Studies on the prevention and control of human immune deficiency virus associated tuberculosis

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Chapter 1: General Introduction
GENERAL INTRODUCTION

The World Health Organization declared tuberculosis (TB) a global public health emergency in 1993 and since then it continues to be a global public health problem. The WHO estimates that as much as one third of the world’s population maybe infected with *mycobacterium tuberculosis* (*M. tb*), the organism that causes tuberculosis infection and disease. In 2012, there were an estimated 8.6 million new cases of TB disease of which 1.1 million (13%) occurred in individuals who were infected with HIV. There were an estimated 1.3 million deaths among individuals with TB with 300 000 of them occurring among HIV-infected TB cases.

**Microbiology and transmission of M.tb**

*M.tb*, the bacterium that causes TB has been in existence for centuries but was first isolated in 1882 by Robert Koch. It is an aerobic, non-motile, non-sporing rod which retains arylmethane dyes on treatment with acid. *M.tb* is slow growing taking 12-24 hours to generate and 2-6 weeks to form colonies. *M.tb* has different lineages including Indo-Oceanic, West African, East African- Indian, East Asian or Beijing, Euro-American and Central Asian. The transmission of *M.tb* is mostly through inhalation. Typically *M.tb* is introduced into the air through an aerosol spray generated through coughing by infectious TB case. The aerosol spray evaporates leaving behind droplet nuclei. The droplet nuclei are inhaled and deposited in the lower airways where they are taken up by alveolar macrophages in which the bacilli multiply. Additional macrophages and neutrophils surround the initial site of infection to form a primary focus. Some bacilli are transported to regional lymph nodes where secondary lesions may occur. The combination of the primary complex and regional lymphadenitis and lymphagitis is called the primary complex. The primary complex can experience any one of four outcomes: i) complete resolution and infection is not established, ii) local spread which can cause local disease iii) haematogenous spread which can cause disease in distant organs - military TB, disseminated TB and iv) apparent resolution with continued survival of mycobacteria within the lesions- clinically latent TB infection – which may reactivate in later years to cause TB disease. Post primary TB usually occurs in the lungs and may result from reactivation of latent infection or re-infection.

**Immunology of TB**

The initial immune response to *M.tb* infection is an innate one with phagocytosis of the bacilli by alveolar macrophages. The interaction of infected alveolar macrophages with other antigen presenting cells initiates an inflammatory response characterised by an influx of neutrophils and other
macrophages around the initial lesion to form an early granuloma. \(^5\)\(^-\)\(^8\) Cell mediated immunity is vital in the body’s efforts to control or contain TB infection. The antigen presenting cells, present in the cellular infiltrate at the site of infection and in the early granuloma activate \(M.\text{tb}\)-specific CD4\(^+\) and CD8\(^+\) T-cells and recruit them to the site of the initial infection. The recruited T-cells form a cellular cuff around infected macrophages, limiting their mobility and activating them for better bactericidal action against the \(M.\text{tb}\). \(^8\)\(^-\)\(^9\) When fully formed the granuloma consists of epitheliod cells, Langhans cells, fibroblasts and lymphocytes surrounding a core of \(M.\text{tb}\) bacilli and dead macrophages.

Within the granuloma \(M.\text{tb}\) can be destroyed, lie in the dormant state which characterise latent TB infection, or can re-activate depending on the continuous interaction between the \(M.\text{tb}\) and the immune system. HIV infection which depletes CD4\(^+\) T- cells results in poor granuloma formation and dissemination of \(M.\text{tb}\) but less infectious disease presumably because of less breakdown of granulomas and cavity formation. \(^8\)\(^-\)\(^10\) The role of the granuloma was initially thought to be limiting the spread of \(M.\text{tb}\) by walling of the bacilli. However, more recently it has been recognised that the granulomas may also contribute to \(M.\text{tb}\) persistence and spread by i) recruiting dendritic cells to the initial site of infection which in turn carry \(M.\text{tb}\) to regional lymph nodes and allow dissemination of \(M.\text{tb}\) elsewhere in the body, ii) creating an environment that favours the growth and persistence of \(M.\text{tb}\) where drugs do not readily reach while iii) the eventual breakdown of granulomas forming cavities leads to spread to other parts of the lung or body and to transmission of \(M.\text{tb}\). \(^5\)\(^-\)\(^8\) A better understanding of the immunology of TB- particularly of the physiological nature of \(M.\text{tb}\) dormancy or latency and what determines progression to active disease is required in order to advance the development of biomarkers, new TB vaccines, diagnostics and drugs and the control of HIV- associated TB.

**Clinical features of TB infection and disease**

The clinical presentation of TB can take different forms ranging from asymptomatic infection which is completely under immune control at one end of the spectrum and severe active disease at the other end depending on the interaction of the host immune system and \(M.\text{tb}\). \(^11\)\(^-\)\(^14\) In addition to site specific symptoms, TB disease presents with non-specific constitutional symptoms such as fever, night sweats, unintentional weight loss, fatigue and loss of appetite. The commonest site of disease is the lung. \(^2\)\(^-\)\(^4\) Pulmonary TB cases may present with cough with or without sputum production, chest pain, shortness of breath and haemoptysis. The commonest sites for extra-pulmonary TB are lymph nodes, pleura,
bones and joints, pericardium, and meninges. Disseminated forms of the disease occur particularly in the presence of immunosuppression.

**Human immune deficiency virus (HIV)**

Infection with the human immune deficiency virus (HIV) is a major cause of morbidity and subsequent mortality worldwide. In 2012, there were an estimated 35.3 million people living with HIV, 2.3 million new infections and 1.6 million deaths from HIV worldwide. Sub-Saharan Africa accounted for 70% of people living with HIV although it is home to only 14% of the world’s population.

HIV is transmitted from person –to-person through sexual contact with an infected partner, vertical transmission between HIV infected mothers and their child, contact with infected needles and sharps and through blood to blood transfusion. The risk of transmission increases with HIV viral load in the index case and for sexual transmission with the presence of genital ulcer disease.

**The immunopathology of HIV**

Following its entry into the human body, viral particles bind to CD4 receptors present on T-lymphocytes, macrophages and dendritic cells using the envelope glycoprotein gp120 receptors on the viral membrane to attach themselves. Chemokine co-receptors on the host cells also bind to the gp120 protein causing conformational changes in the CD4 cell membrane which allow the virus to enter the cell. Once inside the cell, the viral reverse transcriptase enzyme virus converts the single stranded RNA to double stranded DNA for integration into host cell chromosome and uses cellular mechanisms to produce new viral particles. The viral particles leave the cell to infect new T-lymphocytes. On-going viral replication results in progressive depletion of CD4+ T-cells - including TB-specific CD4+ T-cells- as a result of direct infection by the virus, killing of uninfected cells as a result of immune activation, programmed cell death or destruction of precursor cells in the bone marrow and lymph nodes. With the gradual depletion of the CD4+ T-cells, infected persons become susceptible to opportunistic infections, which appear at different levels of immune suppression. TB is often the first opportunistic infection individuals with HIV infection present with.
**The interaction between HIV and TB**

HIV and *M. tb* interact on many levels. (See Table 1)

**Table 1: Interaction of HIV and M.tb**

<table>
<thead>
<tr>
<th>Stage in TB progression</th>
<th>Effect of HIV on TB</th>
<th>Effect of TB on HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>↑ time spent in health facilities and possibility of exposure to TB. 17</td>
<td>↓CD4 count and↑ increases viral load and likelihood of HIV transmission 22, 23</td>
</tr>
<tr>
<td>Infection</td>
<td>↑ number of susceptible to infection ↑ infectious individuals. 18</td>
<td></td>
</tr>
<tr>
<td>Progression to primary disease / reactivation</td>
<td>↑ recurrence - HIV associated immune suppression leading to reactivation of latent infection, 19-21</td>
<td>↑ mortality during TB treatment. 40, 41</td>
</tr>
<tr>
<td></td>
<td>↑ recurrent infections. 6</td>
<td>↑ mortality post TB treatment 42, 43</td>
</tr>
<tr>
<td>Clinical presentation and diagnosis</td>
<td>↓ sensitivity of tuberculin skin test (TST) and interferon gamma release assays (IGRAs) in detecting latent TB 24, 25 ↓ sensitivity of Xpert M.TB/Rif (27) ↑ extra-pulmonary disease and disseminated forms 6 ↑ sensitivity of the urine lipoarabinomannan (LAM) test 28 ↑ &quot;atypical&quot; features on chest radiographs 26, 30</td>
<td>TB most common ADI, usually first presentation of HIV</td>
</tr>
<tr>
<td>Treatment</td>
<td>↑ immune reconstitution inflammatory syndrome (IRIS) ↑ adverse events 31, 32</td>
<td>↓ immune recovery 37, 39</td>
</tr>
<tr>
<td></td>
<td>↓ bioavailability of some TB drugs 33-35 ↑ interaction with other drugs - protease inhibitors and rifamycins 36</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>↑ mortality during TB treatment. 40, 41</td>
<td>↑ mortality post TB treatment 42, 43</td>
</tr>
<tr>
<td>Public health and health systems</td>
<td>↑ patient/case loads, staff burn out 44</td>
<td>Poor HIV outcomes 42, 45, 46</td>
</tr>
<tr>
<td></td>
<td>↓ case detection 44</td>
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</tr>
</tbody>
</table>
HIV is the strongest known risk factor for progression of latent TB to active TB and can occur at any CD4 count level.\textsuperscript{15, 47} The risk of developing TB increases early after seroconversion and increases further as the CD4 count declines.\textsuperscript{48, 49} Untreated HIV infection is associated with high rates of morbidity and mortality from TB and other opportunistic infections.\textsuperscript{50, 51} Mortality from all forms of TB was as high as 35\% among HIV infected adults not taking antiretroviral therapy (ART).\textsuperscript{40} With initiation of ART, and restoration of TB specific immune responses patients may develop IRIS. The occurrence of IRIS has been associated with ART initiation at CD4 counts < 50 cells/µl and early ART initiation following TB treatment.\textsuperscript{52-55} With increasing duration on ART, the risk of TB decreases but remains elevated compared to that in HIV uninfected persons.\textsuperscript{56} The effect of ART in reducing the incidence of TB is present all CD4 count levels but is greatest at lower CD4 count levels.\textsuperscript{57} Patients who develop HIV-associated TB are therefore not a homogenous group and control strategies may depend on CD4 count levels and ART use.

Strategies for the prevention and control of HIV-associated TB comprise strategies that can be applied to all populations regardless of HIV status and those that are specific for HIV-infected individuals. The strategies for the prevention and control of HIV-associated TB are discussed starting with measures that can be applied to all populations.

\textbf{PREVENTION OF TB}

\textit{Vaccination}
The only currently licensed vaccine for the prevention of TB, the bacilli Calmette-Guerin (BCG) is an attenuated strain of \textit{Mycobacterium bovis} (\textit{M.bovis}) and has been in use since 1921. Studies have shown that BCG given at birth protected children against TB meningitis and other disseminated forms of the disease but conferred variable protection against adult pulmonary TB ranging from 0- 80\% depending on exposure to environmental mycobacteria.\textsuperscript{58, 59} Revaccination with BCG during adolescence was not protective against TB.\textsuperscript{60, 61} The development of new TB vaccines has focused on three main immunisation strategies – priming where the goal is to modify the existing vaccine BCG to make it more effective or replace it with a new vaccine product, boosting – where the goal is to boost BCG induced immunity in infancy or adolescence and immunotherapeutic – where the goal is to prevent reactivation of latent TB infection or reduce recurrence of TB following TB infection. Researchers agree that any new TB vaccine
would need to demonstrate efficacy in infants, HIV negative adolescents or adults with prior exposure to BCG and in HIV-infected patients and has to be as safe as BCG in HIV uninfected persons. By the middle of 2013, there were at least 14 TB vaccine candidates which were in human trials, with three candidates in trials including HIV-infected populations. The main challenges in TB vaccine development remain the limited knowledge of what constitutes protective immunity against TB and the unavailability of biomarkers of protective immunity.

Preventive therapy

TB preventive therapy is given to individuals with latent TB infection in order to prevent progression to active disease. The most commonly used and widely available regimen for preventive therapy is isoniazid monotherapy which has been shown to decrease the incidence of TB by 60% among HIV-uninfected individuals. A meta-analysis of placebo controlled trials found that IPT reduced TB incidence by 32% overall and by 62% among TST positive HIV-infected individuals. The efficacy of IPT in TST negative individuals not on ART has not been established. The wide scale use of IPT has been limited by concerns about safety and about the ability to confidently exclude active TB – which could result in the development of isoniazid resistance from treating active TB with isoniazid monotherapy. More recently concerns arose that the durability of protection conferred by IPT is limited in areas of high TB transmission with high risk of disease soon after cessation. There is an urgent need to identify biomarkers predicting who is at most risk of developing TB and who is protected following treatment of latent infection. In addition the development of safer and shorter regimens with drugs not contained in the first line TB treatment regimens and suitable for use in high TB and HIV burden settings remains a priority. A new regimen containing high dose rifapentine and isoniazid taken as a once weekly directly observed course for 12 weeks was found to be as effective as nine months of IPT in a four year clinical trial in the United States. Subsequent to this finding, the CDC approved the use of Rifapentine and Isoniazid for the prevention of TB among TST positive adults not taking ART and children older than 11 years in 2011.

Before preventive therapy can be effectively administered, active TB must be excluded through TB screening and diagnosis while the presence of latent infection needs to be determined in order to identify those likely to benefit the most from treatment. Confirming presence of latent infection can be done through the use of immune based tests which detect cell mediated immune responses to TB. Two commonly used tests are the tuberculin skin test (TST) and Interferon Gamma Release Assays (IGRAs).
The TST has been available for more than 100 years, it is cheap and relatively simple to administer. Results have to be read 72 hours later requiring a second visit to the provider.\textsuperscript{2,73,74} The main drawbacks of the TST are subjective interpretation and cross reaction with BCG and environmental mycobacteria. The TST can less sensitive or be rendered anergic in immunosuppressed individuals.\textsuperscript{5,9,73-76} The IGRAs [Quantiferon TB Gold-In- Tube and T-SPOT] were developed to overcome some of the limitations of the TST. The IGRAs have better specificity for TB but similar sensitivity for detecting active TB (assuming individuals with active TB are infected with TB), which was as low as 80\% in HIV uninfected individuals and 60-70\% among HIV infected.\textsuperscript{74} They are expensive, require good logistics and laboratory infrastructure and are prone to conversions and reversions especially among patients with borderline results.\textsuperscript{11,24,25,74,77} IGRAs, like TST, cannot distinguish individuals with active TB from those with latent TB nor predict which individuals will progress from latent infection to active disease. They are not useful for monitoring successful treatment of LTBI, a drawback which they share with the TST.\textsuperscript{11,24,25,73,74} The development of a simple test to detect latent TB and distinguish it from active TB and indicate successful treatment of latent infection is a priority.

\textit{Infection control}

TB infection control refers to a combination of measures aimed at minimising the risk of TB transmission within populations.\textsuperscript{78} These measures are classified as managerial, administrative, environmental and personal protective.\textsuperscript{17,78} Managerial measures include the developing an infection control plan, planning the use of existing facilities or construction of new ones in order to optimise the implementation of infection control measures and conducting surveillance of TB infection and disease among health care workers.\textsuperscript{78} Administrative control measures reduce generation and exposure to infectious droplet nuclei and include identifying individuals with TB symptoms, separating the ones who are likely to be infectious, teaching cough etiquette and respiratory hygiene and minimising time spent in the facilities.\textsuperscript{78} Environmental measures are measures which reduce the concentration of infectious droplet nuclei in a room and include measures to improve ventilation – both natural and artificial – and the use of ultra violet radiation.\textsuperscript{78} Personal protective measures reduce the inhalation of droplet nuclei by health care workers and other people in contact with infectious individuals. They include wearing of N95 masks.\textsuperscript{78} Scaling up these measures in resource limited settings remain a major priority especially in the face of drug resistant TB.\textsuperscript{79,80}
TB CONTROL THROUGH SCREENING, DIAGNOSIS AND TREATMENT

Case detection and treatment has been the cornerstone of the global TB strategy. When the DOTS strategy was launched in 1995, it set targets of 70% for case detection and 85% for treatment. The DOTS strategy had five components – government commitment and political will to address TB, case detection through passive case finding of patients with symptoms, case holding or treatment with short course chemotherapy, directly observed for at least the first two months of treatment, and establishing a reliable system for recording and reporting. DOTS implementation was integrated into health care systems of countries and its main limitations were: variability in implementation across countries with differing health systems capacity, failure to address increasing drug resistance, failure to address the HIV epidemic within TB programmes and insufficient case detection. The Stop TB strategy which was introduced to improve on the DOTS strategy retained case detection and treatment as key components, while the STOP TB partnership post 2015 strategy still has case finding and treatment as key components.

Screening for TB

Screening for TB refers to the evaluation of seemingly healthy individuals in order to detect the presence of TB. The WHO has defined systematic TB screening as “the systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly.” For most target groups, the most widely used screening method is symptom screening followed by evaluation of those found to have symptoms. A number of symptom screening algorithms have been in use in different settings. For HIV infected individuals, the WHO recommends a four symptom screening algorithm. The algorithm is based on a meta-analysis of data from 8148 participants enrolled in nine studies of TB screening among patients with HIV infection. This algorithm had 79.8% sensitivity and 49.6% specificity for TB among HIV-infected patients not taking ART. In this algorithm, any HIV positive patient who reports cough, fever, night sweats and weight loss of any duration may have TB and should be investigated further. Since then follow up studies have been conducted to test the performance of this and other screening algorithms in different settings, among individuals on ART and who are regularly screened for TB and among HIV uninfected individuals. Because of limited sensitivity and the potential to miss cases especially in high TB and HIV burden settings where asymptomatic or subclinical disease has been reported, there are efforts to improve the sensitivity and specificity by combining symptom screening algorithms with other clinical parameters or tests such as body mass index, haemoglobin level and CD4 count levels in the case of...
individuals with HIV. Questions regarding the practical implementation of TB screening and impact on mortality and other TB treatment outcomes remain and will need to be investigated in trials.

**Diagnosis of TB**

Individuals who are suspected of TB based on TB screening or presentation to the health system with symptoms consistent with TB must have the diagnosis of TB confirmed or excluded. Several methods are available for diagnosis of TB and include:

**Microbiological examinations**

- **Smear microscopy** - remains the most widely used method of diagnosing TB particularly in developing countries. It is an affordable, low cost technology which can be used in low resource settings by lower levels health cadres e.g. with training of microscopists. The main limitation of smear microscopy is low sensitivity ranging from 20-65% compared to culture. Sensitivity can be improved by using induced sputum and concentrating techniques such as centrifugation and decontamination with bleach or NaOH.

- **Sputum culture** - is the gold standard for the diagnosis of TB treatment. It involves growing mycobacteria present in sputum on solid or liquid culture media. Culture has better sensitivity compared to smear microscopy and has the added advantage of allowing mycobacterial species identification and drug susceptibility testing where resources permit. Drawbacks include high cost of equipment and maintenance, requirements of biosafety equipment (BSL-3 laboratory required) and a long turnaround time of 4-8 weeks. The liquid culture technique used in South Africa Bactec Mycobacterial Growth Indicator Tube (MGIT) has shorter time to positivity but is more prone to contamination in the laboratory.

- **Nucleic acid amplification or molecular tests** – these include Line probe assays [such as Genotype® M.TBDRplus assay (Hain Life Science GmbH, Nehren, Germany)] and Xpert M.TB/Rif (Cepheid, Sunnyvale, USA), which have been endorsed by WHO for TB detection. These tests detect mycobacterial DNA through different amplification methods, the most widely used being polymerase chain reaction (PCR). These methods have high sensitivity for TB – albeit lower than culture in the case of smear negative disease- and can be used to detect the presence of drug resistance. The main limitations of the NAATs are high cost, complex infrastructure and operational requirements such as electricity, laboratory biosafety requirements and the risk of DNA contamination in the case of the open system nucleic acid amplification tests (NAATs).
Xpert M.TB/Rif is the most widely studied and used NAAT. It is an automated, cartridge based PCR test designed to detect the presence or *M. tb* as well as rifampicin resistance and has a pooled sensitivity of 89% (95% CI 85%- 92%) when used as a replacement test for detecting pulmonary TB and 67% (95% 60% - 74%) when used as an add-on test to detect smear negative TB. The sensitivity is slightly lower in HIV-infected patients – 79% (95% CI 70% - 86%) and 61% (95% CI 40%- 81%) respectively. A systematic review concluded that Xpert M.TB/Rif increased TB case detection by 23% (95% CI 15% - 32%) compared to smear microscopy in studies of adults older than 15 years with or without HIV-infection. Xpert M.TB/Rif is quick and able to give results in under two hours and has improved sensitivity over smear. Xpert MTB/ Rif is now the recommended test for extra pulmonary TB provided an appropriate specimen can be obtained. Its main limitations are the high costs of the machines and cartridges as well the operational requirements of uninterrupted electricity supply and controlled temperature, limiting its use in peripheral laboratories of most resource limited settings. Xpert is also not useful for monitoring response to TB treatment. Two randomised controlled trials (RCTs) have shown that Xpert M.TB/Rif reduced time to treatment for patients both with smear positive and smear negative disease but had no effect on morbidity or mortality. At what level in the health system Xpert MTB/Rif should be placed for most impact on case detection against acceptable costs in various settings still needs to be determined.

**Radiological examinations**

The chest radiograph is the commonest radiological method used in the diagnosis of TB. It remains a widely used method of screening and detecting TB particularly in patients with smear negative disease and maybe the only method of detecting some forms of TB (such as miliary, pleural or pericardial disease) in or outside the lung. The main advantages of the chest radiograph is that it is cheap and able to pick up other disease processes in patients suspected to have TB. However they are not available at all levels of the health system and need to be read and interpreted. The interpretation of X-ray findings tends to be subjective and requires specialised training. Another limitation is that the chest radiographs are not very specific. Although they are sensitive, chest radiographs may even be normal in HIV-infected individuals with TB particularly at low CD4 counts. This limits their utility in high HIV burden settings. Efforts are underway to develop validated automated computer aided chest radiograph reading systems and standardised chest radiograph reading tools to improves access where there are no specialist to read and interpret.
**Antigen detection tests**

Lipoarabinomannan (LAM) test is used for detecting TB disease among immunosuppressed individuals with disseminated disease. The LAM test detects the glycolipid LAM, a component of the mycobacterial cell wall which is released into the blood and eventually ends up in the urine following the breakdown of the mycobacterial cell wall or presence of renal TB. This ELISA based test is now commercially available as a low cost lateral flow strip allowing it to be used as a point of care test. The sensitivity of the LAM test is about 50% and is higher in HIV-infected patients with disseminated disease and low CD4 counts. The LAM test can be combined with other tests or clinical parameters in order to best predict patients at highest risk of undiagnosed TB and death. However, it is not yet clear where to best place the LAM test within the health system and how best to combine it with existing diagnostic tools in order to achieve this.

**TB Treatment**

The goal of anti-TB therapy is to cure the affected patient, render them non-infectious in order to minimise transmission, prevent the emergence of drug resistance and reduce the risk of death. The standard treatment regimen comprises two months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by four months of Isoniazid and Rifampicin. This six month regimen is lengthy and individuals have to continue taking it long after they feel better. The standard TB treatment regimen is not without adverse events. Adverse events may contribute towards increased morbidity and treatment interruption among individuals taking treatment. There are concerted efforts to develop and introduce newer and shorter regimens which are better tolerated. There are a number of drugs products and regimens that are in the TB drug development pipeline. There are at least six classes of new drugs in phase II, III and IV studies- i) Darylquinolones - Bedalaquine has been in trials for both drug sensitive and drug resistant TB. In 2013, this drug was approved by WHO and the FDA for use in drug resistant TB on the basis of phase IIb trial findings, ii) Ethylenediamines (SQ-109), iii) Fluoroquinolones (Moxifloxacin, ), iv) Oxozalidinones (Linezolid for MDR-TB, Sutezolid- PNU100480, AZD5847 ), v) Nitro-dihydro-imidazooxazole (Delamanid ) and vi) Rifamycins (Rifapentine for drug sensitive TB and latent infection). There is a move towards the development and testing in clinical trials of new regimens as opposed to single drug entities which need to be combined with the current optimised background regimen in trials. There is one such regimen already in clinical trials and more are expected in the future.
**TB treatment programmes**

The WHO has traditionally led the global response to the TB epidemic and hosted the Stop TB Partnership for many years. Through the global TB programme, WHO provides leadership on the TB control strategies develops evidence based policies, guidelines and standards for TB control and monitors the implementation of the policies. The current global strategy for TB control is the STOP TB strategy which was launched in 2006. The six components of the strategy are – pursuing high quality DOTS expansion, addressing high TB/HIV, MDR-TB and TB in vulnerable populations, contributing to health systems strengthening based on primary care, engaging all health care providers in TB including those in the private sector, empowering patients and communities with TB and enabling and promoting operational research. The targets of the strategy are to reduce the prevalence of and deaths from TB by 50% from the baseline of the 1990 by 2015 and to eliminate TB as a public health problem by 2050. The failure to diagnose and treat all TB cases, to initiate TB treatment in all those diagnosed, to cure all those treated for TB and the emergence of drug resistant point to challenges faced by TB programmes globally. Health system issues such as adequate financing, human resources training, motivation and retention, supply of good quality TB diagnostics and drugs as well as gaps in recording, reporting, monitoring and evaluation of TB programmes are faced by national TB programmes and limit the extent to which they are effective in controlling TB. The spread of the HIV epidemic has undermined the effectiveness of TB programmes particularly in settings where there are high rates of TB/HIV co-infection.

**TB PREVENTION AND CONTROL FOR HIV-INFECTED POPULATIONS**

Strategies and activities for TB prevention and control among individuals infected with HIV are included in the WHO policy on TB/HIV collaborative activities. These are activities intended to decrease the burden of TB among individuals with HIV infection and the burden of HIV among those with TB. The activities to decrease the burden of TB among the HIV-infected are TB screening or intensified case finding, isoniazid preventive therapy and TB infection control (discussed in previous sections on preventive therapy, infection control and TB screening) and the initiation of ART at higher CD4 count thresholds in to prevent TB. These first three activities can apply to all populations regardless of HIV status and have been discussed previously. With respect to ART initiation, an RCT which compared initiation of ART at < 200 cells/µl compared to 200-350 cells/µl showed that early ART decreased mortality and development of AIDS defining illnesses. A later RCT comparing ART initiation at CD4 counts <350 cells/µl and those initiated at CD4 counts of 350-550 cells/µl confirmed that early ART
initiation was associated with reduction in the incidence of extra pulmonary TB.\textsuperscript{118, 119} A subsequent meta-analysis has demonstrated that ART reduces incident TB across all CD4 count strata with the highest impact at observed at lower CD4 counts.\textsuperscript{57}

The other set of TB/HIV collaborative activities are intended to decrease burden of HIV among TB patients and are discussed here. Current guidance on TB care recommends that all TB patients be tested for HIV, initiated on cotrimoxazole preventive therapy (CPT) and ART early during the course of TB treatment. CPT has a mortality benefit in HIV-infected TB patients.\textsuperscript{120-122} Initiation of ART during TB treatment is recommended to reduce mortality from TB and other AIDS defining illnesses during and after TB treatment. Based on three definitive RCTs, the current recommendations are that ART be initiated after eight weeks of TB treatment provided the CD4 count is > 50 cells/µl below which ART needs to be started immediately.\textsuperscript{123-125} This optimal timing of ART during TB treatment reduces the likelihood of developing IRIS while reducing excess morbidity and mortality from HIV. Current challenges in scaling up TB/HIV collaborative activities are in the area of health systems and organisation of services. There is debate on whether implementation of different service delivery models with respect to TB/HIV collaborative activities has an impact on mortality, morbidity or retention in care among HIV infected TB patients.\textsuperscript{126} Proponents of service integration argue the approach is more patient-centred and more efficient in terms of resource utilisation while those opposed argue that integrated models may result in longer wait times for individuals who do not require both TB and HIV services, increased risk of exposure to TB where TB infection control is poor and that individuals patients may not benefit from being managed by specialised providers for TB and HIV respectively.\textsuperscript{126}

OUTLINE AND SCOPE OF PAPERS

This PhD thesis presents studies on the prevention and control of HIV-associated TB in adults. Chapter 2 is a systematic review of TB incidence among HIV clinic populations taking ART contrasting cohorts from high TB burden and low TB burden settings. This paper discusses the implications of TB incidence rates in this population on the design and implementation of TB vaccine trials including individuals who are HIV-infected and on ART. Chapter 3 describes the incidence of TB among HIV-infected individuals with high CD4 counts and discusses the implications of the findings on ART scale up and TB screening. Chapter 4 explores the willingness of HIV-infected individuals to participate in TB vaccine trials and to be vaccinated with a novel TB vaccine once such a vaccine becomes available. Chapter 5 looks at the eligibility for and use of IPT in a population of HIV-infected individuals with high CD4 counts. Chapter 6
looks at TB screening in an HIV clinic and describes the association between ART and previously undiagnosed TB and the implications for intensified case finding, IPT and TB infection control. *Chapter 7* looks at performance and potential use of urine LAM test for the detection of TB in an ambulatory HIV clinic while *Chapter 8* describes the effect of ART on the risk of having undocumented outcomes following TB treatment under routine TB programme conditions and discusses the potential impact of ART on TB programme performance. *Chapter 9* discusses what the papers contribute to the literature and the implications for current policy and practice as well as future research.
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