

Thibela TB

HIGHLIGHTS OF THE YEAR

- » Over 16,000 participants on INH in the largest trial of its kind in the world.
- » Thibela TB wins a Good Clinical Practice Journal inaugural award for excellence in clinical research.
- » Study re-certified by the Data Monitoring and Safety Board as well as ethics committees for 2007/8.
- » The electronic data capture system deployment continues to attract international attention for its scope and innovation.
- » Encouraging data emerges on the safety of INH in TB prevention.

OVERVIEW

During the 1990s, it became clear in the South African gold mining industry that, despite meeting World Health Organization (WHO) targets for tuberculosis (TB) detection and cure, the incidence of TB among employees had risen sharply and was the principal cause of death in the workforce. It was noted, too, that the five-fold increase in the rates of TB coincided with the onset of the HIV epidemic in South Africa. A comprehensive TB prevention programme which included all aspects of the WHO's TB-control strategy, together with x-ray screening, was not succeeding in reducing the incidence of TB. It thus became imperative that an alternative approach be investigated and plans were formulated to research the likely effects of community-wide TB preventative therapy on the incidence rate of TB in the South African gold mining industry.

The aim of the Thibela TB study is to establish whether community-wide isoniazid preventative therapy (IPT), administered to a whole at-risk community, is more effective than TB preventative therapy that is given to high-risk individuals only, particularly those with HIV/AIDS or silicosis. Thibela TB's primary objective is to accomplish a 60% reduction in the incidence of TB in the community-wide IPT arm, compared to the control arm at 90% power. If successful, such a programme will have the added advantage of reducing the transmission of TB between people,

resulting in fewer cases of TB, which will in turn lead to improved control of the disease.

While the Thibela TB study is being overseen and managed by Aurum in South Africa, it is one of three studies designed by the Consortium to Respond Effectively to the AIDS and TB Epidemic (CREATE), of which Aurum is a member. The research being conducted by Aurum, under the auspices of the Mine Health and Safety Council (MHSC) and CREATE, follows extensive consultation and collaboration with three South African gold mining companies, AngloGold Ashanti, Gold Fields and Harmony, and the Departments of Health, Labour, and Minerals and Energy. Extensive discussion and debate has also been held with representatives from the National Union of Mineworkers and other labour unions representing mineworkers to obtain their support for the study.

GENERAL DESCRIPTION OF THE STUDY

This is an open cluster-randomised study, comparing clusters projected to remain operational for at least five years. In the intervention clusters, community-wide IPT will be offered to all employees without evidence of active TB. Each of the 15 clusters recruited, with shaft sizes ranging from 1,000 to 10,000 men, will have sufficient power to address the study objectives.

REVIEW OF PROGRESS

» Regulatory

The first version of the study protocol was initially approved during 2006. During 2007 recertification was obtained and an amendment to the protocol was approved for implementation. A report to the first Data Safety Monitoring Board was submitted in June 2007. Safety data and adverse incidents are routinely reported to the Ethics Committee and Regulatory Authority, as required.

» Project operations

The Thibela TB project team grew to 162 people by the end of 2007, and regional offices were established in Carletonville, Orkney and Welkom. Each shaft in the study is supported by a site team of up to 35 members of staff. 35 shipping containers were converted to mobile study centres, supported by three mobile digital X-ray units, and are now in place at three shafts to accommodate the recruitment and follow-up of participants. By the end of December 2007, full enrollment teams were allocated to three shafts and dispensing teams to five shafts, supporting ongoing follow-up and safety monitoring of participants.

In addition, each study centre is equipped with state-of-the-art IT infrastructure to accommodate electronic data capture and transfer as well as study management. Following the first implementation during





2006, a second acceleration plan to expedite recruitment was formulated and implemented in Welkom during 2007.

A project of this magnitude and complexity requires regular revision as new lessons are learned and challenges are encountered. The protocol is reviewed and amended to accommodate these challenges where necessary. Various standard operating procedures and guidelines support project implementation and these are reviewed on an ongoing basis to ensure compliance with regulatory and protocol requirements.

Sanofi-Aventis continued their ongoing support for Thibela TB by donating all 2007 and future Isoniazid requirements for the study, as part of their Global Access Corporate Social Investment programme.

» **Community mobilisation**

Community mobilisation remains key to the project, and ongoing stakeholder consultation and communication are essential. In recognition of this, community mobilisation teams, each headed by a dedicated community mobilisation officer, are in place at every intervention shaft in the study. These teams are in turn co-ordinated regionally, together with input from regional community advisory groups. Thibela TB enjoys excellent support from all community stakeholders, including organised labour representatives and mining company management. As part of this success, 106 volunteer peer educators were recruited at the first participation shafts, most of whom have completed their training. Volunteers at the remaining shafts are still in training.

Participant advisory groups were established at the intervention shafts and regular meetings with these groups ensure that the project team stays in touch with the opinions of participants. Various launch and incentive events were hosted throughout the year to mark the start of recruitment at intervention shafts as well as to reward enrolled participants for adherence to their treatment plans. These events are always well attended and the spirit of Thibela TB

is clear on the faces of the people in the community.

During 2007, MARKINOR was contracted to test the Thibela brand. A survey was conducted to gauge the opinions of the mineworkers at both the TauTona and Great Nologwa mines as to their general views on health, their perceptions on TB, the Thibela project in particular, and what else they thought should arise from the project. This was done to inform and improve intervention efforts at later clusters, and to build on the community mobilisation efforts that preceded the work at these shafts. Thibela TB has very successfully shifted attitudes towards TB and TB prevention in the community and has created an enabling environment for the successful implementation of the study.

The community mobilisation programme, amongst others, led to Thibela being short-listed for two categories in the inaugural GCPJ Awards, recognizing excellence in clinical research, organised by the International Good Clinical Practice Journal (www.gcpj.com). The categories were:

- » Clinical Trial which Best Promoted Access to Medicine; and
- » Most Innovative Patient Recruitment Strategy.

We are very proud to report that we have received the GCPJ 2007 award in the category for innovative patient recruitment.

» **Data management**

As expected, data management remains a key challenge in such a large trial. Aurum has implemented Phase Forward's fully electronic data management system, InForm, to handle all aspects of the Thibela TB study. There are no paper case report forms in this study and the volumes of data, being handled to world-class standards, are truly immense: the initial estimate of 1.4 million data fields has increased to at least 58 million data fields captured in the course of the study. These follow about 300 unique rules and 840 data edit checks in order to meet

standards of good clinical practice (GCP) and are warehoused in a database that meets international standards for quality and security. The IT infrastructure is unique in the world of health research and is already receiving international attention from other research groups looking at large-scale EDC solutions. Thibela has presented its work in this field to a number of plenary conference sessions around the world.

» **Training**

Staff training remained a priority and during 2007: 5,139 training hours were logged. Training topics included, among others, clinical TB, GCP, data management and capturing, dispensing, and basic IT skills. At the Thibela Academy team members have online access to training material which can also be accessed from training centres at the regional offices. Assessments of identified topics are completed on an ongoing basis to ensure team members comply with training plan requirements.

» **Quality management**

Thibela has developed SOPs and guidelines to support study activities, and has a monitoring team of four who monitor enrolment and follow-up activities on an ongoing basis according to a monitoring plan. The study is also monitored by CREATE and has had three external monitoring visits with only minor issues identified.

Our Thibela monitoring team also monitors service providers on a continuous basis. As part of this programme, the central warehouse for INH storage and distribution as well as the microbiology laboratory were assessed during 2007.

» **Participant enrolment**

After months of preparation and putting systems in place, trained Thibela study workers welcome volunteers at each intervention shaft. Participant recruitment is done at the crush, hostel areas and access

points, on a one-on-one basis. Consenting individuals are screened for active TB using a symptom questionnaire and chest radiograph. Individuals with no evidence of active TB are offered INH. TB suspects have a sputum sample taken for microscopy and culture, and are referred to the mine health service for further management. Participants are given calendars to record their use of the INH. Retention and adherence activities include using peer educators and providing incentives of small value to participants selected at random at a pick-a-box show once a month.

Enrolment is now in full swing in Carletonville, Orkney and Welkom. Towards the end of 2007, more than 16,000 volunteers across Thibela consented to participate in the study and started on INH. This is the largest clinical study group on INH in the world.

STUDY MEDICATION DISTRIBUTION AND SAFETY MANAGEMENT

Dispensing of INH and pyridoxine is facilitated by dispensing teams at intervention clusters. These teams are comprised of health research co-ordinators, assistants and treatment supporters. Health research co-ordinators are all required to complete an accredited dispensing course for health professionals, which leads to applications for dispensing licences for the respective individuals.

Both INH and Pyridoxine are stored in a central warehouse and dispatched to intervention clusters on a weekly basis where they are repacked according to agreed procedures. In total, close to 50,000 units of 30 tablets each have been dispensed to date.

Full dispensing teams are in place at all shafts, dispensing study medication and reviewing participants for adverse effects. Thus far there have been very few adverse events on the medication, providing researchers with new data on the safety of INH in TB prevention.

SUB-STUDIES

Various sub-studies within the Thibela programme collect endpoint and supporting data for the study:

Baseline prevalence surveys

The Thibela protocol calls for individuals in participating clusters to participate in a baseline survey of radiological TB and silicosis. Recruitment began in Carletonville and in Orkney during 2006 and Welkom followed in 2007. Baseline prevalence surveys enroll approximately 1,000 individuals per shaft and continue for several weeks at each participating cluster. This study was completed at eight clusters towards the end of 2007, enrolling 8,355 volunteers.

TB case ascertainment study (TCAS)

This study, the aim of which is to collect data on the primary endpoint of Thibela TB, is initiated for each cluster on the first working day after the last participant has been enrolled on to the baseline prevalence survey. This study approaches everyone who is known to be on full treatment for TB and invites them to participate. The study enrolled 2,095 participants by the end of 2007.

Foundation for Innovative New Diagnostics Study (FIND)

This sub-study, which is being conducted over 24 months, involves the collection of sputum from individuals being investigated for TB by Thibela or mine health services. The study aims to test newer diagnostic techniques for TB as part of a global initiative to speed up the time to correct diagnosis in TB disease management. The study runs concurrently with TCAS. The project team had enrolled 1,170 participants by December 2007.

POLICY AND ADVOCACY

» The mining industry

The Mine Health and Safety Council has been kept informed on the progress of the

study through quarterly reports, meetings, newsletters and site visits. The recently gained support of the Minister of Minerals and Energy will assist in transforming policy in the mining industry with regard to TB preventive therapy. Dr Churchyard is co-authoring international (ICMM) guidelines for HIV and TB in the mining industry in which the value of TB preventive therapy is highlighted.

» The private sector

Aurum has established partnerships with South African Business Coalition on HIV/AIDS (SABCOHA) and the Global Business Coalition. Through representation by Aurum on SABCOHA's Board of Governors, a link with Business Unity South Africa (BUSA) has also been established. Contact has also been made with the World Economic Forum and the International Labour Organisation's HIV department. The use of IPT in the workplace has been actively promoted at all meetings. Dr Churchyard has also participated in an international workshop to develop guidelines for TB preventive therapy in silica exposed workers.

» National health policy and ensuring government support

Thibela has engaged regularly with the National Department of Health on HIV/TB issues and the use of IPT. Dr Churchyard has contributed to the national HIV/TB review, the national TB strategic plan and the national HIV strategic plan. Results of the study will be presented at relevant meetings of South African research institutions to share INH prophylaxis experience with the local research community.

» Transforming research results into global health policy

Results and lessons learnt from the Thibela study have been presented at international conferences such as the World Lung Conference, the EDCTP Conference, and two Phase Forward International Users Conferences.

Dr Churchyard plays a leading role on a number of WHO committees and working groups where the Thibela experience and IPT strategies are shared.

CHALLENGES

1. The magnitude of the Thibela Project

Thibela is a very large public health project, arguably unique in that it is also a clinical trial. The magnitude and complexity of operations and logistics at the real and practical level has uncovered the large variation from the original assumptions which underpinned planning and thinking when Thibela TB was conceptualised. Sharing the lessons learned and operational characteristics with colleagues in the clinical trials and project management industries has left observers amazed at what is being achieved. The team believes it has mastered the complexities and has a sound understanding of what is required to complete the project and what is achievable, provided resources can be found to match the reality rather than the original assumptions.

2. Organised labour

The study staff has established good working relationships with the regional and shaft union structures. The relationship with the National Health and Safety Committee of the National Union of Mine Workers remains robust and honest, positive and constructive. A policy and advocacy co-ordinator has been appointed who focuses on strengthening the relationship with organised labour across the stakeholder spectrum.

3. Uptake of and adherence to IPT

This remains a key challenge for the project team. The community mobilisation and incentive programme has been intensified to support recruitment and

retention activities. Any early evidence of a positive effect of the project on TB rates is likely to have a positive feedback effect on uptake and adherence once communicated to stakeholders.

4. Mine health companies

Changes in senior management of the mining companies and breaks in communication are a risk to the smooth implementation of Thibela TB. The challenge is to identify changes in management timeously and to ensure adequate briefing of the new managers. Organised labour has been particularly supportive in this and delays have been largely averted thus far.

5. Data management

Data management had already emerged as a challenge during the second year of the study. This challenge has grown in year 3 as the strategy for electronic data capture (EDC) unfolds. Despite the substantial cost involved, the project team is satisfied that early outcomes confirm the EDC route to have been the right decision.

The data management system will prove invaluable to the project and its investigators in meeting the important epidemiological and clinical goals the study has set out to achieve. Although it is a state-of-the-art data management system, the Phase Forward Inform EDC system has never previously been used in such a large public health intervention. Modification and additions to the system were required in order for the system to perform optimally.

PLANS

Strategies for improving participant recruitment and adherence are being developed and implemented on an ongoing basis. These include a jingles sound trailer with adherence messages, and a roadshow featuring well-known actors promoting the topics of adherence and the adverse effects of medication.

As a closing note, Thibela TB is, and will continue to be, a mammoth project that persistently surprises all who work towards its audacious objectives. However, it holds out the promise of being an incredibly significant stride forward in the fight to stop TB. This makes all the challenges and constant re-planning worthwhile. Thanks go out to all the team members, both in South Africa and abroad, for their dedication to this task. Viva Thibela TB! Viva!

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