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GLOBAL
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REPORT OF A TECHNICAL
ADVISORY MEETING ON RESEARCH
ON AIDS AND TUBERCULOSIS

GENEVA
2 - 4 AUGUST 1988



WORLD
HEALTH
ORGANIZATION



REPORT OF A TECHNICAL ADVISORY MEETING
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1. INTRODUCTION

A technical advisory meeting on research on AIDS and tuberculosis was held in Geneva from 2 to 4 August 1988. The meeting had been recommended by the Working Group on HIV Infection and Tuberculosis held from 18 to 19 January 1988 by the Global Programme on AIDS (GPA), the Tuberculosis Unit (TUB) of the Division of Communicable Diseases (CDS) of the World Health Organization, and the International Union Against Tuberculosis and Lung Diseases (IUATLD). The list of participants is provided in Annex 1.

The objectives of the meeting were:

- (1) to review ongoing and planned research on AIDS and tuberculosis (TB);
- (2) to prioritize AIDS/TB research questions, suggest essential studies, and recommend study designs;
- (3) to discuss which studies, if any, are most in need of international collaboration;
- (4) to identify key research questions that may not be covered by ongoing and planned studies, and to recommend a framework for development;
- (5) to identify key areas of TB programmes which need strengthening in order to carry out this research (e.g., surveillance, laboratory) and suggest mechanisms for development;
- (6) to identify a core group of technical advisers to WHO/GPA and WHO/TUB to review and otherwise assist in work related to HIV/AIDS and TB; and
- (7) to identify possible roles for WHO in AIDS/TB research.

The meeting was opened by Dr J. Mann, Director, GPA, and Dr G. Torrigiani, Director, CDS, and closed by Dr A. Rouillon, Executive Director of IUATLD. They pointed out the importance of the interactions between HIV and mycobacterial infection, which has become apparent from the high incidence of diseases caused by mycobacteria observed in AIDS patients. The problems raised by HIV infection in relation to TB control are of major concern, and, in view of the limited knowledge available at present on the interaction of HIV and mycobacterial infections, research on this subject is urgently needed.

The participants decided to concentrate on objectives (1)-(5), with particular reference to issues relevant to developing countries with a high prevalence of HIV infection.

2. BACKGROUND INFORMATION

2.1 Tuberculosis

2.1.1 The magnitude of the problem

Despite the decline in the risk of new Mycobacterium tuberculosis¹ infection, TB remains a global health problem of enormous dimensions. Approximately 8-10 million new cases occur each year and the disease causes approximately 3 million deaths annually. The prevalence of TB is far greater in developing countries than in the developed parts of the world.

¹Hereafter referred to throughout the text as M. tuberculosis.

2.1.2 Current tuberculosis control efforts

Current control efforts in developing countries are based primarily on identification and treatment of infectious (smear-positive) cases of pulmonary disease. Unfortunately, noncompliance with the long period of drug treatment required, the high cost of the most effective drugs, the emergence of drug-resistant organisms, the lack of a suitable and properly managed infrastructure for delivering TB services, and other problems limit the application of case-finding and treatment measures in many developing countries. Bacille Calmette-Guérin (BCG) immunization, especially of newborn infants, is a commonly used adjunct to case-finding and treatment but it has a limited impact on the number of infectious cases. Furthermore, there is a large pool of persons with latent M. tuberculosis infection (two billion or more) from which many new cases will continue to emerge. Treatment of these individuals to prevent the emergence of clinical disease is practised only on a limited scale in developed countries and minimally in developing countries. Preventive therapy programmes are expensive, and have unfavourable risk-benefit ratios in many infected populations. Given these problems, it is not surprising that progress in reducing the world TB problem has been painfully slow.

2.1.3 The epidemiology of tuberculosis infection and disease

A great deal is known about the epidemiology of TB in developing countries, including the annual risk of infection in populations, risk factors for infection and for progression from infection to clinical disease, the age, sex and geographical distribution of clinical disease, and mortality rates (with and without treatment). While the annual risk of new infection has been decreasing in recent years in the industrialized countries and in some developing countries, it is still 1-3% per year in several countries, and more than half of the populations in these countries are infected by the time they reach adulthood. Most cases of TB continue to occur in young adults. More than 60% of TB patients will die within five years if they are not treated.

Sharing airspace with an untreated infectious (smear-positive) case is the major risk factor for acquiring infection. Early case-finding and treatment of persons with pulmonary TB can considerably reduce the duration of infectiousness of cases and thereby further reduce the risk of M. tuberculosis infection in the population.

It has been known for many years that immunodepression (secondary to many causes such as stress or malnutrition) promotes the progression of latent infection to clinical disease. The widespread introduction of a factor which causes immunodepression (such as HIV infection) in a population which already has a high prevalence of latent M. tuberculosis infection would be expected to alter the dynamics of TB in the group.

2.2 Acquired immunodeficiency syndrome (AIDS)

As of 1 August 1988, 108 176 cases of AIDS have been reported worldwide from 177 countries. It is estimated that 250 000 cases have already occurred and that about five million persons are infected with HIV worldwide.

It is now clear that there are three general patterns of HIV/AIDS. Pattern I areas are those in which most cases have occurred in homosexual men and intravenous (IV) drug users. This pattern is seen in North America, Western Europe and parts of Latin America, the Caribbean and Oceania. In Pattern II areas heterosexual transmission is dominant, with almost equal numbers of male and female cases. This is the current situation in sub-Saharan Africa and several areas in the Caribbean. Pattern III refers to areas where there are still relatively few cases and where the transmission pattern has not yet been completely clarified. Most cases in these areas have been infected through exposure in other countries or by international travellers. This pattern is presently seen in Eastern Europe, Asia, the Middle East and the Pacific. In Asia, the problem is of lower magnitude at present, but the prevalence of HIV infection is rising rapidly in high-risk groups.

Sub-Saharan Africa and the Caribbean are of special concern regarding the interaction between HIV and M. tuberculosis infection; the prevalence of HIV has already been found to be 10-25% in several urban areas in Africa, where infection with M. tuberculosis is highly endemic. A similar overlap of doubly infected populations exists in IV drug users in the inner cities of North America and Europe. A very large TB problem exists throughout Asia and the Middle East, and there will be great cause for concern if and when HIV infection becomes more widespread there.

In 1985, another retrovirus, HIV-2, was described in West Africa which shared many of the same properties of HIV-1. The extent of infection with this virus has not yet been well characterized.

2.3 The relationship between tuberculosis and HIV infection

Some of the data on the relationship between TB and AIDS or HIV infection come from developed countries and may not be relevant to the situation in developing countries. Furthermore, the data concern exclusively HIV-1; little is known about the relationship between HIV-2 and TB.

2.3.1 Epidemiological issues

Patients with TB appear to be more likely to be HIV seropositive than the general population. Several groups of TB patients in the Caribbean, Africa and the USA have been reported to have an HIV seroprevalence of 20-50%, which is several times greater than in the general population of those countries. This association is best explained by accelerated progression of latent M. tuberculosis infection to TB owing to the prolonged and severe immunodepression associated with HIV infection.

There is also concern that HIV could be spread through the use of unsterilized injection equipment during the treatment of TB. Streptomycin by injection is frequently used in the treatment of TB in developing countries. There is no evidence that streptomycin injections have transmitted HIV, but the possibility must be kept in mind.

The magnitude of the problem of TB among HIV-infected persons is unknown. Only one study has directly addressed the prospective risk of TB among persons known to have both HIV and M. tuberculosis infection. In this study, an average annual TB incidence of 7.5% was documented in HIV seropositive IV drug users with M. tuberculosis infection between 1984 and 1987 in New York City. This is of concern for developing countries with high HIV infection levels in their adult populations, virtually all of whom also have very high levels of M. tuberculosis infection. If similar rates of TB are found in dually infected persons in developing countries, an enormous potential increase in TB cases may be anticipated.

Several countries have reported national or local increases in reported cases of TB. The extent to which this is related to the HIV epidemic is not clear, but health officials from some of these countries believe that HIV is playing an important role.

2.3.2 Clinical issues

The occurrence of TB in immunodepressed HIV-infected individuals presents diagnostic challenges which may be particularly difficult to deal with in developing countries. The clinical presentation of TB in persons with HIV has often been unusual, with a higher frequency of extrapulmonary and disseminated disease. In HIV-infected TB patients, cavities are less common on chest radiographs, lower or mid-zone pulmonary infiltrations are commonly seen, and lymphadenopathy is often striking. Thus, sputum smears in such persons might be less likely to be smear positive. If developing countries continue to rely primarily on sputum smear results to diagnose TB, a high proportion of TB cases among HIV-infected persons may be missed.

The ability of patients with TB and HIV infection to transmit M. tuberculosis infection needs to be assessed, although the above observations would suggest that these patients as a group might have a lower infection potential as compared to TB patients without HIV infection.

TB in HIV-infected persons has generally responded well to short-course chemotherapy, and there are more limited reports on response to standard 12-month therapy. Also, there are some reports that adverse reactions to drugs used for treating TB are more common in these patients. There are few data on relapse rates. These patients have a high mortality rate, which may be attributable to the development of other opportunistic infections. The role tuberculosis might play as a co-factor in the progression of HIV infection to AIDS is unknown.

Evidence remains inconclusive regarding the rate of adverse reactions after BCG immunization among asymptomatic HIV-infected individuals.

2.3.4 Preventive therapy

Preventive therapy with antituberculosis drugs (Isoniazid [INH]) in tuberculosis-infected HIV seropositives is recommended in the USA, but no data are available on its efficacy, safety, and acceptability in developing countries. Until more data are available regarding the risk of clinical TB among persons with dual HIV/M. tuberculosis infection, using scarce health care resources to provide preventive therapy on a large scale to such persons in developing countries will be problematic and controversial. Given the seemingly high risk of TB in HIV-infected individuals and the technical possibilities for prevention, the issue needs to be addressed urgently and the benefits and feasibility assessed.

3. URGENTLY NEEDED RESEARCH

Given the enormity and serious nature of the TB/HIV problem, the participants urged WHO to take immediate action to assist developing countries to assess the problem as a basis for individual and public health intervention. The participants found that, unless such action is taken, there will be a considerable worsening of the world TB problem and increasing human suffering and death. Thus, it was with a sense of urgency that the participants recommended that the following research studies be undertaken. Within each category the studies are listed in approximate order of priority. More specific information on the design of some of these studies is given in Annex 2. These should be considered as broad examples rather than final designs, since for each research project a detailed protocol will need to be developed, according to specific study conditions and objectives.

3.1 Epidemiological studies

3.1.1 Objective and justification

The objective of these studies is to assess the nature and magnitude of the problem of concurrent infection with M. tuberculosis and HIV.

The impact of such concurrent HIV and M. tuberculosis infection on the number of TB and AIDS cases which will occur is not known but may be considerable. Data from Tanzania, Burundi, Zaire, Uganda and the USA have shown national or local increases in the number of reported cases of TB; some of the increase is undoubtedly attributable to HIV infection. In countries and areas where HIV and M. tuberculosis infection are both highly prevalent, combined surveillance and monitoring for these two infections and diseases is urgently needed to allow public health, social and economic planning.

The research questions given below are divided into those which address the effects of HIV on the TB situation in populations and those which look more specifically at risks to individuals. The latter may provide a direct basis for intervention trials (see section 3.4.2, questions 1 and 2, and section 3.5.2, questions 1 and 2).

3.1.2 Specific research questions

3.1.2.1 Surveillance for TB and HIV in populations

1. What is the prevalence of HIV infection and disease in newly diagnosed TB patients as compared to an appropriately chosen control group?
2. What are the numbers of cases, rates, proportions and trends of smear-positive and smear-negative pulmonary and extrapulmonary TB in newly diagnosed TB patients in areas with high, moderate and low prevalence of HIV and M. tuberculosis infection?
3. Is the downward trend in annual risk of TB in developing countries which began to appear in recent years being altered by the HIV epidemic?

3.1.2.2 Risk of TB and AIDS in individuals

1. What is the risk of developing TB in tuberculin-positive persons with HIV infection and how does this risk compare to that in a similar population without HIV infection?
2. What is the rate at which clinical AIDS develops in a population of persons with HIV infection and TB, and how does this compare to the rate in a group of similarly HIV-infected persons without TB?
3. How infectious are patients with both pulmonary TB and HIV infection as compared to patients with pulmonary TB but without HIV infection?

3.2 Diagnostic studies

3.2.1 Objective and justification

The objective of these studies is to improve diagnostic methods for TB and M. tuberculosis infection using techniques that are applicable in persons with HIV infection. These studies should be designed to provide information that will enable a more accurate and rapid diagnosis of TB.

Central to several of these studies is the development of useful serological tests that will, ideally, separate persons with latent M. tuberculosis infection from those with clinical TB. Given the sometimes atypical clinical presentation of TB in persons with HIV infection, the increased frequency of skin-test anergy, and the suggestion that sputum smears are less often positive, other diagnostic tests are clearly necessary. In addition, a reliable serological test for M. tuberculosis infection could permit testing for this infection at the same time as serological testing for HIV. Such a test would also be useful for future epidemiological studies and offer potential benefit to control programmes and individuals should chemoprophylaxis against clinical TB subsequently prove effective, safe and feasible. If such a test became available and simplified so that it can be used at remote health centres in developing countries, significant progress could be expected for the case-finding activities which are at present one of the important constraints on successful TB control programmes. Research on improved serological techniques to diagnose M. tuberculosis infection and disease should be given high priority.

3.2.2 Specific research questions

1. Can currently available serological techniques improve the accuracy and rapidity of diagnosis of TB and/or M. tuberculosis infection in HIV-infected persons?
2. How valid is the tuberculin skin test in HIV-infected individuals?
3. What is the best means of separating latent M. tuberculosis infection from disease in HIV-infected persons?
4. Can nucleic acid probe techniques for identifying mycobacteria be developed that are applicable in developing countries?

3.3 Clinical presentation studies

3.3.1 Objective and justification

The objective of these studies is to describe the prevalence and clinical features of TB in HIV-infected persons (including persons with AIDS). These studies require comprehensive evaluation of a representative sample of HIV-infected patients who have lung diseases. Tests that have proven useful in diagnosing these diseases in a developed country should be applied in a uniform fashion in a developing country having a high prevalence of both HIV and M. tuberculosis infection.

Identification of TB among HIV-infected persons who have lung disease will serve to define its relative importance and will predict the operational characteristics of diagnostic tests. Moreover, prospective evaluation of HIV seropositive and seronegative persons using a uniform series of diagnostic studies will enable a comprehensive description of clinical patterns. Specific questions relate to the frequency of positive tuberculin test reactions, positive sputum smears, and radiographic patterns of disease. Diagnostic criteria can be developed for use in areas where the full range of studies is not available. This should enable accurate and earlier presumptive diagnosis and empirical therapy.

3.3.2 Specific research questions

1. What proportion of lung disease occurring in HIV-infected persons is caused by M. tuberculosis?
2. How does the clinical pattern of TB in HIV-infected persons differ from that in persons not infected with HIV?
3. How does the clinical pattern of TB differ from the patterns of other lung diseases which are or are not related to HIV?

3.4 Prevention studies

3.4.1 Objective and justification

The objective of these studies is to determine the most effective means of preventing TB in persons infected with both HIV and M. tuberculosis. This is obviously an issue of critical importance because it offers opportunities for intervention (with drugs that are already available).

Unfortunately, under the conditions that prevail in most developing countries, the large-scale application of preventive measures, other than BCG immunization, will not be practical until TB control programmes are considerably strengthened (see section 4.3).

However, in view of the presumed high frequency of TB in dually infected persons, prevention of TB in such persons is clearly a high priority. Isoniazid (INH) preventive therapy, which is of proven efficacy in other risk groups, has not been evaluated in persons with HIV infection.

There are at least two problems that might reduce the public health effectiveness of INH in HIV-infected persons: the tuberculin test may be falsely negative and thereby not identify all persons with M. tuberculosis infection; and because of atypical presentation, persons who appear latently infected may have clinical disease. It is likely that treating TB with INH alone in those persons would be ineffective and promote development of drug resistance. For this reason, and in order to find shorter and more feasible prophylactic regimens, both INH alone and multiple drug preventive therapy regimens should be evaluated.

3.4.2 Specific research questions

1. Is INH effective for chemoprophylaxis in dually infected persons?
2. Are short-duration drug combinations effective in preventing TB in dually infected persons?
3. Does prior BCG immunization protect against TB in persons with HIV infection?

NB: It will be necessary to determine the risk of developing TB in tuberculin-positive persons with HIV infection before or in the course of chemoprophylaxis studies (see Epidemiological studies 3.1.2.2, question 1).

4. Is BCG immunization associated with a greater risk of adverse effects in HIV-infected persons than in persons not infected with HIV?

3.5 Treatment studies

3.5.1 Objective and justification

The objective of these studies is to determine the safety, efficacy and acceptability of treatment regimens for TB in persons with HIV infection. The limited information available suggests that the bacteriological response to treatment in TB patients with HIV infection is very good, especially with regimens containing rifampicin and INH. However, there is less information on the outcomes of treatment with the INH-thiacetazone-streptomycin regimen which is commonly used in Africa. In addition, in this setting there have been anecdotal reports of an increased risk of severe adverse reactions to thiacetazone.

Because of HIV-related immunodepression, it is not certain that TB chemotherapy will be as effective in HIV-infected persons. Thus, the rate of treatment failure and relapse must be assessed. Of additional concern is the suggestion that adverse drug reactions increase in frequency. Finally, there is concern that incomplete sterilization of needles used for streptomycin injections could serve to transmit HIV.

3.5.2 Specific research questions

1. How safe and effective is standard chemotherapy for TB in persons with HIV infection as compared to those without HIV infection?
2. Should long-term maintenance chemotherapy be given to TB patients with HIV infection?

4. PLAN OF ACTION

In order to carry out the high-priority research projects recommended by the participants, it will be necessary to attract resources, create organizational structures, develop more detailed plans and timetables, and promote collaborative arrangements.

Annex 3 illustrates the interrelationships among the specific studies suggested in this document and shows their sequencing, however, specific timetables have not been developed.

4.1 Recommendations on the role of WHO

WHO must play a major role if these research proposals are to be carried out. The specific areas in which WHO could provide assistance include the following:

1. Encouraging the research outlined in this report. This can be accomplished through distribution of this report (or a summary) and announcements of proposed research funding to persons involved in relevant scientific areas. Communication with key scientists and institutions would also be useful;
2. Funding to support TB research. In addition to soliciting research grants, projects will require a review mechanism. The preferred method for reviewing and ranking proposals would be by creating a committee made up of persons with knowledge and experience in the relevant areas;
3. Identification of other (non-WHO) sources of funding. Personnel from the WHO Global Programme on AIDS (GPA) and the Tuberculosis (TUB) unit should gather information concerning potential funding sources and make this information known to investigators. By making widely known WHO's interest and support for projects related to HIV and tuberculosis, additional funding might be forthcoming from other sources;
4. Coordinating and facilitating interactions among investigators and clinicians in relevant areas;
5. Organizing a serum or tissue bank. This might be very useful, in particular for facilitating diagnostic and clinical studies;
6. Coordination of communication among programmes in the field; meetings and other means of information exchange could be extremely useful;
7. Strengthening of existing research capabilities in target countries. By allocating a portion of any study support funds to improvement of the research capabilities of specific targeted countries, a more long-lasting effect could be achieved that would outlive a specific research project.

4.2 Strengthening of tuberculosis control capacity in WHO

The participants urged WHO to develop, plan, and coordinate a global programme of research and technical assistance on AIDS and TB for countries which are attempting to combat the increasing incidence of TB resulting from the worldwide AIDS epidemic. An advisory committee could be formed, to include representatives of GPA, TUB, IUATLD, and consultants from outside organizations with expertise in TB and AIDS. In addition, there should be representation from national programmes concerned with the TB/AIDS problem, especially in Africa, Asia and Latin America. This committee should develop objectives for the programme and a timetable for action, and describe funding and staffing needs. The committee should assist WHO in soliciting support for the programme of activity, help solicit proposals for projects to be given funding and/or technical support, advise regarding priorities for funding and technical assistance, and coordinate technical assistance from national and international organizations and between countries.

4.3 Strengthening of tuberculosis control capacity at the country and local level

Although much of the proposed research can be conducted now in carefully selected areas, an overall strengthening of national TB control programmes, especially in high prevalence areas, will be necessary to implement programmatic changes suggested by the results of these studies. Without the ability to act on the results of the research, conducting these studies would be an ineffective exercise.

At the national level, carrying out research and technical assistance activities in TB/AIDS will require close cooperation and coordination between national TB and AIDS programmes. The participants strongly supported GPA's promotion of the inclusion of persons involved in national TB programmes on national AIDS committees. Each country should be urged to include a strategy for dealing with the TB/HIV problem in its national programmes on AIDS and on tuberculosis control. Support from the national AIDS programme for these activities should be considered. Information, resources, and personnel necessary to carry out these activities may not belong exclusively to one programme but to both of them. Ethical, legal and social issues related to research and service delivery in AIDS/TB will need to be resolved by both programmes. Cooperation can be mutually beneficial because TB programmes can assist AIDS programmes in identifying and counselling HIV-infected individuals and in providing public education about AIDS and HIV infection. AIDS programmes can assist TB programmes by identifying HIV-infected individuals with TB or M. tuberculosis infection who are in need of diagnostic evaluations, treatment, preventive treatment and follow-up.

Close collaboration between the TB and AIDS programmes at the local level will be essential. It is at this level that a number of operational issues will need to be resolved. It will be necessary to ensure the availability of HIV testing for TB patients, the development of counselling services, and referral for proper treatment and follow-up of other HIV-related diseases.

An important question is the extent to which TB and AIDS programme activities should be integrated within the general health services to achieve the research objectives and the efficient delivery of TB and AIDS services. Because both programmes may be identifying individuals in need of services by the other programme and because information in one programme may be needed by the other, active collaboration between the TB and AIDS programmes will be necessary. However, care should be taken that attempts at integration and collaboration enhance, rather than impair, the effectiveness of each programme. The optimal level of integration and collaboration will have to be determined by national and local circumstances. Factors to be considered include: (1) the epidemiological situation of TB and AIDS in the area; (2) the extent to which the populations served by one programme overlap with the population served by another; and (3) the extent to which health care workers in one programme have the time, skill and motivation to take on extra tasks.

4.4 Selection of research sites

Many of the research questions listed could best be addressed in the setting of a "field station" having trained personnel, adequate facilities, and a suitable patient population. These stations could be based in several different areas having a high prevalence of both HIV and TB infection. Some could perhaps be organized as WHO collaborating centres. Such centres should ideally be able to encompass a broad range of research activities - operational, applied, clinical and basic.

To successfully carry out the research studies proposed in this document, a participating agency or institution should have the potential for identifying a high proportion of the cases in its catchment area, adequate diagnostic facilities for TB and HIV, an adequate number of appropriately trained health care workers to provide TB and HIV-related services, established procedures for managing both infections, and an

adequate supply of standard antituberculosis drugs, and be reasonably successful in keeping patients compliant with therapy and follow-up visits. Specific requirements will be dictated by the nature of the study being contemplated. Some studies may require more or less stringent criteria.

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Annex 1

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EXAMPLES OF DESIGNS FOR SELECTED RESEARCH STUDIES

The following examples give further information in the design of some of the research studies outlined in section 3 of the report.

EPIDEMIOLOGICAL STUDIES1. Surveillance for TB and HIV in populations (SECTION 3.1.2.1, QUESTION 1)

What is the prevalence of HIV infection and disease in newly diagnosed TB patients as compared to an appropriately chosen control group?

1.1 Objective

To determine the prevalence of HIV-1 and HIV-2 seropositivity in a group of newly diagnosed TB patients and a suitable control population.

1.2 Study design

Newly presenting patients with bacteriologically proven TB and a suitable control group should be screened for infection with HIV (HIV-1 or HIV-2). The controls should be selected from the same area and socioeconomic groups, and should also be matched for age and sex. Both groups of patients should be subjected to a diagnostic work-up, with clinical examination (including skin tests with tuberculin [purified protein derivative] and *Candida* and *Trichophyton* antigens) and chest radiography. All subjects should be questioned for a history of past TB treatment, a history of blood transfusions and hospitalization, a family history of TB or AIDS, and for other risk factors for TB or HIV infection.

2. Surveillance for TB and HIV in populations (SECTION 3.1.2.1, QUESTION 2)

What are the numbers of cases, rates, proportions and trends of smear-positive and smear-negative pulmonary and extrapulmonary TB in newly diagnosed TB patients in areas with high, moderate and low prevalence of HIV infection and TB?

2.1 Objective

To determine whether or not there is a correlation between the proportion of newly diagnosed cases with smear-negative pulmonary TB and extrapulmonary TB and the prevalence of AIDS or HIV infection.

2.2 Study design

This study can probably be done in many areas without the need to collect new information. TB morbidity data from various parts of the world, which identify the proportion of cases which are smear-positive, smear-negative and extrapulmonary, can be collected, as can survey data on HIV seroprevalence or AIDS surveillance data. The correlation between the proportion of TB cases which are smear positive, smear negative and/or extrapulmonary, and the prevalence of HIV infection or AIDS can then be calculated.

Demographic variables and HIV risk data should also be collected, if possible.

3. Surveillance for TB and HIV in populations (SECTION 3.1.2.1, QUESTION 3)

Is the downward trend in annual risk of TB in developing countries which began to appear in recent years being altered by the HIV epidemic?

3.1 Objective

To estimate the current annual risk of TB in developing countries and compare it to previous estimates.

3.2 Study design

The key variable to study will be prevalence of tuberculin positivity in children. For example, non-BCG vaccinated children can be given a tuberculin skin test on entry into school. From this prevalence, one can derive the annual risk of infection and compare it to previous figures from the same area. If this is done in countries which have undertaken HIV serosurveys or which have good surveillance systems for AIDS, the correlation between these measures of the HIV epidemic and the annual risk of TB can be calculated.

4. Risk of TB and AIDS in individuals (SECTION 3.1.2.2, QUESTIONS 1 AND 2)

What is the risk of developing TB in tuberculin-positive persons with and without HIV infection? What is the risk of developing AIDS in persons with and without M. tuberculosis infection?

4.1 Objective

To determine the risk of clinical TB which is attributable to HIV infection, and to determine the risk of AIDS in HIV-infected persons which is attributable to TB or M. tuberculosis infection.

4.2 Study design

Prospective studies of cohorts which are similar in all respects, except for the presence or absence of HIV infection, will be necessary to address this issue. These persons should be characterized with regard to HIV serological status and tuberculin reactivity. The cohort should be actively followed with periodic skin tests, serological studies for HIV and TB, immunological studies, clinical symptoms, physical examination, chest radiographs and other diagnostic studies as indicated. Outcomes to be assessed include the development of TB and AIDS, HIV seroconversion, tuberculin skin-test conversion, anergy, and other immunological parameters. Such studies would enable quantification of the rate of increased progression to TB attributable to co-infection with HIV. Studies such as these could also look at the role played by TB, if any, as a possible co-factor accelerating progression to AIDS. Following a cohort of dually infected persons would, in and of itself, provide very useful information as to the risk of TB and AIDS, and could, if the risk was sufficiently high, provide the basis for chemoprophylaxis studies.

5. Risk of TB and AIDS in individuals (SECTION 3.1.2.2, QUESTION 3)

How infectious are patients with both pulmonary TB and HIV infection as compared to patients with pulmonary TB but without HIV infection?

5.1 Objective

To determine if patients with pulmonary TB and HIV infection are more likely to transmit M. tuberculosis to household contacts than TB patients not infected with HIV.

5.2 Study design

A survey should be conducted to determine the prevalence of clinical TB and M. tuberculosis among the household contacts of TB patients with HIV infection. The study group should be adults who have pulmonary TB and are HIV antibody positive. The control group should be adults with pulmonary tuberculosis who are HIV antibody negative. A third control group of persons without TB will probably be necessary to take into account the background prevalence of M. tuberculosis infection in the population. Insofar as is possible, the three groups should be selected to be of similar age and sex and have similar places of residence. Cultures for M. tuberculosis should be performed on all study subjects and isolates should be fully identified.

Following this study, the incidence of TB in household contacts could be assessed by following these contacts over time with periodic health assessments. All household contacts of the cases and the controls should be enrolled in the study and assessed for HIV infection and M. tuberculosis infection and disease. Histories of possible risk factors for HIV infection and TB should be obtained. A tuberculin skin test, a chest radiograph and a physical examination should be performed on all household members. In order to minimize possible biases, the interviews and examinations of household contacts should be conducted "blind" as to knowledge of whether or not the index case of TB for the household is infected with HIV. All cases of suspected TB should be assessed independently, together with a sample of those not suspected to have disease. Any cases of TB found should be treated.

Subsequently, all contacts should be followed regularly (every three or four months) to detect new cases of TB. Chest radiographs and serological testing for HIV infection should be performed regularly.

DIAGNOSTIC AND PREVENTION STUDIES

6. Diagnosis of M. Tuberculosis infection and disease and measures to prevent tuberculosis (SECTIONS 3.2.2 and 3.4.2)

How valid is the tuberculin skin test in HIV-infected individuals? How useful are serological tests for identifying M. tuberculosis infection and/or TB in HIV-infected persons? What is the safety, efficacy, and acceptability of preventive therapy regimens and BCG immunization in HIV-infected persons? Are immunological parameters useful in predicting risk of TB in HIV-infected persons?

6.1 Objectives

- (i) To determine validity of tuberculin skin tests in HIV seropositive persons;
- (ii) to evaluate new tests for M. tuberculosis infection;
- (iii) to determine the efficacy, safety and acceptability of INH for six months or other regimens (e.g., multiple drugs) in preventing the emergence of TB;
- (iv) to evaluate the efficacy of prior BCG immunization in preventing the development of TB in both HIV-positive and HIV-negative individuals; and
- (v) to examine immunological variables that may be of use in predicting the development of TB.

6.2 Study design

HIV-seropositive and HIV-seronegative controls should be identified, ideally from the general population (failing that, by recruitment from the blood donation services or

from antenatal or sexually transmitted disease clinics). Each subject should be tuberculin skin tested (2 TU of RT 23 or other equivalent to 5TU of PPD-S). Subjects should then be randomized to the following groups:

<u>Group</u>	<u>HIV</u>	<u>Tuberculin</u>
A	+	+
B	+	-
C	-	+
D	-	-

Chest radiographs should be performed. Those with evidence of current or old disease should be excluded. All subjects should undergo venepuncture for serological studies (to be defined) and a proportion for immunological studies (lymphocyte transformation, macrophage function, etc.) which will require about 50 ml of blood. These investigations should be done "blind" with respect to HIV or tuberculin status.

Each group that is tuberculin positive should then be randomized to receive either placebo or preventive therapy. Subjects should be followed up at three-month intervals for clinical evidence of TB, and sputum examination should be performed. Chest radiographs should be taken at six-month intervals. If chest radiographs are found to be abnormal, at least three sputum samples should be examined by microscopy and culture for mycobacteria. The tuberculin test should be repeated at yearly intervals. Follow-up should be continued for at least two years after cessation of treatment. Serological/immunological tests should be repeated as necessary.

CLINICAL PRESENTATION STUDIES

7. Clinical pattern of lung disease in persons with HIV infection (SECTION 3.3.2, QUESTION 1)

What proportion of lung disease occurring in HIV-infected persons is caused by M. tuberculosis?

7.1 Objective

To identify the proportions of lung diseases found in association with HIV infection that are due to TB and other infectious diseases, neoplasms, and idiopathic processes.

7.2 Study design

Patients presenting themselves to a health facility with respiratory symptoms should be asked if they are willing to enter the study, which will be described, and to be HIV tested. If they agree, appropriate counselling and HIV testing should be carried out, clinical histories should be taken and they should undergo physical examination. Respiratory investigations should be performed blind with respect to HIV results in a standard manner and should include:

- a chest radiograph;
- serological examination for respiratory pathogens;
- culture of sputum, blood and, where available, pleural fluid by standard microbiological techniques, including mycobacterial cultures;
- fibre-optic bronchoscopy with bronchoalveolar lavage and transbronchial biopsy;
- other investigations as the patient's clinical status dictates.

Appropriate treatment should be started as soon as clinically indicated, but after obtaining appropriate specimens.

8. Clinical pattern of lung disease (SECTION 3.3.2, QUESTION 2)

How does the clinical pattern of TB in HIV-infected persons differ from that in persons not infected with HIV?

8.1 Objective

To compare the clinical features of TB in untreated patients with and without coexisting HIV infections.

8.2 Study design

Newly presenting patients with suspected TB should be screened for infection with HIV. Those found positive (for HIV-1 or HIV-2) should be matched for age and sex with suspected patients not infected with HIV. Both groups of patients should be subjected to a full diagnostic work-up, with clinical examination (including skin tests with tuberculin [purified protein derivative], and Candida and Trichophyton antigens) and chest radiography. All subjects should be questioned for a history of past TB treatment, a history of blood transfusions and hospitalization, a family history of TB or AIDS, and other risk factors for TB or HIV infection.

TREATMENT STUDIES

9. Treatment of TB in persons with HIV infection (SECTION 3.5.2, QUESTIONS 1 AND 2)

How safe and effective is standard chemotherapy for TB in persons with HIV infection as compared to those without HIV infection? Should long-term maintenance chemotherapy be given to TB patients with HIV infection?

9.1 Objective

To determine the frequency of adverse reactions, treatment failure and relapse in TB patients with and without HIV infection.

9.2 Study design

The patients included in the previously proposed study (8) should be put on a standard treatment regimen and response to treatment assessed. Patients should be excluded from the study if they have a previous history of TB, significant other pathology (e.g., diabetes), or other pulmonary opportunistic infections (if detected), or if they are moribund.

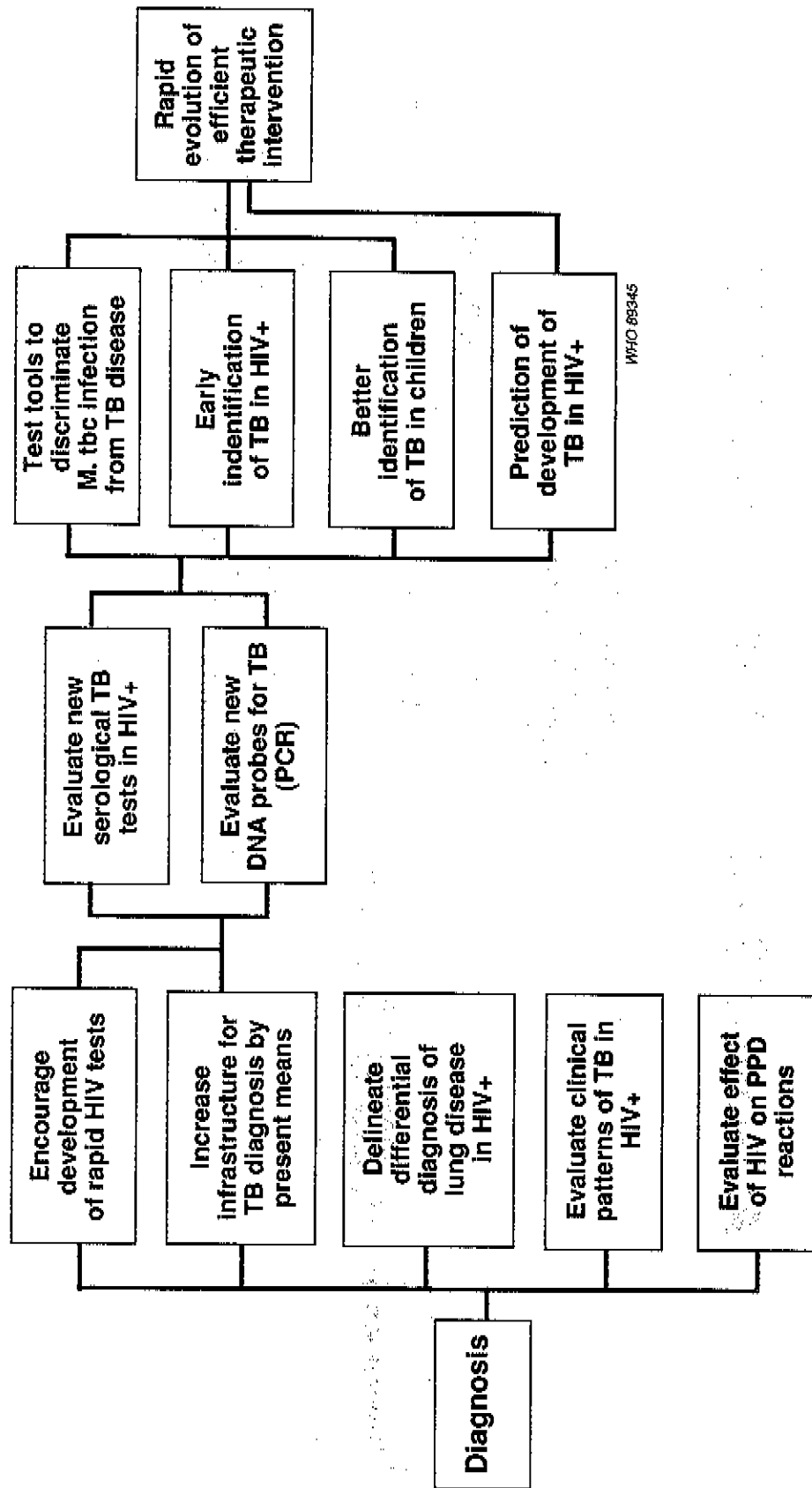
Clinical, radiological and laboratory investigations should be performed. Patients should be followed up regularly (e.g., weekly for the first month and twice monthly thereafter) to assess their bacteriological response to treatment, compliance, and any adverse reactions to the drugs.

At the end of treatment, HIV seropositive patients could be randomized to receive either placebo or maintenance isoniazid in order to answer the second part of the research question.

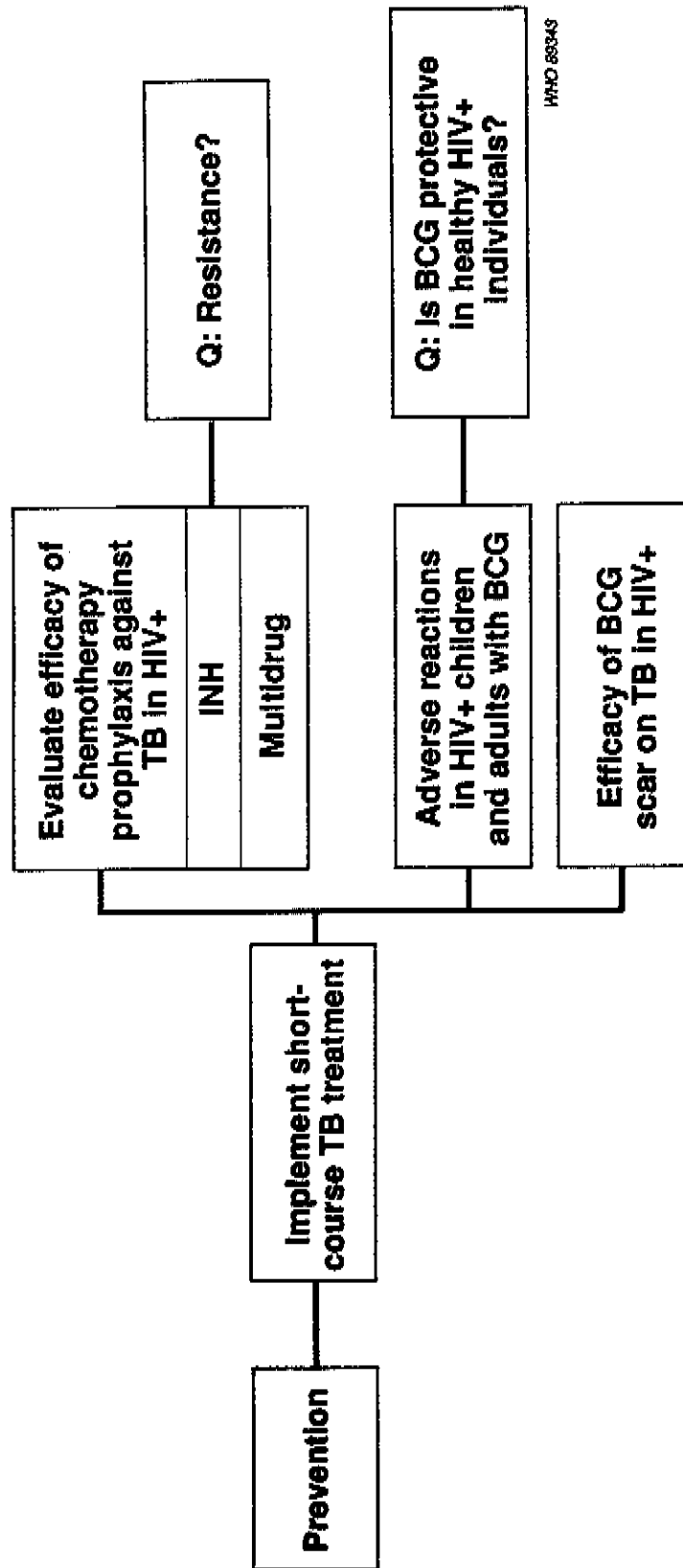
It will be important to follow up defaulters by domiciliary visits.

INTERRELATIONSHIPS BETWEEN SPECIFIC STUDIES

ALGORITHM FOR DIAGNOSTIC STUDIES

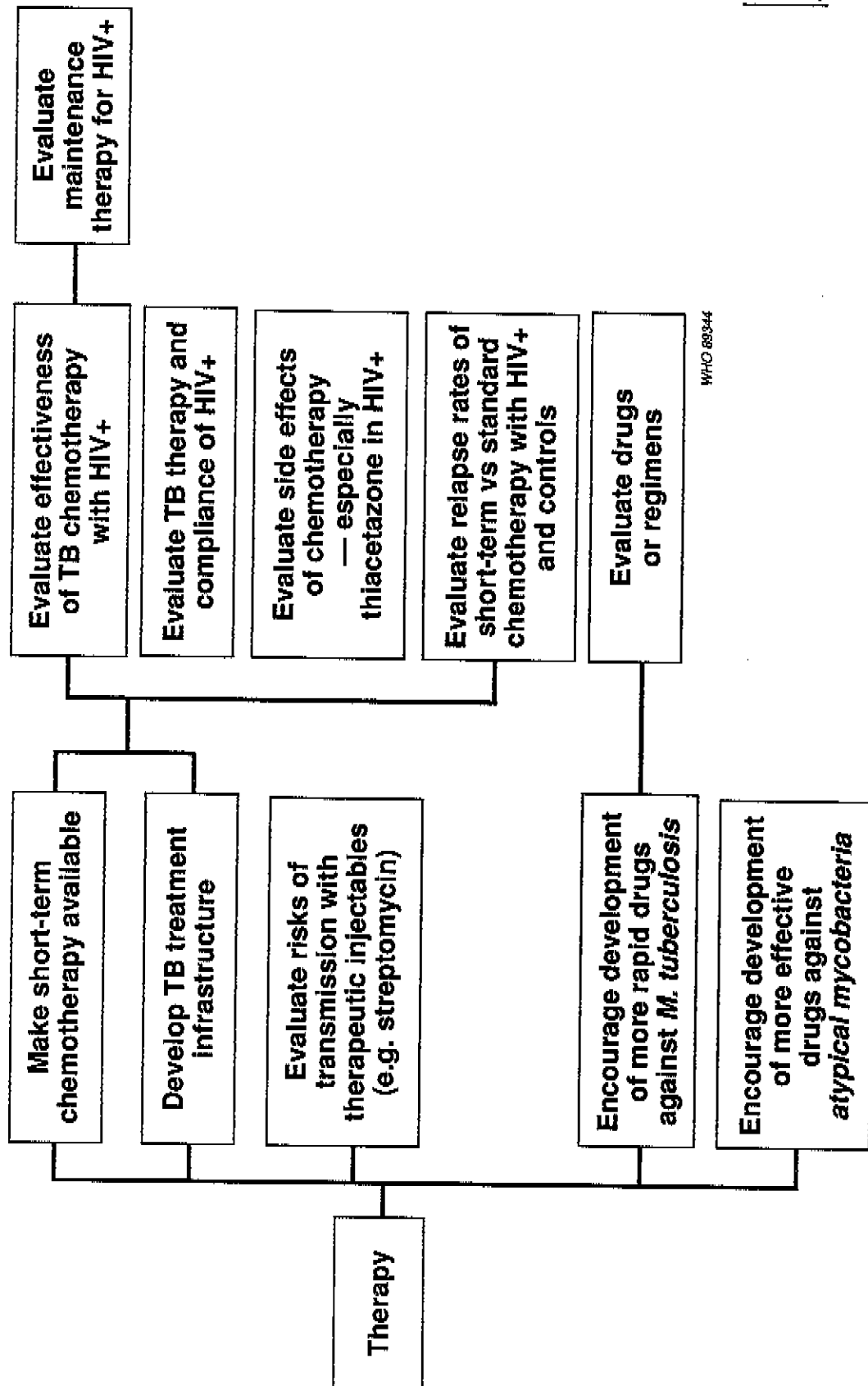


ALGORITHM FOR PREVENTION STUDIES



WHO 88343

ALGORITHM FOR TREATMENT STUDIES



WHO 89344