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 world's population are infected with the TB bacillus, *Mycobacterium tuberculosis*. 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. Mortality due to TB was estimated at 1.87 million in 1997 and the global case fatality rate was 23%. 

The Human Immunodeficiency Virus/Acquired Immunodeficiency 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. 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, 71% live in sub-Saharan Africa. 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. The annual rate of increase of TB cases in this region is estimated at 6%.

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

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.

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. 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\textsuperscript{11,12}. Conversely, in persons co-infected with \textit{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\textsuperscript{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 \textit{Mycobacterium tuberculosis}\textsuperscript{12}. Finally, HIV increases the rate of recurrent TB, which may be due to either endogenous reactivation (true relapse) or exogenous re-infection\textsuperscript{17-21}.

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

\textit{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\textsuperscript{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\textsuperscript{29-31}.

\textit{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\textsuperscript{1,23}. High HIV rates mean high rates of smear-negative pulmonary TB and extrapulmonary TB\textsuperscript{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\textsuperscript{37,38}.

\textit{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\textsuperscript{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\textsuperscript{44-46} such as bacterial infections, infection with \textit{pneumocystis carinii} 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 tuberculosis patients”.

\textit{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\textsuperscript{47}. The risk of recurrent TB is increased in HIV positive patients\textsuperscript{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\textsuperscript{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.

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 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, 16% and 8% in Tanzania, 31.3% and 4.4% in Zaire, and 35% and 9% in Zambia.

Close to 40% of overall TB mortality is early mortality occurring within the first 2 months of anti-TB treatment. 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. 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. 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. 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.

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. 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. 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. 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\textsuperscript{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 overstretched and under-resourced health services through increasing TB notification rates\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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 \textit{Streptococcus pneumoniae} and \textit{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 acceptable in different settings\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{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)\textsuperscript{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%)\textsuperscript{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\textsuperscript{67}. HIV/AIDS is projected to reduce economic growth in countries such as South Africa by 17% by 2010\textsuperscript{67}. If such countries do not take effective measures to combat AIDS, there is likely to be complete economic collapse in 3 generations\textsuperscript{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\textsuperscript{67}. 
TB ranks high among causes of mortality and healthy life lost in adults (3rd among all causes worldwide)\(^8\). 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 \(^7\) 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\(^1\) (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\(^2\).

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\textsuperscript{73,74}. (Table 1)

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

<table>
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<th>Full Implementation of the DOTS Strategy</th>
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<td>- Household contacts of TB patients</td>
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<td><strong>Through prevention of new TB cases</strong></td>
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<td>Isoniazid preventive treatment for PLHA</td>
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</tr>
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<td></td>
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</tbody>
</table>

Adapted from the WHO Guidelines for implementing collaborative TB and HIV programme activities\textsuperscript{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 infections 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 worldwide 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 gonorrhoea 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{96}

**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.\textsuperscript{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%.\textsuperscript{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.\textsuperscript{92} A third trial was conducted in Masaka, rural Uganda,\textsuperscript{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.\textsuperscript{93}

Although superficially, the results of these three landmark trials may appear contradictory,\textsuperscript{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.

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 the hypothesis to explain the results of the Masaka trial 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.

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. 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. In Africa pelvic inflammatory disease associated infertility accounts for 50-80% of all causes of infertility. 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. Gonorrhoea and *Chlamydia trachomatis* causes morbidity both in the Mother and in the newborn. Vertical transmission occurs in 30-50% of infants whose Mothers are infected with *N.gonorrhoea* and if untreated, gonococcal ophthalmia neonatorum, leads to blindness. Syphilis caused by *Treponema pallidum* can cross the placental barrier, infect the fetus and cause congenital malformations. In developing countries where routine screening programs for early detection of cervical cancer are limited or nonexistent, 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.
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. Using sophisticated diagnostic techniques the cost of diagnostics can exceed the per capita national healthcare budgets of many low-income countries.

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, 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, $\beta$ 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. 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[197].

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 indicators (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)

<table>
<thead>
<tr>
<th>Surface Area</th>
<th>118,480 Square kilometers</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of districts</td>
<td>25</td>
</tr>
<tr>
<td>Traditional authorities</td>
<td>202</td>
</tr>
<tr>
<td>Population</td>
<td>10,640,000</td>
</tr>
<tr>
<td>Population growth rate</td>
<td>2.4%</td>
</tr>
<tr>
<td>Population below poverty line</td>
<td>65%</td>
</tr>
<tr>
<td>GDP (USD)</td>
<td>8.9 billion</td>
</tr>
<tr>
<td>Literacy rate (Total/Male/Female)</td>
<td>56%/72%/42%</td>
</tr>
<tr>
<td>Health expenditure (per capita)</td>
<td>10 USD</td>
</tr>
<tr>
<td>UNDP human development index</td>
<td>No. 161 of 192 countries.</td>
</tr>
<tr>
<td>Life expectancy at birth</td>
<td>41 years</td>
</tr>
<tr>
<td>Crude birth rate</td>
<td>47/1000 population</td>
</tr>
<tr>
<td>Crude death rate</td>
<td>22/1000 population</td>
</tr>
<tr>
<td>Maternal mortality rate</td>
<td>620/100,000 population</td>
</tr>
<tr>
<td>Under 5 mortality rate</td>
<td>234/1000 live births</td>
</tr>
<tr>
<td>Infant mortality rate</td>
<td>140/1000 live births</td>
</tr>
<tr>
<td>Total fertility rate</td>
<td>6.8 children/woman</td>
</tr>
</tbody>
</table>
Figure 1. Map showing Malawi in Africa
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%. 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. 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 (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 to 52% in 1888, to 67% in 1991. In 2000, a countrywide survey of TB patients found an HIV-seroprevalence rate of 77%. 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.

Deaths within the first 2 months (early mortality) contributes up to 40% of overall TB mortality in Malawi. 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**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. TB cases</th>
<th>TB cases/100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>7,581</td>
<td>95</td>
</tr>
<tr>
<td>1989</td>
<td>9,431</td>
<td>140</td>
</tr>
<tr>
<td>1991</td>
<td>14,443</td>
<td>155</td>
</tr>
<tr>
<td>1993</td>
<td>17,105</td>
<td>172</td>
</tr>
<tr>
<td>1995</td>
<td>19,155</td>
<td>180</td>
</tr>
<tr>
<td>1997</td>
<td>20,676</td>
<td>181</td>
</tr>
<tr>
<td>1999</td>
<td>24,396</td>
<td>211</td>
</tr>
<tr>
<td>2001</td>
<td>27,672</td>
<td>265</td>
</tr>
</tbody>
</table>
Sexually transmitted infections in Malawi

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

In 2001, the national average for syphilis prevalence was 3.9\%\textsuperscript{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\%\textsuperscript{130}. Malawi adopted the syndrome-based approach to the management of STIs as recommended by the World Health Organization in 1993\textsuperscript{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 Malamulom hospital). There are 16 health centers and 6 maternities.

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\%\textsuperscript{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\%\textsuperscript{129}.

In 2002, HIV prevalence in TB patients in Thyolo was estimated at 77\%\textsuperscript{122}, which was the same as the National average\textsuperscript{132}.

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\textsuperscript{133}. Among commercial sex workers in Blantyre, the HIV prevalence rate is estimated to be 70\%\textsuperscript{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 transmitted 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.
REFERENCES


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