Evidence for treatment policy for HIV-infected tuberculosis patients
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>4FDC</td>
<td>four fixed-dosed combination</td>
</tr>
<tr>
<td>AHRI</td>
<td>Armauer Hansen Research Institute</td>
</tr>
<tr>
<td>ART</td>
<td>antiretroviral therapy</td>
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<tr>
<td>ARV</td>
<td>antiretroviral</td>
</tr>
<tr>
<td>CIDA</td>
<td>Canadian International Development Agency</td>
</tr>
<tr>
<td>DOTS</td>
<td>Directly Observed Treatment Short-course</td>
</tr>
<tr>
<td>DOTS Strategy</td>
<td>The WHO-recommended strategy for detection and cure of TB including: political commitment, microscopy services, drug supplies, surveillance/monitoring, and directly observed treatment</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
</tr>
<tr>
<td>FDA (US)</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FDC</td>
<td>fixed-dosed combination</td>
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<tr>
<td>GCLP</td>
<td>Good Clinical Laboratory Practice</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GDF</td>
<td>Global Drugs Facility</td>
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<tr>
<td>GFATM</td>
<td>Global Fund to Fight AIDS TB and Malaria</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>HAART</td>
<td>highly active antiretroviral therapy</td>
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<tr>
<td>IRIS</td>
<td>immune reconstitution inflammatory syndrome</td>
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<tr>
<td>JCB</td>
<td>Joint Coordinating Board</td>
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<tr>
<td>KEMRI</td>
<td>Kenyan Medical Research Institute</td>
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<tr>
<td>MDGs</td>
<td>Millenium Development Goals</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant tuberculosis</td>
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<tr>
<td>MRC</td>
<td>Medical Research Council (South Africa)</td>
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<tr>
<td>NIMR</td>
<td>National Institute of Medical Research (South Africa)</td>
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<tr>
<td>NTP</td>
<td>national TB control programmes</td>
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<tr>
<td>PDT</td>
<td>product development team</td>
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<tr>
<td>PEPFAR</td>
<td>(US) President's Emergency Plan for AIDS Relief</td>
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<tr>
<td>PK</td>
<td>pharmacokinetic</td>
</tr>
<tr>
<td>PMTCT</td>
<td>preventing mother-to-child transmission</td>
</tr>
<tr>
<td>Q1/Q2/Q3/Q4</td>
<td>quarters by year</td>
</tr>
<tr>
<td>QA</td>
<td>quality assurance</td>
</tr>
<tr>
<td>SAPIT</td>
<td>Starting Antiretrovirals at Three Points in Tuberculosis (South Africa)</td>
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<tr>
<td>SIDA</td>
<td>Swedish International Development Cooperation Agency</td>
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<tr>
<td>SSCC</td>
<td>Serial sputum colony counts</td>
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<tr>
<td>STAC</td>
<td>Scientific and Technical Advisory Committee</td>
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<tr>
<td>SWG</td>
<td>Scientific Working Group</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<tr>
<td>UNDP</td>
<td>United Nations Development Program</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children's Fund</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>UTH</td>
<td>University Teaching Hospital (Zambia)</td>
</tr>
<tr>
<td>UVRI</td>
<td>Uganda Virus Research Institute</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>Extremely drug-resistant tuberculosis</td>
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</table>
This business line aims to produce the evidence needed to drive the management and delivery of TB/HIV care guidelines in disease-endemic settings.

**Global context and needs**

Despite improved availability of TB drugs through the WHO Global Drugs Facility (GDF) mechanism for anti-TB chemotherapy and the universal scale-up of antiretroviral medicines, developing countries are confronted by a soaring disease burden of HIV-driven TB as well as limited evidence on case management strategies – factors which challenge resource-limited health systems to cope effectively.

The Global Plan to Stop TB (2006-2015) recently announced by the STOP TB Partnership presents a major opportunity to address this need. The Global Plan aims to reduce TB incidence, in line with the Millennium Development Goals (MDGs), halving TB prevalence and deaths by 2015 in comparison with their level in 1990.

The Global Plan is underpinned by an investment in research of some US$ 9 billion. As part of this Global Stop TB research movement, TDR is supporting the development of a research agenda addressing unmet needs of HIV-infected TB cases.

In 2007, there were an estimated 9.27 million new TB cases globally, of which 1.37 million cases, or 14.8%, were in people who were HIV-infected. According to WHO, 79% of HIV-infected TB patients live in sub-Saharan Africa, and the annual trend in TB incidence almost parallels HIV prevalence in some countries of sub-Saharan Africa.

This concomitant occurrence of TB with HIV provides an acute need to define optimal timing of ARV therapy during TB treatment and to find alternatives to current drug regimens (particularly those with rifampicin) in order to minimize side-effects from drug interactions.

Independent of HIV status, the long duration of TB treatment is an obstacle to effective TB control. Fluoroquinolone-containing regiments may allow for simpler, shorter regimens; however, these must be evaluated in clinical trials. Similarly there is a need to evaluate the safety and efficacy of fixed-dose combinations of TB chemotherapy in mixed populations of HIV-infected and uninfected TB patients, as well as bioavailability studies.

Another key unmet need is research addressing the frequent occurrence of IRIS (immune reconstitution inflammatory syndrome), especially in TB patients with advanced HIV-related immune deficiency.

Finally, there is a need to invest in basic research to identify biological or pathogen surrogate markers that would facilitate the monitoring of disease and treatment response; identification of such markers could potentially accelerate treatment evaluation, shorten clinical trials and potentially accelerate drug registration.
Strategic objectives

TDR’s new approach to TB/HIV research has been developed in consultation with major research and policy actors to reflect unmet needs in the current global research agenda and, in particular, to respond to the growing burden of TB fueled by the HIV pandemic. Strategic objectives of this business line (BL) aim to provide evidence through the following activities by 2013:

1. Developing evidence to shorten and simplify the treatment of TB in HIV-infected TB patient populations.
2. Developing evidence for timing and optimal management of HIV-infected TB patients.
3. Implementing optimal case management approaches and treatment strategies in resource-limited settings of high-burden countries, in support of the scale-up of antiretroviral therapy (ART).

Partnerships and stakeholders

The alliance with the Stop TB Partnership represents an unprecedented opportunity for major research efforts to be initiated in the control programme context. It provides strong leverage for resources and global consensus for action. Synergies with other role players will be attained quickly, and TDR can position itself to provide intellectual leadership in this field. In leading an initiative, TDR has several comparative advantages including an excellent track record in conducting guideline-informing and quality-assured clinical trials. TDR also is linked to national TB and HIV/AIDS control programmes in high-burden countries and with cadres of nationals trained in conducting research. Also in the context of TDR BL8 activities, other strategic partnerships and synergies have been established with a range of key partners including Merck, GlaxoSmithKline, WHO’s HIV and AIDS departments, the United Nations Development Programme (UNDP), the joint United Nations Programme on HIV/AIDS (UNAIDS), Becton Dickenson, the (US) President’s Emergency Plan for AIDS Relief (PEPFAR), the United States Agency for International Development (USAID), UNICEF, the World Bank, the Bill and Melinda Gates Foundation, the Japanese Ministry of Health and the European Commission.
Progress so far

Progress achieved over the past year has included:

1. Finalization of a first phase of operational research projects on antiretroviral treatment scale-up with five HIV/AIDS high-burden countries, with Zambia and United Republic of Tanzania moving rapidly to incorporate findings into policy and develop Phase II research plans.

2. Attainment of target recruitment for the Phase III clinical trial of a shorter (four-month) and simplified TB regimen including gatifloxacin.

3. All target milestones have been met for clinical trials testing: 1) safety and efficacy of concomitant use of highly active antiretroviral therapy (HAART) in HIV-infected TB patients, and 2) safety and efficacy of a four fixed-dosed combination of TB drugs (4FDC) in HIV-infected and HIV-uninfected TB cases.

4. Publication of three reports from expert consultations on biomarkers, immunomodulation and potential new TB drugs for HIV-infected patients. These reports are intended to stimulate new research and further examination of gaps that need to be addressed for the development of policy. (These and other publications are listed in section 6.1.)

Empowerment, stewardship and leverage

TDR’s strategies reflect the priorities of national TB/HIV control programmes in low-resource settings and embed the evaluation and deployment of new interventions into health systems, along with a culture of research. This helps ensure that research findings will be translated into policy. Already as a result of research activities in 2008, there have been documented improvements in routine TB control programme function of partner countries, including improved case detection for TB and optimized adherence for patients on treatment. The health ministries of partner countries also have contributed staff and staff training, laboratory services and funds to build and equip laboratory facilities and offices for TDR co-sponsored studies. These contributions have been recognized as valuable by partners such as the Stop TB Partnership, whose Executive Secretary in 2008 visited one of the TB-HAART study patient recruitment sites, Temeke Hospital in Dar-Es-Salaam, United Republic of Tanzania.
1. Context, strategic objectives and framework

1.1. Context and rationale

Launch of the new Global Plan for TB Control has positioned the Stop TB Partnership to address the TB epidemic with one of the most comprehensive initiatives in recent history. A new global plan for research is part of the overall initiative, which is underpinned by a planned investment of some US$ 9 billion. In this context, the Partnership has asked TDR to contribute to the development of a research agenda and to the operational deployment of new tools (drugs, vaccines and diagnostics) together with national TB programmes (NTPs) and other key players.

Particularly in sub-Saharan Africa, HIV infection is now a major factor driving the TB epidemic. In 2007, there were 9.27 million new TB cases globally (of which 4.06 million had a smear-positive diagnosis), and the number of prevalent cases was 13.7 million. Among these 9.27 million new TB cases, WHO estimates that around 1.37 million were HIV-positive, with the African Region accounting for 79% of HIV-positive TB cases. Most of the remaining cases are in the South-East Asia Region, mainly in India.

Nigeria and South Africa are among the five countries with the highest global incidence of HIV-infected TB. Certain African countries also account for

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* WHO’s member states are divided into six regions globally: the Eastern Mediterranean Region (EMR), African Region (AFR), the South East Asia Region (SEAR), the Western Pacific Region (WPR), the American Region (AMR) and the European Region (EUR). Also abbreviated are the United Republic of Tanzania (UR Tanzania) and the Democratic Republic of Congo (DR Congo). Source: Global tuberculosis control: surveillance, planning, financing. Geneva: WHO, 2008
a strikingly large number of HIV-infected TB cases relative to their population. South Africa, for example, has 0.7% of the world’s population but 31% of the number of TB cases in the African Region.3

This synergistic coexistence of TB and HIV, ranging from 35–70% of TB cases in sub-Saharan Africa, implies the need to manage both diseases simultaneously. In HIV-infected TB patients, the management of TB alone, without concomitant HIV treatment, is associated with increased mortality during TB treatment.

In spite of intensive efforts to apply the DOTS strategy and meet global targets for effective TB control, at the end of 2006 only 61% (target 70%) of infectious TB cases were detected and 84.7% (target 85%) of detected infectious TB cases were successfully treated. Detection and cure rates are lower in sub-Saharan Africa and other high HIV-prevalence settings. Despite the improved availability of TB drugs through the WHO Global Drugs Facility mechanism (GDF for anti-TB chemotherapy) and the universal scale-up of antiretroviral medicines, resource-limited countries remain constrained in their ability to cope with HIV-driven TB. The convergence of the TB and HIV/AIDS epidemics, as well as rapid emergence of multiple drug-resistant (MDR) TB and extremely drug-resistant (XDR) TB, imply a need to consider innovative treatment approaches.

In 2005, TDR initiated a priority-setting exercise in consultation with international TB and HIV/AIDS research experts. The resulting Scientific Working Group Report on Tuberculosis (TDR/SWG, 2006) was endorsed by the WHO Stop TB Department. The report set an agenda of research needs including:

• Defining the optimal timing of ARV therapy during TB treatment.
• Finding alternatives to current TB drug regimens (particularly rifampicin) that minimize drug interactions with first-line HIV drugs.
• Testing, developing and registering fluoroquinolones that may open possibilities for simpler and shorter regimens.
• Rapidly addressing other research gaps at both “upstream” and “implementation” ends of the research chain. These include: stimulation of research on TB biomarkers that could contribute long-term to improved TB diagnosis and case management; research to understand and address immune reconstitution inflammatory syndrome (IRIS) in HIV-infected TB patients treated concomitantly; verification of safety and efficacy of fixed-dose TB drug combinations (4FDC) already on the market; and definition of optimal case management and treatment approaches for antiretroviral therapy (ART) scale-up among HIV-infected populations (TB +/-) in resource-limited settings.

Looking forward, there also is a compelling need to anticipate and plan for future TB research needs in light of new and emerging trends, e.g. the impact of social factors such as climate change and migration on TB transmission and the need for more rapid development of evidence-based responses to care and management of HIV-infected TB populations ahead of policy decisions.
1.2. Strategic objectives

In response to the aforementioned needs and issues, the goal of this business line was defined as follows:

**To develop evidence for optimizing treatment and case management of TB and TB/HIV co-infection, informing planned standard treatment guidelines revision with respect to three strategic objectives and associated end-products.**

**Objective 1: Develop evidence to shorten and simplify the treatment of TB in HIV-infected TB patient populations by year 2013**

- Shorten TB treatment duration to four months, and register a fluoroquinolone based-fixed-dose anti-TB regimen (2010).

**Objective 2: Develop evidence for timing and optimal management of HIV-infected TB patients by year 2013**

- Evidence base established for concomitant treatment and optimal timing of HAART therapy in HIV-infected patients with newly diagnosed TB (2013).
- Regulatory approval by the FDA and other relevant regulatory bodies in TB high-burden countries secured for the use of rifabutin-containing TB regimen (rifampicin-free regimen) for management of HIV-infected TB patients failing 1st line ARVs (2013).*
- Surrogate markers of TB disease activity identified and evaluated for improvement of case detection, facilitation of the monitoring of response to treatment including the determination of cure, and the detection of relapse, potentially leading to shortening of the observational phase of TB clinical trials (2013).**
- Efficacy and safety data developed on identified immunomodulatory candidates used as adjuncts to TB chemotherapy (2013).***
- Improved understanding of the immunopathology of IRIS, its determinants and biological predictors (2013) ****

**Objective 3: Operational implementation of case management approaches and treatment strategies in resource-limited settings of high-burden countries, in support of the scale-up of antiretroviral therapy (ART) by year 2013**

- Evidence base established for treatment guidelines and optimal access to care for HIV-infected TB patients (paediatrics, pregnant and nonpregnant women). Preliminary evidence developed Q4 2008 and further follow-up activities to evaluate and disseminate the interventions proposed at programme level will be ongoing until Q4 2010.
- Enhanced research capacity embedded into national control programmes of the five countries participating in research, in a manner that is country-owned (2013).

*, **, ***, **** These aspects of Objective 2 are in the BL8 business plan and have specific and relevant research questions defined, and are awaiting funding.
1.3. Strategic framework and operational approach

Table 1 (see next page) notes the indicators for end products and indicators for outcomes that are a measurement of the BL’s performance.

This business line’s strategic model works through existing TB control and research structures within target countries. This model “embeds” research activities within the routine operational activities of the national TB control programmes (NTPs). The model aims at improving the delivery framework of national programmes through optimization of systems and improvement of outreach facilities, and through twinning of traditional research institutions with NTPs. Expertise of national programme staff not previously trained in research methods is thus enhanced, and at the same time the culture of research, which enhances service delivery, is reinforced. The model also has stimulated national governments to develop TB/HIV treatment centres in areas where such facilities did not exist to accommodate the research studies and simultaneously support ART scale-up.

The model therefore accommodates another important strategy of TDR and the Stop TB Partnership, referred to as “retooling”. This is a framework for catalysing accelerated introduction of new health technologies into TB control programmes, targeted at global- and national-level policy-makers and practitioners. As compared to a classical research model, a “learning by doing” culture, as per the model described here, also ensures stakeholder engagement early in the process of evidence development. Evidence generated may thus be perceived as more relevant than knowledge developed in a more classical (academic) model – however important the latter still may be. The empowerment of a cadre of nationals also promotes research leadership and ensures that policy will be updated continuously through the provision of appropriate evidence testable at the delivery phase in “real-life” settings. However, in developing such a model other challenges are evident, particularly the enormous training requirements needed to maintain quality and standards.
Objectives | End-products (by 2013) | Indicators for end-products | Outcomes | Indicators for outcomes |
---|---|---|---|---|
1. Development of evidence to shorten and simplify the treatment of TB in TB- and HIV-infected TB patient populations | Clinical trial data showing safety, efficacy and improved adherence of shorter and simplified TB treatment in TB- and HIV-infected TB patient populations | 1. Registration of 4FDC including gatifloxacin for four-month TB treatment 2. Evidence of safety and efficacy of 4FDC in HIV+ TB cases | 1. Adoption and implementation of evidence for policy by high-burden countries 2. Improved safety and efficacy in mixed populations of HIV+/- TB cases | 1. Number of new countries adopting policy for new drug treatment 2. Number of new countries adopting policy for 4FDC in mixed HIV+/- TB populations |
2. Development of evidence for optimal management of HIV-infected TB patients | Completion of Phase 4 clinical trials conducted by 4 national programmes, showing safety and efficacy of concomitant use of TB-HAART therapy in HIV-infected TB patients | Peer-reviewed publication of evidence on optimal timing of concomitant TB-HAART therapy, and adoption into policy by national programmes involved in trial | Adoption and implementation of policy for optimal timing of concomitant TB-HAART therapy in high-burden TB/HIV countries | Number of countries adopting and implementing policy for optimal timing of concomitant TB-HAART therapy |
3. Safe scale-up of ART in resource-limited settings | Evidence from operational research in five countries to optimize scale-up of ARTs, 2009 | Peer-reviewed publication of research evidence and adoption by national programmes involved in study | Adoption and implementation of policy for optimized scale-up of ART in high-burden countries by 2015 | Number of countries adopting and implementing policy for optimized scale-up of ARTs |
2. Key stakeholders, roles and responsibilities

2.1. Stop TB Partnership

The Global Plan to Stop TB 2006–2015, developed by the Stop TB Partnership, presents a major opportunity to initiate and conduct research of direct relevance to urgent TB control needs. The Global Plan sets out plans for the coming decade designed to reduce TB incidence in line with the Millennium Development Goals (MDGs) and to halve 1990 TB prevalence and deaths by 2015. The new Global Plan is underpinned by a planned investment of some US$ 9 billion to be earmarked for research and development over the coming decade. This represents an unprecedented opportunity for major new research efforts to be initiated in the control programme context.

Together with TDR, the Partnership has launched a global Stop TB research movement. The Partnership has asked TDR to contribute to the development of a research agenda and the operational deployment of new tools (drugs, vaccines and diagnostics) within NTPs and in conjunction with other key players.

WHO's Stop TB Department also links to TDR activities at operational level through a range of activities. These have included the joint conduct of expert meetings and development of a joint agenda for priority research, as reflected in the report of the TDR/WHO co-sponsored Scientific Working Group on TB (TDR/SWG, 2006), and the identification of global TB control needs that will drive appropriate research activities. The Stop TB Partnership, through its research working groups (vaccines, diagnostics and new drugs) and the Special Task Force on Retooling, engages with this BL to ensure the development of “real-life” research activities in response to the global needs.

2.2. National stakeholders

As noted, the strategic model emphasizes embedding of activities in national TB and HIV/AIDS control programmes of participating countries. Therefore, the most key stakeholders for this business line are NTPs of target TB and HIV/AIDS high-burden countries. TDR's TB/HIV research agenda reflects the concerns of these NTPs and accommodates their evaluation and deployment of new interventions and strategies within the context of their operational capabilities. TDR's links with NTPs and its regionally based clinical coordination research support network will facilitate real-life evaluation of the effectiveness and feasibility of the proposed interventions.

The countries in which BL activities are ongoing have been chosen from the high-burden countries identified by the Stop TB and HIV/AIDS departments of WHO. A complete listing of countries where clinical research projects are ongoing is provided in Annex 6.5. Considerations for the country and site selections include:

- High disease burden for both TB and HIV/AIDS;
- Consultation with NTP managers of the African countries identified by the Stop TB partnership and department as being a part of the 22 high-burden countries contributing to 80% of the global TB burden;
- Consultation with the Stop TB Department and the Partnership regarding countries currently receiving quality-assured anti-TB medications supplied by the Global Drug Facility (GDF) of WHO;
- Availability of laboratory support infrastructure or access to the nearest laboratory facilities with uncomplicated logistical access for patients and sample movement;
2.3. Donors and other partners

In addition to the donors which provide undesig- nated funding to TDR as a whole, UNDP, USAID, the Swedish International Development Coopera- tion Agency (SIDA) and the Canadian International Development Agency (CIDA) have provided direct financial support to the activities of BL8. Other key partners in study conduct and development of evidence for policy include the following:

- Pharmaceutical industries: Merck, GlaxoSmith- Kline and Lupin Pharmaceuticals are key suppliers of clinical trial materials and development of safety profiles.

- Academic institutions: University College Lon- don; Medical Research Council (MRC), South Africa; National Institute of Medical Research (NIMR), South Africa; Armauer Hansen Research Institute (AHRI); Kenyan Medical Research Institute (KEMRI); the United Kingdom MRC; and the Uganda Virus Research Institute (UVRI) are partners in providing technical support for several clinical studies.

- Partnership activities continue with WHO’s Stop TB and HIV departments. The recent creation of a research focal point within the Stop TB depart- ment and the Stop TB partnership secretariat presents a good opportunity for initiation of joint activities and exchange of ideas.

- Along with providing support, UNDP has part- nered in development of evidence supporting ART scale-up in resource-limited settings.

- The European Commission has partnered in development of research on neglected priorities.
3. Progress, key achievements and effect on the 2008–2013 plans

3.1. Plan, progress and key milestones

In the context of the strategic objectives already set forward, a Business Plan for 2008–2013 was developed, and the following activities were identified as the highest priorities for immediate action within the context of TDR’s capabilities and experience. These are the only activities currently funded in the TB/HIV portfolio:

- Gatifloxacin TB treatment shortening studies;
- 4FDC safety and efficacy studies;
- TB-HAART studies for optimal timing and concomitant use of anti-TB and ARV treatment;
- Operational/implementation research to optimize the scale-up of ART in resource-limited settings of disease-endemic countries.

Frameworks for monitoring the progress of key activities, and definition of milestones, were defined and presented to last year’s Scientific and Technical Advisory Committee (see Annex 6.3). Over the past year the following milestones have been reached:

1) The initial phase of operational research on antiretroviral treatment scale-up with five HIV/AIDS high-burden countries has been finalized. Countries involved are Burkina Faso, Malawi, Uganda, the United Republic of Tanzania and Zambia. Zambia has already incorporated findings into policy within the country’s PMTCT and TB clinics. The Zambian Ministry of Health and University Teaching Hospital (UTH) are set to explore further (Phase 2) operational research activities to support ongoing treatment scale-up for HIV and AIDS. The United Republic of Tanzania also has developed plans for further activities informed by the initial results.

2) Target recruitment for the Phase III clinical trial on a four-month TB regimen including gatifloxacin has been attained.

3) All target milestones, including expected recruitment targets, have been met for clinical trials of: 1) safety and efficacy of concomitant use of TB-HAART therapy in HIV-infected TB patients (TB-HAART) and; 2) safety and efficacy of a fixed-dosed combination of TB drugs (4FDC) in both HIV-infected and uninfected TB cases. These include meeting the expected recruitment targets for each study at this stage of the trials.

4) Three reports from expert consultations have been published, which are intended to stimulate new research and further examination of: a) the potential role of biomarkers in the management of patients with tuberculosis and the development of biomarkers to predict non-relapsing cure and hence shorter clinical study duration; b) the potential use of rifabutin for improved management of TB in the presence of first-line antiretroviral failure; and c) the potential use of immunomodulation for optimal care of HIV-infected TB cases.

For further details of progress by each area of activity, see Table 2 and Annex 6.3.
### TABLE 2. BL8 MILESTONES AND PROGRESS TOWARD COMPLETION

<table>
<thead>
<tr>
<th>Strategic objectives</th>
<th>Activities (2008–2013)</th>
<th>Milestones and target dates</th>
<th>Progress made</th>
<th>Revised dates (if relevant)</th>
</tr>
</thead>
</table>
| 1. Evidence for TB treatment shortening and simplification | 1.1 Phase 3 clinical trial of 4FDC including gatifloxacin, for four-month TB treatment in five African countries | 1. Completion of multicentre Phase 3 study, Q4 2009  
2. Completion of analysis for Phase 2 serial sputum colony counts (SSCC) trial, Q4 2010  
3. Completion of evaluation of study for evidence base for policymakers, Q4 2014 | Recruitment of 1840 patients in five countries completed October 2008 | On track |
|                      | 1.2 Evidence of safety and efficacy of 4FDC in HIV+patients                              | 1. Completion of patient recruitment, Q1 2009  
2. Interim data analysis, Q1 2009  
3. Completion of the study and data collection on safety and efficacy of 4FDC, Q4 2010 | 1. Patient recruitment near completion (+800 of 996)  
2. Interim analysis in progress | All on track |
<table>
<thead>
<tr>
<th>Strategic objectives</th>
<th>Activities (2008–2013)</th>
<th>Milestones and target dates</th>
<th>Progress made</th>
<th>Revised dates (if relevant)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.2. Pharmacokinetic (PK) TB-HAART w/120-patient sample size</td>
<td>1. Eighty patients recruited for PK study, Q4 2008 2. Completion of recruitment, 2009</td>
<td>PK study slightly delayed due to regulatory re-validation of clinical trial material</td>
<td>Recruitment to be completed Q2 2009 with final results by Q4 2009</td>
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<tr>
<td>3. Operational implementation of improved TB and HIV/AIDS case management and treatment strategies</td>
<td>3.1. Operational research on ART scale-up in five African countries</td>
<td>1. Development of a final report by WHO/TDR for publication, Q1 2009 2. Identification of key lessons leading to next phase and further follow-up studies and evaluations, Q3 2009</td>
<td>Final reports submitted by Burkina Faso, Malawi, Uganda, Zambia, Q3 2008 (except United Republic of Tanzania)</td>
<td>On track</td>
</tr>
<tr>
<td></td>
<td>3.2. Development of research capacity at national programme level</td>
<td>Participating countries demonstrate capacity to conduct and implement operational research activities within national control programmes</td>
<td>A cadre of national control and research officers trained in operational research methods developed</td>
<td>On track</td>
</tr>
</tbody>
</table>
3.2. Implications of progress/delays and global context changes for 2008–2013 plans

The activities of this BL have focused largely on multi-country clinical trials ranging from late Phase 3 to Phase 4 studies. The stringent nature of the recruitment criteria challenged our initial recruitment strategy and led to its modification to meet the recruitment targets. In several instances this has led to an expansion of sites within identified participating countries, and to the consideration of expanding to other high-burden countries. The latter approach is still to be implemented as we explore fully the softer options of within-target country site expansion. The challenges of accelerated recruitment range from financial to human and infrastructural. However, the implications of delaying provision of much-needed evidence for policy and guidelines within NTPs are of far greater concern.

The immediate challenges of recruitment raise broader issues of changes in the global context that need to be addressed. In particular, due to their own need to respond rapidly to new and emerging disease control challenges, TB control programmes cannot wait for classical clinical trials to provide evidence for policy decisions. Evidence-free standard treatment guideline modifications have become common in many high-burden countries. These are yielding unexpected outcomes, both in terms of the proportions of patients attaining target end points for these complex regimens and for safety events, which have increased in frequency as more people access treatment.

In response, there is a need to find innovative approaches to provide evidence for policy more rapidly through clinical trials. One option is a modification of study approaches to approach a “midpoint” between classical regulatory trials and academic trials. Modification of aspects of Good Clinical Practice (GCP) compliance and the development of biosurrogate markers robust enough to predict non-relapsing cure (usually of 18–24 months duration) might potentially shorten study duration and reduce cost. TDR is currently participating in discussions on these topics with its partners, and stands ready to consider other suggestions ranging from interim analysis of already-acquired data to the opening of new study sites in other high-burden countries.
3.3. Planned and proposed activities for 2009 and beyond

Three categories of BL8 activities are: 1) those planned and funded for 2009, 2) those planned as part of the BLs strategic objectives but not yet funded; and 3) proposals for future research directions on current and emerging trends.

3.3.1. Planned and funded for 2009–2010

The following activities, planned as part of BL8 strategic objectives, have funding approval for the duration of the activity:

- Improving the rate of recruitment of all ongoing clinical trials through development of a strategy aimed at optimizing functions across sites (intensified case-finding). This model has been successfully applied in United Republic of Tanzania and Uganda with improved enrolment.

- Developing a new call for operational research activities in support of universal scale-up of ART. The operational research activities present an opportunity for further future engagement with NTPs at the service level. Outputs of each participating country will be integrated into its standard guidelines and policy frameworks.

- Reviewing all expert committee reports on unfunded projects and seeking funding to initiate new activities.

- Identifying training needs of all participating countries and engaging with BL2 in meeting these needs and developing improved quality assurance mechanisms to optimize country-level clinical study procedures.

- Continuing with GCLP training at all sites.

- Engaging with BL7 to optimize TB diagnostics at recruitment sites and to evaluate the impact of optimized TB diagnostics at study sites on overall case detection.

- Clinical audit planned for selected sites to improve site capacity and ensure that procedures are protocol and GCLP–compliant.

- Discussing strategies for improving the human resource base to actualize the activities within BL8.

3.3.2. Planned within current objectives 2008–2013 but not yet funded

With respect to BL8 strategic objective 2, several activities remain unfunded despite a clear recommendation from the TDR Scientific Working Group on TB (TDR/SWG, 2006) that these be pursued in the context of already well-defined research questions. These include:

- Research to obtain regulatory approval by the FDA and other relevant regulatory bodies in TB high-burden countries for the use of a rifabutin-containing TB regimen (rifampicin-free regimen) for management of HIV-infected TB patients failing first-line ARVs (2013).

- Identification and evaluation of surrogate markers of TB disease activity that will improve case detection and facilitate the monitoring of response to treatment, including the determination of cure and detection of relapse – potentially leading to shortening of the observational phase of TB clinical trials (2013).

- Clinical trials to assess efficacy and safety of identified immunomodulatory candidates used as adjuncts to TB chemotherapy (2013).

- Improve understanding of the immunopathology of IRIS, its determinants and biological predictors (2013).
3.3.3. Proposals for future research directions on current and emerging issues (2010–2013)

Issues raised here are not currently part of the BL business plan, but have emerged as areas of concern in the course of implementation so far. Research questions identified would require further refinement through the convening of priority-setting workshops by TDR and its partners.

Climate change, international migration and TB/HIV transmission

Since the convening of the scientific working group in 2005 and development of the BL plan in 2007, the issue of climate change and its impact on health has become a major global priority and a priority of WHO – as reflected in the dedication of World Health Day 2007 to health impacts of climate change (www.who.int/world-health-day/en/). In light of these developments, the Joint Coordinating Board (JCB) and STAC have issued a clear mandate to TDR to explore avenues for conducting research on the impacts of climate change on infectious diseases of poverty and on mitigation and adaptation options.

In relation to TB incidence, it is anticipated that climate change (leading to drought reducing agricultural yields and to flooding of coastal areas, with attendant harms to drinking water supplies) will trigger massive population movements in many African countries. Migration trends alongside poor service provision, crowding of migrating populations and altered “herd immunity” will facilitate the spread of HIV and attendant opportunistic diseases, as well as facilitating efficient transmission of TB variants including MDR TB and XDR TB within vulnerable populations. As a result, gains in infectious disease control achieved over the last half–century, as well as progress towards meeting the MDG goals, may be halted or even reversed.

TDR can proactively anticipate and contribute to efforts at mitigating the above effects of climate change by:

- Commissioning a review of all data on HIV/TB health outcomes from climate change (mini-Cochrane analysis);
- Evaluating the outcomes of predictive models of the outcomes of climate change on infectious diseases and determining gaps for further action;
- Based on evaluation and analysis, defining priorities for engagement by various stake-holders and partners (stewardship function);
- Convening a meeting of experts to outline a plan for essential global research to mitigate and adapt to the impact of climate change on TB/HIV.

Best-practice in primary health care management of HIV-driven TB, as well as in other HIV-driven infections – integrating biomedical studies with operational research on critical socio-behavioural and gender-related factors

An emerging area of concern is the social-behavioural dimension of TB and HIV/AIDS convergence and management, as well as critical gender-related issues of HIV-infected TB patients’ access to diagnosis and treatment. For instance, the current ART entry points for treatment are insensitive to biological differences between males and females, and this may impact on sex-specific morbidity and mortality.

The envisioned TDR research activity would integrate operational research on socio-behavioural issues of disease management with clinical studies of relevant biomedical issues, e.g. systematic documentation of safety information for treatment of co-infection through pharmacokinetic assays and appropriate laboratory evaluations.

An innovative programme of research examining both biomedical and social factors of disease management at the primary health care level would support development of a best practice evidence base for managing TB and TB/HIV co-infected patients, as well for management of HIV/AIDS in conjunction with other (opportunistic) infections such as community acquired pneumonia, pneumocystis carinii pneumonia, cryptococcosis, malaria, hepatitis and leishmaniasis.
4. Leverage, synergies with other TDR business lines and contributions to empowerment and stewardship

4.1. Leverage

In terms of overall financing, the majority of funding for BL8 is provided by TDR, with supporting designated funds from USAID, UNDP, CIDA and SIDA. TDR has continued, as reported last year, to seek more funding from major funding agencies that are operating activities in TDR’s collaborating countries and/or have partnership and technical support agreements with participating NTPs. While this approach is considered important and strategic, it has yet to yield monetary benefits.

The Stop TB Partnership has, however, displayed interest recently in how TDR’s strategies for embedding research in NTPs have improved and optimized TB case detection in the context of clinical trials underway. Interest in building upon this approach may offer the possibility of joint resource recruitment under the auspices of the Partnership’s own global plan and goals. This potential will be carefully explored jointly with the WHO Stop TB Department and the Partnership itself.

Another line of leverage focuses on the development of partnerships at the regional and sub-regional levels. The operational model aimed at “embedding” research activities within the framework of the national control programmes enables TDR access to in-country funds, especially operational research grants provided by the Global Fund to Fight AIDS, TB and Malaria (GFATM). In addition, resources have been leveraged from health ministries of participating countries for patient care, access to complementary medications, in-hospital care and ancillary investigations. TDR’s activities in countries have even stimulated some national government partners to create HIV and TB diagnostic and treatment centres in areas where such facilities did not previously exist, in order to support the universal scale-up of ART access initiative and to accommodate studies undertaken.

Linking activities to national health research institutes also has resulted in the secondment of highly qualified and trained staff and in access to satellite facilities of such institutions at identified recruitment sites. Finally, TDR has been able to leverage transport, laboratory equipment and other logistical support. This is estimated to equal US$ 750 000 – US$ 900 000, including the joint activities conducted with national programmes in five collaborating countries. These efforts will need to be sustained and indicate the feasibility of the operational approach undertaken in carrying out these clinical studies.

4.2. Contributions to global empowerment

As already noted, the core business line research activities are currently being conducted jointly with the national TB and HIV/AIDS control programmes of TB and HIV/AIDS high-burden countries in “real-life” settings, e.g. at the level where patients from the community would normally receive care. This approach has already led to the improvement of skills for a cadre of nationals within NTPs, skills which have developed through TDR studies and collaborations as well as competencies needed to design and conduct research studies.

Additionally, a statistician has been trained and two potential doctoral candidates have been identified from the participating countries who are about to
begin working with studies linked to the TB-HAART research activities. Furthermore, the conduct of these trials has developed a network of clinical trial sites compliant with GCLP guidelines that can be used for future clinical studies. It is expected that through the sustained use of this approach, TDR’s BL8 activities will increase numbers of skilled and trained nationals from disease-endemic countries at both technical and leadership levels.

4.3. Contributions to global stewardship

BL8 has played a major stewardship role through its initiation, conduct and finalization of reports on priority research activities based upon a series of expert meetings it convened or co-convened. These three reports are now available for global consideration, with reference to research priority agenda-setting:

• Report of the expert consultation on immunotherapeutic interventions for tuberculosis;
• Report of the expert consultation on the potential use of rifabutin for HIV-infected TB;
• Report of the expert panel on the use of biomarkers in TB.

Through the stewardship platform, and in line with the long-term objectives set forward in Section 3.3.3, it is the intention of this BL to initiate a review of, and possibly modelling of, the impact of climate change on TB incidence. This would entail the convening of expert panels to review existing evidence and priority activities that would respond to the recommendations of the UN Framework Convention on Climate Change for the health sector (http://unfccc.int/2860.php).

4.4. Elements enhancing sustainability of outcomes

TDR aims at ensuring the sustainability of research outcomes through a strategy of “embedding” research activities within service elements of national programmes so as to ensure uptake, and through the conduct of parallel capacity-strengthening activities already described in the sections on leverage and empowerment.

4.5. Synergies with work of other TDR BLs

The service activities within the Empowerment business line ensure that clinical trials within BL8 receive direct support from BL2 for:

• Preparing for and implementing clinical audits;
• Protocol review and amendments;
• Training of investigators;
• Sourcing and identifying study monitors;
• Trial site preparation and expansion;
• GCP training materials for site investigator reinforcement training.

Future requests and linkages with Empowerment and other TDR BLs relate to:

• Joint activities for country-level operational studies for ART scale-up;
• Training to meet essential service needs within NTPs and provide quality assurance (QA) functions;
• Provision of higher degree study opportunities for national programme staff.

Improvements in TB case detection and adherence to treatment that have been recorded at the recruitment sites of several participating countries illustrate an opportunity and create new collaborative possibilities with BL2 as well as with the business line for quality-assured and accessible diagnostics (BL7). This could involve research demonstrating the impact of optimized microscopy and improved QA mechanisms on case detection.

We further anticipate productive collaboration with BL3 (lead discovery for drugs) through discovery activities for molecules with defined antimycobacterial properties and early Phase 1 studies on potential lead compounds for new TB drugs. Other potential collaborations exist with BL11 (community-directed interventions) in terms of synergising efforts at the community level to scale-up access to treatments and to encourage early diagnosis and improved TB and HIV case detection. Emerging observations about the effect of malaria in pregnancy and on TB/HIV pose challenges that may be addressed through direct collaboration (at least at diagnostic level within primary care centres) with the TDR business line on antimalarial policy and access (BL9).
5. Critical issues and suggested solutions

Challenges faced by this business line include the rapid evolution of scientific knowledge in diverse fora, the prolonged periods needed to generate evidence through classical large-scale clinical trials, and the recent tendency of overburdened NTPs to adopt new interventions even with limited evidence.

For instance, some groups (such as SAPIT in South Africa) have initiated relatively small studies to generate positive indications of concepts such as early initiation of TB-HAART treatment. In light of this, the impact of TDR’s own research on the same issue may be somewhat diminished. This not withstanding, BL8 research activities are poised to make a vital contribution to the global evidence base through a more refined analysis of certain critical questions essential to formal guideline development, e.g. regarding the differential value of early initiation of TB-HAART on specific CD4 strata.

A related issue is the anticipated development of new guidelines and policy changes by several NTPs for earlier initiation of anti-TB and antiretroviral treatment for HIV-infected TB patients. This, in and of itself, could potentially result in ethical concerns about the placebo treatment arm of TDR’s TB-HAART trial. The solution is to accelerate enrolment before implementation of such guideline changes.

In spite of these challenges, it is important to underline the need to systematically collect evidence for future support of guidelines. The emergence of MDR and XDR TB has challenged all the assumptions inherent in the control strategy for TB and has increased the need to closely examine the evidential basis for any revision in treatment guidelines. In that context, the TDR strategy, as reflected by BL8, is of tremendous public health importance.

However, what may be lacking in the BL8 strategy is a simultaneous evaluation of the health systems’ opportunities and constraints in accommodating and optimizing new interventions. An analysis of capacity and cost-effectiveness of the interventions being proposed would serve to highlight their importance and improve the advocacy needed to acquire more resources for these activities.

Another critical issue is the lack of financial and human resources currently available for this BL. In particular, management and monitoring of clinical trials in over a dozen locations across Africa require training of principal investigators and support staff, regular visits by TDR staff to field sites and overall strategic technical input. Several expert panels, including the data safety and management committees of the different studies currently under way and the recently convened Scientific Advisory Committee, have strongly emphasized the need for more resources. The committee in particular was critical of the paucity of the human resource base responsible for this very substantial portfolio.

The need for improved efficiencies in the bureaucracy surrounding fund transfers in the wake of WHO’s adoption of a new Global System of Management is another important issue. The commitment of partner countries to planned activities is undermined when collaborating institutions do not receive promised funds on time. In certain cases, TDR even runs the risk of triggering violations of national regulations for the ethical conduct of trials in countries with ongoing TDR-sponsored clinical studies due to delays in transfers of critical funds. Additionally, since clinical trials are a multi-year process, firm financial commitments from WHO/TDR would ideally be made for the entire trial phase cycle to assure a parallel sustained commitment from country partners. At present, the complex process of annual contract renewal can be problematic for participating countries and health ministries, which need assurance for their own ethical, regulatory and legal processes that when a clinical trial is initiated it will indeed be funded until its conclusion.
6. Annexes

6.1. Publications from BL8 activities (2006–08)


6.2. Scientific Advisory Committee on evidence for treatment policy of HIV-infected TB patients: members and observers

**Members**

- **Dr Faisal ABU-DUHIER**  
  Medical Research Department  
  Ministry of Health, Riyadh,  
  Saudi Arabia

- **Mr Kevin BELLIS**  
  HLSP Ltd  
  Johannesburg  
  South Africa

- **Dr Jeremiah CHAKAYA**  
  Kenya Medical Research Institute, Nairobi,  
  Kenya

- **Dr Abdulamid Isa DUTSE**  
  Aminu Kano Teaching Hospital  
  Kano, Kano State, Nigeria

- **Dr Elizabeth MADRAA**  
  Ministry of Health  
  National AIDS/STB Control Programme  
  Kampala, Uganda

- **Dr Helen McILLERON**  
  University of Cape Town, Medical School  
  Department of Pharmacology  
  South Africa

- **Dr Madhukar PAI**  
  Dept. of Epidemiology, Biostatistics & Occupational Health  
  McGill University  
  Montreal, Canada

- **Dr Robert WALLIS**  
  Pfizer Global Research & Development  
  New London, CT,  
  United States of America

**Observers**

- **Dr Saidi EGWAGA**  
  Ministry of Health, National Tuberculosis and Leprosy Programme  
  Dar es Salaam, United Republic of Tanzania

- **Dr John HORTON**  
  Tropical Projects  
  Hitchin, United Kingdom

- **Dr Roxana RUSTOMJEE**  
  Unit for Clinical and Biomedical TB Research  
  South African Medical Research Council, South Africa

- **Dr Fiona SAMUEL**  
  Poverty and Public Policy Group Overseas Development Institute (ODI)  
  London, United Kingdom

- **Professor Alimuddin ZUMLA**  
  Centre for Infectious Diseases and International Health  
  London, United Kingdom
6.3 Definition of frameworks for monitoring milestones of key activities (2007)

6.3.1. TB-HAART

Fig. 2. Framework for monitoring milestones for TB-HAART drug development
# 6.3.2. 4FDC

<table>
<thead>
<tr>
<th>Generic Stage</th>
<th>Drug development stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Knowledge review</td>
<td>Development decision</td>
</tr>
<tr>
<td>2. Targeted studies to fill critical knowledge gaps</td>
<td>Preclinical toxicology</td>
</tr>
<tr>
<td>3. Initial design of intervention</td>
<td>Human formulation and dosage schedule</td>
</tr>
<tr>
<td>4. Testing intervention under controlled conditions</td>
<td>Phase I trials</td>
</tr>
<tr>
<td>5. Finalization of intervention</td>
<td>Registration / label extension</td>
</tr>
<tr>
<td>6. Testing intervention in real-life settings</td>
<td>Phase IV (safety and effectiveness)</td>
</tr>
<tr>
<td>7. Intervention recommended for disease control use</td>
<td>Drug recommended for control use</td>
</tr>
</tbody>
</table>

![Fig. 3. Framework for monitoring milestones for 4FDC drug development](image-url)
6.3.3. Four-month TB regimen including gatifloxacin

Fig. 4. Framework for monitoring milestones for GAti drug development trial
6.3.4. Operational research for ART scale-up

### FRAMEWORK FOR MONITORING MILESTONES OF DOWNSTREAM RESEARCH (ILLUSTRATIVE FOR BL9,10,11)

<table>
<thead>
<tr>
<th>Generic Stage</th>
<th>Corresponding stage for research on access</th>
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<tbody>
<tr>
<td>7. Recommended for disease control use</td>
<td>Intervention/strategy implemented at scale</td>
</tr>
<tr>
<td>6. Testing in real-life settings</td>
<td>Research on scale up</td>
</tr>
<tr>
<td>5. Finalization of intervention</td>
<td>Intervention/strategy recommended for use</td>
</tr>
<tr>
<td></td>
<td>Interventions/strategy refined</td>
</tr>
<tr>
<td>4. Testing under controlled conditions</td>
<td>Multicentric evaluation of intervention/strategy and its cost-effectiveness</td>
</tr>
<tr>
<td></td>
<td>Pretesting</td>
</tr>
<tr>
<td>3. Initial design of intervention</td>
<td>Design new/improved intervention/strategy</td>
</tr>
<tr>
<td>2. Targeted studies to fill critical gaps</td>
<td>Exploratory research for possible solutions</td>
</tr>
<tr>
<td>1. Knowledge review</td>
<td>Problem/situation analysis</td>
</tr>
</tbody>
</table>

**Fig. 5.** OR for ART scale-up
6.4. Progress and achievements by product areas

1. Evidence base for concomitant treatment and optimal timing of HAART therapy in HIV-infected patients with newly diagnosed TB including co-morbid diseases in all affected populations (including paediatrics and pregnancy) (2013)

Key achievements 2008:
• The recruitment is ongoing in all participating countries.
• Embedded PK study has almost attained the target sample size. Sanofi-aventis requested data on bioavailability for quality assurance of their 4FDC and promised financial support to the study.
• Improved case detection has been recorded by NTPs at TB-HAART recruitment sites through optimization of technician function and the introduction of LED microscopy, including use of the concentration method.
• Several new sites have been opened to accelerate recruitment.
• Service capacity for routine patient care has been upgraded or initiated in several sites.
• Renewal of agreement to manufacture new batches of placebo and active combivir have been finalized with manufacturer.
• Monitoring activities are in place.
• PDT meeting produced recommendations for funding levels and urged approval for the studies to be conducted (May 2008 and May 2009; see PDT summaries and reports).
• Rate of implementation of plans and recruitment targets reviewed at all study site by GCP clinical trial monitor.
• GCP and GLP investigator training was conducted, Q1 2008.
• Several investigators’ meetings were held to review progress and lessons learned.

2. Use of rifabutin-containing TB regimen (rifampicin-free regimen) for management of HIV-infected TB patients failing first-line ARVs (2013)

Key achievements 2008:
• Held an informal expert consultation on the role of rifabutin on management of HIV-infected TB patients who fail first-line ARVs.
• Research priorities were defined with regards to the use of rifabutin for multiple indications among HIV-infected TB patients.
• Negotiations were started with Lupin Pharmaceutical for donation of rifabutin.
• Funding was pursued in ongoing negotiations.
• Efforts were made to develop appropriate questions and definitive protocol.

3. Identification and evaluation of surrogate markers of TB disease activity that will improve case detection and facilitate the monitoring of treatment response, including the determination of cure and the detection of relapse (2013)

Key achievements 2008:
• Held an EC/TDR joint expert consultation on the role of biomarkers in TB/HIV cases.
• Protocol development is ongoing with partners.
• Ongoing negotiations sought funding for these efforts.
• Biobanks are being developed for storage of samples from ongoing trials to facilitate evaluation of identified biomarkers.
4. Efficacy and safety data on identified immunomodulatory candidates used as adjuncts to TB chemotherapy (2013)

Key achievements 2008:

- Pursued funding in ongoing negotiations.
- Study to evaluate the utility of *M. vaccae* in preventing TB among HIV patients now published by collaborators, increasing confidence to evaluate this agent as an adjunctive immunomodulator in HIV-infected TB cases.
- Protocol development with partners continued.
- New collaboration developed with several partners on account of renewed interest in adjunctive immunomodulation, leading to innovative study designs to evaluate the potential utility of immunotherapy for MDR/XDR TB.
- Lupin Pharmaceuticals continues to cooperate with drug provision to and logistics in participating countries.
- All monitoring reports confirmed the adequacy of trial conduct in both participating countries.
- The study has almost attained the target sample size as a result of opening several new sites and optimising functions of programme and research staff.
- Several Good Clinical Laboratory Practice (GCLP) training courses were administered to all investigators in the participating countries, Ethiopia and Nigeria.
- Successful study audit was conducted in Ethiopia and recommendations were implemented.
- Preparations for second DSMC review for interim analysis finalized for Q1 2009.

5. Simplified and shortened duration of TB treatments, including the registration and evidence base for use of a fluoroquinolone-containing fixed-dose combination (FDC) for four months by national TB control programmes (2013)

Key achievements 2008:

- Recruitment targets were met at all sites.
- Adverse events profiles were analysed by Data Safety and Monitoring Board (DSMB).
- Procurement of FDCs for sites was improved.


Key achievements 2008:

- Trial initiation commenced in both participating countries.
- Gained approval from Lupin Pharmaceuticals to manufacture and donate drug supply for expanded weight band.
- Reports received from four of five participating countries.
- Phase 2 quantitative analysis of impediments to ART uptake among PMTCT and TB clients initiated in Zambia, with results planned for 2009.
- Phase 2 studies evaluating an identified adherence tool (quantitative) have been initiated in United Republic of Tanzania.
- Lessons learned workshop and special project team review meeting held to finalize reports and document recommendations from the operational research studies.
- Overall report was finalized and planned for publication as a WHO report, Q1 2009.

7. Implementation research studies within programmes scaling-up ARVs and optimizing TB treatment to improve care and support for people living with TB and HIV/AIDS

Key achievements 2008:

- Reports received from four of five participating countries.
6.5. Investigators, co-investigators and recruiting sites of all BL8 clinical trials and operational research studies

6.5.1 TB-HAART

<table>
<thead>
<tr>
<th>Country (principal investigators)</th>
<th>Recruiting sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Republic of Tanzania</td>
<td>Temeke</td>
</tr>
<tr>
<td>Dr Saidi Egwaga</td>
<td>M'yla</td>
</tr>
<tr>
<td></td>
<td>Amana</td>
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<tr>
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<td>Iringa</td>
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<td></td>
<td>Tanga</td>
</tr>
<tr>
<td>Uganda</td>
<td>Buluba</td>
</tr>
<tr>
<td>Dr Francis Adatu</td>
<td>Iganga</td>
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<td></td>
<td>MildMay Centre</td>
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<td></td>
<td>Bombo</td>
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<td></td>
<td>Mulago Hospital</td>
</tr>
<tr>
<td>Zambia</td>
<td>University Teaching Hospital (UTH), Lusaka</td>
</tr>
<tr>
<td>Dr Peter Mwaba</td>
<td>Chipata</td>
</tr>
<tr>
<td></td>
<td>Kanyama</td>
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<td></td>
<td>Chawama</td>
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<td></td>
<td>Matero</td>
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<tr>
<td>South Africa</td>
<td>Richmond</td>
</tr>
<tr>
<td>Dr Roxana Rustomjee</td>
<td>King George V</td>
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</table>

6.5.2 4FDC

<table>
<thead>
<tr>
<th>Country (principal investigators)</th>
<th>Recruiting sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>St Peter’s Hospital</td>
</tr>
<tr>
<td>Dr Abraham Aseffa</td>
<td>Bole Health Centre</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Mile Four Hospital</td>
</tr>
<tr>
<td>Dr Joseph Chukwu</td>
<td>Aba Health Centre</td>
</tr>
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### 6.5.3 Four-month TB regimen including gatifloxacin

<table>
<thead>
<tr>
<th>Country (principal investigators)</th>
<th>Recruiting sites</th>
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<tbody>
<tr>
<td>Senegal Dr Cheikh Seck</td>
<td>Programme National de Lutte contre la tuberculose, Dakar Fann</td>
</tr>
<tr>
<td>Guinee Conakry Professor Oumou Bah-Sow</td>
<td>Service Pneumo-Phtisologie Conakry, Guinée</td>
</tr>
<tr>
<td>South Africa Dr Roxana Rustomjee</td>
<td>South African Medical Research Council, Durban</td>
</tr>
<tr>
<td>Kenya Dr Joseph Odhiambo</td>
<td>Kenya Medical Research Institute</td>
</tr>
<tr>
<td>Benin Professor Martin Gninafon</td>
<td>Programme National de Lutte contre la tuberculose</td>
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### 6.5.4 Operational/implementation research in support of ART scale-up

<table>
<thead>
<tr>
<th>Country (principal investigators)</th>
<th>Recruiting sites</th>
</tr>
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<tbody>
<tr>
<td>United Republic of Tanzania</td>
<td>Dr Roland Swai NACP, Dar-es-Salaam</td>
</tr>
<tr>
<td>Zambia</td>
<td>Dr Peter Mwaba UTH, Lusaka</td>
</tr>
<tr>
<td>Malawi</td>
<td>Dr Ann Maureen Phoya Ministry of Health and Population, Lilongwe</td>
</tr>
<tr>
<td>Uganda</td>
<td>Dr Wilford Kirungi STD/AIDS Control Programme Ministry of Health Kampala</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Dr Blaise Sondo Comité Ministériel de lutte contre le SIDA Ministère de la santé Ouagadougou</td>
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</table>
6.6. Details of revision of business plans

The business plan did not undergo revision during 2008.

6.7. Responses to specific JCB/STAC requests

This report addresses concerns raised by STAC in 2007 regarding clarity on proposed dates for planned activities, on partnerships and collaborative arrangements especially with the WHO Stop TB Department, and on the basis for selecting countries and sites for planned BL activities.
References/notes


4. The term “health technology” refers to the application of organized knowledge and skills in the form of devices, medicines, vaccines, procedures and systems developed to solve a health problem and improve quality of lives, as defined in WHO 60th World Health Assembly, Fourth Report of Committee B (draft), Geneva, 2007 (A60/62.23, 23 May 2007).


6. The SAPIT study was underpowered statistically. The TDR-sponsored TB-HAART study, still ongoing, is poised to answer more profound questions considered critical to development of formal guidelines. For instance, the TDR study will demonstrate the differential value of early initiation of TB-HAART on specific CD4 strata in terms of improved survival benefits.
The Special Programme for Research and Training in Tropical Diseases (TDR) is a global programme of scientific collaboration established in 1975. Its focus is research into neglected diseases of the poor, with the goal of improving existing approaches and developing new ways to prevent, diagnose, treat and control these diseases. TDR is sponsored by the following organizations: