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Improving the diagnosis of active TB in people with HIV

HIV has led to a dramatic increase in hard-to-diagnose smear-negative pulmonary and extrapulmonary TB. Delay caused by the inherent difficulty diagnosing these forms of TB, combined with an accelerated rate of TB disease progression in people with HIV, results in a very high rate of mortality in coinfecting patients — even in settings where free treatment for both HIV and TB is now available, according to Dr. Graeme Meintjes of the University of Cape Town.

Speaking at the 36th Union World Conference on Lung Health in Paris, Dr. Meintjes said: “We now have free TB treatment, free antiretroviral therapy available from government-run clinics in all the communities that [our hospital] serves and yet we are still seeing extremely high rates of mortality related to coinfection.”

Dr. Meintjes works at GF Jooste Hospital, a secondary level referral hospital serving impoverished communities such as Khayelitsha and Guguletu in the Western Cape, areas with a high incidence of both HIV and TB. Each month, the hospital sees at least 56 HIV-related deaths, 57% of which are due to TB, and this does not include people in the community dying at TB hospitals, hospices or at home. The actual rate of TB related deaths in people with HIV is probably even higher, which, in fact, is supported by evidence from autopsy studies in other settings with a high burden of coinfection. These studies have found that the majority of HIV-related deaths are due either to undiagnosed TB or TB diagnosed and treated too late.

According to Dr. Meintjes, investigations of the TB deaths at GF Jooste, “have clearly identified diagnostic delay as a major factor in the high mortality we are seeing associated with HIV-TB co-infection.” In one study at the hospital, the time to diagnosis was assessed in a group of 125 patients who were ill enough to require hospital admission for suspected TB but who had essentially failed the primary care diagnostic work-up. 83% of the subjects were HIV-infected and 83% were ultimately diagnosed with TB.

“This was an extremely ill group of patients,” said Dr. Meintjes “72% were bed bound for a median of 7 days by the time of admission.” The patients had sought medical attention a median of 14 days after the development of symptoms. Then there was a 30 day delay within the health services with patients having a median of 3 visits to the health services before they were sick enough to require admission.

“One of the important findings was that the time from onset of symptoms to admission (by which point most patients were bed bound) was 60 days. This points to the rapid progression of TB in the context of HIV,” said Dr. Meintjes. He noted that studies of HIV and TB coinfection in South African miners had reached similar conclusions (Corbett). “That means that there is a narrower window of opportunity to diagnose TB in HIV infected people and to start people on treatment before they have clinical deterioration.”

Reasons for the delay in diagnosis of TB

“The fact that traditional methods of TB diagnosis (sputum smear and chest x-ray) are less reliable in HIV-infected patients causes significant delays in diagnosis,” said Dr. Meintjes.

Several published studies have shown that smear negative TB is about twice as common in HIV infected people, with rates of around

50% in some reports. Likewise, extrapulmonary disease is also much more common. And as CD4 counts decline, both extrapulmonary TB and smear negative TB become even more frequent.

Chest x-rays also look different in many people with HIV and TB, particularly in those with advanced immunosuppression.

Dr. Meintjes reviewed data from studies conducted at Somerset Hospital in Cape Town in the 1990s which addressed the radiographic appearance of TB in HIV infection. These studies found that at higher CD4 cell counts, chest x-ray shows typical upper zone opacification and cavitation. But with decreasing CD4 cell counts, a spectrum of abnormal chest x-ray presentations are possible (see graph). Some of these atypical x-ray presentations are now becoming fairly well characterized, and could indicate TB whenever a patient has low CD4 cells (more on this later in the article) (Post 1995).

However, even in those settings where the expertise exists to recognize these atypical x-ray presentations of TB, sometimes chest x-rays provide no useful diagnostic evidence whatsoever. According to another study at Somerset, a full 19% of patients with culture-proven pulmonary TB have normal chest x-rays (Hudson 2000).

In addition, other social or context-specific factors may contribute to the delay in diagnosis. For example, in the survey at GF Jooste Hospital, other reasons for diagnostic delay included male gender (associated with delays in seeking medical attention), being unemployed (which resulted in provider delay), and a tendency on the part of the patient to seek healthcare at multiple providers (leading to discontinuities in care). “There was also a suggestion that there was inadequate investigation at the primary care level – only 37% of patients reported having had the sputum sent,” said Dr. Meintjes.

“Addressing this will require an integrated approach: improving HIV services – getting patients into care and onto HAART prior to advanced immunosuppression; improving TB services by reducing diagnostic delay and offering TB preventive therapy; and, then on the service level, integrating TB and HIV services, to address this high level of mortality that we are still seeing,” he said.

Alternative approaches to TB diagnosis

Dr. Meintjes listed a number of alternative diagnostic techniques used at GF Jooste help speed TB diagnosis in people with HIV.

- Biopsy of Peripheral Lymph Nodes
- Sputum induction using an ultrasonic nebuliser with hypertonic saline
- Ultrasound looking for
- Aspiration of effusions
- TB blood cultures and early morning urine for TB culture
- Bone marrow biopsy particularly in pancytopenic patients
- Fine needle aspiration biopsy has a diagnostic yield of up to 75%
- Core or excision biopsy gave a diagnosis in 85% in one study at GFJooste
- Limitations: patient needs to have large accessible nodes.
- In a study done at Jooste, 27% of patients with a dry cough or who were smear negative on spontaneous sputum were smear positive on induced sputum.

- Also improves the diagnosis of Pneumocystis pneumonia.
- pericardial effusions, particularly with stranding
- abdominal nodes, particularly with nodes larger than 1 cm in size
- splenic hypodensities that suggest splenic abscesses
- ascites
- Both can have a yield of up to 40% in disseminated TB

And as already noted, even if they are not altogether reliable, chest x-rays can still be useful when there are diffuse miliary or nodular infiltrates (predictive of TB in patients with low CD4 cell counts) or to exclude certain other alternative diagnoses (such as PCP).

However, there may be very little time to conduct these investigations in a patient with HIV, and the fact remains that many of these procedures cannot be performed at the primary care level. By the point patients present to a referral hospital, the diagnostic window of opportunity is even narrower. Additionally, any samples obtained must still be sent off for culturing (except in the case of sputum induction for AFB smears). Given the time that culturing takes (up to six weeks) and the rapid rate of clinical progression, culture confirmed diagnoses will still come too late for many patients who are deteriorating clinically.

Slow pace of development of new diagnostic tests

One such case was Ronald Lowe, a professor of law at the University of KwaZulu Natal and one of treatment activist Zachie Achmat's closest friends. Earlier at the TB conference, Achmat recounted how delays in diagnosis cost his friend's life. Lowe had suffered from a persistent fever and cough that initially was diagnosed as bronchitis, but after four weeks of treatment with antibiotics, his illness grew worse. After an HIV and AIDS diagnosis, doctors presumed he had PCP; but again, there was no response to treatment. Four weeks later, a lung biopsy demonstrated evidence of TB. But it was too late – Lowe died three days later.

"This is the fate of countless people with TB and HIV in developing countries," Achmat said. He contrasted how easy it was for Lowe to get his HIV disease diagnosed and even staged.

"He requested an HIV test," said Achmat, "and within 24 hours, Ronald knew that he had been infected with HIV and, more significantly, that he had AIDS (his CD4 count was 108) – still, no one could diagnose his lung disease... It's interesting to compare the tale of two tests. In HIV, 25 years [since its discovery], a virus that no one understood, a virus that mutates, has many clades - you can get a test and have a reliable result in 15 minutes. Why not TB?"

But there were no major developments in lab technology to quickly diagnose smear negative TB at this year's TB conference, other than the promise of collaborations to develop such a test in the future (see this [news report](#)).

Clinical algorithms and empiric treatment

Until an inexpensive, easily applied, point-of-care, rapid diagnostic test is developed that can reliably detect active tuberculosis infection in people with HIV, healthcare workers will have to rely on the available tools - including clinical assessments or algorithms. And when a patient with HIV with what appears to be smear negative or extrapulmonary TB begins clinically deteriorating, "there

comes a point where empiric treatment becomes necessary while waiting for culture results," said Dr. Meintjes.

He presented data from two studies at Jooste conducted to validate the approach of using clinical algorithms as the basis for starting TB therapy.

The first study, previously presented as a poster at the Bangkok World AIDS conference Dr. Doug Wilson recruited 147 patients who had either 2 negative smears or a non-productive cough. If a participant fitted one of several expanded case definitions drawn from WHO and South African national guidelines (see below), samples from different sites were sent for culture, and the subject was given empiric TB therapy.

Case definitions for smear-negative case definitions (Wilson 2004 and in press).

Pulmonary

- Cough for >21 days plus
- Pulmonary opacification or nodular infiltrate on CXR plus
- Exclusion of PCP
No resolution after treatment with broad-spectrum antibiotic (except in patients with diffuse miliary [miliary] infiltrate on CXR, who are started on anti-tuberculosis treatment after cultures are sent

Lymphadenopathy

- Peripheral
- Visceral
- Significant asymmetrical peripheral nodes (long axis = 3 cm) plus
- Fever =38° C on two occasions or
- Drenching sweats for > 2 weeks
- Visceral nodes (mediastinal/hilar or abdominal nodes seen on imaging) plus
- Fever =38° C on two occasions or
- Drenching sweats for > 2 weeks

Serositis

- Pleural effusion
- Pericardial effusion
- Ascites
- Constitutional syndrome (not found to be predictive of TB diagnosis in this study)
- Lymphocytic exudates
- Effusion on ultrasound plus
- Fever =38° C on two occasions or
- Drenching sweats for > 2 weeks
- Lymphocytic exudates plus

- Fever =38° C on two occasions
or
- Drenching sweats for > 2 weeks
- Wasting (BMI of 18.5
or
- documented weight loss >5% body weight within a month)
plus
- Fever =38° C on two occasions
or
- Drenching sweats for > 2 weeks

* 1) Bilateral interstitial infiltrate; 2) exertional dyspnoea (onset < 3 months); 3 hypoxia or de-saturation 5% or more on effort.

Participants had advanced HIV disease (with a median CD4 cell count of 107). They were classified according to the case definitions, and many met more than one. If their cultures came back positive, or if they had a response to treatment as assessed by an independent clinician on chart review, patients were classified as having TB. 130 (88%) were subsequently diagnosed as having TB (103 definite, 2 probably, 25 possible).

With the exception of wasting syndrome, the case definitions were all highly predictive of a final TB diagnosis. Positive Predictive Value for TB Case Definitions

Syndrome (n)	Positive Predictive Value
Pulmonary	89%
Visceral Nodes	96%
Peripheral Nodes	94%
Serositis	89%
Wasting Syndrome	36%

"The wasting syndrome case definition performed far worse than the rest with a positive predictive value of 36% suggesting that there are significant differential diagnoses in this group," said Dr. Meintjes.

Response was monitored objectively using weight (WT), haemoglobin (HB), C reactive protein (CRP) level, Karnofsky performance score (KS) and symptom score response (SSR), assessed at baseline, 2, 4 and 8 weeks (see results in graph).

Response to empiric TB therapy in smear negative TB

"The CRP, Karnofsky performance and symptom score were the most useful predictors of response to therapy with over 80% of patients experiencing response to these indicators by 8 weeks. These indicators could thus be used to objectively assess response to empiric therapy – something which would be particularly useful in a setting where there is no access to TB cultures for diagnostic confirmation," said Dr. Meintjes.

Another study used a similar algorithm in a primary care setting at one of the Medecin San Frontiers clinics in Khayelitsha (See attachment).

Patients suspected of having TB had two smears sent for microscopy and were given an antibiotic. If both smears were negative or they were unable to produce sputum, they were given a chest x-ray and samples were sent for culture. If the x-ray was compatible with TB then TB treatment was started and the patient

followed up assessing the criteria outlined in the previous study. Patients who deteriorated despite TB treatment were to be referred to GF Jooste.

Outcomes

58 patients started empiric TB treatment

- 32 (55%) were subsequently culture positive
- Of the 26 without positive culture results:
 - 5 were "probable TB" (3 with miliary TB and 2 with lymphocytic pleural effusions) and improved on TB treatment
 - 16 were "possible TB," with significant objective responses to TB treatment by 8 weeks in terms of weight gain, symptom improvement and CRP reduction
 - 3 were lost to follow up and did not take TB treatment
 - 2 patients deteriorated despite TB treatment and died after referral to Jooste hospital

53 of the 58 TB suspects (91%) who started on empiric treatment showed objective clinical improvement by 8 weeks, and 96% of the patients who remained in care either improved on TB treatment and /or had a positive culture.

"What is important in this group is that commencing TB treatment empirically rather than awaiting culture confirmation led to patients being commenced on TB treatment a mean of 19 days earlier," said Dr. Meintjes. "This illustrates that clinical algorithms designed to identify HIV infected patients in whom TB is very likely can be used to institute early therapy and reduce morbidity and mortality associated with diagnostic delay – although it is obviously important to include in these algorithms a reasonable attempt to exclude alternative diagnoses during the initial diagnostic work-up and a more intensive work-up if patients deteriorate despite TB treatment."

Another important finding in these studies is the positive response in patients who are culture negative – which underscores the fact that even the gold standard for TB diagnosis can miss cases in people with HIV. Waiting for a positive culture result in these patients would deny them of effective treatment and probably result in their deaths.

Dr. Meintjes concluded by saying that these algorithms need to be adapted to and validated in varying regions according to differential diagnoses, HIV prevalence and other factors. However, in his talk, Achmat called for more immediate action, asking for the experts at the TB conference to not delay reaching a consensus on improved clinical algorithms to more rapidly identify TB in people with HIV. "We can't wait for another year, we have to have it now, and this meeting is the one place where the experience and the possibility of doing this actually exists," he said.

STOP TB Department of WHO issues recommendations for revised clinical algorithms for TB diagnosis

Achmat didn't have long to wait. Shortly after the TB meeting, the STOP TB Department of WHO released recommendations for new diagnostic algorithms to speed the diagnosis of TB in HIV prevalent and resource-constrained settings. These can be seen at [this page](#) on the WHO website.

The Stop TB Department of WHO has asked for comments on the recommendations and the newly developed diagnostic algorithms "from all TB and HIV/AIDS partners and stakeholders including the

academia in order to assist and contribute towards the formulation of sound and responsive public health policy for use by member states." Comments and views should be sent to <mailto:smearnegativetb@who.int> before 9 January, 2006.

HATIP will also be asking its advisory panel comments on these algorithms, and whether they have additional clinical expertise that might speed the diagnosis of smear negative and extrapulmonary TB. We hope to publish another issue with our panelists' comments in the near future.

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about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

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