Epidemiology and control of tuberculosis and sexually transmitted infections in Thyolo District, Malawi

Zachariah, R.

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Rony Zachariah

EPIDEMIOLOGY AND CONTROL OF TUBERCULOSIS AND SEXUALLY TRANSMITTED INFECTIONS IN THYOLO DISTRICT, MALAWI

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CHAPTER 1

INTRODUCTION

EPIDEMIOLOGY AND CONTROL OF TUBERCULOSIS

Tuberculosis and HIV/AIDS in sub-Saharan Africa

Burden of tuberculosis and HIV/AIDS

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global emergency, in recognition of its growing importance as a public health problem. The WHO estimates that 1700 million people or a third of the Worlds population are infected with the TB bacillus, *Mycobacterium tuberculosis*[1].
In 2001, the estimated number of new TB cases globally was 8.5 million, with the global incidence rate growing at approximately 0.4% per annum[2].
Mortality due to TB was estimated at 1.87 million in 1997 and the global case fatality rate was 23%[3].

The Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) is the modern world's greatest pandemic. At the end of 2003, the estimated number of adults and children living in the world with HIV/AIDS was 40 million[4] During 2003, 5 million people were newly infected with HIV and 3 million people died.
Sub-Saharan Africa bears the brunt of this global catastrophe. In 2003, it was home to an estimated 29 million people living with HIV/AIDS (70% of the global total). In that same year there were 3.5 million new infections in the region and 2.4 million AIDS related deaths, representing 77% of global AIDS deaths for that year. The most severely affected countries are in eastern and southern Africa.

The TB and HIV/AIDS epidemics overlap, particularly in sub-Saharan Africa. Of the 11.4 million adults estimated to be co-infected with HIV and *Mycobacterium tuberculosis* worldwide in 2000[2] 71% live in sub-Saharan Africa[5]. With an annual estimated TB incidence rate of 110 per 100, 000 population, this region currently has the highest TB incidence rate in the world[2]. The annual rate of increase of TB cases in this region is estimated at 6%[5]

In 2000, 12% of global TB deaths were attributable to HIV/AIDS, the figure being highest in the African region at 39%[5].

The interaction between HIV and tuberculosis.

TB accelerates the progression of HIV-related immune suppression and is one of the leading causes of death among people living with HIV/AIDS. The diagnosis of TB in HIV positive individuals is difficult, often leading to delays in diagnosis and treatment which in turn contributes to increased death rates[6-9].

Where HIV-TB co-infection occurs, HIV infection is the most important driving force behind the TB epidemic for a number of reasons; Firstly, HIV is the most powerful known risk factor for reactivation of latent MTB infection to active disease[10]. In persons infected with MTB

only, the risk of clinically significant disease within the first year after infection is approximately 1.5%, which thereafter decreases to a fairly stable risk of 0.1% or less per annum after 5 years[11, 12]. Conversely, in persons co-infected with *Mycobacterium tuberculosis* and HIV, the annual risk of active TB is between 5 – 15%, with the risk increasing as the immune system becomes more compromised[13-16] Secondly, in individuals who are HIV positive, there is a higher risk of rapid TB progression to active disease soon after infection with *Mycobacterium tuberculosis*[12]. Finally, HIV increases the rate of recurrent TB, which may be due to either endogenous reactivation (true relapse) or exogenous re-infection[17-21].

The strong link between HIV and TB has several implications for TB control. The main problems include:

Increase in TB case rates. Since the mid 1980's, TB case notification rates have risen up to 400% in many African countries including those with well-organized TB control programmes[22-28]. Many of these countries have TB case notification rates reaching peaks of more than 400 cases per 100,000 people. High TB rates increase the need for human and infrastructure resources in the health sector, the need for TB diagnostic facilities and case holding and enhance the risk of nosocomial TB transmission among patients and health staff[29-33].

Increasing HIV prevalence in TB patients and difficulties in diagnosis. In some countries in sub-Saharan Africa, up to 70% of TB patients are HIV positive[1,23] High HIV rates mean high rates of smear-negative pulmonary TB and extrapulmonary TB [25, 34-36]. Diagnosis of smear-negative pulmonary TB in particular poses diagnostic problems as chest X-rays become atypical with advanced immunodeficiency. For instance the chest X-ray may be normal in some patients with disseminated disease while other patients might be wrongly diagnosed as TB patients[37,38].

HIV-related morbidity and mortality. Countries with a high HIV prevalence have case fatality rates of up to 25% in smear-positive patients and 40-50% in smear negative pulmonary TB patients. A large proportion of these deaths take place early during the course of anti-TB treatment and 2-year survival is low[17,27, 39-43].
At the level of immune deficiency at which HIV-infected individuals develop TB, they are susceptible to a range of HIV-related diseases[44-46] such as bacterial infections, infection with *pneumocystisis carinnii* and toxoplasmosis, which contribute to the increased morbidity and mortality in this group. The impact of HIV on TB mortality is further addressed below under the sub section on the "Impact of HIV on mortality in tuberculoisis patients"

Higher risk of recurrence of TB. Recurrent TB is defined as a case of TB, which has started After a patient, has completed a full course of anti-TB treatment for previous tuberculosis[47]. The risk of recurrent TB is increased in HIV positive patients[17-21]. Increasing numbers of cases of recurrent TB add to the overall case burden that TB control programmes have to tackle. As the drug regimen for recurrent TB is more expensive, the overall costs of anti-TB treatment are increased. In addition, the drug regimen for re-treatment cases is more complicated[47]. Increasing recurrent TB rates challenges the credibility of TB control in the eyes of patients, the community and health staff.

Community perception of the link between TB and HIV. The general public has increasingly begun to associate TB with AIDS. In communities where HIV/AIDS related stigma is present, there could thus be a risk that TB suspects delay accessing health services for fear of being seen to have AIDS. Such delays increase the risk of TB transmission in the community and reduce the chances of a good outcome with anti-TB treatment[48,49].

The impact of HIV on mortality in tuberculosis patients in sub-Saharan Africa

Death rates in patients treated for TB in sub-Saharan Africa have increased in the last 10-15 years, the most important reason being concomitant HIV infection[46]
case fatality rates for all forms of TB are considerably higher in HIV-positive than HIV-negative TB patients and the death rates in the HIV positive group is the main contributing factor to overall TB mortality. The case fatality rates in HIV-positive TB patients and HIV-negative patients in a number of countries where data is available is estimated respectively at 32.5% and 8.95% in Burkina Faso[50], 16% and 8 % in Tanzania[51], 31.3% and 4.4% in Zaire[52] and 35% and 9% in Zambia[53].

Close to 40% of overall TB mortality is early mortality occurring within the first 2 months of anti-TB treatment [46]. In Nairobi, Kenya, nearly one third of the deaths in HIV-positive TB patients who were followed on anti-TB treatment for 6 months occurred during the first month of treatment[54]. In Zomba, Malawi, about half of all the deaths reported in HIV-positive TB patients during 12 months of follow-up occurred during the first month of treatment[44]. In Hlabisa, South Africa, the probability of death for both HIV-positive and HIV-negative patients was greatest during the first two weeks following the start of treatment[56]. These findings could to a certain extent be due to ascertainment bias when late mortality is partly included in the "defaulter" category and when defaulter rates are relatively high. However also in countries such as Malawi where defaulter rates are close to 1%, early mortality constitutes the large chunk of overall mortality.
High mortality during anti-TB treatment in sub-Saharan Africa challenge the credibility of TB control. In HIV-positive smear-positive pulmonary TB patients, the high death rates also mean that treatment is less cost effective in terms of years of life saved than previously calculated for HIV-negative patients[56]

There are several possible ways in which HIV adversely contributes to TB mortality. Firstly, the incidence of HIV related opportunistic infections is high and this contributes to increasing case fatality rates [57-59]. Secondly, biological interactions between HIV and *Mycobacterium tuberculosis* accelerate the course of HIV infection and enhance the suppression of cellular immunity, which is strongly associated with death. This coupled with difficulties in diagnosis particularly in smear negative pulmonary TB contributes to late initiation of treatment and higher case fatality rates[25, 34-38]. Even in the absence of HIV, the diagnosis of smear negative pulmonary TB can challenge the most experienced physicians. As rates of HIV rise, an increase in the proportion of pulmonary TB patients with negative sputum smears may be anticipated, due to the effects of increased immuno-suppression reducing pulmonary cavity formation and sputum bacillary load[38]. In a study in Malawi, that determined the causes of smear-negative pulmonary TB in 352 suspected pulmonary TB cases, 39% had TB confirmed on culture while 22% had other conditions mimicking TB while in 39% of suspects no firm

diagnosis could be made[38]. The use of bronchial lavage and culture improves detection of TB bacilli in those with a lower sputum bacillary load, but such investigations require sophisticated laboratory facilities and expertise which at the moment are beyond the reach of most TB control programs in resource-limited settings. The case fatality rates in smear-negative pulmonary TB in sub-Saharan Africa might thus be a mix of deaths from TB and other HIV related diseases misdiagnosed as TB.

Finally, sub-optimal TB management within health services is likely to contribute to an increased case fatality rates. In particular, HIV increases the demands on already over-stretched and under-resourced health services through increasing TB notification rates[29-33]. Reduced human resource capacity through HIV related deaths of health care workers and absence from work due to repeated illness and attendance at funerals is also a growing problem[60].

Little has so far been done to combat the high mortality observed amongst HIV-positive TB patients in Africa. There are three main options, which are not mutually exclusive.

a) Since HIV related opportunistic infections are known to be an important cause of the high morbidity and mortality experienced by HIV-positive TB patients, interventions to prevent these infections might improve survival[57-59].
Between 1995 and 1998, a cotrimoxazole–placebo controlled trial conducted in Cote d'Ivoire in HIV-positive smear-positive pulmonary TB patients showed a 48% reduction in deaths in the cotrimoxazole group[61]. The incidence of bacterial infections was also lower in the cotrimoxazole group. The results of this study were an important factor in persuading WHO/UNAIDS to issue provisional recommendations that cotrimoxazole be given to all patients in Africa living with AIDS which by definition includes HIV-positive patients with TB[62].
Despite the encouraging results from cote d'Ivoire, African countries are yet to implement cotrimoxazole prophylaxis for TB patients on a widespread national level. The concern is that, prevalence and resistance patterns of commonly occurring pathogens particularly *Steptococcus pneumoniae* and *Salmonella species* might be different from that in Cote d'Ivoire and this might effect the relative efficacy of the drug.
Although several African countries are considering cotrimoxazole prophylaxis for HIV positive TB patients, there is still a need for further evaluation of feasibility, efficacy and acceptability in different settings[63]. The prospect of cotrimoxazole prophylaxis is however of particular relevance in resource-limited settings as the drug is cheap, easy to administer and readily available.

b) Highly Active Antiretroviral Treatment has dramatically reduced mortality rates in HIV-infected patients in western countries[64,65] . There is now a growing positive commitment for treatment and resources are becoming available for antiretroviral treatment through the global Fund to fight AIDS, TB and Malaria (GFATM). World Health Organization has recently released guidelines for scaling-up antiretroviral treatment in resource-limited settings[66] which have included eligibility for HIV-positive TB patients.
However the current prospects for widespread use of highly active antiretroviral treatment in sub-Saharan Africa are faced with the challenge of insufficient human

resources for service delivery, weak health infrastructure, cost of drugs and concerns around adherence and safety particularly among TB patients. It is thus likely to be some time before highly active antiretroviral treatment becomes available on a widespread level within National TB control programs.

c) Reducing delays in diagnosis and treatment of TB through a combination of active case-finding, improved and increased resources for diagnosis and treatment of TB as well as HIV related opportunistic infections is likely to have an effect in reducing mortality.

Other consequences of HIV/AIDS and tuberculosis

The HIV/AIDS epidemic has an immediate effect on the *health sector*, increasing the demand for public and private health services and at the same time taking its toll on health personnel. For example, the share of hospital beds occupied by patients who are HIV-positive exceeds 50% in most Southern African countries. In order just to maintain the numbers of doctors and nurses, training would have to increase by 25 to 40 percent over the 2000-2010 period[67,68].
TB takes its toll on health service delivery in terms of financial, infrastructure and human resources needed for diagnosis, treatment and follow up. [69].

Socially, the number of AIDS orphans is increasing rapidly. By the year 2010, in some countries between 4.1% (Lesotho) and 7.9% (Swaziland) of the total population, or between 12 and 20% of the relevant age group will be under-aged orphans (0-14)[67]. The effects of a large proportion of orphans who do not have appropriate access to shelter, education and nutrition would have its own toll on social pathologies, urban migration, security and health. Individuals with TB are often too sick to work and thus lose income. This has an adverse impact on the education of family members such as the withdrawal of children from school. In many countries, TB is still associated with stigma and a diagnosis of TB is often associated with isolation, abandonment and in certain cases divorce particularly in women. These events have psychological and social costs both to affected individuals as well as the community.

Economically, HIV/AIDS has become the leading cause of mortality and the single most important contributor to the burden of disease among adults (15-59 years) worldwide in 2002. It is the leading cause of disease burden in males (7.4%) and the second in women (7.2%)[68]. AIDS affects the most productive age group, and thus teachers, health care workers, civil servants and the labor force in general. In countries like Botswana, Namibia, South Africa and Zimbabwe, the number of new teachers that require to be trained in order to replace those lost due to AIDS has increased by between 65 and 119 percent in 2000[67]. HIV/AIDS is projected to reduce economic growth in countries such as South Africa by 17% by 2010[67]. If such countries do not take effective measures to combat AIDS, there is likely to be complete economic collapse in 3 generations[68].
The costs of providing AIDS care including management of opportunistic infections, antiretroviral therapy and palliative care (at a modest antiretroviral coverage rate of 10%), will exceed one half of public health expenditure for some sub-Saharan African countries[67]

TB ranks high among causes of mortality and healthy life lost in adults (3rd among all causes worldwide)[68]. The disease affects the most productive and economically active segment of the population with 80% of victims being aged between 15 and 49 years. The cost borne by the patient often exceeds the costs to the health ministry. It is estimated that lost work-time and lost income from TB morbidity are 3-4 months and constitute at least 20% of annual household income. The potential cost of lost productivity due to TB is in the order of 4%-7% of Gross National Product [70] in high burden countries.

Framework for tuberculosis and HIV associated tuberculosis control

The overall aim of TB control is to reduce mortality, morbidity, and transmission. The main intervention is standardized combination chemotherapy for all identified sputum smear-positive TB patients who are the main sources of infection. The framework for effective TB control incorporates a global strategy known as DOTS[71] (Directly Observed Treatment Short-course) The five components of this strategy include:

1. Sustained political commitment
2. Access to quality-assured TB sputum microscopy services
3. Provision of standardised short-course chemotherapy for all cases of TB
4. Uninterrupted supply of quality assured drugs and
5. Standardised recording and reporting system.

The global targets for TB control, adopted by the World Health Assembly in 1991, were to cure 85% of newly detected cases of sputum smear-positive pulmonary TB and to detect 70% of the estimated smear-positive pulmonary TB cases by the year 2000. By 1997, it became apparent that these targets could not be met, and at the World Health Assembly in May 2000 they were postponed to 2005[72].

Due to the strong link between HIV and TB, TB and HIV programmes share mutual concerns: prevention of HIV should be a priority for TB control and TB care and prevention should be a priority for HIV/AIDS programmes. Whereas previously TB programmes and HIV/AIDS programmes have largely pursued separate courses, they need to exploit synergies in supporting health service providers to deliver joint TB-HIV interventions. At the service delivery level, reciprocal synergies exist between different service providers e.g. HIV-positive clients who undergo voluntary counseling and HIV testing have a high rate of TB (and could therefore benefit from TB screening and treatment) and TB patients have a high rate of HIV (and therefore could benefit from voluntary counseling and HIV testing and associated services). Establishing collaborative TB and HIV programme activities will require increased funding and efficiency, increased general health service capacity to deliver interventions (human resources, infrastructure and commodities) and effective coordination of activities on the part of the many role players often involved.
Up to now the efforts to control TB among HIV-infected people have mainly focused on implementing the DOTS strategy for TB control i.e. identifying and curing infectious TB cases among patients presenting to general health services; This targets the final step in the sequence of events by which HIV fuels TB, namely the transmission of *Mycobacterium tuberculosis* infection by infectious TB cases.

The expanded scope of the new strategic framework for TB control in high HIV prevalent populations consists of interventions against tuberculosis (intensified case-finding and cure and TB preventive treatment) as well as additional interventions against HIV (and therefore indirectly against TB) e.g. promotion of condom use, provision of sexually transmitted infection, and antiretroviral treatments[73,74]. (**Table 1**)

Table 1: Interventions to control TB in high HIV prevalent populations.

Full Implementation of the DOTS Strategy **Additional Interventions beyond Effective case finding and treatment**	
Interventions directly against TB	**Interventions against HIV (and therefore indirectly against TB)**
Through TB case detection and treatment: Intensified TB case finding in high-risk groups:- - HIV-positive VCT clients - Intravenous drug users - Patients with STIs - PLHA support groups - Home based care patients - Prisoners - Household contacts of TB patients **Through prevention of new TB cases** Isoniazid preventive treatment for PLHA - Treatment to prevent a first ever episode of TB - Treatment to prevent a recurrent episode of TB	**By preventing HIV transmission** - Condom promotion - Treatment of STIs - Voluntary counseling and HIV testing - Safe injecting drug use - Sexual behavioral changes - Prevention of mother to child transmission of HIV - Safe blood - Universal precautions by health care workers - Targeted interventions to high risk locations, e.g. brothels - IEC activities - Life skills - Antiretroviral treatment **By increasing immune function in PLHA** - Antiretroviral treatment
By providing care for PLHA - Treatment of HIV related diseases (infections and tumors) - Prevention of HIV-related infections - Psycho-social support - Palliative care - Nutritional support	

Adapted from the WHO Guidelines for implementing collaborative TB and HIV programme activities[73,74]

Abbreviations: STI – sexually transmitted infection; PLHA – people living with HIV; IEC – information, education and communication; VCT – voluntary counseling and HIV testing

Operational research questions on HIV-TB in sub-Saharan Africa

Operational research questions linked to HIV-TB include those related to prevention and treatment of HIV related opportunistic infections in TB patients, administration of highly active anti-retroviral treatment and its effects on TB mortality, enhancing early diagnosis and treatment of TB and questions around preventing TB in HIV positive individuals.

Specific questions include:

- What are possible reasons for mortality including early mortality in HIV-positive TB patients?
- Are pathogens causing deaths in HIV-positive TB patients susceptible to cotrimoxazole. Are these pathogens the same as those isolated in Cote d'Ivoire?. How would varying resistance profiles to cotrimoxazole in commonly occurring pathogens particularly *Streptococcus pneumoniae* and *Salmonella species* affect drug efficacy?
- Is it feasible to introduce voluntary counseling, HIV testing and cotrimoxazole prophylaxis within routine program conditions? Is the drug associated with a low rate of adverse side effects or in other words is it a "safe drug" to be made available to TB patients under routine programme conditions? Will introducing cotrimoxazole for HIV positive TB patients reduce overall death rates in a TB control program?
- Will TB patients be compliant with cotrimoxazole prophylaxis during the course of anti-TB treatment? Will these patients still continue being compliant on cotrimoxazole after completing anti-TB treatment at which time the administration of cotrimoxazole is in principle no longer the direct responsibility of the TB control program?
- Does resistance increase with long-term administration of cotrimoxazole prophylaxis?
- Is it feasible to offer highly active anti-retroviral treatment to HIV-positive TB patients and will this intervention reduce mortality rates during anti-TB treatment? What will be the effects of joint administration of anti-TB drugs and anti-retroviral drugs in terms of incidence of side effects and patient management?
- How can TB be diagnosed and treated earlier in high-risk groups e.g. household contacts of index TB cases, HIV positive voluntary counseling and testing clients? Can the diagnosis of smear-negative PTB be improved in resource-limited settings?
- Is it feasible to offer isoniazid preventive treatment to HIV positive voluntary counseling and HIV testing clients and is it possible to ensure high adherence to the regimen?

EPIDEMIOLOGY AND CONTROL OF SEXUALLY TRANSMITTED INFECTIONS

Sexually transmitted infections in sub-Saharan Africa

Burden of sexually transmitted infections

Sexually transmitted infections rank among the top five categories for which adults in developing countries seek health services[75,76]. The most common curable sexually transmitted infgections include gonorrhoea, chlamydial infection, syphilis, trichomoniasis, chancroid, lymphogranuloma venereum and donovanosis. The incurable but preventable sexually transmitted infections include the human immunodeficiency virus (HIV), human papilloma virus, hepatitis B virus, and herpes simplex virus.

The world health organization estimates that 340 million new cases of curable sexually transmitted infections occurred world wide in 1999[76]. This included 12 million new cases of syphilis, 62 new cases of gonorrhoea, 92 new cases of chlamydial infection and 174 million new cases of trichomoniasis. One in four of all these new cases (69 million) occurred in sub-Saharan Africa. This region of Africa also bears the largest burden in terms of the yearly incidence of curable sexually transmitted infections among the 15 to 49 year olds which is estimated at 11-35%[76]. In addition to curable sexually transmitted infections, out of a global total of about 40 million people living with HIV/AIDS in 2003, 29 million (70% of the global total) were living in sub-Saharan Africa.

The interaction between sexually transmitted infections and HIV/AIDS

The interaction of sexually transmitted infections with HIV is complex with the possibility of reciprocal influences on susceptibility, infectiousness and the natural history of infections[77]. Both ulcerative disease and non-ulcerative sexually transmitted infections enhance HIV transmission[77-79].
This interaction between sexually transmitted infections and HIV is bi-directional. 1) sexually transmitted infections increase the susceptibility of a person to get infected with HIV and 2) sexually transmitted infections increase the infectiousness of HIV-infected persons.

Sexually transmitted infections increase the susceptibility of a person to get infected with HIV.
Sexually transmitted infections increase HIV susceptibility by disruption of mucosal tissues, increasing the number of CD4 lymphocytes (the target cell for HIV) and the number of receptors per cell[81-84]. For instance, in women who have gonnorhoea or chlamydial infection, there is a disproportionate increase in the number of CD4 lymphocytes in the endocervix[81].

Sexually transmitted infections increase the infectiousness of HIV-infected persons.
Sexual transmission of HIV depends to a great extent on the inoculum of the virus. The shedding of HIV in genital fluids is increased by sexually transmitted infection related

inflammatory responses and exudates from lesions, making men and women who have a sexually transmitted infection and are HIV positive more infective[85-87].
In a study in Malawi, HIV-1 positive patients with urethritis had an eight-fold increase in the secretion of HIV-1 RNA in semen compared with a control group[88]. In Abidjan, Cote d'Ivoire, a significant increase in the detection of HIV-1 DNA in cervico-vaginal lavage samples from patients with gonorrhoea, chlamydia, cervico-vaginal ulcer, or cervical mucopus was found[87]. A week after sexually transmitted infection treatment, the detection of HIV-1 in these secretions decreased from 42% to 21%. Such changes in detection rate were not observed in women whose sexually transmitted infections were not cured[90]. Treatment of sexually transmitted infections thus affect the biological interaction between these infections and HIV by reducing the shedding of HIV. In addition, HIV-1 vaginal shedding was significantly associated with HSV-2 shedding[90].

Sexually transmitted infection treatment as a way of reducing the probability of HIV transmission.

In order to quantify the effect of sexually transmitted infection treatment at a population level, three community levels randomized controlled intervention trials have been conducted in Africa[91-93].
In Mwanza district of rural Tanzania, treating sexually transmitted infection symptomatic individuals using the syndromic approach reduced HIV incidence in the study population by 42%[91].
In Rakai, Uganda, the intervention involved directly observed mass treatment for curable sexually transmitted infections at 10 month intervals. After 3 mass treatment rounds that spanned 20 months, HIV incidence was similar in the intervention and control communities[92].
A third trial was conducted in Masaka, rural Uganda[93], where all adults living in 18 communities were randomly allocated to receive behavioral interventions alone (Group A), behavioral and sexually transmitted infection interventions (Group B), or routine government health services and community development activities (Group C). After a median follow-up of 3.6 years, it was not possible to show a measurable reduction in HIV-1 incidence. There was evidence in group A of reduced HSV-2[93].
Although superficially, the results of these three landmark trials may appear contradictory[94-95], in fact the 3 studies tested different interventions in different HIV-1 epidemic settings and the divergent results may be complementary rather than contradictory.

The results from the Rakai trial suggest that intermittent mass treatment for sexually transmitted infection alone, offered to the general population is not an effective strategy to prevent HIV infection. This divergent result with regard to the Mwanza trial might be explained by a number of reasons. First, sexually transmitted infection co-factors in HIV transmission may play a larger role in early concentrated HIV epidemics as in Mwanza than in mature epidemics such as in Rakai. This is because early, in HIV epidemics infections take place primarily in core groups of highly sexually active individuals, who have high rates of sexually transmitted infections. Later on, more HIV transmissions occur in stable relationships with lower sexually transmitted infection exposure. Second, as a result of selective HIV-attributable mortality among high-risk individuals, STI prevalence's decline during the evolution of the epidemic with time. Third, the prevalence of incurable sexually transmitted infections particularly herpes simplex type 2 (HSV-2) is higher in sub-Saharan Africa and this enhances HIV transmission. Since no effective treatment for HSV-2 was provided in the Rakai

study, the likely effect of the sexually transmitted infection intervention on HIV transmission is further reduced[93].
Finally, Uganda has experienced a reduction in sexual risk-behavior. This causes a fall in the prevalence of short-duration sexually transmitted infection which in turn will reduce the importance of these curable sexually transmitted infection on HIV transmission.
On of the hypothesis to explain the results of the Masaka trail was that the population attributable fraction of new cases of HIV-1 due to sexually transmitted infection was lower than that in the Mwanza trial. Such an association could have been compounded by the importance of HSV-2 as a cause of genital ulcers. As in the Rakai trial, HSV-2 was a much more common infection than syphilis. Since no effective treatment for HSV-2 was provided, the likely effect of the sexually transmitted infection intervention is further reduced[93].
Since intervention clinics also promoted condom use, there might have been an effect of behavioural change associated with increased condom use.

The extensive observational data however leaves little doubt that sexually transmitted infection facilitate HIV transmission through direct biological mechanisms and sexually transmitted infection control remains an integral part of HIV/AIDS control. Sexually transmitted infection control is a good idea by itself due to its potential contribution to HIV prevention, even if its population impact is uncertain.

Consequences of sexually transmitted infections.

The main consequences of sexually transmitted infections include health, social and economic consequences. The ***health consequences*** of sexually transmitted infections other than HIV/AIDS includes pelvic inflammatory disease , urethral strictures, adverse pregnancy and neonatal outcomes and cervical cancer.
Pelvic inflammatory disease is often the most common cause of admission to gynecological wards in developing countries[96]. Direct sequel of pelvic inflammatory disease includes infertility, ectopic pregnancy with subsequent maternal mortality, chronic pelvic pain and discomfort, risk of repeated infections and hysterectomy[97]. In Africa pelvic inflammatory disease associated infertility accounts for 50-80% of all causes of infertility[97,98].
Urethral stricture occurs in one out of every seven males with gonorrhea and often requires urological intervention in order to prevent further complications caused by restricted urine flow. Gonnorhoea and *Chlamydia trachomatis* causes morbidity both in the Mother and in the newborn[99]. Vertical transmission occurs in 30-50% of infants whose Mothers are infected with *N.gonorrhoea* and if untreated, gonococcal opthalmia neonatorum, leads to blindness[100]
Syphilis caused by *Treponema pallidum* can cross the placental barrier, infect the fetus and cause congenital malformations[100,101]. In developing countries where routine screening programs for early detection of cervical cancer are limited or nonexistent[102-104], this cancer (attributable to the human papilloma virus) is the second most important cause of cancer-related mortality among women.

Socially, consequences of sexually transmitted infections such as infertility may be associated with abusive behavior and divorce. Particularly, in African society, infertility is often associated with complex social interactions. In Tanzania for instance, a husband can return an infertile woman to her parents and ask for a return of the bride price[105].

Economically, sexually transmitted infections (other than HIV/AIDS) account for 0.5% of the global disease burden in adult men and 1% of the burden in women[68]. Using sophisticated diagnostic techniques the cost of diagnostics can exceed the per capita national healthcare budgets of many low-income countries[101].

Framework for sexually transmitted infection control.

The rate of spread of sexually transmitted infection's including HIV, is determined by three factors: 1) the average rate of exposure of susceptible people to infected individuals. 2) the average probability that an exposed susceptible person will acquire the infection (the "mean efficiency of transmission") and 3) the average time that newly infected persons remain infectious and continue spreading infection. In terms of a mathematical model[106], this relationship can be expressed as $R_0 = c \times \beta \times D$ where R_0 (the basic reproduction number) is the number of secondary cases of STI arising from an "average" new case in a totally susceptible population. c represents the "effective mean rate of sexual partner change" within a population, β is the mean efficiency of transmission per exposure and D is the mean duration of infectiousness after acquisition of a new infection. In the presence of considerable heterogeneity in the rate of partner change, the "average" is strongly influenced by core groups (such as sex workers and their clients].
The principles of interventions for control of STI's within a population thus depend on:

1) *Reducing the rate of exposure to sexually transmitted infections.* This can be achieved by lowering the rate of partner exchange (fewer sex partners) and avoiding risky partners and sexual networks
2) *Reducing the efficiency of transmission.* The main stay of this intervention involves use of condoms. Microbicidal agents (alone or combined with spermicides) that could be administered vaginally before sexual intercourse to kill sexually transmitted infection pathogens and HIV also reduce the efficiency of transmission. Promoting safer traditional sexual practices that involves a modification of traditional practices that increase the efficiency of transmission is part of this strategy.
3) *Shortening the duration of infectiousness.* The main interventions in this respect include providing accessible and acceptable services for detection, and treatment of sexually transmitted infections. This will reduce population prevalence of infection, Early diagnosis and treatment of sexually transmitted infections, avoiding sex or using condoms until cured and assisting partner notification and treatment are important aspects of individual case management.

   For HIV infection and most other viral sexually transmitted infections, therapy has not been yet been clearly shown to shorten the duration of infectiousness. Thus, interventions currently target the rate of exposure and the efficiency of transmission.

Sexually transmitted infection - syndromic management

Most developing countries have adopted the syndromic approach for sexually transmitted infection management as recommended by the world health organization [107]. The

syndromic approach of treating sexually transmitted infections is based on identifying a syndrome – a group of symptoms and easily recognized signs associated with a number of well-defined etiologies. Once a syndrome has been identified, treatment can be provided for the majority of the organisms responsible for that syndrome.
The syndromic approach is particularly useful in developing countries where laboratory facilities for diagnosis are often unavailable and human resource skills limited. The approach allows same day treatment and avoids the need for repeated visits by the patient.
Sexually transmitted infection syndromes can be managed easily and rapidly using clinical flowcharts (also known as algorithms or decision trees) for diagnosis and treatment. The world health organization recommends that national sexually transmitted infection control programs incorporate diagnostic and therapeutic flow charts into their management guidelines[107].
There are many advantages of using flow charts. First, it rationalizes and standardizes diagnosis, treatment and referral. Second, data collection and analysis is simplified which in turn facilitates surveillance, planning (such as the purchase of drugs/supplies) and training. Finally, standardization of treatment delays the development of anti-microbial resistance of sexually transmitted organisms.

One of the main disadvantages of the syndromic approach is that the strategy does little to diagnose asymptomatic infections and diminish the sub clinical sexually transmitted infection pool. In women, symptoms are poorly predictive for vaginal discharge[108,109].

Interventions in core groups such as commercial sex workers

Those individuals with the highest rates of partner change, epidemiologically referred to as "core groups" (such as commercial sex workers) disproportionately increase the rate of spread of sexually transmitted infection within a population. Infection spreads fastest among such dense sexual networks which have sexual links between many people over a short period of time.
Commercial sex workers in developing countries are particularly vulnerable to sexually transmitted infections and HIV infection. Because of high infection rates and large numbers of sexual partners, sex workers are considered a core group or "high frequency transmitters". Targeted interventions[110] in this group could thus have considerable effect in slowing the spread of the HIV epidemic at a relatively low cost[111]

During a female sex worker intervention in South Africa, including monthly presumptive treatment of bacterial sexually transmitted infection, gonococcal and chlamydial rates decreased from 25% to 10% and from 11% to 6% respectively. Genital ulcer prevalence decreased from 10% to 4% among female sex workers and from 6% to 1% among miners[112]. In Thailand where 100% condom use was promoted in brothels, there was a marked reduction in the rates of sexually transmitted infection[111]. A similar targeted intervention among commercial sex workers in Abidjan showed a decline in HIV and sexually transmitted infection prevalence[114].

Operational research questions on sexually transmitted infections control in sub-Saharan Africa.

Sexually transmitted infection control is an integral part of AIDS control. Sexually transmitted infection control requires a thorough understanding of specific sexually transmitted infection prevalence in different population groups, the efficacy of antibiotic regimens used in the sexually transmitted infection syndromic management and sexual and health seeking behavior among patients with sexually transmitted infections including core groups. Specific questions on STI/HIV/AIDS control include:

- What is the prevalence of pathogens causing sexually transmitted infections in men and women. For those that are treatable, what are their drug sensitivity patterns? Is the prevalence different in rural and urban areas?
- What is the health seeking and sexual behavior of men who contract sexually transmitted infections? How can delays in diagnosis and effective treatment be limited?
- Can alternative care providers be included in sexually transmitted infection control strategies and how can collaboration with these groups be enhanced?
- What is the prevalence and pattern of sexually transmitted infections among core groups such as commercial sex workers? Among commercial sex workers who have such infections (and those that do not), what proportion use condoms "always"? Are there factors that are associated with "no condom use" in this high risk group?
- What is the prevalence, incidence and pattern of sexually transmitted infections among prison inmates?
- How can partner notification and treatment be improved?
- Is it feasible to integrate routine screening of sexually transmitted infections at sites where HIV and TB screening is done?

Setting of the studies: Malawi - country profile.

The republic of Malawi is located in Southeast Africa, landlocked by Mozambique on the Southeast, Tanzania in the North and Zambia in the west (Figure 1)
Its 118,480 sq. km area takes the shape of a narrow elongated plateau with rolling plains, rounded hills, and mountains in the south and the north. Twenty percent of the area is occupied by lakes (Figure 2).

There are three main administrative regions (North, Central, South) which are divided into 25 districts. Districts are further divided into 202 traditional authorities headed by a traditional chief.
The population in 1999 was estimated at 10,640,000[115]. Malawi is one of the most densely populated countries in Africa with 105 persons per km^2. It is one of Africa's poorest countries with 65% of the population living under the poverty line[116].

Malawi is one of the few African countries in which both the allopathic and traditional sectors of health are officially recognized. The latter are thought to play an important part in health delivery because of their geographic and cultural accessibility. The traditional sector is particularly known for its traditional birth attendants and traditional healers who are licensed by government.

Malawi has very poor health indictors (Table 1). Life expectancy at birth is 41 years: 23% of children die before they reach the age of 5 years; and nearly 6 out of every 1,000 women die in childbirth. The main human development and health indicators for Malawi are shown in table 1.

Table 1: Human development and health indicators – Malawi (2002)

Surface Area	118,480 Square kilometers
No of districts	25
Traditional authorities	202
Population	10,640,000
Population growth rate	2.4%
Population below poverty line	65%
GDP (USD)	8.9 billion
Literacy rate (Total/Male/Female)	56%/72%/42%
Health expenditure (per capita)	10 USD.
UNDP human development index.	No. 161 of 192 countries.
Life expectancy at birth	41 years
Crude birth rate	47/1000 population
Crude death rate	22/1000 population
Maternal mortality rate	620/100,000 population
Under 5 mortality rate	234/1000 live births
Infant mortality rate	140/1000 live births.
Total fertility rate	6.8 children/woman

Figure 1. Map showing Malawi in Africa

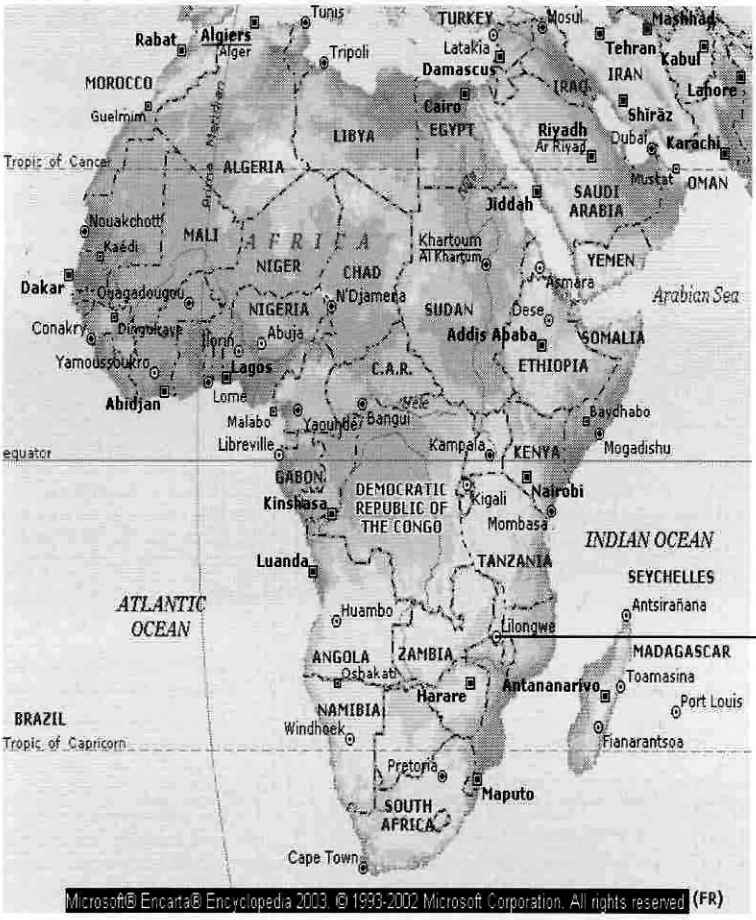
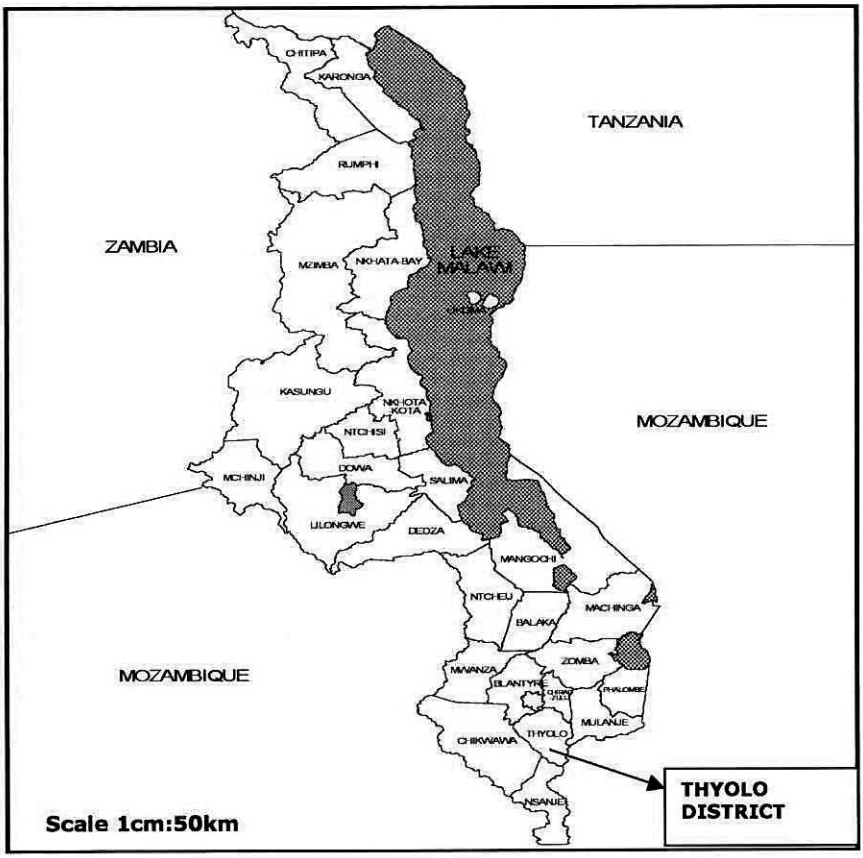


Figure 2.Map of Malawi.



HIV/AIDS and tuberculosis in Malawi

HIV/AIDS

Malawi has one of the highest levels of HIV infection in the world. In 2003, out of a population of about 10.5 million, there were an estimated 900,000 people living with HIV and AIDS. In the same year, there were an estimated 87,000 deaths due to AIDS in the most productive age group (15-49 years). The HIV prevalence in this age group is estimated at 14.4%[117]. Among antenatal women tested, HIV seroprevalence rates varied from 4% to 36% in various sentinel sites, were higher in the south than the north, and were higher in urban and semi-urban sites than in rural sites.

The cumulative number of AIDS orphans (children who have lost their Mother or Father or both parents to AIDS and who were alive and under 15 years at the end of 2001) is approximately 400,000, with more than 60,000 being added to this pool each year.
The impact of the epidemic on bed occupancy rates in hospitals is dramatic. In a recent study carried out in Blantyre, 70% of medical patients admitted to hospital wards were HIV positive and 45% had AIDS[118]. 68% of all deaths in hospital were related to TB, AIDS or severe bacterial infections.

HIV-TB epidemic

The HIV epidemic has fuelled a severe secondary epidemic of TB. TB case notifications have risen by 250-300% between 1987 and 2001[119] (Table 2).
HIV prevalence in TB patients has also shown a rising trend at different individual sites in the country. This increased from 26% in 1986[120] to 52% in 1888[121], to 67% in 1991[122]. In 2000, a countrywide survey of TB patients found an HIV-seroprevalence rate of 77%[123].
High rates of HIV infection have also led to increasing numbers of patients with "difficult to diagnose" smear-negative pulmonary TB and extra pulmonary TB, an increasing case fatality rate in patients with all types of TB and an increasing rate of recurrent disease.
Treatment outcomes have been monitored in patients (new and relapse) with smear-positive PTB since 1984. Initially cure rates were high (between 85 – 90%), and then began to decrease in the 1990s. In the last ten years, cure rates have remained between 63 - 69%.
In Malawi treatment completion, default and transfer out rates have been less than 10%. Treatment failure rates have also remained low at 1%, signifying a low rate of drug-resistant TB. Death rates have however risen from 10% in 1990 to above 20% from 1996 onwards. In 1998 the country had the highest death rates among TB cases being treated in Africa[124]. Deaths within the first 2 months (early mortality) contributes up to 40% of overall TB mortality in Malawi[125]. With such high death rates that are attributed to HIV, it is impossible for Malawi to reach its World Health Organization targets of a cure rate of 85%.

Interventions to reduce the high current death rate is a major priority for the national TB control programme. Such interventions which will have to be incorporated into the diagnosis and management of TB should at least include: the diagnosis and treatment of HIV-related diseases, prevention of opportunistic infections using adjunctive cotrimoxazole and restoration of immunity using antiretroviral therapy. Voluntary counseling and HIV-testing would have to be offered to all TB patients as an "entry-door" to such interventions.

Table 2: TB case notification rates between 1987 and 2001

Year	No. TB cases	TB cases/100,000 population
1987	7,581	95
1989	9,431	140
1991	14,443	155
1993	17,105	172
1995	19,155	180
1997	20,676	181
1999	24,396	211
2001	27,672	265

Sexually transmitted infections in Malawi

In Lilongwe, 4.4% of all patients presenting to the outpatient department have a sexually transmitted infection[124] and HIV seropositivity rates in male patients with sexually transmitted infections range between 53–62% [126-128]. 83% of female clients with sexually transmitted infections are estimated to be HIV seropositive[126].

In 2001, the national average for syphilis prevalence was 3.9%[129]. At Queen Elizabeth Central hospital in Blantyre, the prevalence of a symptomatic sexually transmitted infection among antenatal clinic attendees was as follows: gonorrhoea 5%, chlamydia 3%, trichomonas 32%, syphilis 13% and genital ulcers other than those attributed to syphilis was 7%[130]. Malawi adopted the syndrome-based approach to the management of STIs as recommended by the World Health Organization in 1993[131]. The antibiotic regimens were selected on the basis of clinical efficacy, in-vitro studies and cost considerations.

Thyolo - district profile

Thyolo district is the site in Malawi where the studies presented in this thesis were conducted. The district lies in the South of Malawi (Figure 1) and has a surface area of 1715 sq km. The district has an estimated population of 472,643. Approximately 70% of the inhabitants are illiterate and 80% of all the income is from the agricultural sector (tea and coffee plantations). During the planting and harvest seasons, laborers working on tea and coffee plantations are required to move between different estates (migrant labor)

The district has 2 main hospitals, one of which is a public reference hospital (the Thyolo district hospital) and the other is a private Mission hospital (the Malamulo hospital). There are 16 health centers and 6 maternities[5].
The Government District Health Officer is charged with the provision of services in all government units, and supervision of all health providers and programmes in the District.
Thyolo district is well known for its semi-urban towns and their HIV risk arenas of lively rest houses, nightclubs, bars and readily available and inexpensive commercial sex workers. The large tea and coffee plantations as well as the thousands of migrant laborers patronize the commercial sex industry.

In 2001, the HIV prevalence among pregnant mothers attending antenatal care consultations in Thyolo was estimated at 16.9%[129] against a national average of 19.5%. Syphilis prevalence in the same year was estimated at 10.9% against an estimated national average of 3.9%[129].
In 2002, HIV prevalence in TB patients in Thyolo was estimated at 77%[122],which was the same as the National average[123].
In Blantyre (a city 35 km from Thyolo), 70% of patients with sexually transmitted infections and 40-55% of patients with a sexually transmitted infection in semi-urban areas were estimated to be HIV positive in 1995[133]. Among commercial sex workers in Blantyre, the HIV prevalence rate is estimated to be 70%[135]. HIV prevalence among patients with sexually transmitted infections and commercial sex workers in Thyolo is unknown.

Outlay of this thesis

This thesis describes operational research conducted in Thyolo district in rural southern Malawi.
The first part which includes Chapters 2 to 6, covers research studies on TB mortality and cotrimoxazole prophylaxis for HIV-positive TB patients (TB-HIV). Chapter 2 assesses the feasibility and effectiveness of offering a package of voluntary counseling and HIV testing and adjunctive cotrimoxazole to reduce death rates among HIV positive TB patients. Chapters 3 and 4 include verification of compliance with cotrimoxazole prophylaxis in HIV-infected TB patients *during* and *after* anti-TB treatment respectively. Chapter 5 determines changes in *Escherichia coli* resistance to cotrimoxazole in TB patients and in relation to cotrimoxazole prophylaxis. The final chapter of this part assesses moderate to severe malnutrition in TB patients as a risk factor for early TB deaths.

The second part includes Chapters 7 to 10 and covers research linked to sexually tranmitted infection and HIV control. Chapter 7 is an assessment of the prevalence of *Chlamydia trachomatis* and antibiotic susceptibility of *Neisseria gonorrhoeae* in men with urethral discharge and their behavioral characteristics. Chapter 8 looks at the prevalence of sexually transmitted infections among a core group namely commercial sex workers. The incidence, prevalence and patterns of sexually transmitted infections among male prison inmates is covered in chapter 9. The last chapter of this part (chapter 10) determines HIV prevalence and socio-demographic risk factors associated with HIV infection in the rural setting. It also looks at offering voluntary counseling and HIV testing for blood donors as a possible entry point for broader prevention and care strategies related to HIV and sexually transmitted infections.

Chapter 11 covers a general discussion on some of the principal findings, implications of these studies on policy and practice in Malawi, and areas for further research.

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CHAPTER 2

Voluntary counseling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi.
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Voluntary counselling, HIV testing and adjunctive cotrimoxazole reduces mortality in tuberculosis patients in Thyolo, Malawi

Rony Zachariah, Marie-Paule L. Spielmann, Christina Chinji[a], Patrick Gomani[b,e], Victor Arendt[c], Nicola J. Hargreaves[d,e], Felix M. Salaniponi[e] and Anthony D. Harries[e]

Objectives: To assess the feasibility and effectiveness of voluntary counselling, HIV testing and adjunctive cotrimoxazole in reducing mortality in a cohort of tuberculosis (TB) patients registered under routine programme conditions in a rural district of Malawi.

Design: 'Before' and 'after' cohort study using historical controls.

Methods: Between 1 July 1999 and 30 June 2000 all TB patients were started on standardized anti-TB treatment, and offered voluntary counselling and HIV testing (VCT). Those found to be HIV-positive were offered cotrimoxazole at a dose of 480 mg twice daily, provided there were no contraindications. Side-effects were monitored clinically. End-of-treatment outcomes in this cohort (intervention group) were compared with a cohort registered between 1 July 1998 and 30 June 1999 in whom VCT and cotrimoxazole was not offered (control group).

Findings: A total of 1986 patients was registered in the study: 1061 in the intervention group and 925 in the control cohort. In the intervention group, 1019 (96%) patients were counselled pre-test, 964 (91%) underwent HIV testing and 938 (88%) were counselled post-test. The overall HIV-seroprevalence rate was 77%. A total of 693 patients were given cotrimoxazole of whom 14 (2%) manifested minor dermatological reactions. The adjusted relative risk of death in the intervention group compared with the control group was 0.81 ($P < 0.001$). The number needed to treat with VCT and adjunctive cotrimoxazole to prevent one death during anti-TB treatment was 12.5.

Interpretation: This study shows that VCT and adjunctive cotrimoxazole is feasible, safe and reduces mortality rates in TB patients under routine programme conditions.

Keywords: HIV, tuberculosis, sub-Saharan Africa, voluntary counselling and HIV testing, cotrimoxazole

Introduction

Death rates in patients treated for tuberculosis (TB) in sub-Saharan Africa have risen in the last 10–15 years, the most important reason being concomitant HIV infection [1]. Between 20 and 30% of HIV-infected

From the Medecins Sans Frontieres-Luxembourg, Blantyre, [a]Thyolo District Health Services, Ministry of Health and Population, [b]Malamulo Mission Hospital, Thyolo District, Malawi, [c]Infectious Disease Reference Centre, Central Hospital, Luxembourg, [d]Liverpool School of Tropical Medicine, UK, and the [e]National Tuberculosis Control Programme, Ministry of Health and Population, Malawi.

Correspondence to Dr Rony Zachariah, Medecins sans Frontieres, Medical Department (Operational Research), 70 Rue de Gasperich, L-1617, Gasperich, Luxembourg. Fax: +352 335133; e-mail: zachariah@internet.Lu.

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patients with smear-positive pulmonary TB (PTB) die within 12 months of starting treatment, with even higher death rates reported in those with smear-negative PTB and extrapulmonary TB (EPTB) [1].

Infections are an important cause of the high morbidity and mortality experienced by HIV-positive TB patients during treatment [2–4], and it is believed that interventions to prevent these infections might improve survival. Between 1995 and 1998, a cotrimoxazole (sulphamethoxazole trimethoprim five/one) placebo controlled trial in HIV-positive smear-positive PTB patients in Cote d'Ivoire showed a 48% reduction in deaths in the cotrimoxazole group [5]. The results of this study were an important factor in persuading WHO/UNAIDS to issue provisional recommendations that cotrimoxazole be given to all patients in Africa living with AIDS (by definition this includes HIV-positive patients with TB) [6].

Malawi, a small country in central-southern Africa, is currently experiencing a severe epidemic of HIV infection, linked to which is a twin epidemic of TB. In 2000, a countrywide survey found that 77% of new patients registered with TB were HIV-seropositive [7]. The National Tuberculosis Control Programme (NTP) has reported rising death rates in new patients with smear-positive PTB, and in 1998 the country had the highest death rates reported in Africa [8]. Despite the encouraging results from Cote d'Ivoire, it is uncertain whether cotrimoxazole will have the same efficacy in Malawi because of differing resistance profiles of commonly occurring pathogens [9]. The NTP in consultation with the Ministry of Health and Population concluded that there needed to be more evidence to support a policy of widespread implementation of adjunctive cotrimoxazole for patients with AIDS, including those with TB.

The recommendations from WHO/UNAIDS [6] have made it difficult to ethically justify further efficacy studies using placebo controls. A district initiative was therefore planned with the aim of assessing the feasibility and effectiveness of voluntary counselling, HIV testing and adjunctive treatment with cotrimoxazole in reducing death rates in TB patients, who are registered and treated under routine conditions. The objectives of the study were: (i) to assess the feasibility of introducing voluntary counselling and HIV testing (VCT) within a TB control programme setting; (ii) to determine whether adjunctive cotrimoxazole is safe; (iii) to measure death rates in a cohort of patients offered the package of VCT followed by adjunctive cotrimoxazole to those who were HIV-seropositive (intervention group); and (iv) to compare results with those obtained in a cohort of patients registered for TB in the previous year when no VCT or cotrimoxazole was offered (control group).

Methods

Setting and study design

The study was carried out in Thyolo District, in Southern Malawi, with a population of 650 000. The district has one government hospital, a mission hospital, and 18 health centres which are involved in TB control activities. The design was a 'before' and 'after' cohort study measuring end-of-treatment death rates in a group of TB patients offered an intervention package compared with historical controls who were not offered the intervention package in the previous year.

Diagnosis, registration and treatment of patients with TB

The same standardized methods of diagnosing, registering and treating patients with TB were used for the intervention and control groups. Diagnosis, registration and treatment of TB was carried out according to National guidelines [10]. The different anti-TB treatment regimens and their indications are shown in Table 1. The initial phase of treatment was always administered in hospital, and the continuation phase in the community.

Integrated voluntary counselling and testing services

In order to set-up voluntary counselling and HIV testing services, a new counselling unit (comprising a reception room, two counselling rooms and a waiting area) was constructed. Four full-time counsellors and an additional laboratory technician were also employed. The necessary consumables for performing rapid HIV tests were made available on a continuing basis.

Study populations

Intervention group

Between 1 July 1999 and 30 June 2000, all TB patients who were registered in Thyolo district, at either the government hospital or the mission hospital, were enrolled into the VCT and adjunctive cotrimoxazole treatment study. This cohort of patients was known as the 'intervention group'. All patients were registered and started on standardized anti-tuberculosis treatment, and referred to the hospital HIV-voluntary counselling and testing unit. Patients were offered pre-test counselling, and those who accepted HIV testing were offered post-test counselling. All blood samples were screened for HIV-1 and HIV-2 using a combination of the Capillus (Cambridge Diagnostics Ltd, Galway, Ireland) and HIV-Spot (Genelabs Diagnostics, Singapore Science Park, Singapore) tests. Any discordant sample was retested, and if it remained discordant was sent for ELISA testing at the referral hospital in Blantyre.

Patients who tested HIV-seropositive were offered adjunctive cotrimoxazole, provided there were no contraindications to the medication. Contraindications

Table 1. Tuberculosis (TB) treatment regimens and indications.

TB treatment regimens	Drugs and duration[a]	Indication
Short course regimen	2SRHZ/6EH	New smear-positive PTB and severe smear-negative PTB or extrapulmonary TB
Standard regimen	1SEH/11EH	New smear-negative PTB and less severe forms of extrapulmonary TB
Retreatment regimen	2SRHZE/1RHZE/5$R_3H_3Z_3E_3$	Retreatment of smear-positive PTB relapses and failure cases
Meningitis regimen	2SRHZ/7RH	TB meningitis in adults and children
Paediatric regimen 1	2$R_3H_3Z_3E_3$/6EH	Children with smear-positive PTB and severe smear-negative PTB (new cases)
Paediatric regimen 2	2$R_3H_3Z_3$/6EH	Children with less serious extrapulmonary TB and smear-negative PTB (new cases)

[a]A regimen consists of two phases: initial phase and continuation phase; the number before a phase is the duration of that phase in months; a number in subscript after a letter is the number of doses of that drug per week (if there is no subscript, the treatment with that drug is daily). S, Streptomycin; E, ethambutol; H, isoniazid; R, rifampicin; Z, pyrazinamide; PTB, pulmonary TB.

included known allergies to sulpha-containing drugs, pregnancy, breast-feeding until 2 months and children aged less than 2 years (because of uncertainty about HIV-serostatus). Cotrimoxazole was given at a dose of 480 mg (400 mg sulphamethoxazole and 80 mg trimethoprim) twice daily for the whole course of anti-TB treatment and indefinitely thereafter. Anti-TB drugs and both daily doses of cotrimoxazole were administered by direct observation during the initial phase of treatment. In the continuation phase, anti-TB drugs and cotrimoxazole were given to patients at monthly intervals from their nearest health facility and the drugs were self-administered. Patients received enough pills for 33 days, which included a 3-day safety stock in case the patient was unable to attend the health facility on the specified follow-up date.

Compliance with self-administered cotrimoxazole was assessed in a cohort of TB patients who were attending four of the TB follow-up centres during the continuation phase (months 4–6) of anti-TB treatment [11]. Urine trimethoprim was measured using gas chromatography and mass spectrometry, and was detected in 87 (94%) of 93 TB patients in the cohort.

Side-effects of cotrimoxazole were monitored clinically. A protocol for monitoring side-effects was developed, and all health personnel were trained on how to manage side-effects. A standard reporting form was also available at all health facilities in the district.

Control group

Between 1 July 1998 and 30 June 1999, all TB patients who were registered in the same two hospitals in the district were started on the same standardized anti-TB treatment, and this cohort of patients was known as the 'control group'. This group was not offered VCT or cotrimoxazole prophylaxis, as the intervention had not commenced during this period.

Treatment outcomes

All patients were followed to the end of treatment, and outcomes were recorded according to standard guidelines [12]. Death was defined as a death at any time during the 8–12 months of treatment from whatever cause. Month of death, default or transfer-out was recorded in the file. End-of-treatment outcomes were classified after cross-verification of information contained in TB registers, laboratory registers, medication registers and treatment cards. Reliability of treatment outcomes was verified by conducting independent household visits on a random sample of 40 TB patients from the intervention and control groups. All these outcomes were confirmed correct.

In 160 TB patients (88 in the control group and 72 in the intervention group), information on treatment outcomes was incomplete and cross-verification was not

possible for the following reasons: the treatment register was not properly completed; the treatment card had been misplaced at the health centre; the date of treatment outcome was not indicated. In these patients, an independent household visit was conducted at the end of the study period in order to obtain a reliable end-of-treatment outcome.

Statistical analysis

A previous cohort study in Zomba district, Southern Malawi, had shown an end-of-treatment mortality of 30% in patients with all types of TB [13]. A sample size of 748 patients in each group was calculated to achieve a power of 90%, and to detect a 25% reduction in end-of-treatment mortality (from 30 to 22.5%) with a type I error rate of 5%. This calculation formed the basis of using a 12-month recruitment period for each group.

Data was entered and analysed using EPI-INFO 6.0 and 2000 (Centre for Disease Control and Prevention, Atlanta Georgia, USA). Baseline characteristics of patients in the intervention and control groups were compared using the chi-squared test for categorical variables. Analysis of treatment outcome was carried out between the intervention and control groups according to the intention-to-treat principle. All patients were included in the intervention group regardless of whether they were treated with cotrimoxazole or not. Differences in end-of-treatment outcomes between intervention and control groups were compared using the chi-squared test. The relative risk of death was stratified for type and category of TB as well as anti-TB treatment using the Mantel–Haenszel chi-squared test. Hazard ratios were also used to compare death rates in the two groups per 100 person-months of follow-up, and were stratified in the same way. Overall survival distributions for both groups were estimated using the Kaplan–Meier method and compared using the Cox–Mantel (log-rank) test. All P values were two sided, and the level of significance was set at $P = 0.05$ or less. 95% Confidence intervals (CI) were used throughout.

Results

Characteristics of the study population

A total of 1986 patients was registered in the study: 1061 in the intervention group and 925 in the control group. Characteristics of the two groups are shown in Table 2. The age, sex and hospital at which the patients were registered were similar between the two groups, but the groups differed in terms of type and category of TB, and in terms of anti-TB treatment.

Occupation and physical status on admission were recorded in the intervention group only. The most common occupations were farming in 625 (59%), unskilled work in 173 (16%), business in 71 (7%) and skilled work in 60 (6%) patients. On admission, 231 (22%) patients were moribund (bedridden and unable to stand without support), 703 (66%) felt ill due to clinical symptoms linked to TB/HIV, 87 (8%) felt well and the physical status was unknown in 40 (4%) patients.

Table 2. Characteristics of patients in the intervention (cotrimoxazole) and control groups.

	Cotrimoxazole [n (%)]	Control [n (%)]	P^a
Total	1061	925	
Median age (years)	32 (range 1–93)	31 range (1–85)	
Age-group (in years)			
1–14	85 (8)	81 (9)	0.5
15–44	783 (74)	689 (74)	0.7
45–64	169 (16)	141 (15)	0.7
> 64	24 (2)	14 (2)	0.2
Male	505 (48)	472 (51)	0.1
Site of registration			
District Hospital	616 (58)	569 (62)	0.1
Mission Hospital	445 (42)	356 (38)	0.1
TB type			
Smear-positive PTB	464 (44)	340 (37)	< 0.01
Smear-negative PTB	282 (26)	288 (31)	0.02
EPTB	315 (30)	297 (32)	0.2
TB category			
New TB case	967 (91)	897 (97)	< 0.01
Relapse	39 (4)	22 (2)	0.09
Other	55 (5)	6 (1)	< 0.01
Type of TB treatment			
Short-course	542 (51)	400 (43)	< 0.01
Standard treatment	350 (33)	416 (45)	< 0.01
Retreatment	77 (7)	24 (3)	< 0.01
TB meningitis	21 (2)	11 (1)	0.2
Paediatric	71 (7)	74 (8)	0.3

[a]Chi-squared test. TB, Tuberculosis; PTB, pulmonary TB; EPTB, extra-pulmonary TB.

VCT and adjunctive treatment with cotrimoxazole

Of 1061 patients registered for TB in the intervention group, 1019 (96%) were counselled pre-test, 964 (91%) underwent HIV testing and 938 (88%) were counselled post-test (Fig. 1). Of the 964 TB patients who were tested for HIV, 740 (77%) were HIV positive: this included 294(68%) patients with smear-positive PTB, 223 (86%) with smear-negative PTB and 223 (82%) with EPTB.

Six-hundred and ninety-three patients, comprising 93% of all known HIV positive cases and 65% of all registered TB patients, were given cotrimoxazole after a median of 4 days (range, 1–57 days) from registration. Two-hundred and eighty-three (61%) of 464

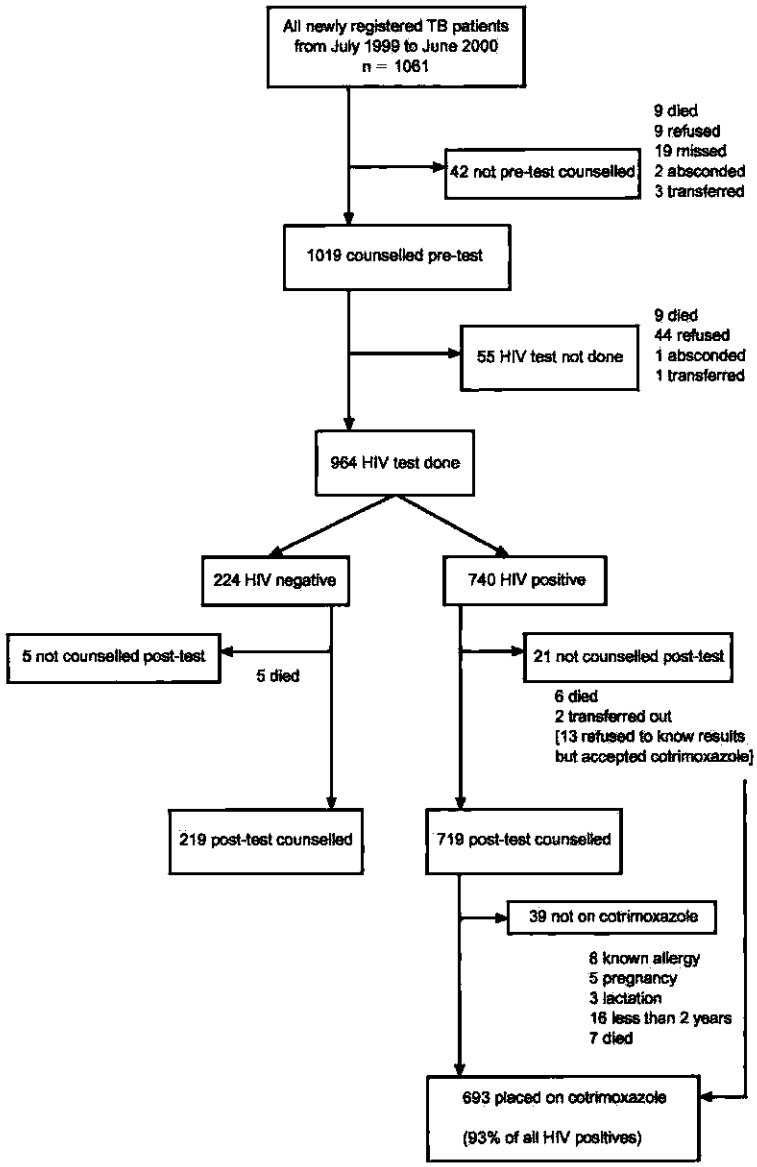

Fig. 1. Study profile of tuberculosis patients in the intervention (cotrimoxazole) group.

registered patients with smear-positive PTB, 200 (71%) of 282 patients with smear-negative PTB and 210 (67%) of 315 patients with EPTB were given cotrimoxazole.

Reactions to cotrimoxazole

Of 693 patients on cotrimoxazole, 14 (2%) had a dermatological reaction. No reactions were serious or involved mucosal membranes, and all were reversible on

discontinuing treatment. All dermatological reactions occurred in the first 2 months of treatment, with 9 (64%) occurring during the first month. In 13 patients cotrimoxazole was discontinued indefinitely, and in one patient it was re-started (by mistake) without problems.

End-of-treatment outcomes and mortality rates

End-of-treatment outcomes in the intervention and control groups – death, treatment success and other outcomes – for all patients and in relation to type, category of TB and treatment regimen are shown in Table 3. Treatment outcomes were known for all except seven patients in the control group.

Death was significantly decreased for all patients in the intervention group, and also for those with smear-negative PTB, new TB and those on standard treatment. Treatment success was also significantly increased for all patients in the intervention group, and for those with smear-negative PTB, EPTB, new TB and those on standard anti-TB treatment. For smear-positive PTB patients, neither death nor treatment success were significantly different between the intervention and the control groups. Other outcomes were similar between the two groups for all patients except those with new TB. The crude relative risk (RR) of death by the end of treatment in the intervention compared with the control group was 0.78 (95% CI, 0.69–0.89; $P < 0.001$). Adjusted for type and category of TB as well as anti-TB treatment, the RR was 0.81 (95% CI, 0.75–0.87; $P < 0.001$).

Death rates per 100 person-months of follow-up and the hazard ratios (HR) in the two groups for all patients and in relation to type, category of TB and anti-TB treatment were also calculated. Results were similar to those obtained using death at the end of treatment as the measurable outcome. The death rate for all registered TB patients was 4.0 per 100 person-months of follow-up in the intervention group and 5.3 in the control group, which corresponds to a 25% reduction in risk of death (95% CI, 12.3–35.8). Adjusted for type and category of TB as well as anti-TB treatment, the HR was 0.76 (95% CI, 0.69–0.83).

Survival curves for both intervention and control groups are shown in Fig. 2. By the end of the first month of treatment, 113 (38%) of 299 deaths had occurred in the intervention group which was not different from the 130 (39%) of 333 deaths in the control group. These results were similar in patients with different types of TB. A significant difference in the survival curve between the intervention and control groups became apparent from 4 months of anti-TB treatment (Log-Rank test, $P = 0.05$), and the overall end-of-treatment survival probability was higher in the intervention group compared with the control group.

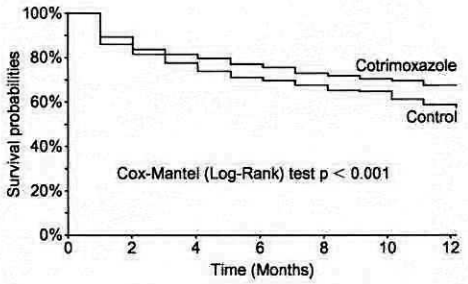

Fig. 2. Kaplan–Meier survival probability in the intervention (cotrimoxazole) and control groups.

In the intervention group receiving VCT and cotrimoxazole 299 deaths (28% of 1061) occurred, whereas 333 deaths (36% of 925) occurred in the control group. The number of TB patients needed to treat with a package of VCT and adjunctive cotrimoxazole to prevent one death during the course of anti-TB treatment is 12.5.

Discussion

This study shows that a package of VCT and cotrimoxazole given as adjunctive treatment to those who were HIV-positive reduced the overall mortality in a cohort of TB patients registered under routine programme conditions in a rural district in Malawi. The intervention appeared to be safe with minimal side-effects. The protective effectiveness of this intervention package was seen mainly in new patients (who comprised > 90% of patients in both groups), and in patients with smear-negative PTB and EPTB. There was no significant benefit in patients with smear-positive PTB.

This was an operational research study using historical controls as the comparison group, as a randomized control trial was not possible. The use of historical controls inevitably leads to problems in deciding what really caused the reduction in mortality. Was it the package of VCT, cotrimoxazole, increased enthusiasm of the programme, the possibility that HIV-positive patients look after themselves better than patients who do not know their HIV-serostatus or that poverty indicators were better in the intervention year compared with the control year? We do not think that poverty, care or programme enthusiasm were any different between the two years, but we do not have firm data to substantiate this.

Although the historical control group was similar in age and sex to the intervention group, there were

Table 3. End-of-treatment outcomes in intervention (cotrimoxazole) and control groups.

	Death [n/total (%)]			Treatment success [n/total (%)][a]			Other [n/total (%)][b]		
	Cotrimoxazole	Control	p^c	Cotrimoxazole	Control	p^c	Cotrimoxazole	Control	p^c
All TB patients	299/1061 (28)	333/925 (36)	< 0.001	701/1061 (66)	524/925 (57)	< 0.001	61/1061 (6)	68/925 (7)	0.1
TB type									
Smear-positive PTB	91/464 (20)	74/340 (22)	0.5	358/464 (77)	253/340 (74)	0.4	15/464 (3)	13/340 (4)	0.7
Smear-negative PTB	105/282 (37)	140/288 (49)	< 0.01	151/282 (54)	122/288 (42)	< 0.01	26/282 (9)	26/288 (9)	0.9
EPTB	103/315 (33)	119/297 (40)	0.05	192/315 (61)	149/297 (50)	< 0.01	20/315 (6)	29/297 (10)	0.1
TB category									
New TB case	267/967 (28)	326/897 (36)	< 0.001	646/967 (67)	505/897 (56)	< 0.001	54/967 (5)	66/897 (8)	0.1
Relapse	11/39 (28)	3/22 (14)	0.2	25/39 (64)	18/22 (82)	0.1	3/39 (8)	1/22 (4)	1
Other	21/55 (38)	4/6 (67)	0.2	30/55 (55)	1/6 (16.5)	0.1	4/55 (7)	1/6 (16.5)	0.4
TB treatment									
Short course	114/542 (21)	98/400 (24)	0.2	403/542 (74)	283/400 (71)	0.2	25/542 (5)	19/400 (5)	0.9
Standard	130/350 (37)	198/416 (48)	< 0.01	193/350 (55)	180/416 (43)	< 0.01	27/350 (8)	38/416 (9)	0.5
Retreatment	25/77 (33)	5/24 (21)	0.3	47/77 (61)	18/24 (75)	0.2	5/77 (6)	1/24 (4)	1
TB meningitis	13/21 (62)	9/11 (82)	0.2	8/21 (38)	1/11 (9)	0.1	0/21 (0)	1/11 (9)	0.3
Paediatric	17/71 (24)	23/74 (74)	0.3	50/71 (70)	42/74 (57)	0.09	4/71 (6)	9/74 (12)	0.2

[a]Includes all patients who have completed treatment, with or without sputum smear-negative results. [b]Includes patients who have defaulted, transferred, failed, or with unknown outcome (seven, all in the control group). [c]Chi-squared test. TB, Tuberculosis; PTB, pulmonary TB; EPTB, extrapulmonary TB.

differences in the proportions of patients according to type and category of TB. Towards the beginning of the intervention period, the NTP had found that patients with recurrent smear-negative TB were being misclassified as new cases of TB [14]. These mistakes were rectified, and this probably explains the increase in TB cases registered as 'other'. The increase in proportion of patients with smear-positive PTB in the intervention group reflects the on-going training and supervision of all TB programme staff around Malawi in improving the diagnosis of TB by sputum smear examination.

Otherwise, the methods of diagnosing and registering TB patients and the anti-TB treatment regimens were the same in both study periods. HIV sero-status was not measured in historical controls. Malawi has witnessed escalating rates of HIV infection in its registered TB patients during the 1990s [7]. Thus, if anything, HIV-seroprevalence might have been higher in the intervention group, which would have had the effect of increasing mortality rates.

The strengths of this study are that a large number of patients were registered in each of the study groups. Rigorous attempts were made to accurately determine end-of-treatment outcomes and month of death/default or transfer-out. End-of-treatment outcomes were known for all patients, except seven in the control group. Default and transfer-out rates were low and in general were similar in the two groups. The study also used the routine district health services for implementation of activities, and the results are therefore relevant, practicable and probably replicable in other parts of the country.

The benefit of cotrimoxazole was seen in the whole cohort of TB patients, but when subgroup analysis was performed the benefit was only apparent in those with smear-negative PTB and EPTB. The lack of effect in patients with smear-positive PTB appears to conflict with the results of the Cote d'Ivoire study [5]. There are several possible reasons for these differences. First, only 61% of smear-positive PTB patients were given cotrimoxazole compared with 71% of patients with smear-negative PTB. This might reduce the cohort benefit of cotrimoxazole in the smear-positive PTB patients. Second, in Cote d'Ivoire, cotrimoxazole had the most significant effect on mortality in those most immunosuppressed [5]. This effect has also been shown in other parts of Africa [15]. HIV-infected patients with smear-negative PTB may be more immunosuppresed than those with smear-positive PTB [16], and thus might be expected to benefit more from cotrimoxazole. Third, patients in our study were offered cotrimoxazole as soon as possible after registration and starting anti-TB treatment. This contrasts with the design in Cote d'Ivoire [5] where patients were offered

cotrimoxazole 1 month after starting anti-TB treatment. We have already documented high early mortality rates in TB patients in Malawi, with nearly 40% of deaths countrywide occurring in the first month of anti-TB treatment [17]. In the current study, a similar high proportion of deaths in both intervention and control groups occurred during the first month, which would negate the overall benefit of cotrimoxazole. Finally, differing patterns of HIV-related disease and differing rates of cotrimoxazole resistance may reduce the efficacy of cotrimoxazole in our patients. There are high rates of *in vitro* cotrimoxazole resistance to a wide range of pathogens in Malawi [9]. Unfortunately we have limited data on the pattern of HIV-related pathogens in Malawi [18], and this aspect was not investigated in our study.

In addition to providing HIV-positive patients with an effective prophylactic intervention, this study also shows that HIV-counselling and testing is feasible under routine conditions in a rural district and has a high patient acceptance rate. HIV-counselling and testing has been shown in sub-Saharan Africa to promote behaviour change and safer sexual practices, and it appears to be a cost-effective intervention to reduce sexual transmission of HIV [19,20]. Patient compliance with cotrimoxazole prophylaxis in the continuation phase of anti-TB treatment (where the drug is self-administered) was found to be encouragingly high [11]. Since June 2000, the package of VCT and cotrimoxazole prophylaxis has continued in Thyolo district, and good links have been established between the hospital counselling services and community care groups. Although cotrimoxazole had a significant benefit, the death rates in patients offered this intervention were still high. The feasibility and effectiveness of other interventions to reduce early mortality (for example, improving access to care, empirical use of antibiotics to treat presumptive bacteraemia and use of corticosteroids) and to improve overall survival, including the possible use of antiretroviral treatment, needs to be explored [21].

For every 12.5 TB patients in our setting, that were offered the package of VCT plus cotrimoxazole, there was one preventable death during the course of anti-TB treatment. Assuming the same level of uptake of VCT countrywide, if the intervention package was adopted by the NTP there might be just over 2000 prevented deaths during anti-TB treatment. In addition, VCT might lead to changes in sexual behaviour and a reduction in HIV transmission. It has, however, been suggested that widespread use of cotrimoxazole for HIV-positive TB patients may increase the risk of drug resistance for the treatment of acute respiratory infections in children (cotrimoxazole is first-line therapy) and for treatment of malaria (sulphadoxine-pyrimethamine is first-line therapy) [22]. The policy debate about whether to introduce the intervention package will have to take into account these considerations. Other issues include: given the high HIV-seroprevalence, whether adjunctive cotrimoxazole should be provided to all TB patients if widespread implementation of VCT is slow; whether the intervention should include all TB patients or just those with smear-negative PTB and EPTB; and who has responsibility for drug administration, adherence and costs after anti-TB treatment.

Whatever the outcome of this debate, providing VCT and adjunctive cotrimoxazole to TB patients is an essential step to reduce the high mortality associated with HIV infection in sub-Saharan Africa. Our findings have important public health implications for TB control in Malawi and in other high HIV-TB burden countries of sub-Saharan Africa.

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CHAPTER 3

Compliance to cotrimoxazole for the prevention of opportunistic infections in HIV infected tuberculosis patients in Thyolo, Malawi.
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Compliance with cotrimoxazole prophylaxis for the prevention of opportunistic infections in HIV-positive tuberculosis patients in Thyolo district, Malawi

R. Zachariah,* A. D. Harries,† V. Arendt,‡ R. Wennig,§ S. Schneider,§ M. Spielmann,* E. Panarotto,† P. Gomani,† F. M. Salaniponi†

* Medecins sans Frontieres-Luxembourg, Thyolo District; † National Tuberculosis Control Programme, Malawi; ‡ Department of Infectious Diseases, Central Reference Hospital, Luxembourg, § Department of Toxicology, National Laboratory of Health, University Center, Luxembourg

SUMMARY

OBJECTIVE: To verify compliance with cotrimoxazole prophylaxis in human immunodeficiency virus (HIV) infected tuberculosis (TB) patients during the continuation phase of anti-tuberculosis treatment, and to assess the sensitivity, specificity and positive predictive values of verbal verification and pill counts as methods of checking compliance.

DESIGN: Cross-sectional study.

METHODS: Cotrimoxazole compliance was assessed in a cohort of TB patients who were attending four TB follow-up centres during the continuation phase of anti-TB treatment between months 4 and 6. Verbal verification of drug intake, physical verification of pill count balance, and urine trimethoprim detection by gas chromatography and mass spectrometry were used for assessing compliance.

RESULTS: Using urine trimethoprim detection as the gold standard for compliance, trimethoprim was detected in 82 (94%) of 87 patients in the cohort. Verbal verification of cotrimoxazole intake and objective pill count balances showed high sensitivity and positive predictive values compared with the gold standard of urine trimethoprim detection.

CONCLUSIONS: In a rural district in Malawi, compliance with cotrimoxazole as an adjunct to anti-tuberculosis treatment in HIV-infected TB patients was good, and can be assessed simply and practically by verbal verification and pill counts.

KEY WORDS: cotrimoxazole; compliance; HIV infection; tuberculosis; Malawi

HUMAN IMMUNODEFICIENCY VIRUS (HIV) positive patients with tuberculosis (TB) in sub-Saharan Africa have high death rates during and following anti-tuberculosis treatment.[1,2] These death rates have a negative impact on cure rates, and challenge the credibility of TB control programmes amongst patients, health care staff and the community. Effective and affordable adjunctive interventions to reduce death rates in sub-Saharan Africa are urgently needed. Tuberculosis is also an early HIV-related opportunistic infection which often brings persons with HIV to medical attention, and it is therefore an opportunity for intervention.

In Abidjan, Cote d'Ivoire, a randomised placebo-controlled trial of cotrimoxazole prophylaxis in HIV-positive patients with smear-positive pulmonary tuberculosis (PTB) showed a significant reduction in morbidity and mortality during anti-TB treatment.[3] Similar encouraging results were reported from Cape Town, South Africa,[4] and UNAIDS has made provisional recommendations that cotrimoxazole prophylaxis be used in those with symptomatic HIV-related disease or persons with CD4 counts of less than 500 in Africa.[5] However, it is uncertain whether the beneficial effect of cotrimoxazole seen in Abidjan and Cape Town will be replicated widely and elsewhere in sub-Saharan Africa because of the differing patterns of HIV-related opportunistic infections and the different prevalence of cotrimoxazole resistance among commonly occurring pathogens.

In view of these uncertainties, the National TB Control Programme (NTP) in Malawi is currently carrying out operational research in two districts to assess the efficacy and feasibility of cotrimoxazole prophylaxis to reduce mortality in patients being registered and treated for TB. This research is being conducted within the routine conditions of district TB control programmes. In assessing whether cotrimoxazole is effective or not, it is important to know that patients are actually taking the drug. The present study was carried out in one of the districts to determine 1) compliance with cotrimoxazole prophylaxis in HIV-positive TB patients during the continuation phase of anti-

Correspondence to: Dr R Zachariah, Head of Mission, Medicins sans Frontieres Luxembourg, Mission Malawi, PO Box 30353, Chichiri, Blantyre 3, Malawi. Fax: (+265) 641 468. e-mail: msflblantyre@malawi.net

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tuberculosis treatment, 2) factors associated with compliance, and 3) the sensitivity and predictive values of verbal verification and pill counts as methods of checking compliance.

METHODS

Study population, data collection and specimens

This operational research study of cotrimoxazole prophylaxis, which is still being implemented, examined a cohort of TB patients registered in the Thyolo district of the southern region of Malawi. In the cotrimoxazole study, all registered TB patients are started on standardised anti-tuberculosis treatment according to national guidelines.[6] Patients undergo voluntary counselling and HIV testing, and are offered cotrimoxazole prophylaxis if they are HIV-seropositive and if there are no contraindications for the medication. Cotrimoxazole prophylaxis is given at a dose of 480 mg (400 mg sulfamethoxazole and 80 mg trimethoprim) twice daily during the whole course of anti-tuberculosis treatment and indefinitely thereafter. Anti-tuberculosis drugs and both daily doses of cotrimoxazole are administered by direct observation during the initial phase of treatment. In the continuation phase of treatment, a sufficient supply of anti-tuberculosis drugs and cotrimoxazole is given to patients at monthly intervals, and the drugs are self administered. All patients receive enough pills for 33 days of cotrimoxazole prophylaxis (which includes 3 days of safety stock), and are expected to report at the follow-up clinic on a fixed day at the end of 30 days of treatment to collect further supplies of anti-tuberculosis drugs and cotrimoxazole.

Cotrimoxazole compliance was assessed in patients attending four TB follow-up centres during the continuation phase of treatment between months 4 and 6. Compliance was assessed as follows. There was a verbal (subjective) verification of cotrimoxazole intake in the previous 24 hours, an objective verification of pill count balance and a record made of the reasons for pill count differences (as explained by the patient). Pill count balances were classified for the purposes of this study as exact (100% correct), satisfactory (one, two or three tablets higher or lower than the expected pill balance) or unsatisfactory (pill balances showing a difference of more than three tablets). The three-tablet cut-off point was used because this signifies one and half days of prophylaxis, which for the purposes of this study was designated as an operationally acceptable difference that can be verified on follow-up visits with respect to the prescribed dose of two tablets daily. A 15 ml sample of urine was also collected for detection of trimethoprim. Urine specimens were stored at −20°C and transported under cold chain to the National Laboratory of Health, Department of Toxicology in Luxembourg for urine trimethoprim detection by gas chromatography/mass spectrometry (set as the gold standard for this study).

Gas chromatography and mass spectrometry (GC/MS) analysis

The GC/MS system[7] combines a separation technique (gas chromatography) and a highly sensitive and specific identification technique (mass spectrometry). Detection of the trimethoprim component of cotrimoxazole (the combination of sulfamethoxazole and trimethoprim) was done by identifying its characteristic fragmentation pattern and retention times. Calibration curves were obtained by spiking drug-free urine specimens with trimethoprim at different concentrations using methaqualone as an internal standard at constant concentration (1 mg/L). Creatinine levels were determined on a Cobas Mira instrument using Merck reagents. Trimethoprim concentrations in urine were standardised and expressed for 1 g of creatinine, although no reference values for trimethoprim levels in urine are available. Trimethoprim is detectable in urine up to 24 hours after the last intake of cotrimoxazole.

Statistical analysis

Data were analysed using Epi-Info (Centers for Disease Control and Prevention, Atlanta, GA). Crude odds ratios with 95% confidence intervals were used to assess whether social and clinical factors were associated with compliance, with the level of significance set at $P = 0.05$ or less.

Sensitivity, specificity and positive predictive values of verbal verification and pill counts were calculated using urine trimethoprim detection as the gold standard.

RESULTS

Demographic characteristics of the study cohort

Of 93 TB patients who should have attended for follow-up in the four main centres during the period of the compliance study, data are available for 87 (94%): two patients did not turn up on the appointed day, two submitted an insufficient amount of urine for analysis and in two patients the specimen bottles leaked during field and international transport, respectively. Of the 87 patients, there were 38 men and 49 women, with a mean age of 32 years. Forty-three patients had smear-positive PTB, 16 had smear-negative PTB and 28 had extra-pulmonary TB. The majority of patients were farmers (57), followed by unskilled employees (15), small scale business people or vendors (12) and skilled employees, students and children (3).

Cotrimoxazole compliance

Trimethoprim was detected in 82 (94%) of the urine samples. The median urine concentration of trimethoprim was 22.7 mg/gm of creatinine (range 0.2–233 mg/gm creatinine). In five urine samples no trimethoprim was detected. Table 1 shows the results of

Table 1 Verbal verification and pill count balances compared to urine trimethoprim detection (gold standard)

Trimethoprim in urine	Present *n* (%)	Absent *n* (%)	Total
Verbal verification (n = 87)			
Cotrimoxazole intake in last 24 hours			
Yes	82 (96.5)	3 (3.5)	85
No	0	2 (100)	2
Pill count balance (n = 87)			
Exact*	51 (96.2)	2 (3.8)	53
Satisfactory†	24 (100)	0 (0)	24
Unsatisfactory‡	7 (70)	3 (30)	10

* Exact balance
† 1–3 pills more or less than expected balance
‡ >3 pills more or less than expected balance

verbal verification and pill count balance compared to the results of urine trimethoprim detection. Of 85 patients who verbally stated that they had taken cotrimoxazole in the last 24 hours, three (4%) had no trimethoprim detected in the urine. Of 77 patients in whom pill count balances were exact or satisfactory, two (3%) had no trimethoprim detected in the urine. Sensitivity and positive predictive values for verbal verification, pill count balance and both assessments together, using urine trimethoprim as the gold standard, were high (Table 2).

Two patients stated that they had not taken cotrimoxazole in the previous 24 hours as they had run out of pills, and 10 patients had unsatisfactory pill count balances. The mean number of pills in excess or deficit from the exact balance was 4.3 (range 0–6). Reasons for unsatisfactory balances included giving some pills out to a sick child, family member or friend (6), losing some pills (2), forgetting to take some doses (1) and not knowing (1). There were no statistically significant social or clinical factors associated with compliance based on urine trimethoprim results, verbal verification or pill count balances.

DISCUSSION

Using urine trimethoprim detection measured by gas chromatography/mass spectrometry as the gold standard for determining cotrimoxazole compliance, the degree of compliance in our TB patients who were taking cotrimoxazole and anti-tuberculosis drugs under routine conditions was high. Similar good results were obtained under research conditions in Abidjan, Cote d'Ivoire.[8] These results are reassuring for the conduct of the operational study in Thyolo, particularly when it comes to assessing the efficacy of this adjunctive intervention. Although the method of detecting trimethoprim in urine is reliable and objective,[7] it is sophisticated and expensive, and is therefore unsuitable as a routine way of assessing cotrimoxazole compliance. Verbal verification, pill count balance and both methods together proved acceptable and robust as alternative ways of assessing compliance, and under routine conditions these are simple and practical to use.

In a rural district such as Thyolo where the majority of patients are farmers, it is understandable that some patients will use cotrimoxazole for treating sick members of the family, will forget to take tablets or will be unable to report at the treatment centre on the exact day of the follow-up appointment. Providing patients with a 3-day excess stock of pills provides a safety net for continued prophylaxis, and in the present study this was not associated with undue abuse of the system.

In the cotrimoxazole operational research study which aimed to recruit TB patients during the course of 12 months, over 1000 patients have been registered for treatment of whom nearly 700 have been started on cotrimoxazole prophylaxis. End of treatment outcomes compared with those observed in historical controls within the same district will help the NTP make a decision about the efficacy or not of this intervention in reducing death rates.

Table 2 Sensitivity, specificity and predictive values of verbal verification and pill count balance

	Sensitivity* (%)	Specificity* (%)	Positive predictive value* (%)
Verbal verification (V)	100	40	96.5
Pill count (P)	91.5†	60†	97.4
Combination of V+P	100	60	97.6

* As compared to urine trimethoprim detection (gold standard)
† Includes those with exact and satisfactory pill counts
‡ Includes those with unsatisfactory pill counts.

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RÉSUMÉ

OBJECTIFS : Vérifier l'adhésion à une prophylaxie au cotrimoxazole chez les patients tuberculeux (TB) infectés par le virus de l'immunodéficience humaine (VIH) au cours de la phase de continuation du traitement antituberculeux, et apprécier la sensibilité, la spécificité et la valeur prédictive positive d'une vérification verbale et des décomptes de comprimés comme méthodes de contrôle de l'adhésion.

SCHÉMA : Etude transversale.

MÉTHODES : L'adhésion thérapeutique au cotrimoxazole a été appréciée dans une cohorte de patients TB qui fréquentaient quatre centres de suivi de TB au cours de la phase de continuation du traitement antituberculeux entre les mois 4 et 6. La vérification verbale de la prise des médicaments, la vérification physique de l'équilibre des décomptes de comprimés et la détection du triméthoprime dans les urines par chromatographie gazeuse et spectrographie de masse ont été utilisées pour apprécier l'adhésion.

RÉSULTATS : Si l'on utilise la détection de triméthoprime dans les urines comme « gold standard » pour l'adhésion, le triméthoprime a été détecté chez 82 (94%) des 87 patients de la cohorte. La vérification verbale de la prise de cotrimoxazole et l'équilibre des décomptes de comprimés ont révélé une sensibilité et une valeur prédictive positive élevée par comparaison au gold standard de détection de triméthoprime dans les urines.

CONCLUSION : Dans un district rural du Malawi, l'adhésion à la prise de cotrimoxazole comme complément à un traitement antituberculeux chez les patients TB infectés par le VIH s'est avérée bonne et peut être appréciée rapidement et d'une façon pratique par une vérification verbale et le décompte des comprimés.

RESUMEN

OBJETIVO : Verificar la adhesión a la profilaxis con cotrimoxazol en pacientes con TB infectados por el virus de la inmunodeficiencia humana (VIH) durante la fase de continuación del tratamiento antituberculoso y evaluar la sensibilidad, especificidad y valor predictivo positivo de la verificación verbal y del conteo de cápsula como métodos de control.

DISEÑO : Estudio transversal.

MÈTODO : Se evaluó la adhesión al cotrimoxazol en una cohorte de pacientes con TB que asistían a cuatro centros, en la fase de continuación del tratamiento antituberculoso, entre los meses 4 a 6. Para evaluar la adhesión se utilizaron la verificación verbal de la toma de drogas, control de la toma de comprimidos y la detección urinaria de trimetoprima por cromatografía gaseosa y espectrometría de masa.

RESULTADOS : Cuando se utiliza la detección de trimetoprima urinaria como el criterio estándar para la adhesión, se detectó la misma en 82 (94%) de 87 pacientes en la cohorte. La 'verificación verbal' de la toma de cotrimoxazol y el 'balance del conteo de píldoras' mostró una gran sensibilidad y un valor predictivo comparados con el criterio estándar de la detección de la trimetoprima en orina.

CONCLUSIÓN : En un distrito rural de Malawi, la adhesión al cotrimexazol como un agregado al tratamiento anti-tuberculoso en los pacientes infectados por el VIH, fue bueno y puede ser evaluado en forma simple y práctica a través de la verificación verbal y del conteo de las píldoras.

CHAPTER 4

Cotrimoxazole prophylaxis in HIV infected individuals after anti-TB therapy in a rural setting.
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Cotrimoxazole prophylaxis in HIV-infected individuals after completing anti-tuberculosis treatment in Thyolo, Malawi

R. Zachariah,* M. P. Spielmann,* A. D. Harries,† P. Gomani,‡ E. Bakali‡

* Médecins Sans Frontières-Luxembourg, Thyolo, Thyolo District, † National Tuberculosis Control Programme/DFID, Lilongwe, Lilongwe, ‡ Thyolo District Health Services, Ministry of Health & Population, Thyolo, Thyolo, Malawi

SUMMARY

SETTING: Thyolo, rural southern Malawi.

OBJECTIVES: To determine 1) the proportion who continue with cotrimoxazole prophylaxis for the prevention of opportunistic infections, and 2) the reasons for continuing or stopping prophylaxis, in human immunodeficiency virus (HIV) infected individuals with tuberculosis (TB) who complete anti-tuberculosis treatment.

DESIGN: A cross-sectional study.

METHODS: A questionnaire study of all HIV-infected TB patients who had been registered over a 3-month period to receive anti-tuberculosis treatment and cotrimoxazole prophylaxis and who had completed anti-tuberculosis treatment 3–6 months earlier.

RESULTS: Of 82 HIV-infected individuals who were alive at the time of interview, 76 (93%) were continuing with cotrimoxazole and wished to do so indefinitely. The most common reason for continuing the drug was to prevent illness associated with HIV, while the most common reason for stopping was long distances to the health facility. Ninety-six percent of patients received cotrimoxazole free of charge from a health centre. Of those who wished to continue indefinitely, the majority (63%) could not afford to pay for the drug.

CONCLUSIONS: In a rural setting, the great majority of HIV-infected individuals continued with cotrimoxazole after completing anti-tuberculosis treatment. Making the drug available and providing it free of charge is essential if it is to remain accessible for longer term prevention.

KEY WORDS: cotrimoxazole; HIV; tuberculosis; Malawi

PATIENTS INFECTED with the human immunodeficiency virus (HIV) and tuberculosis (TB) in sub-Saharan Africa have high death rates during and after anti-tuberculosis treatment.[1,2] Opportunistic infections are an important cause of the high morbidity and mortality experienced by these patients,[3–5] and it is believed that interventions to prevent these infections might improve survival. Prophylaxis with cotrimoxazole has been shown to reduce morbidity and mortality in HIV-infected patients with smear-positive pulmonary tuberculosis (PTB) in Côte d'Ivoire,[6] and in 2000, UNAIDS made provisional recommendations that cotrimoxazole prophylaxis be given to all persons living with HIV/AIDS in Africa.[7]

Since early 1999, Thyolo District, in rural southern Malawi, has been offering voluntary counselling and HIV testing (VCT) to all TB patients, followed by adjunctive cotrimoxazole treatment to those found to be infected with HIV. The district is currently assessing the feasibility and effectiveness of this intervention in reducing death rates.[8] During anti-tuberculosis treatment, HIV-infected TB patients receive anti-tuberculosis drugs as well as cotrimoxazole under the supervision of the TB control programme. This responsibility ceases at the end of anti-tuberculosis treatment, and patients are simply encouraged to continue with cotrimoxazole, the decision being left principally with the patient. Information as to whether patients are continuing with cotrimoxazole prophylaxis after anti-tuberculosis treatment, and possible factors that encourage or discourage continuation of prophylaxis would be useful to the general health services in planning for cotrimoxazole prophylaxis after anti-tuberculosis treatment. It might also give insight into the value of cotrimoxazole as perceived by the patient.

This study was conducted in a cohort of HIV-infected individuals 3 to 6 months after they had completed anti-tuberculosis treatment, in order to determine 1) the proportion of patients still taking cotrimoxazole prophylaxis, and 2) their reasons for continuing or stopping prophylaxis during the same period.

METHODS

Study setting

The study was carried out between February and March 2002 in Thyolo District, in rural southern

Correspondence to: Rony Zachariah, Médecins Sans Frontières-Luxembourg, Luxembourg 1617. Tel: (+352) 332515. Fax: (−352) 335133. e-mail: zachariah@internet.lu

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Malawi, which has a population of 450 000. The district has one government hospital, a mission hospital and 18 health centres involved in TB control activities. In this district, all patients (adults and children) diagnosed with TB are registered and started on standardised anti-tuberculosis treatment according to national guidelines.[9] Patients undergo VCT, and are offered cotrimoxazole prophylaxis if they are HIV-seropositive and there are no contraindications to the medication. Cotrimoxazole prophylaxis is offered at a dose of 480 mg (400 mg sulfamethoxazole and 80 mg trimethoprim) twice daily in adults and according to weight (kg) in two divided doses in children. The drug is taken throughout the whole course of anti-tuberculosis treatment and indefinitely thereafter. Early in the course of initiating cotrimoxazole in our setting, it was observed that several patients complained of severe nausea and vomiting when the drug was given once daily in the morning along with the anti-tuberculosis drugs. Twice-daily dosing was therefore introduced, and continued as patients experienced fewer reactions.

Anti-tuberculosis drugs and both daily doses of cotrimoxazole are administered by direct observation by the health worker during the initial phase of treatment. In the continuation phase, the anti-tuberculosis drugs and cotrimoxazole are given to patients at monthly intervals at their nearest health facility, and the drugs are self-administered.

At the end of anti-tuberculosis treatment, HIV-infected individuals can collect their cotrimoxazole for prophylaxis on a monthly basis from health centres, where a special stock is made available for this purpose, through nurses in areas where home-based care services exist, or from public pharmacies and vendors at a cost. The drugs provided by the health centres and home-based care services are free of charge.

Study population and data collection

All TB patients with known HIV infection who had been registered over a 3-month period to receive anti-tuberculosis treatment as well as cotrimoxazole prophylaxis and who had completed anti-tuberculosis treatment 3 to 6 months earlier were involved in the study.

TB treatment and counselling registers were used to gather information on patients who were alive at the end of their anti-tuberculosis treatment. A household visit was conducted for each patient known to be alive. After obtaining informed consent, interviewer-administered questionnaires which had been pre-tested on a different group of 10 HIV-infected TB patients were used to gather basic socio-demographic data and information related to cotrimoxazole prophylaxis. In the design of the questionnaire, patients were asked to give their main reasons for continuing or stopping cotrimoxazole after completing anti-tuberculosis treatment. In the case of children, the father or mother was interviewed. Cotrimoxazole availability at the patient's home was physically verified by requesting to see the tablet package. The interviews were conducted in the local language by experienced interviewers, and the same team was used throughout the study.

Analyses were performed using Epi-Info software (Centre for Disease Control and Prevention, Atlanta, GA).

RESULTS

Study population, VCT and adjunctive cotrimoxazole prophylaxis

A total of 219 TB patients were registered in the 3-month study cohort. Of these, 212 (97%) received pre-test counselling, 204 (93%) underwent HIV testing and 199 (91%) received post-test counselling. The HIV status was unknown for 15 patients: five refused HIV testing, six died, two were transferred out of the district and two had missed pre-test counselling (Figure).

Of the 204 TB patients who were HIV-tested (66 on standard treatment and 138 on short-course treatment), 149 (69%) were HIV-positive: this included 75 (65%) of 114 patients with smear-positive PTB, 41 (85%) of 48 with smear-negative PTB and 33

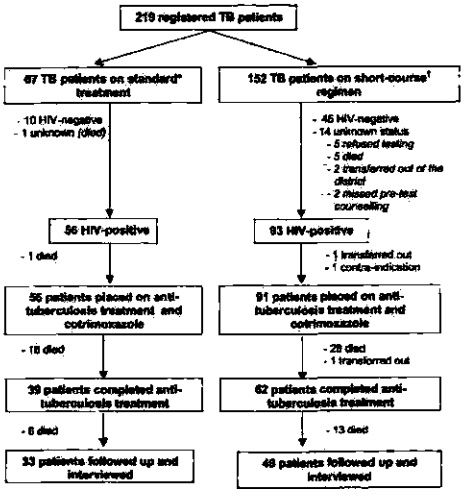

Figure Profile of the study cohort followed up after completing anti-tuberculosis treatment. * 35 smear-negative PTB and 32 EPTB cases on 1SEH/11EH; † 125 smear-positives and 13 severe smear-negatives/EPTB on 2SRHZ/6EH, six children on $2R_3H_3E_3/6EH$, and 8 relapses on 2 SRHZE/1RHZE/ $5R_3H_3Z_3E_3$. PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; S = streptomycin; E = ethambutol; H = isoniazid; R = rifampicin, Z = pyrazinamide. (A regimen consists of two phases—an initial phase and continuation phase. Numbers before the letters indicate the duration of that phase in months; numbers in subscript indicate the number of doses of the drug(s) per week. If there is no subscript, the treatment with that drug is daily.)

(78%) of 42 patients with extra-pulmonary TB (EPTB). Of the 149 HIV-infected TB patients, 146 (98%) were given cotrimoxazole after VCT within a mean period of 2 days after registration (Figure).

Of those placed on anti-tuberculosis treatment and cotrimoxazole, 44 (20% of the registered cohort) died during the course of their anti-tuberculosis treatment, and 19 (9%) died after completing their treatment. One patient was transferred out during treatment and was lost to follow-up.

Of the 82 individuals on cotrimoxazole who were finally interviewed, there were 34 men, 47 (57%) women and one child. The median age was 32 years (range 5 to 58), and the median educational level was 6 years of schooling (range 0–14). Forty-nine (60%) patients were married and 33 were single (unmarried, divorced or widowed, or a child). The commonest occupations were farming in 46 (56%), unskilled work in 17 (21%), business in 10 (12%) and skilled work in six (7%) patients. Two patients had no form of employment and the child was aged 5 years. The majority of the patients (89%) resided in villages, with 62% earning less than the equivalent of US $4 in local currency per week.

Cotrimoxazole after anti-tuberculosis treatment

Eighty-two HIV-infected individuals were alive 3 to 6 months after completing anti-tuberculosis treatment; all of them gave consent for interview. Of these, 76 (93%) were continuing with cotrimoxazole prophylaxis and wished to do so indefinitely; 54 (71%) said they would continue the drug as they were HIV-positive and it would prevent them from getting ill, 10 (13%) felt their life depended on it, 10 (13%) wished to continue because it was free of charge and two (3%) because the doctor advised it.

Of the 76 patients taking cotrimoxazole, 73 (96%) were getting their drug from a health centre and the other three through home-based care nurses. When asked if they could afford to start purchasing cotrimoxazole for continuing prophylaxis, 26 (34%) were willing to try to pay up to US $0.50 for a month's supply, while 50 (66%) said they would have to stop the drug since they would not be able to afford it.

Six individuals stopped cotrimoxazole after completing anti-tuberculosis treatment, three because they moved to a different district that was too far away, one because he had started working and had no time, one felt he was fine and did not need to continue, and one individual had developed a skin allergy to the drug.

DISCUSSION

After completing anti-tuberculosis treatment, the great majority of HIV-infected TB patients in this study continued with cotrimoxazole prophylaxis and wished to do so indefinitely. There are a number of encouraging findings in this respect: first, the great majority of HIV-infected individuals came back of their own free will to the health centres to collect their cotrimoxazole. During the course of anti-tuberculosis treatment, activities linked to cotrimoxazole prophylaxis are integrated within the TB programme, and patient follow-up is the responsibility of the TB officers. The situation is not so clear once the patient has completed anti-tuberculosis treatment when, ideally, this responsibility should be taken over by the HIV programme. While efforts are still underway to try to integrate HIV and TB programme activities, making a stock of cotrimoxazole available at the health centres is an interim measure that will facilitate continuing prophylaxis without adding an undue burden for follow-up. Second, we demonstrated high compliance with cotrimoxazole prophylaxis in HIV-infected TB patients during the course of anti-tuberculosis treatment.[10] Our finding suggests that compliance remains high even after completion of anti-tuberculosis treatment. Third, the counselling process has clearly made HIV-infected TB patients aware of the potential benefits of cotrimoxazole in reducing morbidity and mortality. Emphasis placed on VCT in our setting and the value as perceived by the patient is likely to enhance compliance in the long term.

In Thyolo, cotrimoxazole is provided to patients free of charge both during and after anti-tuberculosis treatment. However, the question as to whether HIV-infected individuals on a country-wide scale should pay for cotrimoxazole or if it should be made available free of charge in Malawi has been raised. In a rural setting such as Thyolo, the majority of patients are either subsistence farmers or unskilled labourers earning less than US $4 per week. Furthermore, HIV-positive TB patients tend to be chronically ill, with a high prevalence of moderate to severe malnutrition.[11] Income generation capacity is low, and most patients end up destitute. Although patients might therefore desire to continue cotrimoxazole indefinitely, the majority would, quite understandably, be unable to afford the cost.

One of the discouraging findings in this study is that despite the fact that the great majority of HIV-positive TB patients were on cotrimoxazole prophylaxis, cohort mortality during anti-tuberculosis treatment remains high. Mortality after completing anti-tuberculosis treatment is also high, with about one in every five HIV-infected individuals dying within 6 months of completing anti tuberculosis treatment.

The National Tuberculosis Control Programme of Malawi has reported rising death rates in new TB patients, and in 1998 the country had the highest TB death rates reported in Africa.[12] Preventing early deaths in patients with TB remains a major challenge in resource-poor countries such as Malawi,[13] and apart from cotrimoxazole, additional effective and

affordable adjunctive interventions to reduce overall death rates, including the possibility of antiretroviral treatment, are urgently needed. Cotrimoxazole prophylaxis is nevertheless the most important adjunctive intervention currently available in resource-poor settings for reducing HIV-related opportunistic infections and promoting survival during and after antituberculosis treatment. Making the drug available for HIV-infected individuals through existing health structures and providing the drug free of charge is essential to ensure that it remains accessible for longer term prevention of opportunistic infections.

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RÉSUMÉ

CADRE : Thyolo, Malawi rural du Sud.

OBJECTIFS : Déterminer, chez les patients infectés par le virus de l'immunodéficience humaine (VIH) et atteints de tuberculose (TB) qui ont achevé le traitement antituberculose, 1) la proportion qui poursuit une prophylaxie au cotrimoxazole pour la prévention des infections opportunistes et 2) les raisons de prolongation ou d'arrêt de la prophylaxie.

SCHÉMA : Etude transversale.

MÉTHODES : Il s'agit d'une étude par questionnaire chez tous les patients TB infectés par le VIH qui ont été enregistrés pendant une période de 3 mois pour recevoir un traitement anti-tuberculose et une prophylaxie au cotrimoxazole et qui ont achevé le traitement anti-tuberculose de 3 à 6 mois plus tôt.

RÉSULTATS : Sur 82 individus infectés par le VIH, 76 (93%) qui étaient en vie au moment de l'entretien poursuivaient le traitement au cotrimoxazole et souhaitaient le faire indéfiniment. La raison la plus fréquente pour la poursuite de la médication a été la prévention de maladies associées au VIH, alors que la raison la plus fréquente pour son arrêt a été une distance importante du domicile au service de santé. Le cotrimoxazole a été administré gratuitement à 96% des patients dans un centre de santé. Parmi ceux qui souhaitaient poursuivre indéfiniment, la majorité (63%) n'étaient pas à même de payer le médicament.

CONCLUSION : Dans un contexte rural, la grande majorité des individus infectés par le VIH poursuivent le cotrimoxazole après avoir achevé le traitement antituberculeux. La mise à disposition de ce médicament et sa gratuité sont essentielles si l'on veut qu'il reste accessible pour une prévention de plus longue durée.

RESUMEN

MARCO DE REFERENCIA : Thyolo, región rural del sur de Malawi.

OBJETIVO : Determinar en los sujetos con tuberculosis (TB), infectados con el virus del inmunodeficiencia humana (VIH), que han completado el tratamiento antituberculoso : 1) la proporción que continúa con una profilaxis con cotrimoxazol para la prevención de las infecciones oportunistas y 2) las razones para continuar o suspender la profilaxis.

DISEÑO : Estudio transversal.

MÉTODO: Estudio por cuestionario de todos los pacientes con TB infectados con VIH, registrados durante un período de 3 meses como habiendo recibido tratamiento anti-tuberculosis y profilaxis con cotrimoxazol y que habían completado el tratamiento anti-tuberculosis 3 a 6 meses antes.

RESULTADOS: De 82 sujetos infectados con VIH, 76 (93%) que estaban vivos en el momento de la entrevista continuaban la profilaxis con cotrimoxazol y deseaban hacerlo indefinidamente. La razón más frecuente para continuar este tratamiento era la prevención de las enfermedades asociadas con el VIH, mientras que la razón más frecuente para suspenderlo era la distancia importante del domicilio al centro de salud. El 96% de los pacientes recibían el cotrimoxazol gratuitamente en el centro de salud. Entre aquéllos que deseaban continuar indefinidamente, la mayoría (63%) no podían hacer frente al pago del medicamento.

CONCLUSIÓN: En un contexto rural, la gran mayoría de los sujetos infectados con VIH continuaban con cotrimoxazol después de haber completado el tratamiento anti-tuberculosis. Asegurar la disponibilidad de este medicamento y entregarlo gratuitamente es esencial si se pretende que permanezca accesible para una prevención de más larga duración.

CHAPTER 5

Changes in *Escherichia coli* resistance to cotrimoxazole in tuberculosis patients and in relation to cotrimoxazole prophylaxis in Thyolo, Malawi.
Trans Roy Soc Trop Med & Hyg, 2002; 96: 202-204

Changes in *Escherichia coli* resistance to co-trimoxazole in tuberculosis patients and in relation to co-trimoxazole prophylaxis in Thyolo, Malawi

R. Zachariah[1], A. D. Harries[2], M. P. Spielmann[1], V. Arendt[3], D. Nchingula[4], R. Mwenda[5], O. Courtelle[3], P. Kirpach[3], B. Mwale[5] and F. M. L. Salaniponi[2] *[1]Médecins sans Frontières–Luxembourg, Thyolo District, Malawi; [2]National Tuberculosis Control Programme of Malawi/DFID, Malawi; [3]Tropical and Infectious Diseases Hospital and Reference Laboratory, Luxembourg; [4]Blantyre Diagnostic Laboratories, Malawi; [5]Queen Elizabeth Regional Reference Hospital/Laboratory Services, Blantyre, Malawi*

Abstract

In Thyolo district, Malawi, an operational research study is being conducted on the efficacy and feasibility of co-trimoxazole prophylaxis in preventing deaths in HIV-positive patients with tuberculosis (TB). A series of cross-sectional studies were carried out in 1999 and 2001 to determine (i) whether faecal *Escherichia coli* resistance to co-trimoxazole in TB patients changed with time, and (ii) whether the resistance pattern was different in HIV-positive TB patients who were taking co-trimoxazole prophylaxis. Co-trimoxazole resistance among *E. coli* isolates in TB patients at the time of registration was 60% in 1999 and 77% in 2001 ($P < 0{\cdot}01$). Resistance was 89% among HIV-infected TB patients (receiving co-trimoxazole), while in HIV-negative patients (receiving anti-TB therapy alone) it was 62% ($P < 0{\cdot}001$). The study shows a significant increase of *E. coli* resistance to co-trimoxazole in TB patients which is particularly prominent in HIV-infected patients on co-trimoxazole prophylaxis. Since a high degree of plasmid-mediated transfer of resistance exists between *E. coli* and the *Salmonella* species, these findings could herald limitations on the short- and long-term benefits to be expected from the use of co-trimoxazole prophylaxis in preventing non-typhoid *Salmonella* bacteraemia and enteritis in HIV-infected TB patients in Malawi.

Keywords: *Escherichia coli*, HIV infections, tuberculosis, chemoprophylaxis, co-trimoxazole, drug resistance, Malawi

Introduction

Non-typhoid *Salmonella* (NTS) bacteraemia particularly with *Salmonella typhimurium* and *S. enteritidis* is known to be among the leading causes of morbidity and mortality in human immunodeficiency virus (HIV)-infected patients with tuberculosis (TB) in Africa (GILKS *et al.*, 1990; BRINDLE *et al.*, 1993; FERNANDEZ GUERRERO *et al.*, 1997; GORDON *et al.*, 2001). Prophylaxis with sulphamethoxazole–trimethoprim (co-trimoxazole) has been shown to reduce mortality and morbidity among HIV-infected patients with sputum-positive TB in Abidjan (ANGLARET *et al.*, 1999; WIKTOR *et al.*, 1999). Protection from NTS bacteraemia and enteritis accounted for much of this beneficial effect, susceptibility of NTS to co-trimoxazole in Abidjan being very high (91%).

The National TB Control Programme of Malawi is currently testing the feasibility and efficacy of co-trimoxazole prophylaxis as an adjunct to anti-TB therapy in reducing overall mortality in HIV-positive TB patients within routine programme conditions in Malawi. The eventual short- and long-term efficacy of co-trimoxazole in reducing morbidity and mortality in Malawi would depend on the baseline levels of co-trimoxazole resistance and particularly the impact of co-trimoxazole prophylaxis on progressive resistance development among a spectrum of common target opportunistic pathogens such as NTS. High resistance to co-trimoxazole in NTS or other opportunistic pathogens could have implications on the potential benefits of co-trimoxazole prophylaxis in HIV-infected individuals and would therefore be important to monitor.

It is known that there is a high degree of rapid plasmid-mediated transfer of co-trimoxazole resistance between faecal *E. coli* and the *Salmonella* species as well as other Enterobacteriaceae (MARSIK *et al.*, 1975; MURRAY & RENSIMER, 1983; BALIS *et al.*, 1996). The level of faecal *E. coli* resistance to co-trimoxazole, which is relatively more simple to measure than that for *Salmonella* in a resource-poor setting such as Malawi, would therefore herald similar resistance patterns in NTS and other Gram-negative bacteria.

The objective of this study was to measure changes in faecal *E. coli* (bacterial flora) resistance to co-trimoxazole in TB patients with time and to determine whether this pattern was different in HIV-positive TB patients who were taking co-trimoxazole prophylaxis.

Materials and Methods

Study setting

The study was carried out in Thyolo district of southern Malawi, which is one of the districts in the country in which the National TB Control Programme of Malawi is currently testing the feasibility and efficacy of co-trimoxazole prophylaxis as an adjunct to anti-TB therapy in reducing overall mortality in HIV-infected TB patients. In this study of co-trimoxazole prophylaxis, which is still being implemented since July 1999, all registered TB patients are started on standardized anti-TB treatment according to National Guidelines (MOHP, 1999). Patients undergo voluntary counselling and HIV testing and are offered co-trimoxazole prophylaxis (800 mg of sulphamethoxazole and 160 mg of trimethoprim) if they test HIV-seropositive and if there are no contraindications to the medication.

Study population and specimen collection

To determine whether there were changes in co-trimoxazole resistance with time, 2 serial cross-sectional resistance studies were conducted in 1999 and in 2001 using stool specimens collected from cohorts of new TB cases selected randomly before starting anti-TB therapy. In these 2 studies, stool specimens were collected immediately after registration and before start of anti-TB therapy. None of the patients was taking co-trimoxazole prophylaxis.

In order to compare resistance patterns with patients who were taking co-trimoxazole, another study was carried out in 2001 on a cohort of TB patients selected randomly while visiting health facilities for monthly drug collection. This cohort of patients was receiving anti-TB therapy and included a proportion of HIV-seropositive patients that were receiving adjunctive co-trimoxazole over 6–8 months.

HIV status was not known for the first serial resistance study in 1999 as HIV testing and counselling

Address for correspondence: Dr R. Zachariah, Head of Mission (Mission Malawi), Médecins sans Frontières–Luxembourg, P.O. Box 38, L-7201, Bereldange, Luxembourg; phone +265 644409, fax +265 641468 (Malawi), e-mail zachariah@internet.lu

were not available until July 1999. In the other 2 subsequent studies, HIV-status results were available. A structured questionnaire was used to gather information on basic socio-demographic data. All patients were residents of the rural district, and stool specimens were collected after obtaining voluntary informed consent, confidentiality of results being respected.

Laboratory methods

Initial inoculation of stool specimens for culture was done on MacConkey 3 (Oxoid) agar plates. Suspect colonies were subcultured for purity and identified by colony morphology and biochemical tests. Isolates were confirmed to be *E. coli* using the API 20E identification system (API-Biomérieux, Basingstoke, England, UK).

Anti-microbial susceptibility testing to co-trimoxazole was done on modified Mueller–Hinton (Oxoid) agar plates. The Kirby–Bauer disk-diffusion technique was used and inhibition-zone sizes (IZS, nearest whole millimetre) for *E. coli* were read according to National Committee for Clinical Laboratory Standards guidelines (NCCLS, 1998). Interpretation of IZS for co-trimoxazole (23·75/1·25 μg) was as follows: 16 mm, susceptible; 11–15 mm, intermediate; 10 mm, resistant. Antibiograms were validated using standardized control strains of *E. coli* ATCC No. 25922 (American Type Culture Collection, Rockville, MD, USA) on a regular basis. Independent control testing was done on specimens that were transported using microbank tubes (Pro-lab Diagnostics, Neston, Wirral, UK) to the National Infectious Diseases Reference Laboratory in Luxembourg. HIV testing was performed using a combination of the Capillus (Cambridge Diagnostics Ltd, Galway, Ireland) and HIV Spot (Genelabs Diagnostics Pte Ltd, 85 Science park Drive, Singapore) tests.

Statistical analysis

The EpiInfo software (Centers for Disease Control, Atlanta, USA) was used for data analysis. The level of significance was set at 0·05 and 95% confidence intervals (CI) were used throughout in expressing differences in proportions. All laboratory results of resistance levels are expressed to the nearest whole millimetre.

Results

Characteristics of the study population

A total of 443 registered TB cases were studied; 16 patients could not produce stool specimens at the time of specimen collection and were excluded. Data are therefore available for 427 TB patients.

Of the 427 patients there were 210 male and 217 (51%) female patients, the mean age being 33 years. Over half (240 patients) of the study group had smear-positive pulmonary TB (PTB), 91 had smear-negative PTB and 96 had extrapulmonary TB. The overall HIV seroprevalence (all TB types) in all those that had undergone HIV testing in 2001 ($n = 286$) was 75%.

Co-trimoxazole resistance

Of the 427 stool specimens that were collected, 406 (95%) grew *E. coli* on culture. In the 2 serial studies conducted on newly registered TB patients (before starting anti-TB therapy or co-trimoxazole) co-trimoxazole resistance among isolates was 60% in 1999 ($n = 118$), and increased significantly ($P < 0·01$) to 77·1% ($n = 144$) in the similar cohort in 2001 (Table). There was no significant difference in co-trimoxazole resistance between HIV-positive (79·0%) and HIV-negative (68·8%) patients in 2001 ($P = 0·23$). Overall co-trimoxazole resistance in patients who had received anti-TB therapy (HIV positive and HIV negative) for 6–8 months (with or without adjunctive co-trimoxazole) was 82·6% in 2001 (Table). In this cohort, resistance in HIV-infected patients receiving adjunctive co-trimoxazole ($n = 113$) was 89·4% (95% CI 82·2–94·4) while in HIV-negative patients ($n = 26$) receiving anti-TB therapy alone it was 61·5% (95% CI 40·6–79·8), the difference being highly significant ($P < 0·001$) (Table). This resistance was also higher when compared to HIV-positive TB cases that were on neither anti-TB therapy nor co-trimoxazole in 2001 ($P = 0·03$).

There were no significant differences in co-trimoxazole resistance with regards to different age-groups, gender and TB type. Independent quality control testing conducted on 103 isolates transported to Luxembourg showed conformity of laboratory results.

Discussion

This study shows that co-trimoxazole resistance in *E. coli* among TB patients has significantly increased in a 2-year period in a rural district of Malawi. In a resource-poor country such as Malawi where effective and affordable interventions to limit morbidity and mortality in people living with HIV are limited, there has been a growing market demand for co-trimoxazole following its introduction in Thyolo district for HIV-infected TB patients in July 1999. Co-trimoxazole, being a relatively cheap antibiotic, which is easy to administer, has since 1999 become readily available in public pharmacies, from private drug vendors and even at some grocery stores, and it can be purchased without any formal prescription. The uncontrolled availability and widespread use of co-trimoxazole in the Thyolo

Table. Resistance to co-trimoxazole in faecal *Escherichia coli* isolates from tuberculosis (TB) patients in Thyolo, Malawi

Patient group	Resistant/total isolates	%	*P* value[c]
TB patients on registration in 1999[a]	71/118	60·2	–
TB patients on registration in 2001[a]	111/144	77·1	
HIV positive	83/105	79·0	0·23
HIV negative	22/32	68·8	–
TB patients on follow-up in 2001[b]	119/144	82·6	
HIV positive (receiving co-trimoxazole)	101/113	89·4	0·001
HIV negative (not receiving co-trimoxazole)	16/26	61·5	–

[a]Specimens collected during TB registration, patients being on neither anti-TB therapy nor co-trimoxazole. HIV status was not known at the time of registration in 1999 and for 7 patients on registration in 2001.
[b]Specimens collected during 6–8-month follow-up visit. HIV-positive patients had received anti-TB therapy and adjunctive co-trimoxazole while HIV-negative patients had received anti-TB therapy alone. HIV status was not known for 5 patients in this group.
[c]*P* values are for HIV-positive as compared to HIV-negative patients.

community could explain the relatively rapid increase in co-trimoxazole resistance in *E. coli* between 1999 and 2001. In Malawi, sulfadoxine-containing antimalarials (Fansidar) and co-trimoxazole are the first-line drugs recommended for malaria and respiratory tract infections in children respectively, and this might also contribute to a high baseline resistance to co-trimoxazole.

Co-trimoxazole resistance in *E. coli* isolates from HIV-infected TB patients who had been receiving adjunctive co-trimoxazole was significantly higher than in HIV-negative TB patients (on anti-TB therapy alone) and is most likely linked to the prophylactic use of co-trimoxazole in these patients (MURRAY *et al.*, 1982; MARTIN *et al.*, 1999).

These findings of high *E. coli* resistance to co-trimoxazole may also herald high levels of resistance in NTS and other Gram-negative bacteria and would limit the protective effect of co-trimoxazole against these Enterobacteriaceae. As the beneficial effects on morbidity and mortality of co-trimoxazole prophylaxis in HIV-infected TB patients in Côte d'Ivoire were mainly linked to protection from NTS bacteraemia and enteritis, limited benefits of adjunctive co-trimoxazole might be expected in this regard in Malawi. However, co-trimoxazole prophylaxis provides a protective effect against other HIV-related opportunistic pathogens, such as *Pneumocystis carinii*, *Isospora belli* and *Toxoplasma gondii*, and might therefore still be effective in reducing overall mortality in TB patients within our context.

In the co-trimoxazole operational research study which is still being implemented in Thyolo, over 1000 TB patients have been recruited of whom nearly 700 have been placed on co-trimoxazole prophylaxis. End of treatment outcomes, compared to historical controls, will help the National Tuberculosis Control Programme of Malawi make a decision about the efficacy (or lack thereof) of this intervention in reducing death rates.

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CHAPTER 6

Moderate to severe malnutrition in patients with tuberculosis predicts early death.

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Moderate to severe malnutrition in patients with tuberculosis is a risk factor associated with early death

R. Zachariah[1], M. P. Spielmann[1], A. D. Harries[2] and F. M. L. Salaniponi[2] *[1]Médecins Sans Frontières–Luxembourg, Thyolo District, Malawi; [2]National Tuberculosis Control Programme of Malawi, Community Health Science Unit, Private Bag 65, Lilongwe 3, Malawi*

Abstract

A study was conducted in new patients registered with tuberculosis (TB) in a rural district of Malawi to determine (i) the prevalence of malnutrition on admission and (ii) the association between malnutrition and early mortality (defined as death within the first 4 weeks of treatment). There were 1181 patients with TB (576 men and 605 women), whose overall rate of infection with human immunodeficiency virus (HIV) was 80%. 673 TB patients (57%) were malnourished on admission (body mass index [BMI] <18·5 kg/m^2). There were 259 patients (22%) with mild malnutrition (BMI 17·0–18·4 kg/m^2), 168 (14%) with moderate malnutrition (BMI 16·0–16·9 kg/m^2) and 246 (21%) with severe malnutrition (BMI < 15·9 kg/m^2). 95 patients (8%) died during the first 4 weeks. Significant risk factors for early mortality included increasing degrees of malnutrition, age >35 years, and HIV seropositivity. Among all the 1181 patients, 10·9% of the 414 patients with moderate to severe malnutrition died in the first 4 weeks compared with 6·5% of the 767 patients with normal to mild malnutrition (odds ratio 1·8, 95% confidence interval 1·1–2·7). In patients with TB, BMI < 17·0 kg/m^2 is associated with an increased risk of early death.

Keywords: tuberculosis, *Mycobacterium tuberculosis*, human immunodeficiency virus, malnutrition, mortality, Malawi

Introduction

The association between tuberculosis (TB) and malnutrition has been recognized for a long time. Malnutrition may predispose to TB, and in turn TB often causes malnutrition (MACALLAN, 1999). By the time African patients with TB present for registration and treatment, a significant proportion have a marked degree of nutritional impairment (HARRIES *et al.*, 1988; KENNEDY *et al.*, 1996). Since the 1980s, many countries in sub-saharan Africa have been affected by a severe epidemic of human immunodeficiency virus (HIV) infection. Malawi, a small country situated in the southern region of Africa, is no exception, and in 1999 it was estimated that there were 800 000 adults and children living with HIV/AIDS (acquired immune deficiency syndrome) in a total population of approximately 10·6 million (UNAIDS, 2000). TB is one of the most common opportunistic infections arising as a result of HIV immunosuppression, and in Malawi 77% of TB patients registered country-wide were found to be HIV seropositive in 2000 (KWANJANA *et al.*, 2001). Weight loss is a characteristic feature of HIV/AIDS, and malnutrition in TB patients is likely to be further exacerabated by the concomitant effects of HIV (KOTLER, 2000).

Case fatality rates in TB patients in sub-saharan Africa have risen in the last 10 years, and are highly associated with HIV infection. A substantial proportion of these deaths occur early in the course of treatment (NUNN *et al.*, 1992; GARIN *et al.*, 1997; WOOD & POST, of 1997; CONNOLLY *et al.*, 1998; HARRIES *et al.*, 1998). Factors associated with early mortality are at present not well characterized. We hypothesized that malnutrition in TB patients, by further compromising host immunity and predisposing to life-threatening nutritional deficiencies and superadded infections, is a risk factor for early mortality. We conducted a study in a rural district of Malawi to determine the prevalence of malnutrition in TB patients at the time of initial registration, and to examine the association between malnutrition and early mortality.

Address for correspondence: Dr R. Zachariah, Head of Mission (Mission Malawi), Médecins Sans Frontières–Luxembourg, 70 Rue de Gasperich, L-1617, Luxembourg; phone +265 644409, fax +265 641468 (Malawi), +352 335133 (Luxembourg), e-mail zachariah@internet.lu

Materials and Methods

Study setting and management of TB

The study was carried out on new patients who were registered with TB between November 1999 and March 2001 in Thyolo district, a rural region of southern Malawi. There are 2 hospitals, one government district hospital and one mission hospital, in the district which register and treat patients with TB. New TB patients, as soon as they are registered, are started on standardized anti-TB treatment. In brief, these regimens during the study period in Thyolo were as follows. New patients with smear-positive pulmonary tuberculosis (PTB) and serious forms of extra-pulmonary tuberculosis (EPTB) were given an 8 months' regimen consisting of 2 months' daily supervised streptomycin, rifampicin, isoniazid and pyrazinamide in hospital followed by 6 months of daily unsupervised isoniazid and ethambutol in the community (2SRHZ/6EH). New patients with smear-negative PTB and less serious forms of EPTB were given a 12 months' regimen consisting of one month of daily supervised streptomycin, isoniazid and ethambutol in hospital followed by 11 months of daily isoniazid and ethambutol, which is self-administered (1SEH/11EH). All new patients therefore, regardless of the type of TB, spent the first month of treatment in hospital.

Since mid-1999, all TB patients in Thyolo have been offered voluntary counselling and HIV testing, and those who are HIV seropositive and have no contraindication are offered co-trimoxazole prophylaxis at a dose of 480 mg (400 mg of sulfamethoxazole and 80 mg of trimethoprim) twice daily. All TB patients (while in hospital) also receive a daily nutritional supplement of 1250 kcal in the form of a premix of Likuni-Phala™ (a mixture of maize flour, soya, oil and sugar) in addition to a routine hospital ration of 1200 kcal.

Study population and data collection

A structured questionnaire and record form were used to gather information on basic demographic data, HIV status, length of symptoms before being diagnosed as a case of TB, and type of TB. All patients were weighed on admission, without shoes and with minimum clothing, between 09:00 and 10:00. The same weighing scale was used for all patients, and calibration was carefully controlled. Height was measured (on admission) with the patient standing upright and looking straight ahead. With patients who could not stand unassisted, height was estimated using knee height

(DENKE & WILSON, 1998). A normal body mass index (BMI; weight in kg divided by height in m^2) was defined as 18·5–24·9 kg/m^2. Malnutrition was defined as BMI < 18·5 kg/m^2. Different degrees of malnutrition were defined as follows: mild malnutrition, BMI = 17·0–18·4 kg/m^2; moderate malnutrition, BMI = 16·0–16·9 kg/m^2; and severe malnutrition, BMI < 16·0 kg/m^2 (DENKE & WILSON, 1998). Personnel conducting these measurements were well trained, and the same personnel were used throughout the study. All patients gave voluntary informed consent to participate in the study. All deaths occurring between registration and the first 4 weeks of treatment were recorded, and were regarded as 'early mortality'.

Statistical analysis

Data analysis was done using Epiinfo software (Centres for Disease Control, Atlanta, Georgia, USA), and the Logistic™ software (ANONYMOUS, 1994). The χ^2 test and χ^2 test for linear trend were used to test for differences in proportions and linear trends, respectively. A non-parametric test (the Kruskal–Wallis test for 2 groups) was used to verify differences in means between groups. Crude odds ratios (OR) and adjusted odds ratios (adjusted OR) were used to assess whether BMI and other factors were associated with early mortality. ORs were adjusted using multivariate logistic regression, the level of significance being set at $P \leq 0.05$, and 95% confidence intervals were calculated throughout.

Results

Characteristics of the study population

There were 1319 new adult TB patients who registered during the study period. Of these, 138 patients were excluded from the study: HIV status was unknown in 83, there were spinal deformities in 12 and oedema in 8, and 35 patients died before undergoing height and weight measurements. Of the 1181 patients in the study, 576 were men and 605 (51%) were women; the mean age was 37 years. There were 624 patients (53%) with smear-positive PTB, 250 (21%) with smear-negative PTB, and 307 (26%) with EPTB. 943 (80%) patients were HIV positive. 922 were given co-trimoxazole chemoprophylaxis, which was started as soon as a positive HIV result was available. HIV positive patients with TB had a mean age of 32 years, which was less than the mean age of HIV negative TB patients, 38 years ($P < 0.001$).

Nutritional status on admission.

The mean BMI on admission for all TB patients was 18·2 kg/m^2; for males it was 18·4 and for females 17·9 ($P < 0.001$). 673 TB patients (57%) were malnourished on admission with 414 (35%) having moderate or severe malnutrition (BMI < 17·0 kg/m^2) (Figure).

Nutritional status and early mortality.

Ninety-five patients (8%) in the study died during the first 4 weeks of treatment (early mortality). Factors associated with early mortality are shown in Table 1. Significant risk factors were age >35 years, HIV seropositivity and increasing degrees of malnutrition. Early mortality was 6·3% in patients with normal nutrition, 6·9% in those with mild malnutrition, 10·1% in those with moderate malnutrition and 11·4% in those with severe malnutrition (χ^2 test for trend = 6·8, $P < 0.01$).

A BMI of 17·0 kg/m^2 was used as the cut-off value to determine whether patients with normal nutrition/mild malnutrition and moderate/severe malnutrition had an increased risk of early death. This assessment was used for all patients, and in relation to the factors listed in Table 1. The results are shown in Table 2. For all patients, there was a significantly higher rate of early mortality amongst patients with moderate to severe malnutrition than for those who had normal nutrition or mild malnutrition. This significantly higher early mortality rate was found in relation to male sex, age >35 years, symptoms >3 months' duration, smear-positive PTB, HIV seropositivity, and co-trimoxazole prophylaxis.

Discussion

This study showed that over half of all TB patients in a rural district of Malawi were malnourished at the time of registration, and over one-third had moderate to severe malnutrition; 8% of patients in the study died during the first 4 weeks of treatment. Factors associated with early mortality included increasing degrees of malnutrition, age >35 years and HIV seropositivity. Patients with moderate to severe malnutrition, (BMI <17·0 kg/m^2) had higher rates of early death compared with those whose nutritional status was normal or mildly impaired, and these differences were found regardless of age, HIV serostatus and other factors.

The strengths of this study are that a large number of patients were studied, all patients were offered counselling and HIV testing, the same personnel and the same equipment were used for performing measurements of

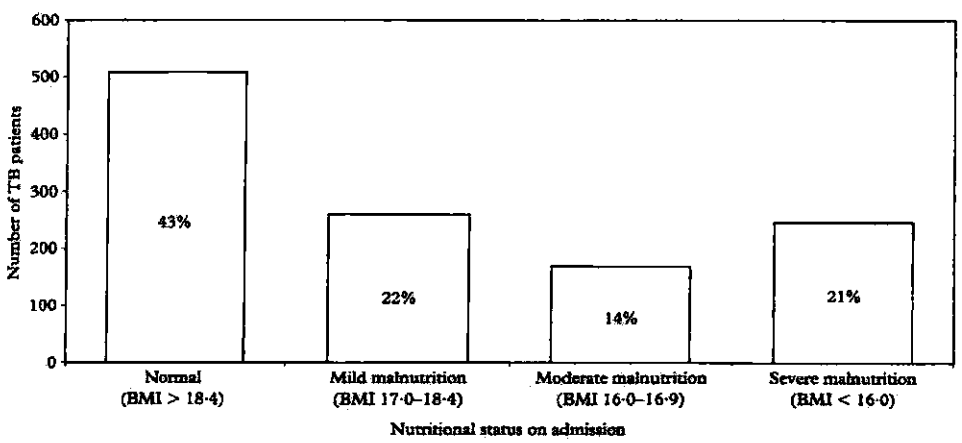

Figure. Nutritional status of patients with tuberculosis (TB) categorized by body mass index (BMI) in Thyolo district, Malawi. (Source: National Tuberculosis Control Programme of Malawi and Médecins sans Frontières–Luxembourg.)

Table 1. Risk factors associated with early mortality (during first 4 weeks of treatment) of patients with tuberculosis

Variables	Early deaths (%)	OR[a]	Adjusted OR[b]	*P*
Gender				
Female	42/605 (6·9)	1	1	
Male	53/576 (9·2)	1·3	1·4 (0·9–2·2)	0·15
Age (years)				
≤35	45/660 (6·8)	1	1	
>35	50/521 (9·6)	1·4	1·5 (1·0–2·4)	0·05
Type of TB[c]				
Smear positive	43/624 (6·9)	1	1	
Others (smear negative, EPTB[d])	52/557 (9·3)	1·4	1·3 (0·9–2·1)	0·20
HIV[e] status				
Negative	12/238 (5·0)	1	1	
Positive	83/943 (8·8)	1·8	4·8 (1·3–17·1)	0·01
Period of symptoms (months)				
<3	63/768 (8·2)	1	1	
>3	32/413 (7·7)	0·9	1·0 (0·6–1·5)	0·87
Co-trimoxazole				
Yes	16/259 (8·6)	1	1	
No	79/922 (6·2)	0·7	2·7 (0·8–8·3)	0·09
BMI on admission (kg/m^2)[f]				
>18·5	32/508 (6·3)	1	1	
17·0–18·4	18/259 (6·9)	1·1	1·2 (0·6–2·2)	0·59
16·0–16·9	17/168 (10·1)	1·4	1·8 (1·0–3·5)	0·05
<15·9	28/246 (11·4)	1·7	2·2 (1·3–3·8)	<0·01

[a]Odds ratio.
[b]Adjusted for gender, type of tuberculosis, human immunodeficiency virus status, co-trimoxazole administration and body mass index on admission; 95% confidence intervals in parentheses.
[c]Tuberculosis.
[d]Extrapulmonary tuberculosis.
[e]Human immunodeficiency virus.
[f]Body mass index; χ^2 for trend = 6·8, P = <0·01.

Table 2. Early mortality (during first 4 weeks of treatment) and nutritional status of patients with tuberculosis

	Normal/mild malnutrition (BMI ≥ 17·0 kg/m^2)		Moderate/severe malnutrition (BMI < 17·0 kg/m^2)			
	No.	Deaths (%)	No.	Deaths (%)	OR[a]	*P*
All patients	767	50 (6·5)	414	45 (10·9)	1·8 (1·1–2·7)	<0·01
Gender						
Female	241	13 (5·4)	243	21 (8·6)	1·5 (0·8–3·0)	0·10
Male	405	29 (7·2)	171	24 (14·0)	2·1 (1·2–3·9)	<0·01
Age (years)						
≤35	407	24 (5·9)	253	21 (8·3)	1·4 (0·8–2·8)	0·20
>35	360	26 (7·2)	161	24 (14·9)	2·3 (1·2–4·2)	<0·01
Symptoms (months)						
< 3	525	37 (7·0)	243	26 (10·7)	1·6 (0·9–2·8)	0·08
> 3	242	13 (5·4)	171	19 (11·1)	2·2 (1·0–4·9)	0·03
Type of TB[b]						
Smear positive PTB	386	19 (4·9)	238	24 (10·1)	2·2 (1·1–4·2)	0·01
Smear negative PTB	160	15 (9·4)	90	9 (10·0)	1·1 (0·4–2·8)	0·87
EPTB	221	16 (7·2)	86	12 (14·0)	2·1 (0·9–4·9)	0·07
HIV[c] status						
Negative	159	9 (5·7)	79	3 (3·8)	0·7 (0·1–2·8)	0·75
Positive	608	41 (6·7)	335	42 (12·5)	2·0 (1·2–3·2)	<0·01
Co-trimoxazole						
Yes	594	40 (6·7)	328	39 (11·9)	1·9 (1·2–3·1)	<0·01
No	173	10 (5·8)	86	6 (7·0)	1·2 (0·4–3·9)	0·70

[a]Odds ratio; 95% confidence intervals in parentheses.
[b]TB = tuberculosis; PTB = pulmonary TB; EPTB = extrapulmonary TB.
[c]Human immunodeficiency virus.

height and weight and, as all patients spent the first 4 weeks in hospital, deaths could be reliably ascertained. However, one of the limitations of the study was the fact that 35 TB patients (who died soon after admission and before any BMI measurements could be carried out) were excluded. We do not know the nutritional status of these patients, but their deaths comprised nearly 30% of the total deaths occurring between registration and the first 4 weeks of treatment. The results in this study do not therefore apply to very early mortality occurring soon after admission.

There are several potential reasons for early deaths of patients with TB: for example, late presentation of patients with severe and extensive TB; life-threatening

HIV-related complications such as severe anaemia and bacteraemia (GILKS *et al.*, 1990; MADEBO *et al.*, 1997; NIYONGABO *et al.*, 1999; GORDON *et al.*, 2001); and the occurrence of a Herxheimer-type reaction due to rapid killing of tubercle bacilli by anti-TB drugs (ELLIS & WEBB, 1983). We have shown that moderate to severe malnutrition is also a risk factor for early death. However, we do not know whether such nutritional impairment in its own right predisposes to early death, or whether it is a marker for extensive TB, severe HIV-related complications or Herxheimer reactions.

Preventing early death of patients with TB will be a major challenge in resource-poor countries such as Malawi (HARRIES *et al.*, 2001). Identification of bacteraemia in many African hospitals is difficult, because of lack of access to blood culture facilities, and ill patients may require an empirical course of antibiotics to treat commonly occurring infections due to *Streptococcus pneumoniae* and non-typhoidal *Salmonella*. Corticosteroids have been suggested as one way to reduce early deaths due to a Herxheimer-type reaction by reducing the toxicity of the disease (ELLIS & WEBB, 1983). Prospective controlled trials have shown a treatment benefit of corticosteroids in tuberculous meningitis and pericardial and pleural disease (ALZEER & FITZGERALD, 1993). However, trials of the use of corticosteroids in sick, malnourished TB patients, especially those with HIV infection, have yet to be carried out and published. Non-antibiotic nutritional interventions such as multivitamins may improve cell-mediated immunity in HIV positive patients (TANG *et al.*, 1997), but efficacy in this group has yet to be assessed in placebo-controlled trials. Anti-retroviral therapy is likely to have a major effect in reducing deaths from TB in HIV positive individuals, but, despite the pressure for widespread introduction of these therapies in sub-saharan Africa, it is likely to be some time before the infrastructure or the funds are available to turn this rhetoric into action.

The results of this study may help in finding solutions to this problem. BMI is a simple measurement for most hospitals to perform. TB patients with BMI < 17·0kg/m^2 form a group which has a higher risk of early death compared with patients whose BMI is 17·0 kg/m^2 or greater.

Although it is unclear what impact interventions in patients with BMI < 17·0 kg/m^2 might have in reducing overall TB mortality, this is nevertheless a group which could be targeted with interventions such as empirical antibiotics, corticosteroids and nutritional supplements in an operational research setting while awaiting the definitive results of phase III randomized controlled trials.

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CHAPTER 7

Behavioural characteristics, prevalence of *Chlamydia trachomatis* and antibiotic susceptibility of *Neisseria gonorrhoeae* in men with urethral discharge in Thyolo, Malawi.

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Behavioural characteristics, prevalence of *Chlamydia trachomatis* and antibiotic susceptibility of *Neisseria gonorrhoeae* in men with urethral discharge in Thyolo, Malawi

R. Zachariah[1], A. D. Harries[2], W. Nkhoma[3], V. Arendt[4], D. Nchingula[5], A. Chantulo[1], F. Chimtulo[6] and P. Kirpach[4] [1]*Médecins sans Frontières–Luxembourg, Thyolo District, Malawi;* [2]*National TB Control Programme of Malawi/DFID advisor, and* [3]*National AIDS Control Programme of Malawi, Ministry of Health, Lilongwe, Malawi;* [4]*Infectious Disease Reference Centre & Laboratory, Central Hospital, Luxembourg;* [5]*Blantyre Diagnostic Laboratory Services, Blantyre, Malawi;* [6]*National Reference Laboratory, Ministry of Health and Population, Lilongwe, Malawi*

Abstract

A study was carried out in 2000/2001 in a rural district of Malawi among men presenting with urethral discharge, in order to (a) describe their health-seeking and sexual behaviour, (b) determine the prevalence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and (c) verify the antibiotic susceptibility of *N. gonorrhoeae*. A total of 114 patients were entered into the study; 61% reported having taken some form of medication before coming to the sexually transmitted infections clinic. The most frequent alternative source of care was traditional healers. Sixty-eight (60%) patients reported sexual encounters during the symptomatic period, the majority (84%) not using condoms. Using ligase chain reaction on urine, *N. gonorrhoeae* was detected in 91 (80%) and *C. trachomatis* in 2 (2%) urine specimens. Forty five of 47 *N. gonorrhoeae* isolates produced penicillinase, 89% showing multi-antimicrobial resistance. This study emphasizes the need to integrate alternative care providers and particularly traditional healers in control activities, and to encourage their role in promoting safer sexual behaviour. In patients presenting with urethral discharge in our rural setting, *C. trachomatis* was not found to be a major pathogen. Antimicrobial susceptibility surveillance of *N. gonorrhoeae* is essential in order to prevent treatment failures and control the spread of resistant strains.

Keywords: sexually transmitted diseases, urethral discharge, men, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, prevalence, health-care seeking behaviour, sexual behaviour, antimicrobial susceptibility, Malawi

Introduction

Sexually transmitted infections (STIs) are known to facilitate the sexual transmission of HIV (CLOTTEY & DALLABETTA, 1993), and effective STI case management is known to reduce the incidence of HIV (GROSSKURTH *et al.*, 1995). The HIV national prevalence in Malawi is estimated at 15% (NACP, 2001), and HIV infection rates among patients with STIs range from 53% to 83% (KRISTENSEN, 1990). As part of its STI and HIV control strategy, Malawi adopted the World Health Organization (WHO) recommended syndromic approach to STI case management in 1993. Based on clinical efficacy, in-vitro studies and cost considerations, a combination of gentamicin (240-mg single intramuscular dose) and doxycycline (100 mg twice daily for 7 days) was recommended as the treatment of choice for men presenting with urethral discharge (MOHP, 1993). Although this regimen is meant to cover for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections (LULE *et al.*, 1994), the relative prevalence of these pathogens in rural communities in Malawi is not known.

Regular monitoring of antimicrobial susceptibility of *N. gonorrhoeae* and other STI pathogens is essential as resistance patterns could change rapidly (LIND, 1990). Because of scarce resources, this is not done in Malawi and there is limited information on the subject.

Control of STIs involves not only providing effective treatment to those that are infected, but should also involve promotion of safer sexual practices during the symptomatic period.

The present study was undertaken in a rural district of Malawi among men presenting with urethral discharge, in order to (a) describe their health-seeking and sexual behaviour, (b) determine the relative contribution of *N. gonorrhoeae* and *C. trachomatis* to urethral discharge, and (c) verify the antibiotic susceptibility of *N. gonorrhoeae*.

Address for correspondence: Dr R. Zachariah, Head of Mission (Mission Malawi), Médecins sans Frontières–Luxembourg, 70 rue de Gasperich, L-1617, Luxembourg; phone +265 644409 (Malawi), fax +265 641 468 (Malawi) +352 335133 (Luxembourg), e-mail zachariah@internet.lu

Material and Methods

Study population, and data collection

This study was conducted in Thyolo district, a rural region in southern Malawi. Between October 2000 and May 2001, all adult males presenting with urethral discharge to the district STI clinic were invited to participate in this study. After obtaining informed consent, a semi-structured questionnaire was used to gather basic socio-demographic data and information on health-seeking and sexual behaviour. All patients were managed according to national STI guidelines (NACP, 1993).

Prevalence of N. gonorrhoeae *and* C. trachomatis

Patients were requested to provide a urine specimen at the time of first attendance. Nucleic acid amplification, by ligase chain reaction (LCR), was used to determine the presence of *N. gonorrhoeae* and *C. trachomatis* in the urine samples.

Antimicrobial susceptibility testing for N. gonorrhoeae

Swabs were also taken from the anterior urethra at the time of first attendance, smeared on a glass slide for Gram staining and placed directly in a transport medium (Amies media, Oxoid, Basingstoke, UK) containing charcoal. The specimens were transported at the end of each day to the laboratory. Plating was done on modified New York City medium (gonococcal selective) containing lincomycin, colistin sulphate, amphotericin-B and trimethoprim lactate. Yeast autolysate was used as a growth supplement and incubation was done in a candle jar for 48 h at 35°C with 5–10% CO_2.

N. gonorrhoeae was identified by colony morphology, Gram staining and oxidase testing. Penicillinase-producing strains (PPNG) were detected using beta-lactam paper strips (Oxoid), which show β-lactamase activity.

Antimicrobial susceptibility was tested on Muller Hinton agar (Oxoid) supplemented with 5% sheep blood, using the disk diffusion technique. Inhibition zone sizes for *N. gonorrhoeae* were read according to National Committee for Clinical Laboratory Standards (NCCLS, 1998). The E-Test strip (AB-Biodisk, Solna,

Sweden) was used for susceptibility testing to gentamicin, and minimum inhibitory concentrations for gentamicin were read as susceptible (≤16 μg/mL) or resistant (>16 μg/mL) (LESMANA *et al.*, 2001).

Antibiograms were validated with standardized *N. gonorrhoeae* control strains (ATCC No. 49226, American Type Culture Collection, Rockville, MD, USA) on a regular basis and the National Reference Laboratory in Malawi provided monitoring and supervision. Additional technical assistance was provided by the Microbiology Laboratory, Reference Centre for Infectious Disease, Luxembourg.

Data analysis

The EpiInfo software (Centers for Disease Control, Atlanta, GA, USA) was used for data analysis.

Results

Socio-demographic characteristics of the study population

A total of 114 adult male subjects with urethral discharge were enrolled in the study. The median age of the study participants was 27 years (range 16–47, SE 0·6). Most patients (79%) came from rural villages, and were married (57%). The mean educational level of participants was 6·5 years in school. Patients included farmers (29%), unskilled employees (34%), skilled employees (6%), business people (24%) and students (7%).

Health-seeking and sexual behaviour

The mean reported time with STI symptoms before presenting at the STI clinic was 27 days; 61% of all subjects reported having taken some form of medication before coming to the clinic. The most frequent single source of medication was traditional healers (43%) (Table 1). Sixty-eight patients (60%) reported having had sexual encounters during the symptomatic period and the majority (84%) had not used condoms. The main reported reasons for not using condoms during sex in the symptomatic period was partner refusal (37%), and having sex with a spouse or with someone in a steady relationship (28%) (Table 1).

Prevalence of N. gonorrhoeae *and* C. trachomatis

From the 114 patients who submitted urine samples for LCR analysis, data are available for 110 patients; 2 patients submitted insufficient urine for analysis and 2 urine containers leaked during transport. *N. gonorrhoeae* was detected in 90 (79%) urine specimens, *C. trachomatis* in 1 (1%) and combined infections were found in 1 (1%) urine sample.

Antimicrobial susceptibility of N. gonorrhoeae

Out of 47 isolates of *N. gonorrhoeae*, 45 (96%) were found to be beta-lactamase producing (PPNG). All but one of these isolates were resistant to penicillin. Forty (89%) PPNG isolates showed resistance to 2 or more antibiotics. Only 3 PPNG isolates were found to be sensitive to tetracycline. All isolates that were resistant to gentamicin were also resistant to tetracycline. The picture is likely to be the same for doxycycline. The susceptibility patterns of isolates to different antibiotics are shown in Table 2.

Discussion

In this study, 61% of all participants presenting at the rural district STI clinic with urethral discharge had first sought care at an alternative source. The search for effective treatment is therefore delayed, and meanwhile the men continue to have sex while symptomatic, the large majority (84%) not using condoms. These different alternative sources of health care could be targeted to improve STI control in the district and reduce delays in effective treatment.

The traditional healer was found to be the most important single source of alternative care in our rural setting as was found in a similar study in an urban setting of Malawi (LULE *et al.*, 1994). In Malawi, traditional healers are generally reputed to be sympathetic, more confidential, and easily accessible. Considering their importance as an alternative care provider, and the potential role they could play in encouraging safer sexual behaviour, it is important to integrate them in control activities and ensure condom availability (to clients) at their sites.

Table 1. Health-seeking and sexual behaviour in adult males with visible urethral discharge ($n = 114$) (Thyolo, Malawi, 2000/2001)

Variable	Number	(%)
Previous medication before coming to clinic	70/114	61
Modern (ampicillin, co-trimoxazole, etc.)	25	36
Traditional (herbs, roots, etc.)	30	43
Both	15	21
Source of previous medication ($n = 70$)		
Public and private clinics	4	6
Drug vendors/public pharmacy	21	30
Traditional healers	30	43
Several of the above	15	21
Mean duration of urethral symptoms (days)	27	–
Sex during symptomatic period = yes	68/114	60
With same partner	37	54
With different partners	31	46
Condom use during sex in symptomatic period ($n = 68$)		
Always	0	0
Intermittent/sometimes	11	16
No condom use	57	84
Reasons for 'no condom use' ($n = 57$)		
Sex with steady partner or spouse	16	28
Refusal by partner	21	37
Condom not available	5	9
Reduces pleasure	3	5
Religious reasons	10	18
Others	2	4

Table 2. Antibiotic susceptibility pattern of *Neisseria gonorrhoeae* isolates ($n = 47$) from men with urethral discharge (Thyolo, Malawi, 2000/2001)

	Susceptible		Intermediate		Resistant	
Antibiotic	*n*	(%)	*n*	(%)	*n*	(%)
Gentamicin	40	(85)	–	–	7	(15)
Penicillin	1	(2)	3	(6)	43	(91)
Tetracycline	5	(11)	4	(9)	38	(81)
Erythromycin	21	(45)	3	(6)	23	(49)
Co-trimoxazole	17	(36)	4	(9)	26	(55)
Spectinomycin	40	(85)	2	(4)	5	(11)
Ciprofloxacin	32	(68)	12	(26)	3	(6)

See Material and Methods for the methodology used.

The National Tuberculosis Control Programme in Malawi conducts training sessions with traditional healers from around the country, and encourages early referral of tuberculosis suspects. Training on STIs and HIV infection could be linked with such an existing initiative, and might be one way of also encouraging earlier referral (by healers) for antibiotic treatment.

This study is the first in Malawi that has used a highly sensitive and specific nucleic acid amplification technique (STARY, 1997) to determine the presence of *C. trachomatis* and *N. gonorrhoeae* in the urine of men presenting with urethral discharge. Infection with *N. gonorrhoeae* was confirmed in 80% of urine specimens whereas *C. trachomatis* was found in only 2% of specimens. In contrast to previous suggestions (TAYLOR-ROBINSON *et al.*, 1995), *Chlamydia* was not found to be a major pathogen in men presenting with urethral discharge in our rural setting. A similar low prevalence of *C. trachomatis* was found in Blantyre, an urban town in Malawi, where *Chlamydia* antigen was found in only 26 (5·2%) of 497 urine specimens tested (LULE *et al.*, 1994). We had not screened for other possible organisms associated with urethral discharge such as *Ureaplasma urealyticum*, *Mycoplasma hominis* and *Trichomonas vaginalis*.

Only 47 isolates from 90 patients positive for *N. gonorrhoeae* by LCR were available for susceptibility testing. This might be explained by the fact that *N. gonorrhoeae* is a very fastidious organism and, despite use of a transport medium, undocumented delays did occur between collection of specimens in the district STI clinic and inoculation at the laboratory in Blantyre. Specimens were transported once a day and could have been subjected to the rapid changes in ambient temperature that are characteristic of the region.

We used the E-Test for testing the susceptibility of *N. gonorrhoeae* to gentamicin and found it easy and practical to use in our developing country laboratory setting. The disc diffusion method, although most widely available and least expensive, is not considered reliable for gentamicin susceptibility testing, and agar dilution assays are quite complicated to perform for routine surveillance (DALY *et al.*, 1997).

None of the antibiotics tested in our study approached the 95% sensitivity recommended for effective 'blind treatment' (WHO, 1989). The clinical cure rate for gentamicin treatment of *N. gonorrhoeae* was 95% in 1993 (LULE *et al.*, 1994) as compared to 92% in 1996 (DALY *et al.*, 1997). Our study, which is the first since 1996 in Malawi, shows that only 85% of *N. gonorrhoeae* isolates are currently susceptible to gentamicin. Although clinical cure rates might differ from in-vitro susceptibility patterns, this finding is of concern since selection of resistant strains may rapidly limit the usefulness of gentamicin for the treatment of *N. gonorrhoeae* in our setting. There is therefore a need to search for alternative antibiotics for the syndromic treatment of urethral discharge caused by *N. gonorrhoeae*.

All isolates tested in 1996 (DALY *et al.*, 1997) were fully sensitive to ciprofloxacin, ofloxacin and cefixime. We had not tested susceptibility to ofloxacin and cefixime but found 6% resistance and 26% intermediate susceptibility to ciprofloxacin. This could be due to the rising indiscriminate use of this agent which is now readily available (without prescription) at some public pharmacies. Ciprofloxacin is relatively expensive and 'cost considerations' often encourage the use of inadequate, or low dosages that will help force the selection of strains exhibiting resistance or reduced susceptibility (HANDSFIELD & WHITTINGTON, 1996).

The great majority (96%) of *N. gonorrhoeae* isolates in the rural district of study were PPNG strains, the majority of which exhibited multi-antimicrobial resistance. Continuing surveillance of antimicrobial susceptibility of *N. gonorrhoeae* is essential in order to detect emerging resistance, prevent treatment failures and control the spread of resistant strains within the population.

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CHAPTER 8

Sexually transmitted infections and sexual behavior among commercial sex workers in a rural district of Malawi.
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Sexually transmitted infections and sexual behaviour among commercial sex workers in a rural district of Malawi

R Zachariah MBBS DTM&H[1], **M P Spielmann** SRN SNM[1], **A D Harries** MD FRCP (OBE)[2], **W Nkhoma** MD MPH[3], **A Chantulo** DipMed[4] and **V Arendt** MD MPH[5]

[1]*Médecins sans Frontières—Luxembourg, Thyolo District, Malawi,* [2]*National TB Control Program/DFID advisor,* [3]*National AIDS Control Program,* [4]*STI services, Thyolo District, Ministry of Health and Population, Malawi and* [5]*Department of Tropical and Infectious Diseases, Luxembourg*

Summary: In Thyolo District, Malawi, a study was conducted among commercial sex workers (CSWs) attending mobile clinics in order to; determine the prevalence and pattern of sexually transmitted infections (STIs), describe sexual behaviour among those who have an STI and identify risk factors associated with 'no condom use'.

There were 1817 CSWs, of whom 448 (25%) had an STI. Of these, the commonest infections included 237 (53%) cases of abnormal vaginal discharge, 109 (24%) cases of pelvic inflammatory disease and 95 (21%) cases of genital ulcer disease (GUD). Eighty-seven per cent had sex while symptomatic, 17% without condoms. Having unprotected sex was associated with being married, being involved with commercial sex outside a known rest-house or bar, having a GUD, having fewer than two clients/day, alcohol intake and having had no prior medication for STI.

The high levels of STIs, particularly GUDs, and unprotected sex underlines the importance of developing targeted interventions for CSWs and their clients.

Keywords: Malawi, sex worker, STI, condom

Introduction

Commercial sex workers (CSWs) constitute a group often socially stigmatized and economically disadvantaged with a high rate of sexual partner change. They are a core group that are known to be highly vulnerable to sexually transmitted infections (STIs) and to infection with HIV, and consequently are at a high risk of transmitting these infections to their clients and other sexual partners[1].

Thyolo District, in rural southern Malawi, is well known for its semi-urban towns and their HIV risk arenas of lively rest-houses, nightclubs, bars and readily available and inexpensive CSWs. The district is characterized by large tea and coffee plantations, as well as thousands of migrant labourers who patronize the commercial sex industry.

From late 1999, as part of a comprehensive district HIV prevention strategy, regular STI clinic services began to be offered through a mobile team to CSWs in three of the main semi-urban towns Thyolo. This was on the basis that targeti interventions with CSWs could contribute to low community STI prevalence[2,3]. This intervention turn might reduce the sexual transmission ar incidence of HIV[4–6] within the general populatic In a country like Malawi where the national H prevalence is estimated at 15%[7], and HIV rat among patients with STI range from 53–83%[9], S control is of major public health importance.

Information on the prevalence and patterns STIs among CSWs as well as sexual behaviour this group would be relevant in guiding STI conti strategies. Condom use in itself is considered critical measure in preventing the acquisition ar transmission of STIs and HIV[9]. Its use in comme cial sex establishments in Thailand has led reductions of more than 80% in STI incidence ar an apparent decline in HIV incidence[10].

This study was conducted among CSWs in ord to (a) determine the prevalence and pattern of ST (b) describe sexual behaviour including condo use among those who have an STI and (c) identi socio-demographic and behavioural risk factc associated with 'no condom use'.

Correspondence to: Dr R Zachariah, Head of Mission (Mission Malawi), Médecins sans Frontières — Luxembourg, 70 rue de Gasperich, L-1617, Luxembourg
E-mail: zachariah@internet.lu

Material and methods

Study setting

The study was conducted between May 2000 and June 2001 in three semi-urban towns (Thyolo, Luchenza and Bvumbe) of Thyolo District, a rural region in southern Malawi. Prostitution is illegal in Malawi[11]. However, CSWs are readily available in bars and rest-houses and are registered as food handlers, bar girls and cleaners. CSWs are not paid by these establishments but are provided with rooms at these sites and are permitted to live at the location as long as they serve drinks and meals and are readily available for commercial sex activity to clients. Their income is, therefore, dependent on sexual activity with clients at the site. For the purpose of this study this group of individuals were considered as CSWs.

All workers at public locations offering food, drink or accommodation facilities (which includes food handlers, bar girls and cleaners) are required by law to be registered at the community police station. They are also required to produce a valid medical clearance certificate that needs to be shown to the communal police on a monthly basis or on request. The mobile clinic service was conducted once a week during daylight hours at a designated rest-house facility. Peer outreach workers were involved in encouraging the CSWs to attend the clinic.

Study population and data collection

All CSWs presenting during an STI mobile clinic were examined and those with an STI were interviewed after obtaining informed consent. Interviewer-administered questionnaires, which had been pre-tested, were used to gather basic socio-demographic data, as well as information on sexual behaviour and condom use. A genital examination which included detailed screening for STIs and speculum examination was performed on all CSWs. A room was made available for all medical examinations and confidentiality of data was ensured. Examinations were carried out by a team of two trained STI clinicians, and the same team was used throughout the course of the study. A patient card which contained details of STI management was filled out for each patient and subsequently used during weekly follow-up visits. Confidentiality was ensured and all patients were diagnosed and managed using national STI guidelines adapted from the syndrome-based approach (clinical assessment of signs and symptoms) as recommended by the World Health Organization[12]. All CSWs that have been screened and treated are issued with medical clearance certificates.

Statistical methods

Analysis was done using the EpiInfo software (Center for Disease Control, Atlanta), and the LOGISTIC software[13]. The measures of risk were determined by crude odds ratio (OR) and adjusted ORs. Odds ratios were adjusted using multivariate logistic regression, and all related P-values were based on the likelihood ratio statistic. Reported 'no condom use' during sexual encounters in STI symptomatic period was designated as the dependent variable for identifying potential risk associations. The level of significance was set at $P = 0.05$ and 95% confidence intervals (CIs) were used throughout.

Results

Characteristics of the study population

A total of 1817 new female CSWs were involved in the study, of which 448 (25%) were diagnosed with an STI. Of these, 19 were excluded; questionnaires were incomplete in six cases and 13 individuals did not want to participate in the interviews due to lack of time. Of the 429 STI patients whose data were complete, the mean age was 24 years and the mean educational level was three years in school. There were 255 (59%) individuals who were registered as beer servers, 86 (20%) as cleaners, and 60 (14%) as food handlers. Twenty-eight (7%) individuals were not registered as rest-house or bar workers in the semi-urban towns. There were 17 (4%) patients who were married while the great majority (422) were either single, divorced or widowed. Of all CSWs 92% earned less than $7 US/week. One hundred and thirty-seven (32%) patients diagnosed with an STI had received some form of medication before presenting at the mobile STI clinic. The commonest sources for medication included the traditional healer (40%), private pharmacies (31%) and a health facility (19%).

STI prevalence and pattern

There were 448 (25%) new STI cases out of a total of 1817 CSWs. Of these, there were 237 (53%) cases of abnormal vaginal discharge with or without dysuria, 109 (24%) cases of pelvic inflammatory diseases (PID), 95 (21%) cases of genital ulcer disease (GUD) and seven (2%) cases who had combined GUD and PID.

Sexual behaviour and condom use

Of all STI patients, 374 (87%) reported having sex during the STI symptomatic period. Of these, 22 (6%) used condoms always, 290 (78%) used condoms intermittently while 62 (17%) did not use condoms. The reasons for not using condoms included client pressure (30), having sex with a regular partner (20), having no knowledge about the usefulness of condoms (seven), condoms not being available (three) and reduction of pleasure (two). Out of those using condoms intermittently,

120 (41%) did so due to client pressure not to use condoms. The median reported time with STI symptoms before being seen by the mobile STI clinic was six days (range one day to two years). The mean number of clients per day was two.

Risk factors associated with 'no condom use'

Significant risk factors associated with 'no condom use' while having sex in the symptomatic period included being married, being involved with commercial sex outside a known rest-house or bar, having an ulcerative genital disease, having fewer than two clients per day, indulgence in alcohol and having had no prior medication for STI symptoms (Table 1).

Discussion

This study shows that at least one-quarter of CSWs have an STI at any one time with just over 20% of those with an STI having GUD. The great majority of those with an STI (over 85%) engaged in sex while symptomatic. Of those, nearly 20% engaged in unprotected sex, and various risk factors were associated with this behaviour such as being married, being involved with commercial sex outside a known rest-house or bar, having an ulcerative genital disease, having fewer than two clients per day, indulgence in alcohol and having had no prior medication for STI.

Although the prevalence of HIV among CSWs in our setting is not known, it is likely to be high[9]. The finding that GUDs constituted a considerable proportion of STIs in the study population is of particular concern as they facilitate the acquisition and transmission of HIV by acting as portals of entry[4]. Very high GUD rates of up to 49% in male STI patients presenting to the Thyolo District Hospital STI clinic have also been reported[14]. The additional finding that GUD was associated with unprotected sex among CSWs merits that the National AIDS Commission develops a specific focus for decreasing the incidence and prevalence of GUDs.

Prostitution is illegal in Malawi and this legal restriction confines commercial sex activity to well known rest-houses and bars where CSWs are resident and working under cover as bar girls, waiters and cleaners. In our setting this offered an important advantage in that CSWs were readily accessible for STI and HIV control activities through mobile clinics. This service was also considered

Table 1. Risk factors associated with 'no condom use' in commercial sex workers during sexually transmitted infection symptomatic period ($n = 374$)

Variables	Condom=No. (%)	OR	†Adjusted OR (0.95, CI)	*P*-value
Age				
<20 yrs	15/111 (14)	1	1	
>20 yrs	47/263 (18)	1.4	1.4 (0.7–3.0)	0.4
Marital status				
Single/divorced/widowed	46/357 (13)	1	1	
Married	16/17 (94)	108	76 (9.0–645)	<0.001
Education				
<8 years in school	61/372 (16)	1	1	
>8 years in school	1/2 (50)	5.1	2.1 (0.1–45)	0.6
Income				
>4 US$/week	56/360 (16)	1	1	
<4 US$/week	6/14 (43)	4.1	0.6 (0.1–5.1)	0.5
Occupation site				
At a known rest-house/bar	52/350 (15)	1	1	
Outside	10/24 (42)	4.1	5.2 (1.3–2.1)	0.02
Period of STI symptoms				
<14 days	52/330 (16)	1	1	
>14 days	10/44 (23)	1.6	0.7 (0.2–2.2)	0.5
Type of STI				
Non-ulcerative	49/321 (15)	1	1	
Ulcerative disease	13/53 (25)	1.8	2.7 (1.2–6.1)	0.02
Clients/day				
>2 clients	5/142 (4)	1	1	
<2 clients	57/232 (25)	8.9	7.0 (2.5–19.9)	<0.001
Alcohol				
No	38/309 (12)	1	1	
Yes	24/65 (37)	4.2	2.6 (1.2–5.5)	0.01
Previous medication for an STI				
Yes	15/126 (12)	1	1	
No	47/248 (19)	1.7	2.5 (1.1–5.9)	0.02

†Adjusted for age, marital status, education, income, occupation site, period of symptoms, type of STI, clients per day, alcohol and previous medication for an STI

'CSW friendly' as the medical team was authorized to issue medical clearance slips which avoided common harassment or unofficial fines on these workers by local police inspectors. It also saved time and money for travel and queuing up at the district hospital.

Client pressure was the most important single reason for unprotected sex by CSWs in our study. Those who had fewer than two clients per day were also at a significantly higher risk of no condom use than those who had more clients. This is most likely related to economic pressure by clients within a competitive sex industry where some men ironically still prefer to pay for sex without condoms. This situation of limited assertiveness for safe sex due to client pressure constitutes a serious obstacle to preventing CSWs (and their clients) from acquiring and transmitting STI and HIV infections.

Mass awareness campaigns that are adapted to target the clients as well as promoting the female condom which could facilitate independent and assertive behaviour on safer sex by the female CSWs are measures to be considered.

The strength of this study is that all CSWs attending the STI mobile clinic were systematically screened, 96% of all those with an STI were interviewed and everyone was managed for STIs. However, one of the limitations of the study is that the information on sexual behaviour and condom use is self-reported. We tried to minimize this limitation by ensuring that the interviews were conducted by well trained and experienced counsellors who were conversant with the approach on sexual issues within the particular population. The estimated STI prevalence rates in this study would principally reflect rates among individuals that are resident at commercial sex establishments in semi-urban towns and who attended our mobile clinics.

Our experience with mobile STI clinics in Thyolo has been encouraging in that CSWs are readily accessible at fixed sites. Their high rate of partner turnover, the high levels of STIs and unprotected sex in this group underlines the importance of developing targeted interventions for them and their clients.

CSWs in Malawi currently provide a window of opportunity for the prevention of STI and HIV transmission. If this window of opportunity closes, STI and HIV transmission will continue through CSWs and their clients, more people will get infected and will eventually die of AIDS.

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R Zachariah, M-P Spielmann and A Chantulo designed and supervised the study, coordinated the collection and analysis of data. AD Harries, W Nkhoma and V Arendt also assisted in the design of the study protocol and interpretation of the data. All authors participated in the writing of the paper.

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CHAPTER 9

Sexually transmitted infections among prison inmates in a rural district of Malawi.

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Sexually transmitted infections among prison inmates in a rural district of Malawi

Rony Zachariah[1], Anthony D. Harries[2], Austin S. Chantulo[1], Alban E. Yadidi[3], Wilfred Nkhoma[4] and Olive Maganga[5] *[1]Medecins sans Frontieres-Luxembourg, Thyolo District, Malawi; [2]National TB Control Program/ DFID Technical Advisor, Lilongwe, Malawi; [3]Prison Medical Services, Ministry of Justice, Zomba, Malawi; [4]National AIDS Control Program, Ministry of Health and Population, Lilongwe, Malawi; [5]STI Services, Thyolo District, Ministry of Health and Population, Thyolo, Malawi*

Abstract

As part of a comprehensive human immunodeficiency virus (HIV) prevention strategy targeting high-risk groups, sexually transmitted infection (STI) clinics are offered to all prisoners in Thyolo district, southern Malawi. Prison inmates are not, however, allowed access to condoms as it is felt that such an intervention might encourage homosexuality which is illegal in Malawi. A study was conducted between January 2000 and December 2001 in order to determine the prevalence, incidence, and patterns of STIs among male inmates of 2 prisons in this rural district. A total of 4229 inmates were entered into the study during a 2-year period. Of these, 178 (4·2%) were diagnosed with an STI. This included 83 (46%) inmates with urethral discharge, 60 (34%) with genital ulcer disease (GUD), and 35 (20%) inmates with epididymo-orchitis. Fifty (28%) STIs were considered incident cases acquired within the prisons (incidence risk 12 cases/1000 inmates/year). GUD was the most common STI in this group comprising 52% of all STI. This study shows that a considerable proportion of STIs among inmates are acquired within prison. In a setting of same-sex inmates, this suggests inter-prisoner same-sex sexual activity. The findings have implications for HIV transmission and might help in developing more rational policies on STI control and condom access within Malawi prisons.

Keywords: human immunodeficiency virus, sexually transmitted infections, control, prison, condom, Malawi

Introduction

Prison inmates are at high-risk of contracting human immunodeficiency virus (HIV) while serving their sentences (DOUGLAS *et al.*, 1989; GAUGHWIN *et al.*, 1991; BREWER, 1999) and acquired immune deficiency syndrome (AIDS) is becoming a common problem in African prisons (OIP, 1998). In Malawi, although the prevalence of HIV among prison inmates is not known, AIDS is an important cause of death while serving sentences (NYIRENDA *et al.*, 1998, 2000).

In western countries, high-risk factors for HIV transmission in prisons include sexual abuse, homosexual activity, and intravenous injection of drugs. In Malawi, homosexuality, or 'unnatural offences' as it is described in the Malawi penal code, is not considered a societal norm and is currently illegal (LAWS OF MALAWI, 1969), carrying a prison sentence of at least 14 years. However, homosexual activity and sexual abuse is known to occur in Malawi prisons and might be the main method of transmission of sexually transmitted infections (STIs) and HIV (NACP, 1998; JOLOFANI & DEGABRIELE, 1999).

From late 1999, as part of a comprehensive district HIV prevention strategy targeting high-risk groups, regular STI clinics began to be offered through a mobile team to all prisoners in the Thyolo district of Malawi. This was on the basis that STIs facilitate the sexual transmission of HIV (CAMERON *et al.*, 1989; CLOTTEY & DALABETTA, 1993) and effective STI case-management would reduce the incidence of HIV (GROSSKURTH *et al.*, 1995)

Although condom use in itself is a critical measure in preventing the acquisition and transmission of STIs and HIV (NELSON *et al.*, 1996), providing access to condoms within prisons is against regulations as it is felt that such an intervention might encourage homosexual practices.

The objective of this study was to determine the prevalence, incidence and pattern of STIs among prison inmates in a rural district of Malawi.

Address for correspondence: Dr R. Zachariah, Head of Mission (Malawi), Medecins sans Frontières-Luxembourg, 70 rue de Gasperich, L-1617, Luxembourg; fax +352 335133, e-mail zachariah@internet.lu

Methods

Study setting

The study was carried out in Thyolo, a rural district in southern Malawi with a population of 450 000. The district has 2 prisons located at Thyolo and Bvumbe towns, both accepting male prisoners. Inmates include convicts and remandees (those awaiting court sentences). Both prisons have limited infrastructure and space and prisoners are housed in overcrowded conditions. Due to financial limitations the diet is often poor in quality and quantity (JOLOFANI & DEGABRIELE, 1999). Water and sanitation facilities are generally inadequate and essential items such as blankets and soap are in short supply or often not available.

Study population and data collection

The study was conducted over a 2-year period between January 2000 and December 2001 and involved all male inmates in the 2 prisons. Prisoners were seen each Friday on a weekly basis by a mobile clinic team of district health services and the supporting medical non-governmental organization (Medecins sans Frontieres-Luxembourg). All new inmates who had been admitted to the prison during the previous week were seen (active case finding). The prison admission register was used to identify new prisoners who were admitted between the scheduled mobile clinic days. Inmates who had been in prison for longer than one week were seen if there was a problem which needed attention (passive case finding). After obtaining informed consent, all inmates underwent a medical interview and a general medical examination which included detailed screening for STIs. STIs were diagnosed and treated using national guidelines adapted from the syndrome-based approach (clinical assessment of commonly occurring group of signs and symptoms) as recommended by WHO (1991). Particular attention was paid to identifying urethral discharge (UD), genital ulcer disease (GUD), and scrotal swellings (SS) due to epididymo-orchitis. A patient was diagnosed as having UD if he had a purulent or mucoid discharge from the urethral meatus with dysuria, while GUD was defined as a genital lesion denuded of the normal epithelium (ulcer or sore). SS due to epididymo-orchitis was defined as a swollen, tender scrotum associated with fever and/or urethral discharge and in

which strangulated inguinal hernia and torsion of the testes were excluded.

A prison side-room was made available for all medical examinations and confidentiality of data was ensured. Examinations were carried out by a team of 2 trained STI clinicians, and the same team was used throughout the course of the study. A patient card which contained details of socio-demographic and medical data was filled out for each patient and subsequently used during weekly follow-up visits. Inmates who were STI-free on initial screening, or who had an STI but were treated and declared cured (on follow-up) but still presented on a subsequent examination with a new STI were designated as having acquired the infection within the prison (new STI case). Inmates who had reported sexual intercourse within 7 d prior to initial screening and were found with an STI on examination one week later were assumed to have been in the incubation period. These cases were excluded from being considered new (or incident) cases acquired within the prisons. Provision of condoms was not included in the medical care package, as prison authorities considered this a contravention of prison rules and regulations. The prison authorities did agree to information, education and communication sessions (IEC) for inmates as well as the provision of condoms by the prison administrative officer for all inmates on discharge from the prison.

Inmates who were found to have an STI while in prison were also encouraged by the team to go for voluntary HIV counselling and testing (VCT) services which are available at the district hospital. Patients who could not be managed by the mobile team were referred to the district hospital.

This study received ethical approval as part of a package of operational research studies on tuberculosis, STI and HIV by the National Health Sciences Research Council of Malawi.

Statistical analysis

Prevalence was defined as the total number of existing cases of STIs detected among the total population of inmates during the 2-year study period (period prevalence). Incidence was defined as the number of new STI cases (occurring among inmates who were previously declared free of STIs) related to the total population of inmates at risk. This was expressed as incidence risk (cases per 1000 inmates) per year of the study period. Data entry and analysis was done using Epi-Info software (CDC, Atlanta, GA, USA)

Results

There were 4236 prisoners who were registered during the 2-year study period in the 2 prisons. Of these, 7 inmates did not want to be screened for STIs and were therefore excluded from the study. Of the 4229 male inmates involved in the study, the mean age was 28 years and the mean educational level was 6 years in school. There were 2707 (64%) inmates who were married while 1522 were either single or divorced. Of all inmates, 592 (14%) were unemployed at the time of incarceration, 1310 (31%) were unskilled workers, 1058 (25%) were farmers, 677 (16%) were involved in small-scale business, and 592 (14%) were skilled employees. The majority of inmates (79%) resided in villages.

There were 178 (4·2%) prisoners who were diagnosed with an STI. These included 83 (46%) inmates with UD, 60 (34%) inmates with GUD, and 35 (20%) inmates with SS due to epididymo-orchitis.

Fifty-six STI cases were diagnosed among inmates who were previously declared free of STIs during the 2-year study period. Six of these cases (all GUDs) had presented 7 d after the initial examination but had reported having had sexual intercourse within 7 d prior to incarceration. They were therefore assumed to have been in the incubation period and were not considered as incident cases. Of the 50 (28%) STI cases that were considered to be incident (or new) cases acquired in prison over the 2-year period, there were 26 (52%) cases of GUD, 15 (30%) cases of UD, and 9 (18%) cases of SS. This included 29 new STI cases out of a total of 2224 inmates in the year 2000 (incidence risk, 13 cases per 1000 inmates per year) and 21 cases out of 2005 inmates in the year 2001 (incidence risk, 11 cases per 1000 inmates per year). There were 6 cases of ruptured peri-anal abscesses that had to be referred to the district hospital. These inmates were all under 20 years of age and had admitted to having had anal intercourse while in prison. Of those with an STI, 24 (14%) individuals went for VCT services of which 60% were HIV-positive.

Discussion

This study shows that 4·2% of male prison inmates from a rural district in Malawi had STIs and about one-third of these infections were acquired within the prison. Although the mobile clinic services are able to treat these infections, the main limitation of the current strategy is that condoms cannot be made accessible to inmates.

The National HIV prevalence in Malawi is estimated at 9%, (NACP, 1999) and HIV infection rates among STI patients range from 53–83% (KRISTENSEN, 1990). The finding that GUDs constituted a considerable proportion of STIs in the study population is of particular concern as these facilitate the acquisition and transmission of HIV by acting as ports of entry (CLOTTEY & DALABETTA, 1993).

Since over 60% of all inmates in this study were also married, there is also a direct risk of HIV transmission to spouses and therefore to their newborn babies upon release. Not being able to provide access to condoms in such a setting constitutes a serious obstacle to preventing inmates from acquiring and transmitting STI and HIV infections.

We tried to limit cases that might have been in possible incubation at the time of first STI screening, from being considered incident (or new) cases. It is however possible that some cases of GUDs caused by syphilis and lymphogranuloma venereum (which could theoretically have long incubation periods) might have presented much later. There is therefore a possibility that the proportion of GUD incident cases expressed in this study is overestimated.

Juveniles and destitute inmates are at particular risk of exchanging sexual favours with adult prisoners for food, warm clothing, or for protection (situational homosexuality). This situation is made worse by overcrowding, and dwindling prison resources in our setting. Several recommendations have been made as a part of a wider strategy to address the root causes of this activity and the associated risks for HIV transmission (JOLOFANI & DEGABRIELE, 1999). Some of the recommendations include reducing overcrowding, providing separate cells for juveniles, provision of essential items such as blankets, soap and adequate food on a regular basis, and improving the conditions of service for prison warders. It is however likely to be some time before the infrastructure or the funds for implementing these recommendations become available. In the meantime, increasing awareness among inmates, treating prevalent STIs, and provision of condoms are simple public health measures that would help to alleviate the problem of STI, including HIV transmission, in the specific setting.

The Dakar conference on HIV and AIDS in African prisons highlighted the impenetrable and insular nature of prison environments, as well as legal constraints, as being principal obstacles to improving health conditions in African prisons (OIP, 1998). Our experience on addressing health issues with the prison authorities

in Malawi has, on the contrary, been very encouraging. Through a process of continuing dialogue, prison authorities have demonstrated collaboration and a clear willingness in working with us. Malawi is also one of the few countries in Africa where tuberculosis control activities (NYANGULU *et al.*, 1997) and, now, STI control clinics are being offered within prisons in collaboration with partners and the prison authorities.

The issue of providing access to condoms within prisons is a legal one that challenges established social norms and that lies beyond the jurisdiction of prison authorities. The way forward lies not in making pedantic recommendations that challenge basic societal values, but in dialogue with authorities that will lead to cooperation. What is needed now is a pragmatic approach to bridge the current discrepancy between the reality of prison life and prison regulations which are dictated by existing laws.

Prostitution is also illegal in Malawi but prostitutes and their clients are now encouraged to use condoms. The national policy is to distribute condoms. The intention is not to encourage prostitution, but rather to prevent the spread of HIV. Such tolerance, which allows access to condoms based on the current reality in prisons, is what is urgently required.

The United Nations in 1989 affirmed that prisoners should have access to preventive and curative health services without discrimination on the grounds of their legal situation (UNITED NATIONS, 1989). Public health officials and collaborating partners have a moral and ethical role to assist prison authorities in improving the general conditions for prisoners and prison staff as well as advocate for effective change in policies.

Prison populations in Malawi currently provide a window of opportunity for the prevention of STI and HIV transmission. If this window of opportunity closes, STI and HIV transmission will continue in the prisons, more people will get infected and will eventually die of AIDS.

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CHAPTER 10

HIV prevalence, socio-demographic risk factors associated with HIV infection and voluntary counseling of blood donors in Thyolo Malawi. *East African Medical Journal* 2001, 79:88-91.

R. Zachariah, MBBS (Nig), DTM&H (Lond), DCH (Dublin), Medical and Operational Research Co-ordinator (Mission Malawi), Medecins Sans Frontieres, Luxembourg, P.O. Box 30353, Chichiri, Blantyre 3, Malawi, A. D. Harries, OBE, MBBS, DTM&H MRCP, FRCP, Professor, National Technical and Operational Research Advisor (DFID), National Tuberculosis Programme, c/o British High Commission, P.O. Box 30042, Lilongwe 3, Malawi, W. Nkhoma, Dip. Med.; MPH, PhD, Programme Manager, National AIDS Control Program of Malawi, Ministry of Health and Population, P.O. Box 30377, Lilongwe, Malawi (currently Medical Officer, WHO Office for the African Region, Box BE 773, Belvedere, Harare, Zimbabwe, V. Arendt, MD, MPH, Specialist, Department of Infectious Diseases, Reference Centre, Central Hospital, Rue Barble Luxembourg, M-P. Spielmann, SRN, SPN, Co-ordinator TB/HIV Programme, Medecins Sans Frontieres - Luxembourg, P.O. Box 30353, Chichiri, Blantyre 3, Malawi, L. Buhendwa, MD, MPH, Co-ordinator HIV programme, Medecins Sans Frontieres - Luxembourg, P.O. Box 30353, Chichiri, Blantyre 3, Malawi, C. Chingi, SRN, SNM, Co-ordinator and Chief Counsellor, Integrated Counselling Centre, Thyolo District Hospital, Ministry of Health and Population, Malawi and J. Mossong, MSc, PhD, Biostatistician, Centre for Public Research, 57, route d'Arlon, L-1 140, Luxembourg.

Request for reprints to: Dr. R. Zachariah, Medecins Sans Frontieres - Luxemborg, P.O. Box 30353, Chichiri, Blantyre 3, Malawi.

HIV PREVALENCE AND DEMOGRAPHIC RISK FACTORS IN BLOOD DONORS

R. ZACHARIAH, A. D. HARRIES, W. NKHOMA, V. ARENDT, M-P. SPIELMANN, L. BUHENDWA, C. CHINGI and J. MOSSONG

ABSTRACT

Objectives: **To estimate HIV prevalence in various blood donor populations, to identity socio-demographic risk factors associated with prevalent HIV and to assess the feasibility of offering routine voluntary counselling services to blood donors.**

Design: **Cross-sectional study.**

Setting: **Thyolo district, Malawi.**

Methods: **Data analysis involving blood donors who underwent voluntary counselling and HIV testing between January 1998 and July 2000.**

Results: **Crude HIV prevalence was 22%, while the age standardised prevalence (>15 years) was 17%. Prevalence was lowest among rural donors, students and in males of the age group 15-19 years. There was a highly significant positive association of HIV prevalence with increasing urbanisation. Significant risk factors associated with prevalence for both male and female donors included having a business-related occupation, living in a semi-urban or urban area and being in the age group 25-29 years for females and 30-34 years for males. All blood donors were pre-test counselled and 90% were post test counselled in 2000.**

Conclusions: **HIV prevalence in blood donors was alarmingly high, raising important concerns on the potential dangers of HIV transmission through blood transfusions. Limiting blood transfusions, use of a highly sensitive screening test, and pre-donation selection of donors is important. The experience also shows that it is feasible to offer pre and post test counselling services for blood donors as an entry point for early diagnosis of asymptomatic HIV infection and, broader preventive strategies including the potential of early access to drugs, for the prevention of opportunistic infections.**

INTRODUCTION

In Malawi, the National HIV prevalence rate has been steadily increasing over the past 15 years and is currently estimated at 14% for the 15-49 year age group(1). In the presence of such a high HIV prevalence in the general population, blood transfusions can pose potential dangers for HIV transmission despite routine screening of all blood for HIV. Potential risks of HIV contamination in district laboratories can persist due to laboratory false-negatives, poorly staffed and overwhelmed laboratories which increase the risk of human error and limited availability of highly sensitive rapid screening tests. Donations made during the window period also pose a danger for HIV transmission (despite routine screening) and is an important reason for using highly sensitive blood tests and limiting blood transfusions(2, 3).

In 1999, the Thyolo district health services decided to monitor HIV prevalence rates in various blood donor populations in order to identify socio-demographic risk factors associated with prevalent HIV infection and to consider selective exclusion of donors with a high risk of being HIV positive. The reasoning being that such a strategy should result in a donor pool with a lower prevalence of HIV infection which in turn would lower the potential risks of transfusing HIV positive blood.

Considering also that blood donors can be a representative sentinel group under certain conditions(4,5) it was considered useful to use the data to extrapolate age standardised HIV prevalence rates for Thyolo district which is currently non-existent. Pre and post-test counselling services were also offered to all blood donors through an integrated district counselling centre under the logic that this strategy could serve as an early entry point for diagnosing HIV positive and HIV negative individuals and for introducing primary and secondary preventive action in these apparently healthy individuals(6,7).

This cross sectional study was meant to: (a) estimate HIV prevalence in various blood donor populations; (b) to identify possible socio-demographic risk factors associated

with prevalent HIV infection and (c) to assess the feasibility of offering routine pre and post-test counselling for blood donors. The rural district of study, Thyolo, with 450,000 inhabitants is an economic growth point, well known for its HIV risk arenas of lively nightclubs, bars and readily available and inexpensive commercial sex workers.

MATERIALS AND METHODS

Blood donor population and data collection: The blood donor population consisted essentially of members of villages and communities, neighbours of patients and friends or relatives of a patient requiring transfusion. No pre-donation screening for risk factors for HIV existed and there was no active recruiting for voluntary blood donations in any group of the population. Only data from first time donors was used for this study so that counselled donors who knew their HIV status would be unlikely to return for further blood donations and could have an impact on the estimated prevalence in the donor population.

The counselling unit registers were used to put together information for all consecutive voluntary blood donors for a two year period from January 1999 to December 2000. Variables for identifying risk factors included age group, sex, occupation and residence. Rural villages were defined as countryside villages without institutions and no health centre or school. Semi-urban villages were villages having a health centre and/or a school. A town (urban) has a hospital or a comprehensive health centre, was easily reached by public transport and had a variety of institutions and shops including a supermarket. Occupation based grouping of donors included village farmers, students (secondary school), business, unskilled employees (tea estate workers, guards, cooks, and cleaners on permanent contract) and skilled employees (teachers, nurses, senior civil servants, or senior staff in companies or tea estates). The proportions of donors that were pre and post-test counselled in 1999 and 2000 were calculated.

Counselling and serological methods: All potential donors underwent pre- and post-test counselling (after obtaining voluntary informed consent) by trained and experienced counsellors in an integrated, voluntary counselling unit. Pre-test counselling (which was done before testing for HIV) involved giving basic information about HIV and AIDS, explaining the reasons for recommending the HIV test and the clients right to refuse the test. If consent was given, blood was withdrawn and the person requested to return for post-test counselling. Post-test counselling involves either a negative or a positive blood test. If the test was negative for HIV, the client was given primary preventive counselling on how to prevent contacting HIV and AIDS. If the test was found to be positive, the client received secondary preventive counselling on how to prevent reinfection, on how to prevent transmission to partner(s) and counselling on how to use condoms.

Information on the possibility of continuing supportive counselling and the existence of a home based care and support programme was also given. The laboratory technicians were also trained as counsellors in case of donations being required on weekends or public holidays when the main counselling unit was closed. Confidentiality of results was maintained.

Blood was screened for HIV-1 and HIV-2 using a combination of the Capillus test (Cambridge diagnostics Ltd, Galway, Ireland) followed by HIV Spot (Genelabs Diagnostics Pte Ltd, 85 Science park Drive, Singapore). All tests were performed according to the manufacturers instructions. The choice of tests conformed with World Health Organisation (WHO) strategy 11 for HIV antibody testing which recommends the serial use of 2 simple/rapid assays for diagnosis (of asymptomatic HIV infection) when prevalence of HIV infection is over 10%(8). Any discordant sample was retested and if it remained discordant, was sent for ELISA testing at the referral hospital in Blantyre. There were a total of 12 specimens that remained discordant and these results were excluded from the analysis of this study. A system for laboratory control testing was in place and external control by the regional blood transfusion centre was done on regular basis.

Statistical analysis: Analysis was done using the Epi-info software of the Centre for Disease Control, Atlanta, and the LOGISTIC software (LOGISTIC a Logistic Regression Program for the IBM PC™ Dallal GE, The American Statistician, 422, 272). Direct age standardisation of crude prevalence rates was performed for the adult population (>15years) using Thyolo district, age specific population census figures from 1998(9). Chi -square for trend was used for demonstrating a linear trend in HIV prevalence with urbanisation. The level of significance was set at 0.05 and 95% confidence intervals (CI) were used through out. The measures of risk were determined by crude and adjusted odds ratios separately for males and females. The age group 20-24 years, farmers and rural donors were used as baseline categories as they comprised the majority in their respective groups. Odds ratios were adjusted using multivariate logistic regression, and all p-values were based on the likelihood ratio statistic.

RESULTS

Between January 1999 and December 2000, a total of 1128 first time blood donors were registered. Seven hundred and forty two (66%) were males and 386 (34%) were females; the mean age for male and female donors being 29 and 30 years respectively. Sixty three per cent of donors came from rural villages while 21% came from semi-urban villages and 16% from towns. Forty eight per cent of all donors were farmers, 26% were unskilled employees, 6% were skilled employees, 11% were involved in business and 9% were students. The overall crude HIV prevalence of all registered donors was 22% (Table 1). Age standardised prevalence rates using the district population census figures for adults (>15 years) was 17% (15% for males, and 19% for females) (Table 1).

Table 1

Crude and age standardised prevalence rates in male and female blood donors (>15 years)

Donor	Crude prevalence (%)	Age standardised* prevalence (%)
Males	150/742 (20.2)	15.2
Females	96/386 (24.9)	19.3
Total	246/1128 (21.8)	17.4

* Standardised for age (> 15 years) using district age-specific population census figures (1998)

There was a progressive increase in prevalence by age, peaking in the 30-34 year age group (34%) and 25-29 year age group (49%) in males and females respectively followed by a progressive decrease in the older age groups (Tables 2 and 3). In both males and females, the age group 15 - 19 year, students and donors from rural areas had the lowest prevalence

when compared to other groups. There was a highly significant linear trend in prevalence rates in both males and females associated with increasing degrees of urbanisation (p-values for Chi-square for linear trend <0.001).

Table 2

HIV prevalence and associated risk factors in various subgroups of male blood donors

Variable	HIV+ (%)	Crude OR	*Adjusted OR (0.95, CI)	P value
Male donors	150/742 (20.2)	–	–	–
Age group				
15-19	3/76 (3.9)	0.2	0.3 (0.1-0.9)	0.02
20-24	33/193 (17.1)	1	1	–
25-29	43/168 (25.6)	1.7	1.3 (0.7-2.2)	0.37
30-34	40/119 (33.6)	2.5	2.5 (1.4-4.5)	<0.01
35-39	20/78 (25.6)	1.7	1.4 (0.7-2.8)	0.31
40-44	6/41 (14.6)	0.8	0.8 (0.3-2.1)	0.59
45-49	3/36 (8.3)	0.4	0.5 (0.1-1.8)	0.25
>=50	2/31 (6.5)	0.3	0.3 (0.1-1.2)	0.04
Occupation				
Farmers	49/299 (16.4)	1	1	–
Unskilled employees	55/249 (22.1)	1.5	1 (0.6-1.5)	0.83
Skilled employees	8/41 (19.5)	1.2	0.5 (0.2-1.2)	0.09
Business	34/75 (45.3)	4.2	1.9 (1.0-3.6)	0.04
Student	4/78 (5.1)	0.3	0.2 (0.1-0.8)	<0.01
Residence **				
Rural	57/447 (12.8)	1	1	–
Semi-urban	40/163 (24.5)	2.2	3.0 (1.8-4.9)	<0.001
Urban	53/132 (40.2)	4.6	5.2 (3.1-8.9)	<0.001
Time period				
Jan 99 - Dec 99	65/322 (20.2)	–	–	
Jan 00 - Dec 00	85/420 (20.2)	–	–	

* Adjusted for age group, occupation, and residence using logistic regression.
** Chi square for linear trend = 49.5, P-value <0.001

Table 3

HIV prevalence and associated risk factors in various subgroups of female blood donors.

Variables	HIV+ (%)	Crude OR	* Adjusted OR (0.95, CI)	p-value
Female donors	96/386 (24.9)	–	–	–
Age group				
15-19	5/50 (10.0)	0.4	0.4 (0.1-1.3)	0.12
20-24	21/92 (22.8)	1	1	–
25-29	33/67 (49.3)	3.3	2.5 (1.1-5.7)	0.03
30-34	20/65 (30.8)	1.5	1.2 (0.5-3.0)	0.62
35-39	10/43 (23.3)	1.0	1.0 (0.4-2.7)	0.97
40-44	4/30 (13.3)	0.5	0.5 (0.1-1.8)	0.26
45-49	2/23 (8.7)	0.3	0.5 (0.1-2.7)	0.41
>=50	1/16 (6.3)	0.2	0.3 (0-2.6)	0.20
Occupation				
Farmers	44/239 (18.4)	1	1	–
Unskilled employees	14/48 (29.2)	1.8	2.0 (0.9-4.5)	0.11
Skilled employees	6/21 (28.6)	1.8	0.4 (0.1 - 1.1)	0.07
Business	29/49 (59.2)	6.4	2.5 (1.1-5.6)	0.03
Student	3/29 (10.3)	0.5	0.4 (0.1-1.6)	0.16
Residence **				
Rural	30/263 (11.4)	1	1	–
Semi-urban	32/69 (46.4)	6.7	6.9 (3.4-14.0)	<0.001
Urban	34/54 (63.0)	13.2	13.1 (5.9-29.2)	<0.001
Time period				
Jan 99 - Dec 99	43/191(22.5)	–	–	
Jan 00 - Dec 00	53/195 (27.2)	–	–	

* Adjusted for age group, occupation, and residence using logistic regression.
** Chi square for linear trend=82.1, P-value <0.001

Significant risk factors associated with prevalence for both male and female donors were having a business-related occupation, living in a semi-urban or urban area, as well as being in the age group 25-29 years for females and 30-34 years for males. The reference categories were farmers, rural donors and the age group 20-24 years respectively (Tables 2 and 3). Moreover among males, the age group 15-19 years and students had significantly lower odds of being HIV positive than these reference groups. All blood donors were pre-test counselled while 70% were post-test counselled in 1999 and 90% in 2000 respectively. Out of those who were not post-test counselled in 2000, 61% were farmers, 20% were unskilled workers, 2% were skilled workers, 10% were in business while 7% were students. The specific reasons why post-test counselling was not done in these individuals were not documented.

DISCUSSION

The overall crude prevalence of HIV among blood donors (22%) was alarmingly high highlighting the potential dangers of HIV transmission through blood transfusions. The age standardised prevalence rate for adults of 17% could represent a similar alarming HIV prevalence in the general population (>15 years) in Thyolo district. This estimate was, however, within limits of the assumption that age distribution is the principal manner in which the blood donors differ from the general population since data on occupation and residence profiles for the district are non-existent and has not been included in standardisation. It is also possible that blood donors tend to be healthier than the general population, so that unhealthy individuals (which could be at higher risk of being HIV positive) are under-represented in the sampled population. The high prevalence rates in the younger age groups and particularly in females could be linked to the cultural practices, beliefs and behaviour as well as some of the unprotected sexual initiation rites that facilitate HIV transmission among the predominantly Lomwe tribes of Thyolo(10). The high prevalence in business people might be linked to higher socio-economic status, travel away from homes and increased indulgence in risky sexual behaviour. The highly significant positive linear trend of HIV prevalence with increasing urbanisation and particularly in towns located on the main road in Thyolo could be consistent with increased and extensive risky behaviour(11) in town arenas in the district that are well known for its lively night life, bars and readily available commercial sex workers.

HIV prevalence was lowest among students (5% for male and 10% for female students), among males 15-19 year old(4%) and in donors from rural areas (12.8% for males and 11.4% for females). If active recruitment of blood donors is required for whatever reason, these groups should be preferred. Although all blood donors were pre-test counselled in both years, in 1999 only 70% underwent post test counselling as compared to 90% in 2000. This was because in 1999, both the counselling unit and

laboratory were understaffed and it was not possible to ensure that all donors were pre and post-test counselled the same day. Patients were often requested to return on a different day for post-test counselling incurring additional time and transport costs for the donor and this might be the reason why some of these patients failed to return. In 2000, the post-test counselling rate improved drastically to 90% as additional trained staff were recruited for the counselling unit and laboratory making it possible to offer pre and post test counselling to all blood donors on the same day.

From an economic perspective, the strategy of counselling blood donors adds an important advantage in that HIV tests are used for dual purposes (blood screening and HIV counselling) in a context where resources are limited and HIV tests are expensive. In the presence of the alarmingly high HIV prevalence among blood donors, it is essential to ensure strict criteria to avoid unnecessary transfusions. There is also an absolute need to ensure the availability of highly sensitive HIV rapid tests for blood screening. The information on risk factors for prevalent HIV infection will be useful in advocating pre-donation selection of blood donors in the area of study although this could have limitations due to the already high prevalence and widespread nature of the epidemic.

The experience is particularly encouraging as it shows that it is feasible to implement pre and post-test counselling services for blood donors within a rural district set up and such a strategy could serve to reinforce primary and secondary preventive strategies in apparently healthy HIV positive and HIV negative individuals. It could equally be an important entry point for early diagnosis of asymptomatic HIV infection and the potential of early access to drugs for the prevention of HIV-related opportunistic infections. The potential of preventive therapy against tuberculosis using isoniazid prophylaxis can be considered(12). Patients could also have the possibility of being monitored on a continuing basis and once they develop symptoms (WHO stage 2, 3, 4) or their total lymphocyte count drops to 2000 or less (CD4 count of < 500cells/mm3, if available), they can also be offered co-trimoxazole prophylaxis(13).

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CHAPTER 11

GENERAL DISCUSSION

GENERAL DISCUSSION

The studies presented in this thesis, focus on cotrimoxazole prophylaxis in TB patients, early TB mortality, sexually transmitted infection among specific population groups and voluntary counseling and HIV testing.
In each of these areas, I discuss some of the principal findings, possible limitations, and their influence on policy and practice. Where relevant, I suggest areas requiring further research.

The study on voluntary counseling, HIV testing and adjunctive cotrimoxazole (Chapter 2) showed a very high overall acceptance rate of both interventions among TB patients registered under routine programme conditions. Approximately 90% of all TB patients underwent voluntary counseling and HIV testing and 93% of all those who were HIV positive actually took cotrimoxazole.
A recent study which compared the impact of offering a package of voluntary counseling and HIV testing and cotrimoxazole in Thyolo district with a neighboring district (Mulange) that did not offer such a package showed that there was a significant improvement in TB treatment outcomes in Thyolo[1]. This finding is encouraging in that it further supports offering such a package to TB patients in Malawi.

One of the main encouraging findings was the high acceptability of voluntary counseling and HIV testing among TB patients and this trend has continued after the completion of the operational research study[2]. This is important for a number of reasons. First, TB is an early opportunistic infection which often brings the HIV positive individual to medical attention. There is thus an opportunity for introducing a wide range of prevention and care related interventions. Second, the prevalence of HIV in TB patients in our setting is high like is the case in many other sub-Saharan African countries. Targeting this group of individuals for voluntary counseling and HIV testing is worthwhile as a large proportion of the group might benefit from available interventions[3,4]. Third, according to recent World Health Organization guidelines on scaling up highly active antiretroviral treatment in developing countries, HIV positive TB patients are classified in WHO stage III (active pulmonary TB) or stage IV (extra-pulmonary TB) and would be eligible for antiretroviral treatment on purely clinical grounds[5]. Offering voluntary counseling and HIV testing to this group could thus provide a potential entry-door to highly active antiretroviral treatment[6].
Encouraging findings with respect to the uptake of voluntary counseling and HIV testing have also been reported from Abidjan, Cote d'Ivoire [7] and public health experts have argued that voluntary counseling and HIB testing should be introduced routinely in out-patient TB centers[8,9].
The most encouraging finding was the reduction in mortality of 22 % in the cohort of TB patients who were offered the package of voluntary counseling, HIV testing and cotrimoxazole when compared with a historical control cohort that was not offered these interventions.
Given the ethical impossibility of a placebo-controlled study, Malawi decided to use a historical cohort for comparison. The primary outcome, death while on TB treatment is clear-cut and shows significant improvement in the recent cohort compared to the historical one.

Unlike the Cote d'Ivoire study[10], The Malawi study however failed to demonstrate a mortality benefit among smear positive TB patients and the possible reasons for this difference have been addressed in Chapter 2. The main reason for this difference might however be the smaller proportion of smear positive TB patients in Thyolo who were HIV positive and received cotrimoxazole. This is likely to have reduced the cohort benefit of the drug in these patients when compared to other types of TB.

Although the results of the Thyolo study add to the existing evidence for advocating cotrimoxazole prophylaxis for HIV positive TB patients in sub-Saharan Africa[11], the overall evidence base upon which WHO/UNAIDS[12] released their blanket recommendation on cotrimoxazole remains limited. Both Malawi and Senegal which at the time, were running similar UNAIDS randomized placebo controlled trails as that of Cote d'Ivoire, had to prematurely terminate their studies as UNAIDS felt that the evidence from Cote d'Ivoire study[1] rendered further cotrimoxazole-placebo controlled trials unethical.
The results of the study from Senegal[13] did not demonstrate any effect on morbidity, but inadequate power due to early termination of the study might explain this difference. The study from Malawi faced a similar problem.
Zambia which, at the time was running a randomized controlled cotrimoxazole trial decided to continue their study. They justified their position by saying that it would be unsafe to generalize the results from Cote d'Ivoire to Zambia as cotrimoxazole resistance among common pathogens were relatively higher in their setting[14]. The results of this trail are yet to be published.

Following the encouraging findings from Thyolo, and similar encouraging results from another district in Malawi (Karonga)[15] that was implementing a similar package of interventions, the Malawi Ministry of Health decided to go ahead with a phased implementation of voluntary counseling, HIV testing and cotrimoxazole prophylaxis to the 25 districts in the country.
By July 2003, phased implementation of voluntary counseling, HIV testing and cotrimoxazole prophylaxis to registered TB patients covered 15 of 43 hospitals in Malawi. 16 more hospitals are scheduled to start offering the package by the end of 2004. This phased implementation process is eventually meant to cover all hospitals country-wide.

This decision to scale up voluntary counseling, HIV testing and cotrimoxazole was justified on the basis of the following: First, Malawi had deferred implementing cotrimoxazole prophylaxis for HIV positive TB patients pending the results of its own operational research. The data from Thyolo and Karonga both showed that offering voluntary counseling, HIV testing and cotrimoxazole is feasible, safe and effective in reducing deaths rates in TB patients.
In public health terms, implementing this package on a country-wide level for the 25,000 or so registered TB cases in Malawi (and assuming similar uptakes as in Thyolo) would translate into approximately 2000 prevented deaths during anti-TB treatment per year. The Ministry of Health thus considered this intervention worthwhile. Second, the evidence from Cote d'Ivoire and the additional operational evidence from Malawi inclined policy makers to think that denying HIV positive TB patients such an intervention (in the absence of other evidence that shows ineffectiveness or harm) would be unjustified.

Third, it was felt that cotrimoxazole was a well known drug in the community and HIV positive individuals were already procuring the drug in a rather anarchic manner from private pharmacies, and vendors. Resistance development is likely to be more a result of such practice than its correct and controlled use in the public service.
It was finally felt that the prophylaxis of opportunistic infections and particularly the use of cotrimoxazole would be a logical first step towards implementing highly active antiretroviral treatment. The package of voluntary counseling, HIV testing and cotrimoxazole would serve as a foundation upon which highly active anti-retroviral treatment could be built.

There are still a number of specific unanswered questions. What really caused the reduction in deaths observed in Thyolo? Was it really the cotrimoxazole, was it voluntary counseling and HIV testing and the subsequent knowledge by health care staff, patient and carer alike of the patients HIV status and subsequently better care for those who were HIV positive?
Another issue is the lack of evidence linked to clinical effectiveness of cotrimoxazole among HIV positive children in Africa. The WHO/UNAIDS guidelines[12] includes the recommendation for empiric cotrimoxazole for infants (which by definition includes HIV positive children with TB) which emerged shortly after the publication of the two Abidjan studies[1,16]. This is remarkable given that neither of the two studies provided any information about the optimal efficacy of cotrimoxazole in children. To date, no randomized trails of cotrimoxazole's efficacy in children have been conducted[17]

The study that assessed compliance to cotrimoxazole during anti-TB treatment (Chapter 3) showed a compliance rate of 94%. An additional finding was that compliance with cotrimoxazole as an adjunct to anti-TB treatment could be assessed simply and practically by verbal verification and pill counts. This study also demonstrated that it is important to provide a excess stock of pills as a safety-net for continued prophylaxis. High compliance to cotrimoxazole prophylaxis during anti-TB treatment has previously been reported under research conditions in Abidjan, Cote d'Ivoire[18]
Since the results of this study became available, subjective verification of compliance pill balance-counting, and a safety stock have been introduced for TB patients receiving cotrimoxazole in Thyolo.

The study that assessed compliance with cotrimoxazole after completing anti-TB treatment (Chapter 4) showed that 93% of individuals were still taking the drug when assessed 3 to 6 months after completing anti-TB treatment. The study also showed that close to 70% of individuals on cotrimoxazole would find it difficult to pay for the drug. In a rural setting where close to 60% of all TB patients earn less than 4 USD per week, this reemphasizes the importance of making sure that the drug is provided free of charge. Since the most common reported reason for stopping the drug was long distances to certain health centers the study raises the importance of ensuring geographical access for long-term prevention.

Although the two studies on cotrimoxazole compliance (Chapter 3 and 4) address the question of compliance in the course of anti-TB treatment and three to six months after, the findings might not necessarily reflect compliance in the longer term. After completing anti-TB treatment, there was a 7% drop out rate to prophylaxis within a three to six months period. Although we can not assume that this would continue to be the trend over time, if indeed such a trend continues, our studies would over-estimate long term compliance. In any case it would

be worthwhile to assess longer term compliance (say after a period of 5 years of starting prophylaxis) with cotrimoxazole.

The study (Chapter 5) which assessed changes in *Escherichia coli* resistance to cotrimoxazole showed that among TB patients, baseline resistance to cotrimoxazole was high (60%) and this increased with time. The increase in resistance (89%) was found to be very significant among HIV-positive TB patients who were taking cotrimoxazole prophylaxis for a period of 6-8 months (89%).
Non-typhoid Salmonella bacteremia particularly with *Salmonella Typhimurium* and *S. enteritidis* is known to be among the leading causes of morbidity and mortality in HIV infected patients in Africa[19-21]. A finding of high resistance to *E.coli* such as in our setting heralds rapid plasmid-mediated transfer of resistance to other Enterobacteriaceae including the *Salmonella* species. It is thus likely that resistance in the latter is also high in Thyolo.
A study from Blantyre, a neighboring district to Thyolo reported the predominance of *non-typhi salmonellae* among adult patients with bacteraemia[22]. Mortality in those that had *non-typhoid salmonella* bacteraemia (n-100) was extremely high (47%) and so was the rate of recrudescence (43%)[23]. In that particular study, resistance levels of *Non-typhoid salmonella* to cotrimoxazole was 73% among adults[23] and 72% among children[24] . In Cote d'Ivoire, susceptibility of *non-typhoid Salmonella* to cotrimoxazole was high (91%) and protection from *non-typhoid Salmonella* bacteremia and enteritis accounted for much of the beneficial effect of cotrimoxazole seen in that setting[1,14]. The results of the Thyolo study (and those from Blantyre) suggests that baseline resistance of *non-typhoid Salmonella* to cotrimoxazole is rather high and the protective effect of the drug wanes with time[25]. This would herald limitations to the short and long terms benefits to be expected from the use of cotrimoxazole prophylaxis in preventing *non-typhoid Salmonella* related morbidity and mortality in Malawi.

There are several questions and concerns related to the development of cotrimoxazole resistance associated with wide-spread implementation of prophylaxis in high HIV prevalence settings such as Malawi.
The list of pathogens (other than *E.coli)* whose epidemiology could be altered by cotrimoxazole exposure includes *Streptococcus pneumoniae, Staphylococcus aureus, Haemophilius influenzae,* and *Neisseria species.* We do not know the baseline cotrimoxazole susceptibility levels among these organisms nor do we know the eventual impact wide-spread cotrimoxazole prophylaxis would have on its development.
Cotrimoxazole is still first-line therapy for a variety of childhood infections under the World Health Organization integrated management of Childhood Infections (IMCI) guidelines[26]. Malawi currently follows these guidelines and resistance development could impair the effectiveness of the IMCI program and thus merits surveillance.
Widespread use of cotrimoxazole is also likely to foster the growing or already high sulfadoxine-pyrimethamine (Fansidar) resistance in *Plasmodium falciparum*, an organism which globally kills approximately one million children each year – the most attributable to any single childhood pathogen[27]. Cotrimoxazole and sulfadoxine-pyrimethamine are close pharmacologically, and share extensive in-vitro cross-resistance [28,29]. Malawi currently uses sulfadoxine-pyrimethamine as first line therapy for malaria and wide-spread use of cotrimoxazole prophylaxis is likely to reduce the useful life of sulfadoxine-pyrimethamine as an effective first line treatment for Malaria. Contrary to expectations, sulfadoxine-pyrimethamine has retained good efficacy (80%) after 10 years as the first line antimalarial

drug in Malawi[30]. Resistance to this drug is however growing or already high in most African countries and it has been suggested that malaria treatment needs to change to artemisinin-class combination therapies[31].
There is also the concern on whether cotrimoxazole prophylaxis could impede the acquisition of natural malaria immunity by infants. Because of maternal antibodies, infants in areas of high malaria incidence are often born with immunity to malaria[32]. As this passive immunity wanes, natural immunity emerges after exposure to infectious mosquitoes. Cotrimoxazole reduces both clinical malaria and asymptomatic parasitemia and, in so doing, could hypothetically attenuate the normal acquisition of immunity. This creates an ethical dilemma since HIV-exposed infants discontinuing prophylaxis, after a negative HIV test at one year of age, might be more vulnerable to severe malaria than if they had never received prophylaxis.

Whatever might be the eventual answers to these questions and concerns, a number of issues are clear. First, the protective effect of cotrimoxazole prophylaxis with respect to bacterial pathogens (and other pathogens) is likely to be time-bound. Currently, there are no alternative choices to cotrimoxazole that have the advantages of providing protection against a range of opportunistic pathogens; being cheap; easy to administer, and relatively safe in terms of incidence of side-effects. There is thus a need to seek for alternative therapies for prophylaxis of opportunistic infections as cotrimoxazole becomes progressively obsolete for this purpose. Second, resistance of *P falciparum* to sulphadoxine-pyrimethamine is already high or rapidly rising in many African countries and it is high-time to move on to the artemisinin-class combination therapy[31,33,34]. The World Health Organization has formulated policy that elevates such therapy as the policy standard for all malaria infections in areas where *P.falciparum* is the predominant infecting species of malaria[34]. Although the high current cost of artemesinin compounds is still a limitation, this barrier must be tackled through advocacy for price reductions combined with access to international funds through the Global Fund to fight TB, AIDs and Malaria.
The best long-term solution for the prevention of HIV related opportunistic infection would be to improve the immune status of individuals and reduce susceptibility to opportunistic infections through the administration of highly active antiretroviral treatment.
Countries in sub-Saharan Africa who currently face the challenge of a high HIV prevalence as well as high HIV-related morbidity and mortality need to drive forward in this direction.

The study that tried to test the hypothesis of an association between malnutrition in TB patients and early TB deaths (Chapter 6) showed that more than half (57%) of all TB patients were malnourished and over one third (37%) had moderate to severe malnutrition. TB patients who were malnourished and had a body mass index of less than 17.0 kg/m^2 had an increased risk of dying in the first month following registration than those who had a higher body mass index.
Despite the fact that nutritional status was assessed in a very large number of TB patients (1181), one of the main limitations of the study is that close to 30% of all early deaths recorded in the study occurred before height and weight measurements could be done. Since these individuals were thus excluded from the analysis, we are unable to ascertain how the nutritional status of these particular individuals might have influenced the association between early mortality and malnutrition.
In the Thyolo study, HIV positive TB patients had a significantly higher risk of dying in the first month and a larger proportion of HIV positive TB patients had moderate to severe

malnutrition than HIV-negative patients. Similar findings have been described in Burundi[36]. Early mortality and its association with low body weight has also been described in South Africa[37]. Another study[38] conducted among hospital inpatients in Bujumbura, Burundi, showed that in patient malnutrition was associated with TB and HIV independently and these variables were in turn associated with higher in-patient mortality rates.
Although we have demonstrated that a body mass index of less than 17.0 $kg/^{M2}$ is associated with early deaths, we do not know if in our setting, it is the nutritional impairment in its own right that predisposes to early death or whether malnutrition is a simple marker of extensive TB, severe HIV related complications, undiagnosed opportunistic infections, or other adverse factors. These questions remain largely unanswered and merit further study.

Whatever the eventual answers to these questions might be, the body mass index is a simple measurement that can be performed in hospitals managing TB patients and those with a body mass index of $17kg/M^2$ or less should be considered a priority for targeting care related interventions. The results of this study have helped alert the Ministry of health and partners in Malawi on the need for considering nutritional supplementation for TB patients as an important aspect of implementing joint HIV-TB activities in Malawi. Continued funding for providing nutritional rehabilitation for TB patients in Thyolo has been made available since the results of this study were published.

The study (Chapter 8) that looked at urethral discharge in men presenting to the district hospital sexually transmitted infection clinic showed; that the majority (61%) of men first seek care at an alternative source, the great majority of individuals with symptoms continue to have sex without using condoms and that the susceptibility of *Neisseria gonorrhoeae* to gentamicin was below the 95% mark recommended by the World Health Organization for the syndromic management of sexually transmitted infections[39]. The most important alternative source of care was the traditional healer
The mean period with symptoms before presenting at the sexually transmitted infection clinic was relatively long (estimated at about 4 weeks) and the majority of these men (84%) continued to have unprotected sex while symptomatic. These findings are particularly worrying in a setting where the prevalence of HIV among sexually transmitted infection clients range from 53 to 83%[40] with a high subsequent risk of sexually transmitted infection and HIV transmission to sexual partners.
The important role of traditional healers in the care of sexually transmitted infections in Malawi has been demonstrated in other studies study in Thyolo[41] and Lilongwe[42]. The important role of this group of alternative care providers as regards TB treatment has also been demonstrated in Malawi[43].
Malawi is one of the few countries where traditional healers are licensed and officially recognized within health services. Despite this, the allopathic and traditional systems of care have led parallel paths over the years. This study and other related studies[41-43] led the MOH in Malawi to try to bridge existing gaps between the two service providers. In Thyolo, the district coordinator for sexually transmitted infection control and the Non Governmental Organization (MSF) now involve traditional healers in planning and activities related to sexually tranmitted infection control. Condoms are also made available at the 48 or so traditional healer sites in Thyolo and these are distributed free of charge to clients with sexually transmitted infections. Traditional healers are also encouraged to refer clients with sexually transmitted infections to

the district clinic. These strategies are integrated along with Information, education and communication sessions encouraging wider use within the community at large.
The National TB control program has been conducting yearly training of all traditional healers country-wide in Malawi and encourages early referral of TB suspects. Efforts are being made to link such an existing initiative to trainings on HIV infection and STI control. This might be one way of encouraging early referral of clients with sexually transmitted infections for effective antibiotic treatment.
This study conducted was the first since 1996 and clearly showed that none of the antibiotics recommended for the syndromic management of sexually transmitted infections approached the 95% mark as recommended by the World Health Organisation[39]. The study led to calls for a complete re-evaluation of the existing syndromic management protocol in Malawi.
Although this study provided important insight into some existing gaps in the current control strategy for sexually transmitted infections, it is not designed to provide specific recommendations on antibiotic treatment in men with urethral discharge. Since the focus was on men, there are also unanswered questions as regards the prevalence, patterns and particularly the antibiotic susceptibility of sexually transmitted infections in women. Further studies including clinical efficacy studies are thus justified.

The study on sexually transmitted infections and sexual behaviour among female commercial sex workers (Chapter 8) attending a mobile STI clinics in bars and brothels showed that one out of every four commercial sex workers, in the setting had a sexually transmitted infection, and that the great majority of these individuals (87%) continued to have unprotected sex while symptomatic.
Relatively recent data from Accra, Ghana [44], and Cotonou, Benin [45] adds weight to the growing body of evidence demonstrating the importance of core and bridging groups in the HIV epidemic in sub-Saharan Africa. The data from these two studies strongly suggest that transactional sex accounts for the majority of HIV cases among adult men, in settings where overall HIV prevalence in the general population is still under 5% (moderate). Men then act as a bridging population, transmitting HIV from the core group of commercial sex workers to their other non-commercial sexual partners [44, 46]. In situations such as these, where there is a significant difference between HIV prevalence in sex workers, their clients, and the general population, interventions targeted at commercial sex workers and their clients could substantially delay the onset and reduce the magnitude of a widespread epidemic in the general population[47].

The scenario is likely to be similar even if less marked in Southern African countries (including Malawi) where the HIV epidemic is more explosive and still on the rise. A study carried out among commercial sex workers in KwaZulu-natal, South Africa showed an HIV prevalence of 56% in this population[48]. The difference between this and the HIV prevalence in the general population of this region at the same time of the survey (20-25%) suggest that, even in explosive epidemics, interaction between commercial sex workers and their clients and subsequently between these men and other women who are not commercial sex workers may be of importance in the dynamics of HIV transmission.
The study in Thyolo and studies in West Africa have clearly shown that it is possible to implement successful preventive interventions targeting commercial sex workers[49-50]. More recently it has also been shown that clients of commercial sex workers are also a reachable population in terms of increasing condom use and decreasing rates of sexually transmitted

infections [44,51,52]. An important aspect of this approach is to involve pimps and bar owners in the sexually transmitted infection and HIV control strategy[53] and focus on strong peer education and empowerment[54].
In Thyolo like in many other settings, the use of condoms by commercial sex workers often depend on client pressure. This situation of limited assertiveness for safe sex is a serious obstacle to preventing these workers (and their clients) from acquiring and transmitting sexually transmitted infections and HIV infections. The introduction of the female condom is likely to facilitate independent and assertive behaviour on safer sex by commercial sex workers and this female devise was found to have a high acceptability in this group[55]. Access to both male and female condoms are now part of the sexually transmitted infection control package offered to sex workers and their clients in Thyolo.

Despite the importance of sexually transmitted infections and HIV control interventions among commercial sex workers, sub-Saharan African countries, including Malawi, do not routinely target this group. Existing interventions are often isolated and run by non governmental organizations or research groups. Given the convincing evidence accumulating about the central role of transactional sex in the HIV epidemic, scaling up interventions that target commercial sex workers (both in intensity and geographical coverage) is urgently required. Preventive and curative services for this group of individuals should be organized with the same goal of nation-wide access as for other public health priorities.

The study on sexually transmitted infections among male prison inmates (chapter 9) revealed a sexually transmitted prevalence of 4.2% and an incidence of 12 new cases/1000 inmates/year. Another study conducted in a district setting in Ttcheu, Malawi revealed a sexually transmitted infection prevalence rate of 11% among new male prisoners[56]. In the Thyolo study, about one third of all cases of sexually transmitted infections were acquired within prison walls. In a prison which accommodates only male prisoners, this suggest inter-prisoner same-sex sexual activity.
Providing access to condoms within such prisons is however not allowed as it is felt that such an intervention will encourage homosexuality which is illegal and carries a prison sentence in itself of at least 14 years[57] in Malawi.
The issue of providing condoms in prisons is thus one that challenges established social norms and existing laws which lie beyond the jurisdiction of prison authorities. In trying to address the issue of condoms in prisons, we avoided recommendations that would directly challenge the existing law but rather tried to find a pragmatic solution that would bridge the discrepancy between the reality of prison life and prison regulations that are dictated by existing laws.
The Dakar conference on HIV/AIDS in African prisons high-lighted an impenetrable and insular nature of African prison environments as well as legal constraints as the principal obstacles to improving health care for prisoners[58]. Our experience shows that through a process of continuing dialogue the prison authorities in Malawi demonstrated collaboration and a real willingness to work with us. Although we were not allowed to openly distribute condoms to male prisoners, prisoners are now allowed access to condoms through the medical staff present on daily basis.
The TB program in Malawi has similarly demonstrated how they have been able to work with prison authorities to improve the diagnosis and treatment of TB in 22 prisons country-wide[59]. The results of this study from Thyolo helped prison authorities to seek additional help in the management of sexually transmitted infections in prisons in Malawi. Another Non

Governmental Organization (Banga La Tscholo) has started a phased approach to introduce STI control services in the 22 prisons country-wide. Discussions are also being held about setting up voluntary counseling, HIV testing and packages of care for those prisoners who are HIV-infected.

The study conducted on blood donors (Chapter 10) showed that HIV prevalence in blood donors was alarmingly high (22%) raising concerns on the potential dangers of HIV transmission through blood transfusions. What was particularly interesting was the very high uptake (90%) of voluntary counseling and HIV testing among blood donors. In a setting where almost one fourth of all donors are HIV positive, offering voluntary counseling and HIV testing would offer an early opportunity for the early diagnosis of HIV infection to individuals that otherwise might not have made contact with the health services. . This opportunity can be used as an entry-point into prevention and care programs.
In 2003, a country-wide situation analysis carried out by the Ministry of health[60] revealed that a total of 60561 HIV tests were done on blood for transfusions in Malawi. The HIV prevalence among those tested was 15% and thus a total of over 9000 HIV positive individuals can be identified and provided an early entry point into possible HIV prevention and care activities.
What has not been addressed in this paper is the problem of incident cases and those in the window period of infection. The use of improved questionnaires to assess recent risk behaviour, implementation of the P24 antigen test and change from blood donors who are family members to true voluntary altruistic blood donors have been suggested[61]

The different research studies presented in this thesis were all conducted in close collaboration with partners from the Ministry of Health and population. This made it easier for the Government to share ownership of the findings. The strategy also made it easier to disseminate the results within and outside Malawi, and to translate the lessons learnt from the research into policy and practice.
The Ministry of health in Malawi and particularly the national TB control programme has a culture of performing operational research, and this encourages non governmental organizations and individuals alike to follow an evidence based approach towards improving and even changing existing strategies in health care.

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SUMMARY

This thesis describes operational research conducted in Thyolo district in rural southern Malawi. The studies were carried out within the framework of a district HIV/AIDS and sexually transmitted infection control program of an Non Governmental Organization (Medecins sans Frontieres-Luxembourg). All the studies were all conducted during the tenure of the author in Malawi.

Chapter 1 gives an overview of HIV/AIDS, Tuberculosis and sexually transmitted infections in terms of; burden of disease, interactions between TB and HIV and between sexually transmitted infections and HIV, the consequences of these diseases, the framework for control and some of the main operational research questions linked to these diseases in sub-Saharan Africa.
This chapter also provides background information on Malawi and the extent of the TB-HIV and sexually transmitted infection epidemics. This is followed by a short description of Thyolo district, which was the main site of the studies included in this thesis.

Chapter 2 describes the feasibility and effectiveness of offering voluntary counseling, HIV testing and adjunctive cotrimoxazole prophylaxis in reducing mortality among TB patients registered under routine programme conditions in the rural district of Thyolo. The study was designed as a "before" and "after" cohort study using historical controls.
A total of 1986 patients was registered in the study; 1061 in the intervention group (which received voluntary counseling, HIV testing and cotrimoxazole) and 925 in the historical control cohort (which received no such interventions). In the intervention group, 1019(96%) patients were pre-test counselled, 964 (91%) underwent HIV testing and 938(88%) were post-test counselled. The overall HIV-seroprevalence rate was 77%. A total of 693 patients were given cotrimoxazole of whom 14(2%) manifested minor dermatological reactions. The adjusted relative risk of death in the intervention group compared with the control group was 0.81($p<0.001$). The number needed to treat with a package of voluntary counseling, HIV testing and adjunctive cotrimoxazole to prevent one death during anti-TB treatment was 12.5.This study shows that voluntary counseling, HIV testing and adjunctive cotrimoxazole is feasible, safe and reduces mortality rates in TB patients under routine programme conditions.

Chapter 3 describes compliance to cotrimoxazole prophylaxis in HIV infected TB patients during the continuation phase of anti-TB treatment. The study also describes the sensitivity, specificity and positive predictive values of verbal verification and pill counts as methods of checking compliance.
Cotrimoxazole compliance was assessed in a cohort of TB patients who were attending follow-up centres during the continuation phase of anti-TB treatment between months 4 to 6. Verbal verification of drug intake, physical verification of pill count balance, and urine trimethoprim detection by gas chromatography and mass spectrometry were used for assessing compliance.
Using urine trimethoprim detection as the gold standard for compliance, trimethoprim was detected in 82 (94%) of 87 patients in the cohort. "Verbal verification" of cotrimoxazole intake and objective "pill count balances" showed high sensitivity and positive predictive values compared with the gold standard of urine trimethoprim detection.

The study shows that compliance to cotrimoxazole as an adjunct to anti-TB treatment in HIV-infected TB patients was good, and can be assessed simply and practically by verbal verification and pill counts.

Chapter 4 is a cross-sectional study that verified compliance to cotrimoxazole among HIV infected individuals who completed anti-TB treatment 3-6 months earlier. The study determined the proportion of individuals who continued with cotrimoxazole prophylaxis for the prevention of opportunistic infections, and the reasons for continuing or stopping prophylaxis.
76(93%) of 82 HIV infected individuals who were alive at the time of interview were continuing with cotrimoxazole and wished to do so indefinitely. The most common reason for continuing the drug was to prevent illness associated with HIV while the most common reason for stopping was long distances to the health facility. 96% of patients received cotrimoxazole free of charge from a health center. Of those who wished to continue indefinitely, the majority(63%) could not afford to pay for the drug.
The study shows that in the rural setting of study, the great majority of HIV-infected individuals continued with cotrimoxazole after completing anti-TB treatment and that making the drug available and providing it free of charge is essential if it is to remain accessible for longer term prevention of HIV related opportunistic infections.

Chapter 5 presents the findings of a series of cross-sectional studies that were carried out to determine whether faecal *Escherichia coli* (E.coli) resistance to co-trimoxazole in TB patients changed with time and whether the resistance pattern was different in HIV positive TB patients who were taking co-trimoxazole prophylaxis.
Co-trimoxazole resistance among *E.coli* isolates in TB patients at the time of registration was 60% in 1999 and 77% in 2001 ($p<0.01$). Resistance was 89% among HIV infected TB patients (receiving co-trimoxazole), while in HIV negative patients (receiving anti-TB therapy alone) it was 62% ($p<0.001$).
The study shows a significant increase of *E.coli* resistance to co-trimoxazole in TB patients which is particularly prominent in HIV infected patients on co-trimoxazole prophylaxis. Since a high degree of plasmid mediated transfer of resistance exists between E.coli and the Salmonella species, these findings could herald limitations on the short and long term benefits to be anticipated from the use of co-trimoxazole prophylaxis in preventing *non typhoid salmonella* bacteraemia and enteritis in HIV infected TB patients in Malawi.

Chapter 6 is a study conducted in new patients registered with TB to determine the prevalence of malnutrition on admission and the association between malnutrition and early mortality (defined as death within the first four weeks of treatment).
There were 1181 patients with TB, (576 men and 605 women), whose overall HIV-infection rate was 80%. 673 (57%) TB patients were malnourished on admission (body mass index < 18.5 kg/m^2). There were 259 (22%) patients with mild malnutrition (body mass index 17.0-18.4 kg/m^2), 168 (14%) with moderate malnutrition (body mass index 16.0-16.9 kg/m^2) and 246 (21%) with severe malnutrition (body mass index < 15.9 kg/m^2).
95 (8%) patients died during the first four weeks. Significant risk factors for early mortality included increasing degrees of malnutrition, age > 35 years, and being HIV-positive. In all patients (n-1181), 10.9% of 414 patients with moderate to severe malnutrition died in the first

four weeks compared with 6.5% of 767 patients with normal to mild malnutrition (OR 1.8, 95% CI; 1.1-2.7).
The study shows that in patients with TB, a body mass index < 17.0 kg/m^2 is associated with an increased risk of early death. This group of patients should receive nutritional rehabilitation and should be prioritised for other care related interventions.

Chapter 7 presents the findings of a study conducted among men presenting with urethral discharge to Thyolo district hospital. The study looked at health seeking and sexual behavior, the prevalence of *Neisseria gonorrhoeae* (N.gonorrhoeae) and *Chlamydia trachomatis* (C.trachomatis), and antibiotic susceptibility
Out of a total of 114 patients, 61% of reported having taken some form of medication before coming to the sexually transmitted infection clinic. The most frequent alternative source of care was the traditional healer. 68 (60%) patients reported sex during the symptomatic period the majority (84%) not using condoms. Using ligase chain reaction on urine, *N.gonorrhoeae* was detected in 91 (80%) and *C.trachomatis* in 2 (2%) of urine specimens. 45 of 47 *N.gonorrhoeae* isolates produced penicillinase, 89% showing multi-anti-microbial resistance.
This study emphasis the need to integrate alternative care providers and particularly traditional healers in control activities, and to encourage their role in promoting safer sexual behaviour.
In patients presenting with urethral discharge in our rural setting, *C.trachomatis* was not found to be a major pathogen. The high resistance of *N.gonorrhoeae* reiterates the importance of anti-microbial susceptibility surveillance of in order to prevent treatment failures and control the spread of resistant strains in Malawi.

Chapter 8 describes a study conducted among commercial sex workers. The study was carried out in order to; determine the prevalence and pattern of sexually transmitted infections, describe sexual behaviour among those who have a sexually transmitted infection and identify socio-demographic and behavioural risk factors associated with "no condom use".
Consecutive new commercial sex workers presenting to a mobile clinic underwent detailed examination for sexually transmitted infections and those found with an infection were interviewed after obtaining informed consent.
There were 1817 female commercial sex workers of whom 448 (25%) were diagnosed with a sexually transmitted infection. Of these, there were 237 (53%) cases of abnormal vaginal discharge with or without dysuria , 116(26%) cases of pelvic inflammatory disease and 94 (21%) cases of genital ulcer disease.
The great majority (87%) engaged in sex while symptomatic with 17% engaging in unprotected sex. Having unprotected sex was associated with being married, being involved with commercial sex outside a known rest-house or bar, having an ulcerative genital disease, having less than 2 clients per day, indulgence in alcohol and having had no prior medication for sexually transmitted infections.
The high levels of sexually transmitted infections particularly genital ulcer disease and unprotected sex among commercial sex workers underlines the importance of targeted interventions for them and their clients. The findings could help to re-orient or even develop strategies on promoting safer sex in high-risk populations.

Chapter 9 presents findings on the prevalence, incidence and patterns of sexually transmitted infections among male inmates of two prisons in Thyolo. Out of a total of 4229 inmates that were studied during a 2 year period, 178(4.2%) were diagnosed with a sexually transmitted

infection. This included 83(46%) inmates with urethral discharge, 60(34%) with genital ulcer disease and 35(20%) inmates with epididymo-orchitis. 50(28%) infections were considered incident cases acquired within the prisons (Incidence risk=12 cases/1000 inmates/year). Genital ulcer disease was the most common infection in this group comprising 52% of all sexually transmitted infections.
This study shows that a considerable proportion of sexually transmitted infections among inmates are acquired within prison walls. In a setting of same sex inmates, this suggests inter-prisoner same-sex sexual activity. Prisons in Malawi do not allow access to condoms as it is felt that this would encourage homosexuality which is illegal. The findings have implications on HIV transmission and might help in developing more rational policies on the control of sexually transmitted infections and condom access within Malawi prisons.

Chapter 10 presents data on HIV prevalence in various blood donor population and socio-demographic risk factors associated with prevalent HIV. The study also assesses the feasibility of offering routine voluntary counselling services to blood donors.
Crude HIV prevalence was found to be 22 % while the age standardized prevalence (>15years) was 17%. Prevalence was lowest among rural donors, students and in males of the age group 15-19. There is a highly significant positive association of HIV prevalence with increasing urbanization. Significant risk factors associated with prevalence for both male and female donors included having a business-related occupation, living in a semi-urban or urban area, and being in the age group 25-29 for females and 30-34 for males. All blood donors were pre-test counselled and 90% were post-test counselled in 2000.
HIV prevalence in blood donors is alarmingly high, raising important concerns on the potential dangers of HIV transmission through blood transfusions. Limiting blood transfusions, use of a highly sensitive screening test, and pre-donation selection of donors is important. The experience also shows that it is feasible to offer pre and post test counselling services for blood donors as an entry point for early diagnosis of asymptomatic HIV infection and broader preventive and care strategies.

Chapter 11, which is the final chapter of this thesis, covers a general discussion on some of the principal findings, implications of these studies on policy and practice in Malawi, and areas for further research.

SAMENVATTING

In dit proefschrift wordt operationeel onderzoek beschreven dat is uitgevoerd op het platteland van het Thyolo district in het zuiden van Malawi. De studies werden verricht in het kader van het HIV/AIDS en SOA (Seksueel Overdraagbare Aandoeningen) bestrijdingsprogramma van een Niet Gouvernementele Organisatie (Médecins sans Frontieres-Luxembourg).

In hoofdstuk 1 wordt een overzicht gegeven van HIV/AIDS, tuberculose en SOA. Ziektelast ('burden of disease'), interacties tussen tuberculose en HIV en tussen SOA en HIV, de gevolgen van deze ziekten en het kader van de bestrijding worden besproken. Enkele van de belangrijkste operationele onderzoeksvragen die te maken hebben met deze ziekten zoals deze voorkomen in landen ten zuiden van de Sahara, worden aangegeven.
In dit hoofdstuk wordt ook achtergrondinformatie over Malawi gepresenteerd en wordt de omvang van de epidemie van tuberculose-HIV en van SOA beschreven. Hierna volgt een korte beschrijving van het Thyolo district; het belangrijkste gebied voor de in dit proefschrift beschreven onderzoeken.

In hoofdstuk 2 worden de haalbaarheid en de effectiviteit beschreven van het aanbieden van counseling (begeleiding) op basis van vrijwilligheid, het testen op HIV en het daarna, indien noodzakelijk, aanbieden van cotrimoxazol profylaxe om de sterfte te verminderen onder jonge tuberculosepatiënten die onder het standaard tuberculose bestrijdingsprogramma vallen van het plattelandsdistrict van Thyolo.
Het onderzoek was opgezet als een cohort studie waarbij een historische groep als controle diende. In deze studie deden in totaal 1986 patiënten mee; 1061 in de interventiegroep (die counseling op vrijwillige basis kregen, op HIV werden getest en cotrimoxazol kregen) en 925 in de historische controlegroep (die deze interventies niet kregen). In de interventiegroep kregen 1019 (96%) patiënten counseling vóór de test, 964 (91%) werden getest op HIV en 938 (88%) kregen counseling na de test. De totale HIV seroprevalentie was 77%. In totaal kregen 693 patiënten cotrimoxazol van wie 14 (2%) lichte dermatologische reacties vertoonden. Het gecorrigeerde relatieve risico op overlijden was 0,81 ($p<0,001$) in de interventiegroep vergeleken met de controlegroep. Om één sterfgeval te voorkomen was het noodzakelijk om 12,5 patiënten een totaal pakket aan te bieden van counseling op basis van vrijwilligheid, het testen op HIV en vervolgens het geven van cotrimoxazol. Deze studie laat zien dat counseling op basis van vrijwilligheid, het testen op HIV en vervolgens het geven van cotrimoxazol haalbaar en veilig is en dat het mortaliteitscijfer onder de tuberculosepatiënten die deelnemen aan het standaard tuberculose-bestrijdingsprogramma vermindert.

In hoofdstuk 3 wordt de therapietrouw aan cotrimoxazol bij seropositieve tuberculosepatiënten beschreven gedurende de continuatiefase van de tuberculosebehandeling. De studie beschrijft eveneens de sensitiviteit, de specificiteit en de positief voorspelbare waarde van het mondelinge navragen en het natellen van de pillen als methoden om therapietrouw te controleren.
De therapietrouw aan cotrimoxazol werd beoordeeld bij een cohort van tuberculosepatiënten die een follow-up centrum bezochten tussen maand 4 en 6 van de continuatiefase van de tuberculosebehandeling. Om de therapietrouw te beoordelen werd gebruik gemaakt van drie

methoden: het mondelinge navragen over de medicatie inname, het daadwerkelijk natellen van de pillen, en het testen van de urine op trimethoprim met behulp van gas chromatografie en massa-spectrometrie.
Het onderzoek in de urine op trimethoprim gold als de gouden standaard bij de bepaling van therapietrouw. Trimethoprim werd bij 82 (94%) van de 87 patiënten van de cohort gevonden. Het "mondeling navragen" over de cotrimoxazol inname en het daadwerkelijke "natellen van de pillen" toonden een hoge sensitiviteit en positief voorspellende waarde in vergelijking met de gouden standaard van de trimethoprim bepaling in de urine. De studie toonde aan dat de therapietrouw voor cotrimoxazol goed was wanneer het werd toegevoegd aan de tuberculosebehandeling bij seropositieve tuberculosepatiënten en dat de therapietrouw eenvoudig aangetoond kan worden door het mondeling navragen en het natellen van de medicatie.

In hoofdstuk 4 komt een dwarsdoorsnede onderzoek aan de orde waarbij de therapietrouw aan cotrimoxazol onderzocht wordt bij seropositieve personen die 3-6 maanden eerder hun behandeling voor tuberculose voltooiden. De studie berekende het percentage personen dat doorging met cotrimoxazol profylaxe om opportunistische infecties te voorkomen en toonde aan waarom werd doorgegaan of gestopt met de profylaxe.
Van de 82 seropositieve personen die in leven waren op het tijdstip van het interview namen 76 (93%) nog steeds cotrimoxazol en wilden hier zeker mee doorgaan. De meest genoemde reden om met de medicatie door te gaan was te voorkomen een aan HIV gerelateerde ziekte te krijgen, terwijl de meest genoemde reden om te stoppen de lange afstand naar het gezondheidscentrum was. Van de patiënten kreeg 96% cotrimoxazol kosteloos via een gezondheidscentrum. De meerderheid van de patiënten (63%) die zeker door wilden gaan met de medicatie konden zich niet veroorloven hiervoor zelf te betalen. Het onderzoek toont aan dat op het platteland het grootste deel van de seropositieve patiënten doorging met cotrimoxazol nadat de tuberculose behandeling beëindigd was. Het toont eveneens aan dat het essentieel is om deze medicatie kosteloos te verstrekken zodat het beschikbaar blijft voor het op langere termijn voorkómen van aan HIV gerelateerde opportunistische infecties.

In hoofdstuk 5 worden de resultaten weergegeven van een serie dwarsdoorsnede onderzoeken die werden uitgevoerd om te bepalen of de fecale *Escherichia coli* (*E. coli*) resistentie tegen cotrimoxazol bij tuberculose patiënten in de loop van de tijd verandert en of het resistentiepatroon bij seropositieve tuberculosepatiënten die cotrimoxazol profylaxe namen anders is. De resistentie tegen cotrimoxazol onder *E. coli* isolaten bij tuberculosepatiënten ten tijde van registratie was 60% in 1999 en 77% in 2001 ($p<0,01$). De resistentie onder seropositieve tuberculosepatiënten die cotrimoxazol kregen was 89%, terwijl bij seronegatieve patiënten die alleen behandeld werden voor tuberculose dit 62% ($p<0,001$) was. De studie laat een significante stijging zien van de resistentie van de *E. coli* tegen cotrimoxazol bij tuberculose patiënten, deze is vooral zichtbaar bij seropositieve patiënten die cotrimoxazol profylaxe krijgen. Omdat er een grote mate van door plasmiden overgedragen resistentie tussen de *E. coli* en de *Salmonella* soorten bestaat, geven deze bevindingen aanwijzingen dat de voordelen van cotrimoxazol profylaxe op korte en langere termijn wel eens beperkt zouden kunnen zijn. Met name ter preventie van bacteriemieën door *Salmonella* anders dan *S. typhi* en van enteritis bij seropositieve tuberculose patiënten in Malawi te voorkomen.

In hoofdstuk 6 wordt een onderzoek beschreven dat is uitgevoerd onder nieuwe tuberculosepatiënten, om de prevalentie te bepalen van ondervoeding bij opname en de relatie te bepalen tussen ondervoeding en vroege mortaliteit (dit is gedefinieerd als overlijden binnen de eerste vier weken van behandeling). Er waren 1181 tuberculosepatiënten, (576 mannen en 605 vrouwen), van wie in totaal 80% met HIV geïnfecteerd was. Bij opname waren 673 (57%) tuberculosepatiënten ondervoed (body mass index < 18,5 kg/m^2). Er waren 259 (22%) patiënten licht ondervoed (body mass index 17,0-18.4 kg/m^2), 168 (14%) matig ondervoed (body mass index 16,0-16,9 kg/m^2) en 246 (21%) waren ernstig ondervoed (body mass index < 15,9 kg/m^2).
95 (8%) van de patiënten stierf in de eerste vier weken. Significante risicofactoren voor vroege sterfte waren onder meer: toenemende mate van ondervoeding bij >35 jarigen en HIV positief zijn. Van alle patiënten (n=1181) stierven 10,9% van de 414 patiënten met gemiddelde tot ernstige ondervoeding in de eerste 4 weken, vergeleken met 6,5% van 767 patiënten die een normale voedingstatus hadden of licht ondervoed waren (OR 1,8, 95% CI; 1,1-2,7).
De studie laat zien dat bij patiënten met tuberculose een body mass index van < 17,0 kg/m^2 is gerelateerd aan een verhoogd risico van vroegtijdige sterfte. Deze groep patiënten zou additionele voeding moeten krijgen en zou als eerste in aanmerking moeten komen voor andere, aan zorg gerelateerde, interventies.

In hoofdstuk 7 worden de bevindingen weergegeven van een studie die is uitgevoerd onder mannen, met een afscheiding uit de urethra opgenomen in het districtsziekenhuis van Thyolo. In het onderzoek is gekeken naar het gedrag bij het zoeken naar medische behandeling en naar seksueel gedrag, het vóórkomen van *Neisseria gonorrhoeae* (*N. gonorrhoeae*) en *Chlamydia trachomatis* (*C. trachomatis*), en de gevoeligheid voor antibiotica.
Van de in totaal 114 patiënten had 61% enige vorm van medicatie genomen voor hij naar de SOA kliniek kwam. De alternatieve bron van zorg waar het meest frequent gebruik van werd gemaakt was de traditionele genezer. Gedurende de symptomatische periode hadden 68 (60%) patiënten seksuele contacten, van wie de meerderheid geen condoom had gebruikt. Door de urine te testen met de ligase chain reaction test werd in 91 (80%) van de urinemonsters *N. gonorrhoeae* vastgesteld en *C. trachomatis* bij twee (2%) monsters. 45 van de 47 *N. gonorrhoeae* isolaten produceerde penicillinase en 89% was ongevoelig voor meerdere antibiotica. Deze studie benadrukt de noodzaak om alternatieve genezers, en in het bijzonder traditionele genezers, te integreren in behandelactiviteiten en hun rol bij het bevorderen van veilige seks aan te moedigen. *C. trachomatis* was geen belangrijke ziekteverwekker bij patiënten met afscheiding uit de urethra in de plattelandscontext van dit onderzoek. De veel voorkomende resistentie van *N. gonorrhoeae* benadrukt het belang van surveillance naar antibiotica resistentie om het mislukken van de behandeling te voorkomen en om de verspreiding van voor antibiotica ongevoelige stammen in Malawi in te dammen.

In hoofdstuk 8 wordt een studie beschreven die is uitgevoerd onder commerciële seks-werkers. De studie is uitgevoerd om de prevalentie en het patroon van SOA's te bepalen, om het seksuele gedrag te beschrijven van diegenen die een seksueel overdraagbare infectie hebben en om sociaaldemografische- en gedrags-risicofactoren die gerelateerd worden aan het niet gebruiken van condooms te identificeren.
Alle commerciële sekswerkers die zich achtereenvolgens aanmeldden bij een mobiele kliniek kregen een uitgebreid onderzoek op SOA's en diegenen die een infectie hadden werden na het verkrijgen van informed consent geïnterviewd.

Er waren 1817 vrouwelijke commerciële sekswerkers van wie er 448 (25%) gediagnosticeerd werden met een SOA. Van hen hadden 237 (53%) patiënten abnormale vaginale afscheiding met of zonder dysurie klachten, 116 (26%) patiënten hadden een infectie van de onderbuik en 94 (21%) patiënten hadden een zwerende genitale ziekte.
De grote meerderheid (87%) had seksuele contacten gedurende de symptomatische periode en 17% had onbeschermde seks. Het hebben van onbeschermde seks was geassocieerd met getrouwd zijn, het hebben van commerciële seks buiten een bar of "resthouse", het hebben van een zwerende genitale ziekte, het hebben van minder dan twee cliënten per dag, overmatig alcohol gebruik, en het niet eerder hebben gekregen van medicatie voor SOA's.
Het belang van gerichte interventies voor commerciële sekswerkers en hun cliënten wordt benadrukt door de hoge aantallen SOA's onder hen, in het bijzonder zwerende genitale ziekten, en het feit dat zij onbeschermde seks bedrijven. De bevindingen kunnen helpen om strategieën te heroriënteren of zelfs om strategieën te ontwikkelen die gericht zijn op veilige seks bij hoge risicogroepen.

In hoofdstuk 9 worden de bevindingen weergegeven over de prevalentie, incidentie en manieren waarop SOA's worden overgedragen bij de manlijke bewoners van twee gevangenissen in Thyolo. Van een totaal van 4229 gevangenen die werden onderzocht gedurende een periode van twee jaar werden 178 (4,2%) gediagnosticeerd met een SOA. Hierbij zijn inbegrepen 83 (46%) gevangenen met een afscheiding uit de urethra, 60 (34%) met een zwerende genitale ziekte en 35 (20%) gevangenen met epididymo-orchitis. Van 50 (28%) geïnfecteerden werd aangenomen dat zij geïnfecteerd zijn in de gevangenis (incidentie = 12 gevallen/1000 gevangenen/jaar). 52% van alle SOA's waren zwerende genitale ziekten. Dit was de meest voorkomende infectie in deze groep.
Deze studie toont aan dat een aanzienlijk deel van de SOA's bij gevangenen binnen de gevangenismuren wordt verworven. Binnen de context van gevangenen die dezelfde sekse hebben suggereert dit seksuele contacten tussen gevangenen van hetzelfde geslacht. Het is niet toegestaan binnen de gevangenissen van Malawi condooms te verstrekken daar dit gezien wordt als een aanmoediging tot homoseksualiteit, en homoseksualiteit is illegaal in Malawi. De bevindingen hebben implicaties voor HIV transmissie en kunnen mogelijk helpen om een rationeel beleid te ontwikkelen voor de bestrijding van SOA's en het verstrekken van condooms in de gevangenissen van Malawi.

In hoofdstuk 10 worden de data beschreven over de prevalentie van HIV bij verscheidene bloeddonorgroepen en de sociaaldemografische risico factoren die verband houden met het vóórkomen van HIV. De studie beoordeelt eveneens de haalbaarheid van routinematige counseling op vrijwillige basis aan bloeddonoren.
De ongestandaardiseerde HIV prevalentie was 22% terwijl de leeftijd gestandaardiseerde prevalentie (>15 jaar) 17% was. De prevalentie was het laagst onder plattelandsdonoren, studenten en bij mannen tussen de 15-19 jaar. Er is een belangrijke significante positieve relatie tussen de HIV prevalentie en de toenemende verstedelijking. Significante risico factoren verband houdend met het hebben van een HIV infectie voor zowel manlijke als vrouwelijke donoren zijn: het hebben van een zakelijk beroep, het wonen in een semi-stedelijk of stedelijk gebied en het behoren tot de leeftijdscategorie tussen de 25-29 jaar voor vrouwen en tussen de 30-34 voor mannen. In 2000 werden alle bloeddonoren geïnformeerd over HIV vóór de HIV test en 90% werd begeleid na de test.

De HIV prevalentie bij bloeddonoren is opvallend hoog, hetgeen grote zorgen baart over het potentiële gevaar van HIV transmissie via bloedtransfusies. Het is belangrijk om bloedtransfusies te beperken, gebruik te maken van een zeer gevoelige screenings test voor HIV en donoren vooraf te selecteren. Ervaring laat zien dat het mogelijk is om counseling aan te bieden aan bloeddonoren vóór en na het testen op HIV als beginpunt bij vroege diagnose van a-symptomatische HIV infectie en voor het aanbieden van verdere preventieve- en zorgstrategieën.

Hoofdstuk 11, het laatste hoofdstuk van dit proefschrift, betreft een algemene discussie over een aantal van de belangrijkste bevindingen, de implicaties van deze studie voor het beleid en de praktijk in Malawi, en mogelijkheden voor verder onderzoek.

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