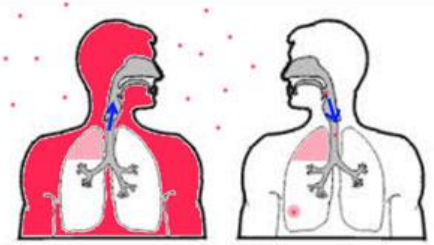
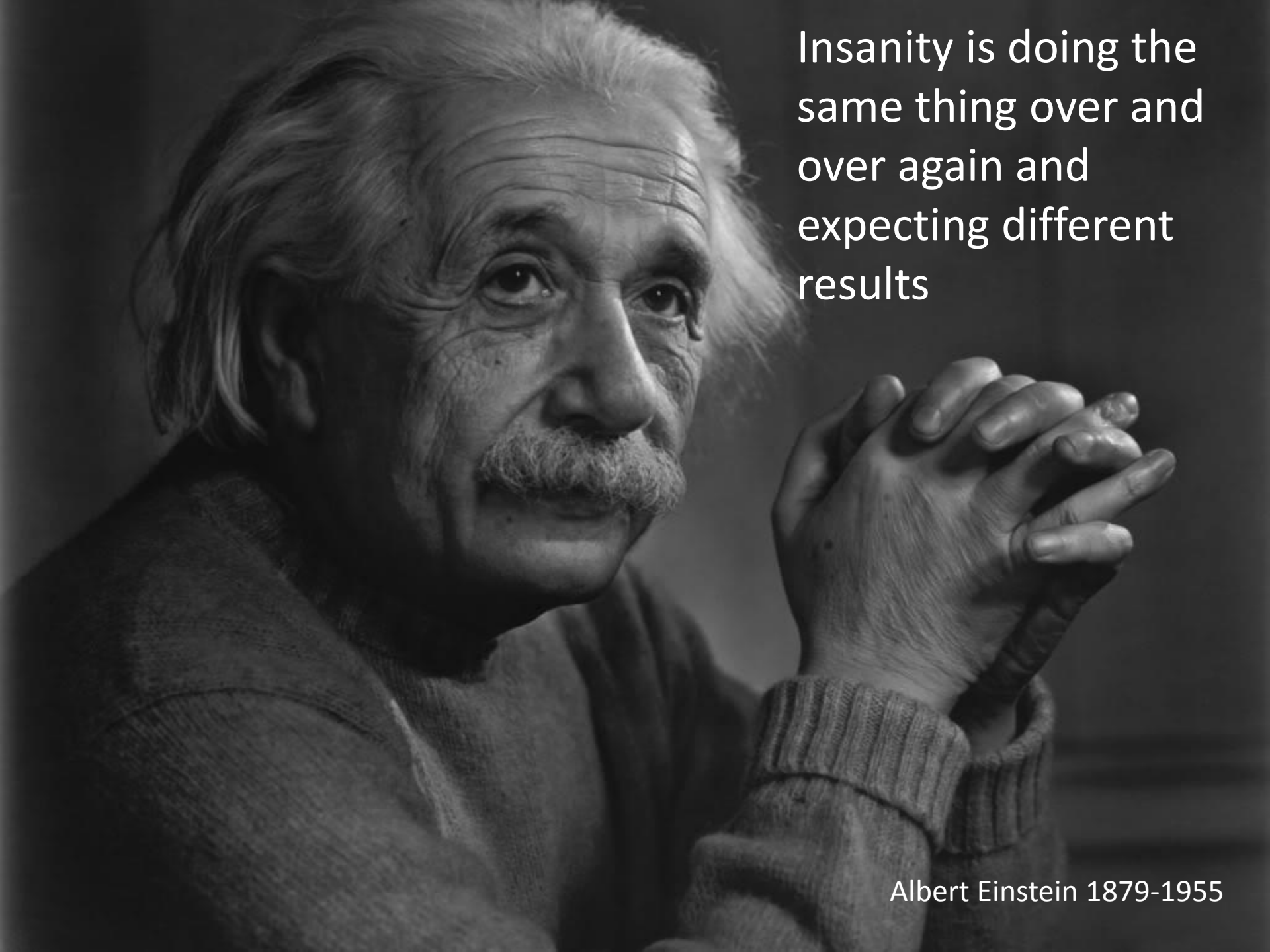
		
Step 1: Contact	**Step 2: Generation of Infectious Particles**	**Step 3: Infection and Disease Progression**
A person with active TB and a susceptible person come into sufficiently close contact for airborne transmission of *M. tuberculosis* to occur.	The person with active TB aerosolizes particles of appropriate quality (size, etc.) containing bacilli of sufficient number and virulence to transmit infection.	The susceptible host has an immune background that facilitates initial infection, non-sterilization of the corresponding granuloma, and eventual progression to infectious disease.
Catalyst: Increased contact rates	*Catalyst:* Increased infectiousness	*Catalyst:* Increased susceptibility

Figure 1. The cascade of tuberculosis (TB) transmission and disease.


Insanity is doing the same thing over and over again and expecting different results
Albert Einstein 1879-1955