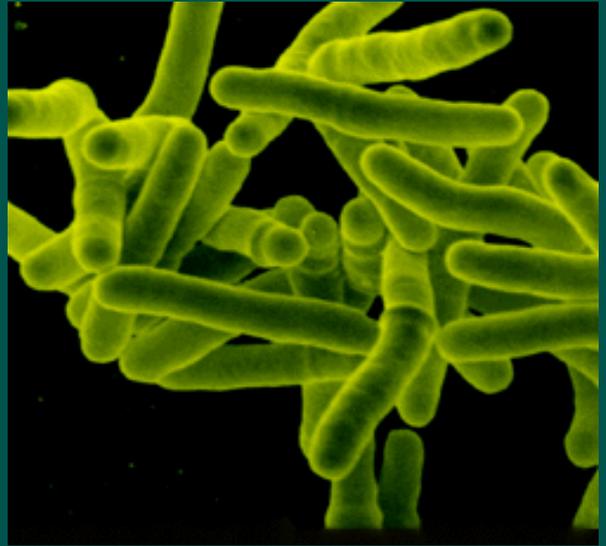


NIAID Research Agenda

Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis



NIAID Tuberculosis
Working Group

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Preface

The National Institute of Allergy and Infectious Diseases (NIAID) remains firmly committed to leading and supporting a robust program of tuberculosis (TB) research, and is prepared to expand this effort with the availability of additional resources. Although concern about the development and spread of multidrug and extensively drug-resistant TB (MDR/XDR TB) is warranted, drug-sensitive TB continues to be the primary cause of TB-related morbidity and mortality worldwide. Basic biomedical research to more fully understand TB, to characterize *Mycobacterium tuberculosis* (*Mtb*), the bacillus that causes TB, and to develop improved diagnostics, new drugs, and better vaccines must continue to provide a solid foundation in the urgent fight against TB. In addition, to the degree that resources allow, a vigorous well-directed research program also must address growing public health concerns and clinical management needs related to MDR/XDR TB.

Recognizing the growing challenges TB researchers are asked to address, it is imperative that research priorities are carefully chosen and coordinated. To prepare this research agenda focused specifically on MDR/XDR TB, NIAID consulted U.S. and international TB experts, academia, activist groups, and other government agencies. While it concentrates on only a portion of the scientific challenges associated with TB, this agenda identifies high-priority research needs that complement the robust basic research and product development program NIAID supports for TB in general. Continuation of basic biomedical TB research is the foundation for an expanded research program to address the special challenges of drug-resistant tuberculosis. The agenda is a Web-based “living document” that can be updated as scientific and public health events and opportunities evolve.

The Challenge of MDR/XDR TB

TB can be resistant to one or more chemotherapeutic agents. MDR TB is defined as resistance to at least the first-line drugs isoniazid and rifampin. XDR TB is defined as MDR plus resistance to any fluoroquinolone, and at least one of the second line injectable drugs, capreomycin, kanamycin or amikacin (1, 2). Such extensive resistance markedly limits treatment options because few effective and reasonably well tolerated alternative drugs are available. Resistance to drugs currently used to treat TB is rapidly becoming a global public health emergency. The continued spread of MDR/XDR TB has the potential to paralyze TB care programs and public health infrastructure in resource limited countries. It is also a serious threat to industrialized nations such as the U.S. where individual care and treatment costs and larger social and economic disruptions could become major public policy issues.

TB treatment program deficiencies resulting in interrupted drug supply, patient non-adherence to a lengthy treatment course, and co-morbidities and co-infections compromise the effectiveness of TB therapy by causing the delivery of sub-optimal drug levels. This can lead to treatment failures and the development of drug-resistant strains of *Mtb* (acquired resistance). In addition, in countries with high rates of TB, new drug-resistant cases can result from the transmission of already resistant organisms between individuals (primary resistance). This adds special urgency to the need for effective infection control and in-patient management, especially for countries with limited hospital infrastructure.

Currently, in most TB endemic countries, the drug resistance profile of the infecting *Mtb* is not determined; therefore, therapy for TB is empiric and changes in treatment regimen are instituted only after relapses or initial treatment failures. As a result, by the time patients are identified as having non-responsive, drug-resistant TB, they have usually experienced multiple episodes of TB and their health has deteriorated significantly. In most cases a determination of the drug resistance profile of the

infecting *Mtb* is not determined. Even patients who have been infected with drug-resistant TB are initially treated with standard first line therapy; therapy is switched to standardized second line drug regimens only after patients are being considered non-responsive to treatment,. This iterative, standardized, and passive approach to TB control has led to many cases of advanced TB disease and death in affected persons.

The recent reports of XDR TB in HIV co-infected patients in KwaZulu-Natal, South Africa (3), as well as the incident surrounding a U.S XDR TB patient have renewed global awareness of drug-resistant TB and the threat it poses to both individual patients and public health, to the challenges facing TB control programs, and also to HIV/AIDS treatment programs in countries with high rates of HIV co-infection (4). Of 554 cases of TB identified at the government district hospital in Tugela Ferry, KwaZulu-Natal (KZN), 221 (41%) were MDR TB. Further, of these, 53 (24%) were resistant to the second-line drugs kanamycin and ciprofloxacin, fulfilling the definition of XDR TB (3). Of the 53 patients with XDR TB, 44 were tested for HIV and all were found to be co-infected with HIV and 15 were receiving anti-retroviral therapy (ART); 52 (98%) died within a median of 16 days following sputum collection for culture and drug susceptibility testing. Nosocomial transmission was reported to be the likely source of infection in most patients, as the majority of these patients had never been previously treated for TB. Two thirds had recently been hospitalized at the same hospital and 85 percent were infected by the same *Mtb* strain family. Several health care workers who came in contact with these patients also were among the fatalities associated with XDR TB in Tugela Ferry (3).

Although reports of XDR TB in HIV co-infected patients in rural KwaZulu Natal, South Africa have received the greatest attention, XDR TB has been detected in all regions of the world (6), including in countries as diverse as South Korea, Latvia, Iran, and the United States, each of which has a low (<1 %) prevalence of HIV infection (5,6,7). In an analysis of a 2000-2004 global survey of supranational reference laboratories in 48 countries using the initial CDC/WHO standardized definition of XDR TB (MDR plus resistance to 3 of 6 classes of second line drugs), 20 percent of 17,690 isolates examined were MDR *Mtb*, and 2 percent of all isolates were XDR *Mtb* (5,6).

While XDR *Mtb* isolates have been identified in all surveyed regions, their true global distribution, prevalence and consequences for treatment success are not known due to limited culture and drug susceptibility testing capabilities in endemic countries. However, estimates of population-based prevalence to date suggest that the proportion of MDR *Mtb* isolates that meet the definition of XDR is 19 percent in Latvia; 15 percent in South Korea; and 4 percent in the United States (5, 6). It is important to note that the epidemiological and clinical characteristics, as well as the clinical consequences of MDR and XDR TB likely differ significantly between areas of high and low HIV and TB prevalence. Both MDR and XDR TB treatment success rates are substantially lower in patients co-infected with HIV. In areas of high TB and HIV prevalence, the presence of TB drug resistance carries the danger of markedly reducing the benefit of both TB and antiretroviral treatment programs

Globally, an estimated 424,203 cases of MDR TB occurred in 2004, with China, India, and the Russian Federation accounting for 62 percent of the burden (8). MDR TB represented 2.7 percent of new and 18.5 percent of previously treated cases of TB (4.3 percent overall) (8). Although MDR TB still responds to second line drugs, successful treatment requires up to two years of therapy, and often involves drug administration on an in-patient basis. In addition, MDR TB therapy is not easily tolerated, it is at least ten times more expensive than treatment of drug-susceptible TB, and cure rates are often well below 60 percent. While current drug regimens for MDR TB average approximately US \$4,000 per patient, the cost of XDR TB treatment has been estimated to be more than twice this amount, depending on the extent of drug resistance and the need for hospitalization (9, 10, 11).

Additionally, guidelines for the treatment of MDR and XDR TB have not been optimized and are not fully standardized (12). Standardization of effective regimens is difficult because *Mtb* may be resistant to different combinations of first and second line drugs.

As is evident from an analysis of the global prevalence of all forms of drug-resistant TB and given the less than optimal state of TB treatment programs in endemic countries, there is a clear need for studies to determine the distribution and prevalence and the medical consequences of both MDR and XDR TB to implement more effective TB control activities worldwide. Increased research efforts also are urgently needed to expedite the development of new and more effective tools to prevent, diagnose, and successfully treat drug-susceptible and drug-resistant TB, among adults, children and adolescents, particularly including those co-infected with HIV.

Status of the National Institute of Allergy and Infectious Diseases Intramural and Extramural TB Research Program (FY06)

The NIAID, through its extramural and intramural programs, supports a globally relevant TB research agenda focused on all aspects of TB science, including drug-susceptible and drug-resistant TB, as well as TB in HIV co-infected persons. Extramurally supported fundamental TB research includes studies to better understand the basic biology of *Mtb* and the host-pathogen interaction, including latent *Mtb* infection in human hosts and in animal models of infection and disease. NIAID supported translational and clinical research is focused on the identification and development of new interventions: diagnostics, drugs, and vaccines. To better understand TB in special populations, NIAID's research agenda includes efforts to study TB in children and immune suppressed persons and to clarify the interaction of HIV and *Mtb* to improve TB prevention and treatment in adults and pediatric populations. To date, NIAID's investment in fundamental, translational, and clinical science has led to the development of several new TB drug, diagnostics, and vaccine candidates.

- FY 2006 NIAID TB expenditures (10% intramural; 90% extramural): ~ \$ 119.7 M (319 Projects)
 - 156 projects in basic/clinical research: \$ 50.6 million
 - 100 projects in drug discovery and development: \$ 41.8 million
 - 39 projects in vaccine discovery and development: \$ 19.7 million
 - 24 projects in diagnostic discovery and development: \$ 7.6 million

NIAID's extramural TB resources provide a framework for research to respond to the growing global MDR and XDR TB crisis and are available throughout the extramural divisions at NIAID (Table 1). NIAID's Research Agenda on Biodefense Category B and C Priority Pathogens (<http://www3.niaid.nih.gov/Biodefense/Research/categorybandc.pdf>) includes fundamental and translational research to diagnose, prevent and treat drug-resistant TB. Current initiatives which include Category C organisms are open to TB researchers (<http://www3.niaid.nih.gov/biodefense/research/funding.htm>). In addition, NIAID supports international HIV/AIDS clinical research networks and is developing international databases that can include research on HIV/TB, and the datasets can contribute to the clinical evaluation of new TB drugs, vaccines, and diagnostics in co-infected persons.

NIAID intramural laboratories are conducting important TB and MDR/XDR TB research in the United States and internationally to add to our knowledge about this disease. At the NIH Clinical Research Center (CRC), NIAID scientists have the resources to conduct pharmacokinetic and pharmacodynamic (PK/PD) analysis of anti-tuberculosis agents in patients, including individuals co-infected with HIV

and receiving antiretroviral drugs. Currently active clinical protocols to admit, treat, and study patients with mycobacterial diseases, including MDR/XDR TB can be expanded to include studies on PK/PD, immune parameters affecting treatment, imaging, and the identification of biomarkers to provide data that complement extramural research programs in the discovery and development of new therapeutic options for TB (see Table 1). In cooperation with partner organizations in South Korea, Mali and India, NIAID has helped establish clinical research centers to study drug-susceptible TB and MDR/XDR TB with biosafety level 3 laboratories and other advanced capabilities. Uniquely, in South Korea through a partnership with the Bill and Melinda Gates Foundation, NIAID scientists already are assessing new treatment strategies to improve MDR/XDR TB survival. At the South Korea site or other international sites, scientists are studying: host factors predisposing to pulmonary, extra-pulmonary, and skeletal TB; the interaction of TB and filarial co-infection; the epidemiology of MDR/XDR TB; HIV/TB co-infection and strategies for the treatment of co-infected patients; host/pathogen factors that influence disease progression; and, factors that contribute to TB drug resistance. These research sites offer additional opportunities to evaluate drugs not currently licensed for TB (such as moxifloxacin, linezolid, capreomycin, or clofazimine) for the treatment of XDR TB, and to undertake other priority MDR/XDR TB research.

In addition to NIAID, several other NIH Institutes and Centers, the US Centers for Disease Control and Prevention (CDC), and other US Federal Agencies support essential and complementary research and product development, disease and drug resistance surveillance, and research training programs of relevance to MDR/XDR TB. Communication and coordination among these partners is extensive and has continued for decades. Collaboration is facilitated through the US Federal TB Task Force, the WHO/Stop TB Partnership, and the NIAID-CDC Joint U.S. Partnership Implementing TB Elimination Research (JUPITER). Through its extramural programs, NIAID also supports an array of public-private partnerships to develop new tools to control TB. In addition to directly providing support for U.S. international TB research, NIAID provides significant financial contributions to the Global Fund for AIDS, TB and Malaria, which supports the development and expansion of endemic control programs for TB and HIV care in many countries throughout the world.

Although these collaborations provide a foundation that NIAID and its partners leverage to address the most urgent research and development needs for MDR/XDR TB, it is recognized that the development of additional tools to combat drug-resistant TB and TB in HIV co-infected persons would be expedited if interactions between academic and pharmaceutical scientists were strengthened – an important objective for the private sector as well as the government.

Current Research and Resource Gaps

In preparing this targeted research agenda, extramural and intramural research staff reviewed the current NIAID TB research portfolio. This review identified particular research needs and opportunities within NIAID's overall mission that, if given intensified attention, will provide data to help frame and strengthen the global response to MDR/XDR TB. The major research priorities for NIAID's current TB program include:

- Understanding latency
- Developing surrogate markers of infection, disease, and response to therapy
- Identifying correlates of immunity and markers that signal transition from latent to active TB
- Discovering and developing new diagnostics, drugs, and vaccines for all forms of TB and all persons at risk, including children and those co-infected with HIV

The research needs for MDR/XDR TB articulated in this document are in addition to, and complement the needs and priorities that have already been identified as part of the global fight against TB. Research priorities and global funding gaps focused on the development of new health care interventions also have recently been published by the StopTB Partnership in which NIH/NIAID staff participates as members.

Targeted research needs for MDR/XDR TB within NIAID's TB program were identified in six critical areas, all of which pertain to HIV co-infected and HIV negative persons, as well as pediatric and other special populations affected by all forms of TB:

1. Developing and testing reliable technologies to rapidly diagnose all forms of TB and to identify drug resistance
2. Defining the most effective use of existing second-line TB therapies and other antimicrobials available to treat drug-resistant TB, and developing new chemotherapeutic agents, particularly against MDR/XDR TB
3. Understanding the basic biology and immunology of host and pathogen that underlie the development and spread of drug-resistant strains of *Mtb*
4. Understanding the epidemiology, as well as operational and programmatic elements that contribute to the development and spread of drug-resistant strains of *Mtb*
5. Determining the influence of the overall immune status and other host factors, and the influence of HIV co-infection on the development of drug-resistance and the outcome of TB chemotherapy
6. Developing effective chemoprevention strategies and developing and evaluating effective vaccines for drug-sensitive and drug-resistant TB

Recommendations for Priority Research in MDR/XDR TB

By using or expanding its existing research capabilities, and by leveraging resources across agencies of the U.S. Government that are involved in TB research and care, NIAID is prepared to address the research gaps that limit a more effective response to the global tuberculosis crisis. In particular, NIAID can provide leadership of and contribute to the fundamental, translational, and clinical research efforts needed to address the growing challenge of MDR/XDR TB. Only through a carefully managed program of additional targeted research and scientific innovation will the global public health community gain the knowledge, drugs, diagnostics and vaccines needed to save the lives of those infected with MDR/XDR TB, and to prevent the further emergence and spread of all forms of tuberculosis. It is expected that these scientific areas will offer new opportunities for young investigators to receive infectious disease training in international TB care and research either through training and/or research grants.

To address the six targeted research areas listed above, NIAID recommends specific activities to advance scientific understanding, improve clinical care for those infected with MDR/XDR TB, and to prevent both acquired and primary TB infection in persons at risk. These activities build on current NIAID capabilities and existing collaborations, for example, with the CDC/National Center for

HIV/AIDS, Viral Hepatitis, STD and TB Prevention (NCSSTP) and other members of the U.S. Federal TB Task force, as well as coordination with other global research funding organizations such as the Bill and Melinda Gates Foundation and the StopTB Partnership. In the absence of additional funding for targeted MDR/XDR TB research, selected activities can be implemented through small shifts in available resources without compromising existing TB program activities. Enhanced progress in future years will be dependent on the level of funding available to support the overall NIAID TB research program, as well as targeted studies on MDR/XDR TB, where appropriate.

1. Diagnostics

Diagnosis of clinical TB remains primitive and in much of the world relies on the relatively insensitive direct microscopic visualization of acid-fast bacilli in patient sputum or on clinical diagnosis alone. Direct microscopic visualization does not diagnose non-pulmonary or smear-negative cases, which are frequently seen in pediatric populations and HIV co-infected individuals.

Diagnosis of drug-resistant TB requires bacterial culture and drug sensitivity testing (DST) within a clinical microbiology infrastructure that is not widely available in resource-limited endemic areas. The WHO supranational reference laboratory (SRL) network supports 25 highly proficient laboratories on 6 continents; however, until the recent recognition of the XDR TB problem in rural KZN, South Africa, only two SRLs existed for the entire African region. Where it is technically feasible, drug-susceptibility testing remains a slow process requiring at least 2-3 months from specimen collection until results are available. In most areas of the world in practice and by policy, culture and DST are not performed except for treatment failure or for re-treatment cases. Thus, great delay in the diagnosis of drug resistance and the empiric treatment of TB are the rules rather than the exceptions, even when such testing is available.

As highlighted by the rapid progression of XDR TB patients in KwaZulu Natal to severe disease and high mortality (70 percent of patients died within 30 days of initial sputum collection), the time to diagnosis of XDR TB is a major limitation in recognizing the presence of drug-resistant *Mtb*, in treating the individual patient effectively, and in reducing the risk of transmission of infection to others. Development of new microbiological diagnostics to rapidly identify drug-sensitive and drug-resistant *Mtb*, and of new immunologic diagnostics to rapidly diagnose TB disease is often hampered by limited access to patient samples or well-characterized clinical specimens with which to determine assay feasibility. Therefore, to expedite the development of microbiological and immune tests to rapidly diagnose TB and assess the response to existing therapies, studies to test new and already available diagnostic methodologies need to be supported. The most urgently needed diagnostic tools are those that are suitable for use in field sites with limited technical and personnel infrastructure, that allow diagnosis of large numbers of patients, including children, and that are compatible with integrated HIV and TB care programs.

Specific Activities:

- 1.1. Determine genetic and physiologic alterations in a global sampling of MDR and XDR strains of *Mtb* associated with resistance to second-line TB chemotherapeutics.
- 1.2. Enhance support for development of new microbiological and immunological diagnostics for all forms of TB and suitable to diagnose TB in HIV+, HIV-, and pediatric patients.
- 1.3. Establish laboratory support for quality assurance, diagnosis, culture, susceptibility testing, strain typing, and preservation at all NIAID-supported study sites involving TB and TB/HIV

patients. Ensure appropriate communication and coordination with national TB control programs for diagnosis, referral and treatment of MDR/XDR TB cases.

- 1.4. Improve access to existing clinical sites where MDR and XDR TB are prevalent and emphasize/support MDR/XDR studies for clinical validation of new microbiological and immunological diagnostics for HIV+ and HIV- adults and children.
- 1.5. Facilitate early interaction among microbiologists, basic scientists and clinicians in the US and in TB endemic countries to assure that newly developed diagnostics have the potential to be applied to field situations.

Expected outcomes:

- Contribution of data and infrastructure by NIAID funded clinical sites to the global assessment of the burden of TB, but especially MDR/XDR TB.
- Improved availability and access to more rapid diagnostics and laboratory capabilities in endemic regions.
- Improved access to clinical networks for testing and validation of new TB diagnostics.
- Expanded pipeline of microbiologic diagnostics to rapidly identify drug-sensitive and drug-resistant TB, and immunological diagnostics to identify TB and response to therapy, in immune competent and immunosuppressed individuals.

2. Improving Chemotherapy for MDR/XDR TB

Current chemotherapeutic regimens for drug-sensitive (first line therapy) and MDR/XDR TB (second-line therapies) have not been fully optimized. Drug combinations and treatment durations, based on clinical outcomes and the lack of relapse, were developed empirically in clinical trials for first line therapies, and in observational studies for second line therapy. The typical duration of treatment is 6 months for first line, and 12-24 months for second line regimens. Pill burden, length of treatment, drug intolerance/toxicity and program inadequacies are the principal reasons for treatment failure, and contribute to the development of resistant strains. Furthermore limited experience with the clinical pharmacology, clinical outcome, difficulties with parallel treatment programs for TB and HIV, and the effect of co-administration of second-line therapies with antiretroviral drugs (ARVs) complicate the treatment of resistant TB.

Existing broad spectrum antimicrobial agents have unexplored therapeutic potential in MDR/XDR TB and should be evaluated. However, these evaluations must be coupled with targeted studies to rule out the potential for rapid development of drug resistance, as patients may have been exposed to these agents as part of broad spectrum treatment for earlier non-tuberculous infections. Accelerated efforts to develop, test, and bring to market new TB drugs and regimens are critical if chemotherapy for MDR/XDR TB is to be improved. These efforts must address the current gap of limited support for IND-enabling studies for new chemical entities, as well as the need for pharmaceutical industry sponsorship of the production and marketing of new drugs.

Specific Activities:

- 2.1. Study the pharmacology of second-line anti-tuberculosis drugs in healthy volunteers, MDR/XDR TB patients and TB/HIV co-infected patients, as well as in special populations such as pregnant women and children who may or may not be receiving ART.
- 2.2. Study pharmacokinetic interactions between second line TB drugs and HIV therapies.

- 2.3. Support preclinical and clinical evaluation of available broad spectrum agents and new drugs for the treatment of MDR/XDR TB, including studies on the pre-existence of resistance to these agents in *Mtb*.
- 2.4. Investigate optimal use of first- and second-line regimens to shorten the time patients remain infectious and contribute to *Mtb* transmission in health care and community settings.
- 2.5. Increase preclinical evaluation of novel drug combinations in standardized animal models to guide clinical selection of new drugs and regimens.
- 2.6. Increase collaboration among HIV/AIDS and TB basic, translational and clinical scientists in drug and regimen development and testing.
- 2.7. Enhance and support centers capable of conducting clinical trials of chemotherapeutic agents and regimens in MDR/XDR TB patients, including patients with HIV co-infection.
- 2.8. Identify markers for response to therapy as surrogates/correlates of clinical efficacy in drug-sensitive and MDR/XDR TB drug trials.
- 2.9. Establish an NIAID-sponsored repository of representative global MDR/XDR TB strains to determine *in vitro* and *in vivo* microbiological activity of promising single and combination therapies.
- 2.10. Maintain and expand NIAID resources for screening and evaluating new chemicals against *Mtb* and validated drug targets to support and advance discoveries of drugs against resistant TB.
- 2.11. Expand the investment in medicinal chemistry programs aimed at optimizing novel series of molecules with activity against MDR/XDR TB.
- 2.12. Provide support for IND-enabling studies in formulation, preclinical pharmacology and toxicology to expedite transition of drug candidates into clinical testing.
- 2.13. Enhance and support novel programmatic treatment strategies, including community based treatment and adherence support programs designed to increase therapeutic success and decrease patient default in second line TB drug treatment programs.

Expected outcomes:

- Improved understanding of the pharmacology of current second-line TB regimens in HIV+ and HIV- patients with TB.
- Determine the presence and clinical significance of pharmacokinetic drug interactions between second line therapies for TB and antiretroviral drugs.
- Additional therapeutic options for the treatment of MDR/XDR TB with currently available drugs not standard for TB treatment.
- Strategies for optimizing the use of currently available drugs to prevent the emergence of additional MDR/XDR TB and limit transmission of *Mtb*.
- Increased collaborative studies between TB and HIV researchers.
- Clinical trials protocols and clinical development plans to provide guidance for advancing drugs specific for MDR/XDR TB indications and compassionate use protocols.
- Availability of predictive animal models to investigate new drug and combination drug therapy according to human drug exposures.
- Expanded pipeline of new chemical compounds in late stage preclinical or early stage clinical development.
- Expedited development of shorter treatment regimens to facilitate adherence and improve treatment outcomes.
- Clinical trial designs to expedite the determination of drug efficacy.
- Defined hand-off points from NIAID to collaborative partners/programs to expedite drug and regimen development, testing and approval.

3. Basic Biology

Many gaps remain in our fundamental understanding of the development of drug resistance and the spread of drug-resistant strains of *Mtb* in communities. Factors that have not been completely elucidated include 1) the mechanisms of development of drug resistance in mycobacteria; 2) the exact location and physiology of bacterial populations in human tissues and organs both for active and latent TB; 3) the phenomenon of mycobacterial tolerance to antibacterial agents; 4) the optimization of the pharmacodynamic response to anti-mycobacterial drugs; 5) the determinants of host survival; and 6) variation by world region and by co-morbidities of these parameters. Most of these questions are already the subject of intense investigations as part of on-going research programs at NIAID and other agencies, but significant research is still needed to provide a solid foundation of understanding of the development of drug resistance in TB.

Specific Activities:

- 3.1. Develop consortia to conduct MDR/XDR TB specific laboratory research, using advanced bio-safety measures (BSL3/4):
 - 3.1.1. Characterize the genetic and physiologic determinants of drug resistance in MDR and XDR *Mtb* strains.
 - 3.1.2. Determine whether MDR/XDR *Mtb* strains are more transmissible and exhibit greater virulence and/or pathogenicity in animal models and in humans.
 - 3.1.3. Determine whether drug-resistant strains respond differently to the host immune response and interact differently with host cells compared to drug-sensitive strains; determine the different innate and adaptive immune parameters that may underlie infection with drug-sensitive and drug-resistant *Mtb*.
- 3.2. Determine the location of *Mtb* in host tissues and whether the location contributes to the development of latency and non-responsiveness to therapy.
- 3.3. Determine whether PK/PD parameters defined *in vitro* and in animals are predictive for modeling the clinical efficacy of single and combination therapies.

Expected outcomes:

- Understanding of how MDR/XDR *Mtb* strains interact with the host immune response and how these differences impact vaccine and drug efficacy.
- Improved understanding of virulence and pathogenicity of MDR/XDR *Mtb* strains.
- Improved understanding of the development and maintenance of protective immunity to MDR, XDR, and drug-sensitive *Mtb*.
- Improved preclinical and epidemiological tools to analyze development of drug resistance in TB to inform translational science approaches.

4. Epidemiology

The global epidemiology of drug-resistant TB, particularly XDR TB is not known and the true magnitude of the problem probably is markedly underestimated. Few data are available from countries with the largest burden of TB, such as China and India. In addition, except for the recent reports of XDR TB from rural KZN, South Africa, little information is available regarding the presence of MDR

and XDR *Mtb* strains in countries with a high prevalence of TB and HIV, such as countries in sub Saharan Africa. Predictors of drug-resistant TB transmission in community and health care settings are poorly understood, as are the interaction of MDR/XDR TB and HIV, and the contribution of the degree of immune suppression to TB acquisition in individuals and populations. Furthermore, key factors associated with transmission of drug-resistant TB in health care settings are not well known.

Specific activities:

- 4.1. Coordinate the efforts of existing national and international centers to study the epidemiology of MDR/XDR TB.
- 4.2. Construct mathematical models to understand the genesis and dynamics of drug-resistant TB epidemic growth in setting with high and low rates of HIV co-infection.
- 4.3. Identify clinical and epidemiologic risk factors for and predictors of MDR/XDR TB development and transmission, particularly in TB endemic countries.
- 4.4. Investigate the relationship between molecular strain patterns and drug resistance.
- 4.5. Study strategies to reduce risk of transmission of drug susceptible and drug-resistant TB in families, community and health care settings, particularly with high prevalence of HIV co-infection.
- 4.6. Determine whether host characteristics (such as co-morbidities, HIV infection, or genetic polymorphisms) influence the acquisition of certain drug-resistant strains of *Mtb*, facilitate the development of clinical resistance during therapy, or affect subsequent patient morbidity and mortality.
- 4.7. Improve infrastructure for, and adherence to, WHO-recommended infection control guidelines for all NIAID-supported study sites involving TB and TB/HIV patients.
- 4.8. Help support development of TB genomic sequencing capabilities for epidemiologic research and control purposes in TB endemic countries where feasible and where appropriate.

Expected outcomes:

- Identification of host factors that predispose to drug resistance.
- Creation of models and scenarios explaining epidemics of drug resistance.
- Identification of predictors of acquired and primary drug resistance in humans.
- Quantification of risk factors for transmission of MDR/XDR *Mtb* strains.
- Development and measurement of validated transmission reduction strategies in community and health care settings and recommendations of viable control strategies for host countries.
- Characterization of survival patterns among patients with MDR, XDR, and drug-susceptible TB, and understanding of the host or strain characteristics that affect morbidity and mortality.
- Appropriate and improved management and isolation of TB patients, and protection of health care workers at all NIAID supported international sites.

5. Clinical Management of MDR/XDR TB in Patients With or Without HIV

Effective clinical management of HIV/AIDS patients co-infected with TB is a critical component of the global fight against HIV and TB. HIV infection predisposes to the development of active TB, and TB worsens the prognosis of AIDS. Limited expertise has been gained to date in the management of MDR/XDR TB in general, and in particular in HIV co-infected persons. Critical components of the management of MDR/XDR TB are to improve our understanding of whether 1) the extent of disease and the degree of immune suppression affect the response to HIV and TB therapy; and 2) whether

these factors contribute to the development of clinical drug resistance to TB therapy. Effective management of MDR/XDR TB in HIV co-infected patients will not only affect the health of the patient, but also limit the spread of TB in this population and in the general community.

Specific Activities:

- 5.1. Evaluate therapeutic options for treating MDR/XDR TB patients with second line chemotherapies in the context of ARV therapy.
- 5.2. Develop common protocols for multi-site studies of XDR TB using updated PK/PD information and expert consultation.
- 5.3. Evaluate the reciprocal effects of HIV and TB treatment on immune reconstitution inflammatory syndrome (IRIS) and the clinical response to each disease.
- 5.4. Determine the influence of HIV-related morbidities (such as diarrhea, mal-absorption syndrome, hepatitis, diabetes mellitus, and parasitic infections) on drug metabolism, on the rate of disease progression and clinical outcomes in MDR/XDR TB co-infected patients.
- 5.5. Evaluate and optimize treatment strategies for HIV and TB in all populations.

Expected outcomes:

- Availability of standardized, effective treatment regimens for MDR and XDR TB.
- Increased understanding of second line TB drug toxicities and options for prevention and clinical management of MDR and XDR TB.
- Increased understanding of the interplay between IRIS and TB therapy in HIV infected patients, and improved management of IRIS.
- Improved treatment success rates and reduction of mortality of MDR and XDR TB patients with and without HIV infection.

6. TB Prevention and Adjuncts to Therapy

Though not available at this time, an effective vaccine is the ultimate goal in the global fight against all forms of TB is. Furthermore, it is not known whether vaccine efficacy would be affected by the strain of *Mtb* or drug resistance phenotypes; thus, evaluation of vaccine candidates against MDR/XDR *Mtb* strains is necessary. In countries with a high incidence of TB, chemoprophylaxis for persons with latent *Mtb* infection has contributed to the decrease in cases of active TB. Studies are underway to determine whether HIV co-infected patients with latent TB may also benefit from TB chemoprophylaxis in conjunction with ART. Chemoprophylaxis for latent TB is available; however, preventive chemotherapy for suspected latent MDR/XDR TB remains to be investigated. Additionally, synthetic vaccines also have the potential to contribute to chemotherapeutic regimens for active TB and shorten the duration of treatment, and are therefore gaining support in the research community.

Specific Activities:

- 6.1. Expand efforts to develop transmission-blocking chemo-preventive/vaccination strategies for MDR/XDR TB outbreaks.
- 6.2. Expand efforts to investigate optimal use of available vaccines and develop vaccines for use in MDR/XDR TB outbreak situations.
- 6.3. Assess the importance of factors associated with MDR/XDR *Mtb* strains and strain variability on vaccine efficacy.

- 6.4. Expand efforts to investigate preventive chemotherapy, particularly for MDR/XDR TB and in HIV co-infected patients and children.
- 6.5. Expand research on antigens and adjuvants for open access to the research community.
- 6.6. Assess the impact of immunomodulatory therapy on both host defense and vaccine efficacy.
- 6,7. Utilize clinical samples from vaccine trials for systematic and extensive mechanistic studies of immune responses to vaccines.

Expected outcomes:

- Vaccine efficacy models for evaluating activity against diverse MDR/XDR TB strains.
- Animal models to assess vaccine candidates that prevent infection and block transmission.
- Surrogates/correlates of protection to estimate TB vaccine efficacy.
- Effective chemoprophylaxis against MDR/XDR TB, HIV co-infected persons and children.
- Adjunctive therapies for MDR/XDR TB

TABLE 1

AVAILABLE RESEARCH PROGRAMS AT NIAID TO ADDRESS RECOMMENDED ACTIVITIES

(see also <http://www3.niaid.nih.gov/research/resources/>)

<i>Activity</i>	<i>Resource/URL</i>	<i>Contact</i>
Investigator initiated grant applications in all areas of TB and HIV/TB research. Response to currently active Initiatives for fundamental and translational science in MDR/XDR TB.	NIAID's Biodefense & Emerging/Reemerging Infections Programs that include Category C organisms; Partnership initiatives for the development of product candidates: www3.niaid.nih.gov/Biodefense/Research/funding.htm#B	
Screen for and test new drug candidates in <i>in vitro</i> microbiological assays and in animals.	Screening, microbiological activity, animal testing and preclinical development of new TB chemotherapeutics: www.taacf.org/ www.niaid.nih.gov/daids/pdatguide/overview.htm www.niaid.nih.gov/daids/dtpdb/integras.asp www3.niaid.nih.gov/biodefense/Research/invitro.htm http://nihroadmap.nih.gov/raid/	B. Laughon C. Sizemore B. Spinelli M. Kurilla M. Ussery M. Nasr
Evaluate the pharmacology of existing and new drug candidates in animal models of TB disease.	<i>In vitro</i> and <i>in vivo</i> PK/PD models, testing of individual drugs and drug regimens	B. Laughon
Characterize the biochemistry, virulence, <i>in vitro</i> and <i>in vivo</i> growth characteristics and pathogenicity of drug-resistant <i>Mtb</i> strains	Animal models of <i>Mtb</i> infection and disease, histopathology, generation and testing of mutant strains http://webhost.nts.jhu.edu/target/	C. Sizemore
Characterize the genome and drug resistance markers of drug-resistant <i>Mtb</i> strains	Sequencing, molecular genetics, bioinformatics www.niaid.nih.gov/dmid/genomes/brc/ www.niaid.nih.gov/dmid/genomes/mscs/default.htm www.niaid.nih.gov/dmid/genomes/pfgrc/default.htm www.niaid.nih.gov/dmid/genomes/prc/	M. Giovanni
Partner with on-going clinical trials to access human specimens for the evaluation of new diagnostic tests relevant to MDR/XDR	www3.niaid.nih.gov/research/topics/HIV/prevention/clinical/default.htm www.case.edu/affil/tbru/trials.htm	B. Laughon M. Makhene G. Jacobs
Correlate human immune response genes with susceptibility to <i>Mtb</i> infection and disease for TB and	Population Genetics Contract	N. Nabavi

Activity	Resource/URL	Contact
MDR/XDR TB		
Extend TB T cell epitope prediction algorithms to include common HLA molecules found in MDR/XDR TB endemic regions	Epitope Discovery Contract	A. Deckhut Augustine
Expand TB T cell epitope discovery efforts to include MDR/XDR TB infected persons and household contacts	Epitope Discovery Contract.	A. Deckhut Augustine
Compile existing B cell and T cell epitope information from <i>Mtb</i> strains to identify points of possible variation and inform diagnostic development	Immune Epitope Database and Analysis Resource www.immuneEpitope.org	A. Deckhut Augustine
Accelerate production of CD1b molecules for tetramer production and characterization of host immune responses to vaccines or natural infections with all forms of TB.	NIH Tetramer Facility www.niaid.nih.gov/reposit/tetramer/index.html	A. Deckhut Augustine
Test addition of vaccine candidates to chemotherapy in animal models of TB	Murine and guinea pig models of infection and disease, immune assays www.cvmb.colostate.edu/microbiology/tb/top.htm	C. Sizemore
Evaluate adjuvant candidates in therapeutic and preventive studies in animals.	Adjuvant Discovery Program Murine and guinea pig models of infection and disease, immune assays www.cvmb.colostate.edu/microbiology/tb/top.htm	D. Winter C. Sizemore
Support analysis of human immune responses to and immunopathology of TB to inform surrogate marker and vaccine development.	Human Immunology Centers	H. Quill
Access to appropriate NIAID Clinical trials contracts	Leverage resources through participation in on-going trials with new product candidates (vaccines, diagnostics, drugs)	M. Makhene R. Mason
NIAID DIR clinical protocols	Template protocols for MDR and XDR tuberculosis http://clinicaltrials.gov : NCT00341601, NCT00425113, NCT00374517	M. Paulson

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