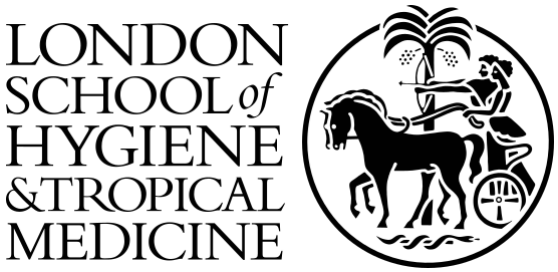

THE IMPACT OF IMPROVED STD CASE MANAGEMENT ON HIV INFECTION AND SEXUALLY TRANSMITTED DISEASES IN MWANZA REGION, TANZANIA

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ABSTRACT

Observational studies have suggested that the transmission of the human immunodeficiency virus (HIV) is enhanced in the presence of other sexually transmitted diseases (STDs). Based on this STD/HIV co-factor hypothesis it has been suggested that interventions aimed at reducing the prevalence of STDs may be able to reduce the incidence of HIV infection.

This thesis presents the results of a community based randomised controlled trial of the impact of improved STD case management on the incidence of HIV infection. The trial was carried out in the Mwanza Region of North-Western Tanzania between 1991 and 1995. It involved 12 rural communities which were formed into six matched pairs. Within each pair, one community was randomised to receive the intervention which comprised improved STD case management services integrated into the existing primary health care (PHC) structure, and health education campaigns to improve treatment seeking behaviour for STDs.

The impact of the intervention was studied in a cohort of about 1000 adults aged 15 to 54 years from each of the communities. Over the 2 years of follow-up, there were 130 HIV seroconversions, 48 (1.16%) in the intervention group and 82 (1.86%) in the comparison group, equivalent to annual incidences of 0.58% and 0.93%. The crude relative risk (RR) for seroconversion in intervention compared to comparison communities was 0.57 (95% CI 0.42-0.76, p=0.004). After adjustment for potential confounders, the RR was 0.62 (95% CI 0.45-0.85, p=0.013), equivalent to a reduction of 38%.

There was also a reduction in the prevalence of active syphilis (adjusted RR = 0.67; 95% CI: 0.47-0.96, p=0.04 at RPR titre of >=1:8), and of symptomatic urethritis in men (adjusted RR = 0.51, 95%CI: 0.25-1.03, p=0.06). No impact was observed for gonococcal / chlamydial infection or overall urethritis in men. There was no impact on the prevalence of STDs in pregnant women, studied by means of two consecutive cross-sectional studies at antenatal clinics.

The results of this trial provide additional strong evidence for the STD/HIV co-factor hypothesis, and demonstrate that improving STD services can substantially reduce the incidence of HIV infection in populations with high STD prevalences. They suggest that the control of STDs should form an important component of HIV prevention programmes. Reliable drug supply and frequent support supervision to health facilities are essential prerequisites for such STD control programmes.

CONTENTS

Tables

Figures

Maps

Annexes

DEDICATION

Decisions in life often depend on chance and on opportunities which come up, sometimes completely unexpectedly. But they are very much influenced by persons one meets along the way. This has very much been true of my life and professional career. The experience in Mwanza represented some of the best years of my life to date. I am deeply grateful to those who gave me the opportunities, and who influenced me to seize them when the time had come. To them I dedicate this thesis:

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Katua Munguti helped to plan the sexual behaviour surveys, one of the supplementary studies needed to interpret the results of the trial. He and his team implemented this survey in the field.

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Role of the Author

As in any programme of this size, many people contributed to the conduct of this research study. This section briefly describes my role in the programme.

I was the director of the study from the preparatory phase in Mwanza (1991) to its completion (1995). The overall design of the trial was developed in 1989/90 by Richard Hayes, Angus Nicoll, David Mabey and others, but I was closely involved in the detailed planning and implementation of the study from 1991 onwards. I was based full time in Mwanza throughout the study. My responsibilities included the scientific management and administration of the programme; the development and administration of the programme office; recruitment, training and supervision of project staff; and relationships with the Tanzanian MoH, the local authorities and the collaborating institutions.

I made major contributions to the design and planning of the intervention and of the three supplementary studies described in this thesis, and to the planning of the main cohort study. I was responsible for the detailed management of the main cohort study, the STD intervention, and for one of the supplementary studies (the follow-up study on STD patients who did not return for a test of cure). I provided managerial assistance for the other supplementary studies on sexual behaviour and on STD prevalences in rural antenatal clinic attenders. I supervised data-collection in the main cohort study including quality control, and facilitated the interaction between the collaborating laboratories and the rest of the trial team. After the data collection phase was completed, I supervised the analysis, interpretation and dissemination of the results of the study.

Chapter 1 Introduction: Scope of the thesis

This thesis concerns a community-based randomised controlled trial which investigated the hypothesis that sexually transmitted diseases (STDs) enhance the transmission of the human immunodeficiency virus (HIV), and that the improved case management of STDs will reduce the incidence of HIV in the general population. This research, the Mwanza STD/HIV Intervention Trial, was conducted in north-western Tanzania from 1991 to 1995.

Chapter 2 presents a review of the relevant literature on the epidemiology and public health importance of STDs in sub-Saharan Africa, on the options available to control them, and on the association between STDs and HIV infection. Emphasis is laid on methodological issues encountered when studying the link between the two types of diseases. A synopsis of the epidemiology and the public health relevance of HIV infection and AIDS is provided. This is kept very brief, as STDs, their control and their possible association with HIV infection are the main focus of the thesis.

The literature review is followed in chapter 3 by a description of the background to the trial, which includes information on the study area, the organisation and management of the trial and on the collaborating institutions which contributed to its implementation.

Chapters 4 to 6 describe the aims, the design and the results of the trial, respectively. Chapter 7 discusses the methodology and findings of the study and the implications of the results.

The thesis ends in chapter 8 with a series of conclusions and recommendations. The latter include policy and programmatic recommendations, as well as recommendations for future research.

The Mwanza trial has also been used to study a variety of related issues, for example patterns of sexual behaviour, risk factors for STDs and HIV infection, the performance of risk scores as a screening tool for the detection of cervical infections in women, the performance of a screening tool to detect urethritis in men, the adult mortality due to HIV infection, and the performance of a verbal autopsy tool. These related studies are not discussed in this thesis. A full list of publications from the Mwanza STD/HIV Intervention and Research Programme and related studies is given in Annex 5.

Chapter 2: Literature review

2.1 Sexually transmitted diseases and reproductive tract infections

2.1.1 Definitions

Sexually transmitted diseases

Sexually transmitted diseases (STDs) is the collective term for a whole group of infectious disorders for which sexual intercourse is an important route of infection. The group includes bacterial, viral, protozoal, mycotic and parasitic infections (Mabey and Richens 1996). Many are associated with genital symptoms and signs; for example gonorrhoea or chancroid. Others do not usually lead to pathologic changes of the genital organs; for example HIV infection or hepatitis B. In the context of this thesis, the term STDs is used for infections which frequently cause genital symptoms or signs, and mostly refers to viral, bacterial, mycotic or protozoal infections.

Reproductive tract infections

The term reproductive tract infections (RTIs) is restricted to diseases of the genital system. Not all infections of the genital tract require sexual transmission. Some, such as bacterial vaginosis or infection with *Candida albicans*, appear spontaneously, although sexual transmission may also occur. Therefore, the terms STDs and RTIs are not synonymous. However, this thesis is concerned with a programme for the control of STDs, and in line with common terminology in this programmatic context, candidiasis and bacterial vaginosis may be included under the term STDs (WHO 1994).

STD syndromes

Different STD aetiologies often lead to a similar pattern of pathology. Such a set of symptoms and signs is called a syndrome, and from a clinical point of view it is convenient to categorise different STDs by the syndrome they may cause (Meheus et al 1990). Important syndromes with which this thesis is concerned are the vaginal discharge syndrome, the urethral discharge syndrome, the lower abdominal pain syndrome and the genital ulcer syndrome.

The vaginal discharge syndrome (VDS) in women and the urethral discharge syndrome (UDS) in men, which together form the group of genital discharge syndromes (GDS) (Mosha et al 1993), are all characterised by an excretion of watery or purulent exudate. Infections of the female genital tract may also involve the urethra, but urethritis in women is usually mild, and the term UDS is normally used as a synonym for GDS in men therefore.

In women, infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are primarily located in the cervix of the uterus and are frequently asymptomatic (Hook and Handsfield 1990, Stamm and Holmes 1990). If they lead to a noticeable amount of inflammatory cervical exudate, this appears as VDS.

The proportion of women complaining of VDS in whom a microbiological aetiology can be identified, seems to vary widely between different parts of the world and seems to be very low in some countries, for example in a rural population in Bangladesh (Sarah Hawkes, personal communication 1998). The fact that many women who complain of VDS are not infected with an RTI or STD may be of concern for the design of STD control programmes.

As a frequent complication of some infections in women, bacteria may ascend to the upper reproductive tract and involve the Fallopian tubes, the ovaries and the pelvic cavity. The resulting syndrome is defined as pelvic inflammatory disease (PID) or, because the inflammation can clinically only be suspected, as lower abdominal pain (LAP) syndrome (WHO 1994).

A variety of STD aetiologies are associated with the genital ulcer syndrome (GUS), which is defined by a disruption of the integrity of the skin or the mucosal membranes of the reproductive organs (Piot and Plummer 1990). The appearance of the ulcers can be extremely variable, making a clinical diagnosis unreliable in the absence of diagnostic tests (De Schryver and Meheus 1992, Ndinya-Achola et al 1996).

2.1.2 Synopsis of STDs and RTIs frequently seen in East Africa

Infections leading to GDS

Gonorrhoea: This is an acute infectious disease of the epithelium of the urethra and cervix caused by *Neisseria gonorrhoeae* (NG). The infection may ascend into the upper genital tract, and lead to epididymitis in men, or to endometritis, salpingitis and PID in women. The infection may occasionally involve the rectum or other areas of the body and give rise to bacteraemia, resulting in metastatic complications (Hook and Handsfield 1990). NG is a gram-negative diplococcus which can be diagnosed microscopically in a gram-stained smear, or, with higher sensitivity, by culture. The bacterium has a tendency to develop antimicrobial resistance rather quickly, and has become resistant already to many of the drugs used for the treatment of gonorrhoea (Piot and Islam 1993, West et al 1995).

Infection with *Chlamydia trachomatis*: Location of the infection, symptoms, signs and typical complications are similar to gonorrhoea. Different strains of *Chlamydia trachomatis* (CT) exist. GDS is mainly caused by serovars D - K, whilst serovars A - C are found in trachoma, and serovars L1 - L3 in lymphogranuloma venereum (Mabey and Richens 1996). Diagnosis of the small gram-negative bacteria by microscopy or culture, by polymerase chain reaction (PCR) or ligase chain reaction (LCR) is highly sensitive and specific, but is possible only in specialised laboratories. Methods which are simpler to use, such as an antigen-detection enzyme immunoassay (EIA) are still too costly and sophisticated to be employed routinely in developing countries (Noble 1997). Treatment is possible with a variety of antibiotic drugs including doxycycline (Mabey and Richens 1996).

Trichomoniasis: Infection with the flagellate protozoan *Trichomonas vaginalis* (TV) is one of the most frequent aetiologies of VDS, and may also lead to urethral discharge in men (Rein and Mueller 1990). There are many asymptomatic infections, particularly in men. In a cross-sectional survey in a rural community of Mwanza Region, 11% of the men were found to be infected (Buve et al 1996). The vaginal discharge caused by TV is typically copious, greenish-yellow and frothy, but this sign is not specific. The diagnosis is made by microscopy of a wet preparation of the vaginal or urethral excretion, or by culture. For treatment, metronidazole is the drug of choice (Rein and Mueller 1990).

Genital candidiasis: The yeast infection of the genital tract is caused by *Candida albicans* (CA), which may be transmitted sexually or spread from the intestine (Mabey and Richens 1996). The discharge may contain cheesy material adhering to the surface of the vaginal wall or glans penis. In men, the infection leads to balanitis (Stolz et al 1990). Asymptomatic infections occur in men more often than women. An immediate diagnosis can be made microscopically by wet preparation or a gram-stained smear. Treatment options include antimycotic pessaries and creams such as nystatin, or the use of antimicrobial dyes such as Gentian violet.

Non-specific urethritis: A variety of bacteria are responsible for non-gonococcal, non-chlamydial and non-trichomonal urethral infections in men[1]. The type of discharge is not pathognomonic. A species specific diagnosis is difficult, and the diagnosis is usually based on the presence of polymorpho-nuclear cells in the gram-stained urethral smear and exclusion of NG or CT infection. The infection usually responds to treatment with tetracycline or erythromycin (Bowie 1990).

Bacterial vaginosis (BV): This condition is characterised by vaginal discharge associated with an increase of vaginal pH, decrease of the physiologic lactobacilli flora and the presence of a variety of bacterial species including *Gardnerella vaginalis*, *Mycoplasma hominis* and anaerobic bacteria such as *Bacterioides* spp. *Peptostreptococcus* spp, *Prevotella* spp and *Mobiluncus* spp., usually without an inflammatory tissue response of the vaginal wall (Spiegel CA 1991). Asymptomatic BV occurs frequently. Diagnosis has been based on the combination of microscopic presence of vaginal epithelial cells coated with bacteria (clue cells), increase in pH and fishy odour in the KOH test (Easmon et al 1991). More recently, a standardised quantitative morphological classification system has been introduced, using gram-stained smears of the vaginal flora (Hillier 1993). BV can be treated with clindamycin or metronidazole.

Infections leading to GUS

Syphilis: This systemic disease is caused by the spirochete *Treponema pallidum*, and is characterised by periods of florid manifestations and years of symptomless latency. Primary and sometimes secondary signs and symptoms involve the genital tract, but in principle the disease is

[1] Chlamydia infection and trichomoniasis of the male urethra are sometimes also summarised under the term 'non-specific urethritis'. Strictly speaking, the term should be limited to infections where the causative agent cannot be identified by means of routine laboratory methods

systemic. The infection is usually transmitted sexually, but vertical transmission from mother to foetus occurs frequently. Primary syphilis is characterised by a usually painless ulcer (chancre) appearing usually within 3 weeks of infection. This chancre heals within 4 to 8 weeks. Secondary syphilis appears 6 to 12 weeks after infection, and is characterised by cutaneous rashes of different parts of the body, which heal spontaneously after some time, but relapses occur. One genital manifestation of secondary syphilis is the extremely infectious condylomata lata, characterised by hypertrophic flat papules. The secondary stage is followed by latent (asymptomatic) syphilis which may last a few years or the rest of the patient's life. During this stage, syphilis may continue to smoulder as a systemic infection involving bones, viscera, the vascular system or the central nervous system. Clinical manifestations of this process are defined as tertiary syphilis (Sparling 1990).

Clinical diagnosis is not always straightforward. Neither the primary ulcer nor the secondary manifestations are pathognomonic, except for condylomata lata. Primary syphilis can be diagnosed through demonstration of *T. pallidum* by darkfield microscopy of ulcer exudate. This method is highly specific, but its sensitivity is low.

Diagnosis can be assisted by a variety of serological tests. The tests used in the studies described in this thesis are the Treponema Pallidum Haemagglutination Assay (TPHA) and the Rapid Plasma Reagin (RPR) test. The latter is similar to the Venereal Disease Research Laboratory (VDRL) test, but does not require the use of a microscope. A patient becomes TPHA positive 1 to 4 weeks after infection, and usually remains positive for decades even if effectively treated (Larsen et al 1995). The test is highly specific, but cross-reaction occurs with non-syphilitic treponemal infections such as yaws (Schulz et al 1990, Arya 1996).

Seroconversion to the RPR test occurs 1 to 2 weeks after that for the TPHA test. The test turns negative some months after treatment, but stays positive in untreated patients. However, if treatment is given during the late latent phase, the test often remains positive, usually at a lower titre (Larsen et al 1995, Goeman et al 1995). The RPR test is non-specific, and false positive results may be observed in pregnant women, and in patients with malaria or some other conditions. The combination of a positive TPHA and a positive RPR test result suggests untreated or recently treated syphilis, and is often referred to as 'active syphilis' in epidemiological studies (Mabey 1986, Mosha et al 1993). A positive TPHA test result alone can be interpreted as indicating past or present syphilis. The combination of a positive TPHA and a negative RPR test result indicates a syphilis infection which was treated successfully in one of

the early stages. For the treatment of syphilis, benzathine-penicillin, a long-acting penicillin is used (Musher 1991). So far, no cases of antimicrobial resistance have been described.

Chancroid: This is a localised disease, characterised by genital ulcers and often by suppuration of the inguinal lymphatic nodes, and is caused by *Haemophilus ducreyi*, a slender gram-negative bacterium. In contrast to the syphilitic chancre, chancroid ulcers are usually non-indurated, painful and may be multiple. However, clinical misclassification as syphilis or herpes infection occurs, as do mixed infections (De Schryver and Meheus 1992, Ndinya-Achola et al 1996). Untreated infections may lead to phagedenic ulcers with massive tissue destruction. Diagnosis can be made by culture or PCR, both of which require a specialised laboratory. Recommended treatments include erythromycin, ciprofloxacin and trimethoprim-sulfamethoxazole (Ronald and Albritton 1990).

Genital herpes: Infection with *Herpes simplex* virus type-2 (HSV-2) is sexually transmitted. Infection is lifelong, symptomatic episodes occur at irregular intervals, and the recurrent lesions are always infectious. The periods between the manifestation of genital lesions are defined as latency. Latency can be established after both symptomatic and asymptomatic initial infection. Recrudescent productive infection with viral shedding is usually associated with genital lesions, but may be clinically asymptomatic (Corey 1990). Genital lesions start as grouped vesicles which erode and usually form painful ulcers which coalesce. Identical genital lesions can be caused by *Herpes simplex* virus type-1 (HSV-1). Diagnosis is possible using a specific antigen-detection enzyme immunoassay on ulcer exudate. Cure is not possible, but the size of the lesions and the duration of the episode may be mitigated by systemic therapy with acyclovir (Corey 1990).

Lymphogranuloma venereum (LGV): This disease, also known as lymphogranuloma inguinale, is caused by a subgroup of *Chlamydia trachomatis* (serovars L1-L3). The symptomatology starts with a transient vesicular lesion, which ulcerates and quickly heals. This is followed by usually unilateral painful enlargement of inguinal lymphatic nodes, which turn into fluctuant abscesses and erupt. Healing with scarification may occur after a prolonged interval; chronic inflammation may lead to blockage of the lymphatic vessels with resulting oedema and possibly genital elephantiasis (Perine and Osoba 1990). The disease is comparatively rare in East Africa. It can be diagnosed with a chlamydia antigen detection EIA using material from the discharging abscess or serologically. Treatment is possible with tetracycline or erythromycin.

Other common RTIs

Genital warts and human papilloma virus infection: Genital warts often appear as small moist pedunculated growths (condylomata accuminata). They are usually caused by human papilloma virus (HPV) types 6 and 11. They occur most commonly in the coronal sulcus and the subpreputial area in men, and on the vulva, vaginal wall and the perineum in women. Genital warts can be treated topically with podophyllum, or through surgical intervention (Oriel 1990).

HPV type 16, more often than types 6 and 11, is associated with cervical carcinomas (Oriel 1990). These seem to occur frequently in sub-Saharan Africa, and cervical intraepithelial neoplasms with proven HPV infection were repeatedly observed at the STD reference clinic in Mwanza (Philippe Mayaud, personal communication 1995). However, the issue of genital carcinoma is not subject to this thesis.

Balanoposthitis: Inflammation of the glans penis and the preputium may be caused by a variety of aetiologic factors including lack of hygiene or a tight prepuce, but can also accompany candidiasis, trichomoniasis, gonorrhoea or ulcers of the preputium (Stolz et al 1990).

2.1.3 Global epidemiology and public health importance of STDs

The burden of STDs in the world, and particularly in developing countries, is enormous. The World Health Organization estimated that in 1995, 333 million new cases of syphilis, gonorrhoea, chlamydial infection, and trichomoniasis occurred world-wide (WHO 1995).

According to the World Development Report 1993, the burden of disease in women of child bearing age caused by STDs (without HIV infection) is the second highest of all groups of diseases, surpassed only by maternity related disorders. The annual loss of Disability Adjusted Life Years (DALYs) in women due to STD related mortality and morbidity has been estimated at 17.2 million (World Bank 1993).

It is their complications and sequelae rather than the acute episodes which make STDs such an important public health problem for women and their offspring: acute and chronic pelvic inflammatory disease, infertility, puerperal sepsis, ectopic pregnancy, abortion, stillbirth, low

birthweight and blind or diseased children (Wasserheit 1989, Laga 1994). These are discussed further in section 2.1.5.

Available data on the prevalence and/or incidence of STDs in developing countries are limited and confined to selected groups and often samples of convenience (Over and Piot 1993). The estimates given above are not accurate therefore. However, there is much evidence that the proportion of the population at risk is increasing in many developing countries. The spread of STDs is strongly influenced by social and economic factors. Poverty and urbanisation are growing rapidly in many developing countries, are often associated with migrant labour and increased demand for prostitution, and are frequently the driving forces behind both STD and HIV epidemics (Laga 1994).

By contrast, in many industrialised countries, STD prevalences and incidences were declining until the end of the last decade and mostly remain at a very low level thanks to more favourable economic and social conditions, the existence of a functional health care infrastructure, and effective control measures. For example, in 1989 the incidence of gonorrhoea was around 40 per 100,000 in Denmark, whilst it was estimated at 3000 - 10,000 per 100,000 in large cities in Africa (De Schryver and Meheus 1990). On the other hand, high incidences of STDs have been reported from some populations of the US, with particularly high rates of syphilis and gonorrhoea in the southern states. Annual notification rates of primary and secondary syphilis are rising and exceed 60 per 100 000 in some places. In these areas, the epidemic is concentrated in the poor heterosexual black population (Mushinski 1995, Nakashima et al 1996). Since about 1990, almost all countries of the former Soviet Union are experiencing a major STD epidemic. For example, in the Russian Federation, the annual notification rate of syphilis has risen from 4 per 100 000 in 1988 to 263 per 100 000 in 1996, equivalent to 62-fold increase (Trichonova et al 1997).

2.1.4 Epidemiology of STDs in sub-Saharan Africa

STDs are a public health problem all over Africa, but are much more common in countries situated south of the Sahara than in the north of the continent. The STD related burden of disease per 100,000 women has been estimated as being more than 7-fold higher in sub-Saharan Africa than in North African and Middle East countries (World Bank 1993). The reasons for this difference are not fully understood (Piot et al 1990). Doubts remain concerning the quality of the

data from North Africa, so that definite conclusions are difficult to draw. In sub-Saharan Africa, the overall combined incidence of syphilis, gonorrhoea, chlamydial infection, and trichomoniasis has been estimated at 254 per 1000 person years at risk (WHO 1995).

However, as in developing countries elsewhere, these figures reflect only estimates, generated by extrapolation of data from patchy sources. Many STD patients do not report to official facilities, diagnosis is mostly not based on laboratory results, and in most countries there is no compulsory registration or reporting of STDs (Adler 1996).

Most epidemiological studies have been conducted in groups which are comparatively easy to reach, such as antenatal clinic (ANC) attenders (table 2.1), or certain high risk behaviour groups (table 2.2). The paucity of studies performed in general populations is striking (table 2.3).

The available studies in various countries show high prevalences of most STDs even in low risk populations, and as one would expect higher prevalences in sex workers. For low risk populations, the prevalence of active syphilis frequently ranges between 4 and 12%, but levels as high as 18% have been observed in war-torn Mozambique (Lindstrand et al 1993, Vuylsteke et al 1993iii). Infections with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have frequently been observed in 2 - 10 % of the population, although again extraordinarily high levels have been reported, exceeding 15% in some communities (Arya 1973, Vuylsteke et al 1993iii). Cost-effective treatment of gonorrhoea has become difficult, as high levels of antimicrobial resistance against many drugs has been reported (Lind 1990, West et al 1995). More than 30% of the women in a population commonly have at least one type of RTI, and sometimes the prevalence exceeds 50% (Vuylsteke et al 1993iii, Mayaud et al 1995). Many STDs in both men and women, particularly those caused by gonococcal, chlamydial and syphilitic infections are asymptomatic (Arya 1973, Piot and Islam 1994, Grosskurth et al 1996). Asymptomatic infections with *Haemophilus ducreyi* occur as well, and may contribute to the transmission of chancroid (D'Costa et al 1985). Observations from Tanzania are in line with findings in other countries in sub-Saharan Africa (tables 2.1 and 2.3).

In sex workers, the prevalence of active syphilis ranges between 14% and more than 70% (table 2.2). Prevalences of trichomoniasis, candidiasis and chlamydial infection are mostly similar to those observed in low risk population studies, but gonorrhoea and genital ulcers usually occur much more frequently, which underlines the importance of this group for STD control programmes (Over and Piot 1993).

Table 2.1: Prevalences of various STDs from selected studies among **pregnant women** in sub-Saharan Africa

Population	Country	STD	N	Prevalence	Reference
Urban	Ethiopia	Active syphilis	337	11%	Friedmann et al 1977
Rural	The Gambia	Active syphilis NG CT TV CA HSV-2 (cult.)	100	1% 6.7% 6.9% 32% 35% 0%	Mabey et al 1984
Urban	South Africa	NG	1200	11.7%	Welgemoed et al 1986
Rural	South Africa	Active syphilis NG CT TV CA BV	193	12% 5.7% 11% 49% 38% 6.2%	O'Farrell et al 1989
Rural	Zambia	Active syphilis	925	8.0%	Hira et al 1990
Rural	Mozambique	Active syphilis NG / CT GUS Any STD	 201	15% 16% 6% 51%	Vuylsteke et al 1993 (iii)
Urban	Mozambique	Active syphilis	202	18%	Lindstrand et al 1993
Urban	Burkina Faso	Any STD Active syphilis NG CT TV CA BV GUS Genital warts	645	32% 3.6% 1.6% 3.1% 14% 14% 13% 0.8% 3.0%	Meda et al 1997
Rural	Tanzania[1]	Active syphilis NG CT NG/CT TV CA GUS Any STD Any RTI	964	10.1% 2.1% 6.6% 8.4% 27.4% 14.3% 0.9% 39.2% 49.1%	Mayaud et al 1995

Active syphilis: combination of positive TPHA or FTA with RPR or VDRL tests,
NG *Neisseria gonorrhoeae*, CT *Chlamydia trachomatis*, TV *Trichomonas vaginalis*,
CA *Candida albicans*, HSV *Herpes simplex virus-2*, GUS Genital ulcer syndrome.
[1] Mwanza Region 1992

Table 2.2: Prevalences of various STDs from selected studies among **high risk** behaviour groups in sub-Saharan Africa

Population	**Country**	**STD**	**N**	**Prevalence**	**Reference**
Urban sex workers	Kenya	NG			
high income			71	16%	D'Costa et al
intermediate			51	28%	1985
low income			71	46%	
Urban sex workers	Kenya	Active syphilis			
high income			71	14%	
intermediate			51	31%	
low income			71	52%	
Urban sex workers	Kenya	GUS			
high income			71	2.8%	
intermediate			51	11.8%	
low income			71	8.5%	
Urban sex workers	Kenya	Chancroid or			
high income		carrier of	71	0%	
intermediate		*Haemophilus*	51	7.8%	
low income		*ducreyi*	71	8.5%	
Urban sex workers	The Gambia	Active syphilis	31	71%	Mabey 1986
Urban sex workers	Zaire	Active syphilis	1233	16%	Nzila et al
		GUS		5%	1991
		NG		23%	
		CT		13%	
		TV		22%	
		CA		10%	
		Genital warts		3%	
		Any STD		75%	
Urban promiscuous men	Djibouti	Active syphilis	105	14%	Fox et al 1989
		NG		34%	
		CT		6%	

Legend: see table 2.1

Table 2.3: Prevalences of various STDs from community based studies in sub-Saharan Africa

Population	Country	STD	N	Prevalence	Reference
Rural men	Uganda[1]	NG	166	4.2%	Arya et al 1973
Rural women		NG	168	2.3%	
Rural men		NG	270	8.9%	
Rural women		NG	295	18%	
Rural men	Somalia	Active syphilis	187	4.2%	Osman et al
		CT		6.0%	1990
		NG		0%	
Rural women	Somalia	Active syphilis	200	16%	
		CT		18%	
		NG		0%	
Rural villagers	Uganda	Active syphilis	294	11%	Wagner et al
		HD antibodies		10%	1994
		HSV-2 antibody		68%	
Rural adolescent girls (aged 17-19 y)	Nigeria (Rivers State)	Active syphilis	158	2.6%	Brabin et al
		CT		10.5%	1994
		NG		1.9%	
		TV		8.3%	
		CA		35.9%	
		Any STD		20.9%	
		Any RTI		43.8%	
Urban men	Tanzania[2]	Active syphilis	597	9.3%	Mosha et al
		GUS[4]		0.2%	1993
		GDS[4]		1.0%	
Urban women	Tanzania[2]	Active syphilis	590	12.4%	
		GUS[4]		1.0%	
		GDS[4]		1.0%	
Rural men	Tanzania[3]	Active syphilis	978	7.0	
		GUS[4]		1.7	
		GDS[4]		2.6	
Rural women	Tanzania[3]	Active syphilis	1046	7.9	
		GUS[4]		0.4	
		GDS[4]		2.1	
Rural men	Tanzania[5]	NG[4]	5876	2.2%	Grosskurth et al
		CT[4]		0.7%	1996
		NG/CT[4]		2.7%	

Active syphilis: combination of positive TPHA or FTA with RPR or VDRL tests.
NG *Neisseria gonorrhoeae*, CT *Chlamydia trachomatis*, TV *Trichomonas vaginalis*, CA *Candida albicans*, HSV-2 *Herpes simplex* virus type-2, GUS Genital ulcer syndrome, GDS Genital discharge syndrome.
[1]Two different rural communities [2]Mwanza town 1990/91, [3]Mwanza Region 1990/91, [4]Minimum prevalences (self reported and clinically confirmed infections), [5]Mwanza Region 1992

2.1.5 The epidemiology and public health importance of STD sequelae

Many STDs may lead to serious complications, particularly in women and their off-spring. Epidemiological data about the incidence of these events in sub-Saharan Africa are scarce, but it is expected that the risk is at least as high as in industrialised countries (Wasserheit 1989). The data given below refer to observations from industrialised countries, except where specific reference to developing countries is made.

Pelvic inflammatory disease: About 10 - 15% of women with untreated chlamydial cervicitis and up to 20% of women with untreated gonococcal cervicitis develop PID (De Schryver and Meheus 1992, Wasserheit 1989). The bacterial flora seen in BV can often also be recovered from peritoneal fluid and tubal specimens of women with PID, suggesting that BV may frequently be the antecedent of pelvic infection. The risk of PID is particularly high in intrauterine device users and in women with cervical infection in whom abortion is performed (Wasserheit 1989).

PID frequently results in tubal blockage or tubal scarring, both intraluminal and peritubal, leading to complications which have devastating consequences for the health of women in countries with insufficient health care systems. These complications include infertility, chronic pelvic pain, and ectopic pregnancy. The risk of these complications increases with increasing numbers of PID episodes (Wasserheit 1989).

Chronic pelvic pain: The chronic lower abdominal pain following peritubal scarring is often so severe that it may have a debilitating effect on women. This condition develops in 15 - 20% of women who had PID (Wasserheit 1989).

Infertility: The prevalence of infertility seems to be higher in sub-Saharan Africa than in all other continents, often exceeding 20% and reaching a level of 50% in some communities (Muir and Belsey 1980, Rosenberg et al 1986). It has been estimated that 80% of infertility in Africa is attributable to STDs (Belsey 1976). Infertility may result from gonococcal but even more often from chlamydial infection (Mabey et al 1985), probably because acute gonococcal PID is more severe and patients are more likely to seek treatment. The social consequences of infertility for women may be severe in societies where much of the social value of an individual is attached to the capability to reproduce (Wasserheit 1989). Infertility and pregnancy wastage may result in divorce, or prostitution in order to survive (Laga 1994).

STDs are also associated with male infertility. Untreated or inadequately treated gonococcal or chlamydial infection in men frequently leads to epididymitis which is the leading cause of male infertility in Africa (De Schryver and Meheus 1992). In a study of infertile couples in Lagos, Nigeria, 40% of the husbands had oligo- or azoospermia, and most of them reported a history of untreated or undertreated urethritis (Osoba 1984). In a community based study in Uganda, 29% of the men in the general population had evidence of chronic orchitis or epididymitis, 22% of which was bilateral (Arya et al 1973). The commonest late complication of urethritis is urethral stricture which may also represent a considerable handicap to conception (Osoba 1984).

Ectopic pregnancy: The risk of ectopic pregnancy has been estimated to be increased up to tenfold in women who had one or more episodes of PID, as compared to women without a history of PID, and postinfectious ectopic pregnancy occurs more often in developing than in industrialised countries (Muir and Belsey 1980). Because diagnostic and therapeutic possibilities are far more limited in developing countries, the mortality of ectopic pregnancy is also much higher (Wasserheit 1989). Precise epidemiological data are lacking, however.

Puerperal upper reproductive tract infections: Deliveries conducted in the presence of an STD, notably cervical infections and bacterial vaginosis, can frequently lead to endometritis and generalised sepsis (Plummer et al 1987, Brunham et al 1990).

Abortion and stillbirth: Pregnancy wastage is frequently associated with STDs. Early spontaneous abortion is associated with gonococcal and *Herpes simplex* virus type-2 infection, and 2nd and 3rd trimester abortion and stillbirth with syphilis (Schulz et al 1987, Wasserheit 1989). In various African studies it has been shown that 20% to 40% of pregnancies in women with untreated syphilis result in perinatal death (Ratnam et al 1982, Schulz et al 1987, Hira et al 1990). Based on the same studies, it has been estimated that 10% to 40% of all perinatal deaths are caused by syphilis in countries with a syphilis seroprevalence of around 10%.

Premature delivery and low birth weight: The incidence of low birth weight is higher in developing than in industrialised countries, and is as high as 30% in many areas. RTIs are an important contributing factor for low birth weight (Wasserheit 1989). Low birth weight, which is a major risk factor for infant mortality, occurs because of intrauterine growth retardation or premature delivery, and STDs are frequently associated with both. Bacterial vaginosis, chlamydial and gonococcal infection may all result in premature rupture of membranes. (French

and McGregor 1997). Preterm delivery occurred in 12% of pregnancies of mothers with untreated syphilis in a study in Zambia (Hira et al 1990).

Congenital syphilis: About 30% to 40% of infants born to mothers with active syphilis are infected with *Treponema pallidum* as a result of intrauterine transmission (Wasserheit 1989, Temmerman et al 1993). About half of them have the signs of congenital syphilis which frequently leads to neonatal death or permanent disability and disfigurement (Schulz et al 1987, Temmerman et al 1993). Diagnosis at birth is difficult, and the problem is therefore often underestimated (Temmerman et al 1993).

Ophthalmia neonatorum (ON): During delivery, about 30 - 50% of mothers infected with *Neisseria gonorrhoeae* and about 30% of those infected with *Chlamydia trachomatis* pass the infection on to their babies (Wasserheit 1989). In many cases this results in purulent eye infection (ophthalmia neonatorum). Gonococcal ON in particular, if untreated, often leads to blindness (Schulz et al 1987). This could be prevented by ocular prophylaxis, but in many African countries prophylaxis has been discontinued or is incompletely applied. It has been estimated that the incidence of ON ranges between 0.5% and 5% of all neonates in Africa, depending on the prevalence of cervicitis due to NG or CT among pregnant mothers (Meheus 1988, Laga 1994). The incidence of blindness from gonococcal ON in Africa is unknown, but the overall prevalence of blindness is low. It has been speculated that this is due to high mortality among blind children (Schulz et al 1987). The seriousness of gonococcal eye infection was demonstrated in a study from Mozambique, which documented that 26 of 89 adults and 2 of 176 babies lost sight in one or both eyes as a result of gonococcal eye infections (Bastos dos Santos et al 1992).

It follows from the facts described in sections 2.1.3 - 2.1.5 that the STD epidemic in the developing world in general, and in sub-Saharan Africa in particular represents one of the most important public health problems (World Bank 1993) and is characterised by a high incidence and prevalence in many populations, a high rate of serious complications, a high rate of asymptomatic infections, and an alarming problem of antimicrobial resistance (Laga 1994, Lind 1997).

2.1.6 STD case management

Appropriate STD case management comprises four steps: correct diagnosis, effective treatment, health education to achieve treatment compliance and sustainable risk reduction, and effective partner notification (Meheus et al 1990, Mayaud et al 1994, Adler et al 1996).

Approaches to STD case management

There are in principle three distinct approaches to STD case management: clinical, aetiological and syndromic case management. These approaches differ mainly in the way the diagnosis is made.

(i) Clinical case management attempts to arrive at a specific diagnosis based on clinical examination, and to treat the assumed aetiology. This traditional approach has been widely used by care providers without access to laboratory services. However, the low sensitivity and specificity of this approach has been emphasised by various authors (e.g. Meheus et al 1983, Dangor et al 1990 et al, Ndinya-Achola et al 1996, Chilongozi et al 1996). The high rate of misclassification and the resulting inappropriate treatment has been demonstrated for example in a study from Kenya, where in 168 patients with clinical ulcers, the specific clinical diagnosis was compared with laboratory results. Sensitivity, specificity, and positive predictive value for the clinical diagnosis of chancroid were 93%, 16% and 41%, and for the diagnosis of syphilis 25%, 88% and 25%. As can be expected, treatment was frequently inadequate, particularly for syphilis (Ndinya-Achola et al 1996).

(ii) Aetiological case management is based on laboratory diagnosis. A number of obstacles make this approach largely inappropriate for Africa and most developing countries elsewhere: Laboratories frequently do not exist, or where they exist, quality control systems are insufficient (Mayaud et al 1994, Ndinya-Achola et al 1996, Adler 1996). For some STDs, such as *Chlamydia trachomatis* infection, available tests are expensive, sophisticated or not sufficiently sensitive (Noble 1997). Unfortunately, cheap, simple and sufficiently sensitive and specific diagnostic tests for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are not available (Piot and Islam 1994).

(iii) Syndromic case management is based on the diagnosis of the syndrome (section 2.1.1). In principle, all likely aetiological causes of that syndrome are treated simultaneously at the place and time of first contact of the STD patient with the health sector. The approach has been strongly promoted by the World Health Organization (WHO 1991).

Syndromic STD case management

Because the major possible causes of an STD syndrome are covered, the syndromic approach is by definition highly sensitive. Delays in the initiation of treatment are avoided, as patients do not need to wait for laboratory results (Mayaud et al 1994, Chilongozi et al 1996). The increased costs due to overtreatment are outweighed by the savings on laboratory costs. In a study of 1500 hypothetical STD patients with different syndromes using decision-theory analysis, it was demonstrated that both clinical and laboratory based case management cost two or three times as much as the syndromic based approach (WHO 1993). The treatment of STDs can be standardised with the help of algorithms, thus enabling paramedical staff to make use of it, and this approach facilitates procurement and logistics in control programmes. WHO has published a complete set of syndromic treatment algorithms and recommendations for the selection of drugs (WHO 1994).

Syndromic case management allows STD treatment services to be integrated within the existing primary health care system of sub-Saharan Africa. This integration is essential because most STD patients in developing countries have no access to the few specialised services which may be available (Wasserheit 1989, Piot and Islam 1994, Laga 1994, Mabey 1996). The validity and the operational feasibility of this approach in sub-Saharan Africa has been demonstrated in several studies (Vuylsteke et al 1993ii, Piot and Islam 1994, Mwijarubi et al 1993, Chilongozi et al 1996)

The validity of specific algorithms depends on the correct choice of drugs to be included in the algorithms. Algorithms have to be adjusted therefore to the specific situation in a country or region, in terms of the underlying pattern of aetiologies and the antibiotic susceptibility of STD pathogens in that area (Mayaud et al 1994, Wilkinson 1997). At least one specialised clinic and reference laboratory is required to monitor these parameters (Adler et al 1996).

The syndromic approach has also a number of disadvantages and unsolved problems.

Patients are frequently treated for infections which they do not have, thus exposing them to possible side effects unnecessarily. Physicians who are familiar with an approach whereby treatment should only follow a full microbiological diagnosis, have difficulties in accepting a method which they perceive as unscientific (Kumar et al 1995).

The main problem, however, lies in the management of the vaginal discharge syndrome (Laga 1994, Adler 1996). The most dangerous infective agents of the female reproductive tract, *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT), are frequently asymptomatic. This has two consequences: If the treatment of these infections is included in the algorithm for VDS, the syndromic approach has a high sensitivity for these infections in women presenting with VDS, but a very low specificity, as many women will be treated unnecessarily; for example 90% in a study from Zaire (Vuylsteke et al 1993i). On the other hand, as a result of asymptomatic infections, the syndromic approach has a low sensitivity to detect NG and CT among women in the community who have these infections, but the sensitivity would be zero if the treatment of NG and CT were not included in the algorithm.

An attempt to overcome this problem has been made through the introduction of a risk assessment step into the algorithm for the management of VDS, hoping that this would increase the algorithm's specificity for NG and CT infection without losing much sensitivity (Vuylsteke et al 1993i, WHO 1994, Mayaud et al 1995). The validity of this approach was recently evaluated in women presenting with vaginal discharge at the STD reference clinics in Mwanza. Unfortunately the sensitivity was only about 46% and 62% in pregnant and non-pregnant women respectively (Mayaud et al 1997ii). A final solution to this problem will only be possible once cheap, simple and accurate diagnostic tests are available for use at peripheral health facilities (Piot and Islam 1994).

Health education

The great importance of health education during the process of case management is underpinned by the fact that STD patients are at high risk for repeat infections and HIV, because of their sexual behaviour or that of their partners (Meheus et al 1990). HIV prevalences in STD patients sometimes reach very high levels, e.g. 35% in Abidjan, 63% in Kampala or 55% in Lusaka in different studies (Somse, Hellamann, Tembo as cited by Nkowane 1991). The contact of a health

worker with an STD patient should be regarded as a privileged moment for education about risk reduction and condom use (Piot and Islam 1994).

Whilst the concept of health education is clear, implementation does not seem to be easy (Wilkinson 1997). The few studies which have been conducted so far in developing countries to investigate the performance of integrated STD services demonstrated that health education is actually given far too rarely, for example in only 30% of STD cases in some health facilities in Honduras, 20% in Ivory Cost, or 30% in India (Mertens et al 1993, Kantharaj et al 1995), and 29% in Malawi (Chilongozi et al 1996).

Partner notification and treatment

Partner notification is an essential part of good STD case management (Wellington 1994, Mayaud et al 1994, Adler et al 1996). It can be achieved through active efforts of health personnel to locate the sexual partner(s) of STD patients (provider referral), or through health education of the STD patient (index case) to persuade his or her sexual partner(s) to seek treatment at the health facility (partner referral).

Few studies have investigated the effectiveness of these approaches in Africa. It seems that the proportion of partners treated seldom exceeds 30% (Hayes et al 1997), and that provider referral in particular has a very low cost-effectiveness (Adler et al 1996). In a study in Nigeria, 156 STD patients were notified through partner referral, and 74 of these (47%) attended a clinic. Home visits by clinic staff to another 56 patients yielded only a further 4 successful provider referrals (Asuzu et al, 1984). On the other hand, in a programme in Harare, successful partner referral was achieved in only 23 % of 1513 sexual contacts, and subsequent provider referral yielded a further 17% (Winfield and Latif 1985).

2.1.7 Options for STD control in developing countries

STD control has two major objectives: (i) to prevent infections through behaviour modification and the use of barrier methods; and (ii) to keep the duration of infection as short as possible through optimal case finding and management (Laga 1994, Adler 1996). To assist the design of control strategies, operational models have been developed to define the overall proportion of STD cases in the community that are successfully treated by the health services, and the stages at which failure occurs (Buve et al 1993, Fransen 1993, Laga 1994, Adler et al 1996).

An example is the Piot-Fransen model shown in figure 2.1 (Hayes et al 1997), based on real data on STDs in women obtained from a variety of studies conducted in East and Central Africa (Vuylsteke et al 1993i , Newell et al 1993, Mulder 1994, Buve et al 1996).

In the absence of improved STD treatment services, about half of all sexually active women in the model community have a reproductive tract infection at any point of time, but only about half of them are symptomatic. Only about two-thirds of these symptomatic women seek treatment, and even fewer go to a health unit or other medically trained care provider. Of the 30% of infected women who present for treatment at a typical peripheral health facility, as few as one in five may be treated appropriately. Not all of these will complete their treatment, and not all will be cured. Of those cured, at most 40% will persuade their partners to seek treatment.

Under these conditions, only 1 to 5% of the infected women will be cured, and many of these may be rapidly reinfected because their partners remain untreated. The situation in men is little better, especially considering that a high rate of asymptomatic infections is also observed in men (Arya 1973, Grosskurth et al 1996, Buve et al 1996).

Classically, STD control programme planners have focused on the last steps of the model, neglecting the initial ones, which may be crucial in determining the final outcome of the programme (Laga 1994).

It is clear from the model that the majority of individuals with an STD in sub-Saharan Africa do not reach the health system, and that improved STD case management alone can reach at most about 30% of those infected (figure 2.1, part b). The magnitude of this problem was not yet known in the late 1980s when the Mwanza trial was designed to study the impact of STD control through the improvement of health services.

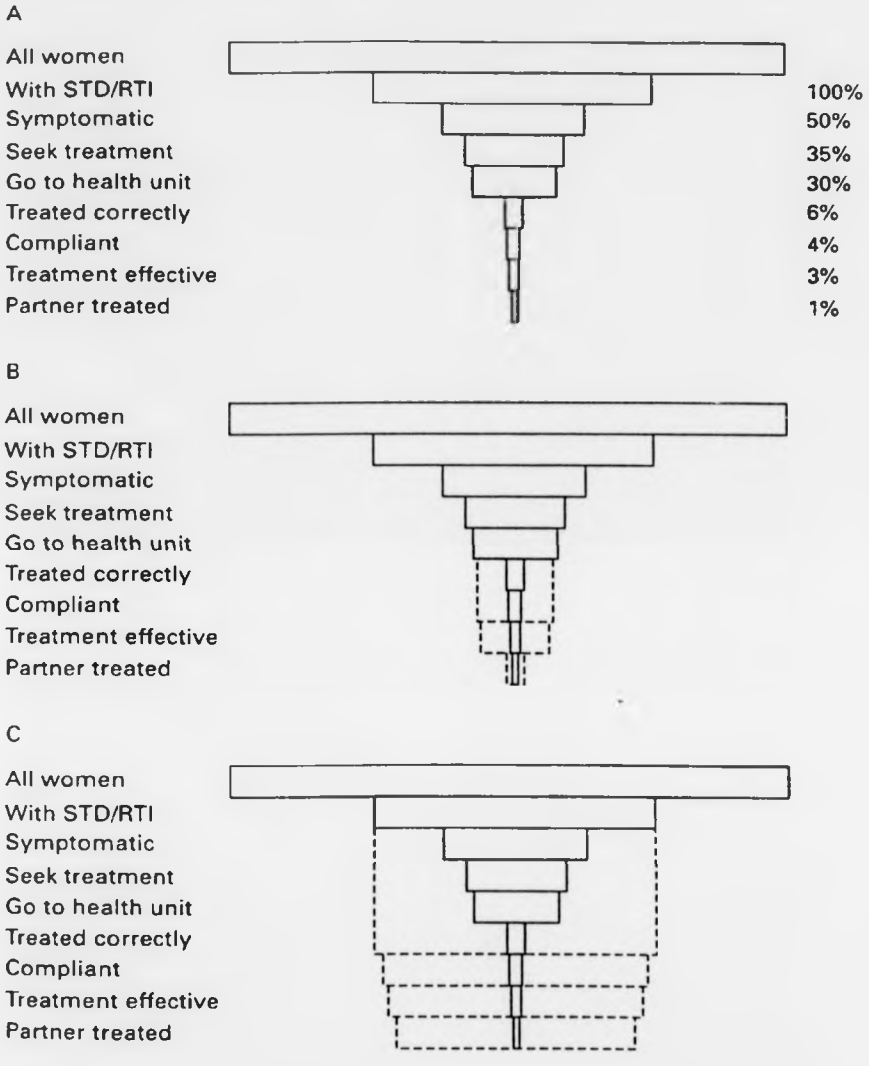


Figure 2.1: Piot-Fransen model of obstacles to and possible strategies for effective STD control

The model shows overall STD/RTI prevalence and proportions of infected patients reaching different steps towards possible effective cure. The model uses a population of rural women in a hypothetical community in sub-Saharan Africa as an example. Data are illustrative and based on observations from Uganda, Tanzania and Zaire (Hayes et al 1997)
A situation in the absence of improved STD services, B potential effect of improved STD case management services, C potential effect of mass STD treatment

The model can be used to systematically consider the options available for improved STD control (Laga 1994, Adler et al 1996, Hayes et al 1997). These are:

- primary prevention of STDs in those who are not (yet) infected
- screening for individuals with asymptomatic infections
- screening for patients with symptomatic but neglected STDs
- improvement of treatment seeking behaviour
- improvement of STD treatment services
- improvement of partner notification and treatment

Additional options are the mass treatment of STDs and targeted interventions through the provision of special intervention packages for sex workers and other members of the 'core group' (Brunham 1991, Moses et al 1991, Over and Piot 1993).

Mass treatment of STDs is a controversial option for STD control. It has the advantage of reaching not only individuals with symptomatic STDs and their sexual partners, but also asymptomatic and neglected cases (figure 2.1, part c). Disadvantages are the unnecessary treatment of uninfected persons, the potential creation of antimicrobial resistance in STD and non-STD microbes, and the enormous logistical requirements. A mass treatment intervention is costly, but may nevertheless be very cost-effective (Wawer et al 1996, Adler et al 1996, Hayes et al 1997).

The core group concept of STD control is based on the assumption that a relatively small proportion of the population is responsible for the maintenance of the STD epidemic, and that this group of transmitters is particularly important for disease control. The core is an epidemiological concept rather than a precisely defined group. Some sex workers are a relatively easy to reach part of the core, but the core comprises many other individuals (Hethcote and Yorke 1984, Over and Piot 1993).

Using a computer simulation model, Over and Piot showed that curing a certain number of cases of gonorrhoea in the core prevents many more secondary and tertiary cases of gonorrhoea in the general population than curing the same number of people in the noncore population. If this dynamic benefit is studied in a one-time intervention, the effect peaks several months afterwards, then decreases, but is still noticeable for a considerable time (Over and Piot 1993).

Core group interventions are most successful if they combine several intervention strategies as a package, e.g. health promotion through peer education, improved STD case management, and regular screening (Over and Piot 1993, Adler et al 1996). Unfortunately, core groups are often difficult to define or locate in rural populations, limiting the applicability of this approach in many parts of Africa.

2.1.8 STD control programmes in sub-Saharan Africa

Until recently, the health programmes of developing countries have not given a high priority to the control of STDs. The same applies to international health agencies and to donor organisations (Rosenberg et al 1986, Over and Piot 1993). Although STDs on their own have such severe consequences for the health of the population in developing countries (sections 2.1.3 - 2.1.5), it was only the emergence of HIV infection, and the suspicion that there is an epidemiological synergism between STDs and HIV infection, that has pushed STDs high up on the health policy agenda (Laga 1994).

As from the early 1990s, almost all countries in sub-Saharan Africa declared the control of STDs to be a major target of their health policies. However, few have made a serious attempt to put this policy into general practice. Implementation is hampered by inadequate health services, expensive medications, and a variety of sociocultural factors. Another obstacle is posed by the multiplicity of the factors affecting acquisition and transmission of STDs which means that the health sector alone would be overburdened with the control of this problem, and that a high degree of intersectoral cooperation is therefore required (Gelmon and Moses 1994).

Against this background it is not surprising that there is no country so far which has accomplished a comprehensive STD control programme which would cover the majority of its population or which would include most of the options described in section 2.1.7.

However, some reports of successful STD control efforts are available from different sub-Saharan African countries. These are highlighted below, using the framework described in section 2.1.7.

Primary prevention

Adaptation of sexual behaviour towards risk reduction is very difficult to obtain and, once achieved, to maintain. Programmes to increase awareness have largely failed to achieve a sustainable impact on sexual behaviour. Primary prevention is particularly difficult to achieve in many developing countries, because sexual behaviour is very much determined by social and economic factors. Not uncommonly, women have sex on a commercial basis against their will and are unable to effectively negotiate the use of condoms. Improving the status and the economic situation of women could contribute substantially to the control of STDs and HIV infection (Adler 1996). Against this background, primary prevention is a difficult task.

Nevertheless, it has been demonstrated that behaviour changes and increased condom use in the general population are possible, provided the price of condoms is affordable (Piot and Islam 1994). Social marketing has proven to be the most successful approach. For example in Zaire, it has been employed successfully in a large scale mass media based promotional programme which was able to increase annual condom sales from 20 000 to more than 18 million within one year (Kyungu 1992). Primary prevention in high risk behaviour groups through intensive condom promotion has also been shown to be successful (Laga et al 1994ii, Ettiegne-Traore et al 1996).

More recently, the focus of attention has shifted to primary prevention among adolescents. For example, as in several other areas, a school health education programme was established in 40 schools of Kabale District, Uganda. An operational evaluation showed that the programme was well accepted in the community and by the students themselves. Self reported risk behaviour improved significantly over a period of 2 years, as demonstrated by two consecutive cross-sectional surveys conducted among 400 primary school students (Bagarukayo et al 1995).

So far, no results on the impact of health promotion interventions based on well designed trials have been reported anywhere in Africa. The first trial to investigate the impact of an educational intervention aiming at sexual behaviour changes in the general adult population is presently being conducted in 18 parishes of the Masaka district of Uganda (Kengeya-Kagondo et al 1996). A trial to determine the impact of an adolescent reproductive health intervention has started recently in 20 communities of the Mwanza Region in Tanzania (LSHTM and AMREF 1996).

Screening

It has been repeatedly recommended that both STD case management and regular STD screening should be integrated within family planning, antenatal and mother and child health services (Wasserheit 1989, Meheus et al 1990). Whilst cheap and simple screening tests for gonococcal and chlamydial infections are still awaited, it would for many years have been possible to screen all women for serological syphilis and for neglected or mildly symptomatic syndromes. Although the benefits are so obvious, however, large scale implementation of regular screening for syphilis has only been accomplished in a few places.

An exemplary evaluation study, which describes the status-quo of STD services in antenatal care in many countries, has been performed in East Africa. In Kenya, syphilis screening in pregnancy is part of the national health policy. During the time of the evaluation, an estimated 90% of all pregnant mothers attended ANC services in Nairobi. Blood taken at various ANC clinics was sent for syphilis screening to a central laboratory. Women were informed about their results a few weeks later. If they were positive, they were sent to a specialised STD clinic. Due to various logistical problems, a syphilis screening test was actually done for less than 10% of the women. Only a small proportion of seropositive women were able or willing to attend the STD clinic. Even after an intervention improving the logistical situation, only 62% of women were screened, and a result was available for only 87% of these. 4% (eleven women) had active syphilis. Of these, only one woman was adequately treated (Temmerman et al 1993).

However, successful screening is possible and can be cost-effective, as demonstrated in a study in Zambia. An intervention trial was conducted at three centres in Lusaka involving 5007 prenatal attenders to investigate the effectiveness of health education given to pregnant mothers, and of prenatal syphilis screening which was performed on the spot using the RPR test. The prevalence of active syphilis in the study population was 8%. Compared to two control centres during the one year study period, the proportion of mothers attending for prenatal visit at the intervention centre improved from 9% to 43%, and adverse pregnancy outcomes were reduced by two-thirds (Hira et al 1990).

Improvement of treatment seeking behaviour

There are no reports of interventions to improve treatment seeking among STD patients, although it has been acknowledged that the problem is a serious one (Buve et al 1993, Mulder 1994, Hayes et al 1997).

Improvement of STD treatment services

Most African countries have adopted a strategy of integrating improved STD case management into their primary health care (PHC) system, usually based on the syndromic approach for STD case management. Very few have been successful in establishing such intervention programmes on a large scale. Positive examples have been reported from Zimbabwe, Zambia, Mozambique, and Rwanda but even in these countries the improved services are still restricted to the capital and a few districts (Wellington 1994, Hira et al 1990, Bastos dos Santos et al 1992, Steen et al 1996).

The example of Mozambique shows that the strategy is feasible even under the extremely difficult circumstances of a post-war situation. Available documentation describes that improved STD case management was introduced at 20 health centres which served a population of about 1.2 million inhabitants. The intervention comprised the creation of a management structure in the Ministry of Health, the establishment of a training programme for PHC workers, of a supply procurement system and of a reference centre, a monthly supervision system, the distribution of an information leaflet to patients, and condom promotion. At some of the health centres, regular syphilis screening was introduced for pregnant mothers. An operational evaluation covering a one-year period showed that about 34,000 STD patients and about 5,000 (15%) sexual partners had been treated, and that fewer than 5% of the patients required referral to the reference clinic (Bastos dos Santos et al 1992). Impact data from this intervention are not available.

Improvement of partner notification and treatment

There are no reports on interventions which aim exclusively at improving partner treatment coverage. Usually such efforts are part of improved case management (Winfield and Latif 1985, Asuzu et al 1984, Wellington 1984). The different approaches to improve partner notification and their effectiveness are outlined in section 2.1.6. It seems that for developing countries, partner referral and the use of a simple coded contact referral card is the most effective solution (Mwijarubi et al 1993, Mayaud et al 1994, Adler et al 1996).

Targeted interventions for sex workers and other core groups

This is probably the area where most STD control activities are being implemented at present in sub-Saharan Africa. However, with a few exceptions, there is still no large scale coverage. Most of the interventions combine treatment of STDs with health promotion and condom distribution.

Sex worker intervention projects have been launched in many locations, including Nairobi, Kinshasa, Abidjan and Mwanza (Moses et al 1991, Laga et al 1994ii, Ettiegne-Traore et al 1996, Matasha et al 1992). The interventions and evaluation results are described in section 2.3.5.

Truck drivers and their assistants are regarded as another important component of the core group (Over and Piot 1993). Truck driver intervention projects have been launched since the early 1990s in various countries, notably Cameroon, Nigeria, Zimbabwe, Kenya, and Tanzania, but few reports have been published (Jackson et al 1997, Mwizarubi et al 1994). Some of these projects have achieved a high degree of coverage. For example, in a nation-wide project in Tanzania, five different NGOs have covered different parts of the country and adopted a standard intervention approach which includes condom provision at truck stops, health education through leaflets, stickers on lorries and other promotional materials, health education to sex workers at truck stops, and improved STD case management in clinics at transport companies and at some of the truck stops (Mwizarubi et al 1994).

Mass treatment

For STD control, mass treatment of the general population is still a theoretical concept. A trial to test this concept is underway in the Rakai district of Uganda (see section 2.3.5).

2.2 HIV infection and AIDS

2.2.1 Definition and synopsis

The acquired immunodeficiency syndrome (AIDS) was first described in the US in 1981, when an unexpectedly frequent occurrence of cases of atypical pneumonia caused by *Pneumocystis*

carinii and of Kaposi's sarcoma was noted in homosexual men (Friedmann-Kien 1981, Gottlieb et al 1981, Siegal et al 1981). AIDS is characterised by a marked reduction of those T-lymphocytes which carry the CD4-receptor molecule, a progressive destruction of lymphoid tissue, severe impairment of immune function, and a variety of opportunistic infections (Pantaleo et al 1997).

The retroviral aetiology of AIDS was revealed in 1983 (Barre-Sinoussi et al 1983). The newly discovered virus was initially named human T-cell lymphotropic virus type III (Hahn et al 1984). In 1986, the term was replaced by human immunodeficiency virus type-1 (HIV-1). The laboratory detection of serum antibodies against the viral antigen became possible as from 1984. These antibodies are not protective, but their occurrence is diagnostic of HIV-1 infection in adults, and can be used to study the prevalence of the infection in epidemiological studies.

The typical course of HIV infection includes three phases: primary infection, clinical latency, and clinically apparent disease which comprises different stages (Pantaleo et al 1997). The median incubation period from infection to AIDS is around 10 years in industrialised countries, and may be somewhat shorter in sub-Saharan Africa. Once a patient develops AIDS, death will usually occur within 2 to 3 years. The survival time from AIDS to death seems to be shorter in sub-Saharan Africa; for example in a rural cohort from Uganda it was 9 months on average (Morgan et al 1997).

Combination therapy with antiretroviral drugs can suppress viral replication, but is unlikely to be introduced on a large scale in developing countries for the foreseeable future because of the prohibitive costs. Efforts to develop a protective vaccine are underway, but no breakthrough has been achieved so far (Clements 1997).

In 1985 a second related human immunodeficiency retrovirus (HIV-2) was discovered in two AIDS patients from West Africa (Clavel et al 1986). Its core antigens resemble those of HIV-1, but both agents differ substantially in their envelope glycoproteins. The West African virus is genetically more closely related to the simian immunodeficiency virus (SIV). Antibodies against HIV-2 are specific and distinct from those against HIV-1, but still so similar that cross-reactions occur in many diagnostic assays.

2.2.2 Global epidemiology of HIV-infection and AIDS

According to estimates by UNAIDS, 30.6 million people were living with HIV infection world-wide by December 1997. Of these, 12.1 million were women and 1.1 million were children. In 1997, 5.8 million new infections occurred, around 16 000 a day. Over 50% of those infected were 15-24 years old. It has been estimated that more than 40 million people will be living with HIV in the year 2000 (UNAIDS 1997).

Since the beginning of the pandemic in the early 1980s, it has been estimated that 11.7 million people have died from AIDS, among them 4.0 million women and 2.7 million children. 8 million children became orphans because their mother or both parents died from AIDS.

More than 90% of HIV-infected people live in developing countries (UNAIDS 1997). The pandemic is composed of distinct epidemics in different parts of the world. HIV prevalence and incidence are still increasing in most parts of the world, but incidence appears to have declined in some populations, for example in gay men in North America, Australia and Western Europe, in young men in Thailand and in pregnant women in southern Zaire and Uganda (UNAIDS et al 1996, Mertens and Burton 1996).

Estimates for average HIV prevalence among adults aged 15 - 49 years in developing regions ranges from 0.13% in North Africa and Middle East, and 0.5% in Latin America and South and South East Asia, to 7.4% in sub-Saharan Africa. Estimates of adult HIV prevalences in industrialised countries are 0.07% for Eastern Europe, 0.1% for Australia, 0.3% for Western Europe, and 0.6% for North America (UNAIDS 1997).

2.2.3 Epidemiology and public health importance of HIV infection and AIDS in sub-Saharan Africa

Transmission

HIV can be transmitted sexually, vertically (from mother to child) and parenterally. In sub-Saharan Africa, the predominant mode of transmission is heterosexual intercourse, accounting for more than 90% of HIV infections in adults (Mann et al 1992, UNAIDS et al 1996). Less

than 1% of adult HIV infections have been estimated to occur as a result of homosexual intercourse (Mann et al 1992).

Vertical transmission has become a major problem in areas with high HIV prevalences among women of child bearing age. Vertical transmission rates vary between different studies and different geographical settings, most studies report that between 25% and 30% of babies born to HIV-positive mothers will carry the infection (Working Group on MTCT HIV 1995). Other sources describe this proportion to be within a range from 25% to 40%, with a central estimate of one third (Mann et al 1992). Transmission by breast feeding has been documented, but it is difficult to estimate the proportion of vertical transmissions due to this mode (Mann et al 1992).

Transmission through transfusion of blood or blood products accounts for only a small proportion of infections, and has been estimated at 4% in sub-Saharan Africa (Mann et al 1992). However it still represents a public health problem because many health services have no facilities to screen donor blood for HIV infection (Bontick et al 1995). Nonsterile needles and syringes may occasionally contribute to the HIV problem (Piot et al 1988). The proportion of adult HIV infection due to intravenous drug has been estimated at 0.5% (Mann et al 1992).

By contrast, adult HIV infection in Western Europe and the US is due to heterosexual intercourse in 9 - 14%, homosexual contacts in 47 - 56%, blood and blood products 2 - 3%, injecting drug abuse 27 - 33%, and other or unknown courses in 4 - 5% (Mann et al 1992).

The proportion of people with multiple heterosexual partners, the network between heterosexual partners in the community and the presence of some enhancing cofactors are the main determinants of the epidemic (Piot et al 1988, Larson 1989).

The course of the epidemic

Sub-Saharan Africa is the region with the most substantial HIV epidemic. It has been estimated that in 1997 about 3.4 million new HIV infections occurred here among adults, and about 530 000 among infants (UNAIDS 1997).

Countries in East and Central Africa were the earliest to experience the full impact of the epidemic, notably Uganda, Rwanda and parts of Zaire (Piot et al 1984, Serwadda et al 1985,

Van de Perre et al 1984). Already in 1986, Quinn et al listed 17 countries in which the prevalence of HIV infection was substantial, ranging from 0.7% among blood donors in the Congo to 18% among pregnant women in urban centres in Rwanda (Quinn et al 1986). Prevalences in some high risk populations rose particularly fast. For example, the HIV seroprevalence among prostitutes of low socio-economic status in Nairobi, Kenya reached 66% by 1986 (Kreiss et al 1986).

At present, the epidemic is spreading particularly fast in the southern part of the continent. The total number of people living with HIV in the Republic of South Africa increased by one third from 1996 to 1997, and has now been estimated at 2.4 million. In Francistown, Botswana, 43% of pregnant women tested HIV positive in 1996, and 32% in Harare in 1995. In Beit Bridge, Zimbabwe, the prevalence in ANC attenders reached 59% in 1996 (UNAIDS 1997).

Recently, prevalence levels measured at four urban antenatal (ANC) surveillance sites in Uganda have started to decrease, reaching 14% to 16% respectively by 1996, equivalent to a reduction of about 40% compared to previous years (Asiimwe-Okiror et al 1997, Bagenda et al 1995). Similar observations were made in a rural cohort in the Masaka district of Uganda, where the prevalence in young men aged 13-24 years fell from 3.5% in 1990 to 1% in 1990 (Mulder et al 1995). Uganda started to react to the epidemic rather early, and it has been speculated that the observed decrease may be a result of a decade of health promotion. However, stabilising or even decreasing prevalences may also result from other factors, such as saturation of the population at risk, changes in virulence of HIV, or changes in infectiousness of people infected with HIV (Mertens and Burton 1996).

The prevalence of HIV infection is still increasing in most rural populations in sub-Saharan Africa. Because most Africans still live in rural areas, the population at risk is very large (Barongo et al 1992).

Impact of the epidemic

HIV infection and AIDS has become the leading cause of adult death in many cities of the continent (Van de Perre 1995). The increase in adult mortality has been dramatic, but many HIV-related deaths seem to occur unexpectedly and before patients have developed full blown AIDS (Todd et al 1997), and this may be a potential obstacle for health promotion and

awareness raising programmes. The overall crude death rate is expected to more than double over the next 10 years in countries of East Africa, reaching 24 per 1,000 by the year 2010. For Botswana and Zimbabwe 5 to 6-fold increases of the crude death rate have been predicted, reaching 29 per 1,000 by 2010. Crude death rates are expected to double in various parts of West and Central Africa (Stanecki and Way 1996). Life expectancy, which had increased substantially in many developing countries during the past 3 decades, is expected to drop to previous levels (Stanecki and Way 1996, UNAIDS 1997).

It is expected that infant mortality and the mortality of children under 5 years of age will increase substantially in sub-Saharan Africa, particularly in urban centres, thus reversing the successes of primary health care efforts of the two last decades, and placing additional burdens on families and health services (Nicoll et al 1994). A rise in infant mortality by 140% because of AIDS has been predicted for Zimbabwe between now and the year 2010 (UNAIDS 1997), and is expected to reach 71 per 1,000 (Stanecki and Way 1996). For other countries in East and South Africa, increases of infant mortality by 40% to 120% have been predicted whilst increases by 10% to 35% are expected for countries in West and Central Africa (Stanecki and Way 1996).

In East and Southern Africa, child mortality rates have already risen by between 25% and 85% due to AIDS mortality, and are expected to have increased 1.8 to 4 times by the year 2010 compared to estimates in the absence of AIDS, and will reach levels between 110 per 1,000 (Kenya) and 240 per 1,000 (Malawi). The most extreme increase is expected to occur in Zimbabwe, where child mortality has been estimated at 38 per 1,000 without AIDS and is expected to reach 153 per 1,000 in the year 2010. Increases for West and Central Africa are expected to range between 15% and 70% (Stanecki and Way 1996). The amount of suffering hidden behind these dry figures can hardly be imagined.

The likely overall demographic impact of the epidemic has been controversial. Some authors predicted that the epidemic will eventually lead to negative population growth in Africa. Other modellers predicted a reduction of population growth from an average of 3% to 1.1 to 2.2% (Anderson et al 1986, Bongaarts et al 1989, Stanley at al 1989, Way et al 1991, as cited by Over and Piot 1993). It is expected that the growth rate will become negative in countries with comparatively low infertility rates and high AIDS related mortality rates, for example in Botswana and Zimbabwe (Stanecki and Way 1996).

All authors agree that the increase in mortality is predominately due to increased deaths among young adults, and that this will have a severe effect on the health system, the economy and the social situation in many African countries (Over and Piot 1993). The substantial mortality increase among young adults has been demonstrated empirically in cohorts from Masaka, Uganda and Mwanza, Tanzania. For example, in the Masaka cohort with an HIV prevalence of about 10%, over 80% of deaths among those aged 13-44 were attributable to HIV infection, and the mortality in HIV seropositive adults was 15-fold higher than in seronegative adults (Mulder et al 1994). Figures from the Mwanza cohort were consistent with this observation: the increase in mortality in seropositive adults aged 15 - 54 years was 16 fold (Todd et al 1997).

HIV-2 infection

The modes of transmission of HIV-1 and HIV-2 are very similar (Piot et al 1990, Miyazaki 1995). In Africa the spread of HIV-2 has been limited mainly to West African countries, although occasional reports of infections in Angola, Tanzania and Mozambique have been published (Santos-Ferreira et al 1990, Schmutzhard et al 1989, Barreto et al 1993). Simultaneous infection with HIV-1 and HIV-2 has frequently been observed (De Cock et al 1988).

Although HIV-2 prevalences reached high levels in some risk groups during the 1980s, for example up to 64% of prostitutes in some West African cities (Denis et al 1987), HIV-1 prevalence has meanwhile exceeded that of HIV-2 in some West African countries. It is likely that transmissibility and pathogenicity of HIV-2 are lower than for HIV-1 (De Cock et al 1993). Intermittent screening of sex workers in Mwanza, Tanzania from 1991 to 1995 did not reveal any HIV-2 infection (Klokke and Grosskurth, unpublished data).

Heterogeneity

The HIV epidemic in Africa is characterised by marked heterogeneity. Extremely high prevalences are observed in some parts of the continent, whilst other areas continue to have relatively low prevalence rates. This phenomenon cannot be explained merely by the different stages of the epidemic. Even in populations where HIV-1 has been present for a long time, the spread of the virus is very heterogeneous (Piot et al 1990).

For example, HIV-1 prevalences among 4486 pregnant women attending 2 urban antenatal (ANC) services in Rwanda in 1989 and 1990 increased annually by 3 - 5% and reached 26% and 31% respectively in 1990 (Bucyendore et al 1993). In urban Malawi 18% of 461 urban pregnant women were infected in 1989, and the annual rise in prevalence during the previous years was estimated as 3 - 4% (Miotti et al 1990).

In contrast, the prevalence of HIV-1 infection remained low and stable in some other African cities even many years after the introduction of the epidemic: for example, 3% of 4205 ANC attenders from 4 urban sites in Shaba, Zaire were infected in 1991, and the prevalence did not increase over a 2 year period (Magazani et al 1993). Similarly the rate in pregnant women remained stable at 8% from 1985 to 1989 in Kinshasa, Zaire (N'galy et al 1989).

It could be argued that these figures may be distorted by selection bias. Population based HIV-1 prevalence studies would be more conclusive for the comparison between different areas. However, the data available are consistent with the observation of a markedly heterogeneous spread of the HIV epidemic.

The reasons for this heterogeneity are not well understood. Several factors seem to be at work and may include: demographic variables such as the male to female ratio in the population, behavioural variables such as the size of and rate of contact with, core groups, biological variables such as male circumcision, political and economic variables such as the official response to the epidemic or civil unrest and war, and differences in the prevalence of factors such as STDs which may enhance HIV transmission (Piot et al 1990).

2.3 The association of STDs and HIV infection

2.3.1 The STD/HIV co-factor hypothesis

As described in section 2.2, the HIV epidemic in sub-Saharan Africa has spread very rapidly, and with marked heterogeneity. This led to research questions as to the possible underlying cause of these observations.

By the mid 1980s, it was postulated that other sexually transmitted diseases (STDs) might enhance the transmission of HIV and contribute substantially to the rapid spread of HIV-1 in sub-Saharan Africa (Quinn et al 1986, Piot and Laga 1989, Cameron et al 1989). This "co-factor effect" of STDs on HIV transmission might have two components: Among persons not infected with HIV, STDs may potentially increase the susceptibility to HIV infection. Among persons infected with HIV, the presence of STDs may potentially increase their infectiousness for HIV (Mertens et al 1990).

This STD/HIV co-factor hypothesis seemed plausible from both epidemiological and biological points of view: STDs are very common in sub-Saharan Africa, and ulcerated or inflamed skin may render a patient either more infectious or more susceptible for viral transmission (Cameron et al 1989, Piot and Laga 1989).

The potentially great public health significance of this hypothesis led to the formulation of the secondary hypothesis that an intervention which is effective in reducing the prevalence of STDs will lead to a reduction of HIV incidence.

There may be other potential associations between STDs and HIV infection: (i) STDs may influence the natural history of HIV infection, (ii) HIV infection may change the clinical course of STDs, (iii) and HIV infection may increase the susceptibility to other STDs (Mertens et al 1990). Such associations are beyond the scope of this thesis.

2.3.2 Methodological issues in research on the co-factor hypothesis

Support for the STD/HIV cofactor hypothesis came from a number of observational studies. However, such studies encounter a variety of methodological problems. The issues involved have

been discussed extensively by Mertens and colleagues (1990), by Laga and colleagues (1991 and 1994i) and by Wasserheit (1992).

Issues of validity: confounding and bias

An association, if proven, may not be causal. An alternative explanation could be that persons with multiple sexual partners are at risk of acquiring both HIV infection and STDs. Both groups of infections share the same mode of transmission. Therefore the association may be completely confounded by sexual behaviour, and the presence of other STDs could merely be a marker for high risk behaviour rather than a causal factor.

It is therefore necessary that study design and analysis should control for the confounding effect of sexual behaviour (Mertens et al 1990, Laga et al 1994i, Wasserheit 1992).

However, in observational studies, complete control for this type of confounding cannot be achieved. This would require data for each subject on their number of HIV infected sexual partners, the degree of exposure to these partners and their level of infectiousness. It is not possible to measure sexual behaviour in such detail. Recall bias and deliberate incorrect response add to this dilemma. This means that residual confounding by sexual exposure will remain even if great care is taken to control for it (Mertens et al 1990).

Residual confounding means that persons are misclassified in terms of their sexual exposure. This misclassification may be differential or non differential with respect to their HIV or STD infection status. It can be shown that misclassification of the confounding variable results in overestimation of the degree of association between STDs and HIV infection if the misclassification is non-differential. If it is differential, the degree of association may be either over- or under-estimated (Mertens et al 1990).

Another type of bias is caused by the nature of the laboratory tests used to diagnose HIV infection and STDs. None of the tests used in epidemiological studies have a sensitivity and specificity of 100%. This fact will lead to misclassification of the infection status of some of the study participants. If it is non-differential, as would usually be expected, the resulting effect of this type of misclassification would be a dilution of the measurable effect, thus biasing the study results towards finding no association (Mertens et al 1990).

Issues of the direction of causality

Studies which investigate the co-factor hypothesis would not only need to demonstrate that there is an epidemiological association between the two types of infection, but also that STDs preceded the HIV infection. However, in observational studies, it may be impossible to establish whether the STD or the HIV infection occurred first. This is particularly the case in cross-sectional and case-control studies. In such studies, both infections occurred in the past, and therefore the sequence of events is not clear. It could be that the HIV infection preceded the STD, and that a proven association between the two types of infection indicates that STD symptoms, for example genital ulcers, are manifestations of HIV infection (Mertens et al 1990). HIV infected subjects may be more susceptible to STDs as a consequence of impaired immune function (Piot et al 1989, Pepin et al 1989).

Intervention studies

For all these reasons, observational studies may not provide conclusive evidence for the existence of an enhancing effect of STDs on HIV transmission.

The only way to control reliably for confounding variables would be through a randomised trial which seeks to determine whether an intervention against STDs reduces the transmission of HIV. Randomisation into an intervention and a control arm would help to ensure that confounding factors are distributed equally and could not bias the result of the study (Mertens et al 1990, Laga et al 1994i).

Biological plausibility

If the co-factor hypothesis were correct it could be expected that the enhancing impact of STDs on HIV transmission would manifest itself through biological mechanisms.

There seem two be two separate biologically plausible explanations for how STDs may facilitate HIV transmission: (i) Inflammatory processes and exudates from STD related lesions may increase the shedding of HIV in genital fluids; (ii) STD-related lesions may facilitate the access

of HIV to CD4 receptor cells, thus leading to an increased susceptibility to HIV infection (Laga et al 1994i).

It would give much support to the co-factor hypothesis if it could be shown that the viral load is increased in the genital tract in the presence of an STD, and that it decreases after treatment. Such an observation could not be regarded as a definite proof of the hypothesis, as the actual mechanism of HIV transmission is not yet fully understood. Recently data have become available from studies comparing viral shedding in HIV infected subjects with and without STDs (see section 2.3.6). Such data were not available at the time the Mwanza trial was formulated.

2.3.3 Cross-sectional and case-control studies

Probably the first work demonstrating an association between other STDs and AIDS was a case-control study conducted in homosexual American men in 1982, at a time when the aetiology of AIDS was not yet known. The study involved 50 AIDS patients and 120 controls. Controls were recruited from patients of STD clinics and general practices. Among other risk factors, AIDS was associated with a history of syphilis (Jaffe et al 1983).

This observation stimulated intensive research. Many cross-sectional and case-control studies have been conducted since, most of which showed that either a history of STDs or a clinical diagnosis of STDs were more prevalent among HIV-infected persons than in the various control groups. Unfortunately, in many published studies no effort was made to control for confounding factors. In some other studies, control for confounders did not include sexual behaviour. A selection of studies from sub-Saharan Africa is listed in table 2.4.

The strength of the association between present or past STDs and HIV infection, as measured through the odds ratio (OR) in these studies, varies widely. The strongest OR has been reported in a study from Rwanda and relates to a history of STDs (OR=11.2), but no adjustment for other variables was made in that study (Van de Perre et al 1987). Some of the observational studies were conducted in sex workers. Results from such studies may not be generalisable to other populations (Mertens et al 1990).

Table 2.4: Selected cross-sectional and case-control studies of the association between STDs and HIV infection

Locality / Country	Study population	N	HIV-1 prevalence	Risk factor for HIV infection investigated	OR (95% CI)	Reference
Cross-sectional studies						
Kigali / Rwanda	rural population	207	3.4%	history of any STD past 2 yrs	11.2 [1] (3.5 - 35.9)	Van de Perre et al 1987
Harare / Zimbabwe	wives of HIV+ve men	75	60.0%	husband had history of GUS past 2 years	1.9 [1] (1.0 - 4.8)	Latif et al 1989
Mwanza / Tanzania	men	2000	2.4 - 8.7%	GUS ever	1.1 [2] (0.7 - 1.9)	Barongo et al 1992
				GDS ever	2.2 [2] (1.4 - 3.5)	
	women (general population)	2161	2.8 - 15.2%	GUS ever	1.1 [2] (0.5 - 2.5)	
				GDS ever	1.7 [2] (0.9 - 2.5)	
Rakai / Uganda	rural women	4718	14.2 - 26.7%	Any bacterial vaginosis	1.5 [3] (1.2-1.9)	Sewankambo et al 1997
				Severe bacterial vaginosis	2.1 [3] (1.5-2.9)	
				Trichomoniasis	1.0 [3] (0.9-1.2)	
				Active syphilis	1.65 [3] (1.3 - 2.1)	
Case-control studies						
Nairobi / Kenya	men attending STD clinic	340	11.2%	history of GUS	7.2 [4] (3.8 - 13.8)	Simonsen et al 1988
				current genital ulcer	2.0 [4] (1.0 - 4.1)	
Nairobi	female sex workers	124	67%	history of GUS	3.3 [5] (1.2-10.1)	Plummer et al 1991
				history of CT infection	2.7 [5] (0.92-7.8)	

GUS genital ulcer syndrome, GDS genital discharge syndrome, CT *Chlamydia trachomatis*
[1] no adjustment for confounding factors; [2] adjusted for all other significant risk factors;
[3] adjusted for age, number of sexual partners past year, other STDs
[4] adjusted for socio-demographic factors and frequency of contact with sex workers;
[5] adjusted for socio-economic status

The association of present STDs with HIV infection could have several possible explanations. It may be the result of the sexual behaviour which led to both types of infection. Or it could be due to the co-factor effect of past STDs, because present STDs are more likely to occur in subjects who had STDs previously, because of their higher risk behaviour.

Of interest was the rather unexpected finding in a cross-sectional study from Uganda that bacterial vaginosis (BV) is associated with HIV-infection (Sewankambo et al 1997). In principle, BV is not marked by inflammatory changes of the vaginal walls (French and McGregor 1997). However, this study from Uganda showed that the adjusted odds ratio of HIV infection associated with any vaginal flora abnormality was 1.52, for moderate BV it was 1.5 and for severe bacterial vaginosis it was 2.08. All these observations were significant.

Because of the methodological problems described in section 2.3.2, none of these studies gives conclusive evidence that STDs enhance HIV transmission (Laga et al 1991, Sewankambo et al 1997).

2.3.4 Prospective observational studies

The methodological problems described above can be overcome, at least in part, if initially HIV negative individuals are recruited into a cohort study and followed prospectively in order to determine the association between STDs and HIV infection. The major advantage of this strategy is that the time sequence of events can be established (Mertens et al 1990). It is also easier to control for the confounding effect of sexual behaviour, because recall bias can be minimised, or because more information can be collected about risk behaviour.

The first prospective study giving some evidence in support of the STD cofactor hypothesis was performed in Nairobi in a cohort of 422 heterosexual men with STDs who were clients of prostitutes known to have 85% prevalence of HIV-1 infection (Cameron et al 1989). 88% of the men were HIV negative. 293 of these HIV-negative men were followed-up for at least 2 weeks from the time of the reported sexual exposure. 8% of these seroconverted a few weeks after they had experienced an STD and had been treated for it. Newly acquired HIV infection was independently and significantly associated with frequent sex worker contact (relative risk: RR = 3.2), with genital ulcer syndrome (RR = 4.7) and with lack of circumcision (RR = 8.2).

Furthermore, there was a subgroup of 73 initially seronegative men who reported only one single contact with a sex worker before they acquired the STD. Again, 8% of them seroconverted within some weeks. In this subgroup the link between a particular exposure at a particular time (genital ulcer in the sex worker, indicated by the consecutive ulcer in the client) and the outcome (HIV infection in the client) seemed to be quite clear. No seroconversion was observed in the absence of genital ulcers. Unfortunately, all seroconverters also lacked circumcision, so that reciprocal confounding of these factors cannot be excluded.

Again in Nairobi, in 1991 Plummer et al showed that the association between genital ulcer syndrome and HIV-1 seroconversion existed also in women. This was demonstrated in a cohort of 595 sex workers, of whom 196 were initially seronegative. The authors were able to follow up 124 women for at least 12 months. Women were regularly screened and treated for STDs. Seroconversion occurred in 67%, corresponding to an extremely high annual incidence of 47%.

After adjustment for number of sex partners and condom use, multivariate analysis confirmed independent and significant associations between HIV-1 infection and oral contraceptive use (RR = 4.5) and genital ulcer syndrome (RR = 3.3). There was also an almost significant association with cervical infection due to *Chlamydia trachomatis*.

In 1993, Telzak et al reported results from a cohort study of 758 heterosexual men attending an inner-city STD clinic in New York City. None of them reported a history of injected drug abuse. HIV-1 seroconversion occurred in 1.8% of all men, and after adjustment for sexual exposure was significantly associated with genital ulcers (RR = 3.0).

In a survey of 1607 initially HIV negative male factory workers followed for 1738 person-years of observation, 51 men seroconverted (2.9%). After adjustment for various confounding factors including number of partners and reported visits to sex workers in a Cox regression analysis, seroconversion was significantly associated with recently having genital ulcers (hazard ratio HR=3.6), but not with other STDs (Mbizvo et al 1997).

Using the results from the two Nairobi cohorts, it was possible to make estimates for the size of the cofactor effect of genital ulcers for single exposures. Under the assumption that the observed associations in the Nairobi cohorts were due to a genuine cofactor effect (and not the result of residual confounding), Hayes and colleagues calculated that the observed data were consistent with a 10 - 50 fold increase in the probability for male to female HIV transmission, and a 50 -

300 fold increase for female to male transmission. The authors concluded that, although subject to wide margins of error, these estimates support the potential role of STD control as an effective intervention strategy against HIV (Hayes et al 1995i).

There are some longitudinal studies addressing the possible link between non-ulcerative STDs and HIV-1 seroconversion. Based on earlier cross-sectional and case-control studies, it was expected that an association would be much weaker than that for genital ulcers. However, it could also be expected that, if a causal link did exist, their population attributable fraction (PAF) for HIV infection could be larger than that of genital ulcers, as the non-ulcerative STDs are much more prevalent (Wasserheit 1992, Laga et al 1993).

The first cohort study providing some evidence for an enhancing effect of non-ulcerative STDs on HIV infection was conducted among sex workers in Kinshasa (Laga et al 1993). 431 initially HIV-1 negative women working as sex workers in Kinshasa were followed for a mean duration of 2 years with monthly STD check-ups and 3-monthly HIV-1 serology tests. During this period 9.8% of the women seroconverted for HIV.

A nested case-control study was performed within this cohort. During the period of HIV-1 acquisition, cases had a much higher incidence of gonorrhoea, chlamydial infection and trichomoniasis than controls who did not seroconvert. After adjustment for the level of sexual exposure, these infections remained significantly associated with HIV seroconversion (giving ORs of 4.8, 3.6 and 1.9 respectively). Genital ulcers were much less common than other STDs, but also appeared more often among cases (Laga et al 1993).

2.3.5 Intervention studies

Randomised controlled trials

Whilst longitudinal observational studies to test the STD/HIV co-factor hypothesis are methodologically stronger than cross-sectional and case-control studies, residual confounding cannot be excluded, as explained in section 2.3.2. However, intervention studies, in which participants or groups are randomised to different levels of STD control, while other preventive activities are kept equal in the different treatment arms, offer an opportunity to control for any

confounding effects (Mertens et al 1991, Laga et al 1994i), and are therefore better able to produce valid results than other study designs.

Such randomised controlled trials (RCTs) have a double rationale: they represent a valid test for the co-factor hypothesis, and they are also able to measure the effectiveness of a specific intervention programme. RCTs are recognised as the gold standard for the evaluation of public health interventions (Hayes et al 1997).

To date, only three randomised controlled trials of improved treatment of STDs have been conducted or are in progress, all of them in East Africa. The first trial was completed in Mwanza Region, Tanzania in 1995, and is the subject of this thesis (Grosskurth et al 1995). Two further randomised trials are in progress. A trial in Rakai District, Uganda is investigating the impact of intensive STD control via periodic mass treatment for STDs among adults in the general population (Wawer et al 1996). Nearby, in Masaka District, Uganda, a further trial is comparing groups receiving health promotion, health promotion together with improved syndromic treatment services for STDs, and a comparison group receiving a community development intervention (Kengeya-Kayondo et al 1996). Investigators from the three trials conducted a joint technical workshop in 1996, and produced a technical document on randomised trials of STD treatment for HIV prevention (Hayes et al 1997). Further details of the Rakai and Masaka trials are given in the discussion (chapter 7).

Uncontrolled intervention studies in core groups

Intervention studies in sex workers and other high risk behaviour groups are important to test the operational concept of core group interventions, to identify the best strategy of intervening in the core, and to evaluate the performance of specific intervention programmes.

Some intervention studies in sex workers have been conducted or are under way. These studies either do not have a controlled design, and compare infection rates before and after the intervention, or they compare different types of intervention, rather than comparing an intervention with a do-nothing alternative. This is done mainly for ethical reasons: because sex workers are often highly mobile, and as close follow-up is required, it would be difficult to justify withholding intervention activities from the control group.

That a well-designed targeted intervention for sex workers may lead to a major decline in HIV and STD incidence has been demonstrated impressively in a cohort study conducted by Laga and colleagues in Kinshasa. From a study population of female sex workers, with high STD prevalences and an HIV prevalence of 35%, 531 initially HIV-seronegative women were enrolled. The intervention was provided through a special health care centre in an area where the women lived and worked. It consisted of free monthly screening and treatment for STDs and provision of condoms. Health promotion was provided through group sessions conducted at 3-monthly intervals. This intervention was started in 1988 and interrupted in 1991 because of political turmoil. The impact evaluation was conducted through monthly screening for STDs and 3-monthly screening for HIV seroconversion.

Over the 36 months of the study period, there was a statistically significant decline in the incidences of gonococcal infection, trichomoniasis and genital ulcer syndrome, but not of chlamydial infection. The incidence of HIV infection declined from 11.7/100 women-years (wy) during the first 6 months to 4.4/100 wy during the last 6 months ($p=0.003$). Regular condom use with clients increased simultaneously from 11% to 68%. Risk factors for HIV seroconversion after multivariate analysis were irregular condom use, trichomoniasis and genital ulcer syndrome during the probable period of HIV acquisition. In women who attended more than 90% of their monthly appointments, the incidence was much lower when compared to those who attended less regularly (Laga et al 1994ii). Because of the study design, it was not possible to distinguish whether the observed effect was due to the health promotion or the STD treatment component, or both. The study was conducted primarily to evaluate an intervention package, rather than to provide information on the co-factor hypothesis.

A comparison of two different interventions is presently being studied in Abidjan (Ettiegne-Traore et al 1996). Sex workers report once a month to a confidential clinic where they receive free STD treatment, health education, and free condoms. They are randomised into those who are examined only when symptomatic and treated according to a basic case management strategy, and those who are examined systematically every month and treated according to an intensive diagnosis and case management strategy.

The outcome is being assessed at six-monthly intervals through testing for HIV, gonorrhoea, chlamydial infection and trichomoniasis. Preliminary results of this study, comparing a pilot period without intervention and the first 6 months intervention interval, show a high HIV incidence (20%) before the intervention, and a marked decrease of HIV incidence to 7% after 6

months of intervention. The authors do not report whether there was also a reduction in STD prevalence or incidence. No significant difference in STD prevalence or incidence was observed between the two intervention groups, but the study was still in its initial phase (Ettiegne-Traore et al 1996).

Another successful core group intervention has been documented in Nairobi where a population of more than 1000 predominantly HIV-1 positive female sex workers have been exposed to an intervention which started in 1985 and is still ongoing. The intervention comprises STD diagnosis and treatment through a special health clinic, and health promotion both individually and through public meetings. A major aspect of the health education component is to counsel the women on how to promote condom use among their clients.

For a study of the cost-effectiveness of the intervention, data were collected on the operational performance of the programme and the number of clients per sex worker, and epidemiological data on the infection status of both women and their clients. A number of assumptions about transmission probabilities, the possible co-factor effect and condom efficacy were made. It was estimated that the programme prevented between 6000 and 10 000 new cases of HIV infection per year among clients and contacts of clients. The operating costs were estimated at US $ 8 to US $ 12 for each case of HIV infection prevented, a figure which compares extremely favourable with other public health interventions (Moses et al 1991, World Bank 1993).

A trial to study the impact of monthly presumptive STD treatment of sex workers from a mining community has recently been completed in South Africa (AIDSCAP/FHI et al 1997), and another is underway in Kenya (Richard Hayes, personal communication 1998). Preliminary results of the South African trial showed a 70 - 85% reduction in prevalence of gonorrhoea, chlamydial infection and genital ulcers, despite continued exposure and a high incidence of subsequent infection. Reported condom use increased considerably. Interestingly, the study also demonstrated that the prevalences of symptomatic and asymptomatic gonococcal and chlamydial infections and of genital ulcers in men from the mining community were significantly reduced at follow-up, less than a year after the baseline survey. This was the first intervention study investigating the impact of a core group intervention on STD prevalence and HIV incidence in the surrounding general population (AIDSCAP/FHI et al 1997).

2.3.6 Studies of viral shedding

Several research teams have investigated whether the secretion of HIV in genital fluids is increased in the presence of STDs.

The group of Ndinya-Achola, Plummer, Kreiss and colleagues reported a study of 92 HIV-infected sex workers from Nairobi, in which they found a significant correlation between cervical inflammation and cervical shedding of HIV (odds ratio OR=8.7) (Kreiss et al 1994). In an earlier study of 97 HIV-infected women attending an STD clinic, they observed that cervical shedding was significantly associated with cervical mucopus (OR=6.2) and cervical ectopy (Clemetson et al 1993). In both studies, no statistically significant association was seen between cervical or vaginal HIV shedding and the diagnosis of particular RTI agents.

More recently, the same group conducted a cross-sectional study in Mombasa, Kenya in 318 HIV-infected women attending an STD clinic. HIV shedding was measured in vaginal and cervical secretions, using PCR amplification. A variety of possible risk factors for HIV shedding were also investigated. HIV-1 infected secretions were found in 51% of endocervical and 14% of vaginal specimens. After adjustment for CD4 count, cervical HIV shedding was significantly associated with the use of oral contraceptives, and vaginal shedding with vitamin A deficiency. After including these two factors in a logistic regression model, gonococcal cervicitis was significantly associated with cervical HIV shedding (OR 3.1), and candidiasis with vaginal HIV shedding (OR 2.6). Vaginal HIV shedding was also significantly associated with moderate or high vaginal polymorpho-nuclear cell counts (ORs 2.2 and 3.8 respectively). *Trichomonas vaginalis* and *Chlamydia trachomatis* were not associated with HIV shedding (Mostad et al 1997).

Cohen and colleagues conducted a study in Malawi of the effect of gonococcal and chlamydial urethritis on the concentration of HIV-1 in semen. HIV-1 was found in the seminal plasma of 135 HIV-1 positive men. 86 of these men had urethritis, whilst the others were controls without urethritis. Samples were analysed at baseline and 1 and 2 weeks after treatment. The viral load of HIV-1 was eight times higher in the urethritis group, a statistically significant difference, despite similar CD4 cell counts and viral load in blood plasma in both groups. The increase was particularly large in cases of gonococcal infection. After successful treatment, seminal HIV shedding decreased significantly over the next 2 weeks. No change was observed in blood plasma viral RNA concentrations. The authors conclude that urethritis increased the infectiousness of

men with HIV-1 infection, and that targeted interventions against urethritis may be an effective public health strategy (Cohen et al 1997).

2.3.7 Computer simulation studies

The possible co-factor effect of STDs on HIV transmission has also been the subject of computer simulation studies.

Over and Piot were probably the first to use computer simulations to look at the interaction between STDs and HIV infection. However, their work concentrated on the effect of the hypothetical association on public health issues such as the cost-effectiveness of interventions against HIV infection and STDs. For this purpose, they *assumed* certain co-factor effects, for example a five-fold increase of HIV transmission probability in the presence of genital ulcers, a 3-fold increase for gonorrhoea and a 2-fold increase for chlamydia infection, and then studied case numbers and disability-adjusted-life-years (DALYs) saved because of new STD and HIV cases which were averted as a result of an STD intervention.

For example, they showed that, *if* the co-factor hypothesis and the assumptions on the size of the enhancing effects were true, the one-time cure of 100 core cases of gonorrhoea would avert thousands of new cases of gonorrhoea within the next 2 years, a substantial number of new HIV cases, and would save thousands of DALYs mainly because of the preventive effect on HIV transmission (Over and Piot 1993).

To study the transmission dynamics of HIV infection and STDs, and to determine whether HIV infection rates observed empirically in sub-Saharan Africa would be possible without the existence of an STD co-factor effect, Robinson and colleagues applied an age-structured stochastic simulation model (SIMULAIDS). For this purpose, they used detailed data on HIV and STD prevalences, sexual behaviour and other demographic characteristics available from a cohort study of a rural population of 10 000 in the Masaka district of Uganda. Assumed HIV transmission probabilities per sexual contact in the absence of STDs were in the order of 0.001, based on observations from elsewhere.

The authors showed that without any co-factor effect, it was not possible to reproduce the HIV prevalence and incidence rates actually observed in the cohort. The scenario most consistent with

the observed data assumed that the transmission of HIV per sexual contact was enhanced 100-fold during all episodes of ulcerative STDs, and 5-fold during episodes of non-ulcerative STDs in females. For the first 10 years of the epidemic, over 95% of HIV infections were attributable to STDs under this scenario. The role of STDs decreased considerably with the progression of the HIV epidemic (Robinson et al 1997).

Chapter 3: Background

3.1 The study area

3.1.1 Geography of Mwanza Region

Mwanza Region stretches along the southern shores of Lake Victoria, the largest of the African lakes, and includes the Ukerewe Islands (map 3.1). The area is situated 190 - 360 kilometres south of the equator, on a plateau about 1100 m above sea level. The region extends about 260 km from East to West and up to 170 km from North to South (Leverenz and Gover 1997).

The region has about 2 million inhabitants (Bureau of Statistics 1992[1]), of whom about two hundred thousand live in the regional centre, Mwanza town, which is the second largest town of Tanzania. There are also five semi-urban centres with a population of about 15, 000 each, serving as district administrative headquarters. The great majority of the population lives in rural villages or in communities with widely scattered compounds. A compound is a group of houses which is occupied by one or more families, and surrounded by their farm land.

3.1.2 Vegetation and climate

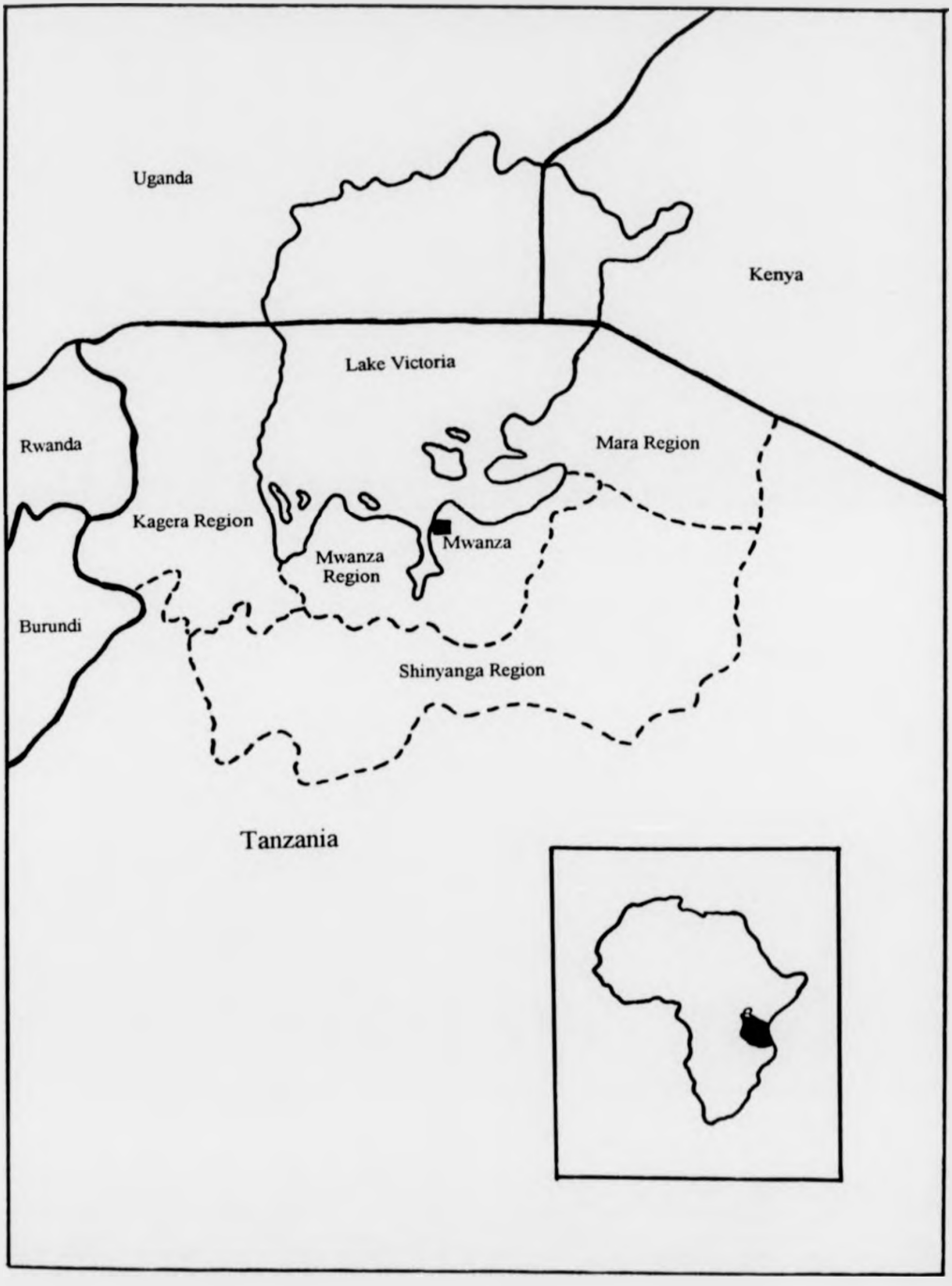
The landscape is semiarid and comprises mostly cultivated bushland, small spots of marshland and little patches of forest. Huge boulders of smooth rock can be seen in many places.

The mean annual rainfall is about 900 mm with 70% of the rain falling during the main rainy season from March to May, and 30% during a second but weaker rainy season from October to December. During the rains, many villages become inaccessible, and even the main long distance truck routes may occasionally be blocked for some days.

Average temperature oscillates between 20 degrees Celsius during the rains and 30 degrees during the dry season, and usually does not drop below 18 or exceed 35 degrees.

[1] Data from 1988 population census, extrapolated to 1991 assuming a 3% per annum population increase

MAP 3.1 MAP OF NORTH-WESTERN TANZANIA SHOWING MWANZA REGION AND NEIGHBOURING AREAS



3.1.3 Ethnicity, language and religion

The region is almost entirely occupied by ethnic groups of Bantu origin, with the Sukuma being by far the most numerous. Wakerewe and Wakara inhabit the islands of the Ukerewe archipelago, the most densely populated rural area of Tanzania. Other ethnic groups from neighbouring regions and other parts of Tanzania can be found in Mwanza town and in centres along the main roads. These include Wahaya, Chagga and others, but also Indians and Arabs.

Each of these ethnic groups has its own language, but Kiswahili is the official national language and is commonly used as lingua franca. People with secondary school education can usually also communicate to some extent in English.

About 60% of the population in Tanzania are Christians, 30% are Moslems and 10% belong to other religious groups (Bureau of Statistics 1997). The proportion of Moslems in rural Mwanza is only about 5% (Munguti et al 1997).

3.1.4 Economy and traffic

The population lives mostly on subsistence farming. The main products are rice, maize, cassava and beans. Cattle breeding is common, and other livestock include goats, sheep and poultry. Cotton and maize are the main cash crops. Inhabitants of lake shore communities and of the islands of Ukerewe engage in fishing, farming, or both.

Some small scale industrial development can be seen in Mwanza town, comprising a fish processing factory, boat yards, a cotton ginnery, a textile factory, and a brewery. Some gold mining is done in the western part of the region, partly under government auspices, partly by private petty miners, and in recent times partly by foreign companies.

Mwanza town is an important traffic junction, situated on one of the main truck and bus routes from Kenya to Central Africa. There are a railway connection to the capital, Dar es Salaam, and shipping lines to neighbouring Kagera Region and to Uganda and Kenya.

3.1.5 Administration

Together with the neighbouring regions of Mara, Kagera and Shinyanga, Mwanza Region forms the Lake Zone of the United Republic of Tanzania.

The region comprises six districts, with Mwanza Municipality and its rural outskirts forming one of them. Districts are divided into divisions, wards and communities.

The administrative system in Tanzania has recently been revised, as part of a whole range of political changes which also included the introduction of a multi-party system. However, from independence until 1996, and thus throughout the time of the trial, the lowest administrative unit was the 'balozi', or 10-household unit. The leader of this unit was the representative of the state and of the ruling party at the lowest level. This balozi leader was usually a male inhabitant of the community, appointed by the administration.

During the time of the trial, the one-party system still prevailed, with representatives being in key positions at all levels of the administration. This hierarchical system was broadly accepted by the population. It assisted the flow of instructions and information from the centre to the periphery and vice versa. For the trial, this system was extremely helpful as it facilitated community mobilisation, enumeration of the cohort and follow-up of study participants.

At regional and district level, the administration is run by civil servants, headed by a regional commissioner and in Mwanza by the six district commissioners, who work under the Central Government. The health sector is administered by the Regional Medical Officer Mwanza (RMO) and the six District Medical Officers (DMOs).

3.1.6 Health services

The teaching hospital for the Lake Zone, Bugando Medical Centre (BMC), is situated in Mwanza town. It is one of Tanzania's four teaching and referral hospitals, and comprises a variety of clinical services and several training institutions, notably schools for assistant medical officers, for x-ray technicians and for nurses. The hospital had a well organised HIV laboratory which played a major role in the trial implementation.

At the time, Mwanza town also had one municipal and two private hospitals. There are also two government health centres with busy antenatal clinics, and eight dispensaries. STD clinic services were integrated into the outpatient department of the Sekou Toure Municipal Hospital and one of the antenatal clinics (Makongoro Centre), and served as reference and training units for the trial (see section 5.2.9).

Regional health services are supervised by the Regional Medical Officer (RMO). The RMO is assisted by a team of senior officers, of whom the Regional AIDS Control Coordinator (RACC) is responsible for AIDS and STD control activities. The RMO and the RACC are physicians. Almost throughout the trial period, the RACC had to deputise for other functions, and had limited capacity to play a role in the intervention. However, a Regional STD Intervention officer was appointed and seconded to the programme.

At each of the five rural district headquarters, there is a district hospital, and the region also has three mission hospitals. However, the majority of the rural population depends on the services of health centres and dispensaries. Some dispensaries are run by mission health services, but most are government facilities. In total, the region had 23 functioning rural health centres and 150 dispensaries at the time of the trial.

A health centre is staffed by about 8 - 12 trained personnel and is managed by a medical assistant (MA). A dispensary has 2 - 3 trained staff and is led by a rural medical aide (RMA). Both cadres have a formal training of three years, but the MA is usually a secondary school leaver. Except for delivery care, there are usually no beds for inpatients. Drugs are supplied through standardised kits as part of the national Essential Drug Programme (EDP).

Dispensaries do not have laboratory facilities. Some, but not all health centres are staffed by a laboratory technician, and are equipped with a microscope. However, there is no system for quality control, the equipment is often damaged, and the supply of reagents irregular.

Public health services in each district are supervised by a health management team. This is headed by the District Medical Officer. Issues of AIDS control are addressed by the District AIDS Control Coordinator (DACC), who is mainly expected to organise educational activities. Unfortunately, due to very limited funds and the lack of transport, the DACC's capacity is very

limited. In the context of the trial, a new cadre was created, the so-called District STD Control Coordinator.

In Mwanza town, several registered private medical practitioners exist, but at the time of the trial, there were no such practitioners in any of the participating rural communities. The same applied to pharmacies. Traditional healers still play a substantial role in health care in both urban and rural areas.

3.1.7 HIV infection and STDs in Mwanza Region

Precise epidemiological data on HIV infection and STDs were not available until early 1991, but were urgently needed to assist with the sample size calculations for the intervention trial.

In 1990 and 1991, a regional cross-sectional survey was conducted by a collaborative team involving LSHTM, AMREF and TANERA (see section 3.2.3 and table 3.2). The survey involved a random selection of 20 communities or urban wards from each of 3 strata: rural villages, roadside settlements and urban areas. Random cluster sampling was used to enrol 2000 participants aged 15 - 54 years from the rural communities, and 1000 each from the other two strata (Barongo et al 1992, Mosha et al 1993).

Results of the study showed that about a year before the trial started, the prevalences of HIV-1 infection in rural villages and roadside settlements were 2.5% and 7.3% respectively. In Mwanza town the prevalence had reached 11.8% (Tab 3.1). Women had a higher HIV-1 seroprevalence than men, and they acquired HIV-1 infection at a younger age than men. The prevalence peaked at 20% in urban women aged 25-34 years.

Sentinel surveillance in antenatal clinic attenders from Mwanza town had shown an HIV prevalence oscillating around 12% for some time (Kigadye et al 1993). It was concluded that the HIV-1 epidemic had entered the region some years before and had possibly reached a mature stage in Mwanza town, but was still spreading in rural areas and in settlements along the main traffic routes.

No information was available about the incidence of HIV infection in the region, but a rough estimate was possible based on preliminary data from a cohort study in neighbouring Kagera Region, where an incidence of 1% had been found in rural communities (Killewo et al 1993).

Table 3.1 Sero-prevalences of HIV infection and syphilis (%) and self-reported prevalence and incidence (%) of genital ulcers and/or genital discharge in 3 strata of Mwanza Region 1990/91, about one year before the intervention trial started [1]

	Rural villages		Road-side settlements		Urban wards	
N=	Men 974	Women 1045	Men 431	Women 527	Men 595	Women 589
HIV-1 prevalence	2.4%	2.8%	5.4%	8.7%	8.7%	15.2%
N=	978	1046	434	528	597	590
Syphilis prevalence (TPHA+/RPR+)	7.0%	7.9%	12.3%	13.2%	9.3%	12.4%
Syphilis prevalence (TPHA+)	13.1%	13.5%	22.4%	21.7%	15.9%	20.5%
Genital ulcers: reported prevalence	1.7%	0.4%	0.3%	0.9%	0.2%	1.0%
Genital discharge: reported prevalence	2.6%	2.1%	2.1%	1.4%	1.0%	1.0%
Genital ulcers and/or discharge: ann. incidence	10.5%	5.7%	8.6%%	5.0%	9.6%	4.8%

[1] (Barongo et al 1992, Mosha et al 1993)

The regional cross-sectional survey showed that STDs presented a major health problem in the region. Active syphilis, as assessed through the prevalence of positive TPHA and RPR tests, was very common with prevalences of 8 - 13%, in both men and women (Tab 3.1). TPHA prevalence, giving evidence of past or present infection, reached 18 - 35% in the oldest age group (45 - 54 years), indicating well established endemicity.

About 10% of the men reported at least one STD episode during the past year. In women the self-reported incidence was much lower, but this was thought to be affected by underreporting (Mosha et al 1993).

3.2 The STD/HIV Intervention and Research Programme Mwanza Region

3.2.1 Rationale for an STD/HIV intervention trial in Mwanza Region

The rationale for a trial of the impact of improved STD case management on HIV transmission is discussed in detail in chapter 2.3. Why was rural Mwanza Region chosen as the location for this project?

Preliminary data suggested that the region would provide the necessary epidemiological conditions: a high prevalence of STDs, a well established but not yet matured HIV-epidemic and a rather stable population.

In Mwanza town, there was a branch of the Tanzanian National Institute for Medical Research (NIMR). The institute had laboratories for microbiology and serology and a statistical unit, though all of these needed major inputs in terms of training and equipment. An HIV laboratory, headed by an experienced biochemist, was available at the Bugando Medical Centre (BMC) in Mwanza. The regional and municipal health services of Mwanza were well staffed so that it should be possible to identify suitable personnel for recruitment as field workers. Mwanza town provided sufficient logistic conditions to establish the programme.

3.2.2 AMREF and LSHTM

For the implementation of a large scale intervention trial, it was necessary to identify an organisation which had the necessary capacity and was well accepted both by the government and the population. It was felt that a non-governmental organisation (NGO) with its greater flexibility was preferable to a government institution.

The African Medical and Research Foundation (AMREF) fulfilled these conditions and developed a keen interest to take the task on.

This indigenous NGO was founded in the early 1960s as the Flying Doctor Service of East Africa with headquarters in Nairobi. Over time it had acquired expertise in the fields of primary health care, the control of infectious diseases, training of health workers and production of

health learning materials. By 1990, AMREF had country offices and programmes in Kenya, Tanzania and Uganda, and ran various projects in Sudan, Rwanda and Somalia. Within Tanzania, activities of the foundation were so far limited to Dar es Salaam, Arusha and Rukwa.

AMREF became the main contract holder and implementing agency for the trial, and the collaboration with LSHTM was formalised through a sub-contract. It was agreed that the director of the trial would be recruited by LSHTM and seconded to AMREF as its programme manager in Mwanza.

The programme manager would establish an AMREF office for north-west Tanzania and would be responsible for the implementation of the trial, but also facilitate other AIDS related projects in the Lake Zone which were to be launched in parallel with the trial. For all these components, close collaboration would be established with various partner organisations in Mwanza and elsewhere in the Lake Zone.

These arrangements had been negotiated very effectively by Dr. Angus Nicoll both with AMREF and with government authorities. When the author took over from Dr. Nicoll as programme manager in January 1991, most of these arrangements were in place, ready for the detailed planning and implementation of the intervention trial. The overall programme was named the 'STD/HIV Intervention and Research Programme Mwanza'.

3.2.3 Other collaborating institutions

The STD/HIV intervention trial was a collaborative effort involving many more institutions besides AMREF and LSHTM. Their input covered various aspects of the intervention and the impact evaluation. Details are listed in tab. 3.2. The coordination of all these institutions represented an interesting management task.

Table 3.2 Institutions collaborating on the STD/HIV Intervention Trial Mwanza

Institution	Function	Input provided
LSHTM	Scientific guidance	1. Trial design and planning, 2. secondment of scientific personnel to Mwanza, 3. assistance during implementation and data analysis, 4. logistic support in London
AMREF	Implementing agency	1. Programme management and scientific direction in Mwanza 2. coordination of intervention, 3. training of health workers, 4. training of district STD coordinators 5. supervision of health units, 6. drug supply, 7. coordination of impact evaluation, 8. training of field workers,survey implementation 9. transport and logistics 10. logistic and administrative support through offices in Dar es Salaam and Nairobi
National Institute for Medical Research (NIMR)	Collaboration on impact evaluation	1. Laboratory tests (microbiology and serology), 2. data entry, processing and data analysis, 3. co-management of field work during surveys, 4. provision of staff for surveys
Bugando Medical Centre (BMC)	Collaboration on impact evaluation	1. development of HIV test strategy, 2. HIV serology, 3. quality control for syphilis serology, 4. provision of staff for surveys
Sekou Toure Municipal Hospital	STD reference clinic	1. Monitoring of STD aetiologies and resistance, 2. practical training of health workers
Makongoro Antenatal Clinic	STD reference clinic	1. as for Sekou Toure Hospital
Regional Medical Office	Supervision and coordination at regional level	1. Policy support for implementation in districts, 2. secondment of a regional STD intervention officer to the programme, 3. provision of staff for surveys
Municipal Health Office Mwanza	Supervision and coordination in Mwanza	1. Policy support for STD reference clinics, 2. provision of staff for surveys
District Health Services	Integration of improved STD case management services	1. STD case management at health facilities, 2. provision of District STD Control Coordinators, 3. health education campaigns
Tanzanian Netherlands Support Project on AIDS Mwanza (TANESA, formerly TANERA)	Collaboration on impact evaluation and intervention	1. Joint implementation of initial cross-sectional survey 2. support of intervention in comparison communities in one district after the trial 3. shared provision and maintenance of NIMR equipment
National AIDS Control Programme / MoH	Overall supervision	1. Formulation of policy, supervision, 2. support within MoH
Muhimbili University College of Health Sciences (MUCHS)	Scientific collaboration	1. Consultancies on aspects of STD treatment, epidemiological and behavioural research
Institute for Tropical Medicine Antwerp	Facilitation of supplementary studies	1. personnel support to NIMR (1 senior lab technologist for microbiology 1992-95) 2. scientific input for supplementary studies

3.2.4 Management structure for the trial

The trial was implemented by a management team which comprised the senior staff responsible for the various scientific and operational components. Details are presented in fig. 3.1.

Some of these components were managed by expatriate personnel: the intervention, the main cohort survey, the clinical studies, the laboratories and the statistical unit. The expatriate staff shared responsibility with counterpart Tanzanian colleagues, who received intensive in-service training and most of whom were sent for formal training courses (PhD, MSc) at LSHTM during or soon after the completion of the trial.

The author had organisational responsibility for the overall programme and direct responsibility for the implementation of the intervention and of the main cohort study. These latter tasks were shared with two counterparts, the regional STD intervention officer (Mr. Ezra Mwijarubi) and the cohort study field manager (Dr. Frank Mosha) whom he trained and supervised.

As described in section 3.2.3 and table 3.2, several institutions contributed to the trial implementation. To coordinate their inputs, a Steering Committee was formed which comprised the Director of BMC (Dr. Zacharias Berege), the Director of NIMR Mwanza (Dr. Reverianus Gabone), the Regional Medical Officer (Dr. Awene Gavyole), the Municipal Medical Officer (Dr. Zebedayo Sekirasa) and the author. However, the coordination was achieved mainly through frequent informal contacts between the author and senior staff of the collaborating institutions.

3.2.5 Programme office, clinics and laboratories

As a base for the trial and for AMREF's various other activities, a compound with 2 buildings was rented. It was located near the centre of Mwanza town, and provided 18 rooms for office space. About half of these were used for staff actually working part-time or full-time on the trial.

A seminar room for training courses and meetings was built next to the office, which could accommodate up to 24 participants. Two stores for the supply unit were also erected. All project

cars could be parked in the compound, and cars were maintained and repaired here as well with the help of a contracted car mechanic.

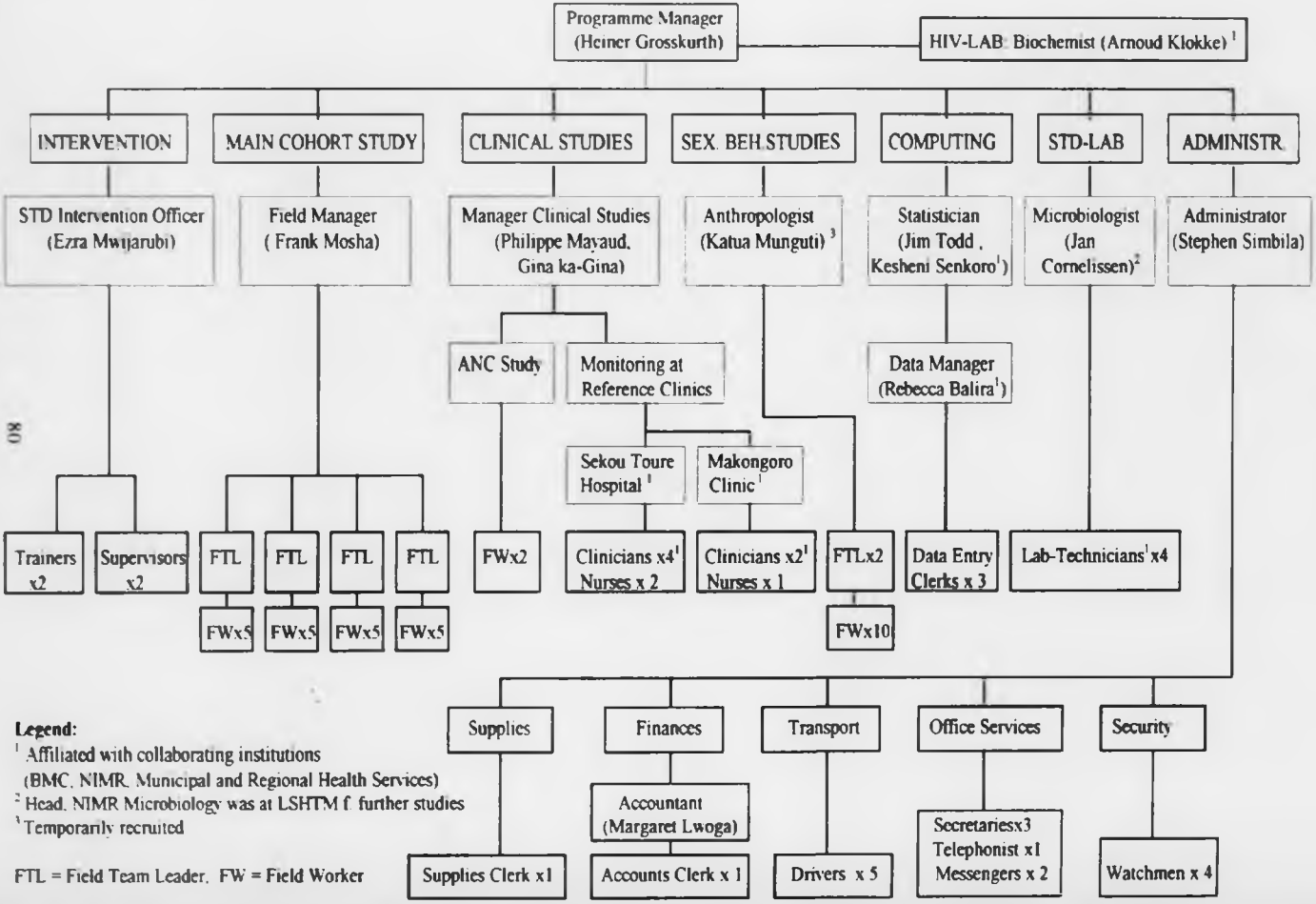
Consultation rooms to be used for STD treatment services at Sekou Toure Hospital and Makongoro Clinic, and laboratories at the two clinics and also at NIMR and at BMC, were refurbished and upgraded with equipment and furniture.

One of the greatest problems for the programme was the irregular electric power supply. Power cuts could occur at any time without warning, and lasted anything between a few minutes and a week. Even worse were sudden or gradual power surges, with voltages anywhere between 60 and 400 Volts. As a result, the electrical and electronic equipment in offices and laboratories were subject to serious damage. In 1993 the situation became so difficult that robust generators had to be purchased and installed both at AMREF's programme office and at NIMR. At NIMR, costs were shared with the TANESA project.

3.2.6 Staff recruitment

Staff recruitment started late in 1990. The personnel involved in the implementation of the trial were either directly employed by AMREF (22), LSHTM (3) or ITM Antwerp (1); fully seconded to AMREF from government institutions (3); or temporarily attached to the programme for particular tasks (39). Other staff collaborated on specific aspects without any change in their institutional affiliation or line of management (23). In total, 79 staff worked on the trial during peak survey times.

Figure 3.1: Management structure for the STD/HIV Intervention Trial Mwanza (April 1993)



Legend:

[1] Affiliated with collaborating institutions (BMC, NIMR, Municipal and Regional Health Services)

[2] Head, NIMR Microbiology was at LSHTM f. further studies

[3] Temporarily recruited

FTL = Field Team Leader, FW = Field Worker

3.2.7 Logistics

Many of the consumables and almost all of the technical equipment had to be purchased from outside Tanzania. The bulk of these purchases and their airfreight was very ably organised by the AIDS Programme Overseas Coordinator at LSHTM, Ms Sarah Henson.

Most shipments went to Dar es Salaam and were cleared and forwarded by the Mwanza Liaison Officer, Mr. Alfred Kiswaga at AMREF's Country Office.

In Mwanza, AMREF's Administrator and Supply Officer, Mr. Stephen Simbila and his team arranged for clearance and storage. They also handled all local purchases.

Two field research teams usually left for their work on Monday mornings, and returned after one or two weeks on Friday afternoons. For the following trips, two other teams went to the field, to alternate with the first two teams, and so on. The same applied for the intervention officers who usually spent one week in the field supervising all the health units belonging to the same intervention community. Equipment and consumables of all the teams were prepared using standard supply lists during the week before departure. The preparations were done jointly by the supplies clerk and the outgoing field team leaders or intervention officers. Maintenance and repairs of vehicles and field equipment were done between two successive trips for each team.

3.2.8 Funding

The initial preparation of the programme from 1989 to 1990 was supported by the Wellcome Trust.

The main donor for the intervention trial was the Commission of the European Communities (EC) through its Directorate General VIII (DG VIII), with ECU 624,000 for phase 1 (1990-93), and ECU 830,000 for phase 2 (1993-96). The last year included a continuation of the intervention after the end of the research work.

The Life Sciences and Technology in Developing Countries Programme of the EC (DG XII) funded a set of supplementary studies, including the sexual behaviour surveys and the cross-sectional STD studies in pregnant women which are briefly described in this thesis.

The UK Overseas Development Administration (ODA) funded the AIDS Research Programme of LSHTM. The employment of the Manager of Clinical Studies (Dr Philippe Mayaud) was supported through this programme, but it also facilitated regular visits to Mwanza of Prof David Mabey and of the Microbiologist Mrs Beryl West in order to provide scientific guidance and support.

The UK Medical Research Council (MRC) funded regular visits of Prof Richard Hayes to Mwanza and supported the Tropical Epidemiology Group of LSHTM through which additional epidemiological and statistical input was provided.

The author as the programme manager of the trial and AMREF's director in Mwanza was recruited by the School, but employed by AMREF and funded by both AMREF and the German Government through its Centre for International Migration and Development (CIM).

The World Health Organization funded the development and printing costs of an STD self learning training manual, which has since been used in the intervention in Mwanza and elsewhere. The operational evaluation of the intervention was supported by AMREF Austria.

Chapter 4 Aims and objectives of the trial

The overall aim of the trial was to test the hypothesis that STDs enhance the transmission of HIV and that improved treatment of STDs reduces the incidence of HIV infection.

The primary objectives of the trial were:

1. to establish a programme for the improved case management of STDs, integrated into the rural primary health care system of Mwanza Region
2. to evaluate the impact of this intervention on the incidence of HIV infection in the general population

Secondary objectives were:

1. to evaluate the impact of the intervention on the prevalence and incidence of STDs
2. to evaluate the feasibility and the cost-effectiveness of the intervention

The integration of the treatment services into the primary health care system aimed at creating a sustainable and replicable intervention. It was not an objective of the trial to evaluate the impact of STD control on HIV transmission under optimised conditions.

Likewise, although the trial would contribute substantial evidence for the STD cofactor hypothesis, if an impact on HIV transmission were observed, it was not an objective of the trial to estimate the size of STD cofactor effects.

This thesis deals principally with the epidemiological objectives of the trial. However, feasibility aspects are addressed in the sections on the operational performance of the intervention (chapters 5.3 and 6.1), and issues of cost-effectiveness in the discussion section (chapter 7.3).

Chapter 5 Methods

5.1 Design of the trial

5.1.1 Overall study design

The study was a community randomised controlled trial of the impact of improved STD case management on the incidence of HIV infection and the prevalence and incidence of STDs in the general population of Mwanza Region, Tanzania.

The intervention was provided through existing health facilities, but included health education of the general population in order to improve treatment seeking behaviour.

The impact was studied in six matched pairs of communities. Within each pair, one community was randomised to the intervention group and one to the comparison group. In each community a cohort of about 1000 adults aged 15 to 54 years was selected from the population by random cluster sampling regardless of their HIV status at baseline, and followed for 2 years.

To facilitate the interpretation of the results of this cohort study, additional data were collected through two sexual behaviour surveys in subsamples of the cohort and two consecutive cross-sectional studies in pregnant women in the same communities.

The operational performance of the intervention was also evaluated, partly through an analysis of health centre records, and partly through a cross-sectional study of patients who did not return for clinical follow-up.

The rationale and details of the study design are described in the following parts of chapter 5.

5.1.2 Rationale for community randomisation

Randomised controlled trials are the accepted "gold standard" for the evaluation of health interventions. Random allocation of study subjects to either an intervention arm or a comparison

arm helps to ensure that both measured and unmeasured confounding factors are equally distributed in the two groups (Mertens et al 1990).

Why was a community-randomised design chosen for this trial rather than randomisation by individuals? There were several reasons:

1. The nature of the intervention: The improved STD treatment services were to be provided through health facilities. The intervention was therefore available to the entire community served by these facilities. It would not have been ethical or feasible to withhold the services from particular individuals when they sought treatment at the facilities.

2. The preventive effect of the intervention on the rest of the community: even the individuals who are not directly benefiting from the intervention are protected because of the overall reduction in STD prevalence in the population. Thus randomisation by community captured the 'mass effect' of the intervention, analogous to the 'herd immunity' achieved through vaccination.

3. The expected bilateral direction of the HIV/STD cofactor effect: it can be assumed that STDs increase both infectiousness of an HIV-infected individual and the susceptibility of an HIV-negative individual. Randomisation by individuals would only allow assessment of the effect of the intervention on susceptibility in the study cohort. Randomisation by community captured the effects of the intervention on both susceptibility and infectiousness, as both HIV-infected and HIV-negative individuals who sought care for an STD were treated.

5.1.3 Definition of study communities

For the purpose of this trial, the 'community' was defined as a group of villages with a health centre located in a central village, and several satellite dispensaries in some or all of the more peripheral villages. In communities within the intervention arm, improved STD services were to be provided in all of these health facilities.

5.1.4 Selection, matching and randomisation of communities

Selection

Mwanza Region had 23 rural health centres and 150 dispensaries at the time of the trial. In 1991, the newly recruited regional STD intervention officer, the field manager of the planned cohort study and the author visited all health centres in the region and about 40 dispensaries, and gathered information on the state of these facilities and the characteristics of the surrounding communities.

Based on this assessment, eight communities with health centres were excluded from participation in the trial for of a variety of reasons: periurban locality, high mobility of the population in a gold mining area, health centre operational but barely utilised by the population, health centre utilised but not by STD patients. From the remaining 15 communities, twelve were selected randomly. The rationale for selecting twelve communities is described in section 5.1.5.

Matching: rationale and criteria

The twelve participating communities differed in terms of their accessibility, their distance from Mwanza town, their distance from main truck routes or from the lakeshore, and in terms of the occupational activities of their populations. It was therefore likely that the communities differed substantially in HIV prevalence and incidence at baseline. With a comparatively small number of communities, a simple randomisation procedure could possibly lead to an imbalanced allocation of communities into the intervention and comparison groups, with for example the average HIV baseline prevalence in the intervention arm being much lower or higher than in the comparison arm, thus making the interpretation of impact data very difficult.

Ideally, for an intervention trial on HIV incidence, communities should be stratified or matched on baseline HIV incidence before randomisation. Pair matching of communities is the extreme form of stratification. Such a matched pair design was chosen for the Mwanza trial.

Pre-trial incidence could only be obtained through an initial cohort study. However, the required time and cost of this would have been prohibitive. HIV prevalence at baseline might have been used as a proxy. Unfortunately, neither prevalence nor incidence data were available for the

study communities before the trial started. Some data on HIV prevalence in the region had been obtained from the cross-sectional survey mentioned in section 3.1.7. This was helpful for the sample size estimate, but could not assist the randomisation process, as that survey had been performed in different communities.

Other variables which may be associated with HIV incidence are the geographical and occupational factors mentioned above. For the Mwanza trial, it was decided to use type of settlement (roadside, lake shore or rural), geographical area (location within low or high prevalence districts) and pre-existing levels of STD attendance at health centres, as matching criteria.

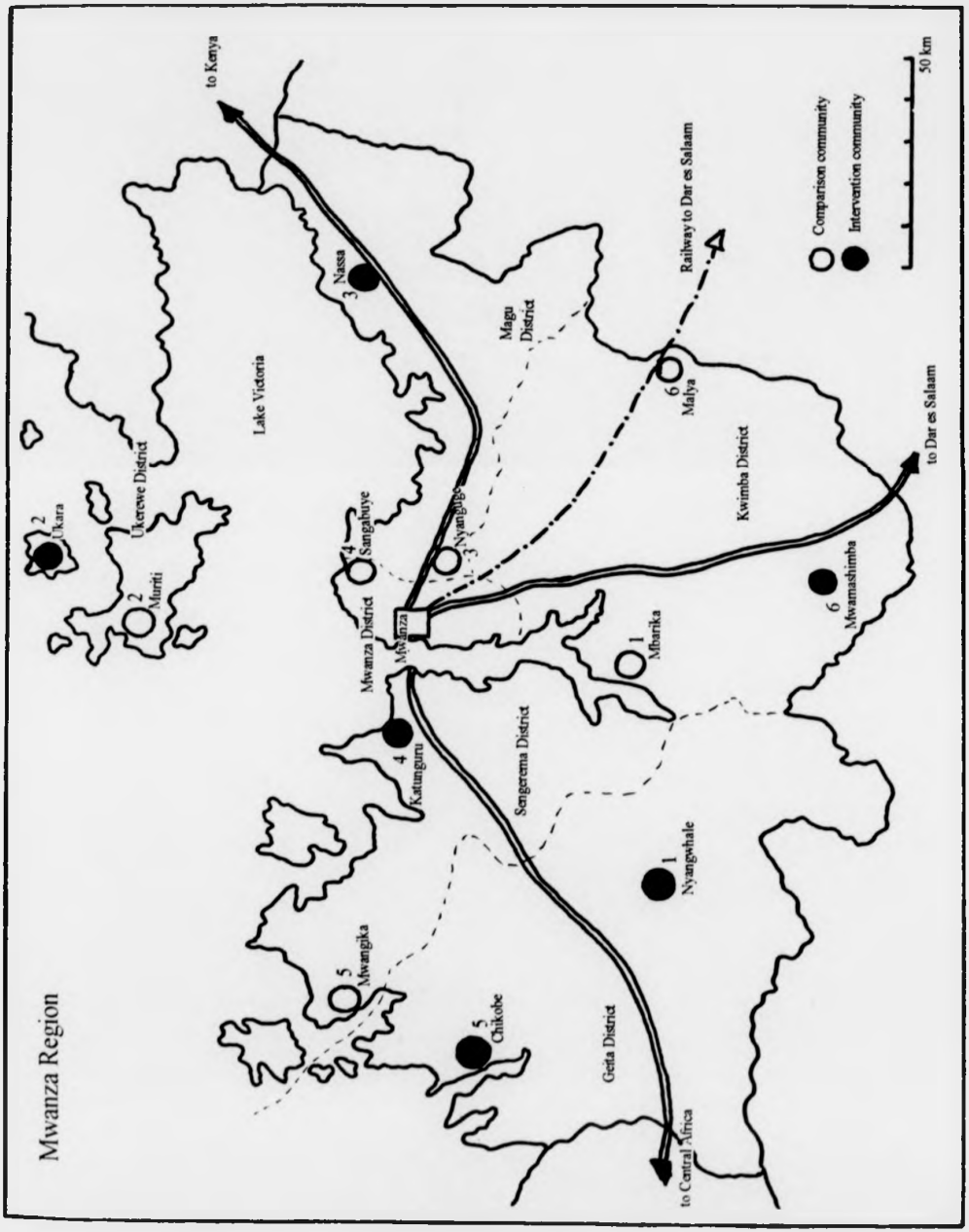
Randomisation of communities

Within each pair, one community was allocated to the intervention group by tossing a coin. The results are listed in table 5.1. The locations of the study communities within the region are shown in Map 5.1.

Table 5.1 Result of the matching and randomisation process

Pair number	Matching criteria	Intervention communities	Comparison communities
1	rural communities, relatively difficult access from Mwanza	Nyangwhale	Mbarika
2	island communities, located in low HIV prevalence district	Ukara	Muriti
3	roadside communities (on a main high way), located in high HIV prevalence district	Nassa	Nyanguge
4	lakeshore communities, easy access from Mwanza, high STD attendance rate at HC	Katunguru	Sangabuye
5	lakeshore communities, difficult access from Mwanza, lower STD attendance rate	Chikobe	Mwangika
6	rural communities, relatively easy access from Mwanza	Mwamashimba	Malya

MAP 5.1 MAP OF MWANZA REGION SHOWING THE LOCATION OF STUDY COMMUNITIES



5.1.5 Sample size considerations for community randomised trials

Two questions followed from the decision to use a community-randomised design:
(i) How many communities were needed in each trial arm? (ii) How many person-years of follow-up were required in each community?

Clearly, these two choices are mutually interdependent. Within certain limits, an increase in the number of person years of follow-up per community (y) would allow a reduction in the number of communities needed (n) in each arm, and vice versa.

The required sample size depends on the incidence of infection in the absence of intervention (I_0), such that a smaller sample size is needed if incidence is higher, since a larger number of events is then expected for a given number of person years of follow-up. It also depends on the degree of the reduction of incidence resulting from the intervention, such that a smaller sample size is needed if the difference between the incidence with and without the intervention is high ($I_0 - I_1$), since a larger difference can be detected more easily.

Furthermore, as in all intervention trials, the sample size depends on the required power of detecting a reduction, and the required level of statistical significance. The higher the required power and level of significance, the larger the sample size.

Lastly, the required number of communities in each arm depends strongly on the variability of incidence between the communities, which can be expressed by the coefficient of variation (k), calculated as the quotient of the standard deviation and the mean of all incidences in one arm of the trial. The greater the variability between communities, the greater is k, and the greater is the number of communities required.

An approximate estimate of the required number of communities in each trial arm can be obtained through the following calculation (Hayes et al 1997):

$$n = 1 + \frac{f\,[\,(I_0 + I_1)/y + k^2\,(I_0^2 + I_1^2)\,]}{(I_0 - I_1)^2}$$

where f is a function of the required power and the required significance[1]. E.g. for 80% power and significance at $p < 0.05$ (in the two-sided test), $f = 7.84$ (Hayes et al 1997).

5.1.6 Sample size estimate for the Mwanza trial

To calculate the required number of communities in each arm (n) and the required number of person-years of observation per community (y), pre-trial information on I_0, I_1 and k are needed. For the Mwanza trial, none of these were readily available, so that plausible estimates had to be used instead.

A value of 1% was assumed for I_0, the annual incidence in the absence of the intervention, based on observations in the neighbouring region of Kagera (Killewo et al 1993).

I_1, the incidence with the intervention, should be lower than I_0 if the cofactor hypothesis was correct. However, it was unclear how much impact could be expected. From a public health perspective, it seemed worth launching an intervention if a reduction of about 50% of the original HIV incidence could be achieved. It was therefore decided to make the sample size sufficiently large to detect a reduction of this order. It followed that the estimate for I_1 should be 0.5%.

To arrive at an estimate for k, the coefficient of variation, it was assumed that the true incidence rates in the communities without the intervention I_0 would follow a normal distribution. Thus for a small number of communities, the lower and upper limits of I_0 would differ from the mean by approximately 2 standard deviations of I_0. It was also assumed that the true incidence rates would vary between approximately 0.5% and 1.5%. Under these assumptions, the standard deviation was SD = 0.25 and k = SD/ mean of I_0 = 0.25/1.00 = 0.25.

It was further assumed, that the degree of variation would be similar in the communities with intervention, giving a range from 0.25% to 0.75%, and k = 0.125/0.50 = 0.25 as before.

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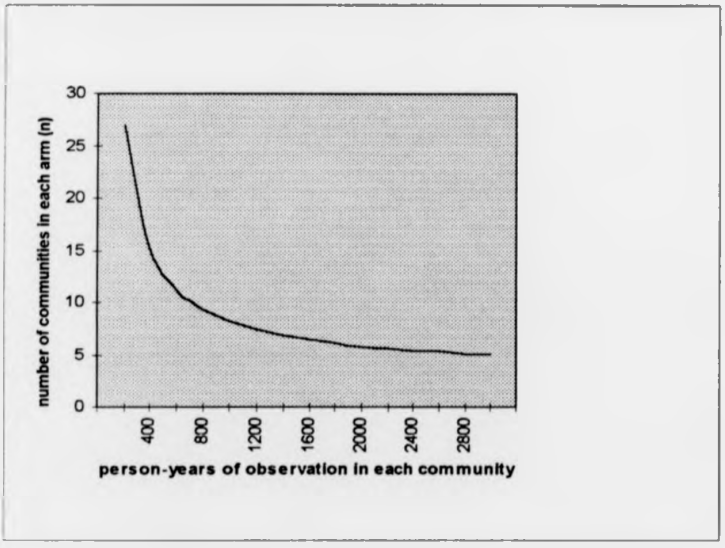
[1] for significance at $p < \alpha$ (z-test) and power = $(1 - \beta)$, f can be calculated as $f = (z_\alpha + z_\beta)^2$, using a table of the percentage points of the standard normal distribution (Kirkwood 1995). For example for $\alpha = 0.05$, $z_\alpha = 1.96$; and for power of 0.8, $\beta = 0.2$, $z_\beta = 0.84$; which gives $f = 7.84$

It was anticipated that the matched design would result in a smaller degree of variation within matched pairs, and so the sample size calculation (based on an unmatched design) was assumed to be conservative.

Using the above formulae, different possible values (n) for the number of communities in each group were obtained for different numbers of person-years of observation (y) per community. The interdependence between these two sample size parameters is displayed in fig 5.1.

Fig 5.1 shows that at least 5 communities were required in each trial arm, and that nothing much would be gained by increasing the person-years of observation in each community beyond 2,000. For a smaller number of person-years, the required number of communities would be larger, the increase being non-linear. The trade-off between the two parameters is clear.

Fig 5.1 Number of communities required in each arm per person-year of observation, to give 80% power of detecting a reduction of HIV incidence from 1% to 0.5%, assuming that the coefficient of variation k=0.25



From a logistical point of view, it was easier to choose a comparatively high number of person-years per community than to increase the total number of communities which participated in the trial. Therefore, a decision was made to aim for 2000 person-years of observation per

community. It followed from the sample size equation in 5.1.5, that the required number of communities would be n = 5.8. Therefore it was decided to select 6 communities for each arm of the trial.

The required person-years of observation were to be obtained by following a certain number of study participants for a certain time period. Again, there was a trade-off between these two parameters: a long follow-up period would have permitted a reduction in the number of study participants, but the benefits of this were limited because of the higher rate of losses to follow-up which was then to be expected. Conversely, an increase in the number of participants would theoretically permit a shorter trial duration. However, this option was subject to logistic limitations. Besides, an impact could reasonably be expected only if the intervention had been in place for some time.

For these various practical reasons, it was decided to recruit about 1,000 cohort participants in each community, and to follow them for a period of 2 years, thus obtaining the required 2,000 person-years of observation.

Incidence calculations can only be based on participants who were HIV-negative at baseline. However, for the sample size estimate this was ignored as baseline HIV prevalence was expected not to exceed 4%.

Losses to follow-up were expected to be in the range of 20 - 30%. This would decrease the number of person-years. However, as follows from the sample size equation in section 5.1.5 when keeping all other parameters equal, the power to detect a halving of HIV incidence would only be reduced to 74 - 77%, a rather modest reduction.

Sample size considerations for the cross-sectional studies on STDs in ANC attenders and the sexual behaviour surveys are discussed briefly in the respective sections (5.4.6 and 5.4.7).

5.1.7 Outcome measures

The *primary outcome measure* was the incidence of HIV infection in the cohort in the intervention and comparison communities, established through a baseline survey and a follow-up survey after a period of 2 years.

Secondary outcomes referred to the prevalence and incidence of STDs and to the sexual behaviour of the study population.

(i) STDs: Data on the prevalences and incidences of different STDs in the two groups of communities were obtained using a variety of approaches, mostly using the same basic format of a cohort study with the baseline and follow-up surveys described above.

1. The cohort was tested for seroincidence and seroprevalence of syphilis.
2. Prevalences of self-reported symptoms of genital discharge and of genital ulcers were determined through interviews of all study participants in the cohort. Symptomatic study participants were examined for signs of genital infections.
3. Urine specimens of all men in the cohort were screened with the leukocyte esterase dipstick test. Men who reported genital discharge, those with signs of discharge detected on examination and all men with a positive dipstick test were examined and urethral smears were taken for the detection of gonorrhoea, chlamydia infection and non-specific urethritis. Thus minimum prevalences of symptomatic and asymptomatic infections were established in the cohort.
4. It was not possible to perform detailed investigations on STDs in women within the main cohort, for ethical and logistical reasons. To determine the impact of the intervention in women, a sample of 100 consecutive antenatal clinic attenders was selected at each of the 12 health centres, at baseline and again after 1 year. All women in these two cross-sectional surveys were examined clinically, and vaginal and cervical specimens were tested for pathogens of reproductive tract infections.

Laboratory methods used in these surveys are described in detail in sections 5.4.4 and 5.4.6.

(ii) Sexual behaviour: The intervention did not aim at inducing changes in sexual behaviour. Nevertheless, it was possible that sexual behaviour differed between intervention and comparison communities already at baseline and that the intervention led to differential changes over time, thus confounding any impact results. It was therefore important to collect data on sexual behaviour at baseline and at follow-up. This was achieved through in-depth interviews of a sub-sample of cohort participants. Details are given in section 5.4.7.

5.2 Design and implementation of the intervention

5.2.1 General principles of the intervention

To make the intervention more sustainable and cost-effective, it was integrated within the existing primary health care (PHC) system: improved STD case management was provided through rural health centres and dispensaries, health educational activities for the general population were performed by the district health management team, and a reference clinic and laboratory were established at government health facilities in Mwanza town.

AMREF/LSHTM played a supportive and facilitating role, providing central services such as training, drug supply and supervision, but even these components were integrated as much as possible into the regional and district health system.

5.2.2 Intervention communities and health facilities

During the trial, the intervention was introduced stepwise into the 6 intervention communities. In each of the communities, this involved one health centre and at least 3 dispensaries. Two communities had 4 dispensaries. At one of these, STD services were discontinued after the first intervention year, because of disciplinary reasons. In total, 25 health facilities participated without interruption. At the end of the trial, the intervention continued in all the intervention communities, and was extended to the six comparison communities, and to other communities of the region thereafter.

5.2.3 Intervention components

The intervention had six components:

1. Training of health workers
2. Improved STD case management at health facilities
3. Supply of effective drugs, essential equipment and consumables
4. Supervision of STD services at health units
5. Health education campaigns in the general population
6. Reference clinic and laboratory

The intervention aimed to provide STD treatment services for the entire population. There was no targeted intervention for high risk behaviour groups, as such groups were difficult to identify. There were no brothels, and except for the two roadside communities, no bars or hotels. However, the operational capacity of the programme was also used to intervene in Mwanza town and in other communities outside the trial area. In such places, identifiable high risk populations often existed and received special attention.

5.2.4 Training of health workers

Selection of trainees

Health workers were selected for training by the respective District Medical Officer (DMO) in collaboration with the Regional STD Intervention Officer (see management structure fig. 3.1). From each of the health facilities, the officer in charge was invited to a STD training course, usually a Medical Assistant (from health centres) or a Rural Medical aide (from dispensaries).

Within two to four months, two additional health workers (HW) followed from each health centre, and one additional HW from each dispensary. For the 25 health units in intervention communities, 65 staff were trained during the trial period, including replacements for transfer or retirement (about 15% in 2 years).

At some of the remote dispensaries, clinical services are provided by auxiliary staff who have a few months training only. Although these HWs are officially not permitted to prescribe, they are in fact the ones who often maintain the clinical routine at such units. The programme obtained permission to include such personnel in the STD training, following the principle of training those who actually do the job.

District personnel (MAs) who were to be become District STD Control Coordinators, and HWs from facilities outside of the trial area, also participated in the training.

None of these HWs had prior exposure to training on STD case management. In Tanzania as in most sub-Saharan countries, STDs are usually covered only superficially during the basic

training of paramedical staff. Even most physicians have only limited skills in the management of this group of infections.

STD training courses

The basic training in STD case management consisted of a one week training course, performed at the seminar room at AMREF's programme office. This was followed within two months by two weeks of practical training at one of the STD reference clinics in Mwanza town.

Training courses were conducted at two monthly intervals, with an average of 6 to 7 courses per year with usually about 15 to 18 participants. Practical training was performed continuously throughout the year.

The training syllabus included the following topics:

1. public health importance of STDs
2. STD syndromes and syndromic case management
3. non-judgmental and caring attitude towards STD patients
4. health education, risk reduction and condom promotion for STD cases
5. partner notification
6. AIDS

Course contents were standardised for all cadres of HWs. Care was taken that teaching was not overloaded with biomedical details. Formal lectures alternated with exercises, group discussions and role plays. The standard training plan is attached as annex 1.

Training manual

Early in 1991, David Mabey (LSHTM) and John Nduba (AMREF Nairobi) developed a self-learning training manual for health workers (Nduba and Mabey 1991).

The manual was provided to all HWs about a month before started their training course, and they were encouraged to study it prior to the course. During the course it was used as the main resource material.

Refresher training

One-and-a-half years after their initial training, health workers were invited to Mwanza to participate in a 3-day refresher course. They used this time to exchange experiences with their peers, and to discuss common problems. Important messages were reinforced, and feedback from supervision and monitoring was given. Because of the limited capacity at the training clinics, no practical refresher training was conducted.

STD training team

Training courses were conducted by the Regional STD Intervention Officer and two senior nurses all of whom had substantial practical experience in STD case management. The Intervention Officer was an MA, who was also regularly involved in the supervision of STD services in the intervention health facilities, so that field experience was constantly fed into the training.

Physicians were usually not involved as trainers. However, the author gave a major input into the design of the courses, and both the author and the Manager of Clinical Studies monitored the quality and the output of the training.

Practical training

The practical training lasted two weeks. It was conducted at the STD reference clinics which were integrated into the outpatient services of Sekou Toure Hospital and the Makongoro Antenatal Clinic (see table 3.2).

Trainees were attached on a one-to-one basis to skilled clinicians who acted as their tutors. They were expected to watch the correct management of at least two cases of each major syndrome by their tutor, and then to manage another two cases of each syndrome on their own, but under supervision. This was roughly equivalent to seeing 30 new STD cases, this number of patients usually presenting within 2 weeks.

5.2.5 Improved STD case management at health facilities

Pre-intervention management of STD patients

Prior to the intervention, STDs were already treated at health facilities. However, health workers were not adequately trained, and lacked effective drugs. They usually tried to establish an aetiologic diagnosis, for example 'gonorrhoea' without having the necessary laboratory support, and treated using drugs from the kits provided to them through the Essential Drug Programme of Tanzania. Treatment was not standardised and ineffective drugs or inadequate doses were often prescribed.

Many HWs showed a reproachful attitude to STD patients, privacy was not maintained, and patients had doubts about confidentiality (Lwihula and Grosskurth 1993). Patients were usually not examined, health education was not given, and little effort was made to extend the treatment to sexual partners.

Improved case management

In the intervention health facilities, through training and regular supervision, HWs were encouraged to manage all STD patients according to the following standard procedure:

1. take a short history
2. perform a clinical examination
3. establish a syndromic diagnosis
4. provide immediate treatment based on a syndromic algorithm
5. give health education and promote risk reduction
6. offer condoms, and promote their use
7. encourage partner notification
8. keep simple records

Clinical examination

This was done through a simple inspection of the genitalia, anus, palms and soles and the oral cavity.

During the first year of the intervention, all health workers were trained in the use of the speculum, and were expected to perform a speculum examination for the diagnosis of vaginal discharge, cervical infections and intravaginal ulcers. However, the available time for practical training was too short for HWs to become confident with the method. As a result, few health workers made use of the speculum. It also became apparent that the speculum examination contributed little to the treatment decision in most cases. Its use was discontinued as from the second year of the intervention.

Syndromic treatment

Health workers used a syndrome-based approach to the management of most STDs. A syndrome is a consistent combination of symptoms and easily recognised signs. Syndromic treatment aims to cover the majority of the microbiological agents responsible for that syndrome in the population in question, usually by prescription of a combination of drugs (WHO 1994).

The rationale, advantages and disadvantages of syndromic STD treatment are discussed in detail in the literature review (section 2.1)

In the Mwanza trial, the following syndromes were diagnosed and treated using standardised algorithms:

1 urethral discharge syndrome (UDS)
2 vaginal discharge syndrome (VDS)
3 genital ulcer syndrome (GUS)
4 balanitis syndrome

A syndromic algorithm was also used for the management of the pelvic inflammatory disease (PID) syndrome, although it is not easy do diagnose this condition by clinical means only. As an

approximation, lower abdominal pain (LAP) was used as a marker syndrome, recognising that this complaint is non-specific and often unrelated to a genuine acute reproductive tract infection.

For some STDs or complications of STDs an unambiguous aetiologic diagnosis is possible, so that monotherapy could be applied, again using standard treatment algorithms:

1. condylomata accuminata (genital warts)
2. condylomata lata (a form of secondary syphilis)

Treatment algorithms were produced in the form of user friendly flow-charts which were supplied to health workers in transparent folders to be kept readily available on their desks.

An example of such a flow-chart is shown in fig. 5.2, and a summary of syndromes, aetiologic agents and treatment regimens is given in Table 5.2.

The algorithms were similar to those recommended by WHO (WHO 1994), except that second and third line treatment options were included for treatment failures. The regimen used for the management of vaginal discharge differed from the one suggested by WHO: a risk assessment step for the diagnosis of cervical infections was not included in the algorithms of the Mwanza trial.

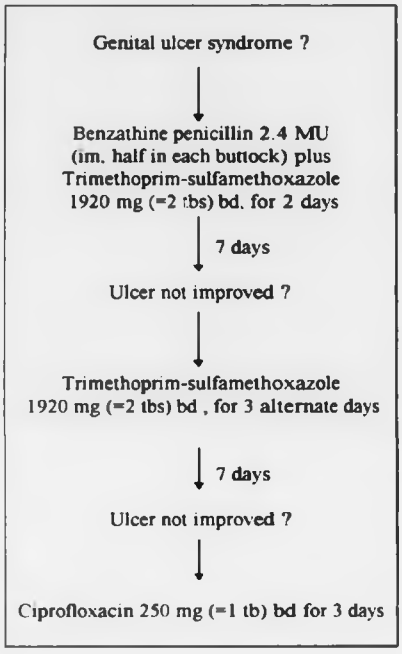
Health education, promotion of risk reduction

Health workers were trained to use a simple check list to guide the health education of their STD patients. Topics to be discussed were:

- the infectious nature of the disease: transmission through sexual intercourse
- some frequent complications: infertility, illness of children, AIDS
- the importance of completing the treatment course
- the reasons and the necessity for treating partners
- risk reduction: how to avoid future infection
- condom demonstration

Condoms were available in sufficient numbers at all health facilities, provided free of charge by the National AIDS Control Programme.

Fig 5.2 Flow-chart for the management of genital ulcer syndrome



Partner notification and treatment

Health workers were encouraged to explain carefully to their patients the reasons why partner treatment was important. Each patient (index case) received small contact cards, one for each sexual partner reported. The card was to be handed to the partner(s), and the patient was asked to encourage them to come to the clinic for treatment. The card carried only the reference number of the index case.

Partners who came forward were offered treatment, even if free of symptoms. Health education was given. A genital examination was offered, but was not a precondition for the treatment.

Table 5.2: Syndromes and their causative agents occurring in Mwanza, with treatment regimens used for each syndrome in the STD intervention

Syndrome	Aetiologies occurring in Mwanza	Treatment regimen used in the STD intervention
Genital ulcer syndrome	• chancroid *(Haemophilus ducreyi)* • syphilis *(Treponema pallidum)* • herpes *(Herpes simplex virus-2)*	1. TMP-SMX 320mg/1600 mg bd for 2 days + benzathine penicillin 2.4 mill.units im stat 2. TMP-SMX 320mg/1600 mg bd alternate days x 3 3. ciprofloxacin 250mg bd for 3 days (no treatment for herpes)
Urethral discharge syndrome in men	• gonorrhoea *(Neisseria gonorrhoeae)* • Chlamydia infection *(Chlamydia trachomatis)* • trichomoniasis *(Trichomonas vaginalis)*	1. TMP-SMX 400mg/2000mg bd for 2 days + doxycycline 100 mg bd for 7 days 2. metronidazole 2g stat + doxycycline 100mg bd for 7 days 3. ciprofloxacin 500mg stat
Vaginal discharge syndrome	• trichomoniasis • bacterial vaginosis (anaerobic bacteria) • cervical infections (gonococcal and chlamydial) • candidiasis *(Candida albicans)*	A if discharge does not appear like thrush: 1. TMP-SMX 400mg/2000mg bd for 2 days + doxycycline 100 mg bd for 7 days + metronidazole 2g stat 2. doxycycline 100 mg bd for 7 days 3. ciprofloxacin 500mg stat B if discharge appears like thrush: nystatin pessaries 1 at night, for 7 days or: application of 1% gentian violet sol
Lower abdominal pain syndrome	if caused by pelvic inflammatory disease: • gonorrhoea • Chlamydia infection • anaerobic bacteria	1. TMP-SMX 400mg/2000mg bd for 2 days + doxycycline 100 mg bd for 14 days + metronidazole 400 mg bd for 7 days 2. ciprofloxacin 500mg stat
Balanitis syndrome	• non-infectious • various skin bacteria • ulcer of glans or fore-skin	A if foreskin retractable and no ulcer seen: application of 1% gentian violet solution B if foreskin not retractable: treat as genital ulcer syndrome
Genital warts	• *Human papilloma virus*	application of 1% podophyllotoxin-ethanol, washing after 3 hours, application 1x per day
Condylomata lata	• Secondary syphilis	benzathine penicillin 2.4 million units im stat

NB: in pregnancy, doxycycline and ciprofloxacin are replaced by erythromycin (500mg td for 7 days)

Legend:
1: treatment given at first visit
2: treatment given if no improvement after 7 days
3: treatment given if no improvement after further 7 days
bd: twice per day, td: three times per day, stat: single dose
im: intramuscular,
TMP-SMX: trimethoprim-sulfamethoxazole

Recording and reporting

At health facilities, simple records of each patient seen were kept using a special STD register book. Standard information was collected and included: a register number, the date, the name, the community of residence, the syndromic diagnosis and the treatment given. Provision was also made to record condom acceptance by the patient, partners treated subsequently, and any follow-up observations (e.g.: improved, cured, not better, worse, 2nd or 3rd line treatment given). It was noted if patients were referred, and which destination health facility they were referred to.

On request of the NACP, a standard monthly report form was completed by the health worker in charge of the facility. Copies were sent to the DMO and the NACP.

5.2.6 Supply of effective drugs, essential equipment and consumables

Drug supply

Drugs were purchased from cheap bulk suppliers in the UK or the Netherlands. They were airfreighted half-yearly to Dar-es-Salaam, cleared by AMREF's country office, forwarded to Mwanza, and administered by the programme's supply officer.

Health facilities kept a standard drug stock which was regularly replenished by the programme. During the initial phase of the trial, drugs were supplied to health facilities by AMREF's intervention supervisors on the occasion of their supervision trips to the intervention communities. After district STD control coordinators (DSCCs) had been trained, the programme supplied drugs to the district level, and DSCCs ensured the supply to health facilities.

The consumption was carefully monitored. Drug stocks were regularly taken at health facilities by supervisors, and observed drug consumption was compared with the expected consumption as calculated from the STD case register books which were kept by health workers. Discrepancies were checked and discussed. Consumed drugs were replaced, initially every six weeks, and later at quarterly intervals.

The effectiveness of the drugs was monitored at the reference clinic and laboratory in Mwanza town (see below).

Other supplies and equipment

Besides the drugs, disposable plastic gloves for examination and batteries for examination torch lights were regularly supplied.

The following items of equipment were regarded as essential for the improved STD services at health facilities:

- a simple desk and two chairs
- an examination bed
- a torch
- a screen to ensure privacy during examination
- a functioning door to close the consultation room
- a mug for drinking water, to ensure directly observed treatment
- a wooden box with padlock to keep the STD drugs
- a register book
- transparent folders with syndromic flow-charts

The intervention programme had to provide chairs, tables and examination beds to about a quarter of the health facilities. A screen had to be provided for about half of them. All these items were produced at low cost by local craftsmen. Several doors had to be repaired. All health facilities received the smaller items listed above.

5.2.7 Support supervision

Objectives

Regular supervision visits to peripheral health facilities were regarded as one of the key elements of the STD intervention. The guiding principle was support rather than mere checking. The visits had four objectives:

1. to provide in-service training
2. to give feedback and motivation
3. to audit the consumption of drugs
4. to replenish the drug stock

Rationale

Experience from another STD intervention programme outside Mwanza Region without a regular supervisory component, had demonstrated that the training of health workers alone, although essential, was not in itself sufficient to ensure successful implementation of the programme at peripheral health facilities (Felix Ndyetabura, NACP Tanzania, personal communication). Health workers found it difficult to put their new skills into practice, particularly to apply the new treatment algorithms, to provide health education to patients reliably and regularly, and to utilise the drugs for the purpose they were intended for. Furthermore, the lack of feedback and in-service training within this programme had a negative effect on the motivation of health workers.

Supervisors

Two Medical Assistants (MAs) acted as regional supervisors in addition to the Intervention Officer (Fig 3.1), one of them on a half-time basis. They were based at AMREF's programme office, and toured all participating health facilities and the respective district health offices regularly, initially every 6 weeks and later at quarterly intervals.

As the intervention programme aimed at complete integration into the district health structure, a new cadre was created: the *District STD Control Coordinator (DSCC)*. The DSCC, usually an experienced MA by background, was a member of the district health management team. The six DSCCs received formal STD training in Mwanza, and in-service training by the regional supervisors. Initially they performed their work together with a regional supervisor, but after 2 years most supervision visits were conducted by DSCCs.

During leave or illness, the *District AIDS Control Coordinator (DACC)* acted as a replacement for the DSCC. However, these two jobs were in principle quite distinct: the DSCC needed to be an experienced clinician, whilst the DACC had mainly an educational task directed at the general population. Since 1989, all districts in Tanzania have been staffed by a DACC.

Supervision checklist

During supervision visits, the regional and/or district supervisors worked with the trained health facility staff. To standardise this process, a checklist was introduced which covered the following points:

- staff availability: any problems anticipated due to illness or leave?
- equipment: is it complete ? are repairs needed ?
- patient register book: is the information complete and consistent ?
- treatments given: have algorithms been followed ?
- clinical discussion: did the health workers see any interesting or difficult cases ?
- in-service training: revise a topic with the HW, see a patient jointly if possible
- statistics: how many patients ? which syndromes ? cure rates ?
- feedback: discuss performance and statistics, compare with rest of the district
- drug consumption: how much has been consumed according to cases treated?
- stock taking: does the physical stock tally with the calculated consumption ?
- reporting: have forms for the district and higher authorities been forwarded ?
- drug replacement: new drugs are provided so that a standard stock is maintained.

Supervision forms

A supervision form, which included the checklist given above, was used to record the performance of STD services at the health facilities, check drug consumption and identify training needs (annex 2).

5.2.8 Health education campaigns

About twice per year, a health education campaign was performed in each village served by an intervention health facility. The campaigns focused on the availability of free and effective treatment at the facility and on the public health importance of STDs. People were encouraged to attend promptly for treatment if they had symptoms.

The campaigns were conducted during market days when a large part of the population was likely come to the village centre. A variety of strategies were used: (i) group discussions were held with local opinion leaders, (ii) health educators and opinion leaders jointly made public speeches, (iii) the population was attracted by means of large picture boards which dealt with STD related topics, (iv) health educators discussed these topics in public, and (v) leaflets were distributed which addressed the importance of early STD treatment and means of risk reduction.

The campaigns were conducted by district health personnel, notably the District AIDS Control Coordinator (DACC), and were facilitated by AMREF through one of the intervention supervisors.

5.2.9 Reference clinic and laboratory

At Sekou Toure Hospital (the Municipal Hospital of Mwanza) and at Makongoro Clinic (the largest antenatal clinic in Mwanza town), improved STD case management was integrated into the outpatient services. Both facilities were used as STD reference clinics. Adjacent laboratories were equipped and refurbished, so that some on-site tests could be done. For all other STD diagnostic tests, specimens were sent to the laboratories of the National Institute of Medical Research (NIMR).

The reference clinics served the following functions within the intervention programme:

- to monitor the aetiology of STD syndromes
- to monitor the antibiotic susceptibility of *Neisseria gonorrhoeae*
- to train health workers in STD case management

This important component was planned and supervised by the Manager of Clinical Studies, Dr Philippe Mayaud, and his counterpart, Dr Gina ka-Gina. The microbiological work was conducted at NIMR by Mr John Changalucha and later by Mrs Beryl West and Mr Jan Cornelissen.

The reference clinics did not routinely function as referral clinics. The great majority of the patients came from Mwanza town.

Monitoring the aetiology of STD syndromes

Monitoring the pattern of STD aetiologies was essential to ensure that the syndromic treatment algorithms covered most of the causative agents occurring in the region. To achieve this objective, vaginal, cervical or urethral specimens were collected from all patients presenting with vaginal or urethral discharge syndromes at the reference clinics. The specimens were used to diagnose infection with *Neisseria gonorrhoeae* by Gram stain and culture, *Chlamydia trachomatis* infection by antigen detection Elisa test, infection with *Trichomonas vaginalis* by wet preparation microscopy, *Candida albicans* by wet preparation and Gram stain, and bacterial vaginosis by Gram stain, pH test and KOH test.

To diagnose genital ulcer aetiologies, swabs were obtained from the ulcer base. *Treponema pallidum*, the bacterium causing syphilis, was diagnosed by dark field microscopy and later by PCR (at LSHTM) ; *Haemophilus ducreyi*, the causative agent of chancroid, was diagnosed by culture; lymphogranuloma venereum (caused by *Chlamydia* species) and infection with *Herpes-simplex* virus type-2 were diagnosed by their specific antigen detection Elisa tests. In addition, blood specimens were obtained from all STD patients for syphilis serology (RPR and TPHA tests). Granuloma inguinale (donovanosis) did not occur in the region.

Treatment decisions at the reference clinic did not depend on the laboratory test results but were guided by the same syndromic algorithms used in the intervention health facilities[2]. This was necessary because some patients did not return to collect their results.

[2] Three exceptions were made to this rule, mainly for ethical reasons:

- In patients with vaginal discharge, the wet preparation microscopy result, usually available within a few minutes, was used to decide whether treatment for *Trichomonas vaginalis* had to be given. This procedure saved many women from taking metronidazole unnecessarily.
- When a patient with urethral discharge returned after 7 days without improvement, third-line (rather than second-line) treatment was given if gonorrhoea had been found at the first visit. This situation indicated the possibility of gonococcal resistance to the first-line drug and a short-cut to third-line treatment seemed justified. Reinfection was excluded, if possible, before this decision was taken.
- RPR test positive patients were treated for syphilis, even if presenting with a non-ulcerative STD.

Monitoring the antibiotic susceptibility of Neisseria gonorrhoeae

It was essential to monitor the effectiveness of the drugs used for treating gonococcal infections. Resistance of *Neisseria gonorrhoeae* to many antibiotic drugs is widespread, and can develop comparatively fast (Holmes 1990, West et al 1995).

Strains of *Neisseria gonorrhoeae* were cultured from patients presenting with genital discharge syndromes. After initial isolation and identification, strains were stored at minus 70°C in Mwanza, and once per year sent to LSHTM for further characterisation and determination of minimum inhibition concentrations (MICs) using an agar dilution technique.

The *training of health workers* is described in detail in section 5.2.4.

5.3 Operational evaluation of the intervention

5.3.1 Monitoring of operational performance

During their regular visits to health facilities, regional and district supervisors monitored the performance of health workers using the supervision checklist described in section 5.2.7, and tried to assist the health workers concerned to solve any problems. They also assessed the reported cure rates of patients with STDs, based on entries from the STD patient register book.

Supervisors completed a supervision form (annex 2), which was discussed during a weekly debriefing session on return from the field with either the Intervention Officer or the Programme Manager. If necessary, decisions were taken at this time to address more substantial problems regarding training, supplies or, occasionally, discipline. The supervision forms were not used for further evaluation.

5.3.2 Evaluation of operational performance based on health facility data

At the end of the trial, that is after the intervention had been in place for two years in each of the intervention communities, all register books were collected from the health facilities and replaced

by new ones. This process lasted one year, because of the phased implementation of the trial (see section 5.4.1)

An experienced STD clinician from Sekou Toure Hospital, who was not involved in the intervention in rural health facilities, was trained by the author to extract all relevant operational data from the register books.

The following parameters were compiled:

1. number of STDs presenting to health facilities by sex and type of syndrome
2. proportion of dual or multiple syndromes
3. proportion of patients with complete follow-up visits
4. proportional cure rates after 1st, 2nd and 3rd line treatment for GUS, UDS and VDS
5. proportion of patients referred
6. proportion of patients who accepted condoms
7. proportion of patients for whom at least one partner was treated

The analysis was performed manually at AMREF's office.

5.3.3 Evaluation of operational performance through home visits of patients with incomplete follow-up: a cross-sectional study

Objectives

Primary objective: to assess the cure rates of STD patients in intervention communities who had been treated syndromically, but who had not returned for a final test of cure,

Secondary objectives: to asses health workers' performance and patients' satisfaction with the improved STD services.

Rationale

As described in 5.3.1, the routine supervisory visits of health facilities helped to monitor whether cure rates were sufficiently high to confirm the adequacy of the drugs and the treatment regimens in use.

However, complete follow-up data were only available from about one third of the patients (see section 6.1). The majority of the patients did not return for a test of cure. It was assumed that most patients were not willing to sacrifice time for further visits if they were already cured. However, it was not clear whether this assumption was correct. It was therefore necessary to perform a survey of patients who did not return for follow-up and to compare the cure rates of these 'non-returners' with those of the 'returners'.

At the same time, this survey offered a possibility to collect information about the patients' perceptions of the STD services.

Study design, selection of participants and sample size

A cross-sectional survey was performed in 1995 through home visits of STD patients from intervention communities who had not returned for follow-up visit to their health facilities.

The necessary sample size was calculated at 250. This was sufficient to detect whether the cure rate in non-returners was unacceptably low (the main research question of this supplementary study). We expected the cure rate to be about 80%, and wished to estimate this with 95% confidence limits of +/- 10%. It was expected that the participation rate in this kind of survey might be low, so that it was decided to define the time span for eligibility in such a way that at least 500 persons would be enlisted.

Eligible study participants were all patients who had been treated for STDs at the six intervention health centres, or at 12 randomly selected intervention dispensaries, within a period of more than 2 weeks but less than 3 months prior to the survey, and who had not completed

follow-up visits for a clinical test of cure. 567 patients fulfilled these criteria, 249 men and 318 women.

367 patients, more than expected, were successfully recruited, 164 men (66% of those eligible) and 203 women (64%).

In order to avoid embarrassment for the patients and to ensure good compliance, the home visits also included 375 patients with diarrhoea, respiratory tract infections and suspected malaria. The study therefore did not have the character of an STD survey. However, except for information on treatment satisfaction, the data from these additional patients were not processed further, as no clear information could be obtained about the original clinical condition.

Survey methods

The survey was conducted by two teams each comprising a team leader, three male and three female interviewers, and a driver. Supervision was provided by the author and the Field Manager. All field research assistants were clinically experienced MAs or RMAs, and had been involved in the main cohort study.

A structured questionnaire was designed in English, translated into Kiswahili, backtranslated into English and pre-tested in a community with STD intervention outside the trial area.

Patients were interviewed in their homes. Great care was taken to ensure confidential interview conditions. Questions concerned the treatment patients had received, their compliance, the treatment results, and present symptoms. Patients were shown a collection of drugs as used in the intervention, and they were asked if they recognised the drugs and remembered how many tablets they had been given, and with what instructions. Other questions addressed the patients' experience with regard to examination, health education, condom promotion and partner notification, and general service satisfaction. Patients who reported symptoms were offered a clinical examination, and treatment if necessary.

5.3.4 Evaluation of the referral system

During the compilation of data from the treatment register books as described in section 5.3.2, a complete list was generated of the 99 patients who had been referred by their local health worker to a higher level health facility during the two years of the trial. The list included the patient's name, the date of referral, the diagnosis, the reason for referral, and the destination health facility.

Permission to access the patient register books of these destination facilities was given by the Regional Medical Officer Mwanza and the various officers in charge of the facilities. Possible alternative health units which a patient might have chosen for referral attendance were also included, for example other health centres or hospitals in the wider area.

A medical assistant who had not been involved in the intervention in rural communities toured all these health facilities, and made a careful attempt to trace the names of the referred patients in the register books. For this purpose, he searched the entries of the month in which the referral decision had been made plus the 3 month period which followed.

If the patient's name could be traced, the MA tried to verify their identity if possible, for example through entries regarding the patient's place of residence. The diagnosis, the treatment, and any available follow-up observations were extracted and recorded.

The data were analysed manually at AMREF's office.

5.3.5 Assessment of the contamination between comparison and intervention communities

It was the primary objective of the intervention trial to investigate the impact of improved STD case management on HIV transmission (chapter 4). It was possible that STD patients from comparison communities might seek and receive treatment from intervention communities. In this case, any impact of the intervention would be diluted.

It was therefore desirable to obtain a good estimate of the proportion of patients who were residents in comparison communities among those seeking treatment at intervention facilities.

This was achieved through a survey of all treatment register books at the end of the two year trial period at each of the 25 intervention facilities, and by extracting the available information regarding the community of residence.

The investigation was performed simultaneously with the analysis of the recorded clinical data described in section 5.3.2.

5.4 Implementation and analysis of the impact evaluation

5.4.1 Phased implementation

After completion of preliminary work, the trial commenced in December 1991. The time plan is shown in fig. 5.3

A period of 2 months was needed to introduce each matched pair of communities into the trial. During this period, the baseline survey was carried out simultaneously in the intervention and the comparison communities, and staff training was conducted. The intervention was launched in the intervention communities as soon as the baseline survey was completed.

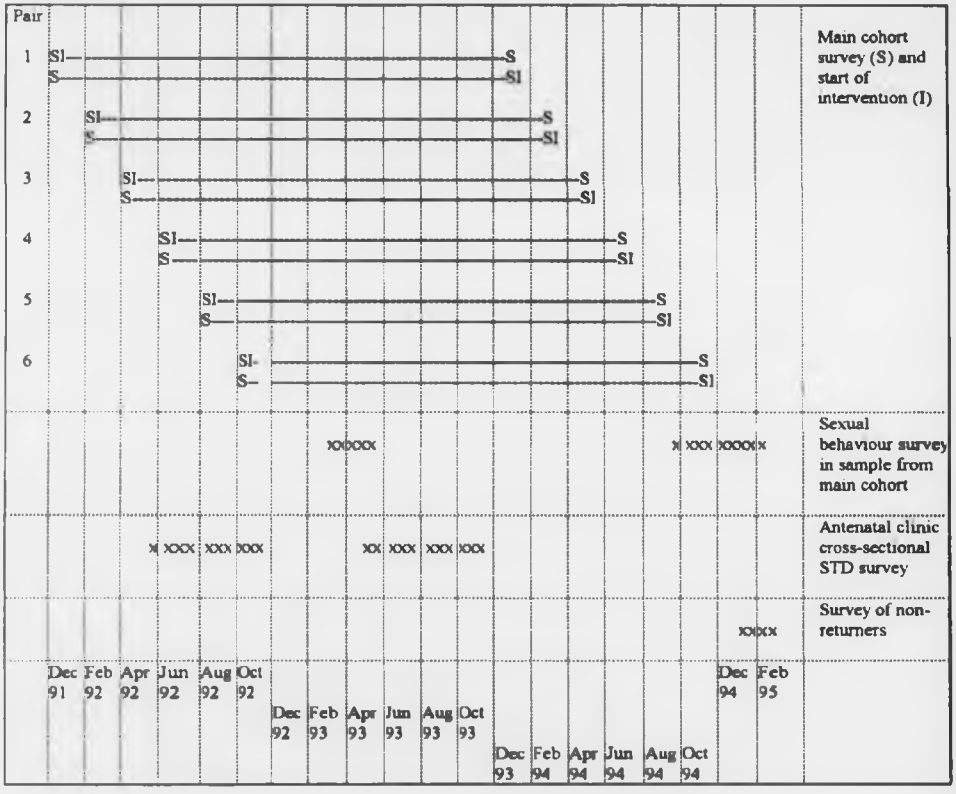
After 2 months, the cohort survey field teams moved to the next pair of communities, and the next batch of health workers from intervention communities came to Mwanza for their STD training course. Twelve months were therefore required to enter all six pairs.

The follow-up survey was conducted in each pair of communities 2 years after the corresponding baseline survey. For each community, the follow-up lasted therefore exactly 2 years. Because of the phased implementation the overall time required from the beginning of the baseline survey to the end of the follow-up survey was 3 years (fig. 5.3).

Immediately after completion of the follow-up survey in each pair, the intervention was introduced into the comparison communities. On completion of the trial, the intervention was

therefore in place in all communities involved in the study. The one year interval between the end of the baseline and the beginning of the follow-up surveys in the main cohort was used to launch the intervention in health facilities within Mwanza town and elsewhere in the Lake Zone, far distant from the trial communities. This approach ensured that the capacity of the programme to implement the intervention was fully utilised throughout the 3-year period of the trial.

Figure 5.3 Phased implementation of the trial. Timetable of main cohort surveys, start of intervention, and supplementary studies



The first sexual behaviour survey was conducted between February and April 1993, four to fourteen months after the baseline survey in the main cohort. The second sexual behaviour

survey lasted from August 1994 to February 1995, two to seven months after the follow-up survey in the main cohort.

The first cross-sectional study among pregnant women was performed from May 1992 to November 1992. The second study followed one year later. A third study of the same type was planned for year 3, but was not implemented due to lack of funds.

5.4.2 Main cohort study: community mobilisation

About 3 weeks prior to the start of the cohort survey in each pair of communities (for both the baseline and the follow-up surveys), the Field Manager and one of the research field team leaders visited the study communities to discuss the plans for the survey. They were accompanied by either the DMO or another high ranking officer from the district administration. The health worker in charge of the local health facility was also involved. The delegation introduced itself with an official document signed by the Director of the National Institute for Medical Research giving information about the study and its approval by the government.

A meeting was held with community and opinion leaders, including officials from the local party office. After obtaining the approval of the community leaders, the random cluster selection was performed jointly with these authorities (see below 5.4.3). A larger meeting followed the next day involving all balozi leaders whose 10-household unit had been selected (see section 3.1.5 on the administrative system in the region). At both meetings, the objectives of the study and the expected benefits for the community were carefully explained, and concerns discussed.

The concern raised most frequently regarded the amount of blood to be taken and fears that the blood samples might be sold abroad. To overcome these anxieties, the survey team demonstrated the size of the blood vials used for taking the specimens. In several communities, it was even agreed that the vials would be burnt in the community after the serum samples had been separated.

The population was informed that blood specimens would be tested anonymously for HIV infection, and that the programme statistician would be the only person who could theoretically

link names with results. Voluntary linked HIV testing was offered for those requesting it, for which a second small blood sample would have to be taken.

5.4.3 Main cohort study: enumeration of the study population

The target was to recruit 1000 participants aged 15 - 54 years through random cluster sampling. Within each community, the cohort was sampled from a study population of approximately 2000 to 3000 adults, defined as those living within 90 minutes walking distance around the health centre.

The twelve study communities were rather large entities, between 20 and 30 km in diameter, with an average population of 25,000 inhabitants, living in several distinct villages. It was assumed that in a scattered rural population, patients from the periphery of the communities might not necessarily use their own local health facility, because of possibly more convenient access to neighbouring villages outside the intervention area. The above definition ensured that, in intervention communities, the population within the more central parts was unlikely to seek care from health facilities without improved STD services, thus reducing 'contamination'. This allowed us to define a sizeable population to be eligible for recruitment into the cohort study (Fig 5.4).

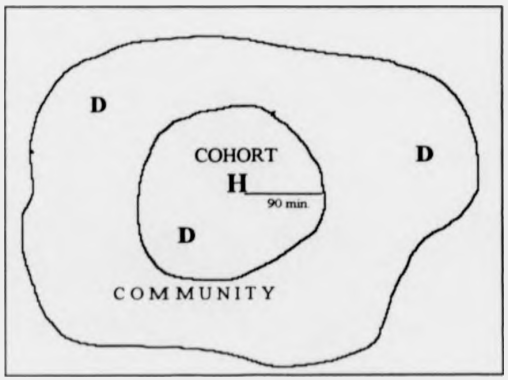


Figure 5.4: Cohort recruitment zone of a study community.
H health centre, D dispensary.

As described in section 3.1.5, the smallest administrative unit was the balozi, which consisted in principle of 10 households. In each study population, 16 - 20 clusters were formed each consisting of three to four neighbouring balozis. Each cluster had a population of 120 - 150 eligible adults. A random sample of seven to nine clusters was selected in each community.

A house to house visit was performed, and with the help of balozi and household leaders a list was made of all adults resident in the selected cluster. Eligibility was defined by age (15 - 54 years) and residence (living in the selected cluster *and* having lived in the community for the last 2 months or longer, or planning to live in the community for the foreseeable future).

All enumerated persons who were present and willing to participate were enrolled in the study, even if this exceeded 1000 participants.

According to the study protocol, if by the end of the baseline survey in a particular community the target of 1000 participants had not been achieved, an additional cluster was to be chosen at random. However, this situation did not arise.

5.4.4 Main cohort study: data collection and laboratory methods

Interview

Nurses and Rural Medical Aides were selected and carefully trained as interviewers. All interviewers were of Sukuma origin and spoke the local language. Each field team had one male and one female interviewer.

Separate structured questionnaires were designed for the baseline survey and later for the follow-up surveys. They were drafted in English, translated into Kiswahili, and backtranslated into English. The Kiswahili versions were pre-tested in pilot studies first among hospital workers and afterwards in two rural communities outside the trial area (see annexes 3 and 4).

Questions concerned personal characteristics, circumcision status in men, history of STDs, treatment seeking behaviour and present STD symptoms. Questionnaires for baseline and follow-up surveys were similar.

The interview was the point of first contact between field research team and cohort participants. At the start of each interview, a standard explanation was given about the objectives of the study and the data and specimens to be collected. It was emphasised that participation in the survey was voluntary and that any information obtained would be kept strictly confidential. The participant was given the opportunity to ask questions about the study. After completion of this procedure, informed oral consent was obtained, and recorded in writing by the interviewer.

If a participant requested to know his/her HIV status, an offer was made to collect an additional small blood sample for a linked HIV test after pre-test counselling. Such a participant was told that the HIV test result would be channelled confidentially to the District AIDS Control Coordinator who would visit the village to feed the result back to the participant after post-test counselling[3].

Serological tests

A sample of venous blood was taken from consenting subjects, serum was separated and a Rapid Plasma Reagin (RPR) test (VD-25, Murex, Dartford, Kent, UK) was performed immediately, so that individuals with positive results could be treated on the spot.

Sera were later tested in Mwanza for HIV-1 antibodies using an enzyme-linked immunosorbent assay (ELISA, HTLV-III-ELISA, Organon Teknika, Boxtel, Netherlands). All positive samples underwent confirmatory testing with a methodologically independent ELISA (Wellcozyme HIV1+2 GACELISA, Murex Diagnostics, Dartford, UK). In case of discrepant or indeterminate results, a western blot test was performed (HIV-1 Westernblot, Epitope, Beaverton, Oregon, USA). For the follow-up survey, HTLV-III-ELISA was no longer available, and the successor product Vironostika HIV MIXT Microelisa (Organon Teknika, Boxtel, Netherlands) from the same company was used instead. The HIV-1 specific component of this ELISA was identical with the previous test (Arnoud Klokke, personal communication)[4].

[3] Only six cohort participants requested to know their HIV test results.
[4] The test used for the follow-up survey differed from the one used for the baseline survey mainly because of its additional HIV-2 specific component. However, surveillance among HIV positive sex workers in Mwanza town in 1992 and 1994 with an HIV-2 specific test failed to show any evidence that HIV-2 had reached Mwanza Region.

Sera were also tested in Mwanza for syphilis serology by the Treponema Pallidum Haemagglutination Assay (TPHA) test (Fujirebio, Tokyo, Japan). An RPR test was performed (as above) on all sera positive for TPHA. Titres (1:2 - 1:32) were determined for RPR positive sera. Only results of syphilis tests conducted in the laboratory were used in the analysis. TPHA seropositivity was considered to indicate past or current syphilis infection, while positivity on both TPHA and RPR tests was considered as indicative of active syphilis, particularly if the RPR titre was >=1:8.

Urine specimens

Male subjects were asked to provide a first void urine sample, which was tested for the presence of leukocytes using a leukocyte esterase dipstick (LED) test (Nephur-Test + Leuco, Boehringer-Mannheim, Lewes, Sussex, England, UK).

Clinical examination

All study participants were seen by the clinician who offered an examination to all those reporting current STD symptoms on interview, to all participants with a positive RPR and to all men with a positive LED test. Symptoms and signs were recorded using a clinical examination form.

Urethral swabs and tests

Men reporting a urethral discharge, men with other complaints who were found to have a urethral discharge on examination and all men with a positive LED test were asked to permit the collection of two urethral swabs.

One of the swabs was smeared on a glass slide which was heat fixed in the field for subsequent Gram staining at the laboratory of NIMR. The presence of intracellular gram-negative diplococci was taken as evidence of infection with *Neisseria gonorrhoeae* (NG). For logistical reasons, it was not possible to attempt isolation of NG during this study.

The second swab was inserted more deeply (2 - 3 cm) and rotated within the urethra. This swab was placed in transport medium at about +4°C, and later frozen at -20°C. These specimens were tested at the NIMR laboratories for *Chlamydia trachomatis* (CT), using an antigen capture enzyme immunoassay (IDEIA Chlamydia, Novo Nordisk Diagnostika, Cambridge, Cambridgeshire, England, UK). A blocking assay was used to confirm a positive test result.

Urethritis was identified as the presence of NG and/or CT infection and/or five or more polymorpho-nuclear (PMN) cells per high power field on Gram stain.

Numbering of study participants and of specimen and data sheets

Each individual who was enrolled in the study was given a unique identity (ID) number which consisted of

1. two digits indicating the community
2. two digits indicating the cluster within the community
3. one digit indicating the balozi within the cluster
4. three digits indicating the individual within the balozi

In addition, all specimens and data sheets for the same individual were marked with an identical sequence number. Adhesive labels printed with these sequence numbers were prepared in the week before the field trip. Questionnaires and clinical examination forms carried both the ID number and the sequence number.

5.4.5 Main cohort study: organisation of surveys

Field teams

Two field research teams worked in parallel, one in each paired community. Teams usually remained in the field for two weeks. They alternated with another pair of two teams, so that the survey could be conducted without interruption for two months in each community.

Each team comprised seven staff: a team leader, two interviewers (one male and one female), two laboratory technologists, a clinician and a driver.

Implementation of field work

It was not possible for the field research teams to transport their equipment including a generator and centrifuge from household to household. A convenient central site was therefore established for members of each cluster to be interviewed and examined, usually at a school house, a party building or somebody's residence. The site was within 15 min walk from each household. After one week, the team moved to the next cluster.

Participants were first seen by an interviewer of the same sex, where their identity was checked, the objectives of the survey explained, consent obtained and the interview conducted. The interview lasted about 10 minutes. Care was taken that conditions of confidentiality were strictly maintained during the interview.

Thereafter the blood sample was drawn by one of the laboratory technicians, and the serum was separated immediately and stored in thick-walled cool boxes at about $+4^{0}C$. Men were requested to provide a sample of first void urine. Laboratory technicians performed the RPR and the LED tests as described above, and reported the results on standardised data sheets to the clinician within one hour after obtaining the specimens.

Study participants were then seen by the clinician for examination and specimen taking as described above.

As a service to the population, treatment for STD syndromes was provided using the syndromic algorithms discussed in section 5.2.5, and for syphilis if the RPR test was positive. Treatment was also given for any other reported ailment. Such treatment was also provided for any other villagers who presented. Occasionally, the team provided assistance if a villager needed referral for a serious or urgent condition.

When eligible individuals failed to attend, repeated home visits were made by the team leader in collaboration with the local balozi leader to encourage attendance. Transport was provided for those too sick to walk. At the end of the field work in a community, one week was used to revisit those clusters where many people had been absent, so that coverage could be increased further. If an individual was definitely not present or unwilling to attend, the reason was recorded.

A rendezvous shuttle service was arranged to transport sera and other specimens to Mwanza twice per week and to bring new ice packs to the field.

5.4.6 Surveys of the prevalence of STDs in pregnant women

Objectives (according to the original protocol)

To determine the prevalence of STD pathogens in pregnant women in intervention and comparison communities at baseline, after one year and after two years.

Rationale

Self-reporting of STD symptoms in women is a problematic criterion for assessing the presence of STDs, because of the frequency of mild and asymptomatic infections and the lack of specificity of genital symptoms in females (Wasserheit 1989). Reliable information on STD prevalence among women therefore requires internal examination and the taking of specimens for laboratory analysis. This is usually not feasible and logistically difficult during a general population survey, but is possible during attendance at antenatal clinics.

Study design, selection of study participants, and sample size

Three consecutive cross-sectional surveys were to be conducted of 100 pregnant women, presenting consecutively to antenatal clinic services at each of the 12 health centres in the intervention and comparison communities, giving a total sample size of 1200 in each survey.

The sample size and power of the survey to detect a significant difference in the prevalence of key STDs between intervention and comparison communities was calculated using a similar equation[5] as the one given in section 5.1.5. For 6 communities in each group, 100 women per community, and with the assumption that k = 0.1, the study had 75% power to detect a reduction of the prevalence of active syphilis from 8% to 4% at the 5% significance level. For 'any STD', the study had 75% power to detect a reduction from 40% to 30%.

Timing

The first cross-sectional study among pregnant women was performed from May 1992 to November 1992. The second study followed one year later. A third study was planned for year 3, but was not implemented due to lack of funds.

Survey methods

The field work was performed by a team comprising an experienced MA and a nurse, under the supervision of the expatriate Manager of Clinical Studies or his Tanzanian counterpart (see the organogram in fig 3.1).

The study participants were enrolled over a 2-week period at each health centre. After obtaining informed consent, subjects were interviewed using a standard questionnaire in Kiswahili which had been piloted in an antenatal clinic in Mwanza town. Questions concerned sociodemographic factors, a full obstetric and gynaecological history, and details of current symptoms. Questionnaires for the two surveys were identical.

A gynaecological examination was performed by the clinician including speculum examination. On this occasion, endocervical and vaginal swabs were taken for various laboratory tests. A blood sample was obtained for the diagnosis of syphilis.

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[5] If the objective is to compare the proportions (p_0 and p_1) of individuals with the outcome of interest in the intervention and control groups in a cluster-randomised trial, the following equation can be used in order to calculate n (the number of clusters required per arm), in terms of r (the number of individuals sampled per cluster), k (the between-community variation in p) and $f = (z_{\alpha/2} + z_\beta)^2$ (Hayes, personal communication 1997): $n = 1 + f\ [\ p_0(1 - p_0) / r + p_1(1 - p_1) / r + k^2 (p_0^2 + p_1^2)\ ] / (p_0 - p_1)^2$

Women found to be infected were treated in collaboration with the health centre staff. If laboratory results were positive, these were fed back to the health centre within two weeks after completion of the field work, and the drugs for treatment were provided.

Laboratory methods

In the field, vaginal swabs were used to prepare saline wet mounts for the diagnosis of infection with *Trichomonas vaginalis* and *Candida albicans*.

Two cervical swabs were obtained for the diagnosis of Neisseria gonorrhoeae infection: one was smeared on a glass slide and heat-fixed for Gram staining, the other inoculated onto commercially available culture kits (Gonoline, Merieux SA, France). A portable field incubator was used, and the specimens shipped to Mwanza twice per week. The diagnosis was confirmed using the Phadebact agglutination test (KaroBio Diagnostics, Huddinge, Sweden).

A third endocervical swab was placed into cooled transport medium, and later tested for *Chlamydia trachomatis* infection using an antigen-detection enzyme immunoassay (IDEIA, NovoNordisk Diagnostics, Cambridge, Cambridgeshire, UK). A blocking assay was used to confirm a positive test result.

Venous blood samples were centrifuged in the field and stored at about +4°C, and later tested for syphilis using the TPHA (Fujirebio, Tokyo, Japan) and RPR tests (VD-25; Murex, Dartford, Kent, UK). No tests were performed for HIV infection.

5.4.7 Sexual behaviour studies

Objectives

To determine the prevalence of behavioural and other risk factors for HIV infection in the trial population at baseline and after 2 years, and to compare these prevalences both between the two arms of the trial and over time.

Rationale

The purpose of the trial as a whole was to determine the impact of the intervention on HIV incidence, and on the prevalence and incidence of other STDs. However, it was possible that a reduction in incidence might be caused by other factors related both to the intervention and to the transmission of HIV or STDs, thus acting as confounding variables.

One of the most important potential confounding variables in the context of this trial was the sexual behaviour of the study population. Two situations could occur: (i) sexual behaviour may have differed between the two trial arms for reasons unconnected with the intervention, and this may have caused a difference in HIV incidence even in the absence of the intervention; (ii) the intervention may have led to a differential change in sexual behaviour between the intervention and comparison communities, which may have caused a difference in HIV incidence between the two arms unrelated to the improvement of STD case management. The latter situation is not strictly one of confounding, but could be one of the mechanisms whereby the intervention has its effect.

In any case, to be able to interpret the results of the trial, it was necessary to measure (and if necessary adjust for) this confounding variable. Data were therefore required on the sexual behaviour of the population in both arms of the trial, both at baseline and at follow-up.

In the main cohort study, it was not possible to collect detailed data on sexual behaviour. This needed to be done in a smaller sample of the study population.

Study design, selection of study participants, and sample size

Two consecutive nested cross-sectional studies were carried out, at baseline and follow-up, in sub-samples of the main cohort, taking a 1 in 8 random sample from each of the communities. For the first of these studies, the sample was chosen from the individuals enrolled at baseline; for the second it was selected from individuals who were seen during the follow-up survey of the cohort[6].

[6] The two sexual behaviour surveys formed part of two larger nested case-control studies of risk factors for HIV infection (baseline) and HIV incidence (follow-up). The results of the first of these case-control

The follow-up study had a power in excess of 90% at the 5% significance level to detect a reduction of the proportion of men with 3 or more partners during the past year from 30% to 15%, under the assumption that k=0.1.

Timing

The first sexual behaviour survey was conducted between February and April 1993, four to fourteen months after the baseline survey of the main cohort. The second sexual behaviour survey was conducted between August 1994 and February 1995, two to seven months after the follow-up survey of the main cohort (fig. 5.1).

Survey methods

Non-medical personnel (mainly teachers and social workers) were selected and carefully trained as interviewers. They were closely supervised by an anthropologist (Mr. Katua Munguti) and by the field manager (Dr. Frank Mosha, see organogram in fig. 3.1).

Structured questionnaires were designed in English, translated into Kiswahili, backtranslated into English and pre-tested in pilot studies. Questions concerned sociodemographic factors, marital partners, non-marital and casual partners, sexual behaviour and sexual practices, and perception of risk. Questionnaires for the two surveys were almost identical.

Approval for the study was obtained from various authorities (see section 5.5.2). Study participants were asked to give informed consent, and were interviewed in or near their houses. Every effort was made to ensure conditions of privacy for the interview, and the confidentiality of the information was stressed. Interviews took about 30 minutes on average.

Interviewers were kept blind to the HIV and STD infection status of the subjects, as determined during the main cohort surveys.

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studies have been published. Data from the second study are currently being analysed. These case-control studies are beyond the scope of this thesis.

5.4.8 Data and laboratory quality control

Data quality

Several methods were used to both promote and monitor data quality. All questionnaires and forms were checked by the field team leader before the end of the week, and mostly before the end of the day. In the main cohort study and the sexual behaviour surveys, team leaders conducted full reinterviews of 5 - 10% of the interviewees, without the interviewer knowing beforehand which of the participants were to be seen again.

The central management team at headquarters arranged for frequent but unscheduled supervisory field visits which were conducted in turn by the author, the expatriate statistician and the field manager. During these visits, they observed the data collection procedures, checked questionnaires and forms and discussed any problems with the field team. Similar supervisory visits were made by the anthropologist and the manager of clinical studies and his counterpart for the sexual behaviour and the antenatal clinic surveys, respectively.

During the baseline survey of the main cohort, field teams were blind as to which trial arm a community was to be allocated to. This was not possible during the follow-up round, but field teams were exchanged between the trial arms in an attempt to prevent bias due to differences between field teams.

To maintain high motivation, feedback was provided by headquarters staff to the field teams during regular meetings when teams returned to base.

Data were double-entered by two different data entry clerks, and the data files compared to identify discrepancies. A check digit assisted with the detection of transcription errors in the identity numbers. Logical checks were performed after data entry, and inconsistencies corrected, if necessary in collaboration with the field team which generated the data.

Quality control for laboratory tests

An external and internal quality control system was established for the various laboratory tests. The programme laboratory technologists of the National Institute for Medical Research

participated in the UK NEQUAS[7] scheme for diagnosis of syphilis and chlamydia infection in which specimens were received 'blind' from a central laboratory in the UK at regular intervals. The laboratory tested these specimens and reported the results back to the central laboratory which sent a critical assessment soon afterwards.

A 10% sample of serological tests performed at NIMR were retested at BMC. For the HIV ELISA tests, a 10% sample of negative sera were retested in the same laboratory, without the technologist being aware that these specimens had been tested already. HIV positive sera were checked using the procedure described in section 5.4.4. A 20% sample of Gram stain specimens were re-read for the diagnosis of *Neisseria gonorrhoeae*. NG cultures were read by a technologist, but regularly checked by the microbiologist and the senior laboratory technician.

5.4.9 Data processing and analysis

Equipment and software used

All data entry and processing were performed at NIMR in Mwanza using IBM compatible computers. EpiInfo (Division of Surveillance and Epidemiology, Centers for Disease Control and Prevention, Atlanta, Georgia, USA) and dBaseIII (Ashton-Tate Corporation, Torrance, California, USA) software packages were used for data management. Analyses were carried out in Mwanza and London, using the Egret (Statistics and Epidemiology Research Corporation, Seattle, Washington, USA) and Stata (Stata Corporation, College Station, Texas, USA) statistical computer packages.

Analysis of HIV impact data

Statistical analysis had to take account of the fact that the unit of randomisation was the community rather than the individual study participant. In principle, the outcome of interest was studied in twelve entities only, and this required the use of statistical methods designed for small numbers of observations. Statistical inference also needed to take account of the variation in HIV

[7] NEQUAS = National Ensurance of Quality Scheme

incidence between communities. Lastly, the matched design needed to be accounted for in the choice of analytical method.

The following procedure was chosen:

1. For each community, the HIV incidence for the 2-year follow-up period was calculated by relating the number of new infections to the number of persons who were HIV-negative at baseline and who were seen at both surveys.

2. The relative risk (RR) of HIV incidence in the intervention community relative to the comparison community was computed separately for each matched pair. A point estimate for the overall RR was calculated as the geometric mean of the six pair-specific RRs. Significance was assessed using the paired t-test on the logarithms of the pair-specific RRs, and the corresponding 95% confidence interval was computed.

3. To obtain an alternative assessment of statistical significance, the non-parametric Wilcoxon sign test was applied.

4. These calculations were done both on crude RRs and after adjustment for possible confounding factors. The adjustment was achieved through logistic regression using data on the individual study participants and by fitting a model which included terms for the matched pair, age group, sex, circumcision in men, travel out of village during the 2-year follow-up period, reported history of STD (ever) at baseline and the community-specific baseline prevalence of HIV infection.

Analysis of STD impact data

Similar analytical methods were used to assess impact on STDs. Relative risks were computed based on prevalences or incidences of STD markers as appropriate. For the adjusted analysis, terms for the community baseline prevalences of the STD under investigation were included in the logistic regression model .

5.5 Ethics

5.5.1 Ethical considerations

Intervention methodology

The syndromic management of STDs implies by definition that most patients are overtreated with the antibiotic drugs prescribed according to the treatment algorithm. In some cases, drugs may cause side effects. The syndromic algorithms used in Mwanza followed WHO guidelines. Drugs were chosen which rarely lead to serious side effects.

Trial design

The intervention was provided to the comparison communities only at the end of the trial, two years after the baseline survey. However, the intervention was launched in additional communities, other than those participating in the trial, and the capacity of the programme to implement the intervention was fully utilised throughout the study and after the trial was completed.

Effective implementation of this type of intervention over a wide geographical area necessitates a phased introduction. The trial exploited this fact by randomising the implementation scheme in such a way that valid comparisons would be made between communities in which the intervention was introduced at an early stage, and matched communities in which it started later.

The ongoing AIDS control efforts of the NACP of Tanzania, launched through the District AIDS Control Coordinator and through public mass media, continued unchanged in both intervention and comparison communities. STD treatment was not withheld in the comparison communities, but continued as before. The services available in the comparison communities were similar to those in many other parts of Tanzania, and in other African countries.

HIV testing

The trial followed the Tanzanian government guidelines on anonymous HIV testing. Health workers and investigators were not aware of the results of individual participants. Linkage of survey results was done using code numbers, and only the senior statistician had access to an electronic file linking these numbers with names. This file was kept in conditions of strict secrecy.

Individuals who wished to know their HIV status received pre-test counselling and a separate blood specimen was taken. The results were fed back to these individuals through a member of the district health management team, after post-test counselling.

All individuals who agreed to provide a blood sample had the immediate benefit of a serological test for syphilis and treatment if necessary.

Other examinations and laboratory tests

In the main cohort survey, for logistical reasons, it was not possible to feed back results of microbiological investigations to the individual patient. However, all symptomatic patients and men with a strongly positive LED test (grades 2+ and 3+) were treated automatically using the syndromic algorithms. Through this procedure, most patients in whom a gonococcal or chlamydial infection was discovered later, would already have been adequately treated

Cross-sectional study of STD patients with incomplete follow-up

Patients with a recently treated STD had to be confident that home visits performed by field workers did not disclose this fact. This was achieved by including patients with other illnesses in the survey. Furthermore, the public was informed that the survey aimed at an evaluation of health services in general and of AMREF's programme in particular, rather than at the health status of individuals.

Health workers had to be confident that the survey would not undermine their authority. The objectives of the survey and the questionnaire were carefully explained to them. They did not participate in the field work, but were involved in the negotiations with the community prior to the survey. Again, emphasis was laid on the fact that the survey was aimed at an evaluation of the programme rather than at an assessment of health workers' personal performance.

Sexual behaviour surveys

The most important aspect was to ensure strict confidentiality. This was achieved by careful selection and training of interviewers who had the skills and natural authority to facilitate a confidential interview situation and to make the study participants feel comfortable with the questions.

Antenatal clinic studies

All clinical or laboratory investigations were of direct benefit to the women participating, as current infections were treated either on the spot, or within two weeks if an asymptomatic infection was discovered through laboratory tests.

5.5.2 Ethical approval

Ethical approval for the trial including the supplementary studies was obtained from the Ministry of Health of Tanzania, and from the ethics committee of the London School of Hygiene and Tropical Medicine. Approval was also obtained from the Tanzanian Institute for Health and Technology, and from the Director General of the National Institute for Medical Research.

The trial was explained in detail to all the regional and district authorities concerned and to local community leaders who gave their approval. Informed verbal consent was obtained from each participant after careful explanation of the study. On advice from the Tanzanian authorities, study participants were not asked to sign a consent form, but a written declaration was signed instead by the field workers who performed the interviews.

Chapter 6 Results

6.1 Operational performance of the intervention

6.1.1 Training of health workers

During the three years of the programme, 16 basic training courses and 5 refresher courses were conducted. The capacity was used for the training of health workers from the intervention communities, from health facilities outside the trial area and, mainly during the third year, from comparison communities (Table 6.1).

Table 6.1 Summary of training courses during the trial period

Year	No. full courses	No. of HWs trained			Total no. of HWs trained	No. refresher courses	Total no. of HWs trained
		Intervention communities	Other health facilities	Comparison communities			
1	6	52	38[1]		90		
2	4	6	50[2]	8[3]	64	3	66
3	6	8	51[2]	48	107	2	44
Total	16	66	139	56	261	5	110

[1] mainly staff from reference clinics and survey clinicians
[2] mainly staff from health facilities in Mwanza town and outside of the region
[3] by end of year 2, in preparation of intervention in comparison communities

6.1.2 Syndromes treated

In the 6 intervention communities, 6 health centres and 20 dispensaries participated in the programme. During the first year, services at one of the dispensaries were discontinued for disciplinary reasons. Data were compiled from the 25 health facilities which participated throughout the 2-year trial period.

Overall, 11,632 STD syndromes were recorded (table 6.2), with almost equal numbers in men and women. A few patients had more than one syndrome. In men, urethral discharge was the

commonest syndrome accounting for two thirds of all cases, followed by genital ulcers in about a quarter of the total. Half of the women sought treatment for vaginal discharge, a third presented with lower abdominal pain and tenderness, and about 10% with genital ulcers. 8899 persons reported with genital discharge and/or genital ulcers.

Table 6.2: Attendance rates and distribution of STD syndromes over 2 years recorded at 25 intervention health facilities in Mwanza Region

STD syndrome	Men		Women	
N = 11,632	N =5,466	47%	N=6,166	53%
Genital discharge syndrome	3662	67 %	3046	49 %
Lower abdominal pain[1)]			2226	36 %
Genital ulcer syndrome	1489	27 %	745	12 %
Buboes without ulcer	164	3 %	31	0.5 %
Other syndromes[2)]	151	3 %	118	2 %
Patients with discharge and/or ulcers	5138	94 %	3761	61%
Patients with more than one syndrome	55	1 %	123	2 %

[1)] Treated as pelvic inflammatory syndrome
[2)] Men: Balanitis, suspected secondary syphilis, genital warts, epididymitis, pubic lice
Women: Suspected secondary syphilis, genital warts, pubic lice; detailed breakdown for other syndromes not available

6.1.3 Treatment effectiveness at health units

During the 2 years of follow-up, data on treatment effectiveness were collected for genital ulcer, urethral discharge and vaginal discharge syndromes from health facilities in the intervention communities. Outcomes were recorded for syndromes rather than patients.

A complete follow-up assessment was available for only 33% of the 8942 ulcer or discharge syndromes treated (table 6.3).

The great majority of these syndromes were clinically cured after 1st line treatment. Some required 2nd or occasionally even 3rd line treatment. Patients with genital ulcer syndromes were more likely to be given 2nd or 3rd line treatment than patients with discharge syndromes. Definite treatment failure was observed in one case of urethral discharge and 2 cases of genital ulcers, all in men. Outcomes for patients who were referred are reported in section 6.1.6.

Table 6.3: Clinical treatment effectiveness for genital ulcer and genital discharge syndromes (GUS and GDS) summarised over two years

	Men				Women			
Syndrome	GUS N=1489		UDS N=3662		GUS N = 745		VDS N=3046	
Assessment completed*)	N 389	26 %	N 1177	32 %	N 235	32 %	N 1136	37 %
of these:								
cured after 1st line trmt.	324	83 %	1153	98 %	191	81 %	1087	96 %
cured after 1st-3rd line	381	98 %	1161	99 %	233	99 %	1104	97 %
definite trmt. failure	2	0.5%	1	0.1%	0	--	0	--
referred	6	1.5%	15	1.3%	2	0.8 %	32	3 %

*) total number of syndromes for which a definite outcome is known.
Possible outcomes were: cured, definite treatment failure, referred.
GUS = genital ulcer syndrome, UDS = urethral discharge syndrome, VDS = vaginal discharge syndrome

6.1.4 Partner notification

Patients were routinely requested to notify their partners, using a contact information card. However, the treatment of a sexual partner was recorded for only 35% of genital ulcer or discharge syndromes in men and for only 33% of these syndromes in women, (table 6.1.4). The treatment of 2 partners was recorded for only 0.5% of the patients. Treatment of more than two partners was never observed.

Table 6.4: Success of partner notification

	Men		Women	
Syndrome	GUS N=1489	UDS N=3662	GUS N = 745	VDS N=3046
Partners treated	432 (29%)	1353 (37%)	255 (34%)	997 (33%)

6.1.5 Condom promotion

Health unit staff were trained to routinely promote and offer condoms to STD patients. However, only 83 (0.9%) of the 8899 patients with genital ulcers or discharge were recorded as accepting condoms.

6.1.6 Follow-up of referred cases

During the 2 years of follow-up, 97 STD patients (55 patients with GDS/GUS) were referred, most of them from dispensaries to health centres, and some from dispensaries or health centres to hospitals including the STD reference clinic.

Only 25 patients (26%) reported to the unit to which they had been referred. The others could not be traced, even at alternative health units. Among these 25 patients, complete outcome assessment was possible in only 5 patients (who were cured). The rest were lost to follow-up after one visit.

6.1.7 Treatment effectiveness and re-infections in non-returners

567 STD patients were eligible for the study of non-returners, 249 men and 318 women. 367 (65%) of these patients could be traced at their homes, 164 men (66% of the eligible men) and 203 women (64%).

The following reasons for non-participation were recorded: wrong address or name (45%), travelling (28%), moved to another village (16%), village inaccessible because of heavy rains (11%), died (0.5%), and refused to participate (0.5%). These reasons were similar in men and women. Non-participants did not differ significantly from participants with respect to type of syndrome or type of treatment received.

The 367 STD patients had presented with 389 syndromes, and had been treated at the intervention health facilities with 1st line treatment (90%), 1st and 2nd line treatment (8%), or 1st, 2nd and 3rd line treatment (2%). After treatment, 240 (62%) of the syndromes were

clinically cured, a further 107 (28%) had been free of symptoms for some time, but were symptomatic again at the time of the survey, and 42 (11%) had not observed any improvement. Among the 28% with recurrence of symptoms, it was not possible to distinguish between those who had genuinely been cured (reinfection) and those who had not been cured but been temporarily asymptomatic (recurrence of symptoms).

To facilitate comparison with the clinical outcomes for the main syndromes reported above for patients with complete follow-up (table 6.3), a breakdown of these findings by sex and main syndrome is given in table 6.5. The overall treatment failure rate for GUS and GDS was 11%. The reported rate of reinfection or recurrence of symptoms was very high, particularly in women, and in most of these cases signs were confirmed on clinical examination.

Table 6.5 Treatment effectiveness for genital ulcer syndrome and genital discharge syndrome based on a survey of STD patients who did not return for follow-up

	Men				Women			
Syndrome Treatment result reported by patients	GUS N=64		GDS N=89		GUS N = 42		GDS N=97	
Cured and no recurrence	52	81%	62	69%	22	52%	51	53%
Reinfection or recurrence of symptoms	9	14%	20	23%	11	26%	34	35%
Not cured	3	5%	7	8%	9	21%	12	12%
Present signs confirmed by clinician	12	19%	22	25%	21	50%	52	54%

6.1.8 Performance of health workers

The study of non-returners was conducted primarily to establish likely cure-rates in this group, but was also used to collect some data on the performance of health workers.

Study participants were interviewed regarding various steps in the provider-patient interaction. The results are listed in table 6. There were no significant differences between the results for different syndromes (data not shown).

Table 6.6 Performance of health workers

	Men N=164		Women N=203		Total N=367	
Patient was examined	114	70%	158	78%	272	74%
Patient received health education	98	60%	110	54%	208	57%
Condoms were offered	73	45%	38	19%	111	30%
Patient received correct treatment	114	70%	117	58%	231	63%
Patient reported full compliance	157	96%	183	90%	340	93%
Patient was satisfied with service	141	86%	164	81%	305	83%

The category 'patient received correct treatment' was assumed if on demonstration of the various drugs available in the programme, the patient pointed at the correct type of drug(s) and recalled the correct dose, or if he/she pointed at the correct type of drug(s) but was not sure about how many tablets he/she should have taken.

As described in the Methods section, examination, health education, condom promotion and the correct syndromic treatment had been intensively emphasised during training courses and supervision visits. All of the above parameters showed results below expectations. The low rate of reported condom promotion among women is particularly worrying. Information on the type and number of drugs received is probably not reliable, but gives rise to concern.

Thirty-three patients (9%) reported that they were asked to pay for the services, although services at primary care level in Tanzania are officially free of charge. All of them paid. The sums involved ranged from the equivalents of US $ 0.40 to $ 6.80 per patient. Fees reported by patients with other diseases ranged from $ 0.02 to $ 2.00.

The proportion of patients in the different communities reporting that they were satisfied with the services at the health unit ranged from 81 to 86 % in STD patients and 59 to 77% in patients with other diseases. Data for men and women were similar.

6.1.9 Monitoring of STD aetiologies at the STD reference clinics

The pattern of STD aetiologies was intermittently monitored at the STD clinic of Sekou Toure Hospital and at the Makongoro ANC Clinic in Mwanza town.

During 1993 and 1994, 3143 patients were seen at the STD reference clinic of Sekou Toure hospital (Philippe Mayaud, personal communication). 25% of these were men presenting with urethral discharge, 39% women complaining of vaginal discharge and 13% women presenting with suspected pelvic inflammatory disease. 14% of the patients presented with genital ulcers, two-thirds of whom were men. 8% of the patients presented with various other complaints.

During different periods, between 55 and 870 consecutive patients with GDS and between 100 and 200 consecutive patients with GUS were sampled, to determine STD aetiologies. The aetiologic pattern for men complaining of urethral discharge was: *Neisseria gonorrhoeae* 40 - 60%, *Chlamydia trachomatis* 5 - 15%, *Trichomonas vaginalis about* 2%, *Candida albicans about 2%* and non-specific urethritis 5 - 15%. Multiple infections occurred in about 20%. In 20 - 35% of the men no aetiology could be demonstrated.

The aetiologies found in women presenting with vaginal discharge included *Trichomonas vaginalis* 20 - 30%, *Candida albicans* 35 - 40%, Bacterial vaginosis 35 - 40%, *Neisseria gonorrhoeae* 5 - 10%, and *Chlamydia trachomatis* about 5%. Multiple infections occurred in 30 - 40%. In 20 - 25 % of the women, no aetiology could be found.

In genital ulcer patients, *Herpes simplex* virus type-2 was clinically suspected in up to 42 %, but could be demonstrated in only 5 - 10%. *Haemophilus ducreyi* was suspected in 20 - 55%, but the infection was proven in 20 - 25%. Syphilis was suspected in 20 - 30%, but a positive dark field result was obtained in only 4%, whereas TPHA+/RPR+ serology was observed in 40 - 50%, but partly in combination with other aetiologies. Mixed infections seemed to occur in 10 - 20 %. In 40%, no aetiology could be demonstrated. There was one man with lymphogranuloma venereum (LGV). None of the patients had donovanosis.

These data supported the effectiveness of the syndromic algorithms chosen for the intervention trial.

6.1.10 Monitoring of antibiotic sensitivity of *Neisseria gonorrhoeae*

The sensitivity of *Neisseria gonorrhoeae* was monitored at yearly intervals to ensure that the drugs chosen for the treatment of gonorrhoea (trimethoprim-sulfamethoxazole, ciprofloxacin) were effective. Monitoring was performed at the reference clinics, as it was not possible to obtain antibiograms from rural health units. The sensitivity was also determined for some drugs prescribed for the treatment of urethral discharge by private providers in Mwanza town (tetracycline, spectinomycine) or by health workers in comparison communities (tetracycline, penicillin) of for those recommended by WHO as alternative options for the treatment of *Neisseria gonorrhoeae* (ciprofloxacin, cephalosporines, spectinomycin) (WHO 1994). Results of this surveillance for 1992 are shown in table 6.7. To give an impression of the changes occurring over time, data for 1996 are shown for comparison.

Intermediate susceptibility to trimethoprim-sulfamethoxazole, the drug in use for 1st line treatment, was found in around 60% of the gonococcal strains. However, at the dose levels used in the treatment algorithms for genital discharge, 96% of the strains were sensitive in 1992. Sensitivity deteriorated slowly, but 90% were still sensitive in 1996. Ciprofloxacin, the drug available for 3rd line treatment, remained fully effective throughout, and the algorithms were not changed therefore.

Table 6.7: Antimicrobial sensitivity of Neisseria gonorrhoeae in 1992 and 1996 (West 1995 et al, and West. personal communication)

	Sensitivity[*)]		
Antimicrobial	*sensitive*	*intermediate*	*resistant*
Penicillin	24% (7%)	26% (33%)	50% (60%)
Tetracycline	5% (0%)	60% (4%)	35% (96%)
TMP-SMX	35% (28 %)	61% (62%)	4% (11%)
Spectinomycin	100% (97 %)	0% (3%)	0%
Azithromycin	100% (100%)	0%	0%
Cefotaxime	100% (100%)	0%	0%
Cefuroxime	100% (100%)	0%	0%
Ciprofloxacin	100% (100%)	0%	0%

*) N=130 strains in 1992; N= 138 strains in 1996; data from 1996 in brackets
TMP-SMX = trimethoprim-sulfamethoxazole

Resistance to penicillin and tetracycline was observed in the majority of gonococcal strains, and increased steeply over time. Their continued use for urethral discharge by other providers in Mwanza town is clearly inappropriate .

6.11 Contamination between intervention and comparison communities

Of the 11,632 syndromes treated at intervention health units, records showed that the patients were residents of comparison communities in only 59 (0.5%) cases. Of these, 45 came from the island comparison community, and had visited the corresponding intervention community within the archipelago, probably in the context of their professional activities (fishing, trading).

6.2 Main cohort: study population

6.2.1 Coverage at baseline and completeness of follow-up

12,537 adults aged 15 - 54 years were enrolled to the study cohort during the baseline survey, representing 85% of eligible individuals in the selected clusters. The great majority of non-attenders were on a journey away from the community, and the coverage was similar in intervention and comparison communities (data not shown).

At follow-up after 2 years, 8845 (71%) cohort members were seen again (table 6.8). Losses to follow-up were 29%, and coverage was similar in men and women, and in intervention and comparison communities.

Reasons for non-participation were also similar in the intervention and comparison arms (table 6.9), except for the category of 'other reasons' which occurred more frequently in the intervention communities. There were two explanations for this discrepancy: (i) at the beginning of the follow-up study, field workers did not record correctly some of the reasons for non-participation in one of the communities; (ii) heavy and long-lasting rainfall made parts of one intervention community inaccessible for several weeks towards the end of the follow-up survey.

Table 6.8 Main cohort study: numbers recruited to cohort, and coverage at follow up

	Intervention	Comparison	Total
Men			
Recruited at baseline	2881	2998	5879
Seen at follow-up	2052	2187	4239
Coverage	71 %	73 %	72 %
Women			
Recruited at baseline	3261	3397	6658
Seen at follow-up	2243	2372	4606
Coverage	69 %	70 %	69 %
Total			
Recruited at baseline	6142	6395	12537
Seen at follow-up	4286	4559	8845
Coverage	70 %	71 %	71 %

Very few persons refused to participate in the follow-up survey. The great majority of the losses to follow-up comprised cohort members who had moved permanently out of the community or who were temporarily absent during the time of the survey.

Table 6.9 Main cohort study: reasons for loss to follow-up

	Intervention		Comparison		Total	
Recruited at baseline	6142		6395		12537	
Losses to follow up:						
Moved out of village	814	13 %	924	14 %	1738	14 %
Temporary absence	291	5 %	459	7 %	750	6 %
Died	87	1 %	109	2 %	196	2 %
Other	664	11 %	344	5 %	1008	8 %
Total	1856	30 %	1836	29 %	3692	29 %

6.2.2 Baseline characteristics of the study population

The average ages of the men and women were 30.9 and 29.9 years, respectively. The male-to-female ratio was 1:1.13. 61% of the men and 68 % of the women were married. More men than women reported having had a school education of standard 4 or above (71% as compared to 47%). 80% of the men and 95% of the women reported farming as their main occupation.

About 19% of the men were circumcised. Female circumcision is not practised among the ethnic groups resident in Mwanza Region.

The baseline survey confirmed that STDs were highly prevalent in this population. 15% of the men and 6% of the women reported having suffered from a genital ulcer at least once in their life. For genital discharge, the corresponding figures were 28% and 8%. Blood tests performed during the baseline survey revealed a TPHA prevalence of 15% in men and 16% in women, indicative of past or present syphilis infection. 11% of the men had the laboratory signs of urethritis, and at least 2.8 % were infected with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*.

HIV test results were available for 12500 (99.7%) out of 12537 enrolled individuals (table 6.10). Overall seroprevalence was 3.7% (95% CI: 3.3 - 4.2%) in men and 4.4% (95% CI: 3.9-4.9%) in women. HIV prevalence was highest in the roadside communities (7.7%), moderate in lakeshore and rural communities (3.8%), and low in the two island communities (1.8%).

Peak prevalences were found in the 25-34 year age group for both sexes (men 5.7% and women 6.2%). Prevalence in women aged 15-24 years was more than twice that in men of the same age group (4.1% as compared to 1.8%). In contrast, prevalence in men aged 35-54 years was higher than in women of the same age (4.2% and 3.1% respectively).

Table 6.10 Main cohort study: HIV seroprevalence at baseline, by stratum, age and sex

Stratum/age	Men Total	HIV+	(%)	Women Total	HIV+	(%)	Overall Total	HIV+	(%)
Roadside									
15-24	309	11	(3.6)	343	25	(7.3)			
25-34	246	27	(11.0)	348	41	(11.8)			
35-44	175	14	(8.0)	210	14	(6.7)			
45-54	174	16	(9.2)	179	5	(2.8)			
Total	904	68	(7.5)	1080	85	(7.9)	1984	153	(7.7)
Rural/lakesh.									
15-24	1410	20	(1.4)	1766	68	(3.9)			
25-34	1170	63	(5.4)	1327	75	(5.7)			
35-44	705	33	(4.7)	732	28	(3.8)			
45-54	610	16	(2.6)	641	15	(2.3)			
Total	3895	132	(3.4)	4466	186	(4.2)	8361	318	(3.8)
Islands									
15-24	378	6	(1.6)	436	11	(2.5)			
25-34	300	7	(2.3)	294	6	(2.0)			
35-44	185	5	(2.7)	234	2	(0.9)			
45-54	195	1	(0.5)	133	1	(0.8)			
Total	1058	19	(1.8)	1097	20	(1.8)	2155	39	(1.8)
Overall									
15-24	2097	37	(1.8)	2545	104	(4.1)			
25-34	1716	97	(5.7)	1969	122	(6.2)			
35-44	1065	52	(4.9)	1176	44	(3.7)			
45-54	979	33	(3.4)	953	21	(2.2)			
Total	5857	219	(3.7)	6643	291	(4.4)	12500	510	(4.1)

6.3 Comparability of intervention and comparison communities

6.3.1 HIV prevalence

Baseline HIV prevalences in the intervention and comparison communities are shown in table 6.11. Prevalences in the intervention group were somewhat lower than in the comparison group, and were therefore adjusted for in the impact analysis on HIV incidence (see section 6.4.1). However, these differences were small both overall (3.7% versus 4.4%) and within each pair of communities. Imbalances between pairs were equally distributed: HIV prevalence was higher in the intervention community in three pairs, and in the comparison community in the other three pairs.

6.3.2 Prevalence of STDs

Distribution of confirmed laboratory diagnoses of STDs within the two groups are shown in table 6.12. Again, there was little difference between intervention and comparison communities.

TPHA test results were available for 12487 (99.6%) and RPR test results for 12437 (99.2%) of study participants. Prevalence of TPHA seropositivity (indicating past or present syphilis infection) was slightly higher in the intervention than in the comparison group (15.8% versus 15.1%). The prevalence of 'active' syphilis (TPHA+ and RPR+ combined) was identical in both groups (6.2%).

1569 (27%) men, who were LED test positive or who reported current symptoms were examined and swabbed. This procedure was used to establish minimum prevalences of urethritis, which were very similar in the two groups (10.2% versus 10.7%). Few men with urethritis reported symptoms, (but the minimum prevalence of symptomatic urethritis was again similar in the two groups (1.0% versus 1.2%). The minimum prevalence of infection with *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* was somewhat lower in intervention than in comparison communities (2.4% versus 3.2%).

6.3.3 Demographic characteristics and risk factors for HIV infection and STDs

With respect to demographic characteristics, there was little difference between intervention and comparison communities in age and sex distribution, marital status, educational level and occupation (table 6.13).

However, some factors known to increase the risk of HIV infection were not distributed equally (table 6.13). The proportion of men who reported ever having a genital discharge or ulcer was lower in intervention communities (31% versus 38%). In the comparison communities rather more individuals reported travelling outside their district during the past year, and this was particularly so in women (men 44% versus 49%; women 24% versus 35%). The proportion of men who were circumcised was lower in intervention communities (14% versus 23%).

With regard to sexual behaviour, comparability of the two trial groups could be assessed through the baseline sexual behaviour survey. Self-reported behaviour is always subject to recall bias; however, there was no reason to assume that this bias was differential between intervention and comparison communities. For both men and women, reported numbers of lifetime sex partners and of sex partners during the past year were similar in the intervention and comparison groups (table 6.14).

6.3.4 Result of matching and randomisation

In summary, the matching and randomisation procedure provided intervention and comparison groups that were generally similar at baseline with respect to HIV and STD prevalence and most of the factors known to increase the risk of HIV and STD transmission. However, some imbalances occurred for reported history of STDs (ever), travel away from the village and male circumcision. These variables were therefore adjusted for in the impact analysis. Adjustments were also made for the slight imbalances in baseline prevalences of HIV infection and STDs.

Table 6.11 Main cohort study: baseline prevalence of HIV infection by community, sex and trial arm, ordered by matched pairs

	Men						Women						Overall					
	Intervention			Comparison			Intervention			Comparison			Intervention			Comparison		
	N	HIV+	Prev. (%)	N	HIV+	Prev. (%)	N	HIV+	Prev. (%)	N	HIV+	Prev. (%)	N	HIV+	Prev. (%)	N	HIV+	Prev. (%)
Matched pair / stratum																		
1 rural	415	14	(3.4)	479	18	(3.8)	500	18	(3.6)	568	11	(1.9)	915	32	(3.5)	1047	29	(2.8)
2 islands	512	12	(2.3)	546	7	(1.3)	548	9	(1.6)	549	9	(1.6)	1060	21	(2.0)	1095	16	(1.5)
3 roadside	441	31	(7.0)	465	37	(8.0)	555	37	(6.7)	524	49	(9.3)	996	68	(6.8)	989	86	(8.7)
4 lakeshore	502	19	(3.8)	473	17	(3.6)	561	38	(6.8)	557	27	(4.9)	1063	57	(5.4)	1030	44	(4.3)
5 lakeshore	489	10	(2.0)	548	26	(4.7)	509	18	(3.5)	570	26	(4.6)	998	28	(2.8)	1118	52	(4.7)
6 rural	512	9	(1.8)	480	16	(3.3)	578	11	(1.9)	622	36	(5.8)	1090	20	(1.8)	1102	52	(4.7)
Overall	2871	95	(3.3)	2991	121	(4.1)	3251	131	(4.0)	3390	158	(4.7)	6122	226	(3.7)	6381	279	(4.4)

Table 6.12 Main cohort study: baseline prevalence of STDs by trial arm

	Intervention			Comparison		
	N	pos.	Prev. (%)	N	pos.	Prev. (%)
Syphilis serology[1]						
TPHA+	6115	968	(15.8)	6372	961	(15.1)
TPHA+/RPR>=1:8	6088	380	(6.2)	6349	391	(6.2)
Urethral infection in men						
LED test positive[2]	2846	728	(25.6)	2990	849	(28.4)
Urethritis[3]	2881	294	(10.2)	2998	321	(10.7)
Symptomatic urethritis[3]	2881	27	(1.0)	2998	36	(1.2)
NG and/or CT infection[3]	2881	69	(2.4)	2998	96	(3.2)

TPHA = Treponema pallidum haemagglutination assay
RPR = Rapid plasma reagin test; 1:8 = titre of RPR test
LED = Leukocyte esterase dipstick
NG = *Neisseria gonorrhoeae*, CT = *Chlamydia trachomatis*
Urethritis = NG and/ or CT infection and/or > 5 polymorpho-nuclear cells per high power field on microscopy

[1] TPHA missing for 27 individuals in intervention and 23 in comparison communities, TPHA/RPR missing for 54 individuals in intervention and 46 in comparison communities;
[2] LED test result missing for 35 men in intervention and 8 in comparison communities
[3] Prevalences of urethritis, symptomatic urethritis and NG/CT infection refer to men only, and are minimum prevalences (because men without symptoms or signs and with negative LED result were not swabbed

Table 6.13 Main cohort study: demographic characteristics and risk factors at baseline by sex and trial arm

	Men				Women			
	Intervention N = 2881		Comparison N = 2998		Intervention N = 3261		Comparison N = 3397	
Demographic characteristics	n	%	n	%	n	%	n	%
Age (years)								
15-24	1008	35%	1095	37%	1227	38%	1326	39%
25-34	851	30%	869	29%	975	30%	999	29%
35-44	533	19%	536	18%	588	18%	592	17%
45-54	489	17%	498	17%	471	14%	480	14%
Marital status								
married	1799	62%	1779	59%	2311	71%	2222	65%
single	819	28%	962	32%	434	13%	591	17%
separ./divor./widowed	263	9%	257	9%	516	16%	584	17%
Education [1]								
Standard 4 and above	1948	68%	2192	73%	1476	45%	1670	49%
Risk factors								
STD ever	903	31%	1147	38%	371	11%	435	13%
Used formal health sector for STD treatment [2]	692	77%	927	81%	200	54%	238	55%
Circumcision in men [3]	403	14%	686	23 %	NA		NA	
Travel outside district (past 1 year)	1255	44%	1482	49%	783	24%	1195	35%
Received blood transfusion (past 5 years)	20	0.7%	22	0.7%	88	3%	73	2%
Received injections (past 1 year)	927	32%	991	33%	1538	47%	1592	47%

[1] Data missing for 1 woman in comparison communities; [2] for cohort members reporting STD ever; [3] Data missing for 6 men in intervention and 5 men in comparison communities
NA not applicable

Table 6.14 Baseline sexual behaviour survey: numbers of sexual partners reported in intervention and comparison communities

	Men				Women			
	Intervention		Comparison		Intervention		Comparison	
No. of lifetime partners	N = 232[1]		N = 279[1]		N = 287[2]		N = 288[2]	
	n	%	n	%	n	%	n	%
0	2	1%	9	3%	9	3%	11	4%
1	16	7%	13	5%	80	28%	75	26%
2-4	42	18%	61	22%	136	47%	152	53%
5-19	101	44%	123	44%	54	19%	47	16%
20+	71	31%	73	26%	8	3%	3	1%
No. of partners past year	N = 237[3]		N = 281[3]		N = 297[4]		N = 299[4]	
	n	%	n	%	n	%	n	%
0	16	7%	27	10%	27	9%	29	10%
1	104	44%	100	36%	231	78%	247	83%
2	51	22%	69	25%	26	9%	19	6%
3-4	42	18%	62	22%	10	3%	4	1%
5+	24	10%	23	8%	3	1%	0	0%

Total number of survey participants: 1117, [1] data missing from 5 men in intervention and 2 in comparison communities, [2] data missing from 11 women in intervention and 13 in comparison communities. [3] no data missing; [4] data missing from 1 woman in intervention and 2 women in comparison communities; for further information on sexual behaviour survey see section 6.4.6

6.4 Impact of the intervention

6.4.1 Main cohort study: impact on HIV infection

HIV results were available at both baseline and follow-up for 8825 of the cohort members. These were 8825/8845 (99.8%) of all those seen at follow up. 276 (3.1%) were already HIV positive at baseline. HIV incidence calculations were therefore based on 8549 initially seronegative individuals, 4149 in intervention communities and 4400 in comparison communities.

Over the 2 years of follow-up there were 130 seroconversions in the cohort, 48 (1.16%) in the intervention group and 82 (1.86%) in the comparison group, equivalent to annual incidences of 0.58% and 0.93%.

HIV incidence varied considerably between matched pairs, but was consistently lower in the intervention community than in the comparison community in all matched pairs (table 6.15 and figure 6.1).

Table 6.15 HIV incidence over 2 years in intervention and comparison communities, and crude and adjusted relative risks

	HIV seroconversions				Relative risks	
	Intervention		Comparison		Crude [1] (95% CI)	Adjusted [2] (95% CI)
Matched pair / stratum						
1 rural	5/568	(0.9%)	10/702	(1.4%)	0.62	0.55
2 islands	4/766	(0.5%)	7/833	(0.8%)	0.62	0.62
3 roadside	17/650	(2.6%)	20/630	(3.2%)	0.82	1.07
4 lakeshore	13/734	(1.8%)	23/760	(3.0%)	0.59	0.54
5 lakeshore	4/732	(0.5%)	12/782	(1.5%)	0.36	0.43
6 rural	5/699	(0.7%)	10/693	(1.4%)	0.50	0.69
Overall	48/4149	(1.2%)	82/4400	(1.9%)	0.57 (0.42-0.76) p = 0.004*	0.62 (0.45-0.86) p = 0.013*

[1] Overall RR was calculated as the geometric mean of the RRs in matched pairs;
[2] Adjusted for age, sex, travel during follow-up period, history of STD (ever) at baseline, circumcision in men and baseline HIV prevalence; *paired t-test on logarithms of Rrs

The crude relative risk (RR) for seroconversion in intervention compared to comparison communities varied from 0.36 to 0.82. The overall crude RR, calculated as the geometric mean

of the RRs in the matched pairs, was 0.57 (95% CI 0.42-0.76, p=0.004). After adjustment for variables showing an imbalance between the two groups at baseline, the RR was 0.62 (95% CI 0.45-0.85, p=0.013). The unadjusted RR was equivalent to a reduction of HIV incidence in the intervention communities as compared to the comparison communities of 43%. For the adjusted analysis, the reduction was 38%. A non-parametric test (Wilcoxon sign test) gave similar results for both the unadjusted analysis and after adjustment for all factors except baseline HIV prevalence (two-sided p=0.03). This test was no longer significant (p=0.11) when a term for baseline HIV prevalence was included, as one of the six pairs showed an adjusted RR>1.

Seroconversion rates by age and sex are shown in table 6.16 and figure 6.2. The reduction in incidence was consistent for all age and sex groups. However numbers of seroconversions in each sex and age sub-group were small, and therefore most of the differences were not statistically significant. Regarding the differences in effect between age/sex groups, there was no significant interaction (test for interaction obtained by logistic regression, ignoring between-community variation: X^2 =2.69, 5 df, p=0.75).

In the comparison group, HIV incidence was highest in women aged 15-24 years and men aged 25-34 years. In the intervention group, the greatest reduction was observed in the same age and sex groups.

Table 6.16 HIV incidence over 2 years by sex and age groups in intervention and comparison groups, with crude and adjusted relative risks

	HIV seroconversions				Relative risks			
	Intervention		Comparison		Crude [1] (95% CI)	p	Adjusted [2] (95% CI)	p
Sex / age group								
Women								
15-24 years	8/721	(1.1%)	17/817	(2.1%)	0.53 (0.39-0.73)	<0.01	0.66 (0.47-0.92)	0.02
25-34 years	8/646	(1.2%)	11/666	(1.7%)	0.71 (0.27-1.88)	0.41	0.77 (0.28-2.12)	0.54
35-54 years	7/795	(0.9%)	8/793	(1.0%)	0.82 (0.45-1.49)	0.43	0.83 (0.46-1.48)	0.44
Men								
15-24 years	7/661	(1.1%)	13/760	(1.7%)	0.76 (0.37-1.54)	0.39	0.77 (0.39-1.51)	0.36
25-34 years	6/650	(0.9%)	15/611	(2.5%)	0.52 (0.27-1.01)	0.05	0.72 (0.49-1.08)	0.09
35-54 years	12/766	(1.6%)	18/753	(2.4%)	0.65 (0.21-2.02)	0.38	0.60 (0.23-1.60)	0.24

[1] The RR for each age/sex group was calculated as the geometric mean of the RRs in matched pairs;
[2] Adjusted for travel during follow-up period, history of STD (ever) at baseline, circumcision in men and baseline HIV prevalence.

Figure 6.1
Seroconversion over two years in the 6 matched pairs of intervention and comparison communities

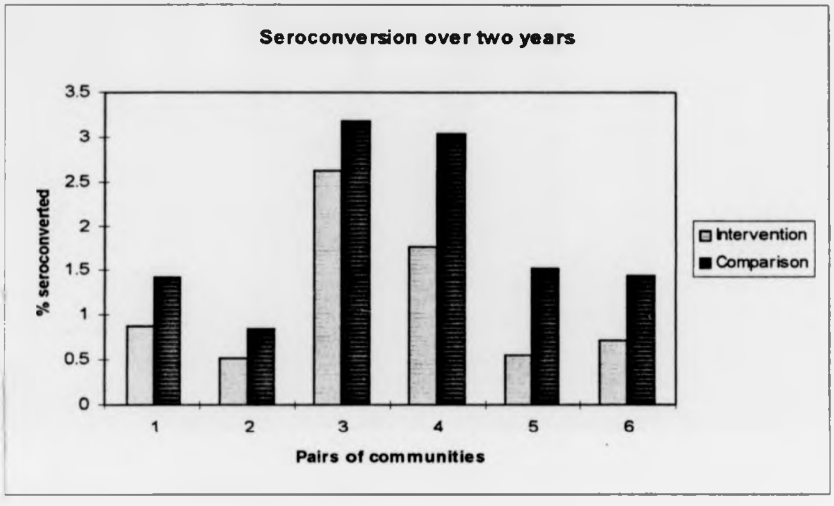
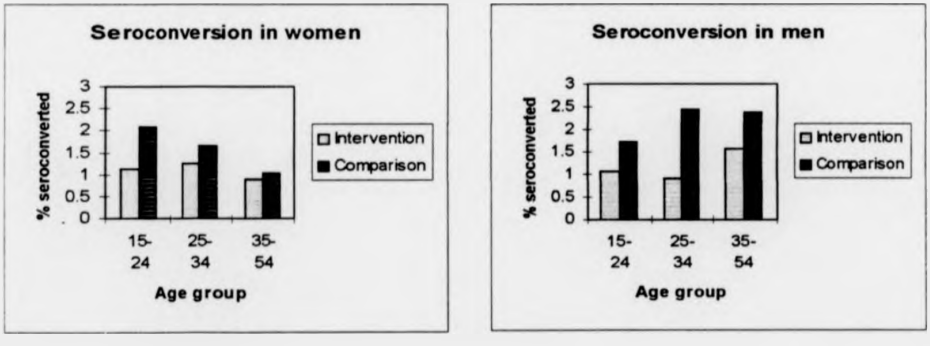


Figure 6.2
Seroconversion over two years by sex and age group, in intervention and comparison communities



6.4.2 Main cohort study: impact on self-reported STD symptoms

4239 men were seen at follow-up, 2052 in intervention communities and 2188 in comparison communities. Data are missing for 1 man from the comparison group. In intervention communities, 236 men (11.5%) reported a genital discharge or genital ulcer during the past year. The corresponding figure in comparison communities was 269 men (12.3%). The crude relative risk (RR) was 0.90 (95% CI: 0.51-1.59). After adjustment for imbalances including reported symptoms (ever) at baseline, the RR was 0.94 (95% CI: 0.57-1.56). The difference was not significant.

4606 women seen at follow-up, 2234 in intervention and 2372 in comparison communities. In intervention communities, 137 women (6.1%) reported a genital discharge or genital ulcer during the past year, and 155 women (6.5%) in comparison communities. The crude RR was 0.96 (95% CI: 0.54-1.72), and the adjusted RR was 1.00 (95% CI: 0.58-1.72). Again the difference was not significant.

6.4.3 Main cohort study: impact on serological syphilis

Availability of serological test results for syphilis

8845 cohort participants were seen at follow-up. Of these, 20 participants refused to give blood, and for a further 53 an unambiguous TPHA result could not be obtained. Thus a definite TPHA and RPR follow-up test result was available from 8772 (99.2%), with 4244 residing in intervention and 4528 in comparison communities. From these individuals, three overlapping categories could be formed, to study different aspects of syphilis serology (tables 6.17 and 6.18):

1. Persons who were TPHA negative at baseline: from the 8772 individuals, 1339 were deducted as they were TPHA positive at baseline and a further 11 as they had no TPHA result at baseline. This provided a group of 7422 persons, 3558 from intervention and 3864 from comparison communities, in whom the *seroincidence of TPHA* could be studied (table 6.17).

2. The whole group of 8772, that is all persons with a definite TPHA and RPR result, to study the follow-up *prevalence of active syphilis* (TPHA+, RPR+) at different titres and to compare it with the prevalence at baseline (tables 6.17 and 6.18).

3. Persons who were RPR negative at baseline: from the 8772 individuals, 709 were deducted who had a positive RPR result at baseline. This provided a group of 8063 persons to study the *prevalence of 'new cases of active syphilis'*, 3893 from intervention and 4170 from comparison communities (table 6.17).

Incidence of TPHA seroconversion

Over the 2 years of follow-up there were 266 seroconversions in the cohort, 108 (3.0%) in the intervention group and 158 (4.1%) in the comparison group, equivalent to annual incidences of 1.5% and 2.0% (table 6.17).

The crude relative risk (RR) was 0.70. After adjustment for factors showing an imbalance at baseline, and for the community prevalence of active syphilis at baseline, the RR was 0.64 (95% CI: 0.33-1.25). This represented a reduction of 36% in intervention compared with comparison communities, but the difference was not statistically significant at the 5% level (p=0.15).

Prevalence of active syphilis

Active syphilis was defined by a combination of a positive RPR and a positive TPHA test. The analysis was conducted using different RPR titres to define the cut-off for "positivity" (table 6.17).

The prevalence of seropositive cases at follow-up was lower in intervention than in comparison communities. For example, if a titre of >=1:8 was chosen as cut-off, the crude relative risk was 0.69 (95% CI: 0.46-1.05, p=0.07). After adjustment for factors showing an imbalance at baseline including baseline prevalence of active syphilis, the relative risk indicated a statistically significant reduction of 33% in the intervention communities (RR=0.67, 95% CI: 0.47-0.96, p=0.04).

Whichever titre was chosen, the prevalence was lower in intervention than in comparison communities, and the adjusted relative risks all showed a statistically significant reduction. The relative risk decreased with increasing titre, from 0.89 at a titre of >=1:2 to 0.54 at a titre of >=1:32. The latter result was equivalent to a reduction of 46%.

The prevalence of active syphilis varied considerably between matched pairs (table 6.18), but was almost always lower in intervention than in comparison communities. Taking an RPR titre >=1:8 again as an example, the prevalence was lower in the intervention community than in the comparison community in 5 of the 6 matched pairs, the RR ranging from 0.40 to 1.12 (table 6.1.8). After adjustment for factors showing an imbalance at baseline including baseline prevalence of active syphilis, the RRs indicated a reduction in all pairs, the RR ranging from 0.36 to 0.84. A non-parametric test (Wilcoxon sign test) gave results (p=0.11 for the crude, and p=0.016 for the adjusted RR) which were similar to those of the t-test.

Prevalence of new cases of active syphilis

An RPR titre of 1:8 or greater was chosen for the definition of a 'new active case'. At follow-up, there were 226 persons with positive results for both tests, who were previously RPR negative, 85 in the intervention group and 141 in the comparison group, representing prevalences of 2.2% and 3.4% respectively (table 6.17).

The crude relative risk was 0.60. After adjustment for factors showing an imbalance at baseline, and for the community prevalence of active syphilis at baseline, the RR was 0.56 (95% CI: 0.30-1.02), equivalent to a reduction of 44% in the intervention as compared to the comparison communities, a result of borderline significance (p=0.06).

Table 6.17 Serological markers for syphilis in intervention and comparison groups, with relative risks for results at follow-up

STD marker	Baseline prevalence		Follow-up incidence / prevalence		Relative risks (RRs)	
	Intervention	Comparison	Intervention	Comparison	Crude [1]	Adjusted [1,2]
					RR (95% CI) p[3]	RR (95% CI) p[3]
TPHA sero-incidence	968/6115 (15.8)	961/6372 (15.1)	108/3558 (3.0)	158/3864 (4.1)	0.70 (0.32-1.50) 0.28	0.64 (0.33-1.25) 0.15
Prevalence of:						
Active syphilis						
RPR>=1:2	536/6115 (8.8)	530/6372 (8.3)	452/4244 (10.7)	525/4528 (11.6)	0.90 (0.76-1.06) 0.15	0.89 (0.80-0.99) 0.03
RPR>=1:4	450/6115 (7.4)	455/6372 (7.1)	316/4244 (7.4)	428/4528 (9.5)	0.77 (0.60-0.98) 0.04	0.75 (0.62-0.91) 0.01
RPR>=1:8	382/6115 (6.3)	394/6372 (6.2)	214/4244 (5.0)	315/4528 (7.0)	0.69 (0.46-1.05) 0.07	0.67 (0.47-0.96) 0.04
RPR>=1:16	291/6115 (4.8)	299/6372 (4.7)	136/4244 (3.2)	224/4528 (4.9)	0.62 (0.38-1.02) 0.06	0.59 (0.39-0.90) 0.02
RPR>=1:32	200/6115 (3.3)	215/6372 (3.4)	91/4244 (2.1)	168/4528 (3.7)	0.56 (0.36-0.87) 0.02	0.54 (0.37-0.79) 0.01
New cases of active syphilis (RPR>=1:8)	NA	NA	85/3890 (2.2)	141/4168 (3.4)	0.60 (0.29-1.25) 0.13	0.56 (0.30-1.02) 0.06

[1] RRs were calculated as the geometric mean of the relative risks in matched pairs;

[2] adjusted for age, sex, travel during follow-up period, history of STD (ever) at baseline, circumcision in men and baseline prevalence of active syphilis;

[3] paired t-test on logarithms of relative risks

NA not applicable

Table 6.18: Prevalence of active syphilis (RPR titre >=1:8) by community pair at follow-up

	Prevalence of active syphilis at follow-up[1]		**Relative risks**	
	Intervention	Comparison	Crude [2] RR (95% CI) p[4]	Adjusted [2,3] RR (95% CI) p[4]
Matched pair / stratum				
1 rural	31/579 (5.4%)	52/712 (7.3%)	0.73	0.84
2 islands	7/777 (0.9%)	19/845 (2.2%)	0.40	0.36
3 roadside	43/678 (6.3%)	55/671 (8.2%)	0.77	0.86
4 lakeshore	43/762 (5.6%)	94/775 (12.1%)	0.47	0.56
5 lakeshore	47/744 (6.3%)	56/811 (6.9%)	0.91	0.79
6 rural	43/704 (6.1%)	39/715 (5.5%)	1.12	0.79
Overall	214/4244 (5.0%)	315/4529 (7.0%)	0.69 (0.46-1.05) p=0.07	0.67 (0.47-0.96) p=0.04

[1] defined as TPHA+, RPR+ (RPR titre >=1:8)

[2] overall RR was calculated as the geometric mean of the RRs in matched pairs;

[3] adjusted for age, sex, travel during follow-up period, history of STD (ever) at baseline, circumcision in men, baseline prevalence of active syphilis;

[4] paired t-test on logarithms of RRs.

6.4.4 Main cohort study: impact on urethritis in men

Of the 4239 men seen at follow-up, 1195 (28%) were eligible for taking urethral swabs, because they were LED test positive (1095), reported urethral discharge at the time of the interview without being LED test positive (66), or were found to have urethral discharge on an examination performed for other reasons (34). 1144 specimens were collected (96% of those eligible), with 29 refusals in the intervention and 22 in the comparison group. A further 6 men did not provide urine, so that it is not clear whether they were eligible for swabbing. The 3095 men from whom swabs were not taken were considered negative in the subsequent analysis; the results reported in this section therefore represent minimum prevalences.

The prevalences of different markers of urethral infection are shown in table 6.19. Observations at follow-up showed that the prevalence of urethritis, defined as the presence of *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT) infection and/or five or more polymorpho-nuclear cells per high power field in the Gram-stained sample, was lower in intervention than in comparison communities, but this difference was not significant.

The prevalence of symptomatic urethritis, defined as presence of biological markers as listed above plus urethral discharge reported either during the past year or reported present at the time of the interview, was lower in the intervention communities. After adjustment for factors showing an imbalance at baseline and for baseline urethritis prevalence, the relative risk was 0.51 for both parameters, equivalent to a halving in the prevalence of these symptomatic infections. The results were statistically significant at the 10% level ($p=0.06$ and $p=0.08$ respectively). The modest reduction in the overall prevalence of urethritis is mostly accounted for by the reduction in symptomatic cases. The prevalence of asymptomatic urethritis, calculated by deducting symptomatic cases from overall urethritis, shows little difference between intervention and comparison communities (4.2% versus 4.5%).

The prevalence of infection with NG/CT was also lower in the intervention communities, both for symptomatic and asymptomatic infections, but numbers of infections were very small especially for symptomatic NG/CT infections, and the differences were not statistically significant. The crude relative risks reflected a reduction, but this was no longer observed after adjustment for factors showing an imbalance at baseline including baseline prevalence of NG/CT.

Table 6.19: Prevalences of urethral infections in men in intervention and comparison groups, with relative risks

STD parameter	Baseline prevalence		Follow-up prevalence		Relative risks				
	Intervention	Comparison	Intervention	Comparison	Crude [1]			Adjusted [2]	
					RR (95% CI)	p[6]		RR (95% CI)	p[6]
Urethritis [3]	294/2881 (10.2)	321/2998 (10.7)	119/2052 (5.8)	152/2187 (7.0)	0.84 (0.31-2.26)	0.68		0.92 (0.53-1.61)[4]	0.73
Symptoms past year	39/2881 (1.4)	52/2998 (1.8)	37/2052 (1.8)	70/2187 (3.2)	0.48 (0.20-1.01)	0.06		0.51 (0.25-1.03)[4]	0.06
Symptoms now	27/2881 (1.0)	35/2998 (1.3)	32/2052 (1.6)	54/2187 (2.5)	0.48 (0.25-1.03)	0.07		0.51 (0.24-1.10)[4]	0.08
NG and/or CT infection	69/2881 (2.4)	96/2998 (3.2)	52/2052 (2.5)	66/2187 (3.0)	0.68 (0.27-1.68)	0.32		0.95 (0.49-1.83)[5]	0.84
Symptoms past year	13/2881 (0.4)	18/2998 (0.7)	21/2052 (1.0)	33/2187 (1.5)	0.48 (0.09-2.39)	0.29		1.12 (0.45-2.77)[5]	0.77
Symptoms now	8/2881 (0.3)	14/2998 (0.5)	19/2052 (0.9)	26/2187 (1.2)	0.60 (0.14-2.63)	0.41		1.29 (0.54-3.07)[5]	0.48

NG = *Neisseria gonorrhoeae*; CT = *Chlamydia trachomatis*

[1] RRs were calculated as the geometric mean of the relative risks in matched pairs

[2] adjusted for age, community pair, travel during follow-up period, history of STD (ever) at baseline, circumcision

[3] defined as NG and/or CT infection and/or >5 polymorpho-nuclear cells in microscopy from urethral swab

[4] also adjusted for overall baseline prevalence of urethritis (symptomatic and asymptomatic)

[5] also adjusted for overall baseline prevalence of NG and/or CT infections (symptomatic and asymptomatic)

[6] paired t-test on logarithms of relative risks

6.4.5 Studies in pregnant women: Impact on STDs in ANC attenders

Study population and coverage

For the two cross-sectional studies performed on pregnant women, the target was to recruit 100 women from each of the 12 antenatal clinics in the intervention and comparison communities.

During the first survey, a total of 1149 women were enrolled. Of these, eight (0.7%) refused to be examined, and were excluded from the analysis. Of the remaining 1141 women, 575 were from intervention and 566 from comparison communities. Mean age was 25.0 years in both groups.

During the second survey, 1239 women were recruited, all of whom agreed to be examined. 614 resided in intervention and 625 in comparison communities. Their mean ages were 25.0 and 24.9 years respectively.

Prevalence of STDs

In both groups of communities, and in both surveys, a very high proportion of the women suffered from an STD (table 6.20): At baseline, 8.4% of women were infected with *Neisseria gonorrhoeae* (NG) and/or *Chlamydia trachomatis* (CT), 28.6% with *Trichomonas vaginalis* (TV), and 8.0% had active syphilis (TPHA+, RPR+ titre >=1:8). 448/1141 (39.3%) had at least one of these STDs. During the second survey, the corresponding prevalences were: 6.6%, 24.6%, 6.6% and 412/1239 (33.3%).

Only 17% of the women with NG and/or CT infection complained about discharge when asked about symptoms before they were examined. These proportions were similar in intervention and comparison communities and in both surveys, and did not differ significantly from women with active syphilis or those who were free of infection (18% and 16% respectively reported having discharge). 26% of the women with TV complained about discharge. When vaginal itching was included in the symptoms indicating a possible STD infection, the proportion of women who complained about discharge or itching was 42% among those with NG/CT, 55% among those with TV, 49% among those with active syphilis, and 38% among those with no infection.

The results for the intervention and comparison communities are compared in table 6.20. There was no significant difference between intervention and comparison groups in the prevalence of any of the STD markers investigated, at either survey. The same was true when different titres for RPR were used to define RPR positivity (data not shown). There was an overall trend for a decrease of STDs in both trial groups, when comparing the data between the two cross-sectional surveys.

6.4.6 Impact on sexual behaviour

Study population and coverage

For the baseline sexual behaviour survey, a random sample of 1 in 8 of the main cohort was selected from each community. 1498 persons were eligible, and 1117 (75%) were interviewed, 535 from intervention and 582 from comparison communities. Only 7 people (1.8%) refused to be interviewed. The main reasons for non-participation were that subjects had moved away from the village since the baseline survey (38%) or were travelling at the time the sexual behaviour survey was conducted (21%). A further 10% were excluded on the basis of doubts as to the correct identity of the individual, 10% could not be traced, 2% had died, and 17% were excluded for other reasons. The numbers and the reasons for non-attendance were similar in intervention and comparison groups (data not shown).

The age and sex distribution of the study population was very similar to that of the main cohort from which the sample was taken.

For the follow-up sexual behaviour survey, a random sample of 1 in 8 was selected from each community, from all those seen at the cohort follow-up survey. 1106 persons were eligible, of whom 987 (89%) were interviewed, 464 from intervention and 523 from comparison communities. Nobody refused to be interviewed. Again, having moved away (35%) and temporary absence (51%) were the main reasons for non-participation, 0.5 % had died and 13% could not be traced. The coverage was higher than previously because the second survey was conducted much sooner after the corresponding survey in the main cohort (average delay 5

months versus 9 months). Again the coverage and reasons for non-participation were similar in both groups.

Sexual behaviour

Data from the baseline sexual behaviour survey are shown in table 6.14. As described in section 6.3.3, reported numbers of lifetime sexual partners and partners during the past year were similar in intervention and comparison groups.

At the follow-up sexual behaviour survey, the numbers of partners reported for the past year were still similar in the two trial groups, and had not changed substantially since the baseline sexual behaviour survey (table 6.21).

Various other parameters of sexual behaviour studied at follow-up did not show any material difference between intervention and comparison communities (table 6.21), including reported sexual intercourse in the presence of STD symptoms, or the use of condoms with casual partners. Some people reported occasional condom use with such partners, but overall condom use was low. Only 3 people (0.3%) reported regular use of condoms, and only 11 (6%) persons of 197 with an STD reported condom use whilst they had the infection.

Table 6.20: Prevalence of STD markers in intervention and comparison groups in two cross-sectional surveys of ANC attenders, with relative risks for the second survey, conducted about 18 months after start of the intervention in the intervention communities

	Prevalences at first ANC survey		Prevalences at second ANC survey		Relative risks for second survey	
STD marker	Intervention N=575	Comparison N=566	Intervention N=614	Comparison N=625	Crude [1] (95% CI)	Adjusted [1,2] (95% CI)
NG and/or CT infection[3]	34/486 (7.0)	47/478 (9.8)	41/614 (6.7)	41/625 (6.6)	0.91 (0.48-1.73)	0.93 (0.49-1.75)
TV infection	164/575 (28.5)	162/566 (28.6)	156/6144 (25.4)	145/625 (23.2)	1.08 (0.92-1.28)	1.09 (0.92-1.28)
Active syphilis[4]	44/575 (7.7)	47/566 (8.3)	42/614 (6.8)	40/625 (6.4)	1.08 (0.68-1.73)	1.08 (0.66-1.79)
Any STD[5]	215/575 (37.4)	233/566 (41.2)	210/614 (34.2)	202/625 (32.3)	1.11 (0.88-1.39)	1.07 (0.79-1.43)

NG = *Neisseria gonorrhoeae*; CT = *Chlamydia trachomatis*; TV = *Trichomonas vaginalis*

[1] RRs were calculated as the geometric mean of the relative risks in matched pairs

[2] adjusted for age

[3] NG/CT diagnosis during the first survey was based on n=964 only, because 177 gonococcal cultures were contaminated

[4] defined as TPHA+ / RPR+ , RPR titre of >=1:8

[5] defined as any of NG, CT, TV or active syphilis

Table 6.21: Results of follow-up sexual behaviour survey

Self-reported sexual behaviour	Men		Women	
	Intervention	Comparison	Intervention	Comparison
No. of partners past year	N = 213	N = 263	N = 246	N = 249
0	10 (5%)	10 (4%)	25 (10%)	26 (10%)
1	90 (42%)	120 (46%)	199 (81%)	187 (75%)
2	58 (27%)	67 (26%)	17 (7%)	29 (12%)
3-4	39 (18%)	51 (19%)	4 (2%)	6 (2%)
5+	16 (8%)	15 (6%)	1 (0.4%)	1 (0.4%)
No. of casual partners past 2 years	N = 213	N = 264	N = 245	N = 248
0	133 (62%)	146 (55%)	218 (89%)	215 (87%)
1	29 (14%)	44 (17%)	14 (6%)	18 (7%)
2	21 (10%)	30 (11%)	7 (3%)	7 (3%)
3+	30 (14%)	44 (17%)	6 (2%)	8 (3%)
Reported being faithful to spouse	N = 216	N = 268	N = 248	N = 255
very faithful	69 (32%)	83 (31%)	119 (48%)	118 (46%)
quite faithful	82 (38%)	105 (39%)	74 (30%)	67 (26%)
not faithful	20 (9%)	19 (7%)	5 (2%)	8 (3%)
no partner	45 (21%)	61 (23%)	50 (20%)	62 (24%)
Sex during dances, weddings (past year)	N = 216	N = 268	N = 248	N = 255
no	193 (89%)	244 (91%)	243 (98%)	250 (98%)
yes	23 (11%)	24 (9%)	5 (2%)	5 (2%)
Sex whilst travelling (past year)	N = 213	N = 263	N = 246	N = 252
no	180 (85%)	222 (84%)	239 (97%)	239 (95%)
yes	33 (15%)	41 (16%)	7 (3%)	13 (5%)
Sex whilst having an STD (past year)	N = 216	N = 268	N = 248	N = 255
had no STD	164 (76%)	197 (74%)	209 (84%)	216 (85%)
had no sex	27 (13%)	48 (18%)	23 (9%)	21 (8%)
had sex	25 (12%)	23 (9%)	16 (6%)	18 (7%)
Condom use with casual pa. (past year)	N = 216	N = 268	N = 248	N = 255
no such partner	185 (86%)	219 (82%)	234 (94%)	247 (97%)
no condom use	28 (13%)	46 (17%)	6 (2%)	5 (2%)
used condoms	3 (1%)	3 (1%)	8 (3%)	3 (1%)

Chapter 7 Discussion

7.1 Choice of study population and site

For a trial of the impact of STD control on HIV transmission, a study population was needed which fulfilled three conditions: a high prevalence of STDs, a well established but still expanding HIV epidemic, and a stable population (section 3.2.1).

In rural Mwanza, these preconditions were met. The baseline survey confirmed that STDs were indeed highly prevalent in the region (tables 6.12 and 6.17) and represented a major public health problem. For example, more than 15% of the study population had serological markers of past or present syphilis, and more than 6% had an active untreated infection. The prevalence of HIV infection in the study population had reached about 4% on average at the beginning of the trial with peak prevalences in roadside communities of about 7.5% (table 6.10). With regard to mobility, only 14% of the cohort had moved out of the community during the two-year follow-up period (table 6.9).

The project area was very large, covering six different districts. The western- and easternmost study communities were situated more than 200 kilometres apart, with a distance of about 150 km in a north-south direction. The ongoing Rakai and Masaka trials, the only other trials of STD treatment for HIV prevention, are both being conducted within much smaller project areas, each covering only one district of Uganda (table 7.1, Kengeya-Kayondo et al 1996, Wawer et al 1996).

The disadvantages of a large project area were the strain it put on field workers and the logistic organisation of the trial, and a comparatively large between-community variation in baseline HIV prevalence (see below). However, it had the advantage that the study communities were well separated, and that only very few subjects from comparison communities gained access to intervention health units, thus minimising contamination (section 6.11). Contamination can represent a major problem for community randomised trials (Mertens et al 1990). The Rakai trial attempted to overcome this problem by means of detailed pilot studies to map geographical patterns of social interaction and sexual networks, and by careful definition of community boundaries. In Masaka, as in Mwanza, geographical separation was chosen to minimise contamination, but distances between separated communities are small.

Another choice which had to be made was whether the trial was to be conducted in a rural or an urban environment. Management and logistics would have been easier in a city, but the implementation of the community randomised design would have been more difficult, and contamination probably inevitable. The preparation of a randomised trial of STD treatment for HIV prevention was well underway in the city of Harare/Zimbabwe in 1993, but had to be given up because pilot studies demonstrated the impossibility of avoiding contamination (Ahmed Latif, personal communication). Besides, most Africans still live in rural areas, which therefore represent a much larger at-risk population than the cities, and it was important to study the operational feasibility and impact of an intervention which, if successful, could potentially bring great benefit to the large rural populations of this continent.

7.2 Intervention

7.2.1 Choice of intervention strategy

Referring to the Piot model of the oucome of STDs in the community (figure 2.1), a range of different STD intervention options could be identified. The decision was made to choose a combination of three strategies: the main focus was on improvement of STD case management, but supported by improvement of treatment seeking behaviour and improvement of partner notification.

This meant putting the emphasis on the last steps of the model, whilst the majority of persons with an STD might not reach the improved services. According to Laga, the initial steps of the model might be more crucial in determining the success of a control programme (Laga 1994).

Alternative strategies for STD control could have included: primary prevention, screening for asymptomatic or neglected infections, targeted interventions in the core group or mass treatment. Why was none of these alternative options chosen for the trial?

Primary prevention programmes are certainly of great importance. However, a trial of a primary prevention programme would focus on modifying sexual behaviour and would therefore not have facilitated investigation of the STD/HIV co-factor hypothesis. At the time when the trial was initiated, the place of primary prevention efforts in AIDS control programmes was universally

accepted, while the role of STD control was still unclear. Interestingly, even after two decades of the AIDS epidemic, there are no published results of any trial to measure the impact on HIV transmission of primary prevention at the general population level. The ongoing Masaka trial is the first to address this issue (Kengeya-Kayondo et al 1996).

Ideally, whole communities might be screened for STDs in order to treat all those infected. However, this is logistically very difficult; and simple and cheap screening tests are not yet available. Also, at the time the trial was planned, the size of the asymptomatic carrier problem was not yet appreciated. For example, the baseline survey results in the main cohort, showing that 85% of men with gonococcal and/or chlamydial infection had no symptoms or signs, were unexpected (Grosskurth et al 1996). A further obstacle to the establishment of STD screening programmes was that in the early 1990s, health policy makers in Tanzania and elsewhere were not yet ready to integrate STD services into family planning, antenatal and MCH services, although this had been suggested as a priority (Wasserheit 1989). The exception was syphilis testing of pregnant women, which was being performed in some places. However, whilst the treatment of syphilis in pregnancy is certainly an important health intervention (Hira et al 1990, World Bank 1993), latent syphilis does not usually lead to sexual transmission, and so the relevance of a latent syphilis screening programme for HIV prevention is unclear.

Over and Piot have emphasised the importance of intervening in the "core group" (Over and Piot 1993). A core group of sorts may have existed in the Mwanza study communities. In the two sexual behaviour surveys, for example, about 3% of women and 15% of men reported more than 2 casual partners during the follow-up period. However, in rural communities in Tanzania it is very difficult to identify those individuals who are part of the core group. There are no bars or hotels in these communities, and open prostitution does not exist. The feasibility and value of core group interventions in these rural areas are therefore unclear. For ethical reasons, the intervention capacity of the programme was used to launch a core group intervention project in Mwanza town independent of the trial. The effect of this on the rural study communities, if any, was in protecting rural visitors to the town. This applied equally in the intervention and comparison communities, and the likely effect would be a dilution of the measured impact of the rural programme.

Periodic mass treatment of STDs for HIV prevention is an appealing option which might have a substantial impact. However, it is a controversial approach, and for the time being would not

offer a sustainable intervention which could realistically be provided on a large scale in Tanzania and most other African countries. It is however very important to test this concept, and this is presently being done in the Rakai trial (Wawer 1996).

Lastly, an intervention through the improved case management of STDs was in line with the expectations of the Government of Tanzania, and with the recommendations of WHO at the time when the trial was designed (Meheus 1990, WHO 1991).

7.2.2 Intervention design

The intervention comprised six components: training of health workers, drug supply, syndromic case management of STDs, regular supervision, the establishment of a reference clinic with laboratory for monitoring and training purposes, and campaigns aimed to improve treatment seeking behaviour. Some of these components are discussed below.

Training

We decided on a one week classroom training course in combination with a practical training period of two weeks at the STD reference clinic. During the course of the intervention, it proved to be extremely helpful that trainers were also regularly involved in the supervision of peripheral health services, as they could feed their field experience directly into the training. Training thus became more practical and linked with the reality of the daily routine.

It is debatable how long STD training courses should last. The intervention team experimented with a shorter course duration of only two or three days, to reduce costs and to increase the output of trained health workers. This attempt was soon given up, because the short time available did not permit adequate training in health education, condom promotion, and partner notification, and there was too little time for exercises on syndromic management. Follow-up of the trainees showed that health workers with this type of short training found it more difficult to apply in practice what they had learned.

The practical training period was also rather lengthy. However, shorter training periods could not ensure that trainees would see all syndromes which occur, and get a chance not only to

observe their tutors at work, but to manage STD cases themselves under supervision. In clinics where more STD patients are seen per day, the practical training can probably be shortened, and this would increase cost-effectiveness. This is an argument for not decentralising STD case management training to too peripheral a level.

Antimicrobial drugs and the role of the reference clinic

The success of STD case management depends largely on the choice of the right drugs, correct prescription practices, and compliance of patients with the treatment prescribed.

Ideally, drugs should be chosen which allow single dose oral treatment, which are highly effective, and which cover different infections with the same antibiotic, as is the case for example with azithromycin. Single dose treatment would allow use of directly observed treatment which would increase patient compliance dramatically. Unfortunately, such drugs are very expensive, and cannot be afforded in most programmes in developing countries. On request of the Ministry of Health, but also to protect the programme against accusations of unsustainability, it was decided to use a comparatively cheap but less than optimal drug, trimethoprim-sulfamethoxazole (TMP-SMX) to treat gonococcal infections and chancroid.

The study has recently been criticised for this (O'Farrell 1998), mainly based on the argument that the failure of the intervention to achieve an impact on the prevalence of male urethritis, and specifically of gonococcal infection (table 6.19) was caused by the choice of this drug. The impact on urethritis is discussed in section 7.5, but the argument as such is of general interest as it highlights the importance for any STD control programme of the services of a reference clinic and laboratory.

The antibiotic sensitivity of *Neisseria gonorrhoeae* to the drugs used for the case management of urethral discharge, vaginal discharge and lower abdominal pain syndromes (table 5.2) needs to be monitored regularly. In the Mwanza trial, this was performed at Sekou Toure clinic in Mwanza town and the Department of Microbiology of the National Institute of Medical Research, Mwanza. Other important functions of the reference clinic were to monitor the actiologies of STDs in the area and to provide practical training for health workers.

Monitoring of the sensitivity of *Neisseria gonorrhoeae* in Mwanza at the beginning of the programme showed intermediate resistance for TMP-SMX, but it was possible to overcome this problem by prescription of a comparatively high dose. This was confirmed not only through antibiotic sensitivity tests but also through the documentation of cure rates at the reference clinic (Philippe Mayaud, personal communication, 1992-95). Over time, the proportion of fully sensitive strains declined from 96% in 1992 to 89% in 1996 (table 6.7).

Unfortunately, resistance patterns may vary widely within the same country or larger region. For example, in 1992, resistance to Tetracycline had already reached 35% in Mwanza, which rendered it obsolete; but the level was only 5% in the STD control programme in Mbeya, in Southern Tanzania, and the drug was still in use in 1995 (Gabriele Riedner, personal communication, 1992 and 1995). By 1994, full resistance to TMP-SMX had reached 60% in neighbouring Uganda (Beryl West, personal communication, 1994).

For the management of an STD control programme, an important question is at what level of resistance treatment algorithms should be changed. If the new first line drug is more expensive than the previous one, one would like to wait as long as possible before the algorithm is adjusted. Conversely, if many patients are not cured on first line treatment, they may lose confidence in the programme and the credibility of the programme may be damaged. Furthermore, the need to prescribe 2nd or 3rd line treatments more often will increase overall costs. It is difficult to define the optimal threshold for the decision. Within the Mwanza intervention team, it has been suggested to switch to a new treatment scheme once the level of resistance to TMP-SMX reaches 20%.

Syndromic case management

The rationale for syndromic STD case management is very compelling. Islam demonstrated that this approach is highly cost-effective and superior to the laboratory and clinical approaches in the developing country context (WHO 1993). Patients are treated at the time and place of their first presentation to a health facility. The sensitivity of the approach is high by definition. Side effects of unnecessarily prescribed drugs (because several aetiologies are treated simultaneously) occur at an acceptably low frequency, if algorithms are designed carefully.

However, syndromic management also has some disadvantages which have been highlighted by various authors (Vuylsteke et al 1993i, Laga 1994), and which also became evident during the course of the intervention programme in Mwanza.

(i) Health workers were trained to treat women with lower abdominal pain as cases of pelvic inflammatory disease (PID), provided that there was no reason to suspect a surgical condition. It is likely that some of the patients with this syndrome had other conditions, particularly recurrent pain due to peritoneal adhesions as a result of previous PID episodes. Syndromic STD case management would lead to overtreatment in such cases. Studies involving more sophisticated diagnostic methods (ultrasound, laparascopy, bacterial cultures) are needed to establish what proportion of this syndrome is associated with genuine PID. Because of the difficulties with the diagnostic assessment of this syndrome, it was excluded from the evaluation of treatment effectiveness (section 6.1.3).

(ii) The main dilemma for syndromic case management lies with the vaginal discharge syndrome. Vaginal symptoms are a poor predictor for the much more dangerous but often asymptomatic cervical infections due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. If the treatment of cervical infections is routinely included in the syndromic management of vaginal discharge (as in the Mwanza programme), many women will be treated unnecessarily. If the treatment decision is based on a risk assessment step, as recommended by WHO (WHO 1994), women will be both under- and overtreated, as the sensitivity and specificity of this method were only about 50%, as shown during an evaluation in Mwanza on behalf of WHO (Mayaud et al 1997ii). Simple and cheap diagnostic tests are urgently needed to address this diagnostic dilemma.

(iii) The operational implementation of the syndromic approach is not straightforward (Wilkinson 1997). This was confirmed in Mwanza: the initial resistance among some health workers, particular those of higher cadres, against the syndromic approach was substantial. Even after the approach became generally accepted, health workers frequently deviated from the algorithms, and fell back into previous habits of treating by clinical impression and with prescriptions which were often underdosed.

Support supervision and the situation of health workers

Supervisory visits revealed that such relapses in treatment practices were often unintentional, and health workers were ready to return to the syndromic algorithms once the issue was discussed with them by the intervention officer. This observation underlines the importance of a functioning supervisory system for the success of the programme.

Supervision became the backbone of the intervention for several other reasons. Supervisors provided in-service training which was as important for the success of the programme as the formal training. They saw complicated cases together with the peripheral health workers, and therefore sometimes provided a means of referral. They organised the drug supply and ensured that drugs were used for the purpose they were meant for.

For some of the health workers, the temptation to sell drugs for other purposes was considerable, and without supervision this problem might have jeopardized the whole programme. In the early 1990s, a pilot programme was launched by the Government of Tanzania, to establish syndromic STD treatment services in 20 health facilities in various areas of the country. Health workers were trained, and supplied with drugs. Supervision was conducted, but only erratically and infrequently. An evaluation after 2 years revealed the failure of this programme: hardly any drugs could be traced at the health facilities although the supply had not been interrupted, and few records had been kept to document the treatment of STD patients (Felix Ndyetabura, personal communication, 1994).

This problem has to be viewed against the difficult socio-economic position of health workers in Tanzania (and many other developing countries). Health workers are grossly underpaid and live under extremely difficult economic circumstances which also explain why in rural health facilities one usually cannot find health workers at their working places after the morning hours. From a health policy point of view, it may be questionable whether a programme to improve the services for a particular health problem, in this case STDs, should be launched, unless structural measures are taken to improve the health sector as a whole, or of the public services in general.

7.2.3 Operational performance of the intervention

Acceptance and coverage

At the follow-up cohort survey, about 12% of the men and 6% of the women in intervention communities reported that they had an STD during the past year (section 6.4.2). About 11400 patients with 11632 syndromes were actually treated at the intervention health facilities during the two years of follow-up. If these figures are compared on the basis of the estimated size of catchment population (about 75000 adults in total), a cautious estimate can be made of the coverage of STD cases achieved by the intervention. This suggested that about 85% of symptomatic STD patients made use of the improved services. This suggested also that the population had still some confidence in the governmental health care system in Tanzania, in spite of the many difficulties it had been through during the past 10 years. It is difficult to decide whether this result was due to the campaigns aimed at the improvement of treatment seeking behaviour, or to the improvement of service quality, or both. In the study of non-returners (section 6.1.8), 83% of the patients reported that they were satisfied with the STD treatment services.

Besides the uncertainty around this estimate because of the imprecise definition of the catchment population, the above proportion of service utilisation may be an overestimate, as there was no record of how many patients experienced more than one STD episode during the year. It may also have been overestimated for another reason: it is possible that the overall incidence of STDs in the intervention communities may have been higher in the first year of the intervention than in the second, as suggested by the decrease in prevalence of symptomatic urethritis and active syphilis (sections 6.4.3 and 6.4.4). The net effect of these two possible errors on the estimated utilisation rate is difficult to assess.

There is evidence that many patients made use of alternative treatment outlets. Pharmacies did not exist in these rural study communities, but traditional healers were frequently consulted (Lwihula and Grosskurth 1994, Newell et al 1993), either instead of or in addition to the formal services. Furthermore, anecdotal evidence showed that some patients delayed treatment seeking up to 9 months. Similar observations were made in the Masaka district of Uganda, where patients reported delays of up to 1 year before seeking STD care. For genital ulcers, delays until onset of treatment were shorter, but were still up to 4 weeks (Mulder 1994). It is important that

the improvement of services is accompanied by health education messages to the public to encourage appropriate treatment seeking behaviour.

Fewer women than men reported having had a genital discharge or genital ulcer during the past year when interviewed in the cohort survey. This was consistent with the observation that fewer women than men presented with genital ulcers or with genital discharge. Many infections in women probably went unnoticed or were genuinely asymptomatic. In areas with high prevalences of reproductive tract infections, women often perceive milder symptoms as 'normal' (Mulder 1994). Again, this demonstrates the need for health education.

Overall services were utilised almost equally by men and women (table 6.2), with the non-specific lower abdominal pain syndrome compensating for the shortfall of discharge and ulcers in women.

Treatment effectiveness

In general, overall clinical cure rates observed at health facilities were high, at 97 to 99%, and did not deteriorate during the two years of the trial. Cases of definite treatment failure were extremely rare (table 6.3). Particularly for genital ulcers, this may change in future, as many more HIV-positive patients progress to higher degrees of immunodeficiency.

Taking into account that the urethral discharge syndrome was treated with less than optimal antimicrobials, the first line treatment cure rate for this syndrome was encouraging.

The cure rates after first line treatment of ulcers may have been underestimated because ulcers did not always heal within one week, and health workers sometimes used second line treatment even in cases where an improvement was seen, recording these cases as first line treatment failures. This was probably the reason why patients with ulcers received 2nd/3rd line treatment more often than patients with discharge syndromes (table 6.3).

On the other hand, overall cure rates in genital ulcer patients may have been overestimated for several reasons: ulcers due to *Herpes simplex* virus type-2 infection are not treatable with the

antimicrobial drugs in use, but will normally heal spontaneously. Similarly, syphilitic ulcers will heal spontaneously, even if not correctly treated.

With regard to 1st line treatment, the drug used to treat chancroid (Trimethoprim-Sulfamethoxazole) might not have been fully effective any longer. However, this seems unlikely, since at the reference clinic in Mwanza town, no case of culture-proven chancroid was reported which did not respond to first line treatment, except for one patient with AIDS (Philippe Mayaud, personal communication 1994). There was no option to study the sensitivity pattern of *Haemophilus ducreyi* in Mwanza. For syphilitic ulcers, resistance to benzathine penicillin has not been described in the medical literature to date (Tartaglione and Russo 1990, Mabey and Richens 1996).

Clinical cure rates could only be determined in patients who returned for follow-up visits until a definite outcome (cured, referred, definite treatment failure) was established. Such patients may not be representative of all patients: cure rates may have been over- or underestimated, if a disproportionate number of those patients who failed to improve either stayed away because of disappointment or came forward as they expected additional treatment. The proportion of patients for whom complete follow-up data were available, was only about 33%. The most likely interpretation was that the other patients were cured and thought that an additional visit to the health unit was unnecessary, and too demanding in terms of time and money.

However, since this was uncertain, an attempt was made to collect information from the non-returners as described in section 5.3.3. This was probably the first community based study in which STD patients were followed up at their homes in order to collect data on the performance of a control programme.

Almost 90% of the non-returners had been free of symptoms after treatment. Unfortunately, the 11% who had not improved had not sought second line treatment. This observation emphasises again the need for careful health education. However, it is encouraging that cure rates in non-returners were not substantially lower than in patients with complete follow up, thus indicating that the algorithms in use were appropriate.

Reinfection and recurrence of symptoms

It is disappointing that more than a quarter of the non-returners reported that they became symptomatic again some weeks after the initial treatment, and that these patients did not seek 2nd or 3rd line treatment (table 6.5). It was not possible to distinguish between recurrence of symptoms after initial improvement or genuine reinfection after initial cure. The latter is more likely, taking into account the rather low rate of successful partner notification and the high prevalence of asymptomatic infections in these communities (Grosskurth et al 1996, Mayaud et al 1995).

The fact that 31% of the non-returners who had originally been treated for genital ulcers either still had these ulcers, or had acquired a new ulceration, was of particular concern.

Partner notification

Only for 34% of the index cases was at least one partner treated, thus putting two thirds of STD patients at risk of reinfection. The reasons are difficult to understand and may include embarrassment, fear of matrimonial conflicts, the casual nature of the sexual relationship or failure of health workers to provide the necessary information. However, most patients in this study confirmed that they were requested to notify their partners.

Low partner treatment rates have been reported from various STD control programmes in developing countries (Wellington 1993), and are also a well known phenomenon in industrialised countries (Cowan 1996).

Referrals

Very few cases (0.8% of all syndromes treated) needed referral, which underlines the fact that peripheral health units are well placed to manage STDs.

Unfortunately, only a minority of the referred patients could be traced at the facilities they were referred to. This is worrying, as such patients may often carry resistant strains. Those who did

not report -probably as a result of the high opportunity costs related to time and transport- fell out of the health care chain, and are likely to spread the infection further in the community.

STD patients should be treated at the place and time of first contact, and drugs for all lines of treatment should be made available at all levels of care. The referral of STD patients should be avoided whenever possible. A genuine alternative for the health worker is to present difficult cases to the supervisor, and to make firm arrangements that such patients can be seen at the specialised reference clinic.

7.2.4 Performance of health workers

During the training of health workers, great emphasis was laid on correct case management, the necessity for health education regarding risk reduction and treatment compliance, and condom promotion. In spite of this, when non-returners were followed up and interviewed about their experience, it became clear that all these parameters showed results below expectation. Only 74% of the patients reported that they had been examined, only 57% received health education, and only 30% were offered condoms (table 6.6). In women, the latter proportion was as low as 19%. Although it is difficult to assess this through an interview which was conducted weeks or months after treatment, it seems that only 63% of the patients had been treated according to the syndromic algorithms.

These observations are consistent with results of a study from South Africa, which showed even worse performance of health workers. For example only 9% of the prescriptions written for STD patients provided adequate treatment, and none followed official guidelines (Wilkinson 1997). The observations in non-returners are also consistent with findings by Buve and colleagues who observed health workers' performance at four intervention health centres in Mwanza region, in order to arrive at more precise estimates for the model described in section 2.1.7. (Buve et al. unpublished data, 1998). This study was conducted about 2 years after the end of the trial. The evaluators observed 84 patients who presented with an STD syndrome. Of these 74 (88%) were diagnosed correctly by the health centre staff, and 48 (65% of 74) received a correct prescription. Assessment of drug stocks revealed that failure to issue a correct prescription was not due to drug shortages.

The reasons for these failures are not fully understood, but may be multifactorial: there may be waning of the effect of training, but lack of time and motivation in the context of health workers' economic situation may also play a role. These results underline again the crucial importance of good quality supervision.

7.2.5 Integration, sustainability and upscaling

The intervention was to be applied in the general population. Specialist care was not available for the majority of the population of Mwanza Region. The task was therefore to design an intervention which made improved STD care accessible to rural villagers. It was much more cost-effective to achieve this through integration of STD services into the existing primary health care structure, than to attempt a vertical approach for example through outreach services. Most people in Mwanza Region can reach a dispensary or health centre within two to three hours.

The principle of integration into the existing services was also in line with the official policy of the Ministry of Health. It fitted into the process of health sector reform in Tanzania, which started around 1992, and aimed at decentralisation and strengthening of district health management teams.

Could the district health system cope with the additional demand? STD services were integrated into the existing primary health care facilities, without additional requirements regarding personnel and physical structure. At the district headquarters, one medical assistant was trained for the post of District STD Control Coordinator (DSCC). All in all, the additional burden was negligible.

Certain components of the intervention were organised vertically, notably the training of health workers, the drug supply, and at least initially the supervision component. There were two reasons for this. Firstly, to investigate the co-factor hypothesis, it was important to keep essential elements of the intervention under control, so that operational success was ensured. This would have been debatable if a system was created which was not sustainable and would not be replicable elsewhere. However, this was not the case: the personnel routinely involved in these components comprised medical assistants and nurses only. Training courses were short and

unsophisticated. The drugs used were inexpensive, and the drug supply was coordinated with the supervision visits.

Secondly, even in a completely integrated programme, unrelated to research, district level health services in developing countries would usually not be in a position to ensure sufficient manpower and expertise for good training and low-cost drug procurement. The few other large scale STD intervention programmes in Africa (see section 2.1.8) have chosen a similar approach for their training and supply components (Bastos dos Santos et al 1992). In Uganda, STD training is being provided for 10 districts through a mobile team of training experts supported by a non-governmental organisation (Dean Shuy, personal communication 1994).

An economic analysis of the Mwanza intervention showed that the single most expensive component in the recurrent costs was the supervision system, as this required transport including fuel and maintenance and outstation allowances for supervisors (Gilson et al 1997). Because regular supervision and in-service training proved to be of paramount importance for the success of the intervention, these costs are unavoidable.

Despite this, the improvement of STD services cost only $0.39 per capita annually, or $10.15 per syndrome treated of which only $2.11 were drug costs (Gilson et al 1997). Both can be further reduced by upscaling the intervention.

Meanwhile, two years after the end of the trial, the intervention has been extended to about 190 health facilities in total, without the need for additional capital investment or personnel at central level.[1]

[1] For completeness, it should be mentioned that in 1996, the drug supply was disconnected from the central project office in Mwanza, and taken over by the Ministry of Health, with funding from the EC. Because of organisational and managerial problems, the supply became erratic soon afterwards, and in 1997, 6 years after the beginning of the intervention, health facilities in Mwanza Region ran out of drugs

7.3 Study design and implementation

7.3.1 Community randomisation

A randomised controlled trial was chosen as the most appropriate study design to assess whether improved STD services had an impact on HIV and STD transmission.

The impact of STD control could, in principle, be tested by individually randomising HIV negative subjects to an STD intervention or to a comparison group. However, if STD treatment is to be provided through existing health services, a community randomised design is dictated by the intervention design.

This design feature had important advantages. STDs are likely to enhance HIV transmission by increasing both the infectiousness of HIV infected individuals and the susceptibility of HIV uninfected individuals (Mertens et al 1990). Randomisation by individual subjects would only measure the effect on HIV acquisition, and therefore fail to capture the full impact of the intervention. In addition, randomisation by community captures the 'mass effect' on transmission which is achieved when whole communities are covered by an intervention against an infectious disease, and which is analogous to the herd immunity which may be observed in immunisation trials (Hayes et al 1997).

7.3.2 Sample size and matching

Randomisation by community had two important consequences each of which required careful consideration and had a major influence on the details of the trial design and the strategy for data analysis (Donner et al 1987).

Firstly, standard sample size formulae for individually randomised trials could not be applied as it could be expected that the main outcome measure would vary between communities, thus introducing an extra component of random error in addition to the binomial variation caused by the random sampling of individuals within the communities. Sample size calculations needed to take account of both types of random error.

Secondly, community randomisation meant that the outcome of interest would have to be analysed at the level of the community as well. In spite of the recruitment of a large cohort of individuals within each community, the trial was based on only 12 communities. With so few units of randomisation, there was a high probability of baseline imbalances between the two trial groups which could have influenced the results. Because HIV incidence was the primary endpoint of the trial, this problem would ideally be addressed through stratification of communities by baseline HIV incidence. The most extreme form of stratification is to form matched pairs of communities.

Sample size

The trial was designed to have 80% power of detecting a reduction of HIV incidence from 1% to 0.5% as statistically significant at the 5% level. The number of communities required for each group and the number of person-years of observation required within each community were calculated using the computation described in chapter 5.1.5.

The key quantity in this computation is k, which is a measure of the degree of variation of the true incidence between communities. Because prior data for k were not available, an assumption had to be made. We assumed that the true incidence without the intervention varied between approximately 0.5 and 1.5%, implying that k=0.25. Under this assumption, the computation showed that at least 5 communities would be required for each group for the trial to give conclusive information (fig 5.1). We decided to choose 6 communities per group, and calculated that 2000 person years of observation (PYO) would be needed for each community, in total 24,000.

Why were 6 communities chosen per group? There was a trade-off between the number of communities and the number of PYO: if only 5 communities per group had been chosen, a much larger cohort would have been required (fig. 5.1). The latter would have been logistically difficult, and in some of the communities it might have been difficult to identify a sufficient number of adults within the cohort recruitment zone of a study community (figure 5.4).

On the other hand, there were several reasons not to exceed six communities per group: Firstly, again from a logistic point of view it was easier to operate in a smaller number of communities.

Secondly, a smaller number of communities reduced the chance of contamination. Thirdly, although for a given value of k, a larger number of small clusters is preferred to a small number of large clusters, since this reduces the design effect resulting from between community variation and increases power for a given total sample size (Gail et al 1996), it was expected that k might be reduced if clusters were larger.

Lastly, it is clear from fig. 5.1, that the required number of communities is more sensitive to losses to follow-up if the choice is made on the left rather than the right side of the diagram: losses to follow-up will in any case lead to a loss of study power, but with a larger number of communities in the study and a smaller number of PYOs in each community, it can more easily lead to inconclusive trial results, as the number of communities may more easily turn out to be insufficient at the time of the follow-up survey.

Matching

The ideal approach -matching on baseline incidence- was not feasible. Matching on baseline HIV prevalence would have been the second best choice as it could be expected that HIV incidence was closely associated with HIV prevalence, as the epidemic in Mwanza Region was still far from reaching saturation. However even that was not possible, as HIV prevalence data were not available from the study communities when the trial was designed. Instead, matching factors had to be chosen which were known from previous studies to be closely correlated with HIV prevalence in this Region (Barongo et al 1992): community location in high versus low prevalence districts, and geographical relationship to main roads, the lakeshore and the islands (table 6.10).

All three East-African trials employed similar matching strategies (table 7.1). In the Mwanza trial, communities were allocated to six matched pairs. In the Masaka trial -a trial with three arms conducted in 18 parishes- six matched triplets of parishes were formed on the basis of known HIV prevalence (Kengeya-Kayondo et al 1996). In the Rakai trial, the 10 study communities were grouped into 3 strata using projected HIV prevalences (Wawer et al 1996).

The baseline survey in Mwanza confirmed that the matching was highly effective. The variation of HIV prevalence was much smaller within pairs than between pairs (table 6.3.1). This resulted also in a substantial increase in study power.

As described above, the initial sample size calculation for the Mwanza trial was based on an assumed value of k=0.25 for the between community variation of baseline HIV incidence. Because incidence figures were not available before the trial, prevalence had to be used as a proxy instead, although this required more caution, since for a trial with HIV incidence as the main outcome measure, HIV incidence was the really important variable. When the baseline survey was completed, the actual size of k calculated over all 12 communities was found to be 0.49, substantially larger than expected (Grosskurth et al 1995i). The potential consequence can be assessed from figure 7.1 which shows the number of communities required for different values of k for given numbers of person-years of follow-up. Without the matched design, the number of communities in each trial arm would not have been sufficient anymore, as for k=0.49 at least 13 communities would be required (fig. 7.1), and the trial would have been inconclusive. However, k was only 0.28 when computed *within* pairs, a result close to the original estimate.

In the Masaka trial, a similar observation was made (table 7.1): k was originally estimated at 0.25, proved to be 0.30 overall, but was only 0.19 when analysed within matched triplets (Kegeya-Kayondo et al 1996, Hayes et al 1997). These figures may still change to some extent, as the calculation was made before the baseline survey was completed. In the Rakai trial, no pre-trial estimate of k was made, but it was recorded as 0.16 at the baseline survey (Hayes et al 1997).

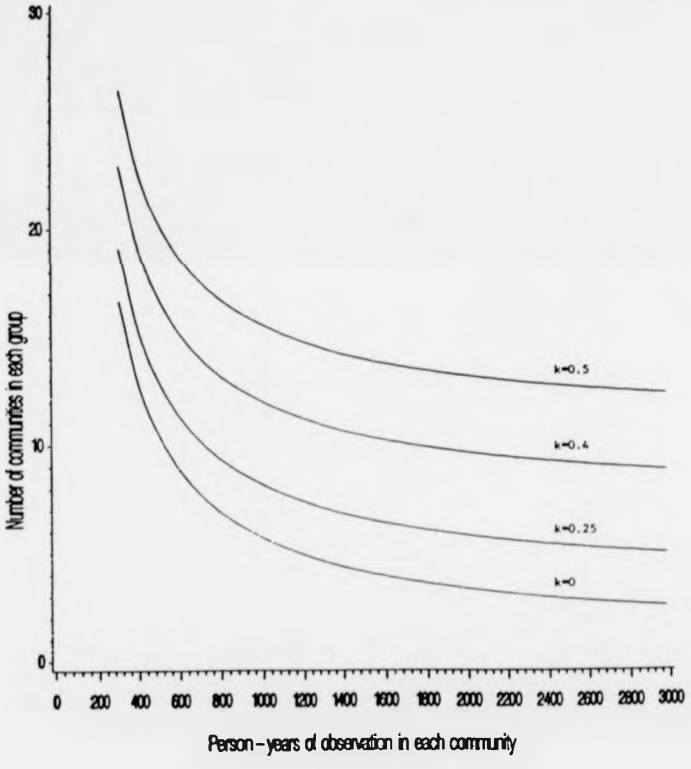
The fact that the Masaka and Rakai trials operate in a comparatively small geographical area - in principle a disadvantage because of the danger of contamination - gave them the advantage of much more homogeneous communities resulting in lower values of k and an increase in study power for a given number of communities.

Table 7.1: Key characteristics of three trials of STD treatment for HIV prevention[4]

	Mwanza trial	*Masaka trial*	*Rakai trial*
Design	RCT	RCT	RCT
Clusters	12 communities (groups of villages)	18 parishes	10 superclusters (groups of villages)
Stratification	6 pairs of communities	6 triplets of parishes	3 strata with 2 or 4 superclusters each
Clusters per arm	6 communities	6 parishes	5 superclusters
Study population (sexually active)	75,000	50,000	12,000
Size of cohort	12,000	18,000	12,000
Coefficient of variation (k) assumed observed [1]: - overall - within pairs/strata	0.25 0.49 0.28	0.25 0.30 0.19	NA 0.16 ?
Activities in intervention arm	Improved syndromic case management	1. IEC only 2. IEC + improved syndromic case man.	Periodic mass treatment
Activities in comparison arm(s)	Continuation of traditional treatment of STDs	Community development intervention	Treatment of STDs at study clinics (self reported or if found infected during survey)
Outcome variables	In cohort: HIV incidence, incidence of syphilis, prevalence of - active syphilis - male urethritis - NG/CT in men In pregnant women: prevalence of - TV, CA, NG/CT	In cohort: HIV incidence, incidence of syphilis, prevalence of - active syphilis - NG/CT in both sexes	In cohort: HIV incidence, incidence of syphilis and genital ulcers, prevalence of - TV in women - BV + CA in women - NG/CT in both sexes In pregnant women + offspring: - all maternal STDs - premature delivery - low birth weight - ophthalmia neonat.
STD laboratory methodologies used	In cohort: NG: gram stain [2], CT: antigen detection EIA [2], urethritis: gram stain[2], Syphilis: RPR, TPHA	In cohort: NG + CT: LCR on urine, Syphilis: RPR, TPHA	In cohort: NG + CT: LCR on urine TV: culture [3], BV + CA: gram stain [3], Syphilis: Trust, TPHA, Ulcers: multiplex PCR for TP, HD and HSV-2

RCT Randomised controlled trial, IEC Information, education, communication, NG *Neisseria gonorrhoeae*, CT *Chlamydia trachomatis*, TV *Trichomonas vaginalis*, BV Bacterial vaginosis, CA *Candida albicans*, HSV-2 *Herpes simplex virus-2*, EIA Enzyme immunoassay, RPR Rapid plasma reagin test, TPHA Treponema pallidum haemagglutination assay, LCR Ligase chain reaction, PCR polymerase chain reaction; [1]regarding HIV prevalence at baseline; [2]on urethral swabs from men; [3]using self administered vaginal swabs [4](Kengeya-Kayondo et al 1996, Wawer et al 1996, Hayes et al 1997, J. Whitworth: personal communication)

Figure 7.1 Number of communities required in each group for different values of the coefficient of variation of HIV incidence (k), for given numbers of person-years of observation (Hayes et al 1995ii)



7.3.3 Randomisation and comparability

From each matched pair, one community was randomly allocated to the intervention group. Within communities, study participants were selected through the random cluster sampling scheme described in section 5.4.3.

The randomisation process was successful in providing intervention and comparison groups that were generally similar with respect to HIV and STD prevalence at baseline (tab 6.11 and 6.12). In three of the community pairs, HIV prevalence was lower in the intervention community, whilst it was lower in the comparison community in the other three pairs.

Imbalances in baseline HIV and STD prevalences

However, small overall imbalances occurred for all HIV and STD prevalences at baseline, and these could potentially act as confounders for the impact variables. In the analysis of each outcome, an adjustment was therefore made for the appropriate corresponding baseline prevalence. For example, overall baseline HIV prevalence was 3.7% in intervention and 4.4% in comparison communities (table 6.11), potentially resulting in an exaggeration of the measured impact of the intervention, and therefore a term for baseline HIV prevalence was included in the logistic regression model for the analysis of HIV incidence.

Imbalances in other potential confounding variables

Most factors known to be associated with the risk of HIV infection and other STDs in this population, including sexual behaviour, were also distributed similarly in the treatment groups (tables 6.13 and 6.14).

The only variables for which there were appreciable differences at baseline between intervention and comparison groups were travel outside the district during the past year in both sexes, circumcision in men and reported STDs (ever) in men.

How could these imbalances influence the results of the impact evaluation? A lack of circumcision has been shown to increase the risk of HIV acquisition in some African studies (de Vincenci et al 1994). Only 14% of the men in intervention communities were circumcised, versus 23% in comparison communities. This difference could potentially lead to a higher incidence in intervention communities, and would therefore reduce the measured impact of the intervention.

Conversely, only 44% of the men and 24% of the women in intervention communities reported having travelled outside of their district during the last 12 months before the baseline survey, whilst the corresponding figures for comparison communities were 49% and 35% respectively. If similar differences also occurred during the follow-up period, this would expose the comparison population to higher risk, as mobility was associated with HIV infection in an earlier study in the Region (Barongo et al 1992).

The same applied to a reported history of STDs. Only 31% of the men in intervention communities reported previous STDs (ever), but 38% of the men in comparison communities. In women, this was more evenly distributed. Because a history of STDs was associated with HIV infection (Barongo et al 1992), and because it could be assumed that a history of STDs would predispose to future infection, the risk of HIV infection was potentially higher in the comparison group.

Thus, imbalances in the history of travelling outside of the district, and history of previous STD episodes, could potentially exaggerate the measured impact of the intervention. Terms for these factors as well as for male circumcision were therefore included in the logistic regression model used in the impact analysis.

7.3.4 Compliance and losses to follow-up

Compliance

The compliance of the local population was remarkably high. The great majority of eligible individuals who were not recruited during the baseline survey, were travelling away from their community. Very few people refused to participate in the study, and the same observation was made during the follow-up survey.

The trial made considerable efforts to encourage compliance through community mobilisation, meetings with official and unofficial representatives, home visits to eligible persons if they failed to present to the study team, and a final revisit to clusters where compliance was below average, before the study team moved on to the next community.

The fact that all interviewers and most of the field team leaders belonged to the Sukuma tribe, the main ethnic group inhabiting Mwanza Region, helped to ensure a positive response. Their training included sessions on how to approach study participants respectfully, and how to address common questions and problems. The survey teams treated any STD and other minor ailments on the spot. This service was not limited to study participants only, but was also provided to people from neighbouring unselected clusters or to people outside the eligible age band. Occasionally quick and effective help was provided in real emergencies. As a result, the programme was generally viewed by villagers as providing good medical care in times of a deteriorating health system. Because it was known that the programme would try to upgrade government health facilities to some extent, and because study teams interacted regularly with the local health staff, the authority of these health workers was not undermined.

Losses to follow-up

Overall losses to follow-up were 29 - 30% in both trial groups, with 14% due to moving away and 6% due to temporary absence of more than two months. Both were fewer than expected, reflecting the relative stability of the population.

However, losses to follow-up were not negligible, and had some implications for the expected power of the study. The actual number of person years of observation (PYOs) was based on only 8549 initially seronegative individuals, from whom 17098 PYOs were obtained, about 71% of the 24,000 of the original sample size calculation. This implied a reduction in the power of the study from about 80% to 74%, a fairly modest reduction (Hayes et al 1995ii).

7.3.5 Quality control

The quality control procedures used within the trial were extensive. They included frequent supervision and support visits to field research teams, measures to shift teams between intervention and control communities during the course of the surveys, and various checks performed at the steps of specimen and data collection and at computerisation. Rapid local data entry and processing facilitated the identification of errors which had not been detected in the field. These were then eliminated in collaboration with the field team leaders, usually within two to three weeks after collection of the original data. For the laboratory work, a system of both external and internal quality control was in place (section 5.4.8).

Similar quality control measures were in place for the supplementary studies on antenatal clinic attenders and the sexual behaviour surveys (sections 5.4.6 and 5.4.7).

7.4 Impact on HIV infection

7.4.1 Validity of impact estimate

The crude relative risk (RR) of HIV infection in the cohort was 0.57 for persons living in intervention communities when compared to those living in the comparison communities. Thus the improved STD treatment services reduced HIV incidence by 43% over 2 years of follow-up. After adjustment for baseline imbalances of possible confounding factors between intervention and comparison communities, including differences in baseline HIV prevalence, the RR was 0.62, equivalent to a reduction in incidence of 38%. The 95% confidence interval for the reduction in HIV incidence ranged from 15% to 55%.

The crude reduction occurred in both sexes, and was observed consistently in all matched pairs of study communities (table 6.15 and figure 6.1). A reduction was also consistently observed in all age groups. It was particularly large in young women and in men aged 25-34 years, the same groups which showed the greatest HIV incidence without the intervention (figure 6.2). After adjustment for baseline HIV prevalence, a reduction was no longer observed in one of the pairs (table 6.15)

The observed annual incidence of 0.9% in the comparison communities was close to the 1% assumed in the study design, and similar to the incidence of 0.8% observed in the rural population of neighbouring Kagera Region (Killewo et al 1993).

The overall reduction was highly statistically significant, both for the crude and the adjusted relative risks ($p=0.004$ and $p=0.013$, respectively). It is therefore very unlikely that chance could explain the observed difference in HIV incidence.

Are there any sources of bias which might account for the observed reduction?

The results might be explained by a lack of comparability between the intervention and the comparison communities. Although this problem should have been minimised by the matching and randomisation process, it possible that with only 12 communities some differences could have occurred. However, as shown in section 6.3, matching and randomisation succeeded in providing intervention and comparison communities that were generally similar at baseline with respect to HIV and STD prevalences and most of the risk factors known to increase the risk of HIV and STD transmission. The most important potential confounding variable, sexual risk behaviour, was evenly distributed between the two groups of communities, at least as far as can be determined with a survey using a structured questionnaire (table 6.14). Some imbalances of baseline variables were identified, but these were adjusted for in the analysis. This adjustment changed the estimated impact on HIV incidence very little.

Losses to follow-up are another potential source of bias. It could be that those lost may differ in their risk from those who were seen at follow-up. However, 71% of the cohort members were seen at follow up, and this proportion did not differ substantially between intervention and comparison communities (table 6.8). These coverage rates are within the range generally considered acceptable in population based studies. Reasons for loss to follow-up were also broadly similar in intervention and comparison communities. It is therefore very unlikely that the comparability of the two groups of communities has been impaired substantially by losses to follow-up.

The testing algorithm used to establish the HIV status of the study participants was highly sensitive and specific. However, a small number of misclassifications are likely to have occurred, as in other studies (see section 2.3.2). There is no reason to assume that this misclassification

was differential with respect to the two study groups. The effect of this misclassification would be to underestimate the impact of the intervention (Mertens et al 1990).

Another possible bias may be caused by study participants in comparison communities travelling to intervention communities in order to seek improved treatment for STDs. The origin of STD patients was carefully monitored. Records showed that only 59 patients (about 0.5% of all STD patients) were residents of comparison communities. Any bias caused by this contamination effect would have been small, and would again lead to a dilution of the measured impact of the intervention.

It can be concluded that the observed reduction in incidence reflects a valid result and can confidently be attributed to the intervention. The question remains whether the impact was caused by the improved case management of STDs or by other effects which stemmed from the intervention.

It was possible that the intervention might have changed the sexual behaviour of the population. Public campaigns in the villages focused on the importance of seeking treatment promptly and on publicising the availability of improved services. However, questions on risk factors for STDs and HIV infection came up in discussions with the public, and the responses of the intervention team included advice on how to reduce risk behaviour. In addition, STD patients were educated by health workers on how to reduce their risk in future, and although only 57% of patients in the study of non-returners reported having actually been exposed to this health promotion, this component of the intervention could have led to a change in the sexual behaviour of the population in the intervention communities.

Unfortunately it did not. For example, only 0.9% of the STD patients accepted condoms, and reported condom use in the study cohort in intervention communities was very low as well. The reported sexual behaviour of the cohort with respect to condom use, number of casual partners during the follow-up period, number of partners during the past year and other parameters measuring risk behaviour did not differ substantially in the two groups of communities, neither did it change over time in either arm of the trial.

It is therefore very likely that the observed reduction in HIV incidence reflected an impact of the STD treatment intervention itself, rather than by changes in sexual behaviour.

When the trial was designed, it was questioned whether health promotion should be included in the intervention, because the objective of the trial was to contribute evidence for or against the STD co-factor hypothesis. For ethical and pragmatic reasons this question was answered in the affirmative. If sexual behaviour adaptation had occurred, this would have to be regarded as part and parcel of the intervention. From a public health perspective it was disappointing that sexual behaviour changes were not achieved. From an epidemiological point of view this strengthened the evidence for the co-factor hypothesis, and for the importance of launching STD control efforts in order to prevent HIV transmission.

Interestingly, during the public discussion of the trial, some commentators thought it had proven the ineffectiveness of STD and AIDS related health promotion. This can certainly not be concluded from the results of this trial. The intervention was not targeted at sexual behaviour changes and it is not easy to influence sexual behaviour. The time required to achieve such an impact is probably much longer than just two years, and would need much more intensive intervention efforts (Slutkin 1993, Adler et al 1996).

7.4.2 Implications for the co-factor hypothesis

The results of the trial provided additional evidence for the hypothesis that STDs enhance the transmission of HIV infection, and that the control of *symptomatic* STDs can substantially reduce HIV transmission in populations where STDs are highly prevalent.

They are consistent with the various observational studies described in sections 2.3.3 and 2.3.4, which had suggested that both genital ulcers and non-ulcerative STDs (notably gonorrhoea, chlamydia infection and trichomoniasis) increase HIV transmission (Cameron et al 1989, Plummer et al 1991, Laga et al 1993). However, the evidence produced by the trial was much stronger than for these previous studies, because the randomised controlled design of the trial made it possible to overcome the problem of confounding which is inherent in observational studies, as described in detail in section 2.3.2 (Mertens et al 1990, Laga et al 1991, Laga et al 1994i).

The results of the Mwanza trial are also consistent with studies demonstrating increased HIV shedding in the semen, or cervical or vaginal secretions, of HIV infected persons in the presence of bacterial STDs (Cohen et al 1997, Mostad et al 1997), and a decrease in viral load in semen after the treatment of urethritis (Cohen et al 1997).

Taking all these findings together, the STD/HIV co-factor hypothesis has now been confirmed beyond reasonable doubt.

The trial was not in a position to shed light on the exact size of the STD/HIV co-factor effect for individual STDs (Hayes et al 1995ii).

The size of the reduction in STD incidence which can be achieved through improved STD case management depends on a variety of factors. The reduction depends not only on the size of the co-factor effect, but also on the prevalences of STDs and HIV infection in the community, the proportion of STDs which are asymptomatic, the treatment seeking behaviour of the population, the compliance of patients, the proportion of partners which can be reached and treated, the effectiveness of the drugs used, and the performance of the health workers involved. This list is probably not exhaustive. It is therefore quite possible that the same type of intervention may have a greater or lesser impact in another setting. There is also some uncertainty about the size of the impact, as the true HIV incidence reduction may have fallen anywhere between 15% and 55%, if the 95% confidence interval around the measured relative risk for HIV transmission is considered.

It would be of great interest to compare the results of the three trials in East Africa, perhaps with the help of computer simulations, in order to arrive at more reliable predictions of how to optimise an STD intervention for HIV prevention in different environments.

7.4.3 Issues of cost-effectiveness

The cost-effectiveness of the Mwanza intervention was evaluated in an associated economic study (Gilson et al 1997). The study related the costs spent on STD control in the intervention communities to the benefit generated by these improved services. This approach took into account that some STDs were also treated successfully through the existing health services in

the comparison communities. Cost-effectiveness was therefore calculated based on *incremental* costs, that is by deducting an estimate of costs spent on STD treatment in comparison communities from the total costs of the intervention. This incremental expenditure prevented about 250 new HIV infections per annum in the catchment population of the intervention communities at a cost of US $ 0.39 per head of population served.

The amount spent to prevent one case of HIV infection was $ 218. Prevented cases of HIV infection were related to the number of disability adjusted life years (DALYs) saved. Using the life expectancy for Tanzania, it was estimated that the intervention costs were $ 10.33 per DALY saved. A sensitivity analysis was conducted by combining various favourable and unfavourable assumptions for the factors influencing cost-effectiveness. In this analysis, the cost per DALY saved ranged from $ 2.50 to $ 48.00.

Even at the unfavourable extreme, this compared favourably with other cost-effective public health interventions (World Bank 1993). It should be noted that the cost-effectiveness estimates did not include the direct benefits obtained by treating STDs and by preventing STD sequelae. The economic burden of STDs is substantial (World Bank 1993).

As discussed in section 7.2.5, the intervention has meanwhile been upscaled and covers about 190 health facilities, without major additional capital investment. It is possible that the quality of the intervention has decreased somewhat, but it is likely that during this process cost-effectiveness has increased substantially, as long as the drug supply remains reliable.

7.5 Impact on STDs

7.5.1 Summary of impact results

A The following parameters were significantly reduced in intervention communities at the 5% or 10% level of significance:

(i) the prevalence of active syphilis, for different cut-offs of the RPR titre. The adjusted relative risk (RR) decreased with increasing titre, ranging from 0.89 (at a titre of >=1:2) to 0.54 (at a titre of >=1:32) (table 6.17), equivalent to a reduction of active syphilis of up to 46%. P-values

ranged from 0.04 to 0.01. For higher titres, the reduction was observed consistently in all pairs of communities.

(ii) the prevalence of new cases of active syphilis, that is of cases which were RPR-negative at baseline. The adjusted RR was 0.56 (p=0.06).

(iii) the prevalence of symptomatic urethritis in men. The adjusted RR was 0.51 both for persons reporting symptoms during the past year (p=0.06) and those reporting symptoms at the time of the interview (p=0.08), equivalent to a halving of the prevalence.

B The incidence of syphilis (TPHA+) during the two years of follow-up was reduced by 36%. The RR after adjustment was 0.64, but this finding was not statistically significant (p=0.15).

C No impact at all was observed (i) on the prevalence of asymptomatic urethritis in men, (ii) on gonococcal and/or chlamydial urethritis in men, even if symptomatic, (iii) on history of self-reported STD symptoms in both sexes in the main cohort study; (iv) and on cervical or vaginal infections in the cross-sectional study at antenatal clinics.

7.5.2 Performance of diagnostic tests

General considerations

False positive or false negative test results would lead to misclassification of the infection status of some of the study participants. What effect would these misclassifications have on the impact estimates? If the misclassification is non-differential with respect to the intervention or comparison groups, as could usually be expected if the laboratory personnel are entirely unaware of the origin of the specimens, the result of this type of misclassification would be a dilution of the measured effect of the intervention, thus biasing the study results towards finding no association (Mertens et al 1990). None of the diagnostic tests used in this trial for the diagnosis of the various STDs had a sensitivity or specificity of 100%. It is therefore likely that the observed impact estimates seen in this trial are biased towards under- rather than an overestimation.

If the misclassification is differential, the association may be biased in either direction (Mertens et al 1990). This may have been the case with self-reported symptoms (see below section 7.5.4).

Serological tests for syphilis

Syphilis versus non-syphilitic treponematosis: Both TPHA and RPR tests may lead to a false positive diagnosis of syphilis in persons with non-syphilitic treponemal infections, notably yaws (Schulz et al 1990, Arya 1996). This could potentially result in the diagnosis of an exaggerated prevalence and incidence of syphilis. The effect on the impact of the intervention would be difficult to predict without detailed data on the distribution of yaws in the two trial groups. It is likely that this distribution would have been equal in the two groups of the trial because of the randomization, and that therefore the misclassification of yaws as syphilis would have led to a dilution of the measured impact (see above). However, yaws was probably eradicated through mass treatment programmes in Tanzania conducted in the 1950s and 1960s, and is believed to no longer exist in Tanzania. No clinical case of yaws was observed during the surveys in any of the 12 communities. Seroscars of old yaws, if they existed at all, may have influenced the prevalence figures of syphilis in the older age groups, probably non-differentially.

Syphilis incidence: The incidence of syphilis was measured by TPHA seroconversion. Even after successful treatment of syphilis, the TPHA test result remains positive throughout life in most cases (Jaffe and Musher 1990, Larsen et al 1995). TPHA incidence can therefore only detect a proportion of all new syphilis cases. Individuals who acquired a fresh syphilitic infection during the follow-up period, but who were already TPHA positive at baseline because of a previous episode, could not be detected.

Persons in whom a new infection was treated as soon as signs and symptoms appeared, may not have seroconverted. Prompt treatment would thus favour the intervention group: true syphilis incidence would be underestimated, and the estimate of the impact on syphilis incidence somewhat exaggerated.

The above observations may imply some inaccuracy in the impact estimate for syphilis incidence.

Active syphilis: Active syphilis was defined by a combination of a positive RPR and a positive TPHA test. Whilst the TPHA test result remains positive after treatment, the RPR test usually reverts to negative within a few months (Jaffe and Musher 1990, Larsen et al 1995). However, this is not always the case, particularly if treatment is given during the late latent phase (Goeman J et al 1995). In such circumstances the RPR titre will usually be low. If cases with low titres are included in the assessment, the measured reduction in the prevalence of active infection will be diluted. Lower titres therefore underestimate the true impact. This was the main reason why the measured impact was found to be smaller for lower titres (table 6.17).

Another reason for this phenomenon may be the fact that the RPR test occasionally leads to false positive results, particularly in areas with a high prevalence of malaria and other parasitic infections. In such cases titres are usually not high (Jaffe and Musher 1990). If false positive RPR test results were observed in conjunction with long-standing positive TPHA results, this would exaggerate the prevalence estimate for active syphilis at low RPR titres in both arms of the trial. The measured impact would be reduced, because persons with active infection would present a smaller proportion of overall RPR-positive individuals.

On the other hand, the RPR titre in persons with untreated long-standing latent infection may also decrease to lower levels (Goeman et al 1995). This would result in an underestimate of the prevalence of active syphilis in both trial groups, if only higher titres are included. However, because long lasting latent cases of syphilis are not associated with symptoms, it is unlikely that this would lead to a differential effect between the two groups, and therefore it is unlikely that the impact estimate would be biased in either direction.

The determination of *new cases* of active syphilis was based on persons who were RPR negative and either TPHA positive or negative at baseline. For this reason, the denominator for this category is larger than for TPHA seroconversion (table 6.17). Conversely, the number of new cases of active syphilis is much smaller than the total number of active syphilis cases, because even at higher titres there would be cases who were already infected at baseline and who would therefore be excluded from the new cases (it is likely that these cases experienced fresh infections during the follow-up period which boosted their RPR titre, since all RPR+ cases observed during cohort recruitment had been treated on the spot by the survey team). The impact on the prevalence of new cases was substantial but because the total number of new cases was

comparatively small for the reason given above, the impact estimate was not quite significant at the 5% level.

Tests employed for the diagnosis of gonococcal and chlamydial infections in men

Probably the most sensitive and specific tests available for the diagnosis of infections with *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) are the polymerase and the ligase chain reactions (PCR and LCR). For logistical and financial reasons, it was not possible to make use of these methods in the trial. Gonococcal culture was also not performed in the main cohort, again for logistical reasons. The tests used (urethral swabs with microscopy on Gram-stained smear to identify intracellular gram-negative diplococci for the diagnosis of NG, and antigen detection assay for the diagnosis of CT) have a comparatively high specificity, but are likely to miss some mild infections (Mardh and Danielsson 1990).

Furthermore, it was not possible to perform urethral swabbing on all men in the cohort. Men were only swabbed if they complained of urethral symptoms, if a discharge was observed by the clinician, or if the LED test was positive. The last of these criteria provided most of the specimens.

The infection rates seen therefore represented only minimal prevalences of NG and CT infection. There is, however, no reason to assume that the prevalence underestimate was differential in the two groups of the trial.

7.5.3 Validity of impact estimates

The observed differences in the prevalences of active syphilis and male urethritis were substantial, and were significant both on crude and adjusted analysis. It is therefore unlikely that chance could explain these reductions.

As discussed for the impact on HIV, however, there might be sources of bias which may explain the observed reduction in syphilis and symptomatic urethritis, or the lack of reduction in the other STD parameters.

Any lack of comparability between intervention and comparison arms should have been minimised by the matching and randomisation process. Nevertheless there were differences in some of the risk factors at baseline which could potentially influence the transmission of STDs. These were identical with those for HIV infection, and are discussed in section 7.4. The differences were adjusted for in the impact analysis for all STD parameters measured in the main cohort study.

The prevalence of NG and/or CT infection, both symptomatic and asymptomatic, was lower in intervention communities (table 6.12). This might have exaggerated the impact if there had been any.

In the impact analysis for each STD parameter, adjustment was made for baseline differences in the parameter under consideration. For symptomatic urethritis, the baseline prevalence of all urethritis was used for adjustment, since the numbers of cases of symptomatic urethritis were small.

Some other potential sources of bias were the same as for HIV incidence: losses to follow-up and contamination. As discussed in 7.4, losses to follow-up were not differential between the two trial arms, and contamination was minimal. It is unlikely that these factors influenced the impact results.

The potential effects of misclassification due to the diagnostic tests used are discussed in section 7.5.2. The net effect of the various misclassifications is likely to have been a modest underestimation of the impact of the intervention on STDs.

An alternative explanation for the observed impact (or lack of impact) could be differential changes in sexual behaviour in the two trial arms, as discussed for HIV infection. However, as described in section 6.4.6, the sexual behaviour survey did not show any evidence for such changes.

It can be concluded that the observed estimates for the impact of the intervention on STDs were valid, and that it is unlikely that the reductions in syphilis and symptomatic urethritis observed in the main cohort were due to changes in sexual behaviour or other sources of bias.

7.5.4 Interpretation of the STD impact results

Self-reported STD symptoms

The intervention showed no impact on the incidence of self-reported symptoms in the past year in either men or women. In the case of women, it is well known that there is a poor correlation between symptoms and the presence of STD pathogens (Mulder 1993, Mosha et al 1993, Mayaud et al 1997). In the case of men, it seemed more surprising that improved STD case management services failed to reduce the incidence of reported STDs. There are several explanations for this observation.

It is likely that the health educational campaigns conducted at community level as part of the intervention and the improved health education given to individual patients resulted in increased awareness of STDs and thus differential recall bias in the intervention communities. Men (and women) in intervention communities may therefore have reported symptoms more often at the follow-up survey, so that the true impact, if any, may have been masked.

A further explanation is that the intervention was more likely to influence STD duration and prevalence than incidence, and that the incidence of self-reported STD episodes did not show a reduction therefore.

There were also many cases who reported symptoms but in whom no STD pathogen could be found. For example, only 27% of men in the main cohort who reported discharge and in whom this discharge was clinically confirmed, had a proven gonococcal and/or chlamydial infection, and of the men who reported discharge, and in whom this discharge could not be clinically confirmed, only 13% had a proven infection (Grosskurth et al 1996). Similar observations were made in an independent cross-sectional survey conducted in another large rural community in Mwanza Region in 1996, where pathogens were found in only 17% of 304 men complaining of urethral symptoms (Buve et al 1996). The same study revealed that urethral symptoms were significantly associated with *Schistosoma haematobium* infection, which is endemic in the region (OR 2.7, p=0.02). An STD intervention cannot have an impact on schistosomiasis. In the trial, the prevalence of schistosomiasis was not investigated, but it is likely that the failure of the intervention to show an impact on reported STD symptoms in men was due partly to the presence of this parasitic infection.

Urethritis in men

The baseline survey revealed that asymptomatic gonococcal and chlamydial infections were highly prevalent in this rural population, and that many more infections were asymptomatic than symptomatic (Grosskurth et al 1996, Mayaud et al 1995). This means that there is a large reservoir of asymptomatic infections in both men and women which keeps STDs in the population at a high level of endemicity. For example, 85% of gonococcal and chlamydial infections in men, and about 90% of the cases of urethritis were asymptomatic at baseline (table 6.12).

It is thus unlikely that an intervention which is designed to improve the management of symptomatic cases, and which only reaches a small proportion of sexual partners, can have a significant impact on the overall prevalence and incidence of urethral infections.

However, the situation was different for symptomatic cases of proven urethritis. A reduction of about 50% was observed. This observation suggests that the timely treatment of symptomatic cases in the intervention communities shortened the duration of these infections and thus reduced their prevalence. The (non-significant) reduction in prevalence of overall urethritis was mostly accounted for by this reduction in symptomatic urethritis.

Unexpectedly, a similar reduction in the prevalence of symptomatic infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* could not be demonstrated. It seems that a substantial proportion of symptomatic urethritis was caused either by non-specific infections, or by specific infections where the urethral pathogens were missed due to the comparatively low sensitivity of the diagnostic tests used in this trial, whilst microscopy was sufficiently sensitive to demonstrate the accompanying increase in polymorpho-nuclear cells (see section 7.4.2). Failure to show a reduction of symptomatic gonococcal and chlamydial infection may have been due also to small numbers and the correspondingly low power of the study to detect such a reduction.

Syphilis

The impact of the intervention on syphilis was considerable. There was a 36% reduction of syphilis incidence, though statistical significance was not reached. The prevalence of active

syphilis was significantly reduced by up to 46%, depending on the cut-off chosen for the RPR titre, and the prevalence of new cases of active syphilis was significantly reduced by 44%. Issues of potential biases caused by the tests used in this study are discussed in section 7.5.2.

The prevalence and the incidence of syphilis in this population are high (table 6.17). It is possible that the overall incidence increased in both groups of communities during the trial as comparared to the time before the trial, since the treatment of all RPR positive individuals at baseline may have rendered many persons with latent infections susceptible to new infections.

Prevalence of STDs in antenatal clinic attenders

The failure of the intervention to show any impact on the prevalence of STDs in the antenatal population after one year of intervention is disappointing. What were the possible reasons?

As mentioned above, cervical infections due to *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) are frequently asymptomatic (Holmes 1990), making it unlikely for an improved case management intervention to have any impact. The prevalence of NG and CT infection was identical in those who did and those who did not complain of vaginal discharge (Mayaud 1995).

Trichomonas vaginalis infection is frequently symptomatic. Even for this condition no reduction could be achieved. It is possible that this is due to inadequate treatment seeking behaviour. Vaginal discharge is so common that it is often regarded as something inevitable or even 'normal' (Mulder 1993). In the ANC attender study, many women, when directly prompted, admitted to vaginal discharge, but only few mentioned this complaint spontaneously (Philippe Mayaud, personal communication 1994).

This is consistent with the observation that only a minority of the many women in the community with symptoms of vaginal discharge voluntarily presented to a health facility. For example, only 46% of the 383 women who reported discharge during the past 2 years at the follow-up survey of the main cohort reported that they had sought treatment from a health facility. This lack of appropriate treatment seeking behaviour did not differ significantly between intervention and

comparison communities (50% versus 43%, p=0.17), and did not show an improvement from baseline (46% versus 51%).

The intervention led to a substantial and significant impact on active syphilis in the main cohort. Why did it not show a similar impact among antenatal clinic attenders? In the case of antenatal clinic attenders, a cohort was not followed, and different women were seen at follow-up than at baseline. Whereas in the main cohort, RPR-positive subjects were all treated at baseline, the antenatal clinic attenders seen in the second cross-sectional survey had not been treated in this way. Thus at the second survey in the main cohort, most subjects presented infections which they acquired during the past two years, whereas many of the seropositive results in antenatal women will have been due to long-standing infections. This observation emphasises the importance of regular antenatal syphilis screening and treatment. Although this measure has been promoted for a considerable time, it is not routinely performed in most parts of Africa (Hira et al 1990, Temmerman et al 1993), including Mwanza Region.

7.6 Implications of the trial

7.6.1 Implications for the choice of STD control strategies

In conclusion, the intervention for the improved case management of symptomatic STDs achieved a substantial and significant impact on syphilis in the general population and on symptomatic urethritis in men.

Unfortunately, the intervention failed to show any impact on STDs in women, partly because these infections were asymptomatic and partly because it was not possible to improve the treatment seeking behaviour of women for symptomatic infections.

It follows that only through comprehensive screening programmes can a reduction in the prevalence of STDs be achieved in the female population. Unfortunately even screening for syphilis is not yet routinely practised in most antenatal clinics in sub-Saharan Africa, as discussed earlier.

Cheap and simple screening tests for NG and CT infections are not available. To overcome this problem, attempts have been made to identify women at risk for such infections through a simple

questionnaire focusing on demographic and other risk factors. Unfortunately, this attempt was not very successful: the sensitivities and specificities of the risk scores developed to detect NG or CT cervicitis ranged between 50% and 70% (Vuylsteke et al 1993i, Mayaud et al 1995).

Another option to reach asymptomatic patients or those who do not seek treatment on their own, would be the treatment of sexual partners. However, in this trial the treatment of only 35% of partners of men with STDs and only 33% of the partners of women with STDs was recorded.

Thus the development of simple and cost-effective screening tests remains an urgent priority, and once such tests become available, screening programmes should be launched on a large scale in addition to programmes for the improved management of symptomatic STDs.

Presumptive treatment of either the whole population or of populations at high risk have been suggested (Over and Piot 1993, Wawer et al 1996). However both approaches have not yet been validated sufficiently, are likely to be expensive, and are still controversial. Preliminary results from the trial in Rakai show that STD prevalences can be significantly and substantially reduced through mass treatment. For example, *Trichomonas vaginalis* infection in women was reduced from 25% in intervention communities to 9% in intervention communities (RR 0.4, 95%CI 0.3 - 0.5); and a significant impact on syphilis was suggested by declining RPR titres (Wawer et al 1996). Data on the impact on HIV transmission are not yet available.

These initial successes argue for more intensive research on mass treatment and presumptive treatment, in different settings and under less than optimal conditions. Because mass treatment is very expensive, it has also been suggested that the impact of a single round of mass treatment in the general population in combination with improved case management services should be investigated (Hayes et al 1997).

7.6.2 Implications for AIDS control programmes

This intervention achieved a substantial reduction in the incidence of HIV infection in conjunction with a major reduction of the prevalence of active syphilis, and of symptomatic urethritis in men. It had little impact on asymptomatic infections. These observations suggest that symptomatic STDs are of particular importance for HIV transmission. The study does not allow

us to determine whether the ulcerative or non-ulcerative infections played the more important role. Whilst the co-factor effect of genital ulcers may be particularly high (Hayes et al 1995i), the attributable risk of HIV infection due to non-ulcerative STDs is considerable and may even be higher, since these STDs are usually much more prevalent (Laga et al 1993). The observed impact on STDs in the Mwanza trial seems to be consistent with the suggestion that both types of STDs are important for HIV transmission.

Rational health policy decisions depend on reliable data on the cost-effectiveness of different health interventions. Because of the urgency of the AIDS epidemic, interventions had to be launched without the benefit of such data. The Mwanza trial has helped to close this gap.

How generalisable are the trial results to other rural populations in Africa? With an adult HIV prevalence of around 4% and an annual HIV incidence of around 1%, the rural population of Mwanza Region is fairly typical of many other parts of sub-Saharan Africa. STD prevalences in Mwanza Region were high, but this is also the case in many other parts of the continent, as has been described in section 2.1.4.

The intervention strategy was chosen for its potential replicability in low-income countries, and was designed to be implemented through routine primary health care services.

In conclusion, the trial has provided evidence to justify the allocation of substantial resources to the control of STDs through improved treatment services in countries with high STD prevalences. This includes most countries in Africa, but is probably highly relevant for some developing countries in Asia and Latin America as well.

It is therefore suggested that STD control should assume a key place within AIDS control programmes in developing countries, together with health promotion for risk reduction and other measures which have a proven efficacy to contain the AIDS epidemic.

Chapter 8 Conclusions and recommendations

8.1 Conclusions

Public health importance of HIV infection and STDs

The incidence of HIV infection in the absence of the STD intervention was considerable in the adult population in Mwanza Region at around 1% per year. It was particularly high in young women. STDs were highly prevalent and represented an important public health problem.

Impact of the intervention

The improvement of STD treatment services in Mwanza Region led to a reduction in HIV incidence in the study population of 43%. After adjustment for possible confounding factors, the reduction was 38% (95% CI = 15% - 55%).

The intervention also had a considerable impact on STDs. The prevalence of active syphilis was significantly reduced by 11% - 46%, depending on the cut-off chosen for the rapid plasma reagin (RPR) test. Symptomatic urethritis in men was reduced by about 50%.

No impact was observed on the prevalence of asymptomatic urethritis in men, suggesting that symptomatic STDs seem to be of particular importance for HIV transmission.

There was no impact on cervical or vaginal infections in pregnant women, whether symptomatic or asymptomatic, suggesting that comprehensive screening programmes would be needed to achieve a reduction in the prevalence of STDs in the female population.

STD/HIV co-factor hypothesis

The trial provided additional evidence for the hypothesis that STDs enhance the transmission of HIV infection, and that the control of STDs can substantially reduce HIV transmission in populations where STDs are highly prevalent. The results are consistent with observational

studies and studies demonstrating increased HIV shedding in cervical or vaginal secretions, or in semen of HIV infected persons in the presence of bacterial STDs, and a decrease in viral load in semen after the treatment of urethritis. Taking all these findings together, the STD/HIV co-factor hypothesis has now been confirmed beyond reasonable doubt.

Design and operational performance of the intervention

These results were achieved through improved STD services which were integrated into the existing primary health care system. Syndromic case management as recommended by WHO and adopted by the Government of Tanzania, was shown to be feasible and effective. The study showed that a reference clinic and laboratory are required to monitor the antibiotic susceptibility of *Neisseria gonorrhoeae*. It was shown that the referral of STD patients leads to low cure rates, because many patients are lost to follow-up.

A reliable supply of drugs and frequent support supervision with a strong in-service training component were essential to achieve satisfactory performance of health services. Factors which seem to impair the performance of health workers include time pressure and difficult socio-economic conditions.

Policy implications

With respect to the control of both STDs and HIV infection, the trial has provided strong evidence to justify the allocation of substantial resources to the control of symptomatic STDs through improved treatment services in countries with high STD prevalences.

An intervention aimed at improving STD case management through the official health sector will be sustainable only if the health services are functional. For example, serious underpayment of health workers is a major obstacle for the improvement of health services including STD treatment services. It is therefore recommended that the introduction of improved STD services should be embedded in measures to improve the situation of health workers and the quality of health services in general, wherever this is necessary.

8.2 Recommendations

Recommendations with respect to AIDS control

Interventions to reduce STDs should form an integral part of AIDS control programmes, particularly in populations with high STD prevalences. Such interventions should be complemented by health promotion aiming at a decrease of risky sexual behaviour, and other measures of proven efficacy to contain the AIDS epidemic.

Recommendations with respect to strategies for STD control

Interventions aimed at a reduction of symptomatic STDs should be a priority.

STD case management services should be integrated into the existing primary health care structure wherever possible.

The syndromic approach for STD diagnosis and case management is preferred whenever other diagnostic methods are not routinely available at low cost.

Regular and frequent support supervision visits to health workers are absolutely essential for the success of the control programme.

STD patients should be referred to higher levels of care only under exceptional circumstances. Instead, health care facilities and -if existent in the community- private providers should have the capacity for second and third line STD treatment, so that all necessary options are available at the place of the first encounter between the STD patient and the health system.

Recommendations for future research

The size of the reduction in STD prevalence and incidence which can be achieved through improved STD case management depends on the size of the co-factor effect, on the initial prevalences of STDs and HIV infection in the community, the proportion of STDs which are

asymptomatic, the treatment seeking behaviour of the population, the compliance of patients, the proportion of partners which can be reached and treated, the effectiveness of the drugs used, and the performance of the health workers involved. It is therefore likely that the same type of intervention may have a greater or lesser impact in other settings. It would be of interest to compare the results of the three trials in East Africa with the help of a computer simulation programme, in order to arrive at more reliable predictions of how to optimise an STD intervention for HIV prevention in different environments.

The development of simple and cost-effective screening tests, particularly for the diagnosis of STDs in women, remains an urgent priority. Once such tests become available, screening programmes should be piloted, and their impact evaluated in randomised controlled trials. If their cost-effectiveness can be proven, screening programmes should be launched on a large scale in addition to interventions for the improved management of symptomatic STDs.

The control of STDs in core groups may be a particularly effective strategy for HIV prevention. STD control programmes should be established in sex workers and other high risk behaviour groups, and their impact on the prevalence of STDs and the incidence of HIV infection in the general population should be rigorously evaluated, for example through a randomised controlled trial.

The mass treatment of STDs may possibly represent a promising option for HIV prevention in the general population. A randomised controlled trial should be performed to investigate the impact of a replicable strategy, for example the combination of a single round of mass treatment with improved STD case management services. Such a trial should be conducted in a population with high STD prevalences and an immature HIV epidemic, marked by increasing HIV prevalences. The reduction in STD prevalences, and the time taken for prevalences to return to their original level, should be recorded.

The Mwanza trial has demonstrated high STD and HIV prevalences in adolescents, particularly in girls and young women. The design and implementation of appropriate interventions to improve the sexual and reproductive health of adolescents through educational programmes and improved access to health services is of high priority. So far there are no data on the efficacy of such interventions in reducing HIV incidence. Trials of such interventions are urgently needed.

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STD training course for health workers: standardised timetable

	Subject	Teaching units (of 45 min)
1.	Public health importance of STDs	2
1.1	Burden on health caused by STDs	
1.2	The STD/HIV cofactor effect	
2.	STD patients and health workers' attitude	3
2.1	Psychological situation of an STD patient	
2.2	How to ensure privacy and confidentiality at the clinic	
2.3	Caring vs. blaming attitudes	
2.4	Local perceptions of STDs and STD symptoms	
2.5	Review	
3.	STD syndromes and their management	18
3.1	Introduction: syndromes and syndromic management (with slide presentation and quiz)	
3.2	Components of good case management: history taking, examination, health education, treatment	
3.3	STD syndromes: introduction, brief discussion of aetiologies, complications, treatment algorithms:	
3.4	Issues of compliance, directly observed treatment	
3.5	Resistance development / ethics of correct prescription and drug dispensing	
3.6	Review	
4.	Health education for STD patients	8
4.1	Importance of good health education	
4.2	Elements of good health education / check list	
4.3	Prevention of re-infection	
4.4	Treatment compliance	
4.5	Condom promotion	
4.6	Partner notification / contact slips	
4.7	Role plays on health education incl. condom promotion and partner notification	
4.8	Review	
5.	Recording and reporting	3
5.1	STD patient register book	
5.2	STD patients tally sheet	
5.3	Operational self evaluation	
5.4	STD report form	
5.5	Review and practical exercises	
6.	Management of the clinic	2
6.1	Integration into routine work	
6.2	Essential equipment for the management of STDs	
6.3	How to organise the clinic room	
6.4	How to organise the clinic	
6.6	Review	
7.	Optional: AIDS	(8)
7.1	Understanding AIDS	
7.2	Clinical synopsis	
7.3	Management of opportunistic infections at the health unit	
7.4	Coping with AIDS in the family and community	
7.5	Management of opportunistic infections in the home	
7.6	Review	
8.	Administrative and other issues	4
	Total course duration	40 (48)

Annex 2

STD/HIV Intervention Mwanza Region **Supervision form: part 1**

Personnel, equipment, performance

Health unit: _____ Date: _____ Quarter: _____

Supervisor: _____

1. Personnel: health workers with STD training

Name:	Function:	present and working Y / N
Name:	Function:	present and working Y / N
Name:	Function:	present and working Y / N

2. Equipment

Item	available and in order?	Item	available and in order?
Examination bed	Y / N	Torch	Y / N
Bed sheet	Y / N	Waiting bench	Y / N
Screen	Y / N	Desk	Y / N
Speculum	Y / N	2 chairs	Y / N
Plastic container	Y / N	Register book	Y / N
Water container	Y / N	Treatmt. flow charts	Y / N
Plastic mug	Y / N	Training manual	Y / N

Repairs or replacement needed: _____

3. Supervision checklist

1. Staff availability: any present or anticipated problem ?		Y / N
2. Register book: is the information complete and consistent ? Which problems ?		Y / N
3. Have algorithms been followed ? What type of problem did you observe ?		Y / N
4. Any difficult cases seen jointly with the HWs? Which ones ?		Y / N
5. Feed-back and training: Which topics did you discuss today with the HWs ?		

STD/HIV Intervention Mwanza Region **Supervision form: part 2**

1. **Summary numbers: syndromes treated, clinical cures, referrals, partners treated**
2. **Drug consumption ('should-be consumption')**

Health unit: **Month/year:**

	Nu of cases	Nu of partn. treat.	TMS forte 960mg	Doxy-cycline 100mg	Metro-nidazole 200mg	Benza. Penicill. 2.4MU	Ciprofloxac. 500mg	Erythro-mycine 500mg	Nu cured	Nu*) of tr.fail. / referrals
Men:GUS 1st line			**x8=**			**x1=**				
GUS 2nd line								**x21=**		
GUS 3rd line							**x3=**			
second. syphilis						**x1=**				
Bubo 1st line			**x8=**	**x28=**						
Bubo 2nd line			**x12=**				**x3=**			
Women: GUS 1st			**x8=**			**x1=**				
GUS 2nd line								**x21=**		
GUS 3rd line							**x3=**			
second. syphilis						**x1=**				
Bubo 1st line			**x8=**	**x28=**						
Bubo 2nd line			**x12=**				**x3=**			
UDS 1st line			**x10=**	**x14=**						
UDS 2nd line				**x14=**	**x10=**					
UDS 3rd line							**x1=**			
VDS 1st line			**x10=**	**x14=**	**x10=**					
VDS in pregn			**x10=**					**x21=**		
VDS 2nd line				**x14=**						
VDS 3rd line							**x1=**			
PID 1st line			**x10=**	**x28=**	**x28=**					
PID 2nd line							**x1**			
Balanitis *)			**x10=**			**x1=**				
total										

Annex 2

STD/HIV Intervention Mwanza Region **Supervision form: part 3**

Calculation of surplus and deficit / consumables supplied / new stock

Health unit: **Month/year:**

	1 old stock	2 count stock	3 real consump	4 should-be consump	5 = (4 - 3) surplus: + deficit: -	6 reasons/ remarks	7 supplied today	8 new stock
TMS forte 960 mg								
Docy-cycline 100 mg								
Metro-nidazole 200 mg								
Erythro-mycin 500 mg								
Benza-Penicill 2.4 MU								
Cipro-floxacin 500 mg								
Gentian violet 1% 0.5 l								
Syringes 10 ml								
Needles f. inject								
Cotton wool								
Antisept solution								
Batteries								
Register book								
Pens								

Date: _____ Supplied (name): _____ Signature: _____

Received (name): _____ Signature: _____

Annex 2

STD/HIV Intervention Mwanza Region **Supervision form: part 4**

Follow-up of referrals

Health unit: _____ **Month/year** _____

Name / sex	Syndrome	Reason for referral	Referred to (name of HC, hospital)	Date of referral	Follow-up results

---

Legend for *part 2* of supervision form:

*) number of total treatment failures recorded = F
number of referrals recorded = R

GUS = genital ulcer syndrome, UDS = urethral discharge syndrome, VDS = vaginal discharge syndrome, PID = pelvic inflammatory disease/lower abdominal tenderness, Bubo = bubo without ulcer, Balanitis = balanitis w. foreskin not retractable

Annex 3

Main cohort study: Baseline questionnaire

(English translation of Swahili form)

Complex: _____

Cluster: _____

Balozi: _____

Person: _____

Trip No: _____

AMREF STD Intervention Study: Questionnaire (1)

INTERVIEWER: *We would like to ask you few questions, which have been authorised by the party, your leaders and also your ten cell leader. All information you give us will be a secret.*

"Please, give me your full name": INTERVIEWER - use CAPITAL LETTERS

Religious name: _____

(NB. if no such name, put a dash)

Birth name: _____

Surname: _____

Full name of the household: _____

Religious name: _____

Surname: _____

INTERVIEWER'S INITIALS: _____

INTERVIEWER'S CODE: _____

Complex: _____

Cluster: _____

Balozi: _____

Person: _____

INTERVIEWER: *please circle the response AND write the relevant letter in the box. Remember to put a cross (X) in the boxes for which a reply is not applicable (such as questions 4, 5, etc.)*

1. Sex — Male/Female — 1. _____

2. How old are you (in years) — 2. _____

3. Now are you married? — No / Yes — 3. _____

4. If answer to Q3 is YES, Are living together, or apart?

   Together / Apart / X = n/a — 4. _____

5. If answer to Q3 is NO, Have you ever married

   No / Yes/X=not appl. — 5. _____

6. If answer to Q5 is YES, Are you divorced / widowed?

   Divorced/Widowed/X=n/a — 6. _____

7. How many injections have you had within twelve months past?

INTERVIEWER: *Explain that it is the total number of injections from hospital and from non-medical people.*

None / 1 / 2 / 3 / 4 / 5 or more — 7. _____

8. Have you ever been transfused within the period of 5 years past?

   No / Yes — 8. _____

9. What is your highest level of education?

   A: Below 4 years of primary education (include no primary education - A)

   B: Four years or above primary education?

   A / B — 9. _____

10. What is the furthest distance you have travelled within the period of twelve months past?

   A. Within this ward?
   B. Within this division?
   C. Witrhin this district?
   D. Within this region?
   E. Out of this region but within the country (Tanzania)
   F. Out of the Country (Tanzania)

   A / B / C / D / E / F — 10. _____

INTERVIEWER: *Ask the interviewee about his / her general health. "We are aware that, there are several people with disease problems in there private parts. In order to understand the extent of the problems, we would like to ask you few questions which would enable us to know whether you have had one of these problems in the past. We will offer you a free treatment incase your problem is curable".*

11. Do you have or have ever had an ulcer in your private parts?

No / Yes 11. _____

(**INTERVIEWER**: Show picture)

If answer to Q.11 is No, write X for Q.12 - 14 and go to Q.15.

12. Did this ulcer start within the past twelve months?

No / Yes / X= n/a 12. _____

13. Is the ulcer still there at present?

No / Yes / X= n/a 13. _____

14. Did you get any treatment?

No / Yes / X = n/a 14. _____

15. Have you ever had

[MALES] pus or watery discharge from the penis

[FEMALE] vaginal pus or abnormal watery discharge, now or in the past?

If answer to Q.15 is No, write X for Q.16 - 18 and go to Q.19

16. Did the discharge start within the past twelve months?

No / Yes/X= n/a 16. _____

17. Do you still have that problem up to now?

No / Yes / X= n/a 17. _____

18. Did you get any treatment for that problem?

No / Yes X = n/a 18. _____

If the answer to either question 14 or 18 is YES,

19. Where did you get the treatment for your problem?

a) Traditional healers? No/Yes X= n/a 19a. _____

b) Drug shop? No/Yes X = n/a 19b. _____

c) Dispensary/Health Center/Hospital?

No/Yes/X=n/a 19c. _____

(INTERVIEWER) *If this includes a coded Health Center/Dispensary, enter code: otherwise enter XXX.*

20. [MEN ONLY] Please may I ask you, are you circumcised?
No / Yes / Don't know / R = refused / X = n/a 20. _____

INTERVIEWER: *Ask the interviewee if he/she has any questions to ask. Thank him/her for his/her cooperation in answering your questions, then explain to him that we shall take some little blood and urine (for males only) to investigate if he/she has diseases which we can offer treatment after a while, as some of the STDs can be diagnosed by investigating blood sample, and explain to him/her that is he/she has an infection we shall offer treatment.*

Explain we need an interval of 2 hours since urine was last passed.

INTERVIEWER: Attach blood sample sticker here _____
and give 9 more stickers with the same number to the interviewee. Then send him / her to the laboratory.

REMEMBER to complete the 'current STD reported at interview' form.

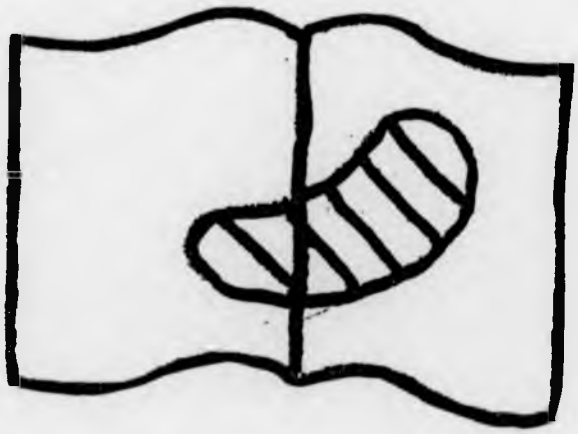
Trip number: _____ Interviewer's code: _____ Initials: _____

Annex 4

Main cohort study: Follow-up questionnaire

(English translation of Swahili form)

Best Copy
Available



Complex/Cluster/Balozi/Person ___/___/___/____

INTERVIEWER: Make sure of the identity of the person in front of you. Copy the complex/cluster/balozi/number and the name from the Balozi list? COPY the check letter.

Name: _____ Check letter ___

Check the age and sex of the person. Do age and sex agree with balozi list? **If not report to team leader.**

Sex Male/Female ___ Age ____

INTERVIEWER: Please check the following points are explained to the study participant.

A. Two years ago people kindly took part in a survey we conducted.
B. This is a follow up to find out about people's health during the last 2 years.
C. Treatment will be provided for persons with curable conditions.
D. The study has been approved by the local / governmental leaders.
E. All responses are totally confidential.
F. We hope the participant will consent to answer the questions.

Informed oral consent obtained.
Interviewers signature _____ Code ___

INTERVIEWER: Look at the Balozi list for this person. **If the list shows MARITAL STATUS = 'M'.**

"When we visited the village 2 years ago you were married and living with your partner. Can you give us the name of your partner at that time." Ask about the spouse(s) of two years ago and **if they belong to the same balozi** find their person number on the list. If more than two wives are mentioned take the first two mentioned.

Name1: _____ ___
ENTER PERSON NUMBER ONLY IF IN THE SAME BALOZI

Are they still living together Yes / No ___
If Not, is the spouse dead Yes / No ___

Name2: _____ ___
ENTER PERSON NUMBER ONLY IF IN THE SAME BALOZI

Are they still living together Yes / No ___
If Not, is the spouse dead Yes / No ___

Please place one sticker here,
put one on the link form,
give another 8 to the participant

Complex/Cluster/Balozi/Person ___/___/___/____

Check letter ___

1. What is your current occupation? ___

A Farmer	B Student/school pupil
C Unskilled manual	D Skilled manual
E Office work	F Business
G Fisherman	H Truck driver
I Gold miner	J Bar-worker/pombe shop worker
K Other (Specify _____)	
X No job	

2. What is your Religion? ___

A = Muslim	B = Catholic
C = Protestant	D = Other

3. What is your tribe ___

A Sukuma	B Gita
C Zinza	D Mkara
E Mkerewe	F Mhaya
G Other	

4. Have you lived anywhere else, for longer than 1 month, outside of this village, during the past 2 years.

Yes/No ___

If YES to Q4,

5. Did you live in

Mwanza	Yes/No/X	___
Another town	Yes/No/X	___
Mining area	Yes/No/X	___
Anywhere else	Yes/No/X	___

"Now I would like to ask you about your health now and in the past two years"

6. Do you have any health problem at present **Yes/No** ___

If YES to Q6,

7. Please tell me about it. Interviewer: Please indicate if the following are mentioned. If not then ask

	Yes/No/X		Duration	Yes/No/X	
7a.	Fever	___	more than 1 month		___
7b.	Chronic cough	___	more than 1 month		___
7c.	Diarrhoea	___	more than 1 month		___
7d.	Weight loss	___	more than 1 month		___

For females only (Questions 8-10). For males put X.

Interviewer: *"We would like to ask you about the health of your children."*

8. Have you any children below the age of 2 years? (Make sure the child was born since the last visit 2 years ago)

Yes/No/X ___

If YES to Q8

9. Soon after birth, did any of these children have a thick yellow or green discharge from their eyes?

Yes/No/X ___

10. During the past two years have you ever delivered a stillborn child? (Explain stillborn is a full term baby who was dead on delivery)

Yes/No/X ___

11. Have you had a genital discharge now or during the last 2 years

Yes/No ⌊__⌋

If YES to Q11,

12. Think of the most recent episode.
How long ago did it start? ⌊__⌋

A = Less than 1 week ago B = Less than 1 month ago
C = Less than 1 year ago D = Between 1 and 2 years ago

13. Do you still have it? Yes/No/X ⌊__⌋

14. Did you get treatment for the genital discharge Yes/No/X ⌊__⌋

If YES to Q14,

15. Where did you go for treatment

15a	First place	⌊__⌋ ⌊__⌋⌊__⌋
15b	Second place	⌊__⌋ ⌊__⌋⌊__⌋
15c	Third place	⌊__⌋ ⌊__⌋⌊__⌋

A = Traditional healer
B = Drugs store/shop
C = Disp/Health centre/Hosp
(Please put code for any govt health unit used, else XX)

16. Have had any genital ulcer now or during the last 2 year

Yes/No ⌊__⌋

If YES to Q16, ask Q17-19

17. Think of the most recent episode.
How long ago did it start? ⌊__⌋

A = Less than 1 week ago B = Less than 1 month ago
C = Less than 1 year ago D = Between 1 and 2 years ago

18. Do you still have it? Yes/No/X ⌊__⌋

19. Did you get treatment for the genital ulcer Yes/No/X ⌊__⌋

If YES to Q19, ask Q20

20. Where did you go for treatment

20a	First place	⌊__⌋ ⌊__⌋⌊__⌋
20b	Second place	⌊__⌋ ⌊__⌋⌊__⌋
20c	Third place	⌊__⌋ ⌊__⌋⌊__⌋

A = Traditional healer
B = Drugs store/shop
C = Disp/Health centre/Hosp
(Please put code for any govt health unit used, else XX)

If any Govt health unit used in Q15 or Q20 then ask about the most recent treatment.

21. Did you get drugs? Yes/No/X ⌊__⌋

22. Were you examined? Yes/No/X ⌊__⌋

23. Did you have to pay a fee? Yes/No/X ⌊__⌋

24. Were you given condoms? Yes/No/X ⌊__⌋

Annex 5 STD/HIV Intervention and Research Programme Mwanza Region: List of publications

1. Publications in refereed scientific journals:

1.1 Directly related to the trial

Hayes R, Mosha F, Nicoll A, Grosskurth H, Todd J, Newell J, Killewo J, Rugemalila J, Mabey D: A community trial of the impact of improved STD treatment on the HIV epidemic in rural Tanzania: 1. Design. AIDS 1995; 9: 916-26.

Grosskurth H, Mosha F, Todd J, Senkoro K, Newell, J, Klokke A, Changalucha J , West B, Mayaud P, Gavyole A, Gabone R, Mabey D, Hayes R: A community trial of the impact of improved STD treatment on the HIV epidemic in rural Tanzania: 2. Baseline Survey Results. AIDS 1995; 9: 927-34.

Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, Mayaud P, Changalucha J, Nicoll A, ka-Gina G, Newell J, Mugeye K, Mabey D, Hayes R: Impact of improved treatment of sexually transmitted diseases on HIV Infection in rural Tanzania: randomised controlled trial. The Lancet 1995; 346: 530-36.

Mayaud P, Grosskurth H, Changalucha J, Todd J, West B, Gabone R, Senkoro K, Rusizoka M, Laga M, Hayes R, Mabey D: Risk assessment and other screening options for gonorrhoea and chlamydial infections in women attending rural Tanzanian antenatal clinics. Bulletin of the World Health Organ 1995, 73 (5):621-630

Grosskurth H, Mayaud P, Mosha F, Todd J, Senkoro K, Newell J, Gabone R, Changalucha J, West B, Hayes R, Mabey D: Asymptomatic gonorrhoea and chlamydial infection in rural Tanzanian men. British Medical Journal 1996; 312: 277-80

Quigley M, Munguti K, Grosskurth H, Todd J, Mosha F, Senkoro K, Newell J, Mayaud P, ka-Gina G, Klokke A, Mabey D, Gavyole A, Hayes R: Sexual behaviour patterns and other risk factors for HIV infection in rural Tanzania: a case-control study. AIDS 1997, 11:237-248

Gilson L, Mkanje R, Grosskurth H, Mosha F, Picard J, Gavyole A, Todd J, Mayaud P, Swai R, Fransen L, Mabey L, Mills A, Hayes R: Cost-effectiveness of improved treatment services for sexually transmitted diseases in preventing HIV-1 infection in Mwanza Region, Tanzania. The Lancet 1997; 350: 1805-09

Munguti, Grosskurth H, Newell J, Senkoro K, Mosha F, Todd J, Mayaud P, Gavyole A, Quigley M, Hayes R: Patterns of sexual behaviour in a rural population in North-Western Tanzania. Social Science and Medicine 1997, 44:1553-1561

Todd J, Balira R, Grosskurth H, Mayaud P, Mosha F, ka-Gina G, Klokke A, Gabone R, Gavyole A, Mabey D, Hayes R: HIV-associated adult mortality in a rural Tanzanian population. AIDS 1997, 11: 801-807

Mayaud P, Mosha F, Todd J, Balira, R, Mgara J, West B, Rusizoka M, Mwijarubi E, Gabone R, Gavyole A, Grosskurth H, Hayes R, Mabey D: Improved treatment services significantly reduce the prevalence of sexually transmitted diseases in rural Tanzania: results of a randomised controlled trial. AIDS 1997; 11:1873-1880

Hayes R, Wawer M, Gray R, Whitworth J, Grosskurth H, Mabey D, and HIV/STD Trials Workshop Group: Randomised trials of STD treatment for HIV prevention: report of an international workshop. Genitourinary Medicine, 1997; 73: 432-443

1.2 Related to other research performed by the STD/HIV Intervention Programme Mwanza Region

Barongo L, Borgdorff M, Mosha F, Nicoll A, Grosskurth H, Senkoro K, Newell J, Changalucha J, Klokke A, Killewo J, Velema J, Hayes R, Dunn D, Muller L, Rugemalila J: The epidemiology of HIV-1 infection in urban areas, roadside settlements and rural villages in Mwanza Region, Tanzania; AIDS 1992, 6: 1521 - 1528.

Mayaud P, Changalucha J, Grosskurth H, ka-Gina G, Rugemalila J, Nduba J, Newell J, Hayes R, Mabey D: The value of urine specimens in screening for male urethritis and its microbial aetiologies in Tanzania; Genitourin Med 1992, 68: 361 - 365.

Mosha F, Nicoll A, Barongo L, Borgdorff M, Senkoro K, Grosskurth H, Changalusha J, Klokke A, Newell J, Killewo J, Velema J, Muller A, Rugemalila J, Hayes R, Mabey D: A population-based study of syphilis and sexually transmitted disease syndromes in north-western Tanzania. 1. Prevalence and incidence; Genitourin Med 1993; 69: 415-420.

Newell J, Senkoro K, Mosha F, Grosskurth H, Nicoll A, Barongo L, Borgdorff M, Klokke A, Changalucha J, Killewo J, Velema J, Muller A, Rugemalila J, Mabey D, Hayes R: A population-based study of syphilis and sexually transmitted disease syndromes in north-western Tanzania. 2. Risk factors and health seeking behaviour; Genitourin Med 1993; 69: 421 - 426.

Nicoll A, Laukamm-Josten U, Mwizarubi B, Mayala C, Mkuye M, Nyembela G, Grosskurth H: Lay health beliefs concerning HIV and AIDS - a barrier for control programmes; AIDS Care 1993, 5: 223-233.

Kigadye R, Klokke A, Nicoll A, Nyamuryekung'e K, Borgdorff M, Barongo L, Laukamm-Josten U, Lisekie F, Grosskurth H, Kigadye F: Sentinel surveillance for HIV-1 among pregnant women in a developing country: 3 years' experience and comparison with a population serosurvey; AIDS 1993,7: 849 - 855.

Borgdorff M, Barongo L, van Jaarsveld E, Klokke A, Senkoro K, Newell J, Nicoll A, Mosha F, Grosskurth H, Swai R, van Asten H, Velema J, Hayes R, Muller L, Rugemalila J: Sentinel surveillance for HIV-1 infection: how representative are blood donors, outpatients with fever, anaemia or sexually transmitted diseases, and ante natal clinic attenders in Mwanza Region, Tanzania? AIDS 1993; 7: 567 - 572.

West B, Changalucha J, Grosskurth H, Mayaud P, Gabone R, Ka-Gina G, Mabey D: Antimicrobial susceptibility, auxotype and plasmid content of *Neisseria gonorrhoeae* in Northern Tanzanbia: emergence of high level plasmid mediated tetracycline resistance. Genitourinary Medicine 1995; 71: 9-12.

Mayaud P, Msuya W, Todd J, Kaatano G, West B, Begkoyian G, Grosskurth H, Mabey D: STD rapid assessment in Rwandan refugee camps in Tanzania. Genitourinary Medicine 1997, 73: 33-38

Jacobs B, Mayaud P, Changalucha J, Todd J, ka-Gina G, Grosskurth H, Berege Z: Sexual transmission of Hepatitis B in Mwanza, Tanzania. Sexually Transmitted Diseases 1997

Mayaud P, Uledi E, Cornelissen J, ka-Gina G, Todd J, Kaatanao G, West B, Rwakatare M, Kopwe L, Manoko D, Klokke A, Grosskurth H, Hayes R, Mabey D: Use of WHO risk-assessment to detect cervical infections in women attending routine urban antenatal clinic services in Mwanza, Tanzania. Submitted to Genitourinary Medicine, December 1997

2. Letters in refereed scientific journals

Grosskurth H, Plummer F, Mhalu F, Mabey D: STD research in Africa, The Lancet 1993; 342: 1415 - 1416.

Hayes R, Grosskurth H, ka-Gina G: Impact of improved management of STD (letter), The Lancet 1995; 346: 1159-60

Ka-Gina G, Grosskurth H, Hayes R: Prevention of HIV spread in developing countries (letter). Lancet 1996, 348: 1742

Grosskurth H, Gilson L, Mills A, Hayes R: Cost-effectiveness estimates of the Mwanza sexually transmitted diseases intervention (letter). Lancet 1998, 351: 989-990

3. Publications in non-refereed journals and series

Mayaud, ka-Gina G, Grosskurth H: STD case management. In: Prevention and Management of STDs in Eastern and Southern Africa. Naresa Monograph, PO 11771, Nairobi, Kenya 1994, ISSN 1023-6783

Grosskurth H, Mayaud P, ka-Gina G, Mosha F, Todd J: Risk assessment for the diagnosis of sexually transmitted diseases. In: Prevention and Management of STDs in Eastern and Southern Africa. Naresa Monograph, PO 11771, Nairobi, Kenya 1994, ISSN 1023-6783

Msuya W, Mayaud P, Mkanje R, Grosskurth H: Health care in unstable situations: Taking early action in emergencies to reduce the spread of STDs and HIV. Africa Health 1996; 18: 24

Ka-Gina G, Nicoll A, Grosskurth H et al : Enhanced detection and treatment of curable sexually transmitted diseases - a proven method for reducing sexual transmission of HIV. PHLS Microbiology Digest 1997: 14(1): 3-7

Grosskurth H: Syndromic case management of sexually transmitted diseases. International Planned Parenthood Foundation Medical Bulletin 1997, 31: 1-2

4. Manuals and text books:

Msuya W, Rajani R, Kudrati M, Grosskurth H: Life first: A practical guide for patients and families with AIDS, AMREF, Dar es Salaam, 1993. English and Kiswahili editions.

Mwijarubi E, Grosskurth H: STD Control efforts in health units. - District STD control efforts. - 2 chapters in Ng'weshemi J, Boerma T, Bennett J, Schapink D (eds): HIV prevention and AIDS care in Africa. KIT Press, Royal Tropical Institute, Amsterdam, 1997

Adler M, Foster S, Grosskurth H, Richens J, Slavin H: Sexual health and care: Sexually transmitted infections. Guidelines for prevention and treatment. DfID Health and Population: Occasional Paper; London, DfID 1998 (2nd edition, in press)