WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

DISTR. : LIMITED
DISTR. : LIMITEE
WHO/TUB/AIDS/90.1
ORIGINAL: ENGLISH

Tuberculosis Programme

Global Programme on AIDS

PREVENTIVE TUBERCULOSIS CHEMOTHERAPY AMONG PERSONS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

Report of the Informal Consultation Geneva, 6-8 February 1990

TUBERCULOSIS PROGRAMME

GLOBAL PROGRAMME ON AIDS

PREVENTIVE TUBERCULOSIS CHEMOTHERAPY AMONG PERSONS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

Informal Consultation

Geneva, 6-8 February, 1990

I. INTRODUCTION

An informal consultation on preventive tuberculosis chemotherapy among persons infected with the human immunodeficiency virus (HIV) was held in Geneva from 6-8 February 1990. The consultation was convened by the Tuberculosis Unit of the Division of Communicable Diseases and the Biomedical Research Unit of the Global Programme on AIDS of the World Health Organization. The list of participants is provided in Annex 1.

The objectives of the meeting were:

1) to review available data on the risk of tuberculosis among persons infected with both causative organisms, as well as information on the efficacy and safety of various preventive therapy regimens and on compliance with therapy;

2) to develop guidelines for study protocols with emphasis on the key elements on which standardization is essential;

3) to consider the possibility of a multinational study and to develop mechanisms for inter-study coordination which will facilitate comparison of study results;

4) to identify the current state of research and funding in this area and the projects most likely to provide useful information and most in need of support; and

5) to develop guidelines for operational studies of the feasibility of tuberculosis preventive therapy as a public health programme.

The meeting was opened by Dr G. Torrigiani, Director of the Division of Communicable Diseases. The first day was devoted to reviewing current knowledge on the prognosis of persons with dual infections with Mycobacterium tuberculosis and HIV, the status of preventive tuberculosis chemotherapy, and the potential impact of preventive tuberculosis chemotherapy for dually infected persons on the AIDS and tuberculosis situations. The second day was spent devising guidelines for future studies. Discussions of these guidelines and accompanying recommendations took place on the third day, along with considerations of the role of the World Health Organization in facilitating and coordinating the necessary studies.

It was agreed that obtaining comparability among otherwise independent trials was more likely to achieve the desired goals expeditiously than a multinational study, mentioned in the third objective. To address the fourth objective, participants were asked to complete a brief questionnaire about characteristics of current and planned trials. The results are summarized in Annex II.

Throughout the consultation, the participants expressed a sense of urgency because of the increasingly gloomy situation with respect to dual infections and a feeling of frustration resulting from technical and administrative difficulties in starting the studies.

II. BACKGROUND INFORMATION

With the spread of the HIV infection epidemic several countries have observed a rapid increase in the incidence of tuberculosis (1,2). Case-control analysis of data from a number of tropical African countries has shown that the increase in pulmonary tuberculosis attributable to HIV infection is often in the order of 30 - 50% and may attain 100% in certain areas where HIV infection is highly prevalent. Clinical observations indicate that extra-pulmonary tuberculosis has increased even more (3,4). In developed countries increases have remained relatively small since both the HIV and the tuberculosis infection prevalences are much lower. However, marked increases have been observed in special risk groups, e.g. drug users in the USA (5,6).

Before the HIV epidemic, developing countries, for which data are available, achieved at best an annual decline of a few percent in tuberculosis, as evidenced by notifications and surveillance of the annual risk of infection (7). The present increase therefore represents a tremendous setback in control efforts. In addition to the direct consequences regarding the case-load, it is likely that the increased incidence of pulmonary tuberculosis will entail a similar increase in the risk of infection which, in turn, will result in an increase in tuberculosis in the entire population in future years.

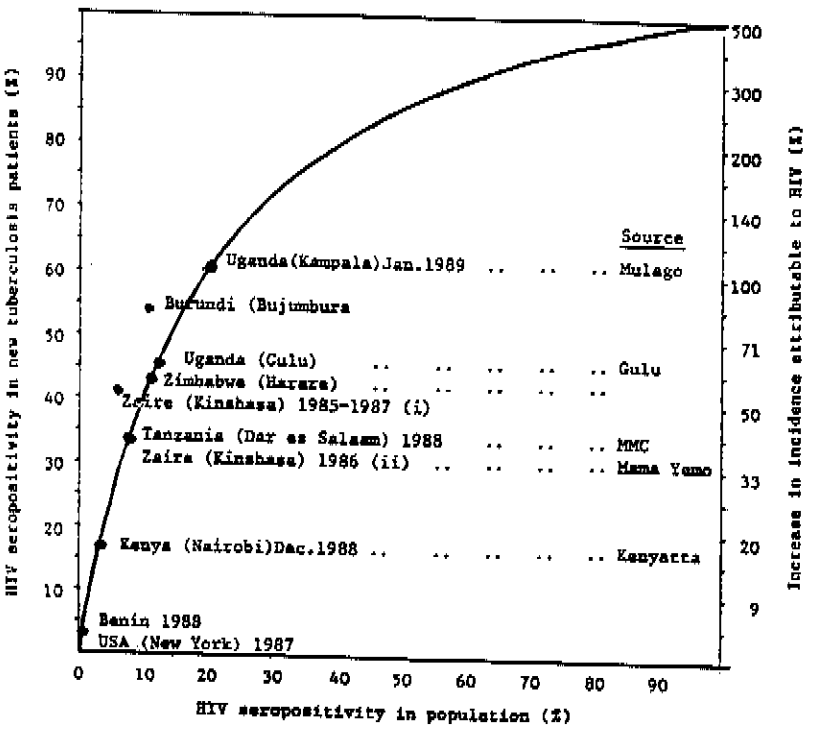
The current tuberculosis control measures - BCG vaccination of the newborn and "passive" case-finding and chemotherapy - even if strengthened, are clearly inadequate to curb the upsurge. Unfortunately, the number of additional tuberculosis control measures that could be applicable is very limited. BCG (re-)vaccination could be considered for adolescents but this would merely be a long-term approach and its effectiveness would have to be determined. For an immediate impact it will be necessary to resort to active case-finding and/or preventive chemotherapy.

Active case-finding, notably through regular follow-up of identified HIV seropositive persons, may reduce transmission of infection in the community but will not immediately reduce the case-load. It would require extensive strengthening of the diagnostic facilities since smear microscopy is not sufficiently sensitive for early case detection (8,9,10). Extrapulmonary tuberculosis would pose an entirely new problem for most national tuberculosis programmes.

Preventive tuberculosis chemotherapy has not been recommended for developing countries in the past, primarily because the limited resources as regards both health staff and drugs had to be reserved for treatment of active tuberculosis cases. In addition, it was difficult to identify high risk groups, aside from tuberculosis contacts, among the vast numbers of tuberculosis infected persons.

The risk of a dually infected person developing tuberculosis is not precisely known but probably is at least six times as high as that of persons infected with tuberculosis alone, and likely very much higher at the later stages of HIV infection. Figure 1 shows HIV positivity among newly diagnosed cases of pulmonary tuberculosis and among comparable population groups in a number of countries. The drawn curve represents a relative risk of 6.0 (11).

Fig. 1 Relationship between HIV seropositivity in the population and in new tuberculosis patients and relative increase in tuberculosis incidence attributable to HIV infection



The high incidence among dually infected persons in countries with an extremely low risk of new tuberculosis infections, indicates that disease is caused predominantly by endogenous reactivation and therefore should be preventable by chemotherapy (12). Furthermore, persons found to be HIV positive are likely to accept medication, especially if they were tested at their own request. Most countries attempt to provide some form of follow-up service for HIV seropositive persons and this can be utilized to increase compliance.

Identification of the HIV infected persons is mainly a management problem whereas identification of the tuberculosis infected persons among those found to be HIV positive is rather a technical problem. For the preventive programme to have a noteworthy impact, in the first place a large proportion of the HIV infected will have to be discovered. This will only be possible if ample facilities for voluntary HIV testing are available and the population has sufficient awareness and motivation to make use of these facilities. In this connection issues of confidentiality and counselling need to be addressed. In many parts of the world, tuberculin sensivity is also caused by BCG vaccination and infection with mycobacteria other than M. tuberculosis. In these situations, any tuberculin reaction size selected to define a "positive" reaction will produce false positive as well as false negative results in varying proportions of tested persons. Selection of an appropriate criterion in HIV infected persons is even more difficult because tuberculin sensitivity tends to decrease in the course of progression of HIV infection to AIDS.

The efficacy of preventive chemotherapy with isoniazid has been well established in numerous controlled trials in a wide variety of populations and in many different countries (13-25; Annex III). It must be stressed that the reduction in tuberculosis reported in these trials is not the potential efficacy of isoniazid but rather the effectiveness of prescribing isoniazid under a variety of circumstances, many of them similar to ordinary programme situations. In those trials in which efficacy could be assessed among persons who adhered to the prescribed regimen, reduction in tuberculosis was close to 90 per cent or better.

In almost all of the trials summarized in Annex III, the dosage of isoniazid was approximately 5 mg/kg with an upper limit of 300 mg daily, given for one year. A lower dosage for a shorter period was given in the Greenland trial; the IUAT trial among persons with fibrotic lesions used three different durations of therapy; and the trial among Alaskan school children compared 1 mg/kg and 5 mg/kg for a total period of 6 months. The optimal duration based on results among tuberculosis contacts (13), Alaskan villagers (13), and persons with fibrotic lesions (25) appears to be somewhat more than 6 months but probably appreciably less than 12 months (26).

Side effects of preventive isoniazid therapy can be acceptably low under programme conditions. The most common symptoms are gastro-intestinal in nature, followed by rashes and dizziness. Drug fever and peripheral neuritis are very rare. The only serious and common side effect is hepatitis. This is rare in children and young adults but can occur in 2-3 per cent of persons over the age of 35 years (27). Serious consequences can be avoided if persons taking isoniazid are monitored at least monthly for symptoms and signs of hepatitis and are motivated to stop medication promptly if any of these occur.

Information from tuberculosis chemotherapy trials and from animal experiments indicates that the use of rifampicin and pyrazinamide in preventive regimens should shorten their duration markedly and perhaps increase their effectiveness (28, 29). The frequency of side effects when these drugs are used in preventive chemotherapy has not been established; a trial by the U.S Public Health Service should provide such information in the near future. The lack of evidence regarding the effect of pyrazinamide on the foetus renders its use among pregnant women problematic.

Because tuberculosis is the only important complication of AIDS that is transmitted from man to man, extensive preventive chemotherapy given to dually infected persons could make a tremendous contribution to the control of tuberculosis in countries where dual infection is highly prevalent.

Preventive tuberculosis chemotherapy is also likely to have an important impact on AIDS control programmes. Prevention of tuberculosis will decrease morbidity among HIV infected persons and probably prolong their lives. Demonstration that there is a treatment with beneficial effects could stimulate voluntary HIV testing and increase the credibility of control programmes. It is even possible that control of tuberculosis infection will slow down the progression of HIV infection to ARC and AIDS.

III. GUIDELINES FOR EFFICACY STUDY PROTOCOLS

The following information is provided to assist investigators in the development of protocols for efficacy studies of preventive tuberculosis chemotherapy in persons infected with HIV. These guidelines cover key elements for which standardization is required to insure that the various studies are sufficiently comparable.

A. Eligibility

Persons who are dually infected with HIV and M. tuberculosis are eligible for these studies. Persons under age 15 may be excluded since dual infection among these will be relatively rare.

For various reasons, some studies will also recruit and enroll persons without serologic evidence of HIV infection, or persons who may not be infected with M. tuberculosis. In some settings where the prevalence of TB infection is very high, it may be practical to recruit all HIV seropositives. In most studies, however, it will be preferable to identify TB-infected persons, or at least to try and exclude a high proportion of uninfected persons.

1. Tuberculosis Infection

A low-dose intradermal tuberculin test in a dosage equivalent to 5 IU (2 "TU" of RT23 with Tween) is the indicated method for identification of persons infected with M. tuberculosis. Accurate administration of the dose and reading of the test result (recorded in millimeters of induration measured in the transverse axis at 72 hours) is required. Training of study staff in the administration and reading of the tuberculin test is indispensable.

Factors that lower the sensitivity (e.g., immunosupppression caused by HIV infection) or the specificity of the test (e.g., BCG vaccination) are to be considered in deciding which test criterion to use in defining tuberculosis infection. Thus, in countries with a high prevalence of tuberculosis infection and where non-specific tuberculin sensitivity is also prevalent, 10 mm induration could be an appropriate criterion (i.e., those with 10 mm induration or more would be classified as infected). In order to maximize the likelihood that study subjects are truly infected with M. tuberculosis, a higher criterion (e.g., 15 mm) may be selected. In other situations (e.g., populations with low levels of non-specific sensitivity), 5 mm induration may be a satisfactory criterion. On the other hand there may be studies in which persons will have to be enrolled independently of their tuberculin reaction. In such studies all participants should be tested at entry and their tuberculin reactions carefully recorded, so that protective efficacy can be analyzed in this respect.

In general it is advisable to tuberculin test in a preliminary study a sample of the potential study subjects, examine the frequency distribution of the observed reactions and then select an appropriate test criterion if this proves possible.

2. BCG vaccination

Prior BCG vaccination complicates the interpretation of the tuberculin reaction, although sensitivity induced by BCG vaccination may wane over time. Thus, large reactions to tuberculin among persons with a remote history of BCG vaccination are likely due to tuberculous infection, at least when tuberculosis infection is highly prevalent.

Since BCG vaccination not necessarily leaves an indelible scar, the presence or absence of a scar may not be a good indication of the vaccination status. Therefore, in all studies, the history of BCG-vaccination should be obtained, including the type of vaccine used, and BCG scars should be looked for and their transverse diameter measured and recorded in millimeters. This will make it possible to verify the accuracy of the history and scar readings as it allows an estimate to be made of the proportion of vaccinated individuals who have neither a scar nor a history of vaccination.

3. HIV infection

The presence of HIV infection should be documented by 2 serologic tests using different mechanisms (e.g., competitive binding and direct assay). Most commonly, this is accomplished by Western blot confirmation of a reactive ELISA test.

4. Informed consent

Study subjects must give informed consent in order to participate in these studies. The procedures and elements of consent must conform with the Declarations of Helsinki as revised at Tokyo and Venice, as well as with local norms. In all cases, procedures for obtaining informed consent must be approved by the local ethical review board.

In some studies, consent may be a two-step process. First, consent for HIV testing and then consent for enrollment in the chemoprophylaxis trial should be obtained.

Study procedures should incorporate counseling and measures to insure confidentiality in accordance with local norms. In all cases, the establishment of procedures to protect study subjects from unwarranted disclosure of HIV status is critical.

B. Exclusions

Exclusions must be made before allocation of the participants to treatment and control groups.

1. Active tuberculosis

Because of the increased likelihood of active tuberculosis among dually infected persons and the risk of development of drug resistance if monotherapy is used in this condition, it is important to exclude persons with active tuberculosis from the study.

Thus, persons with symptoms consistent with tuberculosis (e.g., unexplained fever, cough, and weight loss) should not be entered unless careful examination excludes tuberculosis as a cause of these symptoms.

Persons with abnormal chest X-ray pictures should not be entered, unless careful bacteriologic examination excludes the diagnosis of active pulmonary tuberculosis. This may be accomplished by the finding of three consecutive sputum samples negative for M. tuberculosis on direct smear microscopy and culture. Persons with abnormal chest X-ray pictures and negative sputum smears may be registered provisionally as participants but should not be allocated before the culture results are known to be negative.

The diagnosis of extrapulmonary tuberculosis is more difficult, and extrapulmonary tuberculosis is not uncommon in the presence of HIV infection. However, it is unlikely that asymptomatic persons will have significant extrapulmonary tuberculosis. Persons with persistent generalized lymphadenopathy but no symptoms of tuberculosis are eligible for these studies.

2. Conditions likely to result in death before any possible development of tuberculosis

The most important of these conditions is clinical AIDS (i.e., opportunistic infections and other conditions associated with advanced immunosuppression caused by HIV infection). However, minor HIV-related conditions, such as thrush, herpes zoster, and genital ulcers, are not reasons for exclusion.

3. Pregnancy

The decision to include pregnant women in studies of regimens including pyrazinamide must be taken by the investigator and relevant review boards and ethics committees. The following points may be taken into consideration.

Although no data are available about the possible teratogenic effects of pyrazinamide, its benefits are considered to outweigh the risks in clinically active tuberculosis. WHO and IUATLD do not recommend withholding pyrazinamide from pregnant women with tuberculosis.

Preventive chemotherapy has reduced the incidence of active tuberculosis in several cohorts of subjects with unknown HIV status, and is likely to have some beneficial effect on tuberculosis prevention in HIV positive subjects. However, the magnitude of this effect for pyrazinamide-containing regimens is unknown and may not outweigh possible risks.

Any teratogenic effects are likely to occur during the first trimester of pregnancy. Therefore, if the decision is made to exclude pregnant women, pregnancy tests should be

performed at entry for all women of childbearing age, and those with a positive pregnancy test excluded from participation. Because of the short duration of pyrazinamide administration, repeated pregnancy tests for women entered into a study are not suggested.

In view of the ethical conflicts introduced by withholding possibly beneficial treatment from pregnant women, and the practical considerations in studies where prenatal care clinics are an important source of subject referrals, a possible solution might be to delay recruitment of pregnant women until after the first trimester of pregnancy or after delivery.

Because any birth defects that do occur among children of participating pregnant women may be attributed to the drug, whether or not it is the cause, this may negatively affect participation in the study or public perception of the study and its investigators.

Pyrazinamide has been shown to have teratogenic effects in mice. This is also true for isoniazid. Isoniazid, however, has not been shown to have this effect in human beings and is considered safe in treatment and preventive regimens during pregnancy. Therefore pregnancy is not a contraindication to participation in studies in which pyrazinamide is not included.

4. Documented history of prior tuberculosis therapy or preventive chemotherapy.

5. The presence of any condition for which administration of one of the study drugs is a contraindication.

The usual contra-indications for chemotherapy in tuberculosis patients apply. Persons at a special risk of developing drug reactions, e.g. those with liver disease or chronic kidney failure, should be excluded. Instructions from the national tuberculosis programme should be followed in this respect. Additional tests may be applied but should not necessarily lead to exclusion of the participants.

C. Pretreatment (baseline) investigations

1. HIV serology (see Section III.A.3.)

2. Tuberculin testing (see Section III.A.1.)

3. History and physical examination.

This history should include history of BCG vaccination, tuberculosis contact, chest symptoms, symptoms of gastrointestinal and hepatic disease, tuberculosis medications taken in the past, and symptoms of HIV disease (ARC, AIDS). The physical examination should include measurements of weight, height, temperature, and BCG scar, inspection of the skin and mucous membranes, examination of the abdomen for hepatosplenomegaly, and palpation of the neck, supraclavicular fossa, axillae, etc. for enlarged lymph nodes.

4. Chest radiograph

5. Sputum for smear microscopy and culture (in persons with abnormal chest radiographs or respiratory symptoms such as productive cough).

6. Complete blood count with differential

7. CD4 cell counts to stage HIV infection are highly desirable. However, inability to perform this test should not exclude a center from conducting a study.

8. Liver function tests are desirable in order to exclude persons with liver disease from participation and to provide a baseline for the evaluating of subsequent hepatotoxic drug reactions. However, inability to perform liver function tests does not exclude a center from conducting a study.

9. Pregnancy test for women of childbearing age (for studies in which pyrazinamide is included).

D. Drug regimens and rationale

Among the drugs considered for preventive tuberculosis chemotherapy in HIV-infected persons are isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and possibly long-lasting rifamycin derivatives (e.g., rifapentine). Isoniazid derivatives like aconiazide may also be considered. These drugs can be used alone or in combination with the following advantages and disadvantages:

1. Isoniazid

Advantages: It is the only drug demonstrated to be effective in preventive chemotherapy when given daily in a dose of 5mg/kg (300mg for an adult) for 6 to 12 months. It is inexpensive and specifically active against M. tuberculosis.

Disadvantages: Isoniazid must be given for 6 to 12 months. It may be hepatotoxic. In some countries, there may be a high rate of primary (or initial) isoniazid resistance. If given inadvertently to patients with active tuberculosis, isoniazid monotherapy can lead to acquired drug resistance.

2. Rifampicin + pyrazinamide + isoniazid

Advantages: This three-drug combination is currently the most effective combination for treating tuberculosis. A two-month regimen has been found to be effective in preventing reactivation in patients with culture-negative pulmonary tuberculosis. A combined tablet is available, which makes administration simpler. If given inadvertently to a patient with active tuberculosis, drug resistance is unlikely to develop.

Disadvantages: It is expensive. There is potential additive toxicity of the three different drugs. Furthermore, the safety of pyrazinamide in pregnancy has not been demonstrated (see Section III.B.3.).

3. Rifampicin + pyrazinamide

Advantages : There is experimental evidence that this combination, given for as short a period as two months, has a good sterilizing effect. It avoids the toxic effects of isoniazid and may be as effective for preventive chemotherapy as the triple drug combination (with isoniazid).

Disadvantages: The combination is expensive and may have additive side effects. A combined tablet is not available. The safety of pyrazinamide in pregnancy has not been demonstrated.

4. Rifampicin

Advantages: Rifampicin is a sterilizing drug and, in theory, at least as effective as isoniazid alone in tuberculosis preventive therapy. It has fewer side effects when given daily and the prevalence of primary resistance is low.

Disadvantages: There is a risk of side effects (immune reactions) if taken irregularly. There has been little experience with this drug alone in persons with immune dysfunction. It is expensive. The optimal duration for administration of this drug is unknown. There is also the risk of the induction of acquired drug resistance if given inadvertently to tuberculosis patients.

5. Rifampicin + isoniazid

Advantages: There is clinical experience of this combination in a four-month regimen of chemotherapy. The use of more than one drug decreases the risk of acquired drug resistance. Tablets of the combined drugs are available.

Disadvantages: Isoniazid hepatotoxicity is not avoided. There may be increased toxicity by combining the two drugs. The combination is expensive.

6. Long acting rifamycin derivatives

These drugs are not licensed at present. However, in the future, once weekly or twice monthly administration may be useful operationally.

7. Isoniazid derivatives

Drugs like aconiazide may be as effective, less toxic, and as inexpensive as isoniazid.

E. Dosage and administration

The dosages recommended for chemotherapy are:

	Daily		Intermittent	
	mg/kg	max (mg)	mg/kg	max (mg)
Isoniazid	5	300	15	750
Rifampicin	10	600	10	600
Pyrazinamide	20-30	2000	50*	2500
			50-70**	3500**

* 3 times a week
** 2 times a week

For daily preventive chemotherapy the same dosages are proposed as for chemotherapy. The advantage of daily administration is that less supervision is necessary. Unsupervised preventive chemotherapy is administered daily.

The advantage of intermittent administration are that drug costs are decreased and fully supervised treatment is feasible. It may become more acceptable if the time between each dose can be increased by the use of a long acting rifamycin. The major disadvantage is that it requires resources for supervision.

F. Use of comparison or placebo control groups:

The demonstrated effectiveness of preventive chemotherapy with isoniazid suggests that a group treated with isoniazid alone might be the appropriate comparison group for assessing the value of other regimens. While this is undoubtedly true for immunocompetent persons, it is unknown whether preventive chemotherapy is effective among persons whose immune system has been as seriously affected as it is in HIV infected persons. There is also the possibility that side effects may be more frequent and severe among these persons. A placebo control group is therefore indicated at least for the initial trials of preventive chemotherapy among HIV infected persons.

If it should turn out that preventive treatment has a limited effect, e.g., merely suppresses the development of tuberculosis during the time that drugs are administered, the small benefit for a few may not be worth the costs and side effects to which all may be subject. Only once it has been determined that there is a favorable balance of benefits and risks for a particular regimen this regimen may be used for a comparison group.

As regards the use of an untreated, rather than placebo, control group, the study group felt strongly that this was inappropriate in trials designed to assess efficacy and safety of particular regimens. Only for operational studies of the effectiveness of programmes, including the efficacy of the drug regimen used, could an untreated control group be appropriate.

G. Sample size

Sample size calculations are based on many considerations including the study objectives, durations of follow-up, and stage of HIV infection. Standard sample size calculations are adequate for estimating numbers of subjects needed for trials that compare drug versus placebo regimens. Given the high risk of tuberculosis among dually infected persons it is anticipated that a few relatively small controlled trials will answer the questions of efficacy and acceptability of side effects.

Two or more regimens that are expected to be effective cannot be compared for efficacy in a single small study, but for similar regimens deciding on the best one may well be a matter of judgement based on approximate efficacy, side effects, compliance, costs, and applicability to programme requirements. Replication of results in several small trials could be more informative than statistical significance shown in a single large trial.

H. Monitoring

1. Monitoring (minimum requirements)

During the whole course of the study, participants should be encouraged to visit the treatment centre if any clinical symptoms develop.

During the period of drug administration there should be monthly visits for full medical examination to detect symptoms of diseases and drug toxicity (active and passive) with all specified laboratory testing.

Compliance should be monitored by systematic urine tests, recording of attendance and possibly home visits to check consumption of drugs. An active retrieval system should be available to limit the loss of participants from the trial. Finally systematic X-rays should be performed every 6 months following the start of the trial.

The length of follow-up after the period of drug administration must be determined according to the objectives of the study and the sample size. It should include:

- full medical examinations at least every 6 months plus chest X-ray plus appropriate laboratory tests;

- free medical services between the visits;

- an active retrieval system to prevent loss to follow-up (every effort should be made to find participants who failed to attend the clinic at the appointed time).

2. Among the outcome measures that should be considered are:

- the length of survival (see below);

- development of TB (see below);

- progression of HIV disease, including decreases in CD4 counts and the development of AIDS;

- toxicity: liver toxicity, skin rash, gastrointestinal symptoms and neurotoxicity (peripheral neuritis); all should be carefully monitored with appropriate laboratory tests and clinical examination;

- withdrawals (refusals or medical discontinuation but remain in area);

- lost to observation.

3. Tuberculosis

During the course of the study active tuberculosis will be suspected or diagnosed on the basis of clinical symptoms, X-ray findings or sputum smears. Regardless of whether treatment for tuberculosis is to be started, appropriate biological samples (e.g., sputum, nodal biopsy, cerebrospinal fluid, etc.) should be cultured for identification and drug susceptibility testing, before starting treatment. At least three specimens of sputum, urine or any other appropriate material should be taken to obtain evidence of tuberculosis. Only cases in which M. tuberculosis (M. bovis or M. africanum) is identified will be considered as having tuberculosis.

4. Death

The date, place and as far as possible the cause of death during therapy and follow-up period should be recorded.

IV. CONSIDERATIONS FOR OPERATIONAL STUDIES

The aim of operational studies is to assess the applicability of preventive tuberculosis therapy for HIV infected persons by national AIDS and tuberculosis control programmes, particularly as regards compliance.

A. Prerequisites for initiating operational studies.

- There should be close collaboration between the AIDS and TB programmes in the planning and conduct of these studies.

- The national TB programme should be established and performing its primary tasks of case finding and treatment adequately. A treatment completion rate of 75% or more would indicate adequate implementation of the treatment programme.

- An assessment should be made of the implications of undertaking a study for the national TB and AIDS programmes, including staffing, and for supporting facilities such as laboratory services.

B. Organization of the study team.

C. Identification of HIV-infected persons.

- In most cases this would be accomplished through the national AIDS programme.

- Laboratory evidence is needed to identify HIV-infected persons. The guidelines for efficacy studies should be followed (see Section III.A.3.).

D. Examination for tuberculosis.

- The diagnosis of tuberculosis infection is based on the results of the tuberculin test following standardized procedures for administration and recording (see Section III.A.1.).

- Sputum examination (smear and if possible culture) and clinical examination is required to exclude active tuberculosis.

E. Exclusions.

1. Tuberculosis cases and suspects.

2. AIDS cases.

3. Persons who have had tuberculosis treatment or preventive chemotherapy.

4. Persons less than 15 years of age.

5. Patients with jaundice.

6. Persons who have not given informed consent.

Pregnant women may be excluded from studies in which pyrazinamide is used (see Section III.B.3). In some populations, the prevalence of tuberculin sensitivity may be so high that it is almost impossible and certainly not cost-effective to identify persons free from tuberculosis infection by preliminary tuberculin testing.

F. Basic information on study subjects.

For all study subjects the following information should be recorded: results of history and physical examination, sputum bacteriology, current therapy, AIDS risk group, presence of other medical conditions (including drug abuse and alcoholism), identification data, domicile, and resident status (resident, refugee, migrant, etc.). The following should be done and their results recorded: examination for presence and measurement of traverse diameter of BCG scar (in mm), intradermal low-dose tuberculin test and measurement of transverse diameter of induration (in mm), chest X-ray, laboratory examinations as indicated.

G. Consent, counseling, confidentiality

Informed consent of the participant should be confirmed by the signature of a member of the study team.

Counseling for AIDS must be provided.

Confidentiality should be guaranteed following local norms.

H. Regimen for preventive chemotherapy.

Study regimens may be selected from among those proposed in Section III.D.

The decision on which regimens to use should be based on the chemotherapy regimen currently used in the NTP, the cost of drugs and the prevalence of initial drug resistance (especially as regards isoniazid) in the area.

I. Measures to assess compliance.

- Drug collection and appointment keeping;
- Treatment completion and continuation at 2 and 4 months;
- Other methods applicable: pill count, urine analysis.

J. Measures to improve compliance.

- Registration and treatment card (should differ clearly from that for TB cases);
- Pill calendars;
- Pretreatment motivation and remotivation at each visit to a clinic;
- Interval of visits to a clinic (at least monthly);
- Home visits for defaulters;
- Subsidy for transport;
- Combining drugs in one tablet when 2 or more drugs are used.

K. Monitoring of side-effects.

Patients should be questioned about the presence of side effects of therapy at each clinic visit, as well as any other time of encounter with clinic staff (e.g., home visits). Information on the presence or absence of side effects should be recorded on the treatment card.

Toxicity and side effects may be classified as: (a) no side effect, (b) slight side-effect but medication continued, and (c) severe side-effect requiring suspension of drug taking.

The type of side effect should also be noted. The most commonly expected side effects are: (a) gastrointestinal disturbance; (b) skin eruption; and (c) hepatitis.

A referral system should be developed for cases with severe side-effects.

L. Sample size.

The size of the study group(s) should be calculated according to the usual formulas, considering the expected default rate, the characteristics of the groups (e.g. stage of HIV infection) and the duration of the follow-up period.

M. Outcome measures.

1. Treatment completion rate including treatment continuation rate at 2 and 4 months.

2. Proportion of drugs taken.

3. Proportion of persons who stopped taking prescribed medication prematurely.

4. Incidence of newly diagnosed tuberculosis as determined by linking tuberculosis case register with list of study subjects.

5. Cost analysis: Cost of preventive chemotherapy, cost of identifying HIV(+) persons and cost of treatment for preventable TB cases.

6. The epidemiologic impact of the preventive chemotherapy program and the impact of this program on other tuberculosis services, e.g., case finding and case holding. This analysis would consider the effectiveness of preventive chemotherapy, the coverage among the dually infected persons estimated to exist in the population and compliance obtained.

7. The impact of the preventive therapy program on other AIDS program services, e.g., changes in voluntary HIV testing, educational services, and other AIDS control alternatives.

V. ROLE OF WHO'S TUB AND GPA PROGRAMMES

WHO should vigorously promote studies of preventive tuberculosis chemotherapy in HIV infected persons as a major priority for research. Activities in this area should include dissemination of information and approaching donor countries and funding agencies with the expectation of targeted support. WHO should also petition the World Health Assembly to adopt a resolution calling for increased support for tuberculosis programmes and studies in the area of HIV-associated tuberculosis, in light of the increasingly devastating effect of HIV on the tuberculosis situation in many countries.

WHO should provide technical assistance to local TB and AIDS programmes in the design and conduct of these studies. This support should include review of study protocols, as well as on-site assistance in study implementation, periodic study monitoring, and assistance in analysis and reporting of study data.

WHO should assist local programs in identifying sources of funding for these studies. This is a critically important activity, as local investigators have had difficulty in obtaining funding. Much might be accomplished by direct lobbying of funding agencies on behalf of these projects.

WHO should serve as the international coordinator of these studies, tracking ongoing studies, identifying gaps in needed research, and identifying investigators to fill these needs. For this activity, local investigators should be encouraged to provide WHO TUB/GPA with copies of their periodic status reports summarizing the progress of these studies and available findings. A specific person should be given this responsibility and made accountable for its accomplishment. By keeping close track of ongoing studies, WHO would be in a position to identify the need for companion and other related studies, as well as to suggest potential investigators to initiate these studies.

WHO should take the initiative to keep investigators updated on the progress of these studies. The WHO coordinator should prepare a periodic report summarizing the ongoing activities and mail it to all interested investigators. The coordinator should arrange informal meetings for local investigators at other meetings where they are likely to gather, such as the International AIDS meetings.

While WHO cannot be the primary funder of these studies, in its coordinating role it should utilize the available resources for those studies that are most likely to provide the most important answers in the shortest time possible. Proposals that will strengthen the local tuberculosis and AIDS control programs should receive special consideration. WHO should also urge local programs to devote a portion of their AIDS MTP funds to support these research activities.

WHO should promote institutional strengthening of laboratory support for these studies, as well as continue strengthening tuberculosis case-finding and the provision of short-course chemotherapy.

At present there are several well-equipped, but poorly staffed, mycobacteriology laboratories which were established with assistance from the British Medical Research Council for their tuberculosis chemotherapy trials. Laboratories located in countries experiencing significant increases in tuberculosis in association with the HIV epidemic should be strengthened.

Problems related to the association of HIV and tuberculosis infection have now been reviewed in three WHO-sponsored meetings. In response to the pressing need for research, the Tuberculosis Unit and the Biomedical Research Unit of the Global Programme on AIDS have established a joint research programme with the following priority study objectives: monitoring of the TB/HIV problem in terms of incidence and risk of infection; safety, efficacy and feasibility of preventive chemotherapy in dually infected individuals; safety and effectiveness of BCG vaccination in HIV-infected infants; optimal treatment for HIV-infected tuberculosis patients; and clinical manifestations of tuberculosis in HIV-infected patients, including differential diagnosis of pulmonary disease.

General information on support provided by WHO and a project proposal form may be obtained from the Chief Medical Officer, Tuberculosis Unit, CDS, WHO, Geneva.

VI. REFERENCES:

1. Standaert B, Nirangira F, Kadende P, et al: The association of tuberculosis and HIV infection in Burundi. AIDS Research and Human Retroviruses, 1989, 5 (2): 247-251

2. Slutkin G, Leowski J, Mann J: Tuberculosis and AIDS. The effects of the AIDS epidemic on tuberculosis problems and tuberculosis programmes. Bull. Int. Union Tuberc. Lung Dis., 1986, 63: 21-24

3. Mann JM, Bila K, Colebunders RL et al: Natural history of human immunodeficiency virus infection in Zaire. Lancet 1986, 2: 707-709

4. Fernandez-Guerrero ML, Agundo JM, Buzon L, et al: Visceral leishmaniasis in immunocompromised hosts. Am. J. Trop. Med., 1987, 83: 1098-1102

5. Selwyn PA, Hortel D, Lewis VA, et al: A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N. Engl. J. Med., 1989, 320: 545-550

6. Pitchenik AE, Russell BW, Cleary T, et al: The prevalence of tuberculosis and drug resistance among Haitians. N. Engl. J. Med., 1982, 307: 162-5

7. Styblo K: The potential impact of AIDS on the tuberculosis situation in developed and developing countries. Bull. Int. Union Tuberc., 1988, 63: 25-8

8. Colebunders RL, Ryder RW, Nzilambi N, et al: HIV infection in patients with tuberculosis in Kinshasa, Zaire. Am. Rev. Respir. Dis., 1989, 139: 1082-85

9. Pitchenik AE, Cole C, Russell BW et al: Tuberculosis, atypical tuberculosis and the acquired immunodeficiency syndrome among Haitian and non-Haitian patients in South Florida. Ann. Intern. Med., 1984, 101: 641-45

10. Centers for Disease Control: Diagnosis and management of mycobacterial infection and disease in persons with human immunodeficiency virus. Ann. Intern. Med., 1987, 106: 254-56

11. ten Dam HG, Eriki P: Surveillance of the tuberculosis/HIV problem. WHO Geneva (1989). Unpublished.

12. Rieder HL, Cauthen GM, Comstock GW, et al: Epidemiology of tuberculosis in the United States. Epidemiol. Review, 1989, 11: 79-98

13. Ferebee SH: Controlled chemoprophylaxis trials in tuberculosis. A general review. Adv. Tuberc. Res., 1970, 17: 28-106

14. Debré R, Perdrizet S, Lotte A, et al: Isoniazid chemoprophylaxis of latent primary tuberculosis: in five trial centres in France from 1959 to 1969. Int. J. Epidemiol., 1973, 2: 153-60

15. Mount FW, Ferebee SH: The effect of isoniazid prophylaxis on tuberculosis morbidity among household contacts of previously known cases of tuberculosis. Am. Rev. Respir. Dis., 1962, 85: 821-7

16. Bush OB Jr, Sugimoto M, Fujii Y, et al: Isoniazid prophylaxis in contacts of persons with known tuberculosis. Am. Rev. Respir. Dis., 1965, 92: 732-40

17. Egsmose T, Ang'awa JOW, Poti SJ: The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. Bull. WHO, 1965, 33: 419-33

18. Del Castillo H, Bautista LD, Jacinto CP, et al: Chemoprophylaxis in the Philippines. A controlled pilot study among household contacts of tuberculosis cases. Bull. Quezon Institute, 1965, 7: 277-91

19. Chiba Y, Takahara T, Kondo K, et al: Chemoprophylazis of tuberculosis for adults in Japan. Bull. Int. Union Tuberc., 1963, 69: 91-3

20. Comstock GW, Hammes LM, Pio A: Isoniazid prophylaxis in Alaskan boarding schools. A comparison of two doses. Am. Rev. Respir. Dis., 1969, 100: 773-9

21. Katz J, Kunofsky S, Damijonaitis V, et al: Effect of isoniazid upon the reactivation of inactive tuberculosis. Am. Rev. Respir. Dis., 1962, 86: 8-15

22. Pamra SP, Mathur GP: Effects of chemoprophylaxis on minimal pulmonary tuberculous lesions of doubtful activity. Bull. WHO, 1971, 45: 593-602

23. Grzybowski S, Ashley MJ, Pinkus G: Chemoprophylaxis in inactive tuberculosis: long-term evaluation of a Canadian trial. Can. Med. Assoc. J., 1976, 114: 607-611

24. Falk A, Fuchs GF: Prophylaxis with isoniazid in inactive tuberculosis. Chest, 1978, 73: 44-8

25. Krebs A, Farer LS, Snider WE, et al: Five years of follow-up of the IUAT trial of isoniazid prophylaxis in fibrotic lesions. Bull. Int. Union Tuberc., 1979, 54: 65-9

26. Comstock GW, Ferebee SH: How much isoniazid is needed for prophylaxis? Am. Rev. Respir. Dis., 1970, 101: 780-2

27. Kopanoff DE, Snider DE, Caras GJ: Isoniazid-related hepatitis. A U.S. Public Health Service cooperative surveillance study. Am. Rev. Respir. Dis., 1978, 117: 991-1001

28. Hong Kong Chest Service/Tuberculosis Research Center, Madras/British Medical Research Council. A controlled trial of 2-month, 3-month and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis: Results at 60 months. Am. Rev. Respir. Dis., 1984, 130: 23-28

29. Lecoeur HF, Truffot-Pernot C, Grosset JH. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. Am. Rev. Respir. Dis., 1989, 140: 1189-1193

Annex I

Participants

Dr S. ALLEN, c/o Projet San Francisco, Monsieur le Representant de l'OMS, B.P. 780, Kigali, Rwanda (Telex: 909-22574)

Dr. E. Baende, Project SIDA, P.O. Box 8502, c/o US Embassy, Kinshasa, Zaire

Dr. J-R. Brutus, Coordonnateur Technique, Centres Pour le Développement et la Santé, 16 rue Frères Simmonds, Cité-Militaire, P.O. Box 1666, Port-au-Prince, Haiti

Dr R.E. CHAISSON, Director, AIDS Services, The John Hopkins University, School of Medicine, Suite, 7401, 1830 E. Monument Street, Baltimore, MD 21205, United States of America (Tel: (301) 955 1754, Fax: (301) 955 7404, Telex: (301) 955-7889)

Prof. J. Chrétien, Chaire de Pneumophtisiologie, Hôpital Laennec, 42 rue de Sèvres, 75007 Paris, France

Dr H.J. CHUM, Director, Tuberculosis Control, Ministry of Health, c/o Dr E.A. Duale, WHO Representative, PO Box 9292, Dar-es-Salaam, United Republic of Tanzania (Tel: 21995, Telex: 41110) (Vice-chairman)

Professor G.W. COMSTOCK, John Hopkins University School of Hygiene and Public Health, Training Centre for Public Health Research, PO Box 2067, Coffman Research Laboratory, Hagerstown, MD 21742, United States of America (Tel: (301) 791-3230) (chairman)

Professor J. GROSSET, Faculté de Médecine, Pitié-Salpêtrière, Bacteriologie et Virologie, 91, Boulevard de l'Hopital, 75634 Paris, Cedex 13, France (Tel: (1) 45-84-11-84, Fax: (1) 45-70-20-45)

Dr J. Kalilani, National AIDS Control Programme Manager, c/o WHO Representative, Attention: Dr S.H. Siwale, PO Box 30390, Capital Hill, Capital City, Lilongwe 3, Malawi (Tel: 731-390 or 731-619, Telex: 44624)

Professor K. MCADAM, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom, (Tel: (01) 636-8636, Telex: 8953474)

Dr S. NATAL RIBEIRO, 2nd Floor, Rua do Resende 128, Rio de Janeiro CEP 20231, Brazil

Dr S. NYANGULU, National Tuberculosis Coordinator, c/o WHO Representative, Attention: Dr S.H. Siwali, PO Box 30390, Capital Hill, Capital City, Lilongwe 3, Malawi (Tel: 731-390 or 731-619, Telex: 44624)

Dr R.J. O'BRIEN, Chief, Clinical Research Branch,
Division of Tuberculosis Control, Centre for Prevention Services,
Centre for Disease Control, Atlanta, GA 30333, United States of America
(Rapporteur)

Dr J.A. PILHEU, Second Vice President, LIGA Argentina
Contra la Tuberculosis, Av. Santa Fe 4292, 1425 Buenos Aires, Argentina
(Tel: 774-91-45)

Dr A. ROUILLON, Executive Director, International Union Against
Tuberculosis and Lung Disease, 68 Blvd. Saint-Michel,
75006 Paris, France (Tel: (1) 46-33-08-30, Fax: (1) 43-29-90-87)

DR SERUFILIRA, c/o Monsieur le Représentant de L'OMS
Projet San Francisco Attention: Dr Susan Allen, B.P. 780, Kigali, Rwanda

Dr T. SHIMAO, Emeritus Director, Research Institute of Tuberculosis,
Japan Anti-Tuberculosis Association, Kekkaku,
Yobo Kai Kekkaku Kenkyujo, Kiyose-Shi, Tokyo, Japan (Fax: 0424-92-4600)

Dr R. WALLIS, Case Western Research University, Division of Infectious
Diseases, Dept. of Medicine, 2109 Adelbert Road, Cleveland, Ohio 44106,
United States of America

Secretariat:

Dr P. Crocchiolo, Medical Officer, Biomedical Research, WHO, Geneva, Switzerland

Mr H. ten Dam, Scientist, Tuberculosis, WHO, Geneva, Switzerland

Dr P. Eriki, Director, NTCP, Kampala, Uganda (Consultant)

Dr J. Esparza, Chief Medical Officer, Biomedical Research, WHO, Geneva, Switzerland (Joint Secretary)

Dr S. Grzybowski, Emeritus Professor of Medicine, University of British Columbia, Vancouver, Canada (Consultant)

Dr A. Kochi, Chief Medical Officer, Tuberculosis, WHO, Geneva, Switzerland (Joint Secretary)

Dr F. Luelmo, Medical Officer, National Programme Support, WHO, Geneva, Switzerland

Dr G. Slutkin, Medical Officer, National Programme Support, WHO, Geneva, Switzerland

Dr F. von Sonnenburg, Medical Officer, Biomedical Research, WHO, Geneva, Switzerland

Dr G. Torrigiani, Director, Division of Communicable Diseases, WHO, Geneva, Switzerland

Dr R. Widdus, Medical Officer, Global Programme on AIDS, WHO, Geneva, Switzerland

ANNEX II
SUMMARY OF ONGOING AND PLANNED STUDIES

STUDY AREA	POPULATION RECRUITED	ENTRY REQUIREMENTS	DRUG REGIMEN AND SAMPLE SIZE	PLACEBO CONTROL	METHOD OF DIAGNOSIS OF TB INFECTION	PLAN OF ADMINISTERING MEDICATION	PLAN FOR COMPLIANCE MONITORING	PRIMARY OUTCOME MEASURES
ARGENTINA	Voluntary testing for HIV hospita attendance) M and F	HIV+ and HIV-	6H; 100 2RZ; 100 Placebo; 100	Yes	HIV+ > 5mm HIV- > 10mm to 5IU PPD	Daily	Every 2 weeks	TB toxicity AIDS
ZAIRE	M and F	HIV+ only	6H 2RZ Untreated	No	> 9mm to 2 TU RT23	Daily self-administered	Urine tests Pill counting	TB AIDS toxicity
MALAWI	M and F	HIV+ and -	2HRZ; 2000		> 9mm to 5IU of PPD	Twice weekly observed	Medication supervised	
RWANDA	F only	Both HIV+ and HIV-		Yes	> 9mm to PPD			
BRAZIL	M and F	18-50 yrs HIV +	2RZ; 200	Yes	> 9 mm to 2TU RT23	Daily self-adminstered	Supervision Pill count	Drug toxicity
ZAMBIA	M and F	HIV + No TB	2R; 300 2RZ 300 long acting 300 Placebo 300	Yes	> 9mm to 5IU PPD	Twice weekly Twice weekly Once weekly Twice weekly	Weekly drug administration Urine tests	Death TB toxicity

KENYA	F	HIV+ and HIV-	isoniazid 750 Placebo	Yes	> 9mm to 5IU PPD	Once weekly observed	Urine tests	Death TB Toxicity
HAITI	M and F	HIV+	6H; 250 2RZ; 250 Untreated 250	No	> 4mm to 5IU PPD	Twice weekly	Urine tests Pill count	TB Death Toxicity
UGANDA	M and F	HIV+	6H 150 2RZ 150 2RHZ 150 Placebo 150	Yes	> 9mm to 5IU PPD	Daily self-administered	Routine checks Pill counts	TB Death
INDIA	M and F	HIV+	6H 175 2RZ 175	No	> 9mm to 1TU RT23	Daily self-administered	Appointment keeping Pill counts Urine checks	TB Death
USA (CDC)	M	HIV+	12H 400-500	No	> 4mm to 5IU PPD	Daily observed	Supervision Pill counts Urine checks	TB Toxicity
USA (CDC)	M	HIV+	6H 50 4R 50	No	> 4mm to 5IU PPD	Daily observed	Observed therapy	Compliance Toxicity

ANNEX 3A

Summary of Results of Controlled Trials of Prescribing Isoniazid to Prevent Manifest Tuberculosis

Type of subjects	Number	Outcome	Years of observation	Percent reduction
Children with primary tuberculosis, U.S. (13)	2 750	Tuberculous complications	10	88
Children with primary tuberculosis, France (14)	2 970	Tuberculous complications	3-10	64
Household contacts to old cases, U.S. (15)	2 814	Tuberculous disease	4	54
Household contacts to new cases, U.S. (13)	27 847	Tuberculous disease	10	60
Household contacts to new cases, Japan (16)	2 238	Tuberculous disease	1	30
Household contacts, Kenya (17)	764	Positive bacteriology	3	80
Household contacts, Philippines (18)	327	Abnormal chest X-rays	2	41
Shipboard contacts, Netherlands (13)	261	Tuberculous disease	7	92
Railway workers, Japan (19)	548	Tuberculous disease	6-12	62
Greenland villagers (13)	8 801	Tuberculous disease	6	31
Alaskan villagers (13)	6 064	Positive bacteriology	6	59
Tunisian villagers, urban residents (13)	15 910	Positive bacteriology	1	25
Mental institutions, U.S. (13)	25 210	Tuberculous disease	10	62

ANNEX 3B

Summary of Results of Controlled Trials of Prescribing Isoniazid to Prevent Reactivation of Previously Untreated Inactive Disease

Source of subjects	Number	Outcome	Years of observation	Percent reduction
Mental institutions, New York State (21)	513	Active tuberculosis	6	43
Health Departments U.S. (13)	1 992	Active tuberculosis	5	60
Chest clinic patients, India (22)	317	Positive bacteriology	6	83
Chest clinic patients, Canada (23)	2 405	Active tuberculosis	7-13	53
Veterans hospitals, U.S. (24)	2 389	Positive bacteriology	5	59
Int'l Union against Tuberculosis, Europe (25)	27 830	Positive bacteriology	5	
12 weeks of treatment				22
24 weeks of treatment				65
52 weeks of treatment				75

= = =