Challenges in dealing with the TB epidemic

Jacques H. Grosset
A personal view
Tuberculosis (TB)

- Infectious disease, transmissible through aerosols produced by patients with cavitary pulmonary disease.
- Diagnosis
  - Radiography to detect abnormal shadows
  - Microscopy to detect AFB in the sputum
  - Culture of the microbe and drug susceptibility
  - Molecular methods
- Treatment
  Antibiotic combination that has the possibility to cure >95% of patients
Acid-Fast Bacilli (AFB) after Ziehl-Neelsen staining of a sputum smear

The microbe
- Acid fast staining, a key for rapid diagnosis
- Slow growth (chronicity of the disease)
- High frequency of naturally occurring drug resistant mutants
The current short-course treatment for active tuberculosis

Duration: 6 months
Antibiotics: rifampin (R), isoniazid (H), pyrazinamide (Z), ethambutol (E) for 2 months followed with RH for 4 months (2RHZE/4RH)

Efficacy: > 95% vs. drug-susceptible TB... if
- all drugs are available,
- appropriately prescribed,
- appropriately delivered,
- and actually taken by the patient for the entire treatment duration

... BUT
First, some lessons from the past...
The IUAT trial, 1960

(IUAT Bull. 1964; 34: 82-150)

- At the end of the fifties, a majority of TB “experts” were still convinced that once a TB patient, always a TB patient (like a “leper”): a patient can be “stabilized” but never cured

- To convince those in doubt, a multi-center (Europe, Asia, America, Africa) study was conducted under the auspices of IUAT among 581 smear +ve patients with pulmonary TB to study the efficacy of 18 months daily treatment with 3SHP*/15HP

- The results were unambiguous...

* (S, streptomycin 1g IM; H, isoniazid 300mg per os; P, PAS 10g per os)
A painful finding

• All of the patients (n= 317) who received the prescribed regimen were cured (not a single failure!)

• But ... almost 50% of the patients did not receive or did not take the prescribed regimen for the full duration, and ... did not perform as well

• **Conclusion**: There is a long way between theory and practice! The development of XDR-TB, a man-made phenomenon, was predictable in the sixties!
In addition, many TB programs are detecting no more than 50% of estimated number of cases.
Consequences 1.

<table>
<thead>
<tr>
<th>Forms of TB</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incident</td>
<td>Prevalent</td>
</tr>
<tr>
<td>All</td>
<td>9.4 million (1.1 or 12% HIV +ve)</td>
<td>14 million</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>440,000 (4.6%)</td>
<td>?</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>30,000 (0.3%)</td>
<td>?</td>
</tr>
</tbody>
</table>

* Global TB 2007-2009, WHO
### Consequences 2. Epidemiological impact of treatment failures

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Died</th>
<th>Cured</th>
<th>Chronic*</th>
<th>Epidemiological impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>No treatment</td>
<td>50%</td>
<td>25%</td>
<td>25%</td>
<td>0</td>
</tr>
<tr>
<td>Adequate treatment</td>
<td>1-5%</td>
<td>≥ 95%</td>
<td>1-5%</td>
<td>Very positive</td>
</tr>
<tr>
<td>Inadequate treatment</td>
<td>15%</td>
<td>50%</td>
<td>35%</td>
<td>Negative**</td>
</tr>
</tbody>
</table>

* including failures, treatment abandons, etc. = still sources of infection  
** inadequate treatment produces many more chronic patients, i.e. many more sources of infection in the community than no intervention at all, and a proportion of them are drug resistant!
What could we propose?
Innovation, innovation, innovation!

• Innovative techniques in tuberculosis are urgently needed ...and thus should be funded and implemented

• However, innovative techniques will not substitute for ensuring regularity of drug-taking, which is the key to success...

• except if we discover a magic bullet (vaccine, drug, or long-lasting fixed drug combination) that would only need to be shot once!
How to innovate?

Some examples...
I. The patients to cure

• While everyone is focused on the treatment of MDR-TB, the exclusive* priority should be given to the cure of the fully drug susceptible new cases

• Why?
  - Because the priority is to cut the vicious circle “Treatment failure of new cases-production of MDR-difficulty in treating MDR”
  - Because it is much easier to cure new cases than MDR
  - Because if we are not able to cure easy-to-cure new cases we are not able to cure difficult-to-cure MDR

*in case of flooding in your bathroom what are you doing?
Ia. Improving cure rate of TB

• Stop talking about care or treatment of patients, talk only of “cure”. The only acceptable objective is to **cure every diagnosed patient**

• **How?**
• Make complete treatment available and insure that the patients swallow their medicines from initiation to completion of treatment

• How to make patients swallow their medicines?
  - education: +++ (of doctors, health workers, patients)
  - Real Directed Observed Treatment (DOT)
  - In many places, it would require a complete reorganization or re-invention, for example of “hostellization of patients”

• Develop much shorter drug regimens
1b. Develop much shorter TB drug regimens

- Better use of existing drugs
- Use of new drugs
“New” potential drugs for TB

1. Long-lasting rifamycin derivatives (rifapentine)
2. Fluoroquinolones (MXF)
*3. the new diarylquinoline TMC207 or J
*4. the metronidazole derivatives (Pa-824, OPC-67683)
5. Oxazolidinones
6. Benzothiazinones (BTZ)
*7. Clofazimine
Diarylquinoline R207910 or “J”

• MIC for *M. tuberculosis* = 0.06 µg/ml

• $C_{\text{max}}$ of 0.5µg/ml and $t_{1/2}$ of 24h: after single dose, serum concentrations are above MIC for 3 days!

• Time-dependent activity: the anti-bacterial starts after several days of exposure in vitro and in humans

• No cross-resistance with known drugs

• Inhibit the proton pump of ATP synthase
Bactericidal activity of J combinations in the mouse model of TB

J, diarylquinoline 25mg/kg; R, rifampin 10mg/kg; Z, pyrazinamide 150mg/kg; H, isoniazid 25mg/kg
Daily (5/7) oral treatment; 10 mice per time point
(From Ibrahim et al., AAC 2007; 51:1011-1015)
Early bactericidal activity of J-containing regimens in mice

From Andries et al., Antimicrob Agents Chemother 2010; 54: 4540-4544
Early Bactericidal Activity (EBA) of the Diarylquinoline

(From Rustomjee et al. AAC 2008; 52: 2831–2835)
Time to culture conversion of MDR-TB patients

Proportion of Culture Positive vs Time (in Weeks)

A
Nitroimidazopyran Pa-824

- MIC of 0.12-0.25 μg/ml for \textit{M. tuberculosis}
- Cmax of 20 μg/ml and \( T_{1/2} \) of 12 – 14 hr in mice after 100mg/kg dose in mice
- Concentration dependent activity
- Might inhibit protein and cell wall mycolate synthesis
Lung CFU counts in mice treated with Pa without RIF and INH

(Nuermberger & al. AAC 2006;50:2621-2625)
Figure 2: Bilinear regression showing the fall in mean log_{10} CFU from baseline
CFU=colony forming unit.
The case of clofazimine

- Clofazimine is a rimino-phenazine dye developed by Vincent Barry in the fifties for treatment of TB that became a leprosy drug (100mg/day):
  - Its MIC for *M. tuberculosis* is 0.5 µg/ml.
  - As its half life is about 70 days, it accumulates in the tissues; after 2 months of treatment, the lung concentration in mice and humans is on average 1000 µg/gm (Grumbach 1960; Mansfield 1974)
  - After stopping treatment, it takes ≥ 2 years for tissue concentration to be less than 0.5µg/gm.

- A 9-month drug regimen including gatifloxacin + ethambutol + pyrazinamide and clofazimine throughout achieved in Bangladesh (Van Deun et al., Am J Respir Crit Care Med 2010; 182: 684–692 close to 90% relapse-free cure rate.)
Additive effect of clofazimine to second-line regimen in TB infected mice

A, Amikacin 100mg/kg; M, Moxifloxacin, 100mg/kg ; E, Ethambutol, 100mg/kg ; Z, Pyrazinamide 150mg/kg, C, Clofazimine 25mg/kg

a a single mouse was culture-positive on undiluted charcoal plates with 14 and 17 CFU (drug susceptible)
bone mouse was positive on both undiluted plain (14 and 21 CFU) and charcoal (79 and 81 CFU) plates. This isolate was clofazimine resistant but remained moxifloxacin and ethambutol susceptible
cone colony each on mouse 1 and mouse 2 lung homogenate at 1:10 dilution
An ultra short-course regimen to test

- **Rationale**: Take advantage of both the potent bactericidal activity of RHZE and the Pk of clofazimine (long half life and accumulation in lung tissue)

- **Protocol**:
  1. Combine the most effective drug regimen (RHZE) with clofazimine for a relatively short period of time (2-4 months) to kill majority of bacilli, then stop treatment and let the “accumulated” clofazimine do the job of eliminating persisters
  2. Other possibilities: (i) Substitute the diarylquinoline TMC 207 for clofazimine; (ii) Substitute moxifloxacin for isoniazid after the first two days of treatment
2. Treatment of TB in HIV-infected patients

- HIV-infected TB patients respond as well as immune competent patients to TB treatment
- Is it a dogma or a reality?
Lung CFU counts in Balb/C (B) and nude (Nu) mice treated 5/7 (---) vs 7/7 (→) with RHZE
PHE versus PHEZ in BALB/c and Nude mice

![Graph showing the comparison of PHE and PHEZ in BALB/c and Nude mice.](image-url)
Conclusion 2

• Response to treatment is less active (≤ 1.5 log_{10} less kill) in immune-deficient than immune-competent mice

• As a consequence, irregularity in drug-taking (5/7) + immune deficiency is a risky combination for failure and drug resistance

• These findings support the earliest antiretroviral treatment in TB patients co-infected with HIV
Final conclusion

• More than ever there is a huge amount of TB research to be performed and the research is more difficult than before. The easiest has been done, the most difficult remains to be done.

• Do not believe in dogma, in short-cuts, in easy-going

• Do remember that implementation in the field is more problematic than pure science in the lab.
Acknowledgments

• NIH NIAID N01 30036 (PI William BISHAI)
• NIAID contract N01-AI40007
• NIH NIAID 1R01AI082612-01
• BILL AND MELINDA GATES FOUNDATION
• All members of the Center for TB Research and especially William Bishai, Deepak Almeida, Paul Converse, Si-Yang Li, Eric Nuerberger, Ian Rosenthal, Sandeep Tiagy, Zahoor A. Parry, and Ming Zhang
• And my gratitude to Stewart Cole, Williams Jacobs, Andy Vernon, Rick O’Brien, and Giorgio Roscigno for their collaboration and sharing common objectives.