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research priorities in resource-limited settings

Report of an expert consultation

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Executive summary

Global consensus has been achieved around the new interim policy on collaborative TB/HIV activities. However, the implementation of joint TB/HIV activities has not yet been scaled up. Updating research priorities specifically aimed at informing future policy and improving the implementation of joint TB/HIV activities in the context of antiretroviral therapy programmes should accelerate scale-up.

For this reason, the Secretariat of the Global TB/HIV Working Group of the Stop TB Partnership in collaboration with WHO's Stop TB Department and Department of HIV/AIDS and the UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) convened an Expert Consultation on TB/HIV Research Priorities in Resource-limited Settings on 14–16 February 2005 in Geneva, Switzerland. The specific objectives of the Consultation were 1) to define TB/HIV research priorities and outline their research relevance, methods and feasibility in the context of programme activities and 2) to solicit and promote the building of TB/HIV research capacity at the country level through the involvement of national and international agencies.

Plenary presentations highlight major issues in implementing and evaluating joint TB/HIV activities. Community contribution to the delivery of the TB/HIV package, human resources, the relationship between multi-drug-resistant TB and HIV and special groups such as injecting drug users emerged as areas for which control strategies clearly need to be developed. In addition, research priorities were identified to accelerate the use of the policy on HIV testing in clinical settings and to integrate management strategies for people living with both TB and HIV.

Three discussion groups identified research priorities for five major areas.

- (1) Research priorities for preventive therapy for TB were identified with a distinction between the population and the individual levels.
- (2) Priority areas of research for co-trimoxazole prophylaxis include the role of co-trimoxazole in the context of antiretroviral therapy, delivery strategies and determining the efficacy of and optimal time for initiating co-trimoxazole prophylaxis among people living with HIV/AIDS and TB.
- (3) The major research priority area identified in relation to antiretroviral therapy for people living with HIV/AIDS who have TB or who develop TB is validating the optimal time for initiating antiretroviral therapy. Other research priorities include optimizing regimens and determining their efficacy and safety profile. Validating the definition of immune reconstitution inflammatory syndrome is also a priority.
- (4) Research priorities on intensified case-finding focus on ways to put this TB/HIV collaborative activity into operation to improve TB control.
- (5) The development of new tools and diagnostic algorithms is a top research priority to improve the diagnosis of smear-negative TB in adults and children.

During the Consultation, a wealth of evidence was presented on the implementation of collaborative TB/HIV activities. However, although many questions remain unanswered, participants felt that evaluating the implementation of the current policy package should be given more emphasis than generating more research questions.

The research priorities produced in this Consultation reflected a wide range of expertise and varying geographical needs. Participants felt that mechanisms to avoid redundancy of research should be identified and knowledge disseminated properly. An advocacy package, containing the identified research priorities, should be prepared to share the outcome of this Consultation with countries, stakeholders and research agencies.

Implementation of research priorities should capitalize on the financial momentum in which the Global Fund for AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief, among others, are mobilizing more funds for treatment and research activities. Budgeting to fill the research gaps is therefore essential, and advocating for additional resources to conduct more research aimed at improving TB and HIV control is needed.

The umbrella of research priorities identified in this Consultation provides guidance on what needs urgent attention. Donor and partner agencies and countries should then take these up and should implement the research priorities they consider crucial for improving TB and HIV control in their settings as soon as possible.

Introduction

HIV is the primary reason for failure to meet tuberculosis (TB) control targets in settings with a high prevalence of HIV infection. TB is a major cause of death among people living with HIV/AIDS. Although sub-Saharan Africa bears the brunt of the HIV-fuelled TB epidemic, the rapidly increasing HIV epidemic in countries in eastern Europe and in China will also increase the number of people with TB resulting from HIV infection. In response to this, the Stop TB Partnership, through the Global TB/HIV Working Group, has coordinated the global response that has resulted in WHO publishing an *Interim policy on collaborative TB/HIV activities*¹ that is part of the essential minimum package of guidelines² to address the TB/HIV epidemic.

Although global consensus has been achieved around an interim policy on TB/HIV, the policy has not yet been widely disseminated, and implementation of joint TB/HIV activities has not yet been scaled up. Updating research priorities specifically aimed at informing policy and improving the implementation of joint TB/HIV activities in the context of antiretroviral therapy should accelerate scale-up.

For this reason, the Secretariat of the Global TB/HIV Working Group of the Stop TB Partnership in collaboration with WHO's Stop TB Department and Department of HIV/AIDS and the UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) convened an Expert Consultation on TB/HIV Research Priorities in Resource-limited Settings on 14–16 February 2005 in Geneva, Switzerland. The specific objectives of the Consultation were 1) to define TB/HIV research priorities and outline their research relevance, methods and feasibility in the context of programme activities and 2) to solicit and promote the building of TB/HIV research capacity at the country level through the involvement of national and international agencies.

Plenary presentations highlighted major issues in implementing and evaluating joint TB/HIV activities. The plenary presentations were followed by discussion groups in which TB/HIV research priority areas identified at the third and fourth meetings of the Global TB/HIV Working Group in June 2003 and September 2004³ were discussed in greater detail. Background papers to summarize the latest available evidence on preventive therapy for latent TB, co-trimoxazole prophylaxis, the use of antiretroviral therapy in people with TB (including a database on ongoing and funded studies on drug-to-drug interaction, immune reconstitution inflammatory syndrome and clinical management), intensified case-finding and smear-negative TB were presented during the discussion groups. The products of the discussion groups were then presented in plenary, and research priorities were summarized. Finally, a discussion was held on methods of mainstreaming research priorities within the implementation of collaborative TB/HIV activities at the country level. The report follows this outline.

¹ *Interim policy on collaborative TB/HIV activities*. Geneva, World Health Organization, 2004 (http://www.who.int/tb/publications/tbhiv_interim_policy/en/index.html, accessed 3 June 2005).

² The various publications are available at <http://www.who.int/tb/hiv/en> (accessed 3 June 2005).

³ *The 3rd Global TB/HIV Working Group Meeting, Montreux, Switzerland, 4–6 June 2003*. Geneva, World Health Organization, 2003 (http://www.who.int/docstore/gtb/TBHIV/montreux_june03, accessed 3 June 2005).

Report of the Fourth Global TB/HIV Working Group Meeting, Addis Ababa, Ethiopia, 20–21 September 2004. Geneva, World Health Organization, 2004 (http://www.who.int/tb/publications/tbhiv_addis_report/en, accessed 3 June 2005).

Approach to the research agenda

The Director of the Stop TB Department and the Director of the Department of HIV/AIDS of WHO pointed out that TB and HIV/AIDS cannot be controlled in settings such as Africa without implementing joint TB/HIV activities. Research is essential to achieve these goals.

The Secretariat presented how the agenda for TB/HIV operational research has evolved over the last decade. Joint TB/HIV research complements the respective agendas of TB and HIV research but does not include research that specifically addresses TB and HIV issues with no particular reference to the TB/HIV overlap. TB/HIV research should be aimed at improving preventive measures for and care of people with HIV-associated TB by improving TB/HIV control policies (health system and policy research) and the operations of HIV and TB control (operational research and targeted evaluation). Basic research was not included, largely because it inherently does not target resource-constrained settings. Instead, TB/HIV research for low-income countries ranges from developing new tools that address the particular problems of people living with both TB and HIV/AIDS to clinical trials that answer operational questions in TB/HIV. This was organized in two areas of research: the first aimed at answering specific technical questions (such as whether co-trimoxazole preventive therapy adds protection to antiretroviral therapy) and how these individual interventions could alleviate the burden of TB/HIV. The second aimed at evaluating the whole TB/HIV package (analogous to the multi-country evaluation of the WHO Integrated Management of Childhood Illness (IMCI) strategy).

Gaps in TB/HIV research should be identified, and efforts should not be duplicated. Country representatives requested a clear agenda to pursue in order to set priorities among key interventions. Data from research evaluation should contribute to policy changes in the health system that take both the public and the private sectors into account. TB/HIV research should be embedded within the operational activities in each country.

A clear advocacy strategy is needed to convince governments and major stakeholders that operational research is needed and is an integral component of programme activities.

TB/HIV in children and family-centered programmes needs to be considered throughout the development of the TB/HIV research agenda. Stigma is a major barrier to implementation: stigma from TB was considered to be at least as strong as HIV-related stigma. Stigma is seen in health facilities and among health care workers and should be further explored while implementing joint activities.

State-of-the-art summaries

Several presentations were made on cross-cutting issues. Some of these presentations identified clear research priorities, whereas others (such as the role of the community in delivering the TB/HIV package and issues involving injecting drug users) highlighted a clear need to develop an approach to define the priorities since not enough evidence was available at the time of this Consultation.

HIV testing for people with TB in the context of scaling up antiretroviral therapy: barriers to implementation and research priorities

Although HIV treatment has been declared an emergency, access to HIV testing has not yet been recognized as a priority. The revised *UNAIDS/WHO policy statement on HIV testing*⁴ represents a major step forward in enabling people to exercise their right to know their HIV status. However, issues around scaling up HIV counselling and testing should be addressed at the country level, where limited human resources, insufficient training and lack of health infrastructure may hamper scale-up. Addressing HIV and TB in an integrated manner is complex. If all people with TB are to be tested for HIV, then adequate human resources need to be identified and proper training conducted. For an integrated approach, client-initiated voluntary testing is not sufficient, as it does not take place at the sites at which sick people are seen and cared for. Instead, provider-initiated approaches in clinical settings should be better implemented, and the opt-out option should be made clear. Counselling and testing need to be less medicalized while quality is retained. The UNAIDS/WHO policy needs to be adapted to reflect local realities and regulations.

There is limited experience with HIV testing from the perspectives of users and how disclosure happens. Issues around stigma need to be considered.

Research priorities

1. Conducting studies to define different ways of operationalizing the UNAIDS/WHO policy on HIV testing in clinical settings (including TB): diagnostic and routine testing using the opt-out approach.
2. Analysing structural, environmental and other obstacles to implementing these guidelines.

Referral systems and models for TB programmes to contribute to delivering antiretroviral therapy: what are the operational research questions?

Various models of TB/HIV care that contribute to delivering antiretroviral therapy to people living with HIV/AIDS who have TB or develop TB were presented. Minimum standards and practices for people with TB and HIV should be established and characterize each approach. Delivery models may vary from separate TB and HIV service delivery with a strengthened referral system (such as Malawi) to a semi-integrated model (such as the START initiative in Durban and Tugela Ferry, South Africa) or to a fully integrated approach with one-point service for TB, HIV and TB/HIV (such as Kayelitsha, South Africa).

Whatever the delivery model is, the major impediment to integrating HIV and TB diagnosis care and treatment is the differences and long-held separate traditions and practices of the TB and

⁴ *UNAIDS/WHO policy statement on HIV testing*. Geneva, UNAIDS and World Health Organization, 2004 (<http://www.who.int/hiv/pub/vct/statement/en>, accessed 3 June 2005).

HIV enterprises. TB has long been addressed through a public health approach, with firmly established algorithms and standardized measures and outcomes. In contrast, HIV/AIDS care and treatment focuses on the individual person with a strong human rights perspective and is characterized by rapidly evolving treatment paradigms. Each discipline needs to accommodate the other. Scaling up HIV/AIDS treatment requires the TB model of a public health approach, and HIV infection among people with TB adds new diagnostic and therapeutic challenges to the TB care system. A particular challenge is the potential increased risk of nosocomial transmission of TB in settings with a high HIV prevalence with an integrated delivery approach. The discussion recognized the importance of civil society in promoting a collaborative and integrated approach to delivering TB/HIV services. Both the private sector and community-based organizations should be seen as an integral part of the public health system and available for implementing efforts to diagnose and treat people with TB and HIV.

Addressing the many outstanding unanswered questions in the diagnosis and management of the two diseases in the spirit of accommodation and collaboration will greatly benefit people with TB and HIV and establish a new paradigm for the future.

Research priorities

1. Conducting research to identify and evaluate practical, effective and more rapid new diagnostic tools for both TB and latent TB infection.
2. Developing successful collaborative and integrated management strategies for people with both TB and HIV.
 - a. Evaluating different models of TB/HIV care collaboration and integration and comparing these with standard separate care.
 - b. Establishing outcome measures to enable separate and collaborative models of care to be compared.
 - c. Performing cost-effectiveness studies to examine the most efficient collaborative strategies.
3. Strengthening communication and referral between TB and HIV programmes and service delivery.

Human resource gaps: what can be done and what are the research questions?

Worldwide, there is a linear relation between health outcomes such as high child or maternal mortality and the density of health workers. This mainly affects developing countries. The crisis in health human resources is multifactorial in developing countries and is accentuated where strong vertical programmes do not interlink with general service providers. There is a human resources gap at the peripheral service delivery level.

Building the capacity of human resources contributes to every step of the health policy cycle, which includes planning, costing, implementation and assessment. The TB and HIV communities should help in building a favourable social and political context to strengthen human resources for health as well as for TB/HIV priorities. Retaining and training health care workers is also vital to enable a patient-centred approach to service delivery.

Research priorities

1. Carefully assessing human resources to quantify the staff requirements for joint TB/HIV activities and to define the gaps that currently exist.
2. Defining and evaluating interventions aimed at increasing human resources in TB/HIV.
3. Identifying links with other disease-specific programmes.

How can the delivery of the TB/HIV package be tailored to injecting drug users?

The number of injecting drug users infected with HIV in Ukraine, the Russian Federation and the Baltic states has risen exponentially during the past decade. At the same time, high background rates of hepatitis C and B infection have been identified. Multi-drug-resistant TB accounts for up to 14% of all TB cases, and TB represents the leading cause of death among people living with HIV/AIDS who have TB. Treating both TB and HIV in injecting drug users is challenging but can be successful. In Ukraine, about 420 people living with HIV/AIDS and TB have been denied access to proper TB care management in the past year because of drug addiction. This has resulted in interruption of TB treatment. Despite this alarming picture, no political commitment or organized programme has been generated to tackle the TB/HIV epidemic among injecting drug users. Stigma against injecting drug users, lack of a national TB/HIV policy and reluctance to provide proper care, including substitution programmes for injecting drug users, are the main obstacles for joint TB/HIV service delivery for injecting drug users. It was concluded that operational research on TB/HIV in relation to injecting drug users in countries formerly part of the Soviet Union and other countries with high prevalence rates of TB and HIV among injecting drug users (such as China and Viet Nam) should focus on joint delivery of TB and HIV services adapted to each country's local situation. Finally, providing care and treatment to incarcerated people with TB and HIV (many of whom are injecting drug users) requires special attention.

Research priorities

1. Evaluating different approaches to comprehensive care for injecting drug users with TB and HIV that include providing substitution programmes and syringe-exchange programmes and other strategies for harm reduction.
2. Supporting WHO policy on the need for substitution therapy for injecting drug users with HIV and emphasizing the additional need for the injecting drug users living with HIV/AIDS who have TB in areas with high background rates of hepatitis C and B infection.
3. Determining the best way to deliver isoniazid preventive therapy to injecting drug users given the high level of primary isoniazid resistance and high prevalence of hepatitis C and B infection.
4. Determining the efficacy, feasibility and safety profile of antiretroviral therapy for injecting drug users living with HIV/AIDS who have TB.
5. Addressing the issue of stigma among health care workers and others towards injecting drug use in addition to TB and HIV.
6. Designing and evaluating programmes to provide care and treatment to incarcerated populations with TB and HIV.

Note from the Secretariat

The Stop TB Department and Department of HIV/AIDS of WHO in conjunction with relevant stakeholders have been urged to develop a strategy for delivering a joint package of TB/HIV services to injecting drug users. Adapting this to special country needs, including substitution programmes and reflecting ongoing experience in joint delivery to injecting drug users, was requested.

Multi-drug-resistant TB and HIV: how great is the problem and what should be done?

Although there have been several well-documented outbreaks of multi-drug-resistant TB in institutional settings, little evidence indicates that HIV is associated with multi-drug-resistant TB among the general population. Most studies conducted in the general population have very little power, are not methodologically rigorous and have many potential confounders. More carefully designed and statistically more powerful studies are clearly needed to determine the relationship, if any, between multi-drug-resistant TB and HIV. There are several reasons why multi-drug-resistant TB may be positively or negatively associated with HIV, and these reasons need to be explored further. In the mean time, sound systems need to be set up for monitoring and evaluating multi-drug-resistant TB, HIV and their potential association in various settings in a standardized manner. As institutional outbreaks have been well documented, and possibly underreported, implementing good infection control practices is a clear priority. Two matters are considered to be crucial: a) the need to ensure better management and treatment of people living with HIV/AIDS who also have multi-drug-resistant TB and b) to investigate the potential impact of antiretroviral therapy in this interaction.

Note from the Secretariat

The Stop TB Department will be following a strategy to integrate drug resistance surveys with HIV surveillance among people with TB in various population studies to be conducted among the general population, institutional populations and groups with high-risk behaviour.

Role of the community in delivering the TB/HIV package: what questions does operational research need to answer?

The experience of community members and volunteers in implementing collaborative TB/HIV activities in Kayelitsha, South Africa was presented. Contextual differences between community involvement in TB and HIV were also discussed. Much of the experience of community involvement in South Africa was empowering people for advocacy and better care. The Treatment Action Campaign was very instrumental in mobilizing people living with HIV/AIDS and affected communities and has recently taken up TB on its agenda. In discussion, it was felt that the definition of “community” in TB/HIV should be all-inclusive: not only people living with HIV/AIDS but also other community members. Volunteers will be effective and committed if driven by a “political” or “religious” agenda. Otherwise, an incentive scheme should be set up. A point of concern was that TB is curable, whereas HIV infection is an irreversible diagnosis. HIV activists and community groups may therefore have a more burning agenda than placing a primary focus on TB. This highlights the importance of developing a better understanding of the different dynamics of TB and HIV. Community groups engaged in patient empowerment and advocacy need technical and financial support.

Research priorities

1. Exploring ways to identify modalities to use the appropriate community member or group to improve the quality of the prevention and care package made available.
2. Defining the minimum package of activities community members need to carry out.
3. Exploring best models that facilitate the recognition and inclusion of activities involving the community in the formal public health system.

Note from the Secretariat

The involvement of the community in TB/HIV activities is important, and WHO has considered this one key area of work. For the HIV/AIDS world, the role of the community is mainly related to advocacy-related activities. In contrast, the community experience of TB is primarily situated in service provision, specifically treatment support and supervision. WHO and its partners are currently in the process of defining the concept of community involvement and developing a framework that outlines the potential packages of TB/HIV services that communities can take up.

Approaches and challenges to conducting operational research

Examples of research initiatives to be applied in implementing the TB/HIV research priorities range from the International Union against Tuberculosis and Lung Disease trial model on the efficacy of drugs with local involvement of TB control programmes⁵ to the Tuberculosis Trials Consortium, which began with a simple model and then expanded to include many partners and became more participatory in nature. The example of the WHO Green Light Committee for multi-drug-resistant TB activities was also discussed. Research activities need to be perceived as an integral part of a TB control programme and greatly contribute to the process of developing policy. National programmes and community representatives should be involved in the planning. Involving the HIV/AIDS counterpart is also crucial. WHO was proposed to function as a repository. Capacity-building at the national level is a prerequisite to conducting research that is embedded within programme activities. Implementing simple observational studies and more resource-intense randomized controlled trials will greatly contribute to answering important questions. Duplicating efforts needs to be avoided, and an ongoing database would greatly help. A system to bring all the funding agencies around the same table should be in place. The results of research should be in the public domain, and no embargo should be applied.

The perspectives of donors and partners

Eleven institutions among partners, donors and research agencies reported on ongoing TB/HIV research activities. The presentations are available online at:
http://www.who.int/tb/events/tbhiv_research_priorities_in_resourcelimited_settings_feb05/en/index3.html.

⁵ Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet*, 2004, 364:1244–1251.

Discussion group reports

Three discussion groups developed recommendations relating to the future research needed in each of the five major areas described below. Following general discussion, discussion groups summarized the research priorities for each area. The list of priorities produced summarized the questions that need to be addressed globally and was not intended to identify the specific questions relevant to individual regions or countries. However, selected questions from the list can be given priority to address specific questions relevant to regions and countries with special needs. The research priorities identified are followed by notes from the plenary discussion.

A. Preventive therapy for TB

The following research priorities, which distinguish between the population and individual levels, were developed.

Population level

- 1. Identifying macro-level barriers to implementing isoniazid preventive therapy and mechanisms to overcome these barriers.** Although policy on providing preventive therapy is permissive, uptake of this intervention is still insufficient. It was felt that acceptance of preventive therapy programmes is low at the health ministry level. Fear that drug resistance will emerge and concerns about the short duration of efficacy have been discussed as potential impediments to implementation. Way to better promote implementation of preventive therapy programmes should be identified.
- 2. Evaluating the outcomes of a national isoniazid preventive therapy programme in Botswana: lessons learned.** Botswana is the only country so far that has widely implemented a preventive therapy programme. Evaluation of the programme is instrumental in extrapolating the lessons learned relevant to international policy.
- 3. Establishing the effectiveness in special populations and regions with elevated isoniazid resistance.** Limited data are available on how isoniazid preventive therapy programmes affect the emergence of drug resistance. This lack of information represents a problem in the context of emerging global drug resistance. Participants agreed to follow current recommendations and to evaluate the efficacy of isoniazid preventive therapy in settings with multi-drug-resistant TB. Guidelines should then be revised accordingly.

Individual level

- 4. Developing the optimum algorithm to exclude TB disease.** Recent evidence shows that a screening chest radiograph is not required to exclude active TB (pulmonary and pleural only) in asymptomatic people. However, the results from these studies should be validated in routine conditions. New diagnostic tools for screening TB are welcome and should be included.
- 5. Determining the added benefit of isoniazid preventive therapy among people receiving antiretroviral therapy.** One study supported by CREATE (Consortium to Respond Effectively to the AIDS/TB Epidemic) in Brazil is already specifically looking at the added benefit of isoniazid preventive therapy among people receiving antiretroviral therapy. Co-administering isoniazid with the protease inhibitors and non-nucleoside reverse transcriptase inhibitors may result in increased hepatotoxicity and rash risk, especially when isoniazid is given alone to treat latent TB infection in people living with

HIV/AIDS receiving these types of antiretroviral therapy. This has important clinical implications and should be studied.

6. **Determining whether there are subgroups of people who are likely to benefit.** Evidence is growing that the incidence of TB is higher among people living with HIV/AIDS who have a low CD4 count. Would introducing a CD4 count threshold as a criterion for entering a preventive therapy programme provide public health benefits? As a subset of this question, would the threshold jeopardize the implementation of preventive therapy programmes?
7. **Determining effectiveness among infants and children.** Improved methods need to be developed for excluding active TB and for assessing the effectiveness of preventive therapy programmes in children.

B. Co-trimoxazole prophylaxis

The routine use of co-trimoxazole in developing countries, especially sub-Saharan Africa, has been minimal despite provisional recommendations from WHO and UNAIDS that co-trimoxazole be given to everyone in Africa living with HIV/AIDS, including those who have TB. The *Interim policy on collaborative TB/HIV activities* promotes co-trimoxazole use among people living with HIV/AIDS who have TB.

Four topics were identified as priority areas for research.

1. **Determining the role of co-trimoxazole in the context of antiretroviral therapy.** Studies are needed to better determine the added efficacy of co-trimoxazole among people who are receiving antiretroviral therapy. In particular, better guidance is needed on other criteria (clinical or arbitrary time period) other than CD4 cell count that might guide the decision to stop providing co-trimoxazole whether people are receiving antiretroviral therapy or not. Further evaluation is also required to validate the exact threshold CD4 cell count at which co-trimoxazole prophylaxis should be stopped. Participants felt that a CD4 cell count of more than 200 is a criterion to stop co-trimoxazole prophylaxis among people receiving antiretroviral therapy. However, recent evidence shows that the risk of death increases with higher CD4 cell count. For this reason, co-trimoxazole prophylaxis should also be considered for people living with HIV/AIDS who also have TB if their CD4 count exceeds 200 cells per μl . Studies should also be undertaken to better determine the efficacy, the incidence of side effects (including haematological) and how to manage complications in children.
2. **Among people living with HIV/AIDS and TB, when is the optimal time to start co-trimoxazole (with and without antiretroviral therapy)?** If most deaths during the first months of TB treatment are due to TB, considering initiating antiretroviral therapy during this period is reasonable. Nevertheless, consideration should be given to co-trimoxazole to prevent the approximately 40% of deaths that are not related to TB during the first month of TB treatment. During the continuation phase, most deaths are due to causes other than TB. Similarly, if the risk of death is increased, even among people with a high CD4 cell count, co-trimoxazole prophylaxis should also be considered for people living with HIV/AIDS and TB whose CD4 counts are more than 200 cells per μl .

3. **Establishing the determinants that influence efficacy.** More observational data are needed on co-trimoxazole efficacy in Asia. The relationship between the level of background drug resistance and efficacy should also be determined. Likewise, more studies should be undertaken to determine the impact of the level of adherence and the efficacy of co-trimoxazole prophylaxis whether people are receiving antiretroviral therapy or not.
4. **What are the best delivery strategies to improve the uptake of co-trimoxazole prophylaxis?** Various delivery strategies should be developed to ensure that co-trimoxazole is offered at health care entry points including TB diagnostic centres, voluntary counselling and testing, antiretroviral therapy clinics and clinics for preventing mother-to-child transmission. Collaboration with HIV programmes is essential.

Note from the Secretariat

The Department of HIV/AIDS is revising the interim UNAIDS/WHO policy on co-trimoxazole use among people living with HIV/AIDS. The outcomes from this Consultation will inform the revision.

C. Antiretroviral therapy for people living with HIV/AIDS who have TB or develop TB

TB/HIV co-treatment is far from being a reality for people living with HIV/AIDS who have TB or who develop TB while on antiretroviral therapy. Clear recommendations on the best-informed practice are needed. Given that limited data are available, there is a need to move from evidence-based individual clinical interventions to a public health approach that will be informed by emerging evidence.

1. **Validating the optimal time to start antiretroviral therapy among people living with HIV/AIDS who have active TB (to improve efficacy and decrease toxicity).** No published prospective controlled study has examined the optimal timing of antiretroviral therapy after TB treatment is initiated. The decision about when to initiate antiretroviral therapy among people living with HIV/AIDS and TB must balance the risk of HIV disease progression, morbidity and mortality with the potential risk of drug toxicity and adverse events, including immune reconstitution inflammatory syndrome stratified by the stage of HIV disease.
2. **What are the best antiretroviral therapy regimens, with dose adjustment when required, to use with TB treatment regimens?** Some evidence is available on the pharmacokinetics of efavirenz and nevirapine when co-administered with rifampicin-containing regimens. Additional studies are needed to determine the clinical efficacy and safety profile of regimens containing efavirenz and nevirapine, proper doses in the presence of rifampicin and identifying the best methods of monitoring them.
3. **Determining the efficacy and safety profile of alternative antiretroviral therapy regimens (such as triple nukes).** Participants felt that drug development should be an area of focus for research on effectively treating people living with HIV/AIDS who have TB in resource-constrained settings. In particular, the development of fixed-dose combinations of antiretroviral drugs (mainly efavirenz-containing fixed-dose combinations) for people with TB should also be pursued. Replacing rifampicin with rifabutin should also be considered. If this is the case, studies are needed to determine the feasibility and cost-effectiveness of rifabutin-containing TB treatment regimens for people living with HIV/AIDS who are receiving antiretroviral therapy.

4. **Developing the best clinical definition for immune reconstitution inflammatory syndrome for use in resource-constrained settings (validation studies).** Clinical data available are based on different definitions of immune reconstitution inflammatory syndrome. There is an urgent need to standardize the definition and to identify the risk factors and predictors for immune reconstitution inflammatory syndrome. Clear and standardized guidance on how to prevent and/or treat an episode of immune reconstitution inflammatory syndrome is essential.
5. **What is the cost–effectiveness of different regimens and strategies?**
6. **What are the minimal requirements for clinical and laboratory monitoring for outcomes related to efficacy and safety?**
7. **What are the best strategies (including DOTS) for measuring and enhancing adherence for people receiving tuberculosis therapy and antiretroviral therapy?**

For all these questions, consideration of special populations, including their comorbidity and unique characteristics, is encouraged.

D. Intensified case-finding

Expanding DOTS and improving the existing DOTS strategy is the priority for national TB programmes. However, intensified case-finding for TB, used successfully on a wide scale and with appropriate emphasis, has the potential to increase case-detection rates and improve TB control.

Generally, research should target the following.

1. **Performing prevalence surveys.** National prevalence surveys would help to define the burden of prevalent TB and provide a basis for more accurately estimating case-detection rates and time trends. Further, measuring HIV prevalence in the same surveys enables important questions on the impact of HIV on TB prevalence to be addressed.
2. **Defining the threshold, if any, for starting intensified case-finding activities for national tuberculosis programmes and national HIV/AIDS control programmes.** Targeted intensified case-finding is recommended in populations with a high prevalence of HIV (see the *Interim policy on collaborative TB/HIV activities*) or in congregate populations such as prisoners and miners irrespective of their HIV status. The epidemiological interaction between the HIV prevalence and the TB incidence needs to be understood better to define the best threshold of TB incidence (or prevalence) and HIV prevalence for starting intensified case-finding activities.
3. **Improving case-detection strategies in clinical settings and where there is unmet need.** TB case-finding among people living with HIV/AIDS in clinics and hospitals, as well as household contacts, populations especially vulnerable to HIV infection and congregate settings should be intensified by improving testing algorithms and developing models to deliver this intervention. In particular, operational aspects of delivering intensified case-finding through existing community structures (shops, churches, schools, community-based and home-based care volunteers) should be better investigated. Further, operational research on the feasibility of integrating intensified case-finding with outreach activities, such as needle–exchange programmes, should be a priority in the countries of the former Soviet Union and countries in South-East Asia, where epidemics of injecting drug use, TB and HIV are closely linked. Collaboration between the national TB and

HIV/AIDS programmes is essential to improve TB control in settings with a high HIV prevalence.

4. **Validating screening methods.** The relative sensitivity and specificity of radiology, microbiology (either smear or culture) or specific symptom screening questions and their predictive value for most target groups or at the population level are not known. Research is needed on the operating characteristics of different algorithms that could be used for intensified case-finding using current diagnostic methods for TB.
5. **Establishing systems to routinely record and report additional cases of TB detected through intensified case-finding.**

E. Smear-negative TB

The HIV epidemic has been associated with a significant increase in the incidence of smear-negative pulmonary TB among people living with HIV/AIDS. However, national TB control activities have focused less on diagnostic strategies and on documenting the treatment outcome of smear-negative and extrapulmonary TB cases although they constitute a large proportion of TB cases.

The following areas have been identified as main research priorities.

1. **Improving current diagnostic algorithms to shorten the time required for establishing a diagnosis of smear-negative pulmonary TB and to include diagnosis of extrapulmonary TB.** Revisions of the existing diagnostic algorithm include consideration for HIV status, disease severity, predictors of poor outcome, trial of antibiotics and improved sensitivity. Studies should also be encouraged to determine validity and cost-effectiveness, especially in settings with a high HIV prevalence.
2. **Validating adapted diagnostic algorithms in children.** Children rarely have sputum-smear positive TB, and diagnosing TB in children is difficult. Although a good TB control programme is the best way to prevent TB in children, studies are urgently needed to improve the diagnosis of TB (both pulmonary and extrapulmonary) in children. The best ways and models to integrate this revised algorithm into the WHO Practical Approach to Lung Health (PAL) and Integrated Management of Adult and Adolescent Illness (IMAI) strategies need to be explored.
3. **Developing new diagnostic tools.** The lack of rapid and reliable diagnostic tools has been a main factor in fuelling the problem of smear-negative TB among people living with HIV/AIDS. Research should be conducted to yield simple, rapid, preferably noninvasive and safe diagnostic tools with increased sensitivity. Advancing appropriate technology to increase the utility of such tools in peripheral health institutions in settings with resource constraints or high HIV prevalence is important.
4. **Determining the utility of chest radiography in the diagnostic process.** In particular, the best time for chest radiography in the diagnostic algorithm for smear-negative pulmonary TB needs to be determined to enhance its utility in assisting diagnosis and shortening the time required to establish the diagnosis. Participants felt that earlier use of chest radiography should be encouraged.

- 5. Determining the feasibility of promising techniques, such as the bleach method and fluorescence microscopy.** In the absence of any better alternative to urgently improve smear microscopy in settings with resource constraints or high HIV prevalence, bleach and the fluorescence microscopy methods should be encouraged depending on the availability of resources. Research should inform the best standard techniques and models to expand these methods and to enhance their utility in existing services to improve the smear-negative pulmonary TB problem.
- 6. Developing appropriate technology.** For example, solar-powered fluorescence microscope and culture facilities need to be explored, especially for use in resource-constrained peripheral settings.
- 7. Improving reporting procedures.** Reporting procedures need to be improved for smear-negative and extrapulmonary TB, and the best models to enhance the utility of such data for programme performance need to be designed.

Note from the Secretariat

WHO has been urged to revise current diagnostic algorithms and urgently take measures to improve the diagnosis of smear-negative pulmonary and extrapulmonary TB. Special attention should be given to children.

Coordinating TB/HIV research

The presentations made during the Consultation and the following discussions showed that a wealth of evidence has been collected about implementing collaborative TB/HIV activities. This has led to the development of the essential policy to implement joint activities. In particular, the *Interim policy on collaborative TB/HIV activities* has set out which joint activities should be implemented according to the level of HIV prevalence.

Although many unanswered questions remain, participants felt that, given the evidence available, evaluating the implementation of the current policy should be emphasized more strongly than generating more research questions. The role of research in supporting improved TB and HIV control should be highlighted.

Although the research questions produced in this Consultation reflected a wide range of expertise and different geographical needs, a warning was expressed about the need to better consider sociobehavioural issues when developing research questions.

The group felt that mechanisms to avoid redundancy of research should be identified and knowledge disseminated properly. An advocacy package, containing the identified research priorities, should be prepared to share the outcome of this Consultation with countries, stakeholders and research agencies.

Implementation of research priorities should capitalize on the financial momentum in which the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief are mobilizing more funds for treatment and research activities. Budgeting the research gap is therefore instrumental to advocate for additional resources to conduct more research aimed at improving TB and HIV control.

This Consultation will provide guidance on what needs urgent attention. We hope that donor and partner agencies will take up the priorities identified, but countries should also take action as soon as possible and implement the research priorities they consider crucial for improving TB and HIV control in their settings. Although WHO is not a funding agency, some activities will happen within the coordination of WHO and the UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The Special Programme will also support additional research priorities relevant to its areas of work, including developing country capacity in programmes considered to be crucial. Partner agencies will take up other areas of research. The efforts by partner agencies to implement research priorities should be harmonized to avoid redundancy. This could be achieved by periodically updating the status of implementation of the research priorities identified. Collaboration with the activities supported by the United States President's Emergency Plan for AIDS Relief is essential.

Conclusions

During the concluding session, the following points were agreed on in order to take the recommendations forward.

1. *The Secretariat convened the Consultation at the request of the Global TB/HIV Working Group. Outcomes will be shared with the Core Group, to further seek advice on the way forward. Presentations and the report of the Consultation will be posted on the web. The background papers will be submitted for publication. Fast-track submission has been requested for the background paper on smear-negative TB, which requires revision to incorporate the comments made at the Consultation.*
2. *The outcomes of the Consultation, including the research priorities developed, will be then submitted to WHO's Strategic and Technical Advisory Group for TB and Strategic and Technical Advisory Committee for HIV/AIDS for their consideration and endorsement on the need to develop a strategy on injecting drug users and the community.*
3. *The Secretariat will monitor the implementation of recommendations through a monitoring and evaluation system based on the TB/HIV questionnaire that informs progress on TB/HIV activities. Subgroups to follow-up on specific issues (such as antiretroviral therapy for TB) will be established. Sociobehavioural aspects should be explored further and dealt with at the next meeting of the Global TB/HIV Working Group.*
4. *The Secretariat will pursue the community care option to improve the implementation of joint TB/HIV activities. This will be drawn from the community TB care and HIV community care models to better reflect the special needs required by the implementation of joint activities. Likewise, a strategy needs to be developed for implementing joint activities for injecting drug users (in settings with background hepatitis C and B infection) and for better determining the relationship between multi-drug-resistant TB and HIV.*
5. *Three discussion groups identified research priorities for each of five major areas.*
 - *Research priorities for preventive therapy for TB were identified, with a distinction between the population and individual levels.*
 - *Priority areas of research for co-trimoxazole prophylaxis include the role of co-trimoxazole in the context of antiretroviral therapy, delivery strategies and determining the efficacy and optimal time of initiation of co-trimoxazole among people living with HIV/AIDS who have TB.*
 - *The major research priority area identified in relation to antiretroviral therapy for people living with HIV/AIDS who have TB or who develop TB is validating the optimal time of initiation of antiretroviral therapy. Other research priorities include optimizing regimens and determining the efficacy and safety profile. Validating the definition of immune reconstitution inflammatory syndrome is also a priority.*
 - *Research priorities on intensified case-finding focus on ways to put TB/HIV collaborative activity into operation to improve TB control.*
 - *Developing new tools and developing diagnostic algorithms are top research priorities to improve the diagnosis of smear-negative TB among adults and children.*

6. *Mechanisms for getting research priorities implemented should be explored. Coordination with the operational research training workshop focused on TB/HIV in Malawi in June 2005 will provide an opportunity to translate the research priorities developed into implementation, as participants from a number of African countries will have the opportunity to develop and conduct operational research projects. This course is being organized by the United States Centers for Disease Control and Prevention, the United States Agency for International Development, the Malawi National Tuberculosis Programme and numerous other partners. Links with other similar initiatives will be explored.*

7. *All partners, donors and research agencies have a role in implementing the research priorities developed in this Consultation. Likewise, countries should take advantage of current funding opportunities (such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States President's Emergency Plan for AIDS Relief and others) to take up some of the recommendations as soon as possible. Technical assistance to countries to develop proposals will be coordinated. An advocacy strategy to package the research priorities will be developed and widely disseminated at the field level and at the global and regional levels.*