A Bit of Relevant Personal History - 1

- Seminar in Infectious Diseases - Muhlenberg Hospital, NJ, March 26, 1980
- Invited panel with Donald Armstrong, Chief, Infectious Diseases, Memorial Sloan Kettering Hospital (Infectious Diseases Icon), Lee Reichman (new kid in academia), Others
- Armstrong presented case after case of disseminated tuberculosis in his patients on cancer chemotherapy
- Reichman shyly asked “If you have so many cases of TB in these obviously immunosuppressed patients, why don’t you give INH before treatment?”
- Armstrong, disdainfully and dismissingly looked at the questioner and emphatically answered: “We don’t do that”
Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups

Preventive treatment of persons at high risk and vaccination of children

Collaborative TB/HIV activities, and management of co-morbidities

Treatment of all people with TB including drug-resistant TB, and patient support

The management of LTBI among high risk groups is a key component of the World Health Organization’s new End TB Strategy. It is necessary to end the global TB epidemic and eliminate TB.

But this effective and appropriate modality is usually ignored or forgotten, rather than promoted and enhanced

It is almost like the TB community considers it a taboo

Nomenclature Modifications

• Ideal nomenclature should be simple and accurate enough to be scientifically descriptive, and easily understood by providers and patients alike
• Treatment of latent TB infection rather than preventive therapy, chemoprophylaxis or IPT promotes somewhat greater understanding of the concept
• But, latent is confusing and usually not understood by, or relevant to patients; certainly does not suggest immediacy or urgency

Bottom Line:

• We are TREATING TB INFECTION (TTI), so why not call it that
The Tuberculosis Taboo

Treating TB Infection: History -1

- The first population based study, starting in 1957, was George Comstock’s USPHS randomized controlled trial in household contacts in Bethel, Alaska (described in the report as an "undeveloped area") TB incidence: 578/100,000
- Resulted in a 69% reduction after one year and a community-wide 30% reduction in TB incidence

Treating TB Infection: History -2

- Marked decline in Bethel death rate (from 650 to 0 over 30 years); and incidence rate (from 1,854 to 141 over 28 years)
- The marked reduction in infection and death rates were due to: intensive case finding, hospitalization, ambulatory treatment programs, as well as the fact that much of the Bethel population received isoniazid in the TTI studies

Treating TB Infection: History -3

- The concept of a public health orientated TTI intervention faded following the 1960s
- Difficult logistical requirements and the advent and widespread promotion of DOTS made TTI only secondary
- The recent realization that TB elimination requires additional control measures, has revived the idea of a programmatic role of TTI
- ERS’s European Forum for TB Innovation (2012) reinvigorated promotion of TTI
Treating TB Infection: History -4

- In response to the alarming occurrence of MDR-TB and XDR-TB in the WHO European Region, a Consolidated Action Plan was developed for all 53 Member States, recognizing that TTI may be relevant to reduce the burden of disease, in addition to case finding and treatment.
- Despite its inclusion in the Action Plan and country guidelines, TTI is still largely not implemented, almost like a taboo.

Treating TB Infection: History -5

- In India, China, Russia and South Africa, TTI is a policy for children <5 and PLHIV, but is rarely implemented or reported.
- NTPs often lack funding for CXR to exclude active TB, or to procure tuberculin; and fear poor adherence, side-effects, and development of resistance.
- Worldwide shortages of Tuberculin, Isoniazid or other drugs may impact TTI programs.
- Consequently, even contacts at highest risk of developing TB may not be managed adequately, TTI, thus, practically remaining a taboo.

TB in Contacts

- Since TB is always spread person-to-person by the airborne route, investigating contacts is a very productive way to find new infections and cases.
- An initially paucibacillary infection can be treated and eliminated far more easily when diagnosed, rather than later when it progresses to clinical TB.
TB in Contacts - Risk of Active TB following infection

- 613 Australian close contacts, 2005-2013
- 67 (10.9%) active TB; 14.5% when excluding death, migration, preventive therapy
- Most risk is within first 5 months after infection
- Greatest risk, 56% <5 year age; 28% age 5-14
- Conclusions:
  - Risk is several fold higher than previous estimates; particularly, immediately following infection, and in children

J. Trauer et al, Chest 2016, 149:516-525

TB in Contacts in US - 2012

- Average of 11 contacts of each TB case (21 contacts for the most contagious TB patients) are infected
- Approximately 1% of contacts already have TB disease at the time of examination

Modified from MMWR, 2016 p.1374

Principles of TBI treatment

- Public health approach with individual benefit which should outweigh any individual risk
- Complement to active TB case finding and treatment activities

Modified from WHO Guidelines on the Management of LTBI, 2015
The Tuberculosis Taboo

Inducing drug resistance and ruling out active TB

- There is no significant risk of inducing drug resistance
- Always ask about symptoms of TB
- Do chest radiography
- Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions before treating for TBI

WHO new recommendations on risk groups for TTI beyond PLHIV and children

<table>
<thead>
<tr>
<th>Risk population groups</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>People living with HIV</td>
<td>Strong: systematic testing and treatment should be performed</td>
</tr>
<tr>
<td>Adult and child PTB contacts</td>
<td>Strong: systematic testing and treatment should be performed</td>
</tr>
<tr>
<td>Patients initiating anti-TNF treatment</td>
<td>Strong: systematic testing and treatment should be performed</td>
</tr>
<tr>
<td>Patients receiving dialysis</td>
<td>Strong: systematic testing and treatment should be performed</td>
</tr>
<tr>
<td>Patients preparing for transplantation</td>
<td>Strong: systematic testing and treatment should be performed</td>
</tr>
<tr>
<td>Prisoners</td>
<td>Conditional: Systematic testing and treatment should be considered</td>
</tr>
<tr>
<td>Health workers</td>
<td>Conditional: Systematic testing and treatment should be considered</td>
</tr>
<tr>
<td>Immigrants from high burden countries</td>
<td>Conditional: Systematic testing and treatment should be considered</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>Conditional: Systematic testing and treatment should be considered</td>
</tr>
<tr>
<td>Illicit drug user</td>
<td>Conditional: Systematic testing and treatment should be considered</td>
</tr>
<tr>
<td>Patients with Diabetes</td>
<td>Conditional: systematic testing and treatment is not recommended unless they belong in the upper two groups</td>
</tr>
<tr>
<td>People with harmful alcohol use</td>
<td>Conditional: systematic testing and treatment is not recommended unless they belong in the upper two groups</td>
</tr>
<tr>
<td>Tobacco smokers</td>
<td>Conditional: systematic testing and treatment is not recommended unless they belong in the upper two groups</td>
</tr>
<tr>
<td>Under-weight people</td>
<td>Conditional: systematic testing and treatment is not recommended unless they belong in the upper two groups</td>
</tr>
</tbody>
</table>


US Preventive Services Task Force

- Supports CDC guidance to test for tuberculosis infection in populations that are at increased risk
  - People born in or who frequently travel to countries where TB disease is common
  - People who currently, or previously, live in large group settings
- CDC also recommends testing for TB infection among healthcare workers, contacts of people with confirmed or suspected TB disease, and as part of disease management for people with certain conditions, such as HIV and diabetes, or as indicated prior to the use of certain medications

September 8, 2016
Diagnosis of TBI

- Two tests shift the investigation from the skin to the blood - QFT Gold In Tube® & T Spot TB®
- Advantages:
  - Allows for introduction of new levels of accuracy and controls
  - Allows for one visit
  - Allows for the use of antigens that cannot be injected into the skin
  - No boosting
  - Not affected by prior BCG vaccination

Quality Control - TST vs. IGRA

- Next time you do or order a TST, ask yourself “when was the last time this test was quality controlled?”
- When was the last time you, yourself, or the venerable old TB nurse who has been doing TST for 40 years, or anyone else, was evaluated while doing the test?
- IGRA moves the diagnosis of TBI from the uncontrolled and unmonitored physician or nurse, to the laboratory which is quality controlled excessively

But,

There is no need to diagnose TBI unless one is going to treat TBI
The Tuberculosis Taboo

### Treatment Regimens for TB Infection

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Months of Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>9</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2x wkly**</td>
<td>72</td>
</tr>
<tr>
<td>INH</td>
<td>6</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2x wkly**</td>
<td>58</td>
</tr>
<tr>
<td>RIF</td>
<td>4</td>
<td>Daily</td>
<td>120</td>
</tr>
<tr>
<td>INH-RPT</td>
<td>3</td>
<td>Weekly**</td>
<td>12</td>
</tr>
</tbody>
</table>

**Intermittent treatment

The Tuberculosis Taboo

### Treatment of TB Infection – The 3HP Regimen

- 3 months Rifapentine and Isoniazid (12 weekly DOT doses) is as good as 9 months Isoniazid (270 daily doses) (TBTC Study 26, NEJM 2011)
- Removing required DOT does not have major effect on adherence results (TBTC Study 33)
- Potential for real impact of a 12-dose regimen to treat TBI when combined with use of IGRAs

### USPHS Study 33: Treatment completion by treatment arm: DOT v SAT v eSAT

<table>
<thead>
<tr>
<th>Treatment completion % (N)</th>
<th>DOT</th>
<th>SAT</th>
<th>eSAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>85.4 (261)</td>
<td>77.9 (262)</td>
<td>76.7 (249)</td>
<td></td>
</tr>
</tbody>
</table>

CROI 2015

Updated Courtesy, Bob Belknap, Andrey Borisov, Ruth Moro
May 2016

Compare to 9H completion rates of <50%

- NYC Health Department, 2016
Innovation is also inspiring activism in TB prevention: Priftin® Rifapentine

- Approved for TB infection (FDA, 2014)
- Listed in the Global Drug Facility catalogue (2016)
- Affordable price negotiated in US (2014)
- Subject of ongoing research (FDC and pediatric formulation development)

Rifapentine: Current status

- Currently registered for active and latent TB infection only in the United States
- Sanofi has started filing for registration to treat latent TB infection throughout Asia
- In Europe, the company’s filing with EMA is complicated by the EMA’s requirement for studies in the 0-2 age group
- Sanofi is developing FDCs: adults (P300 H300), dispersible for children (P150 H150) and dispersible rifapentine alone (P100) which will all have to be registered separately

Now,

Let's quickly switch our attention to contacts of MDR-TB and XDR-TB
Why Do We Have Drug Resistance?

- Inadequate treatment
  - Incorrect regimen (lack of drugs or knowledge)
  - Poor adherence

  Treatment failure / relapse with drug resistant TB

  Transmission of drug resistant TB

- It is far easier to prevent TB in an individual infected without disease than to treat a full blown case of TB or drug resistant TB

A Bit of Relevant Personal History -2

- In December 2011, I had the opportunity to visit Estonia to observe their program and meet several MDR-TB patients
- I found a severe MDR-TB problem caused by previously poor programs
- But, I also found a dedicated staff, good programs and effective implementation of the WHO Stop TB Strategy
- This paradox was explained by the fact that each of the MDR-TB patients I met had been infected by a known MDR-TB patient who did indeed receive appropriate treatment but after infecting the contact with MDR-TB

A Bit of Relevant Personal History -2 cont’d

- The tragedy is that the transmission of MDR-TB to contacts occurs prior to diagnosis in the source case
- It is past time to consider the heresy of acting differently
  - when the infected MDR contact has been identified, treat him/her for paucibacillary MDR-TB infection concurrently with the source patient’s treatment for MDR-TB disease rather than waiting for the contact to develop more difficult to treat, transmissible MDR-TB later
### MDR Contacts in Children

- Conservative estimates suggest that in high-burden regions there are at least two child contacts who are less than 5 years of age or who are infected with HIV per MDR-TB source case.
- Thus, more than 1 million vulnerable contacts could be considered for TBI treatment each year.
- In nearly a quarter of households with a case of MDR or XDR-TB, a contact will develop TB disease within 4 years of identification.
- Prevention of progression to MDR-TB disease with TTI could be a practical and cost-effective solution both for individuals and from the public health perspective.

Modified from JA Seddon et al., Lancet 2012

### MDR Contacts in Children - 2

- It is estimated that over 67 million children are infected with TB and therefore at risk of developing disease in the future:
  - 5 million with INH resistance; 2 million with MDR; 100,000 with XDR.
- Every year 25,000 children develop MDR-TB and 1200 XDR-TB.


### But,

- Published guidelines don’t yet accept TTI of MDR-TB case contacts
ECDC Guidance (2012)

• The systematic review concludes that it is not possible with the available evidence to support or reject preventive therapy (for contacts of MDR-TB and XDR-TB)
• More research and particularly clinical trials are warranted before any recommendations in favor of (or against) preventive therapy can be made


• NO Recommendation
• Panel agreed on strict clinical observation and “close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts of MDR-TB cases”

I respectfully disagree…

because, even with supreme effort, including global PMDT, the overall global MDR-TB/XDR-TB cure rate remains less than 50%; which is no better than TB cure in the pre-drug era!
The Tuberculosis Taboo

- It is time to start identifying well defined high risk contacts of MDR-TB patients and to treat them with appropriate fluoroquinolone containing preventive therapy
- After all, MDR-TB treatment would be hard pressed to be any less successful


Richard Brostrom, MD, May 2016

**Image 1:**
The Tuberculosis Taboo

**Image 2:**
The Tuberculosis Taboo

**Image 3:**
The Tuberculosis Taboo
The Tuberculosis Taboo

Thus, WHO needs to update its priority recommendations

- Prevent regular TB which then can be mismanaged into DR-TB and treat contacts of MDR-TB with Fluoroquinoline containing preventive regimen

Modified from WHO, 2016

- So there truly are compelling reasons for adopting and promoting TTI
- But how do we stop treating TB infection from being considered a taboo?

A Bit of Relevant Personal History -3

- One of the major things that I’ve learned in over 50 years of practice dealing with tuberculosis patients, is that in the overwhelming majority of cases, I can convince a patient to take, or not to take, a course of treatment. If I think it is important, I can usually get the patient to think it is important
- In other words, a practitioner must truly believe in a strategy, in order to promote a strategy
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Bottom Line

- A case of TB prevented, is a patient who won’t get sick, won’t infect anyone, won’t be absent from work or school and in whom physician mismanagement or patient non-adherence cannot cause MDR-TB
- The first pillar of WHO’s new End TB Strategy includes treating TB infection in high risk infected persons
- Appropriate treatment of TB infection in drug sensitive patients prevents active TB and consequently prevents MDR-TB and XDR-TB
- Conclusive data regarding treatment of MDR-TB infected contacts is still lacking, but is accumulating rapidly and such treatment, extremely likely, prevents new drug resistant patients

Bottom Line - 2

- It is time to accept accumulating compelling data, and adopt and promote treatment of MDR-TB infected contacts; especially to prevent a disease with a less than 50% cure rate
- So obviously, treatment of TB Infection in drug sensitive as well as drug resistant contacts should no longer be considered the Tuberculosis Taboo

So if it is no longer considered a taboo, what can we call it?
Bottom Line -3

- We now have, within our grasp, a new means for effectively diagnosing and treating TB infection with IGRAs and the 12-dose 3HP regimen
- Accurate one step diagnosis and 12 doses of non toxic medication with a 78-85% adherence rate to treat TB infection, thereby preventing not only TB and secondary cases, but also downstream MDR-TB, seems to me, to be the true “Holy Grail”, and certainly the polar opposite of “taboo”
- We just have to avail ourselves of it and enthusiastically promote and use it

Summary

- Joint use of IGRAs and 3HP are truly the Holy Grail in TB control
- The sooner these modalities are widely adopted and promoted, the sooner TB and even MDR-TB will be controlled and eliminated

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