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Tuberculosis control in Africa in the face of the HIV epidemic

Martin J. Boeree

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Tuberculosis control in Africa in the face of the HIV epidemic

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

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Contents

Abbreviations

ADR	Adverse drug reaction
AFB	Acid fast bacilli
AIDS	Acquired immuno deficiency syndrome
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
CD4	Cluster of Determination 4
CI	Confidence interval
CTX	Cotrimoxazole
DALY	Disability-adjusted life years
DFID	Department for International Development
DOTS	Directly observed treatment short-course
DTO	District TB Officer
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FACS	Fluorescent-activated cell sorter
FBC	Full blood count
GDP	Gross Domestic Product
HAART	Highly active antiretroviral treatment
HIV	Human immunodeficiency virus
IDA	International Dispensary Association
IEC	Information, education, and communication
INTL $	International dollar
IUATLD	international Union against Tuberculosis and Lung Disease
KNCV	Royal Dutch Tuberculosis Association
LJ	Löwenstein-Jensen culture
MMH	Mlambe Mission Hospital
NTP	National Tuberculosis Control Programme
NTS	Non-typhoidal salmonellae
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NORAD	Norwegian Agency for Development Co-operation
NRTI	Nucleoside reverse transcriptase inhibitor
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
PCP	*Pneumocystis carinii* pneumonia
PMG	Programme Management Group
PTB	Pulmonary tuberculosis
py	person-years

QECH	**Q**ueen **E**lizabeth **C**entral **H**ospital
SCC	**S**hort **c**ourse **c**hemotherapy
SD	**S**tandard **d**eviation
SP	**S**ulfadoxine-**p**yrimethamine
STD	**S**exually **t**ransmitted **d**isease
TB	**T**u**b**erculosis
TE	*Toxoplasma* **e**ncephalitis
UNAIDS	Joint **U**nited **N**ations programme on HIV/**AIDS**
UNGASS	**U**nited **N**ations **G**eneral **A**ssembly **S**pecial **S**ession
US$	**U**nited **S**tates dollar
UTI	**U**rinary **t**ract **i**nfection
VCT	**V**oluntary **c**ounselling and HIV **t**esting centres
WHO	**W**orld **H**ealth **O**rganisation
WGO	**W**ereld **G**ezondheids**o**rganisatie
ZN	**Z**iehl **N**eelsen

Chapter I

Introduction and outline of the thesis

Introduction

Tuberculosis (TB) is and has been a major health problem in Africa. In low-income countries like most of the countries in sub-Saharan Africa, the struggle against this disease is difficult and costly. With the introduction of an effective strategy in 1964 introduced by World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) under the inspiration of Dr K. Styblo, many of the African countries were able to decrease the incidence of tuberculosis.[1-4] This strategy was based on the organisation of a National Tuberculosis Programme (NTP), which was to be responsible for case finding and diagnosis, registration, monitoring, and treatment. Until the 1980s this strategy was successful. In the 1980's the first cases of HIV and its association with TB were reported. This co-infection resulted in a catastrophe. Tuberculosis resurged to the same level as in the fifties (figure 1). WHO declared the epidemic a global emergency, an unprecedented step in the history of this organization. Today, tuberculosis kills approximately 2 million people each year. More than 8 million people, of which 2 million in sub-Saharan Africa, will become ill with TB each year. The global epidemic is growing and becoming more dangerous. Someone in the world is newly infected with TB every second. Overall, one third of the world's population is currently infected with the TB bacillus. It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will become ill, and 36 million will die of TB - if control is not further strengthened.

TB is a disease, which is spread through the air. Only people who are sick with pulmonary TB are contagious. When such people cough or sneeze they produce TB bacilli, *Mycobacterium tuberculosis (M. tb),* into the air. A person needs only to inhale a small number of these bacilli to be infected. Left untreated, each person with active, contagious TB will infect on average between 10 and 15 people every year. However, people infected with TB will not necessarily develop illness. The immune system walls off the mycobacteria, which can remain dormant for years. When someone's immune system is weakened, the chances of becoming ill are greater. Since HIV is capable to corrode the immune system, and *M. tb* tends to enhance the multiplication of HIV, HIV and TB form a deadly combination, each accelerating the other's progress. Someone who is infected with HIV and at the same time with *M. tb* is about 35 times more likely to become ill with TB than someone infected with TB who is not co-infected with HIV.

HIV has a negative impact on the treatment outcome of TB. For example in Malawi, the case fatality rate has increased for example from 6% in 1987 to 21% in 1995. In one report in Zomba in the south of Malawi, the case fatality rate was 18% in smear positive TB and 40 – 50% in smear negative and extra-pulmonary tuberculosis.[5] In Malawi, the first case of AIDS was reported in 1986. A study of TB patients in 1986 found that 25-30% were already infected with HIV. In 1995 this number had risen to 75%.

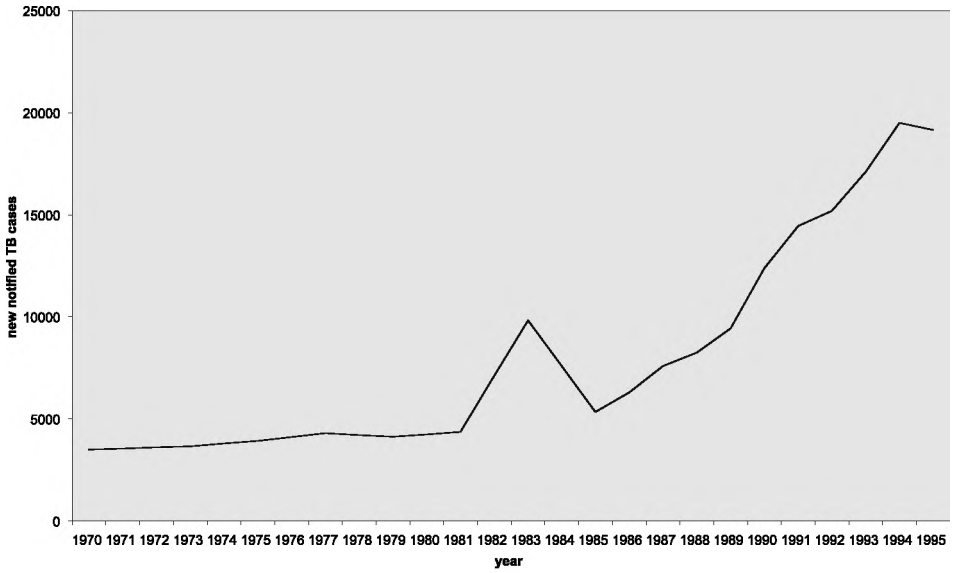
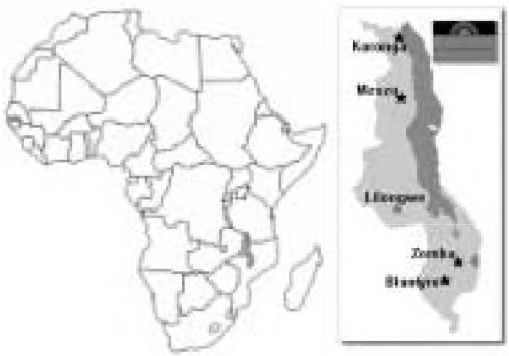


Figure 1 New notified TB cases in Malawi 1970-1995



Statistics (2001)

Total population	11 571 000
GDP per capita (Intl $)*	500
Life expectancy at birth m/f (years)	35.7/36.9
Healthy life expectancy at birth m/f (years)	29.0/30.7
Adult mortality m/f (per 1000)	695/636
Total health expenditure per capita (Intl $)*	38
Total health expenditure as % of GDP	7.6

* International dollar: a common currency unit that takes into account differences in the relative purchasing power of various currencies.

Figure 2

The result is that TB is a leading cause of death among people who are HIV-positive. It accounts for about 11% of AIDS deaths worldwide. In sub-Saharan Africa, HIV is the single most important factor determining the increased incidence of TB in the past 10 years.

Malawi

Situated in south-east Africa, Malawi is bordered by Tanzania on the north, by Zambia on the west and by Mozambique on the south and east. Malawi is approximately 900 kilometres in length and ranges in width from 80 to 160 kilometres. The total area is about 118 500 km^2, of which 94 000 km^2 is land. The remaining area consists of Lake Malawi. Malawi is divided into three main administrative areas, the Northern, the Central and the Southern Regions. Every region is subdivided into districts, five in the Northern, nine in the Central and eleven in the Southern region. Within each district there are administrative subdivisions known as Traditional Authorities, which are presided by chiefs. The smallest administrative unit is the village.

The climate is tropical continental with some maritime influences. Temperature and rainfall vary with altitude and proximity to the Lake. Malawi is a mainly agricultural country: 43% of the population are farmers, while almost another 40% does farming beside their official job. Malawi had its last population census in 1987. In 1987 the official population was almost 8 million, whereas the population grows rapidly and recent estimates approximate 11.3 million. Rapid population growth has meant increasing pressure on the GDP. This is clearly seen with regard to maize production: to achieve minimum food self-sufficiency for the nation there is a current annual shortfall of maize production of about 900 000 tonnes.

There are nine main ethnic groups, a small but economically important Asian community and an even smaller European community. The main ethnic tribes in Malawi are the Chewa, Tumbuka and Yao tribes. Almost 50% of the population is under the age of 15 years. The official language spoken is English, whereas Chichewa is the second official language. The most important religions are Christianity (Protestants and Catholics) and Islam (the Yao tribe). There is a low literacy rate: 56% in adults in 1995 with 72% in men and 42% in women. Secondary school enrolment is low with 22% of males and 12% of females gaining places at secondary school.

Politically, an important change was seen with the transition from a one-party system to a multi-party democracy in 1994 and a new democratically elected government. The new Malawi Government committed itself to poverty alleviation as the central national policy objective. In terms of health, this new government adopted a policy with an objective of developing a sound health care system capable of preventing and curing disease. Due to the high infant, under five, and maternal mortality (as a matter of fact the highest in Africa, table 1), the health needs of mothers and children under five years of age have been given high priorities.

Table 1 Health Indicators in Malawi

Health Indicator	Estimated figures
Crude birth rate (births per 1000 population)	47
Crude death rate (deaths per 1000 population)	23
Maternal mortality rate (per 100,000 live births)	620
Under-5 mortality rate (per 1000 live births)	234
Infant mortality rate (per 1000 live births)	135
Total fertility rate	6.7
Life expectancy at birth	39

Service delivery should be improved by extending coverage, so that basic curative services for common diseases such as malaria, diarrhoea, and acute respiratory infections, would be widely available along with immunisations and family planning. Information, education, and communication (IEC) programmes are claimed to be used to increase effective preventive behaviour. Support of a new College of Medicine within the University of Malawi, is advocated to train a sustainable number of doctors who are less vulnerable for brain drain and to create a more scientific background for improvement of the health sector.

The results of the new health policy up to the present day have been rather disappointing. Still, health parameters show bad or even worse statistics as compared to other countries in sub-Saharan Africa that appear to have similar conditions. Deteriorating economics, rapidly increasing corruption, and poor working moral, are said to be causing this decline in standards. In addition, HIV/AIDS has had a devastating impact on the health systems. Possible causes of this breakdown were an increased patient load, an increasing mortality of the patients, and also of the health care workers themselves, and a reallocation of funds towards expensive and not cost effective measures such as antiretroviral drugs for a limited section of the population.

The National TB Control Programme

History of Tuberculosis Control in Malawi

The first named death from tuberculosis in Malawi was Shadrach Ngumuya in 1877 at Cape Maclear. From then until 1964, TB cases were diagnosed and treated according to available resources, but no actual TB control programme existed.

1964 to 1983 The National Tuberculosis Control Programme in Malawi commenced in 1964 when Malawi became independent. Assistance in the form of equipment, transport and drugs was provided by the United States of America through the University of North Carolina. The programme aimed at controlling tuberculosis (TB) through active case finding, treatment and prevention. However, each district in Malawi worked independently in its efforts to control TB and so the programme lacked coordination. In 1969, a tuberculosis control unit and central registry

was created at the Ministry of Health Headquarters. The aims of this unit were to coordinate activities in the districts and to provide on-going analysis of TB cases in the country. The TB Control Unit was run by a newly appointed TB Control Officer and was further strengthened by the appointment of Regional TB Officers to supervise and coordinate activities in the districts.

1984 to present time In 1984, Malawi received assistance from the IUATLD. This organisation provided drugs for short course chemotherapy of smear-positive TB cases and set in place a standardized reporting and evaluation system in all districts of the country. The National TB Control Programme (NTP) was formed. Countrywide short course chemotherapy for the treatment of sputum positive cases was achieved in 1986. Technical assistance in the form of two consultant visits each year was also established. In 1996, the Department for International Development (DFID), UK, provided assistance to the TB Control Programme in the form of technical assistance on the ground through a technical advisor, capital equipment, training and operational research. This supplemented the assistance from IUATLD. In 1999, the IUATLD formally ended its long term assistance to the Malawi NTP. In its place, donor assistance was provided by DFID, the Norwegian Agency for Development Cooperation (NORAD) and the Royal Dutch Tuberculosis Association (KNCV). These three organizations have provided support to the NTP up to the present time.

The problems of the NTP at present

Today, even though its 11.3 million people struggle daily with poverty, disease, and a terrible lack of resources, Malawi's Tuberculosis Control Programme (NTP) is seen by many as a model for sub-Saharan Africa. Beside the structural approach advocated by the IUATLD, Malawi adopted the DOTS strategy advocated by WHO in 1984 for smear positive cases of pulmonary tuberculosis (PTB). DOTS (Directly Observed Treatment Short-course) consists of five main pillars (see table 2)

Table 2 **The five pillars of DOTS**

1 Government commitment to a NTP
2 Priority to detect infectious disease cases by sputum smear microscopy
3 Standardised regimens of short-course chemotherapy, given *under direct observation* for, at least, the intensive phase of treatment
4 Regular, uninterrupted supply of drugs
5 Monitoring system for programme supervision and evaluation

This led to an increase in cure rates from 74% in 1984 to 90% in 1987 and a short-lived optimism about this new treatment strategy. AIDS struck the country in this very same episode. In

1985 there were 5 334 new cases of TB notified; by 1995 this number rose to 19 155 and cure rates declined to 63%. The NTP as an organisation suffered under the increased burden. In addition, AIDS had a general devastating effect and resulted in a national breakdown in health services. The NTP had to find innovative approaches to this disaster. In order to provide possible solutions an analysis of constraints was made (table 3)

Table 3

Some constraints on the Malawi NTP in 1995

1 Diagnosis
- Up to 30% of smear positive patients in some districts diagnosed in the laboratory register were not being registered and therefore not placed on treatment
- Long delays in the diagnosis of smear positive TB patients who were admitted to hospital with risk of nosocomial transmission to health care workers
- Too many smear-negative TB patients related to sputum smears never being examined
- Possible delay in diagnosis because of consultation of traditional healers
- Difficult diagnosis of forms of extra pulmonary TB such as TB lymphadenitis, TB meningitis
- Possible gender differences in access to health care

2 Treatment
- Congestion of patients in TB wards who were receiving initial phase of treatment
- Improper directly observed treatment
- No follow-up of patients with smear negative and extra-pulmonary TB
- High case fatality rate in HIV related TB
- No perspective for HIV positive TB patients besides treatment of TB
- Possible high default rates in some districts

3 Laboratories
- Irregular supply of slides
- Too little time spent examining smears
- Short-cuts (ie only one of 3 sputum specimens from each patient actually examined)
- Insufficient numbers of laboratory staff
- Poorly maintained equipment
- Viability of smears questionable with long storage

4 Education
- Lack of formal education sessions for patients

5 Supervision
- Lack of regular supervision because of no resources

6 Training
- No regular training seminars for different stakeholders such as health centre staff, traditional healers and village headmen

7 Communications and documentation
- Poor communication between all levels of the NTP; no computers to assist in the collating, disseminating, and documentation of information

The NTP tried to develop a strategy to be able to manage the new problems. A Programme Management Group (PMG) was formed with the Programme Manager (F Salaniponi), a scientific TB Advisor (Prof. AD Harries, MD), the head of the Department of Medicine of the College of Medicine (MJ Boeree, MD), the National TB Officer (T Nyirenda, MD) and a district health officer with a special interest in TB and research (A Banerjee, MD). One of the ideas of the PMG was to organise a specific research programme in collaboration with WHO and DFID. Several research proposals, based on the constraint analysis, were developed and launched. This resulted in a research agenda (table 4).

The research based on this analysis, was to be conducted in order to better define -with data- the problems of TB control in Malawi and to test interventions to solve those problems. The results of this research had to contribute to a continuous adjustment of policy and practice, and therefore, be able to influence and improve the care of TB patients. Two examples of this philosophy are demonstrated in the research on the role of traditional healers (chapters IV and V) and the research to the efficacy on survival and occurrence of disease of cotrimoxazole (CTX) prophylaxis in HIV seropositive PTB patients. Firstly, the finding that more than one third of sputum smear-positive PTB patients had visited a traditional healer before seeking regular medical care with a median delay of 4 weeks, led to the implementation of a new policy towards traditional healers. In a series of meetings in 1997 to 2001 with traditional healers and other influential members of the community, information was collected from thousands of traditional healers, education was given about TB and the NTP, and referral slips were distributed to send TB suspects for sputum examination. Funds were obtained to continue these community education sessions.

Secondly, on the basis of the findings of the study on CTX prophylaxis and other studies in the country, a meeting was held in October 2002. The outcome of this meeting was a policy statement which a) endorsed that Voluntary Counselling and Testing for HIV (VCT) and CTX prophylaxis for HIV seropositive TB patients be continued in those districts where it has been started, b) encouraged VCT plus CTX prophylaxis for HIV seropositive TB patients to be expanded into other districts in a phased approach with results carefully monitored by the NTP, c) urged that the NTP encourage and work with its partners to conduct a randomised controlled trial to determine the efficacy of CTX prophylaxis with and without antiretroviral therapy in HIV seropositive TB patients and d) requested all parties to keep up to date with any new information about the efficacy of CTX prophylaxis in the region and act accordingly if evidence suggests that CTX has harmful consequences.

This introduction is largely based on a document published by the PMG, under auspices of the WHO, the NTP, the IUATLD and DFID.[1]

Table 4 TB Research Agenda

CASE DETECTION

1 **Difficulties faced by TB suspects using present case detection system**
*Role of traditional healer in case detection**
*Gender determination**
2 **Inefficiencies within the passive case finding system**
Health centre and out-patient performance in dealing with cough and TB suspects
Delays between sputum submission and smear examination
*Sputum storage and smear/culture viability**
*Reasons for diagnostic delay**
3 **Laboratory performance**
Knowledge and practice of recommended laboratory procedures
Improvement of smear sensitivity
Assessment of safety procedures
4 **Diagnosis of Pulmonary TB**
Assessing different strategies for screening TB suspects
% of smear positive patients who do not get registered or treated
% of smear-negative PTB patients with no smears done, with false positive smears, with another diagnosis and with genuine TB
Accuracy of chest radiograph diagnosis
*Improvement of strategies in diagnosis of forms of EPTB**
5 **Paediatric TB**
Improved diagnosis
6 **High risk groups**
Prevalence of TB in prisoners
Prevalence of TB in health care workers
Prevalence of TB in secondary school children

CASE HOLDING AND TREATMENT

1 **Treatment delivery**
Decentralised care in urban end rural environments
Use of a unified regimen for all types of TB
Integration of TB/HIV/STD care
2 **Adherence to treatment**
*Assessment of true extent of defaulters**
*Reasons for defaulting behaviour**
Interventions to reduce transfer out rates
3 **Reactions to treatment**
Monitoring adverse reactions on systematic basis
4 **Smear-negative pulmonary TB and extrapulmonary TB**
Assessment of treatment outcome through routine NTP
*Assessment of treatment outcome in a research setting**
*Assessment of treatment outcome in relation to HIV and other clinical parameters**
5 **Mortality**
Treatment outcomes in smear-negative PTB and EPTB, especially in relation to HIV status
*Interventions to reduce mortality in HIV-positive TB patients e.g. cotrimoxazole prophylaxis**
6 **Monitoring of treatment**
Use of simple measures to monitor patient compliance in the continuation phase of treatment
7 **Drug security**
Methods to ensure drug security at all levels

** topics, which led to studies in this thesis, are indicated in italic*

Outline of the thesis

This thesis consists of six studies that were performed in relation to the research agenda mentioned above, in collaboration with the Department of Medicine and the NTP.

We hypothesized that gender was a factor in the access to the health care systems in relation to case finding. This question was addressed in a study described in Chapter II. In the last 10 years in Malawi male notifications have consistently outnumbered female notifications. This hypothesis that women are under notified was tested by an operational research study of gender differences in numbers of TB suspects submitting sputum specimens and numbers of suspects with positive sputum smears.

There are several procedures to diagnose TB lymphadenitis. We asked the question which is the best locally applicable strategy for the diagnosis of TB lymphadenitis; our investigations are described in Chapter III. In a prospective study the results of basic procedures for the diagnosis of tuberculous lymphadenitis are compared with the outcome of histology and/or culture.

In Chapter IV we addressed the question whether traditional healers were responsible for a possible diagnostic delay. Their role and their opinion are analysed in a questionnaire study involving both patients and traditional healers.

In Chapter V we tried to answer the question which aspects of care seeking behaviour and diagnostic processes in smear positive PTB patients are relevant. Amongst the aspects looked at were time of diagnosis, the health institution that was visited, the number of visits made, and the effect of antibiotics.

In Chapter VI, the question of viability of mycobacteria was addressed in a study to see how long sputum samples can be stored at room temperature or in the refrigerator without losing the ability to demonstrate acid fast bacilli in a Ziehl Neelsen stain or to remain positive when a culture for mycobacteria is done. This issue has practical implications for the diagnostic process of smear positive TB in situations of time delay and frequent power cuts.

A major question within the context of his thesis was whether we could accomplish an increased survival in HIV co-infected PTB through prophylaxis with cotrimoxazole with a single dose of 480 mg as compared to the double dosage of 480 mg, a historical control group, and the national case fatality rate (Chapters VII and VIII).

In Chapter IX, the problem of treatment compliance within the NTP is addressed. We were interested in the reasons for default of TB treatment and present status of smear positive PTB patients who were registered to have defaulted treatment.

Finally, a critical review of TB control in the face of the HIV epidemic concludes this thesis in Chapter X. This paper was published in first 1998 and an addendum is given in Chapter Xa updating it with newer developments in the era of antiretroviral treatment.

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Chapter II

Gender differences in relation to rates of sputum submission and smear-positive pulmonary tuberculosis in Malawi

Boeree MJ, Harries AD, Godschalk P, de Mast Q, Upindi B, Mwale A, Nyirenda TE, Banerjee A, Salaniponi FML.
The International Journal of Tuberculosis and Lung Disease
2000; **4(9)**: 882-884

Summary

Objective: To examine gender differences in sputum submission and sputum smear positivity.
Methods: Laboratory registers in all diagnostic units in 8 districts in Malawi were examined for the years 1995 and 1996.
Results: During a 12-month period (averaged between 1995 and 1996), 26 624 new TB suspects submitted sputum samples of whom 3282 (12.3%) were smear-positive. Significantly more males submitted sputum (52%) compared with females (48%), and significantly more males (53%) were smear-positive compared with females (47%, $p < 0.05$). Rates of sputum submission per 100 000 adults were also significantly higher for males (1203) than females (1032).
Conclusion: In Malawi, fewer females are submitting sputum samples and are being diagnosed with smear-positive TB compared with males.

Introduction

Gender is recognised as an important variable in infectious disease epidemiology. A 1998 review[1] on gender differences in tuberculosis (TB) suggested that women in low-income countries were probably under notified. However, the data analysis in that review was based on studies going back 30 years previously. Despite the upsurge of HIV-related TB in sub-Saharan Africa, there has been little recently published data on the relationship between gender and TB case notifications.
In the last 10 years in Malawi, male TB notifications have consistently outnumbered female notifications (Malawi National Tuberculosis Programme [NTP]). We were interested in whether there were any gender differences in 1) the number of TB suspects submitting sputum specimens for examination of acid-fast bacilli (AFB), and 2) the number of suspects with positive sputum smears. We carried out an operational research study to investigate this further.

Methods

Laboratory sputum registers

Every laboratory in Malawi that performs sputum smear microscopy for AFB records results in a sputum register. For each patient submitting sputum, a unique number is given and a record made of the name, address, age, sex, place of submission, category (i.e., new suspect or follow-up patient), number of specimens received and the sputum smear results. Sputum examination is a free service.

Data collection

Eight out of 25 districts were chosen to provide appropriate geographic representation from the north to the south of Malawi. Within each district, all laboratories performing sputum smear microscopy in government/ mission hospitals or health centres were visited. There were 27 laboratories in nine government hospitals, ten mission hospitals and eight health centres. In each laboratory, the laboratory sputum registers were reviewed. The following information was obtained for each of the years 1995 and 1996: total number of new TB suspects submitting sputum specimens, place of submission, number of male and female suspects, and number of male and female suspects with positive sputum smears. From 16 hospitals, 100 males and 100 females consecutively listed in the laboratory register from 1 January in 1995 and 1996 were identified, and ages (if recorded) were obtained.

Population distribution

The population of Malawi and the eight districts was obtained for the year 1996 from population estimates based at the national statistics department. Population numbers were obtained in relation to age and sex.

Calculations and analysis

Data for the two years 1995 and 1996 were combined. The numbers of males and females submitting sputum samples and the numbers who were smear-positive were calculated for a 12-month period. Annual rates of sputum submission and smear-positivity were calculated per 100 000 persons aged 15 years or more using population estimates for 1996. Epi-Info version 6.0 was used for data collection. For gender comparisons, X^2 tests, odds ratios (OR), 95% confidence intervals (CI) and p values were calculated, differences at the 5% level being regarded as significant.

Results

In 1996, the estimated population of Malawi aged 15 years or more was 5 735 730 with 47% males and 53% females. In the eight districts, there were 2 389 852 persons aged 15 years or more, with 48% males and 52% females.

In laboratory sputum registers, age was not recorded for 18% of males and females respectively. Of 2622 males and 2613 females for whom age was recorded, the age distribution is shown in the Figure; 2% of males and 3% of females were aged under 15 years. A significantly higher

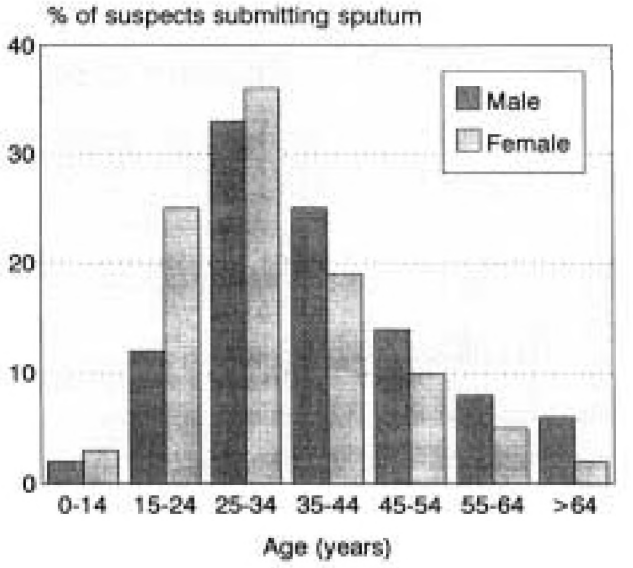

Figure 1 Age distribution of male and female TB suspects who submitted sputums

proportion of females (61%) were aged 15 - 34 years compared with males (45%, $p < 0.05$). During a 12-month period (averaged between 1995 and 1996), 26 614 new TB suspects submitted sputum; of these, 3282 (12.3%) were smear-positive. Significantly more males submitted sputum and were smear-positive compared with females (Table). This significant difference was found at government and mission hospitals, although in the health centres no significant differences were found.

Table 1 Number of males and females submitting sputum and who were sputum smear-positive during a 12-month period according to type of institution.

	Males *n*(%)	Females *n*(%)	OR [95% CI]* *n*(%)
Number submitting sputum	13 784 (52%)	12 831 (48%)	1.15 [1.12-1.19]#
At government hospital	7 651 (51%)	7 305 (49%)	1.1 [1.05 -1.15]#
At mission hospital	4 862 (54%)	4 224 (46%)	1.32 [1.25 -1.41]#
At health centre	1 271 (49%)	1 302 (51%)	0.95 [0.85 -1.06]
Number sputum smear positive	1 751 (53%)	1 531 (47%)	1.31 [1.19 -1.44]#
At government hospital	962 (53%)	861 (47%)	1.25 [1.09 -1.42]#
At mission hospital	638 (54%)	534 (46%)	1.43 [1.21 -1.69]#
At health centre	151 (53%)	136 (47%)	1.23 [0.88 -1.73]

* Odds ratios (OR) with 95% confidence intervals (95%CI) are shown for comparisons between males and females

\# $p < 0.05$ - significant differences between males and females

Annual rates of sputum submission and sputum smear positivity per 100 000 adults aged 15 years and above in the eight districts were respectively 1114 and 137 . Rates of sputum submission per 100 000 adults were 1203 for males and 1032 for females (OR = 1.17, 95% CI 1.14 - 1.20). Rates of smear-positive sputum per 100 000 adults were 153 for males and 123 for females (OR = 1.24, 95% CI 0.97 - 1.59).

Discussion

This study shows that in 1995 to 1996 in eight districts in Malawi, more males than females 1) submitted sputum specimens for AFB examination and 2) were found to be sputum smear-positive. These differences were found at both government and mission hospitals. Similar differences were obtained when results were analysed in relation to rates per 100 000 adults per year.

This study conducted within the operational framework of the Malawi NTP has some limitations. Data validity depends on accuracy of records in laboratory sputum registers and accuracy of sputum smear microscopy, and mistakes may be made under routine conditions (personal observations). We also did not obtain information on the relationship between gender, number of patients presenting to health facilities with a cough and the number submitting sputum for AFB examination. A study at one referral site (Queen Elizabeth Central Hospital, Blantyre),[2] showed that 18% of out-patients complained of cough. Of those with cough, 31% had a cough > 3 weeks and nearly 60% were referred for sputum examination. No gender differences were noted, although this study cannot be said to be representative of the country. However, we believe that the results of the present study (although some pieces of information are missing) are probably representative of the country. The population in the eight districts constituted just over 40% of Malawi's population, the gender distribution reflected that seen in the country, the three regions which serve the main ethnic groups were covered, and large numbers of patients were included. We feel justified in calculating our sputum submission and sputum smear-positive rates per 100 000 for persons aged 15 years and over because age-related data showed that less than 4% of males and females submitting sputum were aged 14 years or below.

It was not unexpected that many more young women aged 15 - 24 years submitting sputum compared with men. HIV infection rates in Malawi are much higher in women aged 15 - 24 years compared with men of the same age (National AIDS Control Programme), and HIV infection is strongly associated with the development of TB.[3,4]

This study suggests that gender differences are important in the epidemiology of TB in Malawi. The NTP needs to obtain more data on male and female patients about the process from onset of cough to sputum submission, diagnosis, registration, treatment and final treatment outcome.

Acknowledgements

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Chapter III

Tuberculous lymphadenitis, a diagnostic problem in areas of high prevalence of HIV and tuberculosis

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HJ Bekedam designed the study, participated in the data analysis and coordinated the writing of the paper.
MJ Boeree collected the data, assisted in the data analysis and interpretation of the results and the writing and the revisions of the paper.
A Kamenya and B Ngwira assisted in the collection of the data and the data analysis.
G Liomba and VR Subramanyam interpreted the pathology and microbiology; they critically reviewed the interpretation of the results.
AD Harries contributed in the design of the study and the data analysis and assisted in the revisions of the paper.

Summary

The human immunodeficiency virus (HIV) epidemic is associated with a marked increase of tuberculosis cases. The influence of HIV on diagnostic methods for tuberculous lymphadenitis is less clear. In an environment of high HIV and tuberculosis prevalence in Blantyre, Malawi, a prospective study compared results of basic procedures diagnosing tuberculous lymphadenitis with the outcome of histology and/or culture. One hundred out-patients, aged 15-55 years, with extra-inguinal lymphadenopathy not responding to general antibiotics, entered the study. Among 52 cases, with whom all procedures were carried out in accordance with the protocol, 38 (73%) were diagnosed as tuberculous lymphadenitis; 84% of the latter (32/38) were seropositive for HIV. Needle aspirate and biopsy smears stained by the Ziehl-Neelsen technique contributed little to detecting tuberculosis, 8% and 11% respectively. In contrast, macroscopic caseation of excised lymph nodes showed a high yield of 82%, which was similar to histology, and higher than that of Löwenstein-Jensen culture (61%). The study suggested that HIV positivity of tuberculous lymphadenitis patients decreased the possibility of histology and culture both being indicative of tuberculosis (odds ratio 0.10; p=0.06). Consequently histology results, often used as the single definitive method, failed to diagnose 18% (7/38) of tuberculosis cases. However, it was reassuring that 4 simple methods, which can safely be carried out at district level, could be expected to diagnose 80-95% of tuberculous lymphadenitis cases in a timely and cost-effective manner.

Introduction

Malawi has high human immunodeficiency virus (HIV) infection rates. In 1993, 32% of mothers visiting the antenatal clinic in an urban area, and 12% in rural areas, were seropositive for HIV.[1] The HIV epidemic is associated with a marked increase in the number of cases of tuberculosis in general,[2] and extrapulmonary cases in particular.[3-5] In Malawi, the number of tuberculosis cases has increased threefold from 6301 to 19 195 over the last 10 years (1986-1995). In the same period, the Queen Elizabeth Central Hospital in Blantyre registered 4 times as many tuberculosis cases in total, and extra-pulmonary tuberculosis increased twelvefold to 893 in 1995.[6] The greater increase at the hospital reflects the higher HIV infection rates in urban Malawi.[7]

The influence of HIV infection on diagnostic methods for tuberculous lymphadenitis is uncertain, despite clear descriptions of the non-reactive histopathology related to HIV infection.[8] To develop recommendations for a protocol that takes into account limited laboratory facilities and availability of personnel at the district level, a prospective study was conducted to compare basic diagnostic procedures for tuberculous lymphadenitis with the results of histology and/or culture. The influence of HIV infection on these findings was assessed. The study took place in a routine out-patient department setting. Except for HIV testing, no additional resource was made available or used to carry out the research.

Methods

Selection of patients

One hundred out-patients aged 15-55 years attending the Queen Elizabeth Central Hospital in Blantyre, Malawi, were selected during the period April 1994 to April 1995. Patients who presented with lymphadenopathy in one or more extra-inguinal sites were issued with general antibiotics for 7-10 d and reviewed after a week. Patients who did not improve on treatment were included in the study. After pre-counselling and consent, blood for HIV testing was taken, and an appointment was made for needle aspiration and lymph node excision.

Procedures

Under local anaesthesia, wide needle aspiration of an enlarged lymph node was performed with a 19-gauge needle.[10] The aspirate was spread on slides and dried in air. The same lymph node was then removed, cut in half, and macroscopically examined for caseation. Fluid from the cut surface of the lymph node was spread on slides and air-dried. Slides were stained by the Ziehl-Neelsen (ZN) method and examined for acid-fast bacilli. Half of the lymph node was fixed in formalin and sent for histological examination. The other half was used to inoculate Löwenstein-Jensen (LJ) cultures. Blood sera were tested for HIV-I and HIV-2 antibodies with Biochem Detect™ enzyme-linked immunosorbent assays (ELSA) and Serodia™ HIV particle agglutination tests.

Definition of tuberculosis lymphadenitis and HIV status

The diagnosis of tuberculous lymphadenitis was established when LJ culture yielded mycobacteria and/or a histology result showed granulomatous and caseating lymphadenitis consistent with tuberculosis (this was the definitive standard technique). Non-tuberculous lymphadenitis was diagnosed when both histology and culture results were inconsistent with tuberculosis.

HIV serostatus was recorded as positive if both the ELISA and particle agglutination test were positive, and negative if both tests were negative. Discordant test results were recorded as indeterminate.

Statistical analysis was done with the aid of EpiInfo, version 6-02. Confidence intervals were calculated at the 95% level. When cell values were 5 or below, Fisher's exact 2-tailed values of p and analogous exact confidence intervals were calculated. Sensitivity, specificity, and positive and negative predictive values were calculated with standard formulae.

Results

From 100 patients enrolled, the following records were available: 83 wide needle aspiration ZN smears; 80 records on macroscopic caseation of excised lymphnodes; 83 biopsy ZN smears; 85 histology reports; 68 LJ cultures; 99 HIV serology results. Incomplete results were related to unrecorded observations, lost specimens, sending incorrect specimens, and the fact that 10 patients failed, for unknown reasons, to report for their surgical procedures. All procedures were carried out in accordance with the protocol for 52 cases; the following analysis focuses on the 52 complete sets of results.

Thirty-eight of these 52 patients (73%) were diagnosed as tuberculous lymphadenitis, and 32 of the 38 (84%) were HIV seropositive. Non-tuberculous lymphadenitis patients had slightly lower HIV seropositivity (11/14; 79%). The HIV status of the 48 patients excluded from further analysis was similar; 85% (40/47) were HIV seropositive. No discordance was observed between the 2 tests for HIV infection.

Acid-fast bacill1i were detected in 3 wide needle aspirates and 4 biopsy smears, and all were confirmed by histology or culture, giving a positive predictive value of 100%. In all these cases, macroscopic caseation of the excised lymph node was observed (Table 1).

Table 1 Sensitivity, specificity and predictive values or diagnostic procedures for tuberculous lymphadenitis compared to histology and/or culture

	Sensitivity	Specificity	Predictive value	
			Positive	Negative
Wide needle aspiration				
Direct smear	8% (3/38)	100%(14/14)	100% (3/3)	29%(14/49)
Biopsy				
Caseation	82%(31/38)	71%(10/14)	89%(31/35)	59%(10/17)
Direct smear	11% (4/38)	100%(14/14)	100% (4/4)	29%(14/48)
Histology	82%(31/38)	100%(14/14)	100%(31/31)	67%(14/21)
Culture	61%(23/38)	100%(14/14)	100%(23/23)	48%(14/29)
Combination[a]	82%(31/38)	71%(10/14)	89%(31/35)	59%(10/17)

[a] Wide needle aspiration direct smear+biopsy caseation+biopsy direct smear.

Macroscopical caseation was observed in 35 cases and tuberculosis was confirmed in 31 of them, giving a positive predictive value of 89%.

All the isolates grown in LJ culture were identified as *Mycobacterium tuberculosis,* based on the time taken for growth, colony morphology, and ZN staining.

Yield of diagnostic procedures

Histology, caseation and culture detected a high proportion of cases (Table 2). The contribution of wide needle aspiration and biopsy smears was low.

Table 2 Yield of diagnostic procedures for tuberculous lymphadenitis

	All	Tuberculosis patients HIV positive	HIV negative
No.of patients	38	32	6
Wide needle aspiration			
Direct smear	3 (8%)	3 (9%)	0
Biopsy			
Caseation	31 (82%)	26 (81%)	5 (83%)
Direct smear	4 (11%)	4 (13%)	0
Histology	31 (82%)	25 (78%)	6(100%)
Culture	23 (61%)	18 (56%)	5 (83%)
Combination[a]	31 (82%)	26 (81%)	5 (83%)

[b] Wide needle aspiration direct smear+biopsy caseation+biopsy direct smear.

Diagnostic yield related to HIV status

All confirmed tuberculosis patients with acid-fast bacilli found in aspirates and biopsy smears were seropositive for HIV. All 6 HIV seronegative tuberculosis patients were histologically diagnosed as tuberculous lymphadenitis. Only 25 of the 32 HIV seropositive patients were diagnosed by histology (Table 2). No statistically significant association was found between the results of aspiration, biopsy smears or histology and HIV status.

Results of histology and culture were both indicative of tuberculous lymphadenitis in 16 of 38 cases; 5 of the 16 were HIV seronegative and 11 were seropositive. With the remaining 22 cases, only one of the 2 procedures gave a positive result for tuberculosis, 7 by culture and 15 by histology. One patient with a histology result consistent with tuberculous lymphadenitis (but a negative culture) was seronegative for HIV; all the other 21 cases were HIV positive. The HIV status of the tuberculous lymphadenitis patients suggests a negative influence of HIV infection on the possibility of both histology and culture being indicative of tuberculosis (odds ratio [OR]=0.10; exact confidence limits zero-1.17; Fisher's exact 2-tailed p=0.06).

Histology and culture: sensitivity and negative predictive values

The results of histology and culture on their own were compared with the combined outcome of both tests to estimate sensitivity and negative predictive values (Table 1).

Histology was indicative of tuberculosis in 31 of 38 diagnosed cases of tuberculous lymphadenitis, giving a sensitivity of 82%. Growth of *M. tuberculosis* occurred with 7 of 21 histo-

logically non-tuberculosis cases. Histological examination therefore had a negative predictive value of 67% (14/21).
Cultures gave positive results for tuberculosis in 23 of the cases, a sensitivity of 61%. Histology was positive for tuberculosis in 15 of the 29 patients with negative cultures, a negative predictive value of 48% (14/29) for culture.

Discussion

Yield of diagnostic procedures

Wide needle aspirations and biopsy smears made only small contributions to the diagnosis of tuberculous lymphadenitis (8% and 11%, respectively). Others have reported higher sensitivities, varying from 28%[9] to 35% for aspiration and 53% for biopsy smears.[10] There are 3 possible reasons for the higher field in other reports. Firstly, other studies included in-patients,[9,10] who present in a later stage of HIV infection and tuberculosis[11] with a more highly compromised immune system; more acid-fast bacilli cells can be detected in their lymph nodes. Secondly, other studies included patients for whom only smears were examined to confirm tuberculous lymphadenitis,[10] thus increasing the number of positive results. Thirdly, our study excluded sputum positive patients since further investigations would not have resulted in different treatment of the patient.[10] A study of out-patients in rural Zambia[12] also reported relatively low yields from smear results, 12% for aspirates and 15% for biopsies.
In contrast to the low yield of aspirate and biopsy smears, macroscopic caseation of excised lymph nodes gave a high yield in our out-patient department setting, similar to that of histology (82%) and higher than LJ culture (61%). The overall positive predictive value of diagnosing tuberculosis by macroscopic caseation was 89%, but it improved during the second part of the study (patients no. 51-100) to give a positive predictive value of 100% (15/15). The improvement could have been due to experience gained, and to the fact that only one surgeon carried out the procedures, instead of 4.This is an encouraging result, but it reminds us of the need for proper supervision and guidance when new protocols are introduced.
Following Perenboom et al.,[10] using a 'step- wise' addition of the 3 diagnostic methods, a cumulative total of 31 of the 38 proven tuberculous lymphadenitis patients was detected retrospectively: firstly, (i) ZN staining of wide needle aspirates diagnosed 3 patients; (ii) macroscopic caseation found 28 more; (iii) biopsy smears did not detect any case of tuberculosis that had not been found by the previous 2 methods.
The contribution of aspiration might be improved by adding an observation described:[9] in 41% of the cases with macroscopic caseation, caseation was also seen in the wide needle aspirate, with a positive predictive value of 100% for tuberculous lymphadenitis. This aspect was not covered in our study, although the surgeons sometimes spontaneously reported (but did not record) macroscopic caseation of the aspirate.

Negative predictive value of histology

In many sub-Saharan African countries, results of histological examination are often used as the standard. Our study revealed a negative predictive value of 67%, implying that tuberculosis was not identified in 33% of patients with negative histology results. If histology had been the only available diagnostic procedure, 18% of the tuberculosis cases would not have been detected and treated. This raises concerns about the effectiveness of histology as a single tool with which to diagnose tuberculous lymphadenitis.

Does HIV infection influence results of diagnostic procedures?

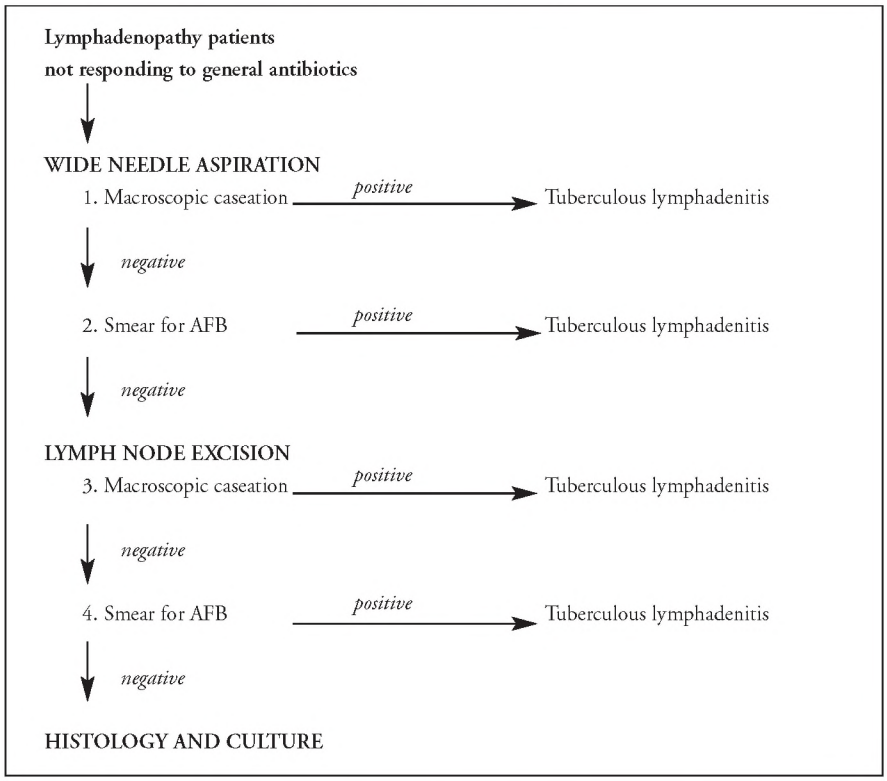
There is no dispute that the HIV epidemic bas contributed to changing patterns of tuberculosis infection. More contentious is the effect of HIV infection on diagnostic methods.[13-17] Although hyporeactive or anergic responses, with numerous bacilli in the lymph nodes of tuberculous lymphadenitis patients infected with HIV, have been described clearly,[9] the influence of HIV on the yield of diagnostic methods for tuberculous lymphadenitis is less certain. Neither Bem et al.[9] nor Perenboom et al.[10] detected any difference in diagnostic yield related to HIV status. Our study suggested that HIV seropositivity of tuberculous lymphadenitis patients decreased the possibility of histology and culture both being indicative of tuberculosis (OR=0.10, p=0.06). In addition, the results tentatively suggested that histology is a more sensitive tool to diagnose tuberculosis in HIV seronegative patients, all of whom were diagnosed by histology, compared with only 78% of those who were HIV seropositive. However, due to the low numbers in general, and especially of HIV seronegative patients, no significant association was found (OR=0; exact confidence limits zero-3.92; Fisher's exact 2-tailed p=0'57). Our finding that HIV infection might decrease the sensitivity of diagnostic procedures for tuberculous lymphadenitis needs further investigation.

Recommendations

Records for only 52 of 100 enrolled outpatients could be used in the analysis. Perenboom et al.[10] were able to acquire complete data for 53% (68/128) of their in-patients. These low return rates reflect the difficulties of research in routine settings outside a research environment. A protocol for diagnosing tuberculous lymphadenitis should therefore be simple and pro-active, reducing the chance of a missed diagnosis due to difficulties in protocol procedures. Therefore, we suggest primarily the use of 4 simple methods to diagnose tuberculous lymphadenitis as shown in the Figure.

These 4 methods have achieved 100% positive predictive values for diagnosing tuberculous lymphadenitis in earlier studies,[10,11] and can easily and safely be carried out at district level. If any of these tests is positive, the diagnosis of tuberculous lymphadenitis can be made and there

Figure 1 Protocol for diagnosis of tuberculous lymphadenitis using 4 simple techniques (developed from the flow chart of Perenboom;[10] AFB=acid-fast bacilli.



is no need to make further investigations, thus saving both cost and time. The recording of caseation of the wide needle aspirate should increase the usefulness of wide needle aspiration in an out-patient department setting. We expect that 80-95% of tuberculous lymphadenitis cases can be diagnosed by these methods in a timely and cost-effective manner in areas with high prevalences of tuberculosis and HIV infection.

Conclusions

The contribution of aspirate and biopsy smears in diagnosing tuberculous lymphadenitis in out-patients was low. In contrast, examination for macroscopic caseation of the cut surface of lymph nodes had high sensitivity. Our study raised concern that sophisticated procedures such as histology and culture, which are developed to diagnose tuberculosis, fail to do so, especially with HIV-associated tuberculous lymphadenitis. Histology missed 18% of the tuberculosis cases, all of whom were seropositive for HIV.

There is a need to develop simple, pro-active methods to diagnose tuberculous lymphadenitis in out-patient departments. Four simple methods, which can easily and safely be carried out at district level, should diagnose 80-95% of tuberculous lymphadenitis cases in a timely and cost-effective manner.

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Chapter IV

Traditional healers and pulmonary tuberculosis in Malawi

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JA Brouwer collected the data, assisted in the design of the studies, and assisted in the writing of the paper.
MJ Boeree assisted in the design of the studies, participated in the data analysis, interpretation and the writing of the paper.
P Kager and CM Varkevisser were supervisors of J Brouwer in the Netherlands and helped in the development of the idea, the data interpretation and the revisions of the paper
AD Harries as the senior scientist in Malawi participated in all aspects of the studies: the design of the studies, the data analysis and interpretation and the write-up of the paper.

Summary

Setting: Queen Elizabeth Central Hospital (QECH) and Blantyre district, Malawi.
Objective: To investigate the use that tuberculosis (TB) patients in Malawi make of traditional healers and traditional medicine.
Design: A questionnaire study was carried out on 89 smear-positive pulmonary TB patients admitted to QECH. Seven traditional healers in Blantyre were also interviewed about their knowledge, attitudes and practice of patients whom they considered to have TB.
Results: Of the 89 patients, 33 (37%) visited a traditional healer before seeking regular medical care. Patients spent a median length of 4 weeks with the traditional healer. During this time, 24 patients did not improve or deteriorated while on traditional treatment. No patient was referred to the medical services by the traditional healer. All traditional healers claimed to know about TB. Four said they would refer a patient to hospital if their treatment was not curative. In 1995, six traditional healers claimed to have cured 116 patients with TB.
Conclusion: It is important to involve traditional healers in the educational activities of the National TB Control Programme. These healers need to be taught to recognise and refer patients with TB, whom they should not treat, but at the same time be encouraged to administer safe treatments for conditions which are more amenable to their practice.

Introduction

TUBERCULOSIS (TB) is a major cause of morbidity and mortality world-wide, with 95% of new cases in 1990 occurring in developing countries.[1] In the World Health Organization (WHO)'s African Region the incidence of TB in 1990 was 1.4 million cases, the majority of which occurred in sub-Saharan Africa.[2] Eighty percent of cases involve persons in their productive years of life (15-59 years), and it has been estimated that 26% of avoidable adult deaths are due to TB.[2]

The human immunodeficiency virus (HIV) infection in sub-Saharan Africa is now strongly associated with TB. In Malawi, in 1989 52% of TB patients were HIV-seropositive[3] and in 1993-1994 in a central hospital in Blantyre 75% were HIV-seropositive.[4] As a consequence of this strong association between the two infections there has been a big upsurge of TB in many African countries, including Malawi, in the last 10-15 years.

Case detection in most sub-Saharan African countries depends on passive case finding. Health workers are taught to suspect pulmonary tuberculosis (PTB) if a patient has a persistent cough for more than three weeks, particularly if there is associated weight loss, fever, chest pain or haemoptysis.[5] Such patients should be referred to the health services for confirmation of the diagnosis, primarily by sputum microscopy examination. In theory, passive case finding of PTB cases should be successful because 90% of smear-positive PTB cases develop a productive cough

soon after the onset of the disease, and this should persuade the patient to seek medical advice.[2] However, under routine conditions, only about a third to a half of smear-positive TB cases are routinely diagnosed. There are various reasons for this failure.

First, it bas been estimated that over half of the existing TB patients in developing countries are not covered by TB services; between 1988 and 1989, service coverage in Africa was estimated at 24%.[1] Second, at the peripheral level health workers often do not consider the diagnosis of TB in patients with a chronic cough, and patients may attend health units several times before a diagnosis is made.[6,7] Third, patients may delay seeking medical advice and help because of other cultural beliefs; in this regard they may initially seek the help of a traditional healer.

The traditional healer is an important and powerful member of the local society, and most villages in Central and East Africa have at least one traditional healer who is easily accessible. There is little information available about the role of the traditional healer in the diagnosis and management of PTB, and we therefore decided to carry out a study.

Methods

Patients

A questionnaire study was carried out between November 1995 and February 1996 on sputum smear-positive PTB patients who had been admitted to the TB ward of queen Elizabeth Central Hospital, Blantyre, to receive supervised anti-TB chemotherapy. Questions concerning the use of traditional healers (in Malawi, such healers deal both with herbs and evil spirits) were asked in the local language (Chichewa), and answers were entered into a questionnaire proforma. Information was entered into an EPI- INFO software package.

Traditional healers

Interviews were carried out with traditional healers living in Blantyre city. Traditional healers were asked about their knowledge of cough and TB, their methods of diagnosis and management and the perceived outcome of their treatment.

Results

Patients

During the study period 89 patients with smear positive PTB were admitted. There were 41 men and 48 women, whose mean age (SD) was 31 (± 9) years. Of these 33 (37%, 15 men and

18 women) had received treatment from a traditional healer before seeking regular medical care. The length of time spent with the traditional healer ranged from two days to two years (median duration = four weeks).

Table 1 Type of traditional medicine

Type of traditional treatment patients (%)	Number of patients (%)
Herbal drink(s) alone	22 (67)
Herbal drink + bath	3 (9)
Herbal drink + bath + necklace	2 (6)
Root powder on tongue	4 (12)
Tattoos	1 (3)
Prayers	1 (3)

The type of traditional medicine taken by the patients is shown in Table 1. The majority of patients were treated with herbal drinks. Fourteen (43%) of the patients paid no charge for traditional medicine; this was because the traditional healer stated he would only charge if the patient was cured. Of the remaining 19 patients, seven (21%) paid less than one US$, eight (24%) paid 1-5 US$, two (6%) paid 6-15 US$ and two (6%) paid 16-30 US$. The outcome of traditional treatment is shown in Table 2. Twenty-four patients (73%) stated they did not improve or deteriorated on traditional treatment. The decision to seek regular medical care for the diagnosis and treatment of PTB was made by the patient in 11 cases (33%), by the patient's family in 12 cases (37%) and as a result of advice from a health care worker in 10 cases (30%). In no case was the patient referred to the medical services by the traditional healer.

Table 2 Patient outcome with traditional medicine

Outcome	Number of patients (%)
No better	19 (58)
Deterioration	5 (15)
Minimal improvement	5 (15)
Temporary improvement	4 (12)

Traditional healers

Seven traditional healers were interviewed, six men and one woman. They all knew about the disease tuberculosis, and the symptoms they mentioned ranged from cough, chest pains and paling hair to haemoptysis, weight loss and swelling of limbs. Six of the healers believed that the cause of TB was adultery in the household, but other causes were also mentioned: sexual inter-

course, germs, stagnant water, alcohol abuse, wrong food, dust, and witchcraft. They all believed they could cure TB. Their treatments included ritual and herbal drinks, mainly (burned) roots, leaves, bark and twigs. The duration of their treatment ranged from two weeks to two months (median four weeks). The charges for their treatment varied from a set charge of 1.25 US$ to a variable charge depending on the amount of time and effort required for a cure. Four traditional healers said they would refer a patient to hospital if their treatment did not cure the patient. In 1995, six of the traditional healers claimed to have cured 116 patients with TB.

Discussion

In this study, over one third of smear-positive PTB patients admitted to Queen Elizabeth Central Hospital, Blantyre, between November 1995 and February 1996 sought help from a traditional healer before approaching the medical services. The proportion of patients may in fact be higher because patients can be hesitant in admitting that they have taken traditional treatment for fear that the health staff would refuse to treat them. Patients who visited a traditional healer spent a median period of four weeks taking traditional medicine; during this time almost three quarters of the patients did not improve or deteriorated. This study of course selected only patients who did not get better with traditional treatment. Those who were cured, if any, would not have been referred to a hospital or a health centre.

The delay in receiving standard anti-tuberculosis chemotherapy has two important consequences. First, the patient may present in an advanced state of the disease and this may contribute to the high early mortality, which is seen in smear-positive PTB patients in Blantyre.[8] Second, the smear-positive patient is a transmitter of infection in the community, and is therefore a considerable public health risk up until the time adequate anti-TB treatment is started.

None of the smear-positive PTB patients had been referred to the medical services by the traditional healer, although two thirds of traditional healers interviewed said that they would refer patients who were not improving. Because of the large number of traditional healers in the community, some of whom are very influential we believe it is important to involve this body of health care providers in the educational activities of the National TB Control Programme (NTP). Traditional healers need to be taught to recognise illnesses such as TB, which in our opinion they should not treat unless there is proven anti-tuberculosis efficacy of the treatment, which they administer. It is prudent to keep an open mind on this issue. There are strong calls from all parts of the globe about the need for new drugs for TB, and in this study over 100 patients in 1995 were claimed by the traditional healers to have been cured by traditional medicine.

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Chapter V

Care seeking behaviour and diagnostic processes in patients with smear-positive pulmonary tuberculosis in Malawi

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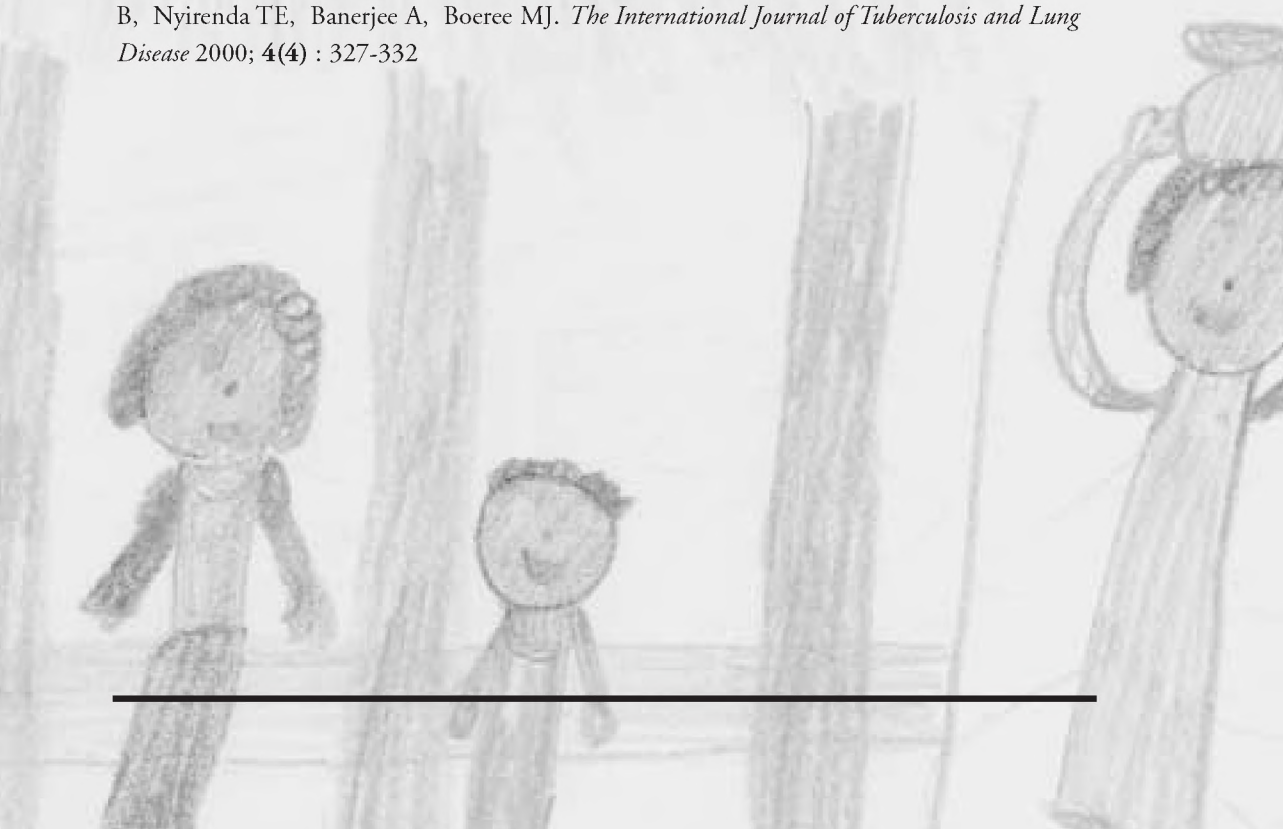

Summary

Setting: Government hospitals in five districts in Malawi.
Objective: To determine care seeking behaviour and diagnostic processes in patients newly diagnosed with smear-positive pulmonary tuberculosis (PTB).
Design: Structured questionnaires completed by interview between January to September 1998.
Results: During the study period 1518 patients were registered with PTB of whom 1099 (72%) were interviewed. The median delay between onset of cough and diagnosis was 8 weeks. There was a variable pattern of care seeking behaviour, with 70% of patients initially visiting a place of orthodox medical care and 30% visiting traditional healers, grocery shops, etc. Of these, 867 (79%) patients had one or more subsequent contacts for help, with these visits targeted more to orthodox medical care. At all stages, antibiotics resulted in symptomatic improvement in up to 40% of cases. There was a median time of 7 weeks between cough and first submission of sputum specimens. Almost all patients received sputum smear results after a median length of 4 days; 474 (43%) of patients were only aware of their diagnosis at the time of receiving smear results, this observation being significantly associated with lack of schooling and not knowing of another person with TB.
Conclusion: More needs to be done to educate communities and non-orthodox care providers about the diagnosis and treatment of TB.

Introduction

TWO OF THE KEY components of a good tuberculosis (TB) control programme are early diagnosis and prompt institution of effective treatment. This is especially important in patients with smear-positive pulmonary tuberculosis (PTB) in order to try and reduce the transmission time of *Mycobacterium tuberculosis* in the community. Studies carried out in Ghana[1] and Botswana[2] have shown long median delays of 3-4 months between onset of symptoms and diagnosis in patients with PTB. The principal reasons for delay are patients seeking alternative ways of treating their cough and the health services failing to perform sputum examination.
Since 1984, the National TB Control Programme (NTP) in Malawi has been supported by the International Union Against Tuberculosis and Lung Disease (IUATLD), and follows guidelines from the IUATLD[3] and the World Health Organization.[4] Case detection is based on passive case finding using sputum smear microscopy as the first-line investigation in a suspect with PTB. In line with the studies in Ghana[1] and Botswana,[2] a study in Malawi in 1988 amongst patients with smear-positive PTB also found a median delay of 4 months between onset of cough and diagnosis.[5] Documented reasons for this delay included prior consultation with traditional healers in over 50% of patients, and a large number of attendances at health centres

before sputum examination was performed. Operational research on case finding activities in Malawi between 1995 and 1996 revealed that many health care staff did not adhere to guidelines on screening PTB suspects,[6,7] and confirmed that a large proportion of smear-positive PTB patients had visited a traditional healer before seeking regular medical care.[8] From 1997 onwards, intensive efforts were made in all districts to train hospital and health centre staff to obtain sputum specimens in patients with a cough for longer than 3 weeks. Efforts were also made to 1) inform the general population about TB with educational talks on the radio, posters, TB messages painted on buses and TB-sponsored football matches, and 2) to brief traditional healers about TB at zonal health centre meetings. One year later, and with training and educational initiatives still on- going, we were interested to obtain up-to-date information about care seeking behaviour and diagnostic processes in patients with smear-positive PTB.

Methods

Setting

The government hospitals responsible for diagnosis and treatment of TB cases in five districts in Malawi were chosen as study sites. There were three hospitals in the Southern region (Queen Elizabeth Central Hospital, Blantyre; Zomba Central Hospital, Zomba; and Mangochi District Hospital), one in the Central region (Ntcheu District Hospital) and one in the Northern Region (Mzimba District Hospital).

Patients

Between 1 January 1998 and mid-September 1998, all patients newly registered with smear-positive PTB at each of the five hospitals were to be interviewed by one of the TB programme's clinical research officers. Structured questionnaires were completed by interview in the local language or English shortly after diagnosis (up to 2 weeks). The questionnaire for each patient included questions about age, sex, TB registration number, history of previous TB treatment, duration of illness and cough, details of first contact for management of the illness, the number of all subsequent contacts and details of management, the time interval between onset of cough and first submission of sputum specimens for smear microscopy, details of the process of receiving results of sputum smear examination, other investigations carried out, and general questions about schooling and about the patient's knowledge of other people ill with TB. Data on patient visits to government and mission hospitals were combined, because at both types of health facility there is a policy of not charging patients with TB.

When all questionnaires were completed, the TB registration numbers of all patients registered with new smear-positive PTB during the study period were compared with the TB registration

numbers of those interviewed in order to determine the proportion of patients who were interviewed.

Analysis

Data from each hospital were entered into Epi-Info version 6.0 software. χ^2 test was used to assess differences in proportions, with differences at the 5% level being regarded as significant. Odds ratios (OR), their 95% confidence intervals (CI) and P values were also calculated where appropriate.

Results

Patients interviewed and clinical features

During the 8-9 month period, a total of 1518 new patients with smear-positive PTB were registered at the five hospitals: 575 in Blantyre, 451 in Zomba, 228 in Ntcheu, 183 in Mangochi and 81 in Mzimba. Interviews were conducted in 1114 (73%) patients: this comprised 318 (55%) patients in Blantyre, 356 (79%) in Zomba, 223 (98%) in Ntcheu, 154 (84%) in Mangochi and 63 (78%) in Mzimba. Reasons why patients were not interviewed were not specifically documented, but included death, early discharge from hospital and absconding. Fifteen patients who were interviewed were subsequently excluded from analysis: seven admitted to a previous episode of TB, five on checking with the TB register had smear-negative PTB or extra-pulmonary TB and three had virtually no information recorded in the questionnaire. Questionnaires were thus analysed for 1099 patients (72% of those registered).

There were 522 males and 577 females, with a mean age of 33 years (range 9-80 years). The median duration of illness was 10 weeks (range 2-100 weeks). The three commonest presenting symptoms of illness were cough (61%), fever (16%) and chest pain (11%). All patients eventually developed a cough. The median duration of cough prior to diagnosis was 8 weeks; 565 (52%) patients had a cough for 8 weeks or less, while 534 (48%) had a cough for longer than 8 weeks.

First contact for help

The places of first contact for help and associated care seeking behaviour are shown in Table 1: 70% of patients visited a place providing orthodox medical care, while 30% visited places practising non-orthodox care (i.e. traditional healers, grocery shops, local vendors, etc). The decision about where to go for help was made solely by the patient in 494 (45%) cases; it was influ-

enced by a close family member (parent, sibling, spouse or partner) in 261 (24%) cases, and influenced by a health care worker in 219 (20%) cases. The commonest reason for attending the place of first contact was because it was the nearest place to home (603 patients, 55%), with the other main reason being a good reputation, pleasant reception and strong medicine (320 patients, 29%); 57% of patients who visited a traditional healer, grocery shop or a vendor and 55% of those who visited a health facility stated that this was because it was the nearest place to home. Most patients (753, 69%) walked to the place of first contact, with others going by bus/mini-bus (18%), bicycle (10%) and motor car (3%). The main way of getting to the nearest place of contact was by walking in 81% of patients: 89% of patients who first visited a traditional healer, grocery shop or a vendor walked compared with 62% of patients who visited a hospital or health centre. Most patients (701, 64%) received pills, but did not know the names or types of pills, which they were given; 112 (10%) patients knew they had been given an antibiotic and 150 (98%) patients attending a traditional healer reported that they were given herbal medicine. Payment was made for treatment by 461 (42%) patients, the median payment made being the equivalent of 1.4 US$ (range a few cents to 24 US$). Payment was made by 51 (9%) patients visiting a government/mission health facility, 158 (86%) patients visiting a private clinic and 252 (77%) patients visiting non-orthodox facilities. In 265 patients (24%) the cough improved with the treatment received - 240 of these patients stated that the cough returned a median of 3 weeks later. There was only one contact for help in 232 (21%) patients, at which point patients were referred for sputum examination. This occurred in 167 patients attending health centres, 45 attending hospitals, 10 attending private clinics, six attending traditional healers and four attending other places.

Table 1 Place of first contact for help in patients with smear-positive pulmonary tuberculosis

Place of first contact	Number (%) of patient in study	Patients at each place of contact (%) who			
		Visited because it was nearest	Walked	Paid for treatment	Found cough improved with treatment
Government/mission health centres	433 (39)	65	70	8	31
Private clinic	183 (17)	42	56	86	28
Government/mission Hospital	157 (14)	44	45	11	18
Traditional healer	153 (14)	48	83	58	6
Grocery/local vendors	145 (13)	67	94	99	20
Other	28 (3)	18	46	71	43
Total	1099	55	69	42	24

Subsequent contacts for help

A total of 867 patients had a median of one further contact for help before a diagnosis of TB was made (range 1-15 contacts), while 262 (24%) patients had three or more further contacts. Details of these contacts are shown in Table 2. Of the 2078 contact visits, 1553 (75%) were to health centres or hospitals, and relatively fewer visits at this stage were made to traditional healers (8%), private clinics (8%) and other sites such as groceries, small dispensaries or private pharmacies (9%). Three hundred and thirty-eight patients did not know what treatment they had received; 529 patients knew they had been given an antibiotic at one of these visits (the antibiotic was known to be co-trimoxazole in 250 patients, penicillin in 103 and doxycycline in 22), and these patients took a total of 841 courses of antibiotics; 204 (39%) patients receiving an antibiotic reported some improvement in the cough.

Table 2 Subsequent contacts for help in patients with smear-positive pulmonary tuberculosis

Place of contact	Number of patients	Number of visits to each place of contact
Government/mission health centres	370	718
Private clinic	125	162
Government/mission hospital	556	835
Traditional healer	93	166
Other (includes pharmacy, grocery store, etc)	137	197
Total	1281	2078

Note: Many patients visited two or more different places of contact for help, which is why the numbers do not add up to 867.

Diagnosis of smear-positive PTB

There was a median time of 7 weeks between onset of cough and first submission of sputum specimens for smear examination. The time was less than 3 weeks in 144 (13%), 3 to 8 weeks in 534 (49%), and longer than 8 weeks in 421 (38%) patients. Information on sputum smear results were given to 1074 (98%) patients after a median length of 4 days (range 1-49 days) from sputum submission. One set of sputum specimens was obtained from 941 (86%) patients (a set of sputum specimens is defined as an on-the-spot sputum, an early morning sputum and a second on- the-spot sputum), 126 (12%) gave two sets, 26 (2%) gave three sets and six gave four or more sets. During the diagnostic process chest radiography was carried out in 151 (14%) patients.

Patient's knowledge about PTB and other related aspects

Six hundred and twenty-five patients (57%) believed that they might have PTB before the diagnosis was made, while 474 (43%) were only aware of the diagnosis when they received their sputum smear results. Details of when the patients thought they had PTB in relation to schooling history and knowing other people with TB are shown in Table 3. Lack of schooling (OR 2.10, 95%CI 1.60-2.77, $p < 0.05$) and not knowing another person with tuberculosis (OR 1.77, 95%CI 1.38-2.28, $p < 0.05$) were significantly more frequent in patients who were only aware of their diagnosis of PTB at the time of sputum smear results compared with those who believed that they might have PTB before the diagnosis was made. Knowing another person with TB was more common in patients interviewed at the two central hospitals in Blantyre and Zomba (478/666 = 72%) compared with patients interviewed at district hospitals (164/ 433 = 38%, $p < 0.05$). Other people known to have TB included a family member or spouse in 387 (60%), a friend in 217 (34%) and a workmate in 38 (6%) cases. Of other persons known to have TB, 54% were said to be well, 15% were ill, 26% had died, and there was no information in the remainder.

Table 3 Patients' knowledge about pulmonary TB in relation to schooling history and knowing others affected with TB

	Patient's knowledge about pulmonary tuberculosis	
	Belief that PTB was the cause of illness before sputum smear results	Only aware of diagnosis after results of sputum smear examination
Number of patients	625	474
Number (%) of patients with*		
No school attendance	137 (22)	176 (37)
School attendance	488 (78)	298 (63)
Primary school only	359	220
Secondary school	129	78
Number (%) of patients who*		
Knew another person with TB	403 (64)	239 (50)

* Percentage of patients within each knowledge category (i.e., believed that they had PTB before receiving sputum results or were only aware of diagnosis alter sputum results).

Discussion

This study shows that in a large number of patients newly diagnosed with smear-positive PTB the median time between onset of cough and diagnosis was 8 weeks. Not all consecutive patients were interviewed according to the study protocol. Some patients died before interview, and in some cases the interviews were not carried out before the patient left hospital. The proportion

of patients interviewed was lower at the central hospitals due to the larger numbers of patients and the fact that clinical research officers had other duties to perform. Nevertheless, nearly three-quarters of all patients had their questionnaires evaluated. Sites were chosen so that all three regions in the country and urban district areas were represented, and we feel the results are a reflection of the current situation at country level.

The pattern of care seeking behaviour was variable. Approximately 70% of patients initially visited a place of orthodox medical care and 30% visited traditional healers, grocery shops, local vendors, etc. In over half of the patients the commonest reason for choosing the first place of contact was proximity to home, reflected in the fact that most patients walked to seek help. Close to 80% of the population in Malawi are said to live within 8 km of a health service point,[9] and over half of the patients who visited a health facility as their first contact gave proximity to home as the main reason for their visit. Unfortunately, we did not document distance from home to first point of contact. However, a distance of up to 8 km, making a round trip of up to 16 km, is still a significant barrier to access if patients are ill and have to walk.[10] Payments were made by over 75% of patients who visited private clinics and places of non-orthodox medical care. Other costs, which were not documented in this study, include the payment for some form of engine-driven transport and loss of earnings from time spent away from work; these may also adversely affect access to care.[10] Most patients received pills of some sort, and either did not know or did not remember the names or type of these medications. However, in about one quarter of patients the cough improved, only to return some time later.

For patients who had more than one visit before a diagnosis of PTB was made, these visits were targeted more towards orthodox medical care. At this stage a large number of patients remembered being given an antibiotic, and over one third of patients reported an improvement again in their cough. It bas been noted in other studies that patients with microbiological TB can lose their respiratory symptoms after a course of antibiotics;[11] this may be due to same antibiotics having a short mycobacteriostatic action or because of bacterial superinfection.[12] Whatever the reason, symptomatic improvement after an antibiotic may contribute to a delay in diagnosis, as bas been found in other parts of sub-Saharan Africa.[13]

At present the NTP spends time and resources in educating traditional healers about TB. This study confirms the importance of traditional healers, although fewer patients admitted visiting traditional healers in this study compared with previous reports from Malawi.[5,8] This study also shows that patients visit grocery shops, local vendors and private clinics, and that in future it will be important to include these personnel in TB education. Experience in rural Nigeria with patent medicine vendors has demonstrated that training in primary care medicine can significantly improve the health care knowledge and behaviour of non-medically trained personnel.[14]

While in general the diagnostic process of sputum examination worked well, a substantial number of patients still had cough present for more than 8 weeks before they submitted their first set of sputum specimens. When sputum samples were submitted, most patients received their results within an acceptable time frame. We were pleased to see that few patients had a chest radiograph, with the diagnostic effort being concentrated on sputum smear examination.

Despite efforts at informing the public about TB, over 40% of patients only realised the diagnosis when told the results of their sputum smear examination. Lack of schooling and not knowing another person with TB were associated with a lack of realisation of the diagnosis. There are initiatives underway in Malawi to inform schoolchildren about important medical conditions such as AIDS, TB and malaria, but it is obviously equally important to target rural people and villagers who may not have access for one reason or another to school education. There needs to be more use of posters, talks and radio broadcasts on a regular basis; widespread coverage of TB issues on World TB day is another practical way of informing communities about TB.

Tuberculosis is a common disease; 642 (58%) patients knew of another person with TB, most commonly a family member. Knowing another person with TB was also more common in the city environment of Blantyre and Zomba, which probably relates to overcrowding, urban poverty and higher prevalence of HIV infection and AIDS.[15] There is growing evidence that a significant number of new cases of TB in sub-Saharan Africa result from recent transmission and casual contact,[16,17] in which case delays between onset of symptoms and diagnosis and treatment should not be tolerated. Although we can be pleased that the median delay between onset of cough and diagnosis in this study was 8 weeks, rather than 4 months as found previously,[5] there are no grounds for complacency, as TB transmission can still occur during this time period. There is also evidence that delay in the diagnosis of TB may compromise the chances of individual cure. Untreated TB in HIV-infected persons may accelerate the decline in immunocompetence[18] and the progression to severe immunodeficiency, and may allow the development of extensive pulmonary tuberculous disease.

One of the important components of global TB control is involvement of communities in treatment and case holding. However, communities should also be involved in case finding.[19] It is unlikely that resource-poor countries will find the resources to change their case detection strategy from passive to active case finding. Therefore, ways to improve passive case finding need to be found. More suspects who never reach treatment need to be identified, and of those who reach treatment the time between onset of symptoms and diagnosis needs to be shortened. More dialogue between the TB programme and other important stakeholders such as traditional healers, village headmen, schoolteachers and patients who are responding well to treatment should be undertaken if we are to improve our case detection rates and reduce the delays in diagnosis.

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Chapter VI

Viability of stored sputum specimens for smear microscopy and culture

Banda HT, Harries AD, Boeree MJ, Nyirenda TE, Banerjee A, Salaniponi FML *The International Journal of Tuberculosis and Lung Disease* (2000); **4(3):** 272-274

Summary

A laboratory study was performed to determine how long sputum specimens from smear-positive tuberculosis patients can he stored at room temperature or in the refrigerator and retain a positive acid-fast bacilli (AFB) smear or a positive mycobacterial culture. Sputum samples from 30 patients were examined up to 4 weeks and samples from 13 patients examined up to 8 weeks. Provided samples had not dried out, all sputum smears remained AFB positive up to 4 and 8 weeks. In both patient groups, at 4 weeks 37-39% of specimens at room temperature grew mycobacteria compared with 54-67% of specimens stored in the refrigerator. These results have implications for tuberculosis programme policy.

Introduction

In Malawi, sputum specimens submitted at rural health centres are transported to hospital laboratories for smear examination. Logistical difficulties can lead to delays in getting sputum examined. Long sputum storage times may result in false-negative sputum smears.[1-3] Sputum specimens are also submitted to the central mycobacterial reference laboratory for culture for patients with previously treated smear-positive pulmonary tuberculosis (PTB) in order to determine drug sensitivity patterns which may influence the choice of drugs for the continuation phase of treatment. There are often delays in transporting specimens from district hospitals to the central reference laboratory, and this can lead to loss of culture viability.[2-5]

We designed two studies to examine how long sputum specimens can be stored, either at room temperature or in the refrigerator, before losing their acid-fastness for smear microscopy or their culture viability.

Methods

Patients and study methodology

Patients with smear-positive PTB registered at Queen Elizabeth Central Hospital, Blantyre, were asked to submit two further sputum specimens into containers before commencing treatment. These specimens were processed on the day of submission (day 0). Thereafter, one sputum container was stored in the refrigerator at 4°C and one at room temperature (20°- 25°C). In the first study (Study 1), the refrigerated and room temperature sputum specimens were processed for smear microscopy and mycobacterial culture on days 2, 4, 7, 9,11,14,21 and 28. When results were obtained for Study 1, a second study (Study 2) was conducted with smaller numbers of patients in which duration of sputum storage was extended up to 8 weeks, with smear and culture examinations performed on a weekly basis.

Smear and culture examination

Sputum smears were examined for acid-fast bacteria (AFB) using Ziehl-Neelsen stain.[6] For mycobacterial culture, each specimen was decontaminated by sodium hydroxide before inoculation into Löwenstein- Jensen (L- J) slopes: examination was at weekly intervals for up to 8 weeks.[7]

Observer variability

There were two technicians involved in the laboratory. Observer variability in smear microscopy and culture was tested using nine portions of sputum from each of three patients (AFB 3+, AFB 2+ and AFB negative). There was no intra- or inter-observer variability in smear or culture results.

Statistical analysis

Differences in culture viability at defined times and between refrigerated and room-temperature specimens were assessed using χ^2 test with Yates correction and χ^2 test for trend. Differences at the 5% level were regarded as significant. Odds ratios (OR), 95% confidence intervals (CI) and p values were also calculated.

Results

Study 1

There were 30 patients: 10 with 3+ AFB, 10 with 2+ AFB and 10 with 1+ AFB. If specimens did not dry out, all those that could be processed remained smear-positive on each examination day from the day of submission up to 28 days of storage, either at room temperature or in the refrigerator. Results of sputum culture-positivity are shown in Table 1. There was a gradual decline in culture-positivity up to 28 days of storage for both room-temperature and refrigerated specimens. A significantly higher proportion of refrigerated specimens were culture-positive at 14 days (OR = 4.0, 95%CI 1.1-4.9, p = 0.03) and culture- positive at 28 days (OR = 3.4, 95%CI 1.1-11.6, p = 0.04) compared with room-temperature specimens.

Table 1 **Sputum cultures up to 28 days after sputum submission**

Initial AFB smear result	Storage of sputum	No. of specimens	Positive sputum cultures for M. *tuberculosis* Day 0 *n* (%)	Day 7 *n* (%)	Day 14 *n* (%)	Day 21 *n* (%)	Day 28 *n* (%)
3+	Room	10	10	9	4	2	3
	Refrigerator	10	10	10	8	8	9
2+	Room	10	10	9	5	7	5
	Refrigerator	10	10	10	9	8	7
1+	Room	10	10	8	6	3	3
	Refrigerator	10	9	9	7	4	4
Combined AFB smears (3+,2+,1+)	Room	30	30 (100)	26 (87)	15 (50)	12 (40)	11(37)
	Refrigerator	30	29 (97)	29 (97)	24 (80)	20 (67)	20 (67)

Two of 540 sputum cultures became contaminated.

Study 2

There were 13 patients: six with 3+ AFB, five with 2 + AFB and two with scanty AFB. Results for smear- positivity and culture-positivity for all patients combined are shown in Table 2. Sputum smears were all positive up to 4 weeks. By 8 weeks three specimens had dried out but the remaining 10 specimens were still smear-positive. There was a general decline in sputum culture-positivity, similar to that found in Study 1. At 4 weeks, positive cultures were found in five (39%) room-temperature specimens and seven (54%) refrigerated specimens. At 8 weeks, positive cultures were found in three (23%) room-temperature specimens and six (46%) refrigerated specimens. These differences were not statistically significant.

Table 2 **Sputum smear and sputum culture results up to 8 weeks after sputum submission**

Type of specimen	Storage of sputum	Weeks from submission of sputum specimen 0	1	2	3	4	5	6	7	8
Sputum smears positive for AFB	Room	13	13	13	12	3	12	12	12	10
	Refrigerator	13	13	13	13	13	12	12	12	10
Sputum cultures positive for *M. tuberculosis*	Room	10	9	8	5	5	2	2	6	3
	Refrigerator	8	10	10	6	7	6	5	8	6

Sputum specimens were examined for 13 patients: 1 sputum specimen became dry at 6 weeks, 3 sputum specimens became dry at 8 weeks, 5 of 234 sputum cultures became contaminated.

AFB = acid-fast bacilli

Discussion

Results show that in a laboratory environment in Malawi all sputum specimens (whether stored at room temperature or in the refrigerator) that could be processed remained smear-positive for AFB up to 4 weeks in the first and second studies, and up to 8 weeks in the second study. The major threat to smear microscopy was in the sputum specimen drying out, and this may have been a result of the study design which involved opening and shutting sputum containers on prescribed days in order to obtain portions of sputum for examination.

Mycobacterial culture viability declined with time, although the ability to grow mycobacteria was better for specimens kept in the refrigerator than at room temperature. In both studies, at 4 weeks between 37-39% of specimens kept at room temperature could grow mycobacteria compared with 54- 67% of specimens stored in the refrigerator. At 8 weeks, the ability to grow mycobacteria had declined to less than 25% for room-temperature specimens and less than 50% for refrigerated specimens. The decline in mycobacterial culture viability was not constant, particularly in Study 2, which probably reflects observer variability in sampling portions of sputum and in decontaminating specimens. In both studies, the proportion of contaminated cultures was small, probably reflecting a rather harsh decontamination process.

This study has implications for the Malawi National Tuberculosis Control Programme. First, specimens for smear microscopy which arrive late in hospital laboratories from health centres should not be automatically discarded by laboratory technicians. Smears can still be positive even if sputum bas been stored for up to 8 weeks. Second, sputum specimens sent to the mycobacterial central reference unit for culture and sensitivity should be kept in a refrigerator prior to transportation. While it is better to avoid delay, at least 50% of refrigerated specimen may show mycobacterial growth even if the delay is up to 4 weeks.

Acknowledgements

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Chapter VII

Co-trimoxazole in HIV-1 infection

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strategies to intervene with appropriate antibiotics early on in the clinical event. Early recognition of pneumococcal and salmonella sepsis is the key to a reduction in early mortality from HIV-1 infection.

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1 Anglaret X, Chêne G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet* 1999; **353:** 1463–68.
2 Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial. *Lancet* 1999; **353:** 1469–75.

Sir—Xavier Anglaret[1] and Stefan Wiktor[2] and their colleagues believe that co-trimoxazole prophylaxis in HIV-infected patients may not be applicable to all parts of Africa, because of differences in the patterns of incident infections and of co-trimoxazole sensitivity of major bacterial pathogens such as non-typhoidal salmonellae (NTS) and pneumococci. We share this view. The investigators report in-vitro co-trimoxazole resistance rates of 14% in NTS isolates in Abidjan. In patients admitted to hospital in Blantyre, Malawi, the most common causes of invasive bacterial disease in HIV-infected adults are NTS and pneumococci, of which the in-vitro resistance rates to co-trimoxazole in the past year have been 83% and 91%, respectively (unpublished data).

In Malawi and some other African countries where malaria is a major cause of morbidity and mortality, sulphadoxine-pyrimethamine is the first-line treatment for *Plasmodium falciparum* infections. In many countries it is a back-up treatment when chloroquine fails. Parasites resistant to sulphadoxine-pyrimethamine are becoming more prevalent.[3] Laboratory data indicate that cross-resistance may exist between pyrimethamine and trimethoprim, and that the widespread use of co-trimoxazole could contribute to the selection or spread of sulphadoxine-pyrimethamine-resistant *P falciparum*.

What is best in West Africa may not have the same benefits elsewhere on the continent. In many countries, 10–25% of adults are HIV seropositive. A policy of co-trimoxazole prophylaxis carries enormous logistical and cost implications. Its effects on the drug-responsiveness of *P falciparum* and invasive bacteria are unknown. It is all the more important that placebo-controlled trials are conducted in areas with high bacterial co-trimoxazole resistance, with attention to the possible impact on malarial sensitivity to sulphadoxine-pyrimethamine, before co-trimoxazole prophylaxis is introduced widely in Africa.

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Sir—Co-trimoxazole prophylaxis in patients infected with HIV-1 prevents *Pneumocystis carinii* pneumonia (PCP),[1] a major cause of morbidity and mortality among AIDS patients in developed countries.[2] This intervention is not widely used in sub-Saharan Africa where PCP is uncommon.[3,4] However, co-trimoxazole also prevents other opportunistic infections that occur commonly in patients with HIV-1 infection in Africa.[4] We read with interest Stefan Wiktor and colleagues Cote d'Ivoire trial[5] that showed the drug improved the outcome of HIV-1-associated tuberculosis.

We assessed the effect of co-trimoxazole on the incidence of opportunistic infections and survival of HIV-1-infected adults with tuberculosis who presented to our HIV clinics between January, 1992, and December, 1996. During this period, we recruited a prospective cohort of patients for whom demographic, clinical, and laboratory data were recorded. Prophylactic co-trimoxazole was not used widely at first because efficacy of the drug was thought to be limited to prevention of PCP. Subsequently, 480 mg daily was given if the CD4+ cell count was less than 200 cells/ L. The case definition of tuberculosis was positive culture or a compatible clinical picture combined with a positive smear or a histological diagnosis. Follow-up was the time from the diagnosis of tuberculosis to December, 1996, which was the date of last visit before the study endpoint, or to death. Survival was assessed by the Kaplan-Meier method. Cox's proportional regression hazards model was fitted to adjust for differences at baseline.

158 patients fulfilled the case definition of tuberculosis. Co-trimoxazole was used by 71 patients. The incidence of opportunistic infections (PCP, cerebral toxoplasmosis, non-typhoid salmonellosis, and bacterial pneumonia) that could be prevented by co-trimoxazole was lower in the treatment group than in the controls (three patients, incidence density 0·3 per 100 person-months *vs* 14 patients incidence density 2·1 per 100 person-months; risk ratio 0·23 [95% CI 0·06–0·84]; p=0·017). Mortality was also lower in the treatment group than in the controls (14 patients, 1·2 per 100 person-months *vs* 36 patients, 5·5 per 100 person-months; p=0·002). The median survival of the co-trimoxazole group was better than that of the controls (28 *vs* 16 months; p=0·03). In the univariate analysis, use of co-trimoxazole improved survival (risk ratio 0·53 [0·30–0·94]; p=0·03). A similar protective effect was found after adjustment for differences at baseline (0·38 [0·23–0·62]; p<0·001). It is noteworthy that the better outcome in patients given co-trimoxazole was achieved despite their lower CD4+ lymphocyte count at baseline (median 174 [IQR 33–199] *vs* 308 [290–745] cells/ L; p<0·001).

Our findings together with those of Wiktor and colleagues[5] indicate a dramatic benefit of prophylactic co-trimoxazole in HIV-1-infected patients with active tuberculosis and confirm that the lower dose of 480 mg daily is also effective in an African context.[1] All patients with tuberculosis should thus be offered HIV testing. Co-trimoxazole is an affordable intervention that would help improve the therapeutic nihilism which surrounds HIV in many African countries.

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Chapter VIII

Efficacy and safety of two different dosages of cotrimoxazole as preventive treatment for HIV infected adults with smear positive pulmonary tuberculosis in Blantyre, Malawi; a randomised clinical trial.

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Submitted

Summary

Background: UNAIDS provisionally recommended the use of cotrimoxazole (CTX) prophylaxis in patients with HIV/AIDS in sub-Saharan Africa as a simple and cheap intervention to reduce the high mortality rates. The efficacy of such a prophylaxis was shown particularly in HIV-positive smear positive pulmonary tuberculosis (PTB) patients in Ivory Coast, and this has made it ethically difficult to justify further efficacy studies using placebo controls. However, further work is needed in this area, and we conducted a study to assess the efficacy and safety of two different dosages of CTX in prophylaxis in similar patients in Blantyre, Malawi.

Methods: The design of the study was a randomised, double-blind trial using two dosages (480 mg and 960 mg) of cotrimoxazole given to 272 and 307 new HIV-positive smear-positive PTB patients, respectively. Patients were followed up for a median of 14.5 months. The primary outcome was survival, and the outcome in the two groups was also compared with the outcome observed in a) an unselected cohort of HIV-positive, new smear-positive PTB patients registered in Zomba, Malawi in 1995 and b) new smear-positive PTB patients registered in the Malawi National Tuberculosis Programme (NTP) in 1999. The secondary outcome was the occurrence of (opportunistic) events, especially bacterial pneumonia.

Findings: There were no statistical significant differences in mortality and bacterial pneumonia in the groups receiving the two different dosages. The case fatality rate at the end of the PTB treatment (8 months) was 15.4% in the CTX 480 mg group and 14.0% in the CTX 960 mg group ($p = 0.63$). This was lower (though not significantly) than the case fatality rate in the Zomba cohort (19.2%, $p = 0.10$) and lower than the case fatality rate of the NTP (21.0%, $p < 0.001$). CTX was well tolerated, and only one patient had to stop prophylaxis because of a serious side effect. Compliance was fair with 2.5% of the patients being non-compliant and 7.8% of the patients defaulted from the study.

Interpretation: This study provided circumstantial evidence that cotrimoxazole prophylaxis may have a beneficial effect on mortality and morbidity in HIV infected smear positive PTB patients. However, our results should be interpreted with caution because of methodological differences with the cohort group in Zomba and the data from the NTP. The efficacy of a dosage of 480 mg CTX was not significant different from a dosage of 960 mg. Both dosages of cotrimoxazole were well tolerated, and the intervention is cheap and easy to implement. These results would support implementation of CTX in this patient group until better strategies are available or evidence is convincingly presented to suggest that its benefit is marginal.

Introduction

The mortality in sub-Saharan Africa of patients who are treated for tuberculosis has increased dramatically in the last decades due to HIV.[1] There is an urgent need for measures to reduce this mortality. At present, the availability of antiretroviral treatment in Africa is limited. Cotrimoxazole (CTX) prophylaxis has several potential benefits. Before the introduction of antiretroviral therapy in the industrialised world CTX prophylaxis was widely used in HIV infected patients with impaired immunity. The decrease in morbidity and mortality was mainly due to preventing opportunistic infection with *Pneumocystis carinii.*[2] In Africa, the reported incidence of *Pneumocystis carinii* pneumonia (PCP), is much lower.[3-5] However, CTX prophylaxis may still be effective in decreasing mortality and morbidity through the prevention of other CTX susceptible (opportunistic) infections.

This assumption was based on existing knowledge of the causes of mortality and morbidity in HIV infected patients in Africa. Mortality is high because of fatal bacterial infections with *Streptococcus pneumoniae* and non-typhoidal salmonellae (NTS).[6-8] Other causes of death and serious illness include cerebral infections with *Toxoplasma gondii*[9,10] and chronic diarrhoea caused by *Cryptosporidium parvum, Isospora belli* and *Cyclospora cayetanensis.*[11] Evidence from studies in the industrialised world showed that the incidence of pneumococcal disease and *Toxoplasma* encephalitis was lower in patients who received CTX prophylaxis for PCP.[12,13] Furthermore, there is a known, recently confirmed,[14] beneficial effect of CTX on *Plasmodium falciparum.*

This led to trials to assess the efficacy of CTX in Africa. In Ivory Coast, the use of cotrimoxazole (CTX) prophylaxis decreased mortality in patients with tuberculosis by 46%.[15] In HIV positive patients without tuberculosis there was no reduction in mortality, but a 43% reduction in hospital admissions.[16] In Senegal,[17] a study in HIV positive patients without tuberculosis showed no beneficial effect, but had small numbers of patients. In a recently completed study in Thyolo district, Malawi, cotrimoxazole showed a significant reduction in mortality in HIV-positive patients with smear-negative PTB and extrapulmonary TB, but not in smear positive PTB.[18] The results of the Ivory Coast study have lead to the provisional recommendation of WHO/UNAIDS that "CTX should be used for prophylaxis in adults and children living with HIV/AIDS in Africa as part of a minimum package of care".[19] These recommendations have made it ethically difficult to justify further efficacy studies using placebo controls. However, extrapolation of the Ivory Coast trial to other regions within sub-Saharan Africa may not be justified because of the relatively low bacterial resistance rates to CTX in Ivory Coast. For example, the resistance of NTS isolates to CTX was only 14%. It has been suggested that these results should be investigated in regions with high bacterial CTX resistance.[20] In Malawi, the rate of resistance of NTS and *Streptococcus pneumoniae* to CTX is much higher (73 and 91% respectively).[6,21]

The most optimal dosage of CTX still needs to be established in terms of efficacy, safety and cost. The WHO/UNAIDS recommends CTX 960 mg daily. In one study in the Netherlands

cotrimoxazole in a dosage of 480 mg had the same efficacy in preventing PCP as CTX in a dosage of 960 mg.[22] In addition to reduced cost of a single dose of 480 mg,[23] side-effects may be less using CTX 480 mg in HIV infected patients, in whom adverse effects to CTX are known to be more frequent.[24] Currently there are no data available on its use in African patients.

We decided to investigate the efficacy of cotrimoxazole in preventing death and disease in HIV infected patients with active smear positive tuberculosis in Blantyre, Malawi. The original design was a randomised placebo-controlled trial. Soon after implementation of the trial the results of the study in Ivory Coast became available.[15] Ethical considerations, especially in light of a vigorous debate at that time about ethical aspects of placebo-controlled studies in Africa[25] lead to our trial being terminated. The trial was then redesigned to compare two different dosages of cotrimoxazole (480 mg and 960 mg). We were interested in comparing case fatality rates, specific morbidity and frequency of drug reactions during anti-TB treatment in patients who received the two different dosages of CTX. We also compared case fatality rates in patients on CTX with those observed in a cohort of HIV-positive new smear positive PTB patients recruited to a study in Zomba, Malawi in 1995 and with the reported case fatality rates in new smear-positive PTB patients registered in the National Tuberculosis Control Programme in 1999.[26,27] We were also interested to document the operational problems encountered with the implementation of this intervention in a health care setting in a developing country with high rates of coinfection with tuberculosis and HIV.

Methods

The setting

The study was carried out at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi from April 1998 until September 2001. QECH is a large 1050-bedded teaching hospital and functions as a primary, secondary and tertiary facility. It is the only government hospital in Blantyre and health care is free of charge; the hospital serves the population of the city as well as that of Blantyre district (estimated population of 830 000 in mid-1998 [source – National Statistics Office]). Health care is provided free of charge. The National Tuberculosis Control Programme (NTP) has an office at QECH managed by a District Tuberculosis Officer (DTO).

Patients

In accordance with current guidelines of the NTP, patients suspected to have active pulmonary tuberculosis were requested to submit three samples of sputum.[28] These samples were examined for acid fast bacilli (AFB) in the hospital laboratory. Patients with a positive smear for AFB were referred to the DTO for registration and treatment according to Malawi National TB

Programme guidelines. Before starting treatment the study clinical officer screened the patients for inclusion in the trial. If the patient was willing to participate he/she was counselled for HIV testing. Patients who fulfilled the following eligibility criteria were candidates for inclusion: patients older than 15 years, serological evidence of HIV infection, pulmonary tuberculosis diagnosed by sputum microscopy reconfirmed in our research laboratory, resident and planning to stay in Blantyre district and surrounding areas for three years, and having given written or verbal informed consent. Patients were excluded on the basis of the following criteria: a diagnosis of active symptomatic bacterial infection other than tuberculosis or protozoal infection, known hypersensitivity to or intolerance to CTX, liver disease, as evidenced by clinically apparent jaundice, inability to comply with protocol requirements, malignancy, inability to leave the bed unassisted to be weighed, being a prisoner, a vendor or a refugee, pregnancy or a previous episode of tuberculosis.

Study methods

Each patient had a careful history and clinical examination. Blood and sputum samples were taken. Eligible patients were randomised to receive either CTX 480 mg or 960 mg during TB treatment and to receive isoniazid or placebo after TB treatment whilst continuing with the assigned CTX regimen. The latter part of the study aims to study the possible impact on secondary prophylaxis of isoniazid on mortality and relapse of tuberculosis. The results of this study will be reported separately.

Randomisation was done using a computer generated randomisation list, using Microsoft Excel. An association of two letters was randomly assigned according to this list to each consecutive patient in order of enrolment. Each combination of syllables corresponded to a simple dose of cotrimoxazole except for one of them, which was a placebo. One group received once daily 480 mg cotrimoxazole in the morning (one active capsule of 480 mg and one placebo capsule); the second group received once daily two capsules of 480 mg cotrimoxazole in the morning.

All study medication was identical in appearance and was manufactured by Genpharmaceutical, Johannesburg, South Africa. The enrolment of the patients and the distribution of the capsules were done by the study clinical officers. Both the patients and the clinical officers (and all other members of the study group) were blinded to the treatment. Treatment for tuberculosis was then started with the standardised anti tuberculosis treatment regimen according to WHO guidelines. This consisted of one month of daily streptomycin (intramuscular), and rifampin, isoniazid, and pyrazinamide (all oral), one month of the same four drugs three times a week, followed by a continuation phase of six months with daily isoniazid and ethambutol ($1SHRZ/1S_3H_3R_3Z_3/6HE$). All dosages were adjusted according to weight. During the two-month intensive phase the patients were admitted in the tuberculosis wards.

The patients were followed up every four weeks at the research treatment clinic until the end of tuberculosis treatment. At each follow-up visit a brief history and clinical examination was

obtained and CTX was given for the next month. Samples of blood and sputum were taken according to protocol.

Patients were discontinued from follow-up after completion of the study period, after death or near-terminal state, after voluntary withdrawal, or after moving out of the district. Patients who did not show up for their scheduled visit or their relatives were visited at home by the study nurse and encouraged to resume attending the clinic. Patients were considered lost to follow-up if they missed two consecutive visits. If patients had died an attempt was made to establish the cause of death although our study originally was not designed to determine these causes. When a patient died the symptoms of the last visit were correlated with the relatives' description of symptoms at the time of death when the death occurred at home.

Compliance was checked by a monthly pill count at each visit. A patient was considered compliant if the ratio of the total number of study drugs actually taken and prescribed was between 0.6 and 1.0

When a serious adverse event related to cotrimoxazole occurred, the CTX was stopped, but the patient was not withdrawn from the study.

Laboratory methods

At enrolment HIV serology was performed using a HIV rapid assay (HIV Spot for HIV-1 and HIV-2, Genelabs diagnostics, Singapore). The samples that tested positive were confirmed by ELISA (Vironostatika, Organon, Boxtel, the Netherlands). A full blood count (FBC) with the measurement of haemoglobin, haematocrit, platelets and white blood cell count with a differential count was done using a Coulter Onyx (Beckman Coulter, Johannesburg, South Africa). A count of CD 4 positive T-lymphocytes was done using a FACScount (Becton Dickinson, Rivonia, South Africa) and later with a manual method (Coulter Onyx, Beckman, Johannesburg, South Africa). Aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) were measured by a kinetic method (Human, Wiesbaden, Germany). Direct bilirubin levels were measured using a colorimetric test (Duomate DBIL, Human, Wiesbaden, Germany). Toxoplasma IgG levels were measured using ELISA (Clark Laboratories, Jamestown, NY, USA.

Sputum samples were stained with the Ziehl-Neelsen staining method and microscopically examined for acid fast bacilli. A sample of the sputum was incubated for culture on a plate with Löwenstein-Jensen medium, which was produced locally. The plates were assessed for the growth of mycobacterial colonies every week until three months. Cases were defined as confirmed tuberculosis if the culture grew mycobacterial colonies and as non-confirmed tuberculosis if the culture remained negative.

CD4 count was repeated after two months, sputum microscopy and culture were repeated after five and eight months, while FBC, ASAT, ALAT and bilirubin were repeated after two months and then after every three months until the end of the study.

Objectives

The primary objectives of this study were to assess i) the effect on survival of the two dosages of CTX for primary preventive treatment in Malawi, with an added objective to compare the mortality rates of the study patients with those found in historical controls[26] as well as patients registered in the NTP in 1999 and ii) to assess the safety of the two dosages of CTX in this setting.

Secondary objectives were to assess i) the effect of primary preventive treatment with the two dosages of CTX on the incidence of bacterial pneumonia and other clinical events and ii) to assess the feasibility to deliver the two dosages in the investigated population.

Outcome

The primary efficacy outcome was death. The secondary efficacy outcome was an occurrence of a clinical event, defined as definite if confirmed bacteriologically, as probable if a patient had a clinical diagnosis of the particular event responded to antibiotic treatment or as possible if it did not respond to treatment. Safety was assessed by the occurrence of adverse events, especially those that are known to be side effects associated with the use of CTX (skin, bone marrow and gastric intolerance).

The Zomba cohort and patients registered in the Malawi NTP

The observational cohort of tuberculosis patients in whom mortality was the main parameter recorded, has been previously described.[26,27] We compared the outcome with patients who were HIV-seropositive and sputum-smear positive. We also compared outcomes with patients who had new smear-positive PTB registered throughout the country in 1999.

Statistical analysis

In the original study design a sample size of 600 patients was calculated to detect a difference of 20% mortality with 80% power and a two-sided significance of 5%; this was left unchanged after the study was redesigned; to show equipotency between the two dosages the sample size would be 40,000 patients which is clearly unrealistic.

The analysis was conducted as an intention-to-treat analysis. Efficacy of the two dosages of CTX was evaluated by comparing the two groups with respect to mortality, incidence of events of pneumonia and other clinical events. The safety of the two dosages was assessed by comparing the incidence of adverse events. Furthermore, Kaplan Meier survival analysis was used with and without stratification to age, CD4 count and confirmation of tuberculosis by culture. The pro-

portional hazards model according to Cox was used to analyse the impact of several variables on the outcomes. An interim analysis was planned after the inclusion of 300 patients to look at effect and attrition. The Data and Safety Monitoring Board of UNAIDS was asked to advise on progression of the trial after the interim analysis. The comparison with the observational cohort in Zomba[26,27] was done using Cox' proportional hazards model. The comparison of the case fatality rates with Zomba and the NTP were done using a χ^2 test. The study was approved by the National Health Science and Research Committee of Malawi and the UNAIDS Ethical Review Board.

Results

Recruitment and follow-up

From March 1998 to January 2001 1795 patients were screened of whom 767 were enrolled in the trial. After enrolment another 188 patients turned out to be not eligible (figure 1). The remaining 579 were eligible for analysis. Two hundred seventy two patients received 480 mg CTX and 307 patients received 960 mg CTX. The groups were comparable (table 1). At the end of TB treatment 42 patients (7.2%) were lost to follow-up: 24 in the CTX 480 mg group and 20 in the 960 mg group. Furthermore, 74 patients were withdrawn from the study at the end of TB treatment, because they missed two consecutive visits (22 patients), because they moved out of the district (32 patients), and because of the wish to withdraw from the study (20 patients).

Death rates in the two groups

The number of cases that died during the tuberculosis treatment until 30 September 2001 was 85. At a cumulative follow-up period of 332 person-years the mortality rate therefore was 25.6/100 person-years. The case fatality rate at the end of tuberculosis treatment was 14.7%. The relative risk of death was 1.14 (95% CI 0.74-1.74) for the CTX 480 mg group as compared to the 960 mg group (mortality rate 27.4/100 person-years versus 24/100 person-years). The survival curves are shown in figure 2. There was a significant association of older age with risk of death, whereas this could not be demonstrated for sex and CD4 count (table 2). The established causes of death did not differ between the two groups (table 3).

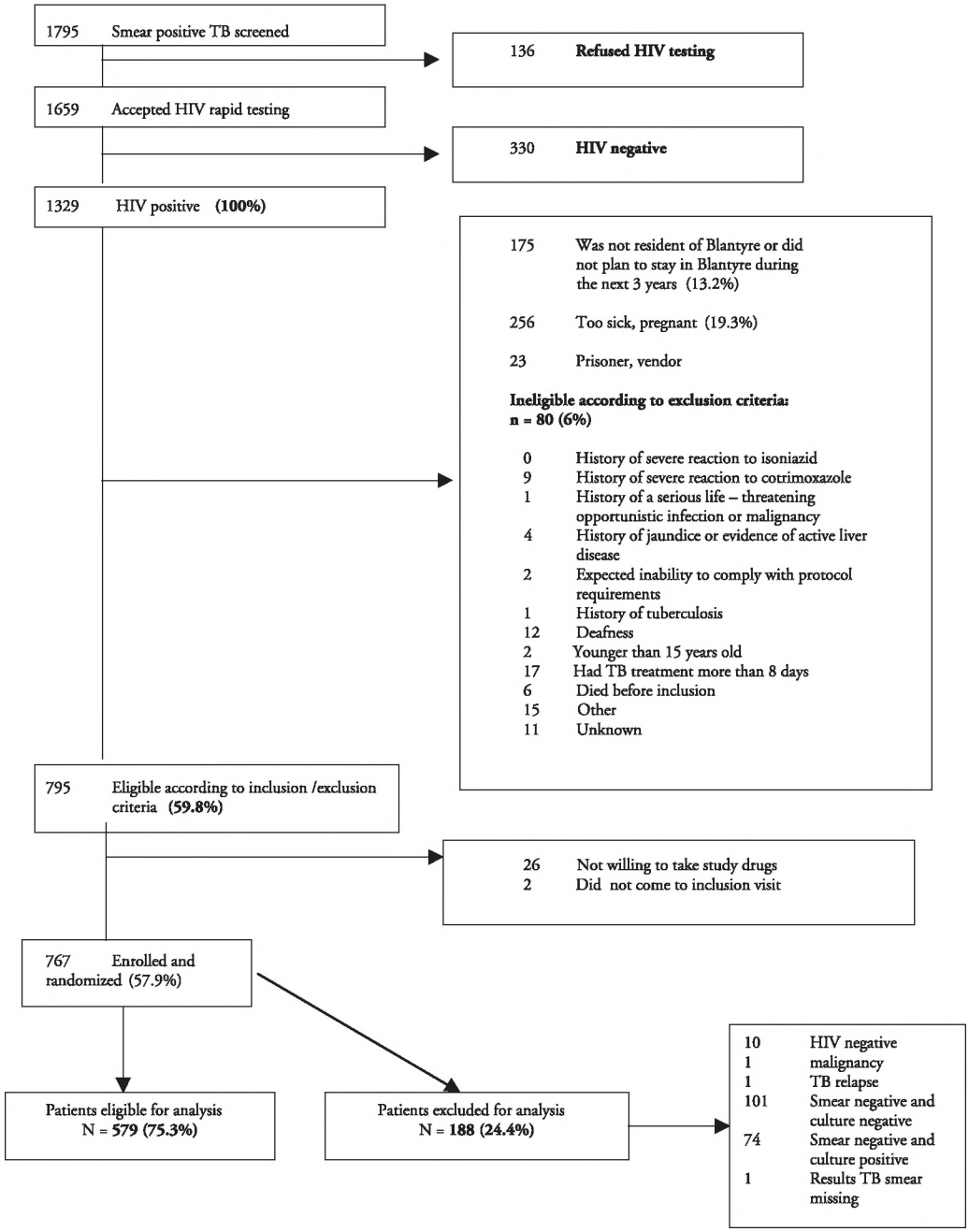

Figure 1 Screening profile. March 9th 1998 – January 26th, 2001

Table 1 Demographical, clinical and biological characteristics of randomized patients according to cotrimoxazole prophylaxis treatment arms

Characteristics at inclusion	CTX 480mg arm	CTX 960mg arm
	N = 272	N= 307
Age in year: mean (SD)	32,4 (30,4)	32,4 (30,8)
Age (year), % (n)		
15-24	19,1 (52)	19,3 (59)
25-34	47,1 (128)	45,4 (139)
35-44	24,0 (66)	26,1 (80)
45+	9,6 (26)	9,2 (28)
Male, % (n)	50,0 (136)	49,5 (152)
Body Mass Index in kg/m2: mean (SD)	17,6 (2,4)	17,3 (2,1)
< 16 (n)	22,8% (62)	24,4% (75)
16-17 (n)	16,5% (45)	17,9% (55)
17-18,5 (n)	26,1% (71)	25,7% (79)
18,5-25 (n)	26,1% (71)	24,4% (75)
> 25 (n)	1,8% (5)	0,3% (1)
Unknown (n)	6,6% (18)	7,2% (22)
CD4 count in cells/mm3: mean (SD)	238 (214)	221 (215)
0-99 (n)	25,7% (70)	28,7% (88)
100-199 (n)	27,2% (74)	28,0% (86)
200-349 (n)	20,2% (55)	19,9% (61)
>=350 (n)	21,7% (59)	17,3% (53)
Unknown (n)	5,1% (14)	6,2% (19)
Hemoglobin level in g/dl: mean (SD)	9.66 (2.00)	9.52 (1.95)
Tb culture results in % (n)		
M. tuberculosis	79,8 (217)	78,8 (242)
Culture negative	18,8 (51)	19,9 (61)
Unknown	1,5 (4)	1,3 (4)

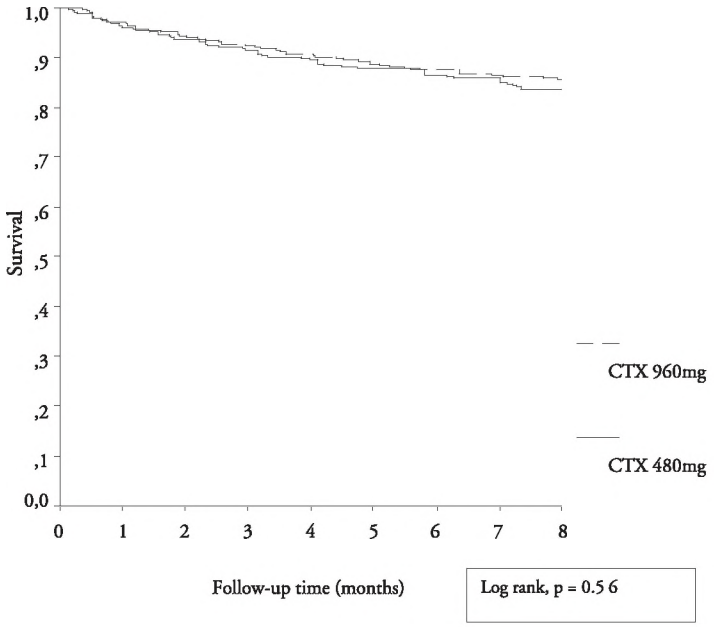

Figure 2 Probability of survival during TB treatment according to treatment arms

Table 2 Incidence rate and rate ratio for mortality during TB treatment period

Mortality	Dead N = 85	Alive N = 494	Hazard Ratio* (95% CI)	Hazard Ratio adjusted* (95% CI)
Age in years as % (n)				
15-24	7.1 (6)	21.3 (105)	ref	ref
25-34	47.1 (40)	46.0 (227)	3.0 (1.27-7.09)	2.74 (1.14.-6.61)
35-44	27.1 (23)	24.9 (123)	3.18 (1.30-7.82)	2.69 (1.04-6.97)
45+	18.8 (16)	7.7 (38)	6.72 (2.63-17.2)	5.22 (1.88-14.54)
CD4 in cells/mm3 as % (n)				
0-199	66.7 (50)	56.9 (268)	1.51 (0.80-2.83)	1.38 (0.72-2.62)
200-349	17.3 (13)	21.9 (103)	1.03 (0.47-2.25)	1.06 (0.48-2.35)
> 350	16.0 (12)	21.2 (100)	ref	ref
Sex, as % (n)				
Male	51.8 (44)	49.4 (244)	ref	ref
Female	48.2 (41)	50.6 (250)	0.89 (0.58-1.36)	1.11 (0.68-1.81)

* Cox regression Model

Table 3 Causes of death during TB treatment according to CTX prophylaxis arms

Causes of death	CTX 480mg	CTX 960mg
Total number of death during TB treatment, % (n)	42 /272	43 / 307
Tuberculosis, % (n)	23.8 (10)	27.9 (12)
Gastrointestinal disease, % (n)	26.2 (11)	18.6 (8)
Pneumonia, % (n)	7.1 (3)	4.7 (2)
Meningitis, % (n)	7.1 (3)	18.6 (8)
Kaposi sarcoma, % (n)	2.4 (1)	0
Anemia, % (n)	2.4 (1)	0
Malaria, % (n)	2.4 (1)	0
Septicaemia, % (n)	2.4 (1)	0
Respiratory infection, % (n)	4.8 (2)	0
Other, % (n)	11.9 (5)	16.3 (7)
Unknown, % (n)	9.5 (4)	9.3 (4)

Table 4 Clinical outcomes during tuberculosis treatment according to cotrimoxazole prophylaxis arms

	CTX 480mg arm N = 272	CTX 960mg arm N = 307	Hazard Ratio* (95% CI)	Hazard Ratio adjusted** (95%CI)	p-value
Patient with at least one clinical events	127	136			
Bacterial pneumonia	18	19	1.07 (0.56-2.06)	1.08 (0.55-2.11)	0.83
Incidence (/100py)	12.3	10.9 ref			
Diarrhoea	18	28			
Incidence (/100py)	12.0	16.2 ref	0.62 (0.33 – 1.16)	0.64 (0.34-1.22)	0.18
Malaria	18	30			
Incidence (/100py)	12.1	17.6 ref	0.69 (0.39-1.24)	0.71 (0.40-1.29)	0.26
Meningitis	3	6			
Incidence (/100Ppy)	2.0	3.4 ref	0.58 (0.15-2.34)	0.59 (0.15-2.36)	0.45
UTI/STD	11	13			
Incidence (/100py)	7.4	7.5 ref	0.99 (0.44-2.20)	1.34 (0.57-3.16)	0.51
PCP	2	2			
Incidence (/100py)	1.3	1.1 ref	0.59 (0.05-6.52)	0.47 (0.02-9.07)	0.62
Septicemia	12	8			
Incidence (/100py)	8.0	4.5 ref	1.76 (0.72 -4.31)	1.92 (0.77-4.74)	0.16

* Cox regression model

** Cox regression model with adjustment for age/ sex/ baseline CD4 count/ *Toxoplasma* serology/ baseline TB confirmation/ CTX arms

Pneumonia and other clinical events

The observed number of patients with one or more events of pneumonia or other clinical events and the adjusted hazard ratios are shown in table 4. There were 62 events of bacterial pneumonia in 37 patients, 8 of them were definite and 54 probable. Thirty events in 18 patients occurred in the 480 mg group and 32 events in 19 patients occurred in the 960 mg group. Figure 3 shows the Kaplan Meier curve of remaining free from a bacterial pneumonia. *Toxoplasma* serology was negative in 90.0%, positive in 8.9% and indeterminate in 1.0%. We did not diagnose a case of *Toxoplasma* encephalitis.

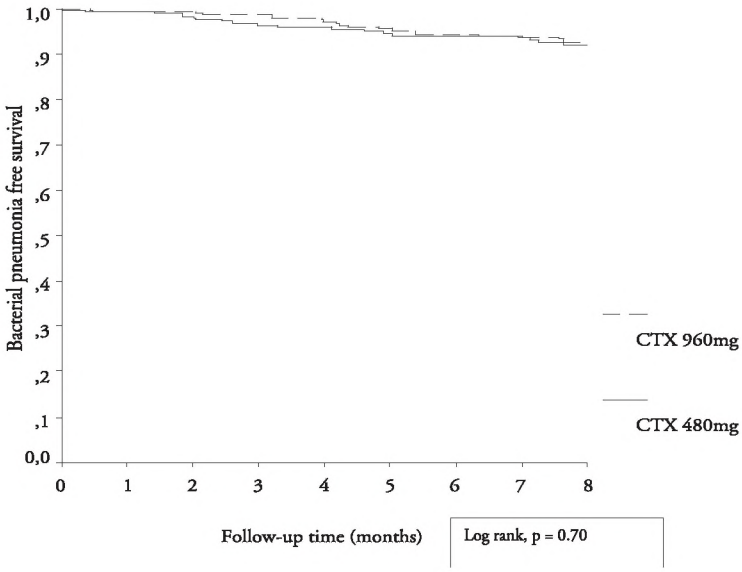

Figure 3 Probability of remaining free of bacterial pneumonia during TB treatment according to treatment arms.

Table 5 Incidence rate and hazard ratio for mortality during TB treatment period for study groups and the Zomba observational cohort, 1995-1996

Mortality	Death	Incidence (/100 py)	Hazard Ratio (95% CI)	Hazard Ratio adjusted* (95% CI)	P value
Patients with:					
No treatment	49	34.1	1	1	
CTX 480mg	42	27.4	0.80 (0.54-1.22)	0.82 (0.54-1.24)	0.35
CTX 960mg	43	24.0	0.71 (0.47-1.08)	0.74 (0.49-1.12)	0.15

*Adjustment on sex and age

Death rates compared to the Zomba cohort and the NTP

In our study groups the mortality was lower compared to the observational cohort in Zomba although the hazard ratio did not show a significant level (table 5). The tuberculosis outcome parameters of our study are summarised in table 6 and compared with the outcome parameters in the Zomba cohort and the general outcome parameters of the NTP. Case fatality rate of the NTP was significantly higher ($p < 0.001$) as compared to our study groups.

Table 6 **Outcome parameters of our study compared with the Zomba observational cohort and the NTP for new smear positive PTB patients**

	CTX 480 mg(%) 1998-2001 n = 272	**CTX 960 mg (%) 1998-2001 n = 307**	**NTP 1999 (%) n = 8 185**	**Zomba 1995 (%) n = 255**
Cured or completed treatment	62.9	58.6	71	69.4
Died	15.4	14.0	21*	18.0**
Failed	3.7	3.9	1	1.2
Transferred			3	5.5
Defaulted***	8.8	6.5	4	5.9

*p < 0,001 as compared to case fatality rate in CTX 480/960 mg (χ^2 test)

**p < 0,10 as compared to case fatality rate in CTX 480/960 mg (χ^2 test)

*** in the study groups default are those patients who were lost to follow up for the study

Adverse effects and compliance

The number of adverse events are outlined in table 7. There were no significant differences between the two groups. Most events, which were thought to be related to CTX, were rash and gastrointestinal discomfort. 14.8% of the side effects occurred in the first month. One patient in the CTX 960 group had to stop the prophylaxis indefinitely because of the occurrence of a Stevens-Johnson syndrome. The patient recovered from this event. The compliance of the patients is shown in table 8.

Table 7 Comparison of adverse drug reaction during tuberculosis treatment according to cotrimoxazole prophylaxis treatment arms

	CTX 480mg Number (%)	CTX 960mg Number (%)	p-value
Total number of patients	272	307	
Patients with at least one clinical ADR	18 (6.6)	20	0.96
Total number of ADR	19 (7.0)	28 (9.1)	0.35
Evidence of CTX side effect	8 (2.9)	13 (4.2)	0.41
Grade1 (mild)	8 (2.9)	10 (3.3)	
Grade 2 (moderate)	0	1 (0.3)	
Grade 3 (severe)	0	2 (0.7)	
ADR during the first month	3 (1.1)	4 (1.3)	1.00
Study drug stopped because of adverse event	0	1 (0.3)	1.00

Table 8 Cotrimoxazole compliance according to CTX prophylaxis treatment arms during TB treatment

	CTX 480mg N = 272	CTX 960mg N = 307	p-value
Medication compliance*, % (n)			
Very low compliance	3.3 (8/244)	2.2 (6/268)	
Low compliance	8.6 (21/244)	9.0 (24/268)	
Normal compliance	73.0 (178/244)	75.0 (201/268)	
Over compliance	15.2 (37/244)	13.8 (37/268)	0.86

* Compliance ratio = number of empty capsules / number of theoretically prescribed in the period. Very low compliance: ratio < 0.6; low compliance: 0.6 ≤ ratio < 0.8; normal compliance: 0.8 ≤ ratio ≤ 1.00; over compliance: ratio ≥ 1.00.

Discussion

This study showed no significant differences in mortality and occurrence of clinical events between 480 mg and 960 mg cotrimoxazole prophylaxis in HIV positive smear-positive tuberculosis patients in Malawi. Furthermore, both dosages of cotrimoxazole were well tolerated with equal compliance. In addition, the overall case fatality rate was reduced significantly as compared to the case fatality rate in the National Tuberculosis Programme although not when compared to the observational cohort in Zomba.

Tuberculosis, gastrointestinal disease and respiratory infection were the most commonly found causes of death. Most of the deaths occurred within the first two months, which has been observed in the Zomba cohort as well and could be a potential target for other interventions

such as antiretroviral treatment.[29] In line with other reports in Africa,[26,30,31] mortality was higher in older age groups suggesting advanced HIV disease as a risk factor. However, this was not reflected in the CD4 measurements as each CD4 category carried equal risk of death during treatment for tuberculosis.

When comparing with the overall countrywide case fatality rate of the NTP for patients with smear positive tuberculosis, our study patients had a significant lower case fatality rate. This difference may in fact be more pronounced taking into account that in the NTP data both HIV positive and negative patients are included; correcting for the lower mortality rate in HIV negative patients (10%)[26] and assuming that 72-80% of smear-positive patients are HIV positive, the NTP mortality figure for HIV positive patients would be 23-25%. These data need to be interpreted with caution as patient characteristics in the various groups differ and our study patients were at the start of the study not very ill and had the benefit of being in a study.

There were no differences in clinical outcomes between the two study groups; bacterial pneumonia, diarrhoea, bacteraemia and malaria were most commonly found, whereas PCP was rare. Although this study was not designed to arrive at a firm diagnosis of clinical events, these findings are in keeping with data from other studies in Africa.[6,8,21,32,33] It is likely that *S. pneumoniae* is among the commonest pathogens in patients with respiratory infection in our wards often becoming invasive;[21] this was also found by others.[8] No study is available on the cause of diarrhoea in Malawi; a recent study to the prevalence of *Cryptosporidium parvum* and *Isospora belli* found similar prevalence rates of 11% and 2.5%, for both pathogens, in patients with diarrhoea and without diarrhoea, respectively (EE Zijlstra, unpublished observations). In contrast to what was found in Malawian children,[34] PCP appears uncommon in adults; similar low prevalence rates have been found by other studies in Africa[3] except for the one report that published about a selected group of patient in Zimbabwe.[5,9,35]

No case of toxoplasmosis cerebri was diagnosed; it is possible that cases were missed as no CT scan was available and patients may have died in the ward or at home of rapidly fatal toxoplasmosis encephalitis. The seroprevalence of anti-toxoplasmosis IgG antibody was however low (9.6%), suggesting a relatively low risk. The incidence of *Toxoplasma* encephalitis (TE) in HIV infected patients directly correlates with the prevalence of *Toxoplasma gondii* antibodies among the general HIV-infected population, the degree of immune suppression, and the institution of prophylaxis against TE.[36]

CTX may also have benefit through its well-recognised effect in treating *Plasmodium falciparum*, and CTX preventive therapy may reduce the frequency of episodes of malaria. Due to the absence of a placebo-controlled arm this hypothesis remains speculation.

We are confident that the use of CTX in HIV infected patients with tuberculosis in this trial was safe. Only one patient had a serious side effect, which led to withdrawal. This patient developed Stevens-Johnson syndrome from which she recovered. The other 36 events of side effects were mild and transient. This result confirms the reports from Ivory Coast,[15] Senegal,[17] and Thyolo District in Malawi.[18] In the group of patients who used 960 mg CTX there were slight-

ly more side effects than in the group who used 480 mg, but this was not statistically significant. There was a fair compliance of CTX use and a good tolerance of the drug in combination with the antituberculous drugs. Most patients chose to continue the prophylaxis after the termination of the study. A considerable number of patients were lost to follow up or chose to withdraw from the study. The reasons for this withdrawal were mainly the burden of too many drugs (TB treatment in addition with the two capsules of CTX) and the alleged stigmatisation of the study towards HIV infection.

Although there are important methodological differences between studies, this study suggests that CTX primary prophylaxis may have a potential beneficial effect on mortality in HIV infected smear positive TB patients and that low dose CTX 480 mg daily may be as effective as CTX 960 mg. The use of a single dose would reduce the costs by more than half. At the International Dispensary Association (IDA, Amsterdam, The Netherlands), which is the most frequently used supplier of drugs in Africa a container of 1000 capsules of CTX 480 mg costs US$ 7.19 (0.72 cent per tablet), while 500 capsules with 960 mg cos t US$ 8.24 (1.65 cent per tablet), which means a cost reduction of 56.4%.[23]

What can be learned from this study? Clearly, as other effective and affordable interventions are still beyond the horizon for the majority of patients, one would like to err on the side where patients who otherwise have a poor prognosis may benefit. In this context it is regrettable that randomised-controlled trials are still not available in southern Africa and that most studies that have been done have methodological problems. High levels of resistance to CTX of common bacteria such as *S. pneumoniae* and low prevalence of other infections to which CTX is targeted (PCP, toxoplasmosis, isosporiasis) should caution against overinterpretation of the currently available data. In addition, implementation of a strategy of wide-spread use of CTX prophylaxis needs to be balanced against unwanted long term effects. The emergence of antibiotic resistance to pathogens is a potential problem after widespread implementation of CTX. In Malawi there is already a very high baseline resistance of the most common pathogens against CTX.[6,21] In a recent study there was an increase of drug resistance to *E. coli* for CTX in Thyolo district in Malawi after the implementation of routine CTX prophylaxis.[37] The clinical consequences of this observation are not clear and needs to be investigated. Other than in Ivory Coast a serious concern is the emergence of cross resistance of *Plasmodium falciparum* to a similar anti-folate combination, sulfadoxine-pyrimethamine (SP), which is now the first-line antimalarial drug in several of the African countries with the highest rates of HIV infection.[20,38] As the only effective and affordable successor to SP, namely the combination of lapudrine and dapson (Lapdap) that will be marketed soon is also an anti-folate this may have severe consequences for malaria control in the community as well as for treatment of the individual. Clearly these issues should be addressed urgently.

Taking all these considerations into account, a meeting was held in October 2002 between the College of Medicine, the national TB programme, interested stakeholders and the Ministry of Health and Population of Malawi to discuss these results as well as operational research data results from Lilongwe, Karonga and Thyolo. The outcome of the meeting was a policy state-

ment which a) endorsed that Voluntary Counselling and Testing for HIV (VCT) and CTX prophylaxis for HIV seropositive TB patients be continued in those districts where it has been started, b) encouraged VCT plus CTX prophylaxis for HIV seropositive TB patients to be expanded in other districts in a phased approach with results carefully monitored by the NTP, c) urged that the NTP encourage and work with its partners to conduct a randomised controlled trial to determine the efficacy of CTX prophylaxis with and without antiretroviral therapy in HIV seropositive TB patients and d) requested all parties to keep up to date with any new information about the efficacy of CTX prophylaxis in the region and act accordingly if evidence suggests that CTX has harmful consequences.

Contributors

MJ Boeree, EE Zijlstra and AD Harries were the principal investigators. AD Harries wrote the protocol. MJ Boeree wrote the paper and supervised the study. EE Zijlstra supervised the study and participated in the writing. D Sauvageot monitored the study and performed the statistical analysis. HT Banda oversaw the data collection and the data entry. All authors contributed to the revision of the various drafts and approved the final draft.

Conflict of interests

None declared

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Chapter IX

True status of smear-positive pulmonary tuberculosis defaulters in Malawi

Kruyt ML, Kruyt ND, Boeree MJ, Harries AD, Salaniponi FM, Van Noord PAH.
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ML Kruyt and ND Kruyt assisted in the design of the study, collected the data and participated in the data analysis and the writing of the paper.
MJ Boeree contributed in the design the study, assisted in the data collection, assisted in the data analysis and interpretation of the results and writing of the paper and its revisions.
AD Harries contributed in the design of the study and the data analysis and assisted in the write-up and the revisions of the paper.
FM Salaniponi assisted in the intermittent evaluations of the study and the revisions of the paper.
PAH van Noord was supervisor of ML Kruyt and ND Kruyt in the Netherlands and contributed in the study design, the data interpretation and critically reviewed the paper and its revisions

Summary

The article reports the results of a study to determine the true outcome of 8 months of treatment received by smear-positive pulmonary tuberculosis (PTB) patients who had been registered as defaulters in the Queen Elizabeth Central Hospital (QECH) and Mlambe Mission Hospital (MMH), Blantyre, Malawi. The treatment outcomes were documented from the tuberculosis registers of all patients registered between 1 October 1994 and 30 September 1995. The true treatment outcome for patients who had been registered as defaulters was determined by making personal inquiries at the treatment units and the residences of patients or relatives and, in a few cases, by writing to the appropriate postal address. Interviews were carried out with patients who had defaulted and were still alive and with matched, fully compliant PTB patients who had successfully completed the treatment to determine the factors associated with defaulter status.

Of the 1099 patients, 126 (11.5%) had been registered as defaulters, and the true treatment outcome was determined for 101 (80%) of the latter; only 22 were true defaulters, 31 had completed the treatment, 31 had died during the treatment period, and 17 had left the area. A total of 8 of the 22 true defaulters were still alive and were compared with the compliant patients. Two significant characteristics were associated with the defaulters: they were unmarried; and they did not know the correct duration of antituberculosis treatment.

Many of the smear-positive tuberculosis patients who had been registered as defaulters in the Blantyre district were found to have different treatment outcomes, without defaulting. The quality of reporting in the health facilities must therefore be improved in order to exclude individuals who are not true defaulters.

Introduction

Malawi has had a National Tuberculosis Control Programme (NTP) since the country gained its independence in 1964 but, like many countries in sub-Saharan Africa, is now burdened with a large and growing tuberculosis (TB) problem, mainly as a result of the epidemic caused by human immunodeficiency virus (HIV). In 1984, the TB programme adopted the DOTS (directly observed treatment, short course) strategy and was supported in this endeavour by the International Union against Tuberculosis and Lung Disease (IUATLD); all districts in the country implemented this strategy over the following 1-2 years. The good recording and reporting system, which is inherent in the DOTS strategy, allowed the TB epidemic to be reliably monitored, and the number of notified cases rose from 5334 in 1985 to 20 630 in 1996 (Malawi NTP, 1996). As the NTP struggled to cope with the increasing number of cases and a deteriorating economic situation, national cure rates for smear-positive TB patients decreased from 86% in 1986 to 63% in 1992, and increased slightly to 68% in 1994 (Malawi NTP).

In Malawi, the TB registers are maintained by the district TB officers (DTOs). Each registered TB patient is given a unique registration number, and the name, age, sex, address, date of diagnosis, type and category of TB are recorded. Patients are treated with standardized antituberculosis regimens, depending on the type and category of TB. Newly diagnosed smear-positive pulmonary tuberculosis (PTB) cases receive 8 months of short-course chemotherapy, comprising 2 months of initial intensive treatment in hospital with daily supervised doses of streptomycin, rifampicin, isoniazid and pyrazinamide, followed by 6 months of unsupervised continuation therapy at home with isoniazid and thiacetazone or isoniazid and ethambutol. The drugs used in the continuation phase may be supplied to patients by the hospital or health centre. Sputum smears are examined after 2 months, 5 months and 8 months of treatment, and the outcome at the end of treatment is recorded according to the guidelines (see Table 1) established by the IUATLD and WHO.[1,2]

In the Blantyre district, which has 15 government health centres providing a TB service to the community, the cure rates in 1991 were less than 50%, with high default and transfer rates among patients.[3] Although cure rates have improved since 1991, the recorded default rates are still unacceptably high at around 10±15%. Defaulters are an extra risk for the population because of possible contagion and the development of drug resistance by tubercle bacilli. The reasons for such defaulting in Malawi and other parts of sub-Saharan Africa are not known, but may include failure to report or record the cure or death of a patient, failure to collect the necessary drugs from the hospital or health centre because the patient was too ill, discontinuation of treatment by the patient after experiencing an initial improvement, and failure to notify the health care system that the patient had transferred to another health centre.

In the present study we investigated the status of patients with smear-positive PTB who had been registered as defaulters in the two principal hospitals, which manage TB in the Blantyre district, and the possible reasons for their defaulting.

Patients and methods

The outcomes of 8 months of treatment of all smear-positive PTB patients who were registered between 1 October 1994 and 30 September 1995 in the TB registers at the Queen Elizabeth Central Hospital and the Mlambe Mission Hospital, Blantyre district, were studied. The name, age, sex, home address and treatment unit of patients who had been registered as defaulters were recorded, and a search was initiated to determine what had happened to them.

Between 31 December 1996 and 31 March 1997 the mortality records of patients admitted to the hospital for the intensive phase of treatment were inspected to determine whether those registered as defaulters had in fact died in hospital. The peripheral unit (usually a health centre) where the patients received the continuation phase of treatment was then visited to determine whether there were any records of the treatment outcome. If there was no such record or the

patient was still registered as a defaulter in the health centre, attempts were made to trace the patient or a relative in the home or workplace. This required making journeys to villages by motorcycle. If there was still no trace of the patient, a letter was written if a post-office box number was present in his/her treatment unit records or the TB register.

In this way we investigated and documented the true 8-month treatment outcome of patients who had been registered as defaulters. According to the IUATLD and WHO definition,[1,2] true defaulters are patients who at any time during the course of treatment had not collected their drugs for two or more consecutive months. All defaulting patients who were still alive, or a near relative, were interviewed (using a structured questionnaire) to determine the following: the current health status of the patient or, if deceased, the date of death; any financial or other difficulties which prevented collection of antituberculosis medication; the distance from the home to the health facility and the time taken to make this journey; and the presence of any other disease besides PTB. In order to determine the factors that could have been associated with defaulter status, a second interview, using another questionnaire, was carried out with the true defaulters and with a group of cured, fully compliant TB patients (matched for age and sex) who had been registered during the same period. This second interview, which was based on the health belief model,[4-6] gathered information about demographic and socioeconomic variables, the patient's health-seeking behaviour and knowledge about antituberculosis treatment, the continuing availability of such treatment, the relations between the health care worker and the patient, the health status of the patient during the continuation phase of treatment, as well as ease of access to the health unit.

Results

A total of 1099 new smear-positive PTB patients were registered at the Queen Elizabeth Central Hospital and the Mlambe Mission Hospital during the 12-month study period; 126 (11.5%) of them had been registered as defaulters. Information about treatment outcomes was obtained for 101 (80%) of these defaulters (Table 1) through a home or village visit (100 cases) and by writing to one patient. Among patients whose treatment outcome was not a true default, we discovered a failure in communication between the district TB officer and the health centre in 70% of cases and between the patient and the health centre in the remainder.

Only 22 patients were true defaulters according to the IUATLD and WHO definition.[1,2] At the time of the first interview, we found that 12 out of the 22 true defaulters had died since the end of their 8-month treatment period, 1 patient had moved out of the area, 1 patient had been wrongly registered in another unit and had defaulted again from treatment, and 8 patients were alive and well. In our first interviews we investigated 20 cases (the 8 who were alive and the relatives of the 12 patients who had died). The most important findings from these interviews are shown in Table 2. We also compared the 8 defaulters who were still alive with a group of age-

and sex-matched cured patients who had been fully compliant with their treatment. The main differences between the two groups were as follows: all 8 compliant patients were married, compared with none of the defaulters; and 7 of the compliant patients knew the correct duration of antituberculosis treatment, compared with none among the defaulters.

Table 1 True 8-month treatment outcomes for 101 study patients who had been registered as defaulters

True outcome	No. of patients
Defaulted from treatment (i.e. patients who during their treatment had not collected drugs for two consecutive months)	22
Cured (i.e. patients who had completed treatment and whose sputum smear results were negative at the end of treatment)	27
Treatment completed (i.e. patients who had completed treatment but whose sputum smear results were not known at the end of treatment)	4
Died (i.e. patients who had died during the 8-month treatment regimen)	31
Transferred (i.e. patients who had transferred to another district and whose treatment outcome was unknown)	17
Total	101

Table 2 Results of interviews with 8 study patients and relatives of 12 patients who had died, concerning 20 defaulters

No. of defaulters	20
No. of males/females	14/6
Mean age (years)	38.9±13.0
Mean time to obtain the medicine (minutes)	147±118
Mean distance to hospital/health centre (km)	7.7±4.7
Mean survival time (months)	11.2±6. 5
Were there difficulties in obtaining medicine in general?	
Yes	89.5%
No	10.5%
Were financial problems incurred to obtain medicine?	
Yes	55.6%
No	44.4%
Were there difficulties in obtaining medicine due to patients' physical problems?	
Yes	36.8%
No	63.2%

Discussion

The true outcome of 8 months of treatment was determined for 80% of the patients who had been registered as defaulters. The remaining 20% could not be traced because either their addresses in the TB register were incorrect and our inquiries in their villages did not help or our letters sent to their post-office box numbers were not answered. Of the 101 patients who were traced, only 22 were true defaulters. The true default rate was therefore considerably lower than that given in the TB register. The possible causes for the different treatment outcomes and suggestions for corrective measures are summarized in Table 3.

Table 3 Possible causes and treatment outcomes for 79 patients who had incorrectly been registered as defaulters, and possible corrective measures

Treatment outcome	Possible causes	Corrective measures
Cured or treatment completed (n= 31)	DTO not visiting health centres [a]	Regular DTO health visits to health centres [a]
	Health centres not communicating with DTO	Educate health centre staff about communicating the results of treatment outcome
Transferred (n= 17)	DTOs failing to communicate with each other	Quarterly DTO meetings at regional level
Died (n= 31)	Difficulties in relatives providing information to health centres	Better follow-up by health centre staff would result from having adequate transport, staff numbers and training

[a] DTO: district tuberculosis officer

About one-third of the registered defaulters had in fact completed their treatment and many of them were cured. The DTO was not aware of this because either the officer had not visited and checked the results in the treatment unit registers, or the patient's transfer to another health centre had not been communicated to the DTO (one-fifth of the cases). Failure in communication between districts was also a problem, and this accounted for a small number of defaulters who should have been registered as "transferred" to another health centre. About one-third of the defaulting patients had died. Over 70% of tuberculosis patients registered for treatment at the Queen Elizabeth Central Hospital were HIV-seropositive;[7] therefore, since the mortality rates among HIV-infected TB patients in sub-Saharan Africa are high[8-11] it is not surprising that many "defaulters" were in fact patients who had died. In the rural areas, with few telephones and difficulties in communication, it is unlikely that relatives would travel to the nearest health

centre to report the death of a patient when there is no incentive to do so. Health centre staff are supposed to follow up all defaulters, but owing to transport difficulties, increasing workload, lack of motivation, concerns about safety in remote areas, and poor record-keeping, few of them do so. Ways to improve communication between health facilities within a district and between different districts must therefore be found.

We investigated the reasons why patients defaulted. Although only a small number of our defaulting patients could be compared with compliant cured patients, we found that unmarried status and ignorance of the duration of antituberculosis treatment were characteristic of defaulting behaviour. The public should be given more information about tuberculosis, especially the total duration of treatment and the need to complete the full course, via intensive health education through health care workers and the use of posters, leaflets and flyers in the local language. Malawi is a poor country, and it is therefore unlikely that substantial socio-economic and demographic improvements can be made in the near future.

This study may raise questions about the reliability of data for other treatment outcomes. Cure rates and treatment completion rates can be verified from the patients' treatment cards, and sputum smear results from the laboratory records. Details of patients who move to another district should be recorded in the TB registers. These treatment outcomes are likely to be correct, although we have not specially investigated this. Deaths cannot always be verified if the patient died in the village, and further research to assess whether death rates are accurate is probably warranted.

Acknowledgements

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Chapter X

Tuberculosis control in the face of the HIV epidemic

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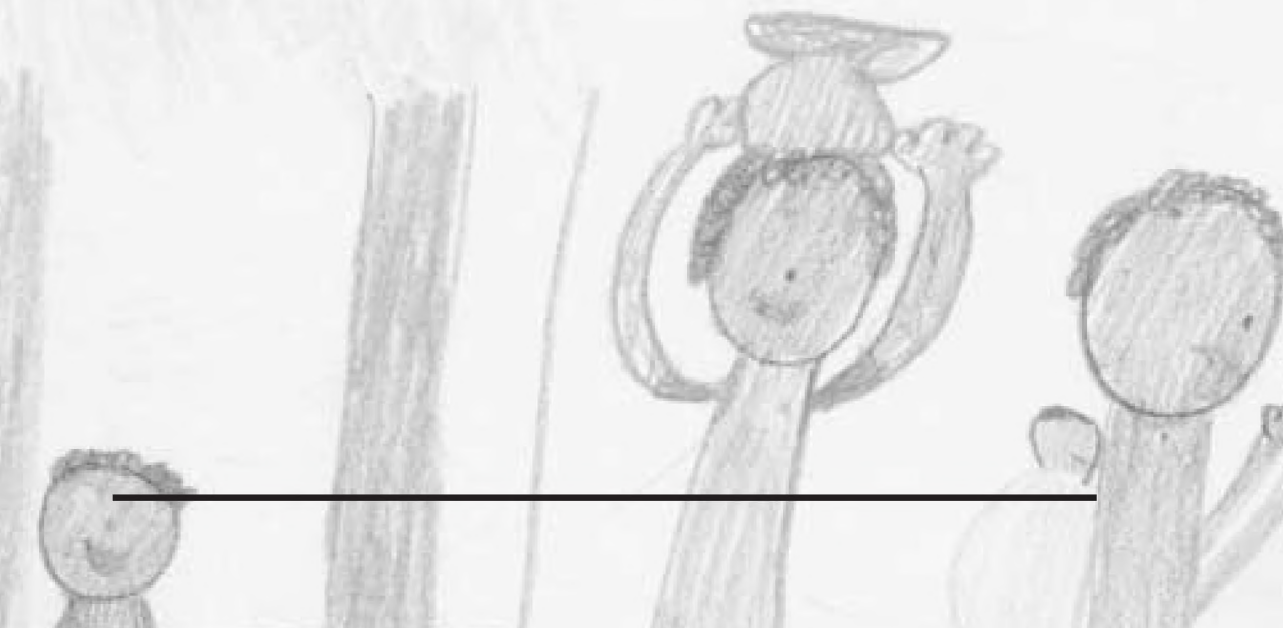

Impact of the human immunodeficiency virus on tuberculosis

The human immunodeficiency virus (HIV) has its greatest impact on tuberculosis (TB) in sub-saharan Africa, although in India and parts of South -East Asia the association between these two infections is becoming increasingly apparent. HIV has its impact in a number of ways, each of which is a threat to good TB control.

TB case numbers

In the last 10 - 15 years, TB case numbers have increased 300 - 400% in high HIV-prevalent countries, mainly because HIV increases the risk of disease reactivation in people with latent *M. tuberculosis* and because HIV infected persons are more susceptible to new TB infections. Along with the increase in case numbers there has been a disproportionate increase in cases with smear-negative pulmonary TB and extra-pulmonary TB. Increased case numbers throw an immense burden on TB control efforts: there is a need for more staff, particularly TB programme officers and laboratory personnel; there is a need for increased laboratory resources, drugs, sputum containers, stationary; where patients are hospitalised for the initial phase of treatment, the wards become overcrowded rendering good nursing care impossible and increasing the risk of nosocomial infection; there is a need for more resources.

Increased morbidity and mortality

HIV-positive TB patients often run a stormy course while on anti-tuberculosis treatment with fevers, chest infections, recurrent diarrhoea, *Candida* and bacteraemia. Adverse reactions to anti-tuberculosis drugs, particularly thiacetazone induced cutaneous reactions, are more frequent leading to interruptions of treatment and occasional fatalities. It is not surprising that HIV-positive patients have a much higher mortality during and after anti-tuberculosis treatment compared with HIV-negative patients. In sub-Saharan Africa, approximately 30% of HIV-positive smear-positive TB patients have died by 12 months of treatment, and about 25% of those who survived will die during the next 12 months.

Recurrence of TB after completing treatment

Recurrence rates (defined as return of clinical evidence of active TB, positive sputum smears or positive cultures of *M. tuberculosis*) are increased in HIV-positive patients. The use of "standard treatment" and treatment interruptions due to drug reactions are associated with recurrence of TB. The proportion of TB recurrence due to disease re-activation or re-infection is unknown.

Drug resistance

Several outbreaks of multi-drug resistant TB (MDR-TB) have been reported from industrialised countries amongst patients with HIV. HIV does not itself cause MDR-TB, but it fuels the spread of this dangerous condition by increasing susceptibility to infection and accelerating the progression from infection to disease. Recent data collated from the World Health Organization (WHO) has shown that MDR-TB is highest in India and South-East Asia and lowest in sub-saharan Africa. However, given the problems faced by many TB programmes in Africa and given the virtual absence of second-line anti-tuberculosis drugs in these countries, MDR-TB is a real and potential threat to TB control.

Tuberculosis Control: the WHO-DOTS Strategy

The overall objective of TB control is to reduce mortality, morbidity and transmission of the disease. At present most TB experts believe that the best way to achieve this is to focus on new cases of smear-positive TB and to i) cure 85% of detected new cases and ii) detect 70% of existing cases. Achieving a high cure rate is the highest priority because TB programmes with high cure rates are thought to attract a large number of existing cases in their catchment area. Giving priority to case finding before achieving a high cure rate increases the TB problem by creating MDR-TB. The strategy for TB control is the provision of short-course chemotherapy (SCC) to, at least, all identified smear-positive TB cases (**Table 1**). There is insistence that any medication which includes rifampicin should be given by direct observation. The success of the TB control strategy depends on the implementation of a 5-point policy package (**Table 2**), the essential ingredients of which were developed by Dr. Karel Styblo of the International Union against TB and Lung Disease (IUATLD) in the early 1980s.

Table 1 Short-Course Chemotherapy Regimens in WHO-DOTS Strategy

INITIAL PHASE (Daily or 3 times a week)	CONTINUATION PHASE
2 EHRZ (SHRZ)	6 HE
2 EHRZ (SHRZ)	4 HR
2 EHRZ (SHRZ)	4 H_3R_3

S = Streptomycin E = Ethambutol Z = Pyrazinamide
R = Rifampicin H = Isoniazid
The number before the first letter of each phase of the regimen is the DURATION in months of that phase.
The number in subscript after the letters is the number of doses per week.

Table 2 TB Control Policy Package

1. Government commitment to a national TB control programme aiming at nationwide coverage.
2. Case detection through passive case finding.
3. Short course chemotherapy to, at least, all smear-positive TB cases.
4. Regular and uninterrupted supply of essential anti-tuberculosis drugs.
5. A monitoring and evaluation system

There is evidence that the DOTS package works and works well. Cure rates are substantially higher in countries which have adopted the DOTS package compared with those using a non-DOTS approach. Even in countries with high HIV infection rates, such as South Africa, Tanzania and Malawi, good cure rates have been achieved.

The WHO-DOTS Strategy in the face of HIV

Although DOTS is a successful strategy, its implementation is not easy. In 1995 the DOTS strategy was only being used nation-wide in 16% of countries in the world. DOTS requires sustained government commitment, a strong national TB programme, a well functioning district health and laboratory service, free drugs and, above all, for resource-poor countries additional resources from the donor community.

HIV adds its own set of problems to this scenario.

1 The targets for cure rates and detection rates are difficult to hit. Cure rates of 85% in smear-positive TB cases are almost impossible to achieve because of high HIV-related mortality. The detection rate target of 70% is also impossible to achieve because a method for estimating the total number of such cases has not yet been found.

2 Hot spots of TB transmission, fuelled by concurrent HIV infection, may occur in places where people are crowded together such as prisons, refugee camps, boarding schools and health care institutions. In such situations, active case finding may be a better strategy for case detection rather than passive case finding with its inherent delays and potential for further TB transmission.

3 Thiacetazone, such a useful and cheap drug in the pre-HIV era, has developed a bad reputation amongst health care workers and most segments of the general population. Many TB programmes in Africa have abolished the drug, in favour of ethambutol, leading to escalation of drug costs and concerns about safety of ethambutol usage in children. Even streptomycin, because intramuscular usage may be associated with HIV transmission and because it is difficult to administer out in the community, is being phased out in some TB programmes.

4 Case holding in hospital TB wards, especially in urban areas, is becoming impossible because of overcrowding, and moves are afoot to decentralise treatment to peripheral health centres and the community. This is a patient-friendly approach. However, the logistics of observed drug administration, drug security (especially of rifampicin), supervision, monitoring and recording in the community are daunting, although not impossible. Any scheme of decentralization needs to be adapted to the local situation and carefully monitored in case there is loss of control.
5 In HIV-positive, smear-positive TB patients the high death rates means that treatment is less cost-effective in terms of years of life saved than previously calculated for HIV-negative patients. In the pre-HIV era, smear-negative PTB was a disease with a good treatment outcome. Evidence is slowly accumulating in sub-Saharan Africa that HIV-positive smear-negative PTB patients have a worse prognosis compared with those who have smear-positive PTB. Yet these patients are ignored in the DOTS strategy despite the fact that their numbers are high. In many countries smear-negative TB cases are not routinely followed up, their treatment outcomes are not reported and they are often given treatment inferior to that given to smear-positive TB cases.
6 It is a sad fact that health care staff in many African countries have the same HIV-seroprevalence rates as the general adult population, and in some urban areas this approaches 30% or more. High absentee rates due to illness or attending funerals, and high death rates due to AIDS threaten the infrastructure and efficient function of the health services, and TB programmes are no exception. Manpower development needs to take this into account, and the concept of one district TB co-ordinator for one district is not enough.

Discussion

Widespread use of isoniazid chemoprophylaxis has been put forward by some experts as an alternative approach to TB control in high HIV-prevalent areas. In controlled trials, isoniazid chemoprophylaxis appears to reduce the occurrence of TB in HIV-infected persons, but the feasibility of using this as a country-wide TB control measure is doubtful. At present, the WHO-DOTS strategy has to be the best way of controlling TB in high HIV-prevalent countries. Countries need to be helped in implementing this strategy with particular emphasis on quality microscopy-based diagnosis, health education, uninterrupted drug supplies and follow-up care. The DOTS strategy must also adapt to the challenges posed by the HIV epidemic if it is to maintain credibility in these areas. Ways of determining the TB case rate must be found, so that the 70% detection rate target has some meaning. In certain circumstances, active case finding should be promoted. The issue of smear-negative PTB must be addressed. Community care schemes must be rigorously piloted and evaluated. Attempts must be made to reduce the high mortality during treatment. There must be enough trained and motivated manpower to cope

with the ravages of the HIV epidemic on the health care workforce. TB programmes should integrate more with AIDS control programmes, because it is becoming apparent that AIDS control is essential for TB control. Operational research, integrated within the national TB programme structure, needs to be carried out under the direction of experienced personnel to try and provide answers to some of these problems. Above all, governments and the donor community need to be persuaded and reminded that good TB control is still very cost-effective, even with increased HIV-related mortality, and requires continued support.

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Chapter XA

Update on tuberculosis control in the face of the HIV epidemic in the era of highly active antiretroviral treatment

Boeree MJ, 2003

Introduction

In the last ten years the development of highly active antiretroviral treatment (HAART) has accelerated. About 16 different drugs from three different classes have evolved from intensive research and more drugs are being developed every year. This has lead to a considerable reduction in mortality from HIV infection.[1,2] Globally, it is estimated that in 2002 from the 36 million people living with HIV/AIDS about 6 million people are in need of HAART now. Instead, only 230 000 have access to HAART, and half of them live in one country, Brazil, where the government offers HAART for free.

The average price of HAART in industrialised countries was about ∈ 10 000 - 12 000 per patient year. This meant that in Africa a wide implementation of HAART was not considered to be realistic. Many efforts were made to put pressure on pharmaceutical companies to decrease the prices of antiretroviral drugs. In 1997, in some of the scientific journals the first cautious papers were published which speculated on introduction of these drugs on a limited scale.[3,4] These publications were the first of a firm debate about the pros and contras of this intervention.[5-7]

The debate

Arguments in favour of the introduction of HAART

- **Inequity.** There are strong moral and ethical pressures on the international community to resolve the appalling disparity between the treated and the untreated, between the rich and the poor. This has lead to the 'great global alliance', which UN secretary general Kofi Annan has called for.
- **Economy**. The HIV pandemic is putting a heavy burden on the economies of the countries involved, those economies that were already vulnerable and in a poor condition. HIV takes away the economically strongest generation, those in the 2nd to 4th decade of their live. The number of orphans is growing beyond control. A major investment is needed to prevent the whole continent falling into an even lower abyss of poverty and misery.
- **Decrease of HIV incidence.** There is evidence that lowering the viral load with HAART may reduce the likelihood of transmitting HIV to others up to 80%.[8] Already established is the effect of a reduction of vertical mother-to-child transmission with antiretroviral treatment.[9] Therefore, a serious attempt to break the chain of transmission can be made.
- **Decrease of mortality.** The average life expectancy for an HIV-infected patient in the absence of treatment is approximately ten years.[10] Rates of progression appear similar by sex, race, and risk category, if adjusted for the quality of care.[11] However and maybe therefore, this period is considerably shortened in Africa, which may be also because of HIV subtype diversity.[12] HAART is expected to reduce HIV-related mortality considerably, as is already established in Europe.[2]

Arguments against the introduction of HAART[13,14,15]

- **Less emphasis on prevention**. The introduction of HAART will draw valuable funds from preventive measures, which are thought to be far more effective in preventing death and saving disability adjusted life years (DALY's) than HAART.[16] The ratio in cost-effectiveness of HAART and of prevention is in some calculations 28:1.
- **Cost**. Two recent studies estimated the cost to mount an effective and appropriate response to the HIV pandemic to be about US $ 7.5 - 9.2 billion annually.[7,17] This is an unprecedented amount of money, which has not been ever donated to health in the developing world. However, when seen in perspective, this is only 0.044% of the combined gross national product of the 22 wealthy donor countries of the Development Assistance Committee of the Organisation for Economic Co-operation and Development (OECD). There is doubt whether these amounts of money will be ever available. Furthermore, there could be a perception that HAART will draw effectively more attention and therefore leverage funds to the whole HIV problem. According to critics, this leverage effect has to be very large to be cost effective.[13]
- **The danger of a further collapse of the health infrastructure**. If HAART was to be implemented, the danger exists that money will be invested in the HAART programme, which was earmarked for other health purposes. This can potentially backfire leading to a further destruction of already fragile health systems that are in some countries at the threshold of total collapse.
- **Transmission may not be inhibited**. A large portion of HIV transmission occurs before the appearance of symptoms, and therefore before the initiation of therapy.[18] Furthermore, patients on HAART live longer; therefore they are potentially able to transmit the virus for a longer period. This effect will be stronger when treatment compliance is not assured. The dynamics of HIV transmission and its epidemiology needs to be established further.
- **The danger of increase of unsafe sexual behaviour.** A recent study has shown that HIV prevalence in Brazil has risen since the implementation of free HAART. This effect is attributed to a decrease of condom use and an increase in unsafe sex practices.[19,20]
- **The danger of the emergence of viral resistance:** When treatment compliance is less than 90%, there is an increased risk of the emergence of viral resistance. This may lead to a re-emergence of HIV infection after an initial decrease.[14]

The status quo of HAART in Africa in 2003

Among all interventions in HIV control, without doubt the greatest improvement in quality of live and the largest reduction in mortality in HIV infected individuals will be achieved with HAART. The major problems of a widespread use of HAART are caused by the costs, the drug delivery and the assurance of compliance.

In April 2001, in anticipation of the United Nations General Assembly Special Session on

HIV/AIDS (UNGASS) that was to be held in New York in June 2001, a new institution of the WHO was established: the Global Fund to fight AIDS, Tuberculosis and Malaria. This body has received pledges totalling US$ 2 billion of new funding and estimated that 7.5 billion US$ per year is needed to meet its targets. Now, with more money possibly available from several institutions such as the Bill Gates Foundation, the Clinical Trial Platform for tuberculosis, malaria and HIV/AIDS (an initiative of the European Union) and others, this may be partly feasible.

WHO recently have proposed guidelines for the scaling up of antiretroviral drugs in resource-limited settings.[21] They recommend starting HAART in adult and adolescent HIV-1-infected patients with a CD4 count of less than 200 cells/µl and/or in WHO stage 4 (in general the stage with the occurrence of opportunistic infections).[22] These first guidelines provide a framework for the national AIDS control programmes in resource-limited settings for the delivery and monitoring of various HAART regimens and the supporting network. Of course, many research questions remain to be answered:[23] is there a clinical advantage to start HAART in patients with a CD4 count > 200 cells/µl, and are there other (and cheaper) laboratory or clinical markers that can successfully guide decisions about when to start HAART.

The framework, in which HAART will be delivered, is essential for an introduction of HAART in Africa to avoid problems that cannot be solved. The minimal conditions, necessary to make this introduction feasible, are that the drugs must become more affordable and that more, and sustainable funds must become available. Secondly, a system for continuous drug delivery, and the assurance of the quality of drugs, must be construed. Finally, a key question will be how to assure the follow-up and monitoring of treatment compliance and adverse events, equivalent to DOTS in TB programmes.

The role of HAART in TB control

HAART has probably a major impact on TB transmission. Some authors are of the opinion that TB control without HIV control is impossible.[6] I have described the negative effects of the HIV epidemic on TB control programmes in Chapter X. One of the specific problems that face the HIV/AIDS control programmes is the relative lack of success of the Voluntary Counselling and HIV Testing Centres (VCT's). Nearly 90% of infected people in Africa do not know their HIV serostatus.[24] Generally this is thought to be due to a shortage of accessible VCT's, poor quality and logistics and a denial of AIDS by individuals, communities and even governments. However, a potential boost in the efficacy of the VCT's could be the link of the counselling and testing with provision of care. This care can consist of standard care, the treatment of STD's, or the availability of prophylaxis with cotrimoxazole and/or isoniazid. Without doubt, the most powerful incentive for patient to have their HIV serostatus determined would be antiretroviral treatment because of its 'curative' element.

HAART will lower the transmission of HIV. For the same reason one can contemplate a decrease of incidence of TB. This will be due to a decreased number of latently infected patients who will develop secondary reactivation PTB, a decreased number of contagious patients and finally less patient-to-patient transmission and therefore fewer newly infected patients who are additionally less susceptible for these new infections when HIV seronegative. Moreover, the number of relapses of TB is also expected to decrease. The first evidence to confirm this theoretical model has already been established. In a study of 264 HIV infected TB patients in South Africa a reduction of 80% in mortality was achieved. According to this study a prevention of 14-20 cases of TB per 100 patient-years of treatment in this patient category would be achieved.[25]

In general, there have been few clinical studies that investigate the simultaneous treatment of HIV and TB. There are some practical and logistical difficulties to consider with the introduction of HAART in TB patients.

1 *Pharmacological difficulties*: There are serious interactions between antiretroviral drugs and rifampicin. More specifically, treatment with protease inhibitors and rifampicin at the same time is pharmacologically complicated and therefore discouraged. The simultaneous therapy of non-nucleoside reverse transcriptase inhibitors (NNRTI's) and rifampicin is feasible, but needs an adjustment of dosages. The exact interactions and adverse effects of this combination need to be studied more carefully. Probably, the only combination with no relevant interactions is between nucleoside reverse transcriptase inhibitors (NRTI's) and the antituberculous drugs.[26]

   Starting both treatments (seven different drugs) at exactly the same time is another concern. When an adverse event occurs, it will be difficult to assess which drug causes this event. Therefore, it is advised to wait a minimum period of, e.g. 2 months with HAART after tuberculosis treatment has begun.

   Another aspect of this approach is the matter of early mortality. There is a high mortality in HIV-seropositive PTB patients, with approximately one third of the mortality occurring in the first months of the TB treatment. A way of trying to lower this early mortality could be to start HAART in the first days of TB treatment. An interesting subject of research is to observe the problems that can be encountered in this early simultaneous treatment.

2 *Logistical difficulties*: how to use the TB infrastructure for HAART drug delivery.

   a) Most of the African NTP's have a long experience in the delivering and monitoring of TB therapy. This infrastructure could be well used for the administration of HAART in general or of HAART restricted to TB patients. Adverse effects of both treatments are best managed in a single programme. A possible disadvantage of such a joint approach would be the overburden of the NTP's. Therefore, these programmes need to be provided with sufficient funding, manpower and training to deal with this enormous task. Furthermore, if the NTP allocations are used for HAART delivery in general one should be aware of the risk of HIV positive patients without TB acquiring TB when undergoing HAART if they had to join the outpatient queues with a mixed population.

b) Another possible solution of drug delivery could be provided by the existing structure of VCT's. In these centres the counselling and HIV testing, the treatment of STD's, the provision of prophylaxis, the delivery and monitoring of TB drugs and the delivery and monitoring of HAART could be offered as a package. Again this will need an enormous effort in strengthening the capacity of these VCT's in terms of human resources, funding and organisation.

c) There is a risk of emergence of resistance of HIV when treatment compliance of HAART is insufficient.[14] Therefore, a similar system of observed treatment is suggested as in DOTS.[5] An additional argument is the expected street value of HAART drugs. Closed observation to prevent HAART drugs being traded at street markets is necessary. Moreover, the lifelong provision of HAART will be a major logistical problem.

3 *When to start*: Another question to be answered is the moment when to start with HAART.[23] WHO recommends that patients with the dual infection of TB and HIV complete their TB therapy prior to HAART, unless there is a high risk of HIV progression and death during that period of TB treatment. The current WHO guidelines recommend starting HAART when the CD4 count is below 200 cells/mm.[3,21] However, TB patients co-infected with HIV have a high early mortality.[27] An important research question is to investigate whether it is possible and clinically feasible to start HAART and TB treatment at the same time.

In my view, a wide-scale introduction of antiretroviral treatment in Africa will be hard to stop. From an ethical and philosophical perspective, withholding a potentially life-saving treatment in one part of the world, while widely available in other parts, is not easy to defend, even if cost effectiveness theories show that the balance points towards prevention only. Until a more definitive solution such as a vaccine is found all efforts should be mobilised to fight this catastrophe, both AIDS and tuberculosis, in all possible ways. All possible measures, such as prevention, prophylaxis, and antiretroviral therapy should be fully exploited. To prevent anarchy and the consecutive emergence of viral resistance, research must be directed towards determining when to start treatment, how to monitor the treatment, which drugs are the best combination, and how to assure adherence to treatment. Furthermore, this research must provide answers about adequate logistics and funds in a cost effective manner. A simultaneous emphasis on the improvement of prevention of HIV transmission through behavioural change will be a continuing challenge.

Inevitably, the fight against AIDS is essential in TB control. While continuing the present classical TB control measures, the battle against the dual epidemic cannot be won without the full employment of all AIDS control measures including HAART.

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Chapter XI

Summary

Samenvatting

This thesis describes some studies and reflections on aspects of tuberculosis control in Africa, specifically in Malawi, in the face of the HIV epidemic. In the research agenda of the National Tuberculosis Control Programme (NTP) in collaboration with the College of Medicine of the University of Malawi several topics have been identified for operational research to improve control measures in the fight against TB and AIDS. Some of these various issues and the studies, which resulted from it, form the basis of this thesis.

In **Chapter I**, a general introduction is given and an outline of the thesis. The problem of TB and HIV is put in epidemiological perspective, globally and in Africa. Some information about Malawi is discussed, especially its political and health situation. An inventory is made of the constraints of the NTP, and the implications that this has for an operational research agenda.
In **Chapter II**, a study is presented of the size of a possible gender difference in TB control. Women in low-income countries are probably undernotified compared to men. In this study we were interested to assess whether there is a sex difference in numbers of sputum submission and numbers of suspects with positive sputum smears in Malawi. We examined the laboratory registers in all diagnostic units in eight (rural, semi-rural and urban) districts for the years 1995 and 1996. We found that during a 12-month period of about 27 000 new TB suspects 52% males and 48% females submitted sputum samples. Of approximately 3 000 smear-positive sputum samples 53% were from male and 47% from female patients. Both differences were statistically significant, and these differences were maintained after correction for gender distribution in the general population. These results supported the suggestion that gender differences are important in control programmes and may reflect differences in access to health care.
In **Chapter III**, a strategy is tested for the diagnosis of tuberculous lymphadenitis in the low resource conditions of health care as seen in sub-Saharan Africa and with the background of a high HIV co-infection rate. In a prospective study the results of four basic procedures diagnosing tuberculous lymphadenitis with the outcome of histology and/or culture are compared. These four procedures were: a wide needle aspiration looking at i) macroscopic caseation and ii) the Ziehl-Neelsen (ZN) stain and a lymph node biopsy again looking at iii) macroscopic caseation and iv) the ZN stain. There were 52 outpatients with extra-inguinal lymphadenopathy in whom all procedures were carried out. Of these, 73% were diagnosed as tuberculous lymphadenitis; 84% of the latter were seropositive for HIV. Needle aspirate and biopsy smears stained by the ZN technique contributed little to detecting tuberculosis, 8% and 11% respectively. In contrast, macroscopic caseation of excised lymph nodes showed a high yield of 82%, which was similar to histology, and higher than that of culture (61%). Results showed that HIV-positive patients with TB lymphadenitis had a reduced frequency of histology and culture being positive for tuberculosis. Histology results, often used as the single definitive method, failed to diagnose 18% of tuberculosis cases. However, it was reassuring that four simple methods, which can safely be carried out at district level, could be expected to diagnose 80-95% of tuberculous lymphadenitis cases in a timely and cost-effective manner.
In **Chapter IV**, a study was carried out on the role of traditional healers and traditional medicine

for patients with TB in Malawi. This was assessed by a questionnaire study on 89 smear-positive pulmonary TB patients admitted to Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. Furthermore, seven traditional healers were also interviewed about their knowledge, attitudes and practice of patients whom they considered to have TB. Of these 80 patients, 37% admitted to have visited a traditional healer before seeking regular medical care. Patients spent a median length of 4 weeks with the traditional healer. During this time, 72% did not improve or deteriorated while on traditional treatment. No patient was referred to the medical services by the traditional healer. All traditional healers claimed to know about TB. Four patients said they would refer a patient to hospital if their treatment were not curative. Six traditional healers claimed to have cured 116 patients with TB in one year. We concluded that it is important to involve traditional healers in the educational activities of the NTP. These healers need to be taught to recognise and refer patients with TB, whom they should not treat, but at the same time be encouraged to administer safe treatments for conditions that are more amenable to their practice. This study was important in being the first study in Malawi to assess the role of traditional healers in causing diagnostic delays for patients with PTB. As a consequence, the Malawi NTP engaged in other studies to investigate traditional healer beliefs and invested in training of traditional healers in all districts around the country. Between 1998 and 2000, just under 6 000 traditional healers were trained about the importance of TB and about the need to refer patients with cough to hospital for further investigation. In its 5-year development plan (2002-2006), the NTP has a budget line of US$ 20 000 per annum for traditional healer training

The results of the study in Chapter 4 contributed to the design of the study described in **Chapter V**. We did structured questionnaires completed by interviews in about 1 000 patients registered with PTB in government hospitals in five districts in Malawi. These questionnaires were to determine aspects of care seeking behaviour and diagnostic processes in smear positive PTB patients. The median delay between onset of cough and diagnosis was 8 weeks. There was a variable pattern of care seeking behaviour, with 70% of patients initially visiting a place of orthodox medical care and 30% visiting traditional healers, grocery shops, etc. Of these, 79% of the patients had one or more subsequent contacts for help, with these visits targeted more to orthodox medical care. At all stages, antibiotics resulted in symptomatic improvement in up to 40% of cases. There was a median time of 7 weeks between cough and first submission of sputum specimens. Almost all patients received sputum smear results after a median length of 4 days. 43% of patients were only aware of their diagnosis at the time of receiving smear results, this observation being significantly associated with lack of schooling and not knowing another person with TB. We concluded on the basis of these findings that more needs to be done to educate communities and non-orthodox care providers about the diagnosis and treatment of TB.

In **Chapter VI,** a laboratory study was performed to determine how long sputum specimens from smear-positive tuberculosis patients can be stored at room temperature or in the refrigerator and retain a positive acid-fast bacilli (AFB) smear or a positive mycobacterial culture. This was important because in remote health centres where facilities are not always available to stain and examine samples, specimens need to be stored and examined in a later stage to diagnose TB. Furthermore,

some samples are submitted for culture and assessment of drug sensitivity to the Central Reference Laboratory in Lilongwe. These samples need to be stored and transported.
Sputum samples from 30 patients were examined up to 4 weeks and samples from 13 patients examined up to 8 weeks. If provided samples had not dried out, all sputum smears remained AFB positive up to 4 and 8 weeks. In both patient groups, at 4 weeks 37-39% of specimens at room temperature grew *Mycobacteria* compared with 54-67% of specimens stored in the refrigerator. These results have implications for tuberculosis programme policy. Laboratory technicians should not discard specimen which arrive late from health centres and specimen should be and can be stored in the refrigerator before transportation to a central laboratory for culture even after 4 weeks.

In **Chapter VII** and **VIII** an important issue of TB control in the HIV positive population was studied and discussed. The mortality in HIV infected TB patients is very high as compared to HIV negative TB patients. Routine antiretroviral treatment is not available at the present time and sub-Saharan Africa is desperately seeking for other cost effective measures to decrease the time to fatale outcome.
Prophylactic treatment with cotrimoxazole (CTX) has shown to be effective in reducing mortality in this patient category. We conducted a randomised, double-blind study to compare the efficacy and safety of two different dosages of CTX (480mg and 960 mg) in preventing mortality and morbidity, particularly bacterial pneumonia. Furthermore, we compared the outcome of our patients with an unselected cohort of TB patients registered in Zomba, Malawi in 1995 and with the treatment outcomes of the NTP in the same period the study was conducted. We found that there were no statistical significant differences in mortality and occurrence of bacterial pneumonia in the groups receiving the two different doses. The case fatality rate at the end of the PTB treatment (8 months) was 15.4% in the CTX 480 mg group and 14.0% in the CTX 960 mg group. This was lower than the case fatality rate in the Zomba cohort (19.2%) and significantly lower than the case fatality rate of the NTP (21.0%). CTX was well tolerated, and only one patient had to stop prophylaxis because of a serious side effect. We felt that the study provided circumstantial evidence that cotrimoxazole prophylaxis has a beneficial effect on mortality and morbidity in HIV infected smear positive PTB patients. Furthermore, the efficacy of a dosage of 480 mg CTX is not significant different from a dosage of 960 mg. Both doses of cotrimoxazole are well tolerated, and the intervention is cheap and easy to implement. In conclusion, after taking all the considerations into account a meeting was held in October 2002 were a statement was made that i) CTX prophylaxis for HIV seropositive TB patients be continued in those districts where it has been started, ii) CTX prophylaxis should be encouraged to be expanded in other districts in a phased approach with results carefully monitored by the NTP, iii) a randomised controlled trial to determine the efficacy of CTX prophylaxis with and without antiretroviral therapy in HIV seropositive TB patients should be encouraged and finally iv) the NTP should keep up to date with any new information about the efficacy of CTX prophylaxis in the region and act accordingly.

In **Chapter IX**, the problem of treatment compliance within the NTP is addressed. The average default rate in the NTP in smear positive PTB in the last ten years was about 11%. We were interested in the true outcome of 8 months of treatment received by smear-positive pulmonary tuberculosis patients who had been registered as defaulters in the QECH and Mlambe Mission Hospital (MMH). In addition, we were interested in possible reasons for default in these patients. The true treatment outcome of 101 patients in 1995 who had been registered as defaulters was determined by making personal inquiries at the treatment units and the residences of patients or relatives and, in a few cases, by writing to the appropriate postal address. Interviews were carried out with patients who had defaulted and were still alive and with matched, fully compliant PTB patients who had successfully completed the treatment to determine the factors associated with defaulter status. Of these 101 patients only 22 were true defaulters, 31 had completed the treatment, 31 had died during the treatment period, and 17 had left the area. A total of 8 of the 22 true defaulters were still alive and were compared with the compliant patients. Two significant characteristics were associated with the defaulters; they were unmarried; and they did not know the correct duration of antituberculous treatment. We concluded that many of the smear-positive tuberculosis patients who had been registered as defaulters actually did not default and were found to have different treatment outcomes. We learned from this study that the quality of reporting in the health facilities had to be improved in order to exclude individuals who are not true defaulters, and that patients must be informed about the duration of anti-TB treatment..

In the last chapters, **Chapter X and Xa**, a covering opinion paper was written about the possible strategies of TB control in the face of the HIV epidemic in sub-Saharan Africa. The first section was written and published in *Tropical Doctor* in 1998. An update of this strategy is given in 2003 with the background of the developments in antiretroviral treatment and the advancements in drug delivery programs.
The problems of TB control in the era of HIV infection are outlined: increased numbers of TB cases, increased morbidity and mortality, increased recurrence of TB after treatment, and the possibility of the emergence of drug resistant TB. The contemporary DOTS strategy of the WHO is explained and critically reviewed in the face of these increasing problems. The targets for cure rates (85%) and detection rates (70%) are difficult to hit because of high HIV-related mortality and because a method for estimating the total number of cases of TB has not yet been found. An argument is made for active case finding in some spots such as prisons and hospitals. The disappearing of some cheap and readily available drugs such as thiacetazone and in some respect streptomycine is mentioned. The problems of case holding in hospitals and the resulting overcrowding of the wards are discussed with possible solutions of ambulatory treatment. The devastating high mortality in smear negative PTB is a demoralizing development that is not targeted in the DOT strategy. Finally, the impact of the epidemic on the health staff itself and the quality of the NTP infrastructure is an additional concern.

In the discussion some options for approach are mentioned: 1) the use of isoniazid chemoprophylaxis 2) the creation of the best conditions (financially, logistically, and operationally) for the WHO-DOTS strategy 3) finding ways of determining the TB case rate 4) promotion of active case finding in some circumstances 5) addressing the issue of smear-negative PTB 6) the rigorously piloting and evaluating of community care schemes 7) an attempt to reduce the high mortality during treatment e.g. by cotrimoxazole prophylaxis 8) ensure enough trained and motivated manpower in the health care workforce 9) integration with AIDS control programmes.

In a 2003 update an overview is given of the intentions to implement Highly Active Anti Retroviral Treatment (HAART) in the treatment of TB patients. The arguments in favour and against that are used in the debate whether to introduce HAART on a wide scale in Africa are discussed. The current progression of HAART programmes in general and more specifically in connection with TB programmes is outlined. Furthermore, the pharmacological and logistical problems of the concurrent use of TB treatment and HAART are discussed. Finally, the chapter ends with a personal view of the way forward in tuberculosis control in Africa in the face of the HIV epidemic in the era of highly active antiretroviral treatment.

Samenvatting

Dit proefschrift beschrijft enkele studies van en bespiegelingen over aspecten van tuberculose (TB) controle in Afrika, speciaal in Malawi, in het tijdperk van de pandemie met het humane immunodeficiëntie virus (HIV). Ook in Malawi veroorzaakt deze co-infectie grote problemen. Het Nationale Tuberculose Controle Programma (NTP) van Malawi in samenwerking met de Faculteit Geneeskunde van de Universiteit van Malawi legden daarom in 1995 de fundamenten van een strategisch plan van aanpak in een poging om de gevolgen van deze problemen te controleren. Dit plan leidde tot een research agenda met verschillende onderwerpen voor operationeel onderzoek om de controle maatregelen in het gevecht tegen TB and AIDS te verbeteren. Sommige van deze onderwerpen en de studies die eruit volgden, vormen de basis van dit proefschrift.

In **hoofdstuk I** wordt een algemene introductie gegeven en een overzicht van de achtergronden van het proefschrift. De epidemiologie van TB en HIV wordt beschreven, zowel globaal als in Afrika. Het hoofdstuk gaat in op sommige aspecten, die van belang zijn voor Malawi, met name de politiek en de gezondheidszorg. Vervolgens worden de problemen van het NTP geïnventariseerd, van waaruit een operationele research agenda kon worden gemaakt.

In **hoofdstuk II** wordt het onderzoek beschreven naar de omvang van een mogelijk man/vrouw verschil in het diagnostische proces naar open TB in Malawi. Bij vrouwen met TB uit landen met lage inkomens wordt waarschijnlijk minder vaak de ziekte daadwerkelijk vastgesteld en dus geregistreerd dan bij mannen. We keken in deze studie vooral naar het man/vrouw-verschil in het aantal monsters ingeleverd sputum en het aantal patiënten met een positive kleuring van sputum voor TB. Hiertoe werden de laboratorium-registers in alle diagnostische units in acht (plattelands- en stedelijke) districten gedurende de jaren 1995 en1996 doorzocht. De sputum uitslagen van ongeveer 27.000 patienten, die werden verdacht van TB, waren in 52% van de gevallen van mannen en in 48% van vrouwen. Van de ongeveer 3.000 sputum-positieve monsters waren er 53% van mannelijke en 47% van vrouwelijke oorsprong. Beide verschillen waren statistisch significant, ook na correctie voor geslachtsverdeling binnen de gehele populatie volgens de bevolkingsregisters. Deze resultaten suggereren dat gelachtsverschillen belangrijk zijn in TB controle en dat deze verschillen mogelijk een weerspiegeling zijn van een verschil in toegankelijkheid van gezondheidszorg.

In **Hoofdstuk 3** is gekeken naar de mogelijkheden om lymfklier tuberculose te diagnosticeren in Malawi met een hoge HIV prevalentie en een laag budget voor de volksgezondheid. In een prospectieve studie werden vier eenvoudige en goedkope diagnostische methoden vergeleken met histologie en/of kweek. De volgende methoden werden beoordeeld en vergeleken: een Ziehl-Neelsen preparaat van een naaldaspiratie en van een lymfklierbiopsie, en de aanwezigheid

van macroscopische verkazing in dat aspiraat of in hetzelfde biopt. Van de 52 patiënten waarbij alle diagnostische methoden werden uitgevoerd werd bij 73% de diagnose lymfklier tuberculose gesteld, 84% van deze laatste groep was seropositief voor HIV. Ziehl-Neelsen preparaten alleen van een aspiraat of biopsie hebben weinig diagnostische waarde: respectievelijk 8% en 11%. Daarentegen is de diagnostische waarde van macroscopische verkazing erg hoog: 82%, dit was even hoog als de histologie en zelfs hoger dan de waarde van een kweek (61%). Bij de vastgestelde patiënten met lymklier tuberculose bleek HIV seropositiviteit een negatieve invloed te hebben op het positief zijn van zowel de kweek als de histologie. Vooral de histologie bleek vaker vals negatief te zijn in deze patiëntengroep. Het blijkt, dat histologie alléén (nu vaak gebruikt als de enige diagnostische methode) 18% van de tuberculose gevallen mist.
Concluderend was het bevredigend, dat een simpele diagnostische strategie met vier simpele onderzoeken 80-95% van de gevallen van lymfklier TB op een snelle en kosten-effectieve wijze kon vaststellen.

In **Hoofdstuk 4** is de rol en invloed van traditionele genezers (traditional healers) onderzocht bij 89 sputumpositieve patiënten opgenomen in het Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. Deze patiënten kregen een vragenlijst voorgelegd. Bovendien werden 7 traditional healers ondervraagd over hun kennis en beleid bij patiënten die zij verdenken van tuberculose. 37% van de tuberculosepatiënten bezocht een traditional healer vóórdat zij hulp zochten in de reguliere gezondheidszorg, gedurende mediaan 4 weken. Geen van hen werd in deze periode naar de reguliere gezondheidszorg doorverwezen. Bij 72% van hen verslechterde hun gezondheidstoestand of bleef deze gelijk. Alle traditional healers kenden het ziektebeeld tuberculose. Vier van hen zouden een patiënt doorverwijzen naar de reguliere gezondheidszorg als hun therapie zou falen. Zes traditional healers beweerden 116 patiënten met tuberculose te hebben genezen in een jaar tijd. We concludeerden, dat het belangrijk is om de traditional healers te betrekken bij onderwijsactiviteiten van het NTP om TB bij hun patiënten te leren herkennen, door te verwijzen en dus niet zelf te behandelen. Tegelijkertijd moeten ze worden aangemoedigd door te gaan met het op een verantwoorde wijze behandelen van aandoeningen die wél door hen behandeld kunnen worden.
Deze studie was belangrijk om dat het de eerste was die de rol van de traditional healer in het TB controle proces beoordeelde. Als gevolg hiervan werden er meer studies uitgevoerd (zie ook hoofdstuk 5). Ook is het NTP is gestart met training van traditional healers in het gehele land en inmiddels hebben tussen 1998 en 2000 ongeveer 6.000 traditional healers een training gehad en wordt er tot 2006 jaarlijks 20.000 US $ voor gebudgetteerd.

De resultaten van de studie in hoofdstuk 4 werden gebruikt voor de studie opzet van **Hoofdstuk 5.** Aan 1000 patiënten opgenomen met PTB in een districtsziekenhuis werd een vragenlijst uitgereikt en aanvullend een interview afgenomen. De vragenlijst was gemaakt om te achterhalen hoe en waarom deze patienten zorg zochten en welke diagnostische procesen een rol speelden. De mediane periode tussen het begin van de hoest en de diagnose tuberculose was 8

weken. Er was nogal wat variatie in de plaats waar voor het eerst hulp werd gezocht. Terwijl 70% direct een conventionele gezondheidsinstelling bezocht, ging 30% eerst naar een traditional healer, de markt of een supermarktje.Van deze laatste groep had 79% meerdere contacten met o.a. de traditional healers. In alle stadia gaven antibiotica klinische verbetering bij tot 40% van de patiënten. De mediane tijd tussen het begin van de hoest en de eerste ingeleverde sputumpreparaten was 7 weken. Bijna alle patiënten kregen de uitslagen van de sputumpreparaten na mediaan 4 dagen. 474 (43%) patienten hadden voor het ontvangen van de sputumuitslag nog geen vermoeden dat hij/zij tuberculose zou kunnen hebben. Deze groep was significant minder geschoold en kende significant vaker geen andere personen met TB. Op basis van deze uitkomsten lijkt de conclusie gerechtvaardigd dat er meer voorlichting en onderwijs noodzakelijk is in locale gemeenschappen en bij niet conventionele verstrekkers van gezondheidszorg zoals traditional healers.

In **Hoofdstuk 6** wordt het onderzoek beschreven naar de tijd, die sputum monsters van sputum positieve tuberculose patiënten bewaard kunnen blijven bij kamertemperatuur of in de koelkast. Omdat in Malawi sommige gezondheidsposten (health centres) erg afgelegen liggen en ze vaak geen mogelijkheden hebben om deze preparaten te kleuren en te beoordelen moeten ze worden opgeslagen om in een later stadium beoordeeld te worden. Bovendien moeten sommige monsters gereed worden gemaakt voor kweek en beoordeling van het resistentiepatroon in het centrale referentielaboratorium in de hoofdstad Lilongwe. Ook deze preparaten moeten worden bewaard en later vervoerd. Er werd een laboratoriumstudie uitgevoerd waarbij de sputumpreparaten van 30 patiënten tot 4 weken werden beoordeeld en de preparaten van 13 patiënten tot 8 weken. Als de preparaten niet uitgedroogd waren bleven ze positief kleuren met Ziehl-Neelsen kleuring tot 4 en 8 weken. Daarnaast konden na 4 weken nog steeds mycobacteriën gekweekt worden in 37-39% van de preparaten bewaard op kamertemperatuur vergeleken met 54-67% van de preparaten bewaard in de koelkast. Deze studie laat zien dat het zin heeft om sputummonsters als ze met vertraging zelfs na 4 weken uit health centres komen nog te beoordelen en niet vroegtijdig weg te gooien.

In **Hoofdstuk 7 en 8** wordt een belangrijk onderwerp aangaande tuberculosebestrijding bij HIV seropositieve patiënten bestudeerd en behandeld. Vergeleken met HIV seronegatieve tuberculose patiënten is de mortaliteit van HIV positieve patiënten erg hoog. Momenteel is medicamenteuze behandeling van een HIV infectie (antiretrovirale therapie) nog niet algemeen beschikbaar in Afrika. Het is daarom, dat alternatieve manieren om de mortaliteit te verlagen, worden gezocht. Eén van deze manieren is het geven van antibiotische profylaxe, met name cotrimoxazol (CTX). In een studie in Ivoorkust bleek CTX profylaxe al effectief in het verlagen van de sterfte.
Daarom verichtten we een gerandomiseerde dubbel-blinde studie om de effectiviteit in het verlagen van sterfte en ziekte van twee verschillende doses CTX (480 en 960 mg) te onderzoeken. Tevens werd het aantal bijwerkingen geregistreerd. Daarnaast werden de uitkomsten vergeleken

met een historisch cohort van TB patiënten in Zomba, Malawi in 1995 én met de landelijke uitkomsten van het NTP.
We vonden, dat er geen statische significante verschillen tussen de groepen met de twee doses waren. Het percentage fatale gevallen aan het einde van de behandeling, de zogenaamde case fatality rate (CFR) was 15.4% in de groep, die 480 mg ontvingen en 14.0% in de groep, die 960 mg kregen. Dit was lager dan in het Zomba cohort (19.2%) en statistisch significant lager dan de CFR van het NTP (21.0%).
CTX werd goed getolereerd, maar één patient moest stoppen vanwege een serieuze bijwerking.

We concludeerden, dat er een positief effect is van beide doses op de vermindering van ziekte en sterfte in de onderzochte populatie. In oktober 2002 werd in een vergadering onder auspiciën van het Ministerie van Gezondheid een richtlijn ontworpen, die invoering van CTX profylaxe aanbeveelt in ieder geval totdat betere maatregelen ter bestrijding van AIDS beschikbaar zijn.

In **hoofdstuk IX** wordt het probleem van de therapietrouw belicht. Het gemiddelde percentage van patiënten, die de TB behandeling niet afmaakt, de zogenaamde default rate, was in de laatste tien jaar ongeveer 11%. Wij waren geïnteresseerd in de werkelijke uitkomst van deze groep aan het einde van de 8 maanden durende behandeling. Tevens wilden we de redenen ontdekken waaròm de behandeling niet was afgemaakt. We onderzochten dit in een groep van 101 open TB patienten, die in 1995 als "defaulter"waren geregistreerd in QECH en in een klein missie ziekenhuis (Mlambe Mission Hospital, Limbe). De onderzoeksopzet bestond uit het zoeken naar de verblijfplaatsen via registers, familie of middels een brief. Vervolgens bezochten we deze plaatsen. Indien we de patienten of de naastverwanten hadden gevonden ondervroegen we ze middels een gestructureerde questionnaire. Van de 101 patiënten waren er slechts 22 daadwerkelijk ware defaulters volgens de definitie. Van de overige 79 hadden 31 de behandeling gewoon afgemaakt, 31 waren overleden en 17 waren verhuisd. Totaal 8 van de 22 ware defaulters leefden nog en konden worden geinterviewed. De uitkomsten van hun vragenlijsten werden vergeleken met 8 vergelijkbare controle patienten, die wél therapietrouw waren. Twee karakteristieken vertoonden een statistisch significante associatie: de defaulters wisten niet de duur van de behandeling en ze waren ongetrouwd. We concludeerden, dat veel open TB patiënten, die geregistreerd waren als defaulters geen echte defaulters zijn. De kwaliteit van de TB registers moet dus voortdurend worden bewaakt. Verder is goede voorlichting o.a. over de duur van de behandeling belangrijk.
In de beide laatste hoofdstukken, **hoofdstukken X en Xa,** schrijf ik een beschouwend artikel over de mogelijke strategiën van tuberculose controle in het tijdperk van de HIV epidemie. Het eerste hoofdstuk werd geschreven en gepubliceerd in *Tropical Doctor* in 1998. Vanwege de actualiteit schreef ik een update in het kader van de ontwikkeling en invoering van antiretrovirale therapie. De problemen van de huidige TB controle worden geschilderd: toenemende TB notificaties, toenemende morbiditeit en mortaliteit, en de dreigende ontwikkeling van resistentie tegen diverse anti tuberculose middelen. De huidige Directly Observed Treatment Short-cour-

se (DOTS) strategie van de Wereld Gezondheids Organisatie (WGO) wordt uitgelegd en kritisch beschouwd. Het is uiterst moeilijk om nu in deze omstandigheden de WGO doelen van 85% genezing en 70% opsporing van alle gevallen van open TB te halen. Het hoofdstuk bespreekt verder de mogelijkheid om in beperkte mate over te gaan naar actieve opsporing van TB, bijvoorbeeld in gevangenissen en ziekenhuispersoneel. Ook worden een aantal problemen genoemd waarmee het NTP te maken heeft: i) het verdwijnen van goedkope en gemakkelijk beschikbare medicijnen zoals thiacetazone en streptomycine, ii) het probleem van de overvolle ziekenhuizen en het meer en meer verschuiven naar ambulante behandeling daardoor iii) de demoraliserende hoge sterfte onder sputum negatieve, gesloten longtuberculose en het feit, dat deze groep niet een doelgroep is in de huidige DOTS strategie, iv) het gevolg van de HIV epidemie op het personeel in de gezondheidszorg zélf en daardoor op de infrastructuur van het NTP.

In de daaropvolgende discussie volgen een aantal opties om de problemen te lijf te gaan: 1) het gebruik van isoniazide profylaxe 2) het scheppen van de beste condities (financieel, logistiek en operationeel) voor de WHO-DOTS strategie 3) het vinden van betere methodes om de ware omvang van TB te detecteren 4) het bevorderen van actieve opsporing van TB patienten in geselecteerde omstandigheden 5) aandacht besteden aan de controle van gesloten longtuberculose 6) het pogen om de hoge sterfte tijdens behandeling te reduceren, bijvoorbeeld met behulp van cotrimoxazol profylaxe 7) het ervoor zorgdragen, dat genoeg getraind en gemotiveerd personeel beschikbaar blijft voor de gezondheidszorg in het algemeen en het NTP in het bijzonder 8) integratie met de AIDS controle programma's.

In de update van 2003 wordt een overzicht gegeven over de plannen voor uitgebreide invoering van zogenaamde Highly Active Anti Retroviral Treatment (HAART) bij HIVseropositieve patiënten in het algemeen en HIV seropositieve tuberculose patiënten in het bijzonder in Afrika. Het artikel gaat uitgebreid in op alle argumenten voor en tegen in dit controversiële debat. Verder worden faramacologische en logistieke problemen van het gelijktijdig gebruik van HAART en antituberculose therapie besproken. Tenslotte eindigt dit hoofdstuk met een persoonlijke mening op "the way forward" in tuberculose controle in Africa in het gezicht van de HIV epidemie in het tijdperk van HAART.

Dankwoord

Dit proefschrift is tot stand gekomen op een wat merkwaardige manier. De onderzoeken waren oorspronkelijk nooit bedoeld om onderdeel te zijn van een proefschrift. Ze zijn gedaan uit enthousiasme voor de tuberculose bestrijding in Malawi en de zeer bemettelijke onderzoeksdrang van het toenmalige hoofd van de Department of Medicine, professor Tony Harries. Tony, your drive caused this all to happen and I will never be able to compete with your energy and working spirit. You remain an example and an inspiration for me: how to do relevant operational research in basic and poor conditions. With you I want to thank Marigo, for your great hospitality during all my trips to Lilongwe. Most of all I would like to thank you both for being good friends.

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Vóór onze gang naar Malawi en dus niet via een klassiek uitgestippeld pad werden natuurlijk wel de fundamenten gelegd voor deze promotie. Deze fundamenten konden niet worden gelegd zonder de intellectuele en stimulerende steun van mijn ouders. Bedankt Pa en Ma!

De allereerste wat twijfelende schreden op het gebied van de wetenschap werden gedaan samen met Herman Hart in Amersfoort met eosinofielen, en samen met Dirkje Postma in Groningen

met gastric asthma. Ik heb echter de waarde van wetenschap steeds meer leren kennen dankzij Huib Kerstjens, die zo aardig is om ook nog mijn paranimf te willen zijn. Ook de andere assistenten wil ik danken: Jaap Strijbos, Nanke Breederveld en Tjip van der Werf. De laatste gaf met zijn proefschrift over tuberculose tijdens de opleiding een voorbeeld dat het wél mogelijk is.
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Curriculum Vitae

Martin Boeree werd op 30 augustus 1958 geboren in Eelde. Vanaf 1961 woonde hij in het schilderachtige Drentse plaatsje Bunne. In 1976 behaalde hij zijn Atheneum-B eindexamen aan het Heymans College in Groningen. Van 1976 tot 1985 studeerde hij geneeskunde aan de Rijksuniversiteit Groningen. Na zijn diensttijd als Luitenant ter Zee Arts KMR 2 JC bij de Koninklijke Marine op Curaçao (NA), begon hij in 1988 met zijn basisopleiding Interne Geneeskunde in het ziekenhuis de Lichtenberg te Amersfoort (opleider Dr Herman Ch. Hart). In 1991 vervolgde hij zijn opleiding tot longarts in het Academisch Ziekenhuis in Groningen (opleider: Prof. Dr Gerard H. Koëter). Na zijn registratie als longarts op 1 januari 1994 werkte hij nog enkele maanden in het Academisch Ziekenhuis in Groningen, bij de GGD in Groningen en Assen en in het ziekenhuis Beatrixoord in Haren. Eind 1994 volgde hij de tropencursus NTA bij het KIT in Amsterdam en na een taalcursus Chichewa vertrok hij uiteindelijk in april 1995 naar Malawi om daar als Senior Lecturer aan de Universiteit van Malawi in Blantyre te gaan werken (hoofd Prof. Dr. Tony Harries). In deze periode was hij tevens adviseur van het Nationale Tuberculose Programma (NTP) van Malawi. Ook werd in 1995 Principal Investigator van de door WHO/UNAIDS gesponsorde studie naar cotrimoxazole/ INH profylaxe bij HIV positieve tuberculose patienten. In 1997 werd hij aangesteld als hoofd van de Department of Medicine.

In 1999 keerde hij terug naar Nederland, waar hij eerst een jaar als algemeen longarts werkte in het Twenteborg Ziekenhuis in Almelo. Sinds 1 januari 2001 is hij verbonden aan de afdeling Longziekten van het Universitair Medisch Centrum Nijmegen St Radboud en is gedetacheerd bij het Universitair Longcentrum in Groesbeek (hoofd destijds Prof. Dr Cees L.A. van Herwaarden, momenteel: Prof Dr. Richard Dekhuizen) en is hij werkzaam op het Medisch Centrum Dekkerswald, met als specialisatie infectieziekten, speciaal de tuberculose en cystic fibrosis. Tevens is hij bestuurslid van de Nederlandse Vereniging van Tropische Geneeskunde, voorzitter van het Concilium Opleiding Tropische Geneeskunde en Vice President van de Federation of the European Societies of Tropical Medicine and International Health (FESTMIH).

Hij is getrouwd met Marianne Schoevers en heeft 2 kinderen: Suzanne en Stijn.