

ZINVID Technical Study Report  
Manhiça Health Research Center  
Final report represents reimbursable costs from 10th of April to 15th of September 2010

The Global Health Bureau, Office of Health, Infectious Disease and Nutrition (HIDN), US Agency for International Development, financially supports this report through TB CAP under the terms of Agreement No.GHS-A-00-05-00019-00.

**Study Title:** Effects of Zinc Sulfate and Vitamin D Supplementation upon the Sensitivity of Tuberculin Skin Tests (TST) among Infants and Children at High Risk for Tuberculosis in Mozambique (ZINVID)

**Contract number:** N/A

**Date of agreement:** July 8<sup>th</sup> 2010

**Principals Investigators:**

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**Period of report 1: 31st of August to 31st of August 2010**  
**Period of report 2: 01st of September to 15th of September 2010**

**Total amount: \$150, 350.00 US**

**Total expense period of report 1 and 2: \$101,831.00 US**

ZINVID is an ancillary study nested in the ITACA study. The main objectives of the ITACA study is to estimate the minimum incidence of TB cases among infants in the Manhiça study area.

ITACA study started recruiting on the 21<sup>st</sup> of June and will finish on the 20<sup>th</sup> of June 2011. So far the ITACA study has recruited 80 infants of whom about 60 children were allocated to the control group of the ZINVID study. Although the contracts ends now, the ZINVID study will continue until we complete the recruitment according to the protocol.

The primary objective of this study (ZINVID) is to assess the proportion of participants positive for infection of TST using two cream supplementation strategies (Zinc sulfate and Calcipotriol- a vitamin D analog) versus conventional methods (TST and IGRA) of detecting TB infection in infants and children at risk.

The secondary objective are: a) to assess the comparative performance of micronutrient supplementation techniques for diagnosing TB infection among children 9-36 months of age in selected subpopulations at risk for immune-suppression of TST:

- a. Those who are diagnosed with *M. Tuberculosis* disease (n≈75)
- b. Those who are household contacts of a smear-positive TB case (n≈400)
- c. Those who have chronic or acute malnutrition (under



*60% weight for height) or failure to gain weight for more than 2 months (n≈400)*  
d. Those *born to HIV+ mothers* (n≈250)

b) To compare the relative cost effectiveness ratio of two distinct micronutrient supplemented TST strategies versus the IGRA for the diagnosis of TB infection in a pediatric population (n≈670).

#### **Study Approvals obtained:**

National Bioethics Committee (CNBS): Ref n° 261/CNBS/10 on July 30<sup>th</sup> 2010

National Drug Authority (NDA) approved on the 6<sup>nd</sup> of October 2010. Ref n° 2147/042.3/DF.

#### **On-site Capacity Building:**

- Quantiferon training was provided by Sebastian Gelderbloem from Aeras South Africa for the six technicians involved in the immunology component of the study. The training was held from the 14<sup>th</sup> to 16<sup>th</sup> July of 2010, funded by under agreement with USAID TB CAP
- The clinical team was trained in TST administration and reading between 9<sup>th</sup> and 14<sup>th</sup> November 2009 by Els Adams (KNCV) and Shireen Surtie (AERAS South Africa) funded by EDCTP grant
- Trainings on gastric lavage and induced sputum techniques were provided by Shireen Surtie between 10<sup>th</sup> and 12<sup>th</sup> May of 2010, co-funded by EDCTP grant
- Case Reporting Forms (CRF\_ completion training done on the 9<sup>th</sup> of September 2010

#### **Expenses:**

USAID TBCAP supported CISM to purchase the following items (see Financial Report) according to the budget and waivers approved by USAID on August 10<sup>th</sup>, 2010:

1. QTF gold tubes
2. Microtainers
3. Other consumables

#### **Study Achievements to Date:**

1. Clinical Trials insurance has been obtained
2. Questionnaires (CRFs) have been finalized
3. ZINVID Open Clinica database ready to use (period of report 2)
4. Study staff at CISM have been trained
5. USAID mission staff have been briefed on study progress and timelines
6. Randomization and blinding schemes have been developed
7. Standard Operating Procedures (SOP) have been drafted and finalized
8. The Data Safety Management has been convened- including the Acting Head of the National Tuberculosis Program, TBCAP partner FHI- Dario Sacur, CDC GAP Director Lisa Nelson, and biostatistics and epidemiological experts from the US and the Netherlands
9. The application to the National Medications Board has completed and approval obtained (period of report 2)
10. Acquisition and consequent delivery of the micronutrient creams to Manhiça has been accomplished. (period of report 2)
11. The randomization envelopes are in place. Sequentially numbered envelopes will be prepared, each containing the allocation of the participant. Each envelope contains 1 or 2 colored papers corresponding to the color of the topic of the dispenser of the creams which should be applied to that child. (period of report 2)
1. The stopping rules have been drafted and shared with the DSMB

The ZINVID will begin to randomize eligible infants to one of three treatment groups starting October 20<sup>th</sup>. Data collection will continue after TBCAP ends and full enrollment will be completed in May, 2011.

### **Delayed Implementation**

There have been several delays in the execution of the micronutrient study. These include challenges both foreseen and unforeseen:

1. As this is KNCV's first randomized double blind clinical trial, it was necessary to find and purchase clinical trial insurance, a specialty product that KNCV's regular insurance carrier did not offer. It took 2 weeks to identify, screen, and negotiate the appropriate coverage to protect KNCV, TBCAP, and USAID
2. As this is a randomized Clinical trial (RCT), it was necessary to establish an independent data safety and management board, which needed to have outside statistical, clinical, and research expertise. This took a week to recruit the expertise.
3. The contract between KNCV and CISM took a bit longer to settle because it was deemed important to establish a clear division between the ZINVID and ITACA study components as well as the study components that are voluntary
4. The KNCV Principal Investigator was not aware of the USAID requirement that equipment over \$5,000 US purchased outside the US requires a waiver. So a waiver was sought on July 14<sup>th</sup> and granted in mid-August
5. The Mozambican National Ethical Review Board had an overflowing agenda for their May meeting and decided to table our protocol review until the June/July meeting. Consequently, the full approval for the study was received on July 29<sup>th</sup>
6. Given that the study is using micronutrient creams for off-label uses in a pediatric population, the study needed to acquire the National Medications Board approval to import and use the creams, even though they are already registered on the national formulary. Written approval took over two months to obtain (October 6, 2010)
7. KNCV was authorized to release funds to CISM in Mozambique on July 19<sup>th</sup>, however the transfer was not completed for an additional three weeks due to technical or communication difficulties between the Finance Units of both entities
8. The US compounding pharmacy contracted to produce the placebo creams and the zinc formulations took over 3 weeks to package the products in the blinded dispensers due to staff holidays
9. There were food riots and a general strike in Maputo in late August which prevented the CISM staff from taking possession of the study creams due to delays in the Mozambican customs clearance department



Despite these delays, the project has moved forward due to positive collaboration among the CISM, KNCV, the National TB Program, FHI, CDC GAP, Aeras Global TB Foundation, and a willingness to provide in-kind and material support to this important study.

To mitigate the impact of the delays, several modifications in the study protocol have been made. A revised protocol has been submitted for review to the National Bioethics Committee to expand the eligible age range from 9-36 months to 9-60 months. In addition, the catchment area of the study

has been expanded to include an additional health center for recruitment. These changes will increase the speed of enrollment and study completion.

### **Outputs & Achievements to Date**

1. The study has increased the capacity of Mozambicans to implement new diagnostics (Quantiferon, gastric lavage, induced sputum) and the CISM is in discussions with other centers to serve as a training site for other institutions that may wish to learn these techniques
2. The study has strengthened the pediatric contact tracing program in Manhica district (previously weak) and enhanced the awareness of the signs and symptoms of TB in pediatric populations
3. The ITACA/ZINVID study has already diagnosed 1 culture positive infant, the first mycobacteriological diagnosis of pediatric TB in the province

Reported by  
Jahit Sacarlal and Ellen M.H. Mitchell  
September 30th 2010

A handwritten signature in blue ink, reading "Jahit Sacarlal", is displayed on a light blue rectangular background.