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**A PILOT STUDY ON THE PREVENTION OF HIV
RELATED TUBERCULOSIS IN ZAMBIA**

BY:

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DECLARATION

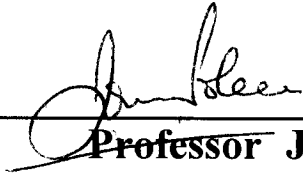
I hereby declare that the work presented in this study for the Master of Medicine degree has not been presented either wholly or in part for any other degree and is not being currently submitted for any other degree

Signed



Student

Signed



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SUMMARY

During the last decade there has been an increase in notification rates of tuberculosis in many developing countries the world over. Epidemiological evidence has linked this increase to the HIV epidemic in many of these countries, the mechanism of which is thought to be either reactivation of a distantly acquired latent infection or re-infection or progression from a recent infection. As a result of this association between HIV and tuberculosis attention has been drawn to the possibility for the use of preventive therapy as a means of reducing the incidence of tuberculosis in the HIV infected individual with a latent tuberculosis infection in developing countries with a high incidence of dual HIV/tuberculosis infection.

To address this issue a randomised placebo controlled double blind trial of two intermittent regimens of tuberculosis preventive therapy with a study sample of about 1000 HIV positive individuals was proposed as a collaborative effort between the University of Zambia and the London School of Hygiene and Tropical Medicine. Prior to beginning this study a pilot study was carried out in order to assess the feasibility of recruiting and following up a cohort of HIV positive individuals in Lusaka.

The pilot study and its findings are presented in this dissertation.

At recruitment an assessment of Knowledge and Attitudes to HIV showed a high level of knowledge about HIV and its transmission. The recruitment of HIV infected patients occurred at a higher rate among those individuals already aware of their HIV status than those who were tested for the first time for the purpose of recruitment into the study suggesting that a voluntary testing centre would be a good recruitment site. Difficulty in excluding active tuberculosis was a major reason for non-enrolment into the study, however no active case of tuberculosis was diagnosed in these patients.

Tuberculin testing at the time of the initial HIV test showed a much lower frequency of positive tuberculin responses in the HIV positive than the HIV negative subjects, indicating that tuberculin testing has limited usefulness as a means of identifying latent tuberculosis in areas with high rates of both tuberculosis and HIV.

Many of the patients recruited did not return to the clinic for follow up. Some of the problems identified in the follow-up included difficulties in finding the patients

within the community as a result of the wrong address being supplied, an inability to locate the given address in the residential areas and a tendency to easily move from one residential area to another. Thus it would be necessary to obtain very detailed information of the patient's residential address as well as that of their next of kin in order to ensure adequate follow-up. More frequent reviews and repeated counselling might also contribute to better follow-up of asymptomatic patients.

Given the future impact that the interaction with HIV was expected to have on the tuberculosis situation in countries like Zambia it was considered important to conduct a study to determine the efficacy of tuberculosis preventive therapy in this setting. The various problems identified during the pilot study indicated that implementation of relevant measures to ensure maximum follow-up of the patients would be critical.

KEY TERMS

Preventive therapy: the use of anti-tuberculosis treatment in order to treat a latent infection.

Tuberculin Test/Mantoux Test: a skin test to determine evidence of prior exposure to tuberculosis infection

ETHICAL APPROVAL

Ethical approval to conduct the study was obtained from both the AIDS Research and Ethics Committee of the Ministry of Health and the Research and Ethics Committee of the University of Zambia.

A PILOT STUDY ON THE PREVENTION OF HIV RELATED TUBERCULOSIS IN ZAMBIA.

1.0 INTRODUCTION

1.1 ZAMBIA

Zambia is a land-locked sub-Saharan African country lying between latitudes 22 to 34 East and longitude 8 to 18 south with an altitude between 900 to 1500 metres above sea-level. It has an area of 7,526,000 sq.km. Zambia shares borders with Zaire and Tanzania in the North, Malawi and Mozambique in the East, Zimbabwe and Botswana in the South, Namibia in the South-West and Angola on the West. The population of Zambia in the last census conducted in 1990 was 7.8 million with a population density of 10.5 per square kilometre and a population growth rate of 3.0%. The population of Zambia is youthful with 48.3% of the population under 14 years and 49.7% between 15 and 64 years (Central Statistical Office 1991). Zambia is a low-income country with 51% of the population living in urban areas. Life expectancy at birth in 1991 was 49 years with an infant mortality rate of 106/1,000 live births. Per capita expenditure on health in 1991 was US\$14 (World Bank 1993). Lusaka is the capital city with an estimated population of 1 million. Health facilities include the University Teaching Hospital which is a tertiary care centre, a military and a mine

hospital, 30 urban health clinics and a growing number of private hospitals and clinics.

1.2 TUBERCULOSIS

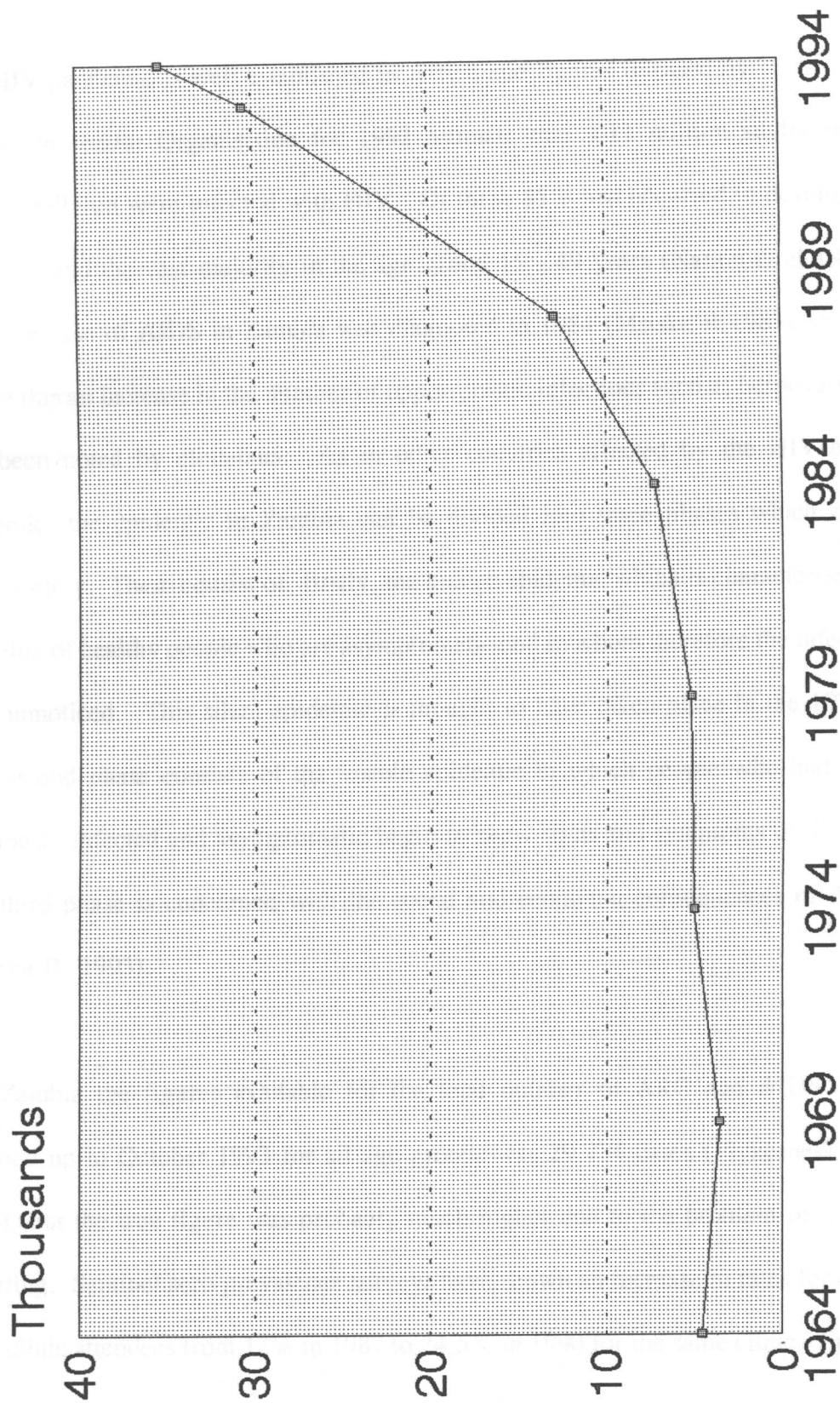
Pulmonary tuberculosis caused by *Mycobacterium tuberculosis* was a major cause of morbidity and mortality worldwide in the last century. Tuberculosis has been known to mankind since antiquity and evidence of a disease similar to tuberculosis has been identified in the mummies of ancient Egypt (Ryan 1992). While the epidemic of tuberculosis in the United States and Western Europe reached its peak at the end of the eighteenth and the beginning of the nineteenth century it is thought that the black population in sub-Saharan Africa was affected only from the beginning of this century (Grzybowski 1991).

Mortality rates in England and Wales declined between 1850 and 1900 even before the introduction of Tb services and this natural decline can be attributed to general socio-economic development with improved housing and nutrition (Pio, 1989). This natural decline has not been observed in many sub-Saharan African countries even despite the use of chemotherapy and other control measures. This can be attributed to a slower socio-economic growth and weak health infrastructure in many of these countries.(ibid)

In the 1990's tuberculosis is still a major cause of morbidity and mortality in the world and has been ranked as the largest cause of deaths from an infectious organism causing approximately 3 million deaths per year. The burden of infection with tuberculosis has been estimated by the World Health Organisation to be about 1.7 billion people or a third of the world's population, with an annual incidence of 8 million new cases. Tuberculosis causes 7% of all deaths in the developing world, and 26% of all avoidable adult deaths (Porter and McAdam 1994). The heaviest burden of infection occurs in the developing world, with countries in Africa, South East Asia and the Western Pacific reporting 95% of the cases notified and contributing 98% of the reported mortality due to tuberculosis (Narain et al 1992).

A trend of increasing notification rates has been reported from many countries, both industrialized and developing, in the last 10 years. Between 1984 to 1993 there was an increase in cases notified to WHO of 14.2% on a global scale, with the African region having an increase of 51.4% for the same period (WHO 1994). In Zambia the case rate remained almost constant from 1960 to 1982 at almost 100/100,000 with minor changes from year to year. A marked increase has occurred in the last 12 years, as shown in figure 1, with an increase in rate from 108/100,000 in 1983 to 400/100,000 in 1994, representing an increase in numbers of cases from 6,974 in 1983 to over 30,000 in 1994.

TUBERCULOSIS CASES IN ZAMBIA 1964 TO 1994



SOURCE: MOH AIDS/STD/TB/LEPROSY PROGRAMME
FIGURE I

1.3 HUMAN IMMUNODEFICIENCY VIRUS (HIV)

The HIV pandemic is well established in Africa and figures released by the World Health Organisation for 1992 estimate that 9-11 million adults and 1 million children were infected with HIV. Of these 85% had occurred in developing countries and the vast majority in the age group 15 - 49 years (Narain et al 1992). The first case of AIDS in Zambia was diagnosed in 1984 (Msiska R 1983), though before this an increase in the number of opportunistic infections such as herpes zoster had been noted by clinicians. As in other countries affected by the HIV/AIDS epidemic, the epidemic in Zambia can be divided into three phases which occur concurrently. These consist of, firstly, the hidden epidemic which is characterised by infection of healthy people who are asymptomatic and in whom therefore the infection goes unnoticed. This silent epidemic is thought to have taken place in the 1970's. The second phase consists of the visible epidemic in which people who had been previously infected and asymptomatic begin to show signs and symptoms of disease. The third phase is concerned with the social and economic consequences of AIDS (Msiska R, 1993).

For Zambia the figures available for the total number of ARC and AIDS cases reported up to October 1993 for all age groups was 29,734 cases (Flykesness et al 1994), but the true figure was probably much higher due to the problem of under-reporting. Sentinel sero-prevalence surveys have shown an increase in rates for antenatal clinic attendees from 12% in 1987 to 24.5% in 1990 for the same clinic. Future

projections by the National AIDS/STD/TB AND Leprosy Programme are that by 1998 the number of adults infected with HIV will have risen from 807,200 in 1993 to 1,237,000 with a total of 147,200 new HIV infections in 1998. Thus the current trend is one of increasing numbers of cases.(ibid)

1.4 HIV AND TUBERCULOSIS INTERACTION

Tuberculosis is a disease that has always been associated with poverty and overcrowding and therefore one factor that may contribute to the observed increase in tuberculosis includes the low socio-economic conditions with poor standards of living that are prevalent in these parts. Much of the reported increases in tuberculosis notification rates in sub-Saharan Africa have, however, been ascribed to concomitant HIV infection. This has been demonstrated by studies showing an increase in tuberculosis in AIDS patients (Quinn et al 1985, Piot et al 1984), autopsy studies showing high rates of tuberculosis in patients dying from AIDS

(Lucas et al 1992) and high HIV seroprevalence rates in TB patients (Narain et al 1992, De Cock 1994). In Zambia, 72% of tuberculosis patients presenting to the chest clinic in Lusaka and 80 -90% of those presenting with pleural and pericardial disease were HIV positive (Elliott et al 1993).

It is clear that the HIV pandemic will continue to exacerbate the problem of tuberculosis in developing countries. This effect will be greatest in countries in which the prevalence of tuberculosis infection in young adults is high as this is the age group

at the greatest risk of HIV infection (Raviglione et al 1995). HIV has become the strongest known risk factor for the progression of a latent tuberculosis infection to active disease. The annual risk of progression to active disease in an individual who is dually infected with both HIV and tuberculosis is 5% to 15% depending on the degree of immunosuppression(ibid). Estimates for mid-1994 were that of the 5.6 million persons dually infected with both HIV and tuberculosis, 3.8 million lived in sub-saharan Africa (ibid).

The mechanism for this increase in tuberculosis cases is thought to be either the reactivation of a distantly acquired infection with *M. tuberculosis*, or re-infection, or progression from a recent infection. The only current available intervention which is likely to reduce the occurrence of HIV associated tuberculosis is the administration of tuberculosis preventive therapy to persons with HIV infection who are latently infected with *M. tuberculosis*.

1.5 PREVENTIVE THERAPY FOR TUBERCULOSIS

Preventive therapy for tuberculosis is based on the treatment of a latent infection in order to prevent reactivation and progression to active disease. Preventive therapy with isoniazid has been used as a control measure for tuberculosis in countries such as the United States where the prevalence of tuberculosis is low and has mainly been used in contacts of TB patients with a positive tuberculin reaction. Several clinical trials conducted in these areas have shown that the efficacy of isoniazid used for

prevention varies from 25 - 92% and the duration of the protective effect lasting up to 19 years and possibly lifelong in the absence of re-infection (O'Brian 1994).

In countries with high tuberculosis prevalence rates, however, preventive therapy has never been considered to be a cost effective means of controlling tuberculosis given the large reservoir of open cases that already exists. Its use in this setting has mainly been limited to infants of mothers with open tuberculosis. With the emerging HIV/TB epidemic, however, there has been renewed interest in the possible use of isoniazid for prevention of TB in the HIV infected individual.

2.0 LITERATURE REVIEW

Several studies have been conducted to demonstrate the efficacy of isoniazid preventive therapy in reducing the incidence of tuberculosis in HIV infected individuals with prior tuberculosis infection.

Selwyn and coworkers conducted a prospective study on the risk of tuberculosis in a cohort of tuberculin positive intravenous drug users in the United States of America. They showed that none of the 27 HIV-infected patients developed tuberculosis after completing a 12 month course of isoniazid preventive therapy with a median follow-up of 25 months, whereas the incidence of TB in those who did not take isoniazid was about 10% per annum.(Selwyn 1989).

Guelar and colleagues studied 839 HIV infected patients in Spain prospectively in order to determine the risk of tuberculosis. Preventive therapy was offered to those with a positive tuberculin reaction (>5mm). They found that active TB developed 7 of 26 patients not receiving INH chemoprophylaxis, in 4 of 61 patients 3 to 27 months after completing 9 months of prophylaxis with INH. No cases of tuberculosis developed in those still receiving INH.(Guelar et al 1993).

Initial results from an isoniazid preventive therapy trial conducted in Lusaka by Wadhawan and colleagues demonstrated that a 12 month course of daily isoniazid was effective in reducing the incidence of tuberculosis in HIV infected individuals in Walter Reed Stage III and IV compared to placebo (11.2 to 2.6 cases per 100 person-

years).(Wadhawan et al 1993)

In another randomized trial of INH versus placebo (pyridoxine) for 12 months in Haiti, Pape and colleagues showed that INH reduced the risk of tuberculosis by 83%. In this study, TB developed in 6 (24%) of 25 patients who received pyridoxine alone versus 2 (5%) of 38 who received INH plus pyridoxine. Thus there were 5.7 versus 3.2 cases per 100 person-years in the placebo and active treatment groups respectively. When the results were stratified by initial PPD reactivity Isoniazid plus pyridoxine showed significant protection in the PPD-positive subjects but not in the PPD-negative group. In this study INH delayed the progression of HIV infection to disease and death for the whole group, with a significant effect in the PPD-positive group but not in the PPD negative patients.(Pape et al 1993)

In Uganda a randomised placebo-controlled trial was carried out using three regimens (Isoniazid for 6 months, Isoniazid and rifampicin for 3 months, isoniazid, rifampicin and pyrazinamide for 3 months) in 2298 HIV infected individuals. Enrolment into the placebo and isoniazid arm was stratified according to size of PPD reaction. The incidence rate for tuberculosis in the anergic subjects was higher than non-anergic subjects for both placebo and Isoniazid groups. Mortality rates were similar in the two study arms when controlled for anergy, though they were greater in the anergic than non-anergic arms. The median length of follow-up in this study was only 351 days. This preliminary data therefore showed that Isoniazid preventive therapy reduced the short term risk of Tb in HIV positive Ugandans. (Whalen et al 1995)

3.0 OBJECTIVES

To assess the feasibility of recruitment and follow-up of patients in a randomised placebo controlled trial on the Prevention of HIV related tuberculosis in Lusaka, Zambia.

3.1 SPECIFIC OBJECTIVES

1. To determine the level of knowledge of HIV and it's prevention among attendees of the University Teaching Hospital Filter clinic and their acceptance of HIV testing.
2. To assess the use of the Filter and Blood Bank Clinics as recruitment sites for HIV positive patients into a clinical trial.
3. To determine the demographic characteristics of patients recruited into a clinical trial.
4. To identify problems associated with the follow-up of patients recruited into a clinical trial in Lusaka.
5. To evaluate the use of measures of compliance to treatment of patients recruited into a clinical trial in Lusaka.

4.0 RATIONALE

In order to examine the efficacy of intermittent isoniazid and a combination of rifampicin and pyrazinamide in the prevention of Tuberculosis a **randomised placebo controlled double blind trial** was planned as a collaborative effort between the University Teaching Hospital, the Ministry of Health and the London School of Hygiene and Tropical Medicine.

The main study titled 'The Prevention of HIV Related Tuberculosis in Zambia' with a sample size of 1050 patients had a proposed recruitment period of eighteen months and a follow-up period of 3 years. This study population was to be HIV positive individuals living in Lusaka. At the time the study was planned there were no facilities for voluntary testing for HIV in Lusaka and therefore it was essential to assess whether the planned recruitment sites would provide an adequate number of patients within the specified recruitment period. It was also important to determine any problems that would arise during the recruitment and follow-up of patients within Lusaka. Thus the pilot study was planned in order to determine measures that would be necessary in order to ensure the smooth running of the main study.

Non-compliance or non-adherence to treatment is a major factor associated with poor outcome to treatment for tuberculosis and has been associated with a 6 times higher risk of subsequent isoniazid-resistant tuberculosis.(Hopewell 1989.) Compliance has been shown to increase as the prescribed length of treatment decreases. Thus the use

of short course preventive therapy would be expected to be associated with improved compliance. The use of various measures of compliance were to be assessed in the study.

5.0 MATERIALS AND METHODS

Study Sample

The estimated sample size for the main study was 1050 patients. For the purpose of the pilot study a sample size of 60 - 100 patients was chosen.

5.1 RECRUITMENT SITES

5.1.1 Adult Filter Clinic

The study clinic was situated in the Adult filter clinic of the University Teaching Hospital in Lusaka. The University Teaching Hospital (UTH) is a 2,000 bed hospital that serves Lusaka and the surrounding areas and is the main reference hospital in Zambia. The hospital runs a general medical clinic, called the filter clinic, which is open to the general public 7 days a week for 24 hours for emergencies. It operates as a "filter" for all non-surgical emergencies attending the hospital during normal working hours of 08:00 to 16:00 hours from Monday through Friday, with a half day on Saturday and open for emergencies only on Sunday.

This clinic has an average attendance of 350 patients per day.

5.1.2 Blood Bank Clinic

The Blood Bank clinic is situated in the Blood Bank and caters for Blood Donors and is run by a clinical officer and provides basic medical care for the blood donors. This clinic has on record the names and addresses of all blood donors who were found to have a positive HIV test on routine screening of donated blood. A proportion of these donors had already received post-test counselling and were attending the clinic on a regular basis.

5.2 TREATMENT REGIMENS

The following three regimens were used during the study;

1. Isoniazid (15mg/kg) - maximum dose 900mg for 6 months

2. Rifampicin (10mg/kg) 600mg maximum dose
plus
Pyrazinamide (50-70mg/kg) 3500mg maximum dose for 3 months

3. Placebo (Calcium Gluconate) 2 tablets for 3 months

All regimens were given twice weekly, either Monday and Thursday or Tuesday and Friday (see Appendix II)

This study was designed to be a double blind study. The drugs used for the pilot study were not however available in a coded form and ordinary tablets were used. In an effort to blind the investigator, the drugs were prepacked in brown envelopes labelled with the code number and dispensed by the study nurse.

5.3 METHODS OF PATIENT SELECTION

5.3.1 Filter clinic

Patients in the Adult Filter clinic sit on benches outside the consulting rooms, in separate benches for females and males. Patients were selected for interview by either picking out every 4th person in the queue as well as by collecting every 4th card from the consulting room. Patients were chosen from both the male and female benches. In addition the clinicians in the consulting rooms were requested to refer any patient with a history suggestive of HIV infection such as Herpes zoster or oral thrush to the study clinic.

5.3.2 Blood Bank Clinic

The Investigator spent every Tuesday morning in the blood bank clinic and interviewed all patients attending the clinic. At a later stage the clinician in the clinic was requested to refer all patients seen in the clinic with a known positive HIV test as attendance in the Tuesday clinic had fallen to very low levels. In addition all

donors on record with a positive HIV test and who had as yet not been offered post-test counselling were contacted by mail, either posted or delivered direct to their residential address, requesting them to attend the clinic.

5.4 RECRUITMENT PROCEDURE

5.4.1 Filter clinic

Patients seen in this clinic were initially treated for their presenting complaints and all necessary investigations, treatment and referrals offered. After the study was underway it was evident that there appeared to be more males than females agreeing to have the HIV test and hence a questionnaire on knowledge and attitude to HIV was introduced during the screening procedure in order to ascertain possible causes for the observed difference. After obtaining verbal consent, this questionnaire was then administered to the patient.

Initial Interviews

As part of the initial introduction to HIV testing and the study a KAB (Knowledge Attitude and Behaviour) questionnaire was administered to all consenting individuals. This questionnaire was designed as a means of gauging the extent of the knowledge of HIV and AIDS, preventive measures against HIV and the individuals attitude to HIV testing. This then enabled the counsellor to fill in any gaps in knowledge and

correct any misconceptions concerning HIV and its transmission during the counselling process. A discussion on general aspects of HIV and AIDS also provided a means by which the subject of HIV testing and the preventive therapy study could be introduced.

The questionnaire consisted of closed questions and was filled in by the investigator during the interview with each client. Verbal consent was obtained from each patient before administering the questionnaire. The first part of the questionnaire covered the demographic details of the respondents such as age, sex, civil status, type of residential area lived in, the number of living rooms and number of occupants. The number of rooms in the house included all living rooms with the exception of the bathroom and toilet.

The second part of the questionnaire consisted of questions designed to elicit the patients main source of knowledge of HIV/AIDS and their knowledge of the transmission and prevention of HIV infection.

On completion of the questionnaire the patients were then asked if they were willing to be tested for HIV and to be informed of their results. The nature of the study and the possible risks and benefits were also explained to the patients. All patients expressing willingness to undergo the HIV test and to be told of their results gave signed consent for the same, were asked questions on previous history of tuberculosis, liver disease, BCG vaccination and drug reactions. They then had blood withdrawn

for the initial screening tests.

5.4.2 Blood Bank Clinic

Patients seen from this clinic and already aware of their HIV status were given information of the nature of the study and offered a repeat HIV test. Those patients giving signed consent to enter the study had the initial screening tests and a chest x-ray done.

5.5 SCREENING TESTS

The following tests were performed in the initial screening process;

5.5.1 HIV TESTING

Blood drawn for the HIV test was sent to the Virology laboratory within UTH and tested with at least two different ELISA tests.

5.5.2 OTHER BLOOD TESTS

The following tests were done on each patient;

a. Blood test

Liver function tests - Bilirubin, Alanine aminotransferase(ALT), aspartate aminotransferase (AST) Alkaline Phosphatase, Protein (total and albumin)

Full Blood Count - haemoglobin, total white count and differential count

b. Urine

Pregnancy Test (Gravindex)

5.5.3 TUBERCULIN TEST

All patients had a tuberculin test on the right forearm using 0.1ml of RT23 Tuberculin (2 tuberculin units TU, Statens Serum Institut, Denmark, equivalent to 5TU of PPD). The test was read when the patient returned to the clinic to collect results of the blood tests within 72 hours. The reaction was observed as a raised papule and was measured by taking the mean of two diameters at right angles of the area of induration. The patients were recruited into the study regardless of the results of the tuberculin test.

5.6 FOLLOW-UP VISIT

All patients on whom the initial screening procedures were performed were requested to return to the clinic for their results within 72 hours.

5.6.1 HIV negative patients

All patients found to be negative on HIV testing had their tuberculin reaction read, were informed of their results and were given post-test counselling on how to avoid infection with HIV by the study nurse, and were reimbursed for their transport costs to the hospital.

5.6.2 HIV positive patients

All patients found to be HIV positive were offered post-test counselling and the tuberculin test was read. Further details on the nature and the rationale of the study were given to the patients. Those patients willing to continue with the study had a detailed history taken, and their demographic details, including both residential and postal addresses recorded. The residential and postal address, where available were also recorded for the next of kin. A full physical examination was done and all patients including those without respiratory symptoms had a chest radiograph done. If there was no clinical or radiological evidence of pulmonary tuberculosis the patients were assigned to one of the treatment arms by the study nurse using a random table of numbers.

5.7 RANDOMISATION PROCEDURE

A sample frame of treatment numbers 1 to 60 was defined. A random table of numbers was used to allocate the treatment numbers to the three regimens and the drugs were packed in brown envelopes and labelled with the appropriate number (1 to 60) by the study nurse .(appendix III)

5.8 INCLUSION AND EXCLUSION CRITERIA

5.8.1 Inclusion criteria

1. Adults of more than 15 years
2. Serologic evidence of HIV infection defined by two ELISA tests
3. No clinical or radiological evidence of pulmonary tuberculosis
4. Informed consent
5. Living in Lusaka

5.8.2 Exclusion Criteria

1. Persons with symptoms consistent with tuberculosis (unexplained fever, cough, weight loss) unless careful examination (i.e x-ray, 3 negative sputum on culture) excludes tuberculosis. Evidence of current active extra-pulmonary tuberculosis.
2. Asymmetrical generalised lymphadenopathy of > 2cm (as a sign of probable extra-pulmonary tuberculosis).
3. The presence of a life-threatening illness
4. Evidence of liver disease (defined as AST and/or bilirubin more than twice the upper limit of normal)
5. A previous history of treatment for tuberculosis.
6. Previous history of adverse drug reaction to the treatment drugs
7. Pregnancy

5.9 PATIENT ENROLMENT

All patients deemed eligible for inclusion in the study were given one month's supply of the appropriate drug, a drug calendar and detailed instructions on drug dose and frequency of medication. In addition, all patients were given K100 towards their transport costs to the hospital and a review date for their next appointment. All the patients enrolled in the study were informed that they were free to visit the study clinic at any time between their reviews if they developed any reaction to the drugs or if they had any concerns about the study or their sero-status.

5.10 INVESTIGATION OF PATIENTS WITH SYMPTOMS OR SIGNS SUGGESTIVE OF TUBERCULOSIS

All patients with a history of a cough for more than 2 weeks, with or without sputum production, or who had an abnormal chest x-ray were investigated to exclude pulmonary tuberculosis. These patients had to submit three early morning sputum specimens for those with a productive cough and were given a 7-day course of antibiotics. They were requested to return to the clinic within 2 to 3 weeks for their sputum results and a repeat chest x-ray, if indicated.

At the follow-up review, those patients with a non-productive cough and with no x-ray abnormalities and who had improved with the antibiotics were included in the study. Any patient who had a productive cough at the first visit had a repeat x-ray

where necessary and if there was no evidence of disease were asked to return after 4 weeks for the sputum culture results. Any patient who had not improved or had radiological or microbiological evidence of tuberculosis was notified and commenced on anti-tuberculous treatment.

Patients with asymmetrical lymphadenopathy of more than 2 cms were referred to the surgical clinic for a lymph node biopsy. Where necessary patients were referred for abdominal ultrasound or echocardiography to exclude abdominal tuberculosis or pericardial effusion respectively.

5.11 FOLLOW-UP VISITS

5.11.1 Frequency of follow-up

The patients were reviewed as follows;

Monthly for the first three months, at 6 months and thereafter at six monthly intervals

Patients were encouraged to attend the clinic at any time between the given reviews for any medical problem or for counselling.

5.11.2 Follow-up procedure

At each subsequent follow-up visit the patients received further HIV counselling as well as information on the nature and aims of the study. A detailed questionnaire was administered to each patient in order to detect any side effects of the study drugs. This included questions designed to detect any evidence of progression of the HIV disease and a complete physical examination.

5.11.3 Follow-up investigations

The following investigations were done during the follow-up period;

Month 1	Repeat HIV
	Full Blood count
	Liver function Tests
	Progression markers(CD4, neopterin, B2-microglobulin)
Month 2	Full Blood Count
	Liver Function Tests
	Progression Markers

Month 3	Full Blood Count Liver Function Tests Progression Markers
Month 6	Full Blood Count Liver Function Tests Progression Markers
Month 12	Full Blood Count Progression Markers Mantoux Chest X-ray
Month 18	Full Blood Count Liver Function Tests Progression Markers
Month 24	Full Blood Count Progression Markers Mantoux Chest X-ray

5.12 DEFAULTER TRACING

Any patient not turning up for their set review had a reminder sent to them , either by way of a letter delivered to their residential address or posted to their postal address. If there was no response to the first reminder a second reminder was sent within the following two weeks.

5.13 MEASURES OF COMPLIANCE

The following measures of compliance were used during the follow-up period;

Drug diaries

Urine testing for drug metabolites

5.13.1 Drug diaries

In order to assist patients to correctly take the treatment on a twice weekly basis the patients were given drug diaries at each visit. The diaries were constructed so that the days on which the patient had to take the drugs were clearly marked with stars and had a space for the patient to indicate the date on which the drugs were taken. The patients were requested to mark on each day when the drugs were taken, regardless

of whether the drugs were taken on the correct day or not and to return the used diaries to the clinic at each visit.

5.13.2 Urine Testing for drug metabolites

Urine testing for drug metabolites of isoniazid was performed using the commercially available Difco urine test strips. These strips consisted of a test strip sealed in a plastic container the end of which had to be cut before use. This strip was then inserted with the cut edge down into the sample of urine. The urine went up the strip by capillary action and on contact with the strip of test material produced a definite blue colour within 20 minutes in the presence of metabolites of Isoniazid.

During the first six months of the study all patients were given a review date to coincide with the day they were due to take the next dose. This was done in order to allow for testing of the urine for metabolites of isoniazid for those on this treatment. The urine testing was performed by the study nurse who was able to determine which of the patients needed this investigation as she was aware of the treatment regimen each patient was taking.

5.14 STATISTICAL ANALYSIS

The data generated during the study was entered into a Dbase III program and analysis done using the EPI-Info 6 statistical program.

6.0 RESULTS

Time Frame

Recruiting of patients for the pilot study took place over a period of 21 weeks.

6.1 KNOWLEDGE OF HIV AND AIDS

A total of 154 questionnaires were administered to patients seen in the filter clinic during the study period and were available for analysis. Not all patients talked to agreed to have the questionnaire, but unfortunately the number who refused was not recorded and thus the acceptance rate of the questionnaire can not be assessed.

The following results were obtained;

6.1.1 Demographic data

a) Sex distribution: 110 males (71.4%), 44 females (28.6%).

b) Age range: 17 to 58 years, mean age 29.2 years.

There was no significant difference in the mean age of females (28.0 years) and males (29.7 years), $p=0.59$.

- c) Civil Status:**
- Married 99 (64.3%)
 - Single 47 (30.5%)
 - Divorced 3 (1.9%)
 - Widowed 5 (3.2%)

d) Residential area and housing: 73.4% of the respondents lived in a high density area, whilst 25.3% lived in a medium or low density area. The mean number of rooms per house excluding the bathroom and toilet was 3.3(2.89 high density, 6.35 low density).

e) Education: The level of education attained by the respondents was as follows;

- Primary education (up to 7 years) 69 (44.8%)
- Secondary education 60 (39.0%)
- College/University education 23 (14.9%)
- No education 2 (1.3%)

Males were more likely to have gone through secondary education and had post-secondary education (university or college) than were the females and the difference attained statistical significance ($p=0.003$, RR 1.68, 95% CI 1.21-2.34).

6.1.2 Knowledge of HIV/AIDS

The second part of the questionnaire contained questions designed to elicit the respondents source of information of HIV/AIDS, their understanding of HIV/AIDS and the way it is transmitted.

6.1.3 Source of Information of HIV/AIDS

The level of awareness of AIDS was very high with 151 of 154 (98.1%) respondents having heard of the condition prior to the interview. Media, including newspapers, television and posters, was the primary source of information among 63% (97/154) of the respondents. Other sources of information included relatives and friends (21.4%), health personnel (12.3%) and school (2.6%). Health personnel in the various institutions were the initial source of information in only 12.3% of the respondents.

6.1.4 Transmission of HIV/AIDS

The following table indicates the responses obtained for questions on the methods of transmission of HIV;

Table 1: Knowledge of routes of transmission of HIV among 154 Respondents

	Yes (%)	No (%)	Do not know (%)
Is HIV an STD?	127 (82.5)	8 (5.2)	19 (12.3)
Can HIV be transmitted by infected blood?	107 (69.5)	14 (9.0)	33 (21.4)
Can HIV be transmitted from mother to child?	115 (74.7)	10 (6.5)	29 (18.8)
Can HIV be transmitted by casual contact?	20 (13.0)	107 (69.5)	27 (17.5)
Do you know of any other way through which HIV is transmitted?	31 (20.1)	108 (70.1)	15 (9.7)

Whilst 98% of the people interviewed had heard about HIV and AIDS, 13% of the

respondents incorrectly identified the correct routes and up to 21 % were unsure of the various means of transmission. Some of the additional methods that were thought to transmit HIV infection included food, clothes and kissing.

A further analysis of those patients responding with "don't know" was done to detect any difference in education level between this group and those who were able to give a definite answer. Patients who were able to give a definite answer, whether or not correct, for all or 3 of the 4 questions had reached a higher educational level than those who were unable to provide a definite answer for 2 or more of the questions. ($p=0.004$, 95 % C.I 0.41-0.79). However this difference became insignificant when comparing those with a definite answer for all the questions and those unsure of one or more question. Those with a higher level of education were therefore able to express a definite opinion more often than those with less education.

There was no statistical difference in knowledge of routes of transmission of HIV between males and females when the results were stratified for age, marital status and type of residential area.

6.1.5 HIV Prevention

Among the respondents, 82.5% (127/154) thought that HIV was a preventable disease, while 5.2% (8/154) did not think this was possible and 12.3% (19/154) did

not know whether or not this was possible. Males were more likely than females to think that HIV was preventable (Fisher's exact test $p=0.03$, 95% C.I 1.15-18.21). In keeping with the knowledge that HIV was a sexually transmitted disease, 81.8% (126/154) thought that sticking to one sexual partner was a method of prevention of HIV. There was no significant difference in attitude to this method of prevention between males and females. However only 48.1% (74/154) thought that the use of condoms was an effective means of preventing HIV infection. In this instance males were more likely to think that condoms were effective in preventing HIV (Chi square 3.60, $p=0.05$, 95% C.I 1.02-2.29)

6.1.6 Treatment

The lack of an effective treatment for HIV and AIDS was recognized by 79.9% (123/154), whilst only 5.8% (9/154) thought there was a cure available and 14.3% (22/154) did not know whether or not a cure was available.

6.1.7 HIV testing

A willingness to undergo HIV testing was indicated by 75.3% (116/154) while 18.8% (29/154) were not willing for the test and 5.8% (9/154) thought they would need to think about it before making a decision on HIV testing. There was no significant difference in the expressed attitude towards HIV testing between males and females ($p=0.12$). However, of the 154 patients initially counselled and who had a

questionnaire on knowledge of HIV/AIDS, 78 of 110 males (71%) had the HIV test, compared to 23 of 44 females (52%). Males were therefore more likely to agree to have the HIV test than were females, a difference that achieved statistical significance (Chi square 7.59, $p=0.005$, 95% C.I 1.09-1.71)

There was no difference in education level, defined as primary education and post-primary education, including college, between those who indicated that they would be willing to have the HIV test and those not willing to do so.

Of the 29 patients who were unwilling to be HIV tested, 18 felt they could not cope with knowing that they were HIV positive, 5 thought it was futile to have the test as there was no known cure for the infection and 6 were convinced that they were HIV negative and hence there was no reason to have the test.

Of 104 patients 33 (31.7%) thought they would share their result with their spouse if found to be HIV positive compared to 40 (38.5%) who would tell their family, including parents and siblings and 16 (15.4%) who would inform their friends. Fifteen patients (14.4%) thought they would keep this information to themselves.

6.2 HIV Screening Procedure

During the recruitment period a total of 341 patients from both the filter clinic (293) and the Blood Bank clinic (48) were initially offered HIV counselling and testing, of whom 212 (62%) consented to have the HIV test and to be screened for possible

inclusion in the study. This contrasts with 75.3% who had expressed willingness to have the HIV test during the initial KAB interview.

The sex distribution of these 212 patients were 47 females (22%) and 165 males (78%). An analysis of HIV status by sex showed there was no significant difference between the HIV positive rate between the two sexes ($p=0.56$). Information on age was not recorded in the first visit and hence it is not possible to analyze HIV status by age.

Table 2: Below shows the numbers of patients screened in each clinic and the HIV results for each Clinic

Table 2: Numbers of patients screened from each clinic with HIV results

	Filter Clinic	Blood Bank Clinic
Number screened	164	48
Number HIV Positive (%)	69 (42%)	42 (87.5)
Number HIV Negative (%)	95 (58%)	6 (12.5%)

From the Blood Bank 12.5% of those initially found to be HIV positive had a negative test on repeat testing. These patients were referred back to the blood bank clinic for further testing and for confirmatory testing in light of the conflicting result obtained though the outcome of a third HIV test on these patients is not known.

Of the patients screened from the filter Clinic, 42% had a positive HIV test. As the cohort of patients tested can not be representative of the general population as they were presenting to the hospital for a medical problem this result can not therefore be extrapolated to the general public.

The patients were requested to return to the clinic within 72 hours for their HIV results, other blood results and reading of the Tuberculin reaction. Table 3 below shows the numbers of patients returning to the clinic for their results according to their HIV result for each clinic.

Table 3: Number of patients returning to the clinic within 72 hours by HIV status for each clinic

	FILTER CLINIC	BLOOD BANK CLINIC
Number HIV Positive	69	42
Number returning to clinic (%)	59 (85.5%)	37 (88%)
Number HIV Negative	95	6
Number returning to clinic (%)	67 (70.5%)	5 (83.3%)

6.3 Tuberculin Testing

The tuberculin reaction was classified as follows;

0 - 5mm Negative

>5mm Positive

Any reaction 5mm or less was taken to be negative in order to exclude any reaction that could be attributed either to a prior BCG vaccination or to sensitization by environmental mycobacteria.

The tuberculin test was read for 162 of the 168 (96.4%) HIV positive and HIV negative patients who were tested and who returned to the clinic within 72 hours.

Effect of HIV status on tuberculin reaction

The results of the tuberculin reaction were analyzed according to the HIV result. For the HIV negative patients 31% (28/89) had a negative tuberculin reaction compared to 60% (44/73) HIV positive patients. Patients who were HIV positive were thus significantly more likely to have a negative tuberculin reaction than were those who were HIV negative ($p=0.0002$). Thus anergy to tuberculin testing may be associated with being HIV positive. (see Appendix V)

Severe immunosuppression may be also accompanied by severe lymphopenia and the results obtained were therefore analyzed by the presence or absence of significant lymphopenia or anaemia. It was not always possible to obtain a differential white count and therefore for the purpose of the analysis the results were classified into two groups according to the total white cell count with low total count of less than $2.5 \times 10^6/l$ and a normal count any value above $2.5 \times 10^6/l$. For haemoglobin a low haemoglobin was considered to be any reading below 9.0g/dl. There was no significant difference between the total white cell count or haemoglobin between patients with a negative and a positive tuberculin reaction.

6.4 Recruitment of patients

6.4.1 Reasons for non-recruitment

The number of HIV positive patients returning to the clinic for their results were 94. Of these, 61 fulfilled the inclusion criteria and were enrolled into the study. The 33 HIV positive patients not enrolled in the study failed to meet the inclusion criteria for various reasons. Table 4 below indicates the reasons for non-recruitment of these patients according to the clinic from which they were recruited.

Table 4: Reasons for non-recruitment of HIV positive patients

REASON OF NON RECRUITMENT	FILTER CLINIC N=57 NO.	BLOOD BANK N=37 NO.
Previous history of TB	2	-
Possible TB	15	3
Currently too ill	1	-
Lives outside Lusaka	2	1
Did not give written consent	-	2
Abnormal LFT's	1	0
Other reasons given	5	1

Eighteen of the 94 HIV positive patients (19%) returning to the clinic were not enrolled due to symptoms suggestive of clinical tuberculosis. The symptoms included;

-history of a productive cough with fever for more than 3 weeks. These patients were requested to submit 3 sputum specimens and were given ampicillin or septrin according to availability and asked to return to the clinic in 3 weeks. Ten of 13 such patients gave sputum specimens, none of which were positive for AAFB on

either sputum smear or culture, and only 5 patients returned for a further review. These patients continued to have cough and hence were given additional courses of antibiotics. One of these patients who continued to attend the clinic had no evidence of tuberculosis but was not enrolled in the study as he was transferred out of Lusaka.

-Abnormal x-ray findings without respiratory symptoms were found in 4 patients (hilar adenopathy 1, parenchymal infiltrates 2, cardiomegaly ? pericardial effusion 1) and these patients were investigated as described above, though none of them returned to the clinic and no evidence of tuberculosis was found on sputum examination. The patient with suspected pericardial effusion did not return to the clinic for echocardiography and was lost to follow-up. Efforts to contact these patients were not successful.

-asymmetrical cervical lymphadenopathy in one patient.

Lymph node biopsy did not reveal any evidence of tuberculosis. The patient was lost to follow-up

6.4.2 Enrolment of patients into study

Of the 61 patients recruited, 31 (51%) were recruited from the Filter clinic and 30 (49%) were recruited from the Blood Bank Clinic. Thus in the Filter clinic, 164 patients were screened in order to recruit 31 patients, compared to 48 patients screened from the blood bank in order to recruit 30 patients.

6.4.3 Demographics of patients enrolled in study

The demographic characteristics of the patients enrolled in the study were as follows;

a. Sex Distribution: Females 11 (18%)

Males 50 (82%)

b. Age Range: Mean Age 29.82 years. A comparison of the mean age of the females and males indicated that the females were on average 6 years younger than the males (females-24.36 years, males-31.02 years).

c. Marital status: Married 36 (59%)

Single 19 (31%)

Divorced 2 (3.3%)

Widowed 4 (6.6%)

d. Educational Level: The following were the educational level of the patients recruited;

No education 5 (8.2%)

Primary Education (up to 7 years of formal school)

14 (23%)

Secondary education 42 (68.9%)

There was no difference in education level or age between the patients who were enrolled in the study and those who were not enrolled.

6.4.5 Symptomatology at Enrolment

At the time of Enrolment into the study the patients had a detailed history taken and a physical examination in order to detect any evidence for the presence of active tuberculosis as well as for any evidence of HIV related disease,

Symptoms of non-productive cough of less than 3 weeks was present in 10 of the patients. One patient with history of a cough for more than 3 weeks was followed up with antibiotics and gave several sputum samples and was only enrolled after all sputum samples were negative on both microscopy and culture. Diarrhoea was reported in 15 of the patients for periods varying from 1 to 4 weeks in the previous 6 months while loss of weight was reported in 29 of the patients. It was not possible for many of the patients to quantify this loss of weight and was done subjectively. A past history of a Sexually transmitted disease was reported in 33 (54.1%) of the patients and this was significantly more common in the males than females (Fisher's exact test, $p=0.008$). A history of joint pains and paraesthesia was present in 9 and 5 of the patients respectively.

A history of contact with a patient suffering from tuberculosis was present in 21 of the patients, with 19 of these contacts having been with a family member (5 sharing

the same room and 14 the same house), while 2 gave a history of a more casual contact with a Tb patient. There was, however, no significant difference in size of tuberculin reaction between those patients reporting a history of contact with a tuberculosis patient and those who had no such history (RR 1.41 95 %CI 0.90-2.21 p=0.09).

On physical examination significantly enlarged extra-inguinal lymph nodes were found in 26 patients (42.6%) and epitrochlear nodes were found in 17 patients(27.9%). A non-specific maculo-papular dermatoses was found in 4 patients while 4 patients had evidence of previous herpes zoster infection and 1 patient had viral warts. No patient had either oral thrush, seborrhoeic dermatitis, hairy leucoplakia, fungal skin infection or Kaposi's Sarcoma.

6.4.6 Distribution of patients in study arms

The patients in the study were assigned to the three treatment regimens using a table of random numbers. The distribution of the patients among the three regimens was as follows;

Isoniazid	22
Rifampicin/Pyrazinamide	19
Placebo	20

6.5 FOLLOW UP OF PATIENTS

The patients were followed up at monthly intervals for the first three months and then at six-monthly intervals thereafter. During the first six months the review dates were given to coincide with the day of the week that the patient was due to take the drugs. This was done as a means of facilitating testing for drug metabolites in the case of the patients on Isoniazid.

At each review the patients were offered further counselling both on HIV and AIDS and on the aims of the study. The patients were followed up from May 1991 to September 1995, though the length of time followed up for each patient varies.

6.6 COMPLIANCE

The two methods used to assess compliance to the prescribed treatment during the study was the use of drug diaries that the patients were required to fill out each time a dose was taken and the use of urine testing strips for the presence of metabolites of isoniazid.

6.6.1 Drug Diaries

During the follow-up clinic a total of 170 diaries were given to the patients returning to the clinic for review. Of these 111 were returned to the clinic by the patients and hence available for analysis. Table 5 below shows for each review month the number of diaries available and a breakdown of when each dose was taken.

Table 5: Analysis of Compliance by Diaries returned to the Clinic

Review Month	No. given out	No. of diaries (total doses)	No. of doses taken (%)	No. of doses taken Correct			
				C	E	L	NT
1	61	39 (328)	312 (93)	318	3	7	23
2	47	31 (248)	235 (95)	224	8	3	13
3	-	25 (200)	199 (99.5)	189	9	1	1
4	-	8 (64)	64 (100)	59	5	0	0
5	-	5 (40)	38 (95)	38	0	0	0
6	36	3 (24)	24 (100)	24	0	0	0

KEY: C = Correct, E = Early, L = Late, NT = Not Taken

As a measure of compliance to treatment by a patient, a drug diary is only of use if the patient can be relied upon to accurately fill out the diary and to return it to the clinic. Thus for the first review only 80% of the patients returning to the clinic returned with the drug diary. The proportion of patients returning to the clinic with their diaries decreased with time such that by the sixth month only 3 of the 36 (8%) patients attending the clinic came with their diaries.

Of the 111 drug diaries returned to the clinic 888 (95.8%) of the total number of possible doses (927) were marked as having been taken, of which 852 (96%) were taken on the correct day.

6.6.2 Urine testing

During the study period a total of 30 urine tests were performed of which 23 were positive for Isoniazid metabolites. A comparison of the drug diaries and the results for the urine testing show that of 18 patients whose diaries indicated that they had taken the dose on the day of review, 15 (83.3%) tested positive with the urine strips. For the other 12 patients there were either no diaries available or the diaries indicated that the dose had not been taken on that day.

Problems encountered with this method of compliance testing were that some patients did not take the drug before coming to the clinic or they had emptied their bladder just before coming to the clinic and therefore were unable to provide a urine specimen and were unwilling to wait until able to do so.

6.7 EARLY LOSS TO FOLLOW-UP

During the follow-up period patients were lost at different times for various reasons. Of the 61 patients initially enrolled in the study, 12 (19.6%) patients never returned to the clinic for any further review. One patient voluntarily withdrew from the study a week after commencing treatment. His reason for withdrawal was that taking the tablets reminded him of his HIV status and thus made him uncomfortable.

One patient developed hepatitis within the first month of treatment and presented with clinical jaundice and raised hepatic enzymes. This patient was therefore taken off treatment and assumed to have reacted to the medication (Rifampicin and Pyrazinamide), though no investigations were done to exclude the possibility of viral hepatitis. He had full recovery of his hepatic function and continued to attend the clinic on various occasions.

Three patients were only seen in the clinic for the first review and did not attend thereafter. One of these patients was known to have died three weeks after his last review though the cause of death could not be ascertained. One patient returned to the clinic for the first review but then withdrew from the study as he did not want any blood drawn for further studies. A further three patients were lost to follow-up after their second month's review. One of these patients who attended the third review later died shortly before his review at six months. The cause of death was an acute respiratory infection of 2 days duration and he died at his home. Four of the patients who attended the clinic for their sixth month's review did not return to the clinic for any further follow-up.

Thus 21 of 61 (34.4%) patients were known to have not taken the full course of treatment and were classified as early defaulters for the purpose of analysis.

6.8 CHARACTERISTICS OF EARLY DEFAULTERS

An analysis of the early defaulters compared to those not regarded as early defaulters was carried out in order to determine any special characteristics of the former group of patients. The parameters examined were the sex, educational level attained, marital status, clinic from where the patient was initially recruited and whether the patient had received active treatment or placebo. For the purpose of analysis the educational level was classified into whether the patients had only completed up to primary level, including no formal education or had gone up to secondary school and/or college. Marital status was defined as single (never married) or ever married (married, widowed or divorced). As the numbers being considered are very small the treatment groups were considered to be either active treatment (Isoniazid or rifampicin and pyrazinamide) or placebo. No attempt was made to differentiate between the two active treatment arms.

There was no significant difference in sex (Relative Risk 1.82, 95% C.I 0.92-3.61 $p=0.1$) or marital status (Relative Risk 0.96 95% C.I 0.66 - 1.40, $p=0.8$) among the early defaulters and those who received all the medication. The patients defaulting from treatment in the first six months were significantly more likely to only have reached primary level of education (RR 2.01 95% C.I 1.04-3.90, $p=0.04$). Similarly the patients recruited from the filter clinic were significantly more likely to default in the early months than those recruited from the blood bank (RR 0.65 95% C.I 0.44-0.95 $p=0.01$). Patients taking either of the active treatments were more likely to

default from treatment early during the study compared to those on placebo and this difference reached statistical significance (RR 1.52, 95% C.I 1.09-2.10 p= 0.02)

6.9 DURATION OF FOLLOW-UP

The 40 patients who took the complete course of treatment were followed up for periods varying from 6 months to 54 months. The total number of patient days of follow-up from time of Enrolment in the study was calculated for all 61 patients using the date of death for those known to have died and the date last seen for all other patients. The total number of days of follow-up for the whole cohort was 40,003 days, giving a total follow-up time of 109.59 years.

At the time the study was completed in September 1995 the number of patients who were still being actively followed up were 15 (24.6%) of the original 61 patients. These patients had been followed up for an average of 3.88 patient years.

6.10 DEFAULTER TRACING

When a patient did not report to the clinic within a week after their scheduled review a letter of reminder was delivered to their residential address by the follow-up team which comprised the study clerk and the driver. Where a postal address was available, the letter was posted. If there was no response from the patient to this reminder another letter was delivered after another week.

Of the 12 patients who did not return to the clinic after commencing treatment, the residential address given by the patient could not be found for 6 of the patients. The address was found by the follow-up team for 6 of the patients and the letters delivered but the patients did not respond. For these patients a total of 3 letters were delivered for each patient but with no response. These patients were then considered to have withdrawn from the study.

For the other patients who attended one or more reviews and then did not return to the clinic, the given address was incorrect for 8 of the patients, while for two patients the address used was that of the place of work, letters were delivered but the patients did not respond. For four patients who had given the correct address and the letters were delivered, there was no response from the patient to three letters. For two patients it was later discovered that they had been out of town for work and hence did not receive the letters until several months had passed. For 9 patients the given address was found but the patient was not known at the address.

7.1 DISCUSSION

7.1 KNOWLEDGE OF AND ATTITUDE TO HIV AND AIDS TESTING

The sex distribution of the respondents was unequal with 71.4% males and 28.6% females. This is unlike the ratio of males to females in the country which in 1991 was 1:1.05 (Central Statistical Office 1991). In terms of sex distribution of attendance at the filter clinic this is almost 1:1. The unequal numbers of female and males respondents (1:3) may have been partly due to a sampling bias towards the male over the females by the investigator.

Of the patients enrolled in the study, the females were on average six years younger than the males. This is in agreement with the finding that females tend to be infected with HIV at a younger age than males (Keenlyside et al 1993). This difference is thought to arise from a more efficient transmission of infection from men to women as well as the tendency for men to have sex with younger women and that women tend to initiate sexual activity at a younger age than males (Flykness et al 1994).

There was a high level of knowledge about the HIV and AIDS in the patients attending the filter clinic at the University Teaching Hospital. This reflects the high level of educational activities of the institutions involved in AIDS education such as the National AIDS/STD/TB and Leprosy control Program and the Anti-AIDS clubs.

These organizations publish information on HIV/AIDS through the news media, both printed and audio-visual as well as through posters and pamphlets. That this is the major route for the dissemination of AIDS information is reflected by the finding from the survey that the major source of information on HIV/AIDS has been the print media and television. Thus the publicity given to the general public on HIV and AIDS has been successful in raising public awareness of this condition.

The rather low level of educational activities being carried out by health personnel (12.3%) could possibly account for the misconceptions expressed by up to 13% of the respondents to questions on methods of transmission of HIV and AIDS. The usefulness of print media to express a message is hampered by a lack of dialogue which would avoid any misconceptions regarding the message being put forward. Thus there is a need for further health education in a setting that allows for dialogue as there still exists misconceptions regarding the routes of transmission of HIV.

Respondents who had reached secondary school or gone to college were able to correctly identify modes of transmission of HIV/AIDS compared to those who had only reached a primary level of education. There was no difference in level of knowledge of HIV/AIDS between males and females when stratified for age, education, marital status or residential area.

HIV was correctly defined as a preventable disease by 82.5% and in keeping with this a similar number (81.8%) thought that sticking to one sexual partner was a method

of prevention. The low number (48.1%) that thought the condom was useful in preventing transmission of HIV reflects the fact that at the time the study was carried out there was poor acceptance for the use of the condom. The question of the usefulness of the condom referred to the male condom as the female condom was not known at the time the study was conducted. Attitudes towards the use of the condom were different between the sexes with males more likely than females to accept the use of condoms as a preventive measure. This may be due to the fact that the use of the condom is dependant on male co-operation and hence the female has little control over it's use.

Knowledge and awareness of risk factors does not always lead to behaviour change as has been demonstrated by a study among commercial sex workers in Thailand which showed that condom use was not systematically influenced by knowledge (Morris et al 1995). The questionnaire used in this study did not, however, deal with issues relating to behavioural change in light of the level of knowledge of HIV and AIDS. Additional questions on behaviour would enhance the usefulness of a questionnaire on knowledge and attitudes of HIV and AIDS.

There is still a considerable stigma attached to being HIV positive in Zambia and hence while 75% of the patients initially thought they would be willing to have the HIV test, only 62% finally agreed to do so. Of the 104 patients for whom data is available, 14.4% felt they would be unable to share the knowledge of their HIV status with anyone if found to be positive, a figure that is much lower than that found at a

voluntary testing centre in Lusaka where 50% felt unable to discuss their HIV status with their family (Baggaley et al 1993). This perhaps reflects the strong family spirit that exists among many people whereby there is need to share problems with friend and family.

There was no statistically significant difference ($p=0.57$) between males and females in their attitude towards sharing a knowledge of their HIV status with a second person. However during the initial screening procedure a number of females expressed reservations on having the HIV test. This was attributed to a fear of being accused of having brought the infection into the home if they were the first found to be HIV positive. This may account for the finding that the proportion of males having the HIV test was significantly more than females.

7.2 HIV RESULTS

The HIV seropositivity rate among the patients tested in the Filter Clinic was 42%. There is no population based data available on the rate of HIV infection in the general population in Zambia. However several Sentinel Surveillances have been conducted among pregnant women attending Ante-Natal Clinics and this rate is assumed to be the best proxy for the sexually active population. In the 1992 surveillance the HIV seropositive rate for pregnant women in all sites tested was 20.7% (Fylkness et al 1994), which is considerably lower than the rate obtained above. The rate obtained in this study is, however, not a reflection on the HIV positive rate in the general population as it consists of persons who are already sick and would therefore be

expected to have a higher rate of infection.

The lack of a significant difference in seropositivity between males and females is an expected finding in countries such as Zambia where the predominant mode of transmission of HIV infection is through heterosexual contact (WHO 1992)¹. It has not been possible to ascertain whether there was any difference in age between those who were HIV positive and negative as the initial questionnaire did not include a question on age. This information is therefore only available for those patients enrolled in the study.

A negative HIV result was found in 12.5% of patients referred from the Blood Bank clinic though these had all previously been found to be HIV positive on routine screening of donated blood. It is not clear whether or not these patients had a repeat HIV test at the time of post-test counselling. According to recommendations on HIV testing issued by the World Health Organisation (WHO 1992)², testing with a single Elisa only is useful for surveillance purposes, but for the purpose of diagnosis at least two tests based on different antigen preparation or principles are necessary. Five patients with a negative result on repeat testing returned to the clinic and were referred back to the blood bank for repeat testing. No further information is available on whether these patients had a repeat test and the outcome of such tests. According to WHO recommendations for HIV testing in countries where the prevalence of HIV infection is equal or greater than 10% with the above scenario where the first test is positive and the second negative in persons who are asymptomatic, the serum should

be regarded as antibody negative (*ibid*).

7.3 TUBERCULIN RESULTS

Tuberculosis preventive therapy in countries with low infection rates is recommended for all HIV infected persons with evidence of *M. tuberculosis* infection as evidenced by a positive tuberculin reaction. (Festenstein F Grange JM 1991) The tuberculin reaction is a delayed-type hypersensitivity reaction and as such mirrors cellular immunity. Anergy to tuberculin testing in an individual with infection by *M. tuberculosis* may occur in malnutrition, disseminated tuberculosis, the use of steroids and cytotoxics, pregnancy, advanced age and HIV infection. (McMurray DN Echverri A 1978). Intradermal skin test with other common antigens such as candidin may be used to test the specificity of the non-responsiveness. The presence of anergy to tuberculin testing in the presence of HIV infection has been reported in patients with active TB, (Johnson et al 1992, Elliott et al 1993).

In HIV infected persons therefore a reaction of 5mm is considered positive as compared to a cut-off of 10 mm in non-HIV infected individuals. In areas with high prevalence rates for *M. tuberculosis* infection, two-step tuberculin testing may be useful to identify anergic patients with *M. tuberculosis* infection. (Hecker et al 1995). A recent report has found that the size of the tuberculin reaction was similar in both HIV positive and HIV negative reactors. In this study the largest numbers of HIV positive cases had reactions less than 1 mm or more than 15 mm. Thus the difference

in cut-off points according to HIV status may be unnecessary. (Gourevitch et al 1995)

Overall there was a significant lower frequency of tuberculin reactivity in the HIV positive than in the HIV negative patients in this study in agreement with the findings in other studies. Thus in areas with high rates of both HIV and tuberculosis infection the tuberculin test would have no role in the identification of those eligible for preventive therapy. In these areas all patients with HIV infection should be considered to be at risk of developing tuberculosis regardless of their HIV status.

7.4 RECRUITMENT OF PATIENTS

7.4.1 Comparison of Recruitment Sites

The rate of enrolment of patients in the study was much higher among the patients from the Blood Bank Clinic than the filter clinic where a larger number of patients (164 vs 48) had to be screened to recruit the same number of patients.

The following factors may account for this difference;

a. Prior knowledge of HIV status

The patients from the blood bank clinic were already aware of their HIV status and had probably gone through all the reaction phases to being HIV positive and had reached a stage of acceptance of their status. Thus these patients

would have been more motivated to seek medical care and therefore be more compliant to treatment. The patients screened and recruited in the Filter Clinic on the other hand still had to go through the phases of acceptance of their HIV status and there may have been denial of the results. The patient who withdrew from the study in the first month as he felt the tablets reminded him of his HIV status was recruited from the filter clinic.

b. Current state of health

Patients screened and recruited from the filter clinic had come to the hospital for a current medical problem whereas the patients from the blood bank clinic were not currently ill and attending the clinic for a routine review. As discussed above, the need to exclude active tuberculosis resulted in the failure to enrol 18 of the 94 (19%) HIV positive patients returning to the clinic. The rate of exclusion due to respiratory involvement at a Voluntary Counselling and Testing centre in Uganda was 10%.(Aisu et al 1995) Patients presenting at the filter clinic were more likely to be excluded on the basis of respiratory symptoms suggestive of tuberculosis than were those from the blood bank clinic ($p=0.01$, 95% RR 0.74CI 0.59-0.93).

Recruitment of HIV positive patients into a clinical trial of a preventive therapy regimen would therefore occur at a faster rate if carried out among patients already aware of their HIV status or who voluntarily seek HIV testing compared to that

among patients who are not aware of their HIV status and need pre-test and post-test counselling. This probably also accounts for the fact that the patients recruited from the filter clinic were more likely to be classified as early defaulters than those recruited from the blood bank clinic.

Recruitment of patients from a clinical setting often requires the exclusion of active TB disease in patients presenting with respiratory symptoms, which is a common presentation in such patients. A voluntary counselling and testing centre would therefore serve as a good source of asymptomatic HIV-positive individuals for possible preventive therapy. Those patients who are sufficiently motivated to seek counselling and testing for HIV would be more motivated to take treatment while they are still asymptomatic.

7.5 EXCLUSION OF ACTIVE DISEASE

Respiratory diseases are a common presentation during the course of HIV infection from asymptomatic disease to AIDS and include bacterial pneumonia, tuberculosis, *Pneumocystis carinii* pneumonia and other conditions with lung involvement such as Kaposi's Sarcoma (Hopewell 1989).

Prior to prescribing preventive therapy in an HIV positive individual in areas with high prevalence rates of tuberculosis it is important to exclude active disease and hence the danger of monotherapy with the risk of development of drug resistance. In

this study, suspected tuberculosis on the basis of either respiratory symptoms and or abnormal chest radiograph was present in 19% of the HIV positive patients who returned to the clinic. In the feasibility study of preventive therapy carried out in Uganda (Aisu et al 1995) 8.6% of tuberculin positive individuals were excluded from the study due either to clinical symptoms suggestive of tuberculosis or the presence of active tuberculosis. Methods to exclude active disease used in this study are mainly directed at diagnosing pulmonary infection and x-ray can not detect extra-pulmonary disease such as abdominal tuberculosis.

The usefulness of sputum smear and culture as a means of excluding tuberculosis in an HIV positive individual may be limited due to the finding of a strong trend towards negative or low grade smear in these patients. Sputum culture takes 6 to 8 weeks before a result is available and in addition HIV positive tuberculosis has been associated with a lower colony count on culture compared to HIV negative disease (Elliott et al 1993). In a similar study conducted in Haiti, however, HIV did not change the diagnostic utility of the sputum smear (Long et al 1991).

Where respiratory symptoms are common and tuberculosis is prevalent, effort has to be made in order to ensure that a case of active disease is not missed. As repeated visits to the clinic would be needed by the patient during this process, staff in the clinic would need to motivate the patients in order to minimize losses during the follow-up. This may be done by repeated counselling on the need to have adequate medical care for all illnesses when HIV positive. Close follow-up and investigation

of these patients will ensure that any active cases are diagnosed early and treatment begun. By so doing any active cases will be referred for treatment.

This process is not always successful as is evident by the finding that in this study 61.5% (8 of 13) patients so investigated did not return to the clinic and efforts to trace them were unsuccessful as the addresses given were either not found or incorrect. Of the 5 patients who did return to the clinic for further treatment no evidence of tuberculosis was found though they continued to have symptoms of cough. All sputum smears were negative for AAFB on both microscopy and culture.

7.6 DEFAULTER TRACING

During a cohort study designed for the purpose of determining efficacy the ability to adequately follow-up the patients is very important. In this pilot study it was evident that number of patients who dropped out of the study increased with increasing duration of follow-up. The ability to find these patients was thus of importance, more so when it is considered that these patients were relatively well at the time of recruitment and would easily forget about their appointment.

Some of the problems encountered in attempting to find these patients included difficulties in finding the residential addresses given by the patients. The high density residential areas and shanty compounds in Lusaka do not have any named streets and the system of numbering of houses does not follow any logical order. Thus when an

address was given by the patient it was often difficult to find the house number given. Attempts had been made at the time the address were recorded to obtain the name of either a grocery shop, bar or tavern that was close to the patients home as a suitable landmark. This was not always helpful as the description offered by the patient was not always correct. Some patients gave an address that could be located, though they were not known at the address and it was not known whether this was either because the name they used in the clinic was different from the one they were known by in their area or because they deliberately gave a wrong address.

People in Zambia tend to have several names and in some cases may be known only by the name of their first child. Thus even where the address given was found the patient was not known as the name used was uncommon. One possible reason for the patient giving a wrong address at the time of recruitment may be the fact that they were not willing for their relatives, friends or neighbours to know that they were having any treatment due to the stigma that is still attached to being HIV positive in Zambia.

People living in high density areas, especially in rented accommodation also tend to be very mobile in that they easily move from one house to another within the same area or to another area as rental charges are increased. Thus even though the initial address given may be correct at the time of trying to trace the patient they may have moved and left no forwarding address. There is also a tendency for patients to migrate back to their village at the time they begin to be chronically ill and hence

these patients are lost to follow-up.

When recruiting patients into a follow-up study it is therefore important to obtain very detailed information of their residential addresses at the time of recruitment, including all their names by which they are known, the names of their children and the addresses of their next of kin and possibly village they originally came from. For patients living in high density areas or shanty compounds it would be necessary, if feasible and the patient willing, to take the patient to their homes in order to determine the exact address.

All measures taken to ensure that the patients are followed up should however take into account the patients wish for confidentiality. One criterion for exclusion from the study was voluntary withdrawal and hence those patients not responding to reminders should be considered to have withdrawn from the study.

In order to increase the follow-up rate it would also be important to provide repeated counselling to the patients in order for them to have a clear understanding of what the study would achieve as well as the benefit to them of constant follow-up. The rate of follow-up decreased quite markedly from the third month to the sixth month review. A period of three months between reviews is a long period especially among patients who are not currently ill. More frequent reviews during the initial treatment months would help to ensure more regularly attendance.

In a study setting other incentives that may be used include delivering patients to their homes after enrolment in order to ensure that a correct address is obtained. Subsequent to the initial counselling, deferred recruitment may help to ensure that only the patients who are sufficiently motivated to return to the clinic at a later time are recruited. The problems of follow-up as a result of the difficulty in finding patients in an urban area might be avoided by conducting a community based study.

7.7 ASSESSMENT OF COMPLIANCE

Various methods may be used to evaluate patient compliance or adherence to a particular treatment regimen. These include pill counts, regular assessment of drug metabolites in the urine, self-reporting on the part of the patient or direct observation of the patient taking the medicine, the use of diaries or monitoring pill collection. Other more sophisticated devices include special electronic bottles which record each time a tablet is removed from the container.

The regimens used in this study were intermittent regimens, taken twice a week and thus the diaries were designed to serve both as a reminder for the patient to take the drugs correctly and as a record of when the drugs were taken in relationship to when they were due to be taken. From the result obtained in this study it is evident that this method is limited in usefulness as a monitor of treatment as it relies on the patient remembering to fill in the form correctly as well as to return it to the clinic. In this study only 65% (111 of 170) of the diaries were returned to the clinic. Patients either did not return to the clinic or else they "forgot" the diaries at home. The low number

of diaries returned by patients at month six review is a reflection of this. However of those patients returning to the clinic with the diaries the number of doses taken of the total number of doses were 93% and above. Thus for those who are compliant to treatment the diaries can serve as a reminder to take the medicine especially with an intermittent regimen.

8.0 CONCLUSION

HIV infection has become the strongest known risk factor for the progression of a latent tuberculosis infection into active disease. Isoniazid preventive therapy offers a possible therapeutic option for individuals found to be HIV positive in areas where the incidence of both tuberculosis and HIV is high and where it is not possible to use the currently available anti-retroviral agent. The major problems identified in the pilot study concerned both the recruitment and follow-up of patients. Thus it would be important in the main study to ensure that detailed information of the addresses of the patient are obtained, including those of the next of kin at the time of recruitment. Repeated counselling to ensure that the patient understands the importance of attending the clinic and of informing staff in the clinic of any change in address may also help to improve follow-up of the patient.

9.0 RECOMMENDATIONS

1. The KAB questionnaire on HIV should be expanded on order to explore the extent to which knowledge of HIV and its mode of transmission affects behaviour.
2. The bias towards screening and recruiting of males should be avoided by ensuring that both sexes have equal opportunity to enter the study.
3. The initial questionnaire should include demographic details such as age and education level in order to have a complete data set of all patients screened.
4. All HIV positive individuals should be considered to be eligible for entry into the study regardless of the results of the tuberculin test due to the high proportion of tuberculin negative reactions in the HIV positive patients.
5. Additional recruitment sites would be necessary for the main study; the rate of recruitment is faster among patients already aware of their HIV status. A voluntary counselling and testing centre would be a suitable site.
6. Exclusion of active tuberculosis is an important pre-requisite to enrolling patients in the study.

7. In order to ensure good follow up it would be important to obtain detailed information of patient's addresses, both residential and business as well as those of their next of kin. Involvement of family members where possible would ensure that information could be available of changes in the patient's state of health or any transfers. Repeated counselling during the course of the study would be necessary.

8. Additional measures of compliance to the use of urine testing and drug calendars such as pill counts may be useful to obtaining an accurate estimate of compliance during the study.

This pilot study was designed principally to identify problems associated with the recruitment and follow-up of HIV positive patients in a randomised placebo controlled trial of tuberculosis preventive therapy in Lusaka. The study also assessed possible sites for the recruitment of these patients. The study identified various logistical problems which would need to be addressed prior to conducting a large scale trial of preventive therapy in Lusaka.

The initial survey done of the patients knowledge and attitudes to HIV/AIDS and HIV testing showed that there was a high degree of knowledge of HIV and its transmission among patients attending the UTH filter clinic. A willingness to be tested was expressed by 75.3% of these patients, though only 65.6% actually had the test. This questionnaire did not explore the effect that a knowledge of HIV and its mode of transmission may have had on the behaviour of the respondents and this is an aspect

that would be important to study.

The difference in ratio between the numbers of females and males may partly be due to sampling bias on the part of the investigator or as a result of a reluctance on the part of females to have the HIV test due to uncertainty of the reaction of their spouses. In a similar study that was conducted in Haiti (Pape 1993), 77% of the participants were women. In this study there was no difference in seropositivity rate between the males and females. In order to have a more representative sample in the main study it will be important to eliminate any bias towards males in the sampling procedure of the patients.

The initial questionnaire used did not include details of the patient's age and other demographic data apart from sex. Hence valuable information was not available as 60% of the patients did not return to the clinic for their results and no further details were collected for the HIV negative patients that did return to the clinic. Hence it would be important to include this information from each patient that is seen at the first contact.

In countries such as the United States (Centre for Disease Control 1990) tuberculin testing is used in order to identify HIV positive patients eligible for tuberculosis preventive therapy. In several other studies conducted in developing countries though Tuberculin testing was carried out (Pape 1993, Whalen 1995), this was not used for the purpose of selecting patients for treatment as it is recognized that skin test

reactivity may not be a reliable marker of M.tuberculosis in patients with HIV infection and immunosuppression. This is borne out in this study by a significant difference in tuberculin reaction between the HIV positive and negative subjects.

The rate of recruitment was higher in patients who were already aware of their HIV status compared to patients who were not aware of their status at the beginning of the study. Thus in order for recruitment for the main study to be carried out within the specified time limit (18 months) it would be necessary to use additional sites to the filter clinic.

Exclusion of active tuberculosis infection was one of the main reasons for non-enrolment of HIV positive patients seen during the recruitment period. The importance of this can not be underemphasised due to the dangers of monotherapy in an undiagnosed case given preventive therapy. The frequency with which patients presenting to the clinic within a hospital setting have respiratory symptoms means that the recruitment process would be more efficient if considering patients who are asymptomatic, such as the partners of patients admitted in the hospital with HIV-related infection or patients presenting at a voluntary HIV testing centre or those who require the test for employment purposes.

A major drawback in this study was the high rate of loss to follow-up due to patients not returning to the clinic. As participation in the study was voluntary some of these patients may have changed their mind and withdrawn from the study. It was not

however, possible to ascertain reasons why some of the patients dropped out of the study as it was not possible to trace them. In a study that would require to carry out an intention-to-treat analysis it would be very important to be able to trace all the patients. In an urban setting such as Lusaka this would require very detailed information of the patient's residential and work address and those of their next of kin. Involving the patients family in the process would also help as they would then provide any information of the patient's health and whereabouts during the study period. However this is not possible unless sanctioned by the patients due to the need to maintain confidentiality. Alternatively the use of institutional settings such as for example factory workers or the military are possible settings for such a study if it were possible to ensure confidentiality and avoid any penalty to those found to be HIV positive.

In a study designed to assess efficacy of a drug treatment it is important to monitor compliance to treatment. In the pilot study, both the use of drug diaries and urine testing for drug metabolites were associated with difficulties. Whilst other methods such as pill counts may be also used to improve the assessment of compliance, the best measure of compliance would be directly observed therapy. Whereas such a measure may be applicable in a study setting it would frequently be impractical in an operational setting.

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APPENDIX I

PILOT STUDY ON THE PREVENTION OF HIV RELATED TUBERCULOSIS IN ZAMBIA

DOSAGE SCHEDULE

ALL DOSES TO BE TAKEN TWICE WEEKLY

NUMBER OF FOR DOSES	TABLETS WEIGHT	DOSE	NUMBER OF ONE DOSE	TABLETS 8
ISONIAZID (15mg/kg)				
	30 kg	400mg	4 (100mg)	32
	40 kg	600mg	6 (100mg)	48
	50 kg	700mg	7 (100mg)	56
RIFAMPICIN (10mg/kg)				
	30 kg	300mg	1 (300mg)	8
	40 kg	450mg	3 (150mg)	24
	50 kg	600mg	2 (300mg)	16
PYRAZINAMIDE (50mg/kg)				
	30 kg	1500mg	3 (500mg)	24
	40 kg	2000mg	4 (500mg)	32
	50 kg	2500mg	5 (500mg)	40
	60 kg	3000mg	6 (500mg)	48
CALCIUM GLUCONATE				
	any weight	1 tablet	1 tablet	8

APPENDIX II

RANDOMISATION CODE

TREATMENT NO	DRUG	TREATMENT NO	DRUG	TREATMENT NO	DRUG
01	INH	21	R/Z	41	C
02	C	22	INH	42	INH
03	INH	23	INH	43	R/Z
04	C	24	R/Z	44	C
05	C	25	R/Z	45	C
06	C	26	INH	46	C
07	R/Z	27	INH	47	INH
08	R/Z	28	R/Z	48	C
09	C	29	INH	49	R/Z
10	C	30	INH	50	C
11	C	31	INH	51	C
12	INH	32	R/Z	52	INH
13	C	33	INH	53	R/Z
14	C	34	R/Z	54	C
15	R/Z	35	R/Z	55	INH
16	INH	36	R/Z	56	INH
17	R/Z	37	INH	57	INH
18	INH	38	R/Z	58	C
19	C	39	R/Z	59	INH
20	C	40	R/Z	60	R/Z

APPENDIX III

Study number _____ Record number _____

Demographic Details

Name

Age |__|__| Date of Birth ___/___/___

Sex |__|

Civil Status a. Married |__|
b. Single
c. Divorced
d. Widowed
e. Separated

Residential Address

Type of Residential Area a. Shanty compound |__|
b. High density
c. Medium density
d. Low density
e. other

No of rooms |__|__|

No of occupants in house |__|__|

Level of education a. lower primary school (grade 1 to 4) |__|
b. upper primary school (grade 5 to 7)
c. secondary school
d. college/university
e. no education

Occupation

Knowledge of AIDS

Have you heard of AIDS? yes Y no N |__|

Where did you first learn most about it? a. Media (newspaper, TV, poster etc) |__|
b. School
c. Health personnel
d. Relatives/friends
e. other (specify).....

Is AIDS/HIV infection an STD? yes Y no N don't know D []

Can AIDS/HIV infection be transmitted by infected blood? []
yes Y no N don't know D

Can AIDS/HIV infection be transmitted from mother to child? |__|
yes Y no N don't know D

Can AIDS/HIV be transmitted by shaking hands or sharing utensils? yes Y no N don't know D

Do you know of any other way by which AIDS/HIV is transmitted? if yes please specify.....

Can you always tell by looking at a person that they have AIDS/HIV infection? yes Y no N

HIV prevention

Can you prevent yourself from catching AIDS/HIV? yes Y no N

Will sticking to one sexual partner prevent you from catching HIV/AIDS? yes Y no N

Will using condoms prevent you from catching HIV/AIDS? yes Y no N don't know D

Do you know of any other way to prevent AIDS/HIV infection? yes Y no N
if yes please specify.....

Is there a cure for AIDS? yes Y no N don't know D

Is there a treatment for AIDS? yes Y no N don't know D

HIV testing

Are you willing to be tested for AIDS/HIV infection and to be informed of your results? yes Y no N would like to think about it D

if no, is it because;
a. you feel that you cannot cope with knowing your result? yes Y no N
b. you fear discrimination? yes Y no N

if yes what kind of discrimination (please specify)

c. do you feel that it is futile as there is no known cure? yes Y no N

d. are you convinced that you are negative? yes Y no N

e. do you have any other reasons for not wishing to be tested? yes Y no N
if yes, please specify

if you are HIV positive will you share this result with anyone? yes Y no N

if yes, with whom; a. your spouse Y/N/D
b. your family Y/N/D
c. your friends Y/N/D

CONSENT FORM

First visit (Adult Filter Clinic)

I have explained the nature of the study to.....

He/She has been informed that because of the strong association that has been observed between Tuberculosis and HIV infection, the study will be carried out to determine whether it will be possible to delay or prevent the onset of Tuberculosis which commonly occurs in patients with HIV infection and that is will also determine whether Tuberculosis will delay progression from HIV infection to AIDS. He/She understands that initial investigations will include a blood sample for HIV test, full blood count and liver function tests, a mantoux test, a pregnancy test and a urine test for glucose. He/She understands that all results will be treated with strictest confidence. He/she has consented to enter the study.

Signature of Investigator

Date ____/____/____/

QUESTIONNAIRE ONE

Q1 P1

SURNAME STUDY NO |_|_|_|_|_|

FORENAMES CARD NO

CLINIC ATTENDING: 1=FILTER CLINIC 2=BLOOD BANK |_|

PRESENTING COMPLAINT

.....

DEMOGRAPHIC DETAILS

SEX (M=MALE, F=FEMALE) |_|

ETHNIC GROUP (A=AFRICAN, O=OTHER)

IF OTHER SPECIFY..... |_|

HAVE YOU EVER SUFFERED FROM TUBERCULOSIS? Y/N |_|

IF YES, IN WHICH YEAR? (MONTH/YEAR) |_|_|_|/|_|_|
(EXCLUDE IF WITHIN 2 YEARS)

WHAT TREATMENT WAS RECEIVED?

WHEN DID THE COURSE OF TREATMENT END?

WHAT IS THE TB NUMBER (IF KNOWN)?

HAVE YOU EVER HAD BCG VACCINATION? Y/N |_|

IS THERE A BCG SCAR PRESENT? Y/N |_|
{LOWER OR UPPER ARM}

HAVE YOU EVER SUFFERED FROM JAUNDICE (YELLOWNESS OF THE EYES)? Y/N |_|

DO YOU DRINK ALCOHOL? 1. YES |_|
2. NOT NOW BUT USED TO
3. NO

IF ANSWERED 1 OR 2:
FOR HOW MANY YEARS? |_|_|

WHAT DO (DID) YOU DRINK? |_|
(1=BEER 2=SPIRITS
3=LOCAL BREW (E.G. KACHASU, 7 DAYS) 4=ALL OF THEM)

HOW MANY TIMES A WEEK DO (DID) YOU DRINK? |_|_|

HOW MUCH DO (DID) YOU DRINK EACH TIME? |_|_|
(APPROXIMATE AMOUNT IN BOTTLES)

STUDY NO |__|__|__|__|__|

HAVE YOU EVER HAD A REACTION TO DRUGS? Y/N |__|

IF YES, TO WHICH DRUG/S

.....

WOMEN ONLY

WHAT IS THE DATE OF YOUR LAST NORMAL MENSTRUAL PERIOD?

|__|__|/|__|__|/|__|__|

WHAT IS THE DATE OF YOUR LAST DELIVERY?

|__|__|/|__|__|/|__|__|

DO YOU PLAN TO FALL PREGNANT IN THE NEXT 3 MONTHS? Y/N

|__|

DO YOU PLAN TO LIVE IN LUSAKA FOR THE NEXT 3 YEARS?

QUESTIONNAIRE TWO

Q2. P1

STUDY NO |__|__|__|__|__|

DEMOGRAPHIC DETAILS

AGE (YEARS) |__|__| SEX (M=MALE, F=FEMALE) |__|

ETHNIC GROUP (A=AFRICAN, O=OTHER) |__|
IF OTHER, SPECIFY

MARITAL STATUS (S=SINGLE, M=MARRIED, P=SEPARATED |__|
D=DIVORCED, W=WIDOWED)

GRADE ATTAINED IN FULL-TIME EDUCATION 1=NO EDUCATION |__|
2=GRADE 1-7
3=GRADE 8-12

DID YOU GO TO COLLEGE/UNIVERSITY? Y/N |__|

OCCUPATION |__|

HOUSING:

NUMBER OF ROOMS |__|__| NUMBER OF OCCUPANTS |__|__|

1. RESIDENTIAL ADDRESS 2. POSTAL ADDRESS
.....
.....

DIRECTIONS FOR RESIDENTIAL ADDRESS (MAP)

NEXT OF KIN: NAME

1. RESIDENTIAL ADDRESS 2. POSTAL ADDRESS
.....
.....

EMPLOYERS NAME

POSTAL ADDRESS

EXAMINATION

Q2 P3

STUDY NO |__|__|__|__|__|

1. FEVER (c) |__|__|. |__| 2. WEIGHT (kgs) |__|__|. |__|

3. HEIGHT (m) |__|__|__| 4. ORAL CANDIDA? Y/N |__|

5. JAUNDICE? Y/N |__| 6. ANKLE OEDEMA? Y/N |__|

7. ENLARGED LYMPH NODES? (>2cm):
IN >1 EXTRA-INGUINAL SITE? Y/N |__|

EPIUROCHLEAR NODES ENLARGED? Y/N |__|

8. SEBORRHOEIC DERMATITIS? Y/N |__|

9. a) MACULO-PAPULAR RASH? Y/N |__|

b) OTHER RASH? Y/N |__|

10. MOLLUSCUM CONTAGIOSUM? Y/N |__|

11. VIRAL WARTS? Y/N |__|

12. HERPES SIMPLEX (L=LABIAL, G=GENITAL,
D=DISSEMINATED, N=ABSENT) |__|

13. SIGNS OF HERPES ZOSTER? Y/N |__|

14. FUNGAL INFECTION a) HEAD? Y/N |__|

b) BODY? Y/N |__|

c) NAILS? Y/N |__|

15. HAIRY LEUKOPLAKIA? Y/N |__|

16. NAIL CHANGES? Y/N |__|

17. HEPATOMEGALY? Y/N |__|

IF YES, cm LENGTH IN MID CLAVICULAR LINE |__|__|

18. KAPOSI'S SARCOMA? Y/N |__|

IF YES, SPECIFY SITE

19. NEUROLOGICAL ABNORMALITIES (e.g. REDUCED ANKLE JERKS)

SPECIFY

.....

.....

STUDY NO |__|__|__|__|__|

20. EXAMINATION OF RESPIRATORY SYSTEM

a) CHEST CLINICALLY CLEAR? Y/N |__|

IF NO, SPECIFY ABNORMALITY PRESENT

.....
.....

OTHER FINDINGS

.....
.....
.....

STUDY NO |__|__|__|__|__|

RESULTS OF INVESTIGATIONSFULL BLOOD COUNT

Hb (g/dl) |__|__|. |__| TWBC (x10⁹) |__|__|. |__|
 Diff% N |__|__| L |__|__| M |__|__|
 B |__|__| E |__|__|

PROGRESSION MARKERS

CD4 |__|__|__| CD8 |__|__|__|__|
 B2 microglobulin |__|__|__|__|
 Neopterin |__|__|__|__|

SPUTUM RESULTS

Sputum present? Y/N |__|
 AFB (microscopy) P/N |__|
 Culture P/N |__|

LIVER FUNCTION TESTS

Bilirubin (umol/L):
 a) Conjugated |__|__|. |__|
 b) Unconjugated |__|__|. |__|
 Total Protein (gm/L) |__|__|. |__|
 Albumin (gm/L) |__|__|. |__|
 Enzymes:
 a) SGOT (umol/L) |__|__|. |__|
 b) SGPT (umol/L) |__|__|. |__|
 c) AlkPhos (umol/L) |__|__|. |__|

HIV RESULTS

Wellcozyme P/N |__| HIVCHECK (or Du-Pont) P/N |__|

MANTOUX TEST

Result (mm) |__|__|

STUDY NO |__|__|__|__|__|

CHEST XRAY

Any findings? (Y/N)

LEFT: UL |__|

ML |__|

LL |__|

RIGHT: UL |__|

ML |__|

LL |__|

Effusion Y/N:

a) Pleural |__| b) Pericardial |__|

Miliary Y/N |__|

PREGNANCY AND GLUCOSE TEST RESULTS

Pregnancy Test P/N |__|

Glucose P/N |__|

OTHER INVESTIGATIONS PERFORMED (please specify test and result):

.....
.....
.....
.....
.....

STUDY NO |__|__|__|__|__|

5. SINCE YOUR LAST VISIT, HAVE YOU:

a) HAD ANY PAIN ON PASSING URINE? Y/N |__|

b) NOTICED ANY CHANGE IN COLOUR OF YOUR URINE? Y/N |__|

IF YES, WHAT COLOUR CHANGE?

6. SINCE YOUR LAST VISIT, HAVE YOU HAD ANY OF THE FOLLOWING:

a) JOINT PAINS? Y/N |__|

b) SWELLING OF JOINTS? Y/N |__|

7. SINCE YOUR LAST VISIT, ON HOW MANY DAYS HAVE YOU HAD ANY OF THE FOLLOWING SYMPTOMS (PUT 00 IF SYMPTOM ABSENT):

a) FEVER Y/N |__|__|

b) NIGHT SWEATS? Y/N |__|__|

c) COUGH? Y/N |__|__|

d) SPUTUM PRODUCTION? Y/N |__|__|

e) CHEST PAIN? Y/N |__|__|

8. SINCE YOUR LAST VISIT, HAVE YOU

a) HAD ANY OTHER ILLNESSES? Y/N |__|

IF YES, PLEASE SPECIFY:

.....
.....
.....

b) BEEN ADMITTED TO THE HOSPITAL? Y/N |__|

IF YES, PLEASE SPECIFY REASON FOR ADMISSION:

.....
.....

STUDY NO |__|__|__|__|__|

PHYSICAL EXAMINATION

1. TEMPERATURE (c) |__|__|. |__| 2. WEIGHT (kg) |__|__|. |__|

3. PALLOR? Y/N |__| 4. ANKLE OEDEMA? Y/N |__|

5. JAUNDICE? Y/N |__|

6. LYMPHADENOPATHY >2 cm: a) EXTRA-INGUINAL? Y/N |__|

b) EPITROCHLEAR? Y/N |__|

7. ORAL THRUSH? Y/N |__|

8. HAIRY LEUKOPLAKIA Y/N |__|

9. HERPES SIMPLEX: a) ORAL? Y/N |__|

b) GENITAL? Y/N |__|

10. HERPES ZOSTER? Y/N |__|

11. SKIN: a) SEBORRHOEIC DERMATITIS? Y/N |__|

b) IMPETIGO? Y/N |__|

c) FUNGAL INFECTION? Y/N |__|

12. HEPATOMEGALY? Y/N |__|

13. SPLENOMEGALY? Y/N |__|

14. KAPOSI'S SARCOMA? Y/N |__|

15. CHEST EXAMINATION: specify any findings

.....

.....

.....

16. NEUROLOGICAL EXAMINATION: specify any abnormalities

.....

.....

.....

17. ANY OTHER FINDINGS

.....

STUDY NO |__|__|__|__|__|

RESULTS OF INVESTIGATIONS

FULL BLOOD COUNT

Hb (g/dl) |__|__|. |__| TWBC (x10⁹) |__|__|. |__|

Diff% N |__|__| L |__|__| M |__|__|

B |__|__| E |__|__|

PROGRESSION MARKERS

CD4 |__|__|__| CD8 |__|__|__|__|

B2 microglobulin |__|__|__|__|

Neopterin |__|__|__|__|

SPUTUM RESULTS

Sputum present? Y/N |__|

AFB (microscopy) P/N |__|

Culture P/N |__|

LIVER FUNCTION TESTS

Bilirubin (umol/L):

a) Conjugated |__|__|. |__|

b) Unconjugated |__|__|. |__|

Total Protein (gm/L) |__|__|. |__|

Albumin (gm/L) |__|__|. |__|

Enzymes:

a) SGOT (umol/L) |__|__|. |__|

b) SGPT (umol/L) |__|__|. |__|

c) AlkPhos (umol/L) |__|__|. |__|

URINE TEST RESULTS

INH P/N |__| Rifampicine P/N |__|

HIV RESULTS

Wellcozyme P/N |__| HIVCHECK (or Du-pont) P/N |__|

OTHER INVESTIGATIONS PERFORMED

OUTCOME QUESTIONNAIRE

O1 P1

To be filled in once:

EITHER when the patient has completed the 36 month follow-up
OR if the patient is withdrawn from the study before 36 months.

STUDY NO |__|__|__|__|__|

1. WAS THE PATIENT A DEFAULTER? Y/N? |__|
IF YES, SPECIFY:

KNOWN TO HAVE MISSED > 2 DOSES? Y/N |__|

KNOWN TO HAVE LOST TABLETS? Y/N |__|

NEVER RETURNED AND ADDRESS NOT FOUND/ Y/N |__|

NEVER RETURNED AND MOVED AWAY? Y/N |__|

2. PATIENT COMPLETED 36 MONTH FOLLOW-UP? Y/N |__|

3. a) DATE LAST CAME |__|__|/|__|__|/|__|__|

b) MONTH LAST CAME (range 01-36) |__|__|

ANSWER THE FOLLOWING QUESTIONS ONLY IF ANSWER TO 2=N (WITHDRAWN)

4. REASON FOR WITHDRAWAL:

a) DEATH? Y/N |__|
IF YES, SPECIFY:

DATE OF DEATH |__|__|/|__|__|/|__|__|

PLACE OF DEATH (1=HOSP 2=HOME 3=OTHER) |__|

CAUSES OF DEATH (1 - 6) |__|

- 1 = RESPIRATORY
- 2 = GASTRO INTESTINAL
- 3 = MENINGITIC
- 4 = WASTING
- 5 = OTHER
- 6 = NOT KNOWN

REMARKS.....
.....
.....

STUDY NO |__|__|__|__|__|

b) TB OUTCOME? Y/N |__|
 IF YES, SPECIFY:

DATE OF DIAGNOSIS |__|__|/|__|__|/|__|__|

DATE OF ONSET OF SYMPTOMS |__|__|/|__|__|/|__|__|

HOW WAS IT DIAGNOSED? :

SPUTUM PRESENT? Y/N |__| NO. OF SAMPLES SENT |__|__|

NO. OF CULTURE POSITIVE |__|__| NO. OF MICROSCOPY POSITIVE |__|__|

SENSITIVITY PATTERN: INH Y/N |__| RIF Y/N |__|

PZA Y/N |__| STREP Y/N |__|

SYMPTOMS:

RESPIRATORY SYMP? Y/N |__| CONSTITUTIONAL SYMP? Y/N |__|
 RADIOLOGICAL FINDINGS? Y/N |__|

IF YES, SPECIFY:
 HILAR ADENOPATHY? Y/N |__| PARENCHYMAL INFILTRATES? Y/N |__|

PLEURAL EFFUSION? Y/N |__| PERICARDIAL EFFUSION? Y/N |__|

OTHER FINDINGS? Y/N |__|

IF YES, SPECIFY:.....

TB TREATMENT GIVEN? Y/N |__|
 IF YES

RESPONSE TO TB TREATMENT

WEIGHT GAIN:

WEIGHT AT DIAGNOSIS |__|__|__|. |__|

WEIGHT AT 2 MONTHS |__|__|__|. |__|

RESPIRATORY SYMPTOMS (1 - 4) |__|

CONSTITUTIONAL SYMPTOMS (1 - 4) |__|

RADIOLOGICAL SYMPTOMS (1 - 4) |__|

- 1 = COMPLETELY BETTER
- 2 = BETTER
- 3 = NOT BETTER
- 4 = WORSE

STUDY NO |__|__|__|__|__|

TB DIAGNOSIS (1 - 4)

|__|

1 = CONFIRMED

2 = PROBABLE

3 = POSSIBLE

4 = UNLIKELY

c) REPEAT HIV TEST NEGATIVE? Y/N
IF YES SPECIFY:

|__|

DATE OF TEST

|__|__|/|__|__|/|__|__|

CONFIRMED BY WESTERN BLOT? Y/N

|__|

INITIAL HIV TEST POSITIVE? Y/N
IF YES, SPECIFY:

|__|

REASON FOR DISCREPANCY

d) DRUG REACTIONS? Y/N
IF YES, SPECIFY:

|__|

DATE OF 1ST REACTIONS

|__|__|/|__|__|/|__|__|

REACTIONS:

SKIN RASHES? Y/N |__|

NAUSEA? Y/N |__|

JOINT PAINS? Y/N |__|

RAISED LFT? Y/N |__|

VOMITING? Y/N |__|

OTHER? Y/N |__|

(IF YES FOR OTHER SPECIFY)

HOW WERE THE REACTIONS DIAGNOSED?

e) PREGNANCY DURING TREATMENT? Y/N
IF YES SPECIFY:

|__|

DATE OF LNMP

|__|__|/|__|__|/|__|__|

STUDY NO |__|__|__|__|__|

f) LOSS TO FOLLOW-UP? Y/N |__|
IF YES, SPECIFY:

DATE DUE TO COME |__|__|/|__|__|/|__|__|

LETTER SENT? Y/N |__|

IF NO, REASON WHY LETTER NOT SENT: |__|

(1=ADDRESS NOT FOUND, 2=OTHER)

IF OTHER, SPECIFY

IF THE REASON FOR LOSS TO FOLLOW-UP IS KNOWN (e.g. moved
house) THEN SPECIFY

.....

g) OTHER REASON? Y/N |__|
IF YES, SPECIFY:

DATE OF WITHDRAWAL |__|__|/|__|__|/|__|__|

REASONS

.....

PREVENTION OF TUBERCULOSIS: TREATMENT CALENDER

EACH DOSE OF YOUR TREATMENT CONSISTS OF:

PLEASE TAKE YOUR MEDICINE EVERY MONDAY AND THURSDAY THE MORNING OF YOUR NEXT CLINIC VISIT. WHEN YOU HAVE TAKEN THE MEDICINE, TICK THE BOX. YOU SHOULD TAKE THE MEDICINE IN THE MORNING, BEFORE BREAKFAST.

IF YOU FORGET AND TAKE IT LATE, PLEASE MARK THE DAY WHEN YOU TAKE IT.

NAME: STUDY NUMBER:

DATE: TREATMENT NUMBER:

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
	*****	*****		*****	*****	*****

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
	*****	*****		*****	*****	*****

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
	*****	*****		*****	*****	*****

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
	*****	*****		*****	*****	*****

IF YOU ARE SICK OR HAVE ANY PROBLEMS WITH THE MEDICINE, PLEASE COME IMMEDIATELY TO SEE DR MWINGA OR DR HOSP AT THE FILTER CLINIC ON MONDAY, TUESDAY, THURSDAY AND FRIDAY MORNING. BRING THIS PAPER AND YOUR CARD WITH YOU.

PREVENTION OF TUBERCULOSIS: TREATMENT CALENDER

EACH DOSE OF YOUR TREATMENT CONSISTS OF:

PLEASE TAKE YOUR MEDICINE EVERY TUESDAY AND FRIDAY THE MORNING OF YOUR NEXT CLINIC VISIT. WHEN YOU HAVE TAKEN THE MEDICINE, TICK THE BOX. YOU SHOULD TAKE THE MEDICINE IN THE MORNING, BEFORE BREAKFAST.

IF YOU FORGET AND TAKE IT LATE, PLEASE MARK THE DAY WHEN YOU TAKE IT.

NAME: STUDY NUMBER:

DATE: TREATMENT NUMBER:

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
*****		*****	*****		*****	*****

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
*****		*****	*****		*****	*****

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
*****		*****	*****		*****	*****

MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY	SUNDAY
*****		*****	*****		*****	*****

IF YOU ARE SICK OR HAVE ANY PROBLEMS WITH THE MEDICINE, PLEASE COME IMMEDIATELY TO SEE DR MWINGA OR DR HOSP AT THE FILTER CLINIC ON MONDAY, TUESDAY, THURSDAY AND FRIDAY MORNING. BRING THIS PAPER AND YOUR CARD WITH YOU.

COMPLIANCE DIARIES

C1 P1

STUDY NO |__|__|__|__|__|

INDICATE WHETHER THE DRUGS WERE TAKEN (Y/N) AND IF THEY WERE TAKEN, SPECIFY WHETHER THEY WERE TAKEN EARLY (E), LATE (L) OR ON THE CORRECT DAY (C).

MONTH 1

DOSE

- 1 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 2 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 3 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 4 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 5 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 6 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 7 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 8 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 9 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|

MONTH 2

DOSE

- 1 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 2 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 3 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 4 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 5 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 6 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 7 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|
- 8 TAKEN? Y/N |__| IF YES, SPECIFY E/L/C |__|

MONTH 3DOSE

1	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
2	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
3	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
4	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
5	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
6	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
7	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
8	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__

MONTH 4DOSE

1	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
2	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
3	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
4	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
5	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
6	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
7	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
8	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__

MONTH 5DOSE

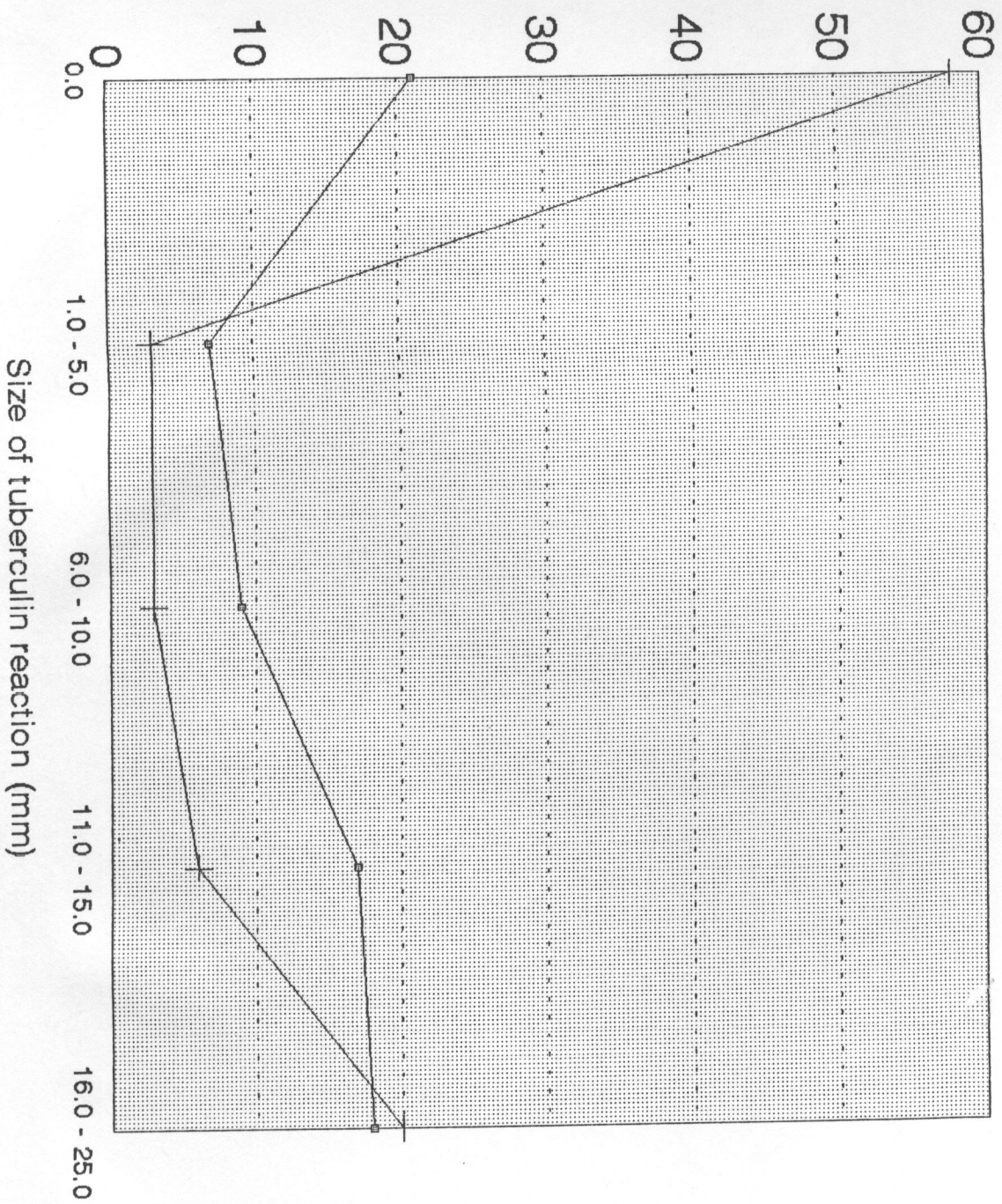
1	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
2	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
3	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
4	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
5	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
6	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
7	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
8	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__

MONTH 6DOSE

1	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
2	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
3	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
4	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
5	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
6	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
7	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__
8	TAKEN? Y/N	__	IF YES, SPECIFY E/L/C	__

TUBERCULIN RESULTS

APPENDIX IV



KEY
—□— HIV NEGATIVES
—+— HIV POSITIVES