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Evaluation of New Tests for Diagnostic Accuracy, Cost-Effectiveness and Effect on Treatment of Tuberculosis in Smear-Negative HIV-positive Patients in Uganda

Academic Thesis
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by
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Abstract

Background
Despite tremendous progress in the control of the global tuberculosis (TB) epidemic during the past decade, it is still a major health problem even today. The burden of TB is particularly severe in sub-Sahara Africa where TB and HIV co-infection is common, especially in those who are smear-negative. Such patients are twice more likely to die from TB than their counterparts because of delayed diagnosis and treatment. This thesis focuses on the evaluation of currently available new tests which have been developed to facilitate rapid diagnosis and early treatment of TB.

Aims
The purpose of this thesis was to increase knowledge about the diagnostic accuracy, cost-effectiveness and effect on treatment of TB of the new tests in smear-negative HIV-positive patients in a context where resources are limited.

Methods
In **study I**, a systematic review was performed to summarize and compare the over-all accuracy for smear-negative TB of the existing traditional TB tests (WHO 2007 TB algorithm) and two new tests: Xpert MTB/Rif test (a molecular-based method) and Microscopic Observation Drug Susceptibility test (a culture-based method). In **study II**, a cross-sectional study was performed to collect primary laboratory data on the diagnostic accuracy for smear-negative TB of Xpert MTB/Rif (GeneXpert), Microscopic Observation Drug Susceptibility test (MODS) and Nitrate Reductase Assay (NRA) in HIV-positive patients. The results of the three tests were compared with traditional solid Löwenstein-Jensen (L-J) TB culture and a new conventional liquid (MGIT) TB culture method. In **study III**, we modelled the cost-effectiveness of using MODS or GeneXpert-based algorithm for diagnosis of pulmonary TB in HIV-positive patients. Finally, in **study IV**, we investigated how best to treat patients with presumptive pulmonary TB who were both Smear and GeneXpert negative.

Results
From **study I**, we found that the sensitivity of the tests for smear-negative TB was moderate (61-73%). The specificity was high for both GeneXpert (98%) and MODS (91%) but moderate for the WHO 2007 TB algorithm (69%). From **study II**, we found that GeneXpert, MODS and NRA had low sensitivity for smear-negative TB in HIV-positive patients (24-49%). However, the specificity of all three tests was high (92-98%). From **study III**, we found that utilizing a MODS-based algorithm for diagnosis of pulmonary TB in HIV-positive patients was more cost-effective than utilizing a GeneXpert-based algorithm (US$ 34 versus US$ 71 per TB patient diagnosed). From **study IV**, we found that a smear and GeneXpert-negative test result had a high negative predictive value for TB. Thus, despite the low-moderate sensitivity of GeneXpert for smear-negative TB, a majority of patients (88%) responded fully to antibiotic treatment and empiric TB treatment was initiated in only a few (8%) of them.

Conclusions
GeneXpert, MODS and NRA are useful for diagnosis of TB in smear-negative patients including those who are HIV-positive. The tests could be used to improve the existing WHO 2007 TB algorithm. But since they have low-moderate sensitivity, additional evaluation for TB is required in those who test negative using these new tests. The high specificity of GeneXpert, MODS and NRA implies they are highly reliable to initiate TB treatment in those with positive results. From an economic view point, utilizing a MODS-based algorithm for diagnosis of TB in HIV patients is more cost-effective than a GeneXpert-based algorithm. Therefore, where resources are limited, MODS could be used as an alternative to GeneXpert. Using an antibiotic treatment trial in HIV patients who are both smear and GeneXpert negative could be useful to reduce empiric TB treatment because of the high negative predicative value for TB of the two combined tests.

Key words: Accuracy, Algorithm, GeneXpert, HIV, MODS, NRA, Smear-negative, TB