New approaches for the diagnosis of smear negative TB among PLWHA in resource constrained settings

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Sputum smear negative pulmonary TB

**WHO 1991**
- At least two negative AFB sputum specimens
  - AND
- Radiographic abnormalities consistent with active TB
  - AND
- Decision by a physician to cure with a full curative course of anti-TB chemotherapy
  - OR
- A patient with AFB smear negative sputum which is culture positive for MTB.

**WHO 2003**
- At least three negative sputum specimens for AFB
  - AND
- Radiographic abnormalities consistent with active TB
  - AND
- No response to a course of broad spectrum antibiotics
  - AND
- Decision by a clinician to treat with a full course of anti-TB chemotherapy
Extrapulmonary TB

WHO 1991

• A patient with histological and/or clinical evidence consistent with active TB AND
• Decision by a physician to treat with a full curative course anti-TB OR
• A patient with one culture specimen from an extrapulmonary site positive for MTB

WHO 2003

• One culture positive specimen OR
• Histological or strong clinical evidence consistent with active extrapulmonary TB, followed by a decision by a clinician to treat with a full course of anti-TB chemotherapy.
Differential diagnoses of smear negative pulmonary TB in PLWHA

- Bacterial pneumonia
- Kaposis sarcoma
- Pneumocystis carinii pneumonia
- Cryptococcosis
- Nocardiosis
- Penicilliosis
- Melioidosis
- Histoplasmosis
- Etc.
Proportion smear negative of all pulmonary cases with HIV prevalence in selected sub-Saharan African countries, 2003.

$R^2 = 0.1601$
TB in Zimbabwe 1996-2000 case-notifications

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<th>Year</th>
<th>PTB-ND</th>
<th>PTB-</th>
<th>PTB+</th>
<th>ETB</th>
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<tr>
<td>2000</td>
<td>21%</td>
<td>30%</td>
<td>31%</td>
<td>18%</td>
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50% increase in case load
Magnitude among PLWHA

- SN pulmonary = 24-61%
- Extrapulmonary = 4-40%
- Institution based studies under routine programme and skewed towards smear+
- Increased mortality than smear +
  - Hazard ratio SNP (2.2) and EP (1.7)
- Autopsy studies show 14-54% of deaths due to TB (including undiagnosed)
Smear microscopy in PLWHA

- Scanty sputum (<10AFB/100HPF) is common in HIV+
- AFB detected in 80% re-examined scanty sputum (Bangladesh) and 95% of scanty sputum were culture + (Nigeria)
- Considering scanty smears as + would result false positives in less than 1% of the patients (Nigeria)
Smear microscopy in PLWHA

- Fluorescence microscopy
  - improves sensitivity up to 18%
  - Cost effective- $40 (on 2 sputa) vs $57 (ZN 3 sputa)
  - Reduce time needed (4 mt vs 10 mt)

- Sputum liquefaction and concentration
  - Bleach method: 16-125% improvement
  - Not tested under programme condition
  - Method not standard
Sputum Culture

• 49% of HIV + TB patients had negative smear on direct microscopy but their sputum was culture positive

• Needs sophisticated infrastructure and expertise and is (?) expensive

• Culture is currently recommended
  – Surveillance of drug sensitivity
  – Treatment failure and relapse
  – Repeated negative smear results
    Could this be a barrier?

• Availability at district level vs CD₄ machine expansion
Use of diagnostic algorithm

- Not validated
- Based on consensus

The current WHO recommended algorithm (2003)
Problems with current practice for PLWHA

- Empiric antibiotics trial for up to 4 weeks
- AFB smear (up to 9) even before empiric antibiotics
- HIV status and severity of disease excluded
- CXR not indicated earlier despite being useful
- Duration: min 13 days; max 44 days
- Number of consultations ranging 5 – 7

In the meantime patients die!
The 4th TB/HIV WG meeting in Addis Ababa, Ethiopia
September 20-21, 2004

"Improvements in the diagnosis and management of smear-negative and extrapulmonary cases of TB need to be explored and existing guidelines reviewed in the context of emerging new diagnostics."
Key features of revised algorithm

- Increased speed and sensitivity
- HIV test for TB suspects
- Severity of disease
- Presumptive TB treatment for seriously ill patients at peripheral institutions
- Antibiotics to treat a clinical condition rather than a diagnostic step
- AFB, sputum culture and CXR together all at a time and as early as possible
The way forward

• Fast track search for new, easy and rapid tools
  *The quest should be a political and a human rights agenda*

• Advocacy and activism for massive investment for the search (Learn from the HIV community)

• Solar-powered technology for settings where there is no electricity
The way forward

• Improve and expand what is at hand
  – Sputum concentration methods
  – Expand fluorescence microscopy
  – Expand sputum culture capacity
  – Speedy, sensitive and validated algorithm
  – Enhanced utility of CXR

*How can the WG on New Diagnostics help?*
Way forward

- Improve and expand existing diagnostics aggressively along the search for NEW tools.
- Expand the actors and level of scientific interest including in resource limited settings
  - More researchers
  - Fellowships for young researchers
  - Programme managers for implementation
  - HIV/AIDS community-activists, researchers etc.
  - Other Working groups
Wish list for what is at hand

– Standardised bleach technique
– Fluorescence microscope: solar powered and with no need for dark room
– District based rapid culture facility
– Solar powered portable CXR
– Effective, efficient and validated clinical algorithms

NOT FOR 2007 or 2010 but for NOW!!!