

PROGRAMME REVIEW

Thibela TB



Highlights of the year

- All pilot studies completed
- Sanofi-Aventis agreed to donate INH in a strong show of support for the study's important public health objectives
- Enrolment of participants into the Thibela study began in July; 5,500 volunteers enrolled by the end of 2006
- Markinor study indicates high level of support for and awareness of study amongst mine workers at participating mines
- Study has received support and praise from the Minister of Minerals and Energy
- Investigators from CREATE, Thibela's primary sponsor, met with Thibela staff for the annual CREATE full group meeting

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 in months 13 to 24 after enrolment, 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, this study is one of three designed by the Consortium to Respond Effectively to the AIDS/HIV 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 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.





The Consortium to Respond Effectively to the AIDS/HIV Epidemic (CREATE) was established in response to increasing awareness by TB and HIV experts that innovative and even radical approaches to TB control will be necessary to reverse the alarming trends of the incidences of these diseases which have been exacting a devastating toll on societies in the developing world. CREATE aims to co-ordinate, organise, implement and evaluate novel strategies to reduce the incidence of TB and related mortality in communities with high HIV infection rates.

CREATE is led by the Johns Hopkins University (School of Medicine, Centre for Tuberculosis Research); research partners are Aurum Institute for Health Research, the London School of Hygiene and Tropical Medicine, the Municipal Health Secretariat (Brazil) and the World Health Organisation. The University of Stellenbosch is also involved.

At the XV International AIDS Conference in Bangkok in July 2004, The Bill and Melinda Gates Foundation announced the award of a \$45 million grant to CREATE which will conduct three, large-scale community studies (including the one conducted by Aurum in the South African gold mining industry) over seven years in Africa and South America. As part of this grant, the Aurum Institute will receive \$14 million over five years.

When announcing the three studies, Richard E. Chaisson, professor of medicine at Johns Hopkins University and principal investigator of CREATE stated, "CREATE's community-level studies will assess bold new approaches for driving down skyrocketing rates of TB in areas with severe HIV epidemics."

The findings of the CREATE research portfolio will be used to develop new global policies to combat TB/HIV, a key criterion of projects supported by The Bill and Melinda Gates Foundation. CREATE will make a major contribution to identifying effective strategies to reduce suffering and death from HIV-related TB worldwide.

Visit the CREATE website at:
www.tbhiv-create.org

In addition to the primary objective stated above, various secondary objectives have been formulated to:

- Achieve a reduction of at least 40% in TB case notification rates in the community-wide IPT arm, compared to the control arm in months 0 to 24 following enrolment.
- Accomplish a 60% reduction in the sputum culture prevalence of TB among HIV infected individuals in the community-wide IPT arm compared to the control arm at the end of follow up.
- Identify and communicate trends in TB case notification following intervention, safety of community-wide IPT, all-cause mortality and the prevalence of isoniazid resistance among TB cases.

Four pilot studies have been completed to date, the results and findings of which will guide the parent study.

Review of progress

Regulatory

Final ethics approval was obtained on 19 April 2006 and the study was allowed to proceed. A protocol consistency review was completed in November and an amended protocol will be submitted for recertification early 2007. A report to the first Data Safety Monitoring Board was submitted in June 2006. Safety data and incidents are routinely reported to the Ethics Committee and Regulatory Authority as required.

Project operations

The Thibela TB project team grew to 130 individuals by the end of 2006, 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.

25 shipping containers were converted to mobile study centres, supported by two mobile digital X-ray units, and are in place at three shafts to accommodate the recruitment and follow up of participants. Another 15 will be converted in 2007 to meet study requirements and a third digital X-ray unit will support the Welkom region. In addition, each study centre is equipped with state-of-the-art IT infrastructure to accommodate data capture and transfer as well as study management.

An initial acceleration plan was implemented to facilitate recruitment within project timelines in the second quarter of 2006 and recruitment began in Orkney in the fourth quarter. A second acceleration plan has been formulated to expedite recruitment in Welkom for implementation in early 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. To date, 15 standard operating procedures and 26 protocol guidelines have been developed and are being reviewed on an ongoing basis to standardise project activities. A separate set of data management procedures has been developed to support data management activities.

During the latter half of the year, a truly significant gesture was made by Sanofi-Aventis which will donate all future Isoniazid requirements for the study as part of their Global Access Corporate Social Investment programme. This very welcome undertaking by the pharmaceutical giant signals clear support for Thibela TB, CREATE and the WHO's Stop TB campaign.

Community mobilisation

Community mobilisation remains key to the project and ongoing stakeholder consultation and communication are essential. We will continue to explore ways and means

of achieving effective stakeholder communication.

In recognition of this, community mobilisation teams, each headed by a dedicated community mobilisation officer, are in place at each 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. The remainder 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 through out the year to mark the start of recruitment at intervention shafts as well as to reward enrolled participants for adherence to their treatment plans. On 18 October, the Minister of Minerals and Energy, the Honourable Buyelwa Sonjica, delighted the Thibela team by visiting our study centre at AngloGold Ashanti's TauTona mine and handing certificates to the first, 1000th and 2000th participants in a gesture of appreciation to the mineworkers who are standing up to be counted in the fight against TB.

Towards the end of 2006, a critical group survey of Thibela TB participants was conducted by the independent company Markinor. This survey highlighted the marked shift in attitude towards fighting TB that has come about in the population as a result of the Thibela initiative. What is particularly remarkable is that the shift in attitude has been accompanied by a translation into action, as can be seen from the numbers of mineworkers volunteering to take part in the study.

Thibela TB hosted a very successful CREATE annual meeting in September 2006. Researchers from all CREATE projects,

leadership and core structures met to discuss project progress, challenges and strategies to ensure ongoing progress.

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 on 25 April 2006 in Carletonville and in Orkney on 15 August, and continued for several weeks at each participating cluster.

This survey was completed in three participating clusters, which included four shafts. In all, 2,800 volunteers were enrolled in the baseline prevalence survey during 2006.

Participant enrolment

After months of preparation and putting systems in place, trained Thibela study workers were ready to welcome our first volunteers at the TauTona mine in Carletonville on 17 July 2006. 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 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 in the second region began at Great Nologwa, Orkney, on 6 November. The mine manager and his management team enrolled on 21 November and by the end of 2006, 4,506 volunteers across Thibela were on INH preventative treatment. Their progress is monitored on a monthly basis.

Dispensing

Two full dispensing teams are in place, dispensing study medication and reviewing participants for adverse effects. Up to 150 participants are seen per day.



The first Thibela volunteer



The Thibela drummers



Minister Sonjica, together with Dr Fazel Randera, visits Thibela at AngloGold Ashanti.



INH compliance testing was initiated in October 2007 with individuals being randomly selected for a urine test to confirm adherence or otherwise. Various participant follow up strategies are being implemented and new initiatives are under investigation.

TB Case Ascertainment Study

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 for the cluster. This study approaches everyone who is known to be on full treatment for TB and invites them to participate.

The project team screened 1,109 patients attending TB clinics. Of these, 1,037 were seen by the team and 470 were eligible for enrolment. In turn, 356 (76%) of these individuals consented to participate.

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 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 the TB Case Ascertainment Study. The project team has thus far screened 397 individuals of whom 151 were eligible: 148 (98%) agreed to participate and sputum was collected from 126 (85%).

Data management

As expected, data management was a key challenge during 2006. 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 will 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 will withstand scrutiny for quality and diversity, not only of the study itself but also of the research work which will follow. In all, 16 processes were developed, tested, implemented and are being supported by various service providers to facilitate data capture and management, the IT infrastructure for which is unique in the world of health research and is already receiving international attention. Thibela presented its work in this field to the plenary session of the Phase Forward International user group conference in Las Vegas in October, to critical acclaim.

Training

Staff training was a priority during 2006 and 1,008 hours were spent training the team who collectively attended 3,310 individual training sessions. Training topics included, among others, clinical TB, good clinical practice, data management and capturing, dispensing as well as 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

Regular quality reviews of operations and processes are vital to maintaining GCP standards in any study. Thibela TB follows these principles and, in particular, is breaking new ground in the areas of clinical observational monitoring and source data verification. The data management system plays a key role in this achievement and the team plans to write up the lessons learned.

Six monitoring reports were issued during the second half of 2006 with most findings relating to the informed consent process and study procedures. Corrective action was implemented as indicated. The study was monitored twice by CREATE during the year.

Challenges

- **Organised labour:** The project has received outstanding public support from organised labour, which is a key stakeholder in this project. Activities are monitored and the team liaises closely with the appropriate role players and stakeholders. The lesson here is, however, never to take support for granted and to maintain good communications with all stakeholders throughout the study.
- **Uptake of IPT:** This remains a key, and proven, challenge for the project team. The community mobilisation programme, including recruitment and retention aspects, receives ongoing priority.
- **Data management:** This emerged as a challenge during the second year of the study. Thorough assessment and consultation led to the development of a strategy for the electronic capturing of data. Despite the substantial cost involved, the project team is satisfied that the early outcomes confirm this 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.
- **The project schedule** fell behind as a result of extended stakeholder negotiations during the first year and an acceleration plan to catch up on schedule was implemented in March 2006. This resulted in an increase in the workload of the operational team, particularly given the concurrent activities being conducted in two regions. Careful management was necessary to keep both teams on track and included:
 - The roll-out of a fast track and concurrent communication plan in Orkney

- Duplication of enrolment team resources and facilities
- All target dates for Orkney brought forward by six months
- All target dates for data management were brought forward by six months

- **Co-ordination with health service providers** is proving to be a challenge and issues relating to the confidentiality of participants' health care records require ongoing consultation. Memoranda of understanding documenting the roles and responsibilities of all parties were approved for signature by all three mining companies.

Plans

Strategies for participant recruitment and adherence are being developed and implemented on an ongoing basis, two of which are an SMS campaign and a roadshow featuring well known actors promoting the topics of adherence and the adverse effects of medication.

As a closing note, Thibela is and will continue to be a mammoth project that continues to surprise 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 replanning 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!



Certificate for participant number 1,000



Thibela team members and enthusiastic supporters



Members of the Thibela team