This project is part of the EDCTP2 Programme supported by the European Union.
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When we designed the HPTN 071 (PopART) study it was revolutionary. The intervention involved reaching out to the entire population — visiting all homes in a community to provide a combination HIV prevention package, and linking to universal treatment for individuals living with HIV. With our previous experience in the ZAMSTAR study we could not ignore TB. And so PopART was designed with a community intervention that mirrored ZAMSTAR’s innovations, but modified according to the lessons we had learned. The scale of this intervention meant that we were testing every member of the population for HIV, as well as screening every member of the population for TB. It was true active case finding.

The TB side of the intervention was not popular with everyone. Many of the study team were much more familiar with working in HIV and so found the TB element of the study difficult to grasp. Our Community HIV Care Providers (CHiPs) also struggled as they were wholeheartedly focused on HIV — collecting sputum proved to be a new challenge. However, we managed to win everyone round.

The TREATS project is so important as it will allow us, for the very first time, to measure the effect of a combination TB and HIV intervention delivered to the entire population in seven urban, high prevalence communities, and to compare this with seven matched communities that did not receive this intervention. It also allows us to measure several endpoints including: the incidence of TB infection in young people; the prevalence of active TB; TB notification and TB disease incidence in a random cohort of 18-44-year-olds. TREATS enable us to bring all this data together in order to understand the epidemiology of TB better.
Working in the field of TB is challenging. Our tools for diagnosing TB infection are limited — this has hampered our understanding of the population dynamics of TB. And the tools necessary for large scale surveys, such as prevalence surveys, are expensive and difficult to use in this setting. The TREATS project will allow us to use the newest available tools to maximise additional scientific value. TB is also a feared and stigmatised disease. A social science component built into the TREATS project will help us understand what worked well and what worked less well in the intervention, and ultimately to better understand stigma related to TB. This will enable us to design better TB services for the future. Mathematical and economic modelling will provide generalisable answers for how we can most effectively undertake these large scale interventions in the future.

For me personally, the TREATS project brings together 20 years of research into a combined strategy — to end both TB and HIV at community level.

It is a unique opportunity to assess an intervention on a massive scale. The TREATS consortium brings together a fantastic team of some of the best TB researchers and modellers, TB diagnostics companies and communications experts in TB. The study, I am sure, will involve many challenges. But it will also provide amazing data, and hopefully practical solutions to end TB.

HELEN AYLES, TREATS PROJECT DIRECTOR
INTRODUCTION

Tuberculosis (TB) is the leading infectious cause of death worldwide. 1.6 million people died of TB in 2017. For people living with HIV, TB is the most significant co-infection. In 2017 an estimated 0.3 million people died of HIV-associated TB. TB continues to disproportionately affect the most vulnerable individuals and communities. If ambitious global goals to ‘End TB’ are to be met, progress to tackle the TB/HIV co-epidemic must be accelerated.

In response to this, the Tuberculosis Reduction through Expanded Antiretroviral Treatment and Screening for active TB (TREATS) trial was launched in November 2017.

TREATS has been set up by a consortium of organisations, some of which are already running the largest ever trial of a combined HIV/TB prevention strategy. This trial, called HPTN071, or PopART, was conducted across 21 communities in Zambia and South Africa, covering around one million people in total. PopART involved universal testing and treatment for HIV through house-to-house visits across the 21 communities on an annual basis over four years — from 2014 to 2018. As part of PopART, all members of these communities were also screened for TB.

Building on PopART, TREATS will measure the impact of a combined TB/HIV intervention — of population level active case-finding for TB, combined with universal testing and treatment for HIV — on TB incidence, prevalence and incidence of infection. The aim is that its findings will help inform new policies and approaches for tackling the TB/HIV epidemic. As the global health community works towards ambitious new goals to ‘End TB’, TREATS’ findings will provide invaluable information for accelerating effective interventions on the TB/HIV co-epidemic.
The project is funded by the European & Developing Countries Clinical Trials Partnership (EDCTP), a public partnership between countries in Europe and sub-Saharan Africa, and the European Union.

The EDCTP programme is supported under Horizon 2020, the European Union’s Framework Programme for Research and Innovation.
THE PROJECT

The TREATS project will measure the TB specific outcomes of the PopART trial and is running for 48 months from November 2017. The project consists of three primary outcomes measures of the burden of TB:

- **Incidence of TB infection** measured in a cohort of adolescents and young adults
- **Prevalence of active TB disease** measured in a prevalence survey of individuals aged 15 years and older
- **An analysis of routinely collected data including TB notification data**

Nested within the study are qualitative and economic data collection and evaluation of improved diagnostic tools for TB. Underpinning these activities are data management and statistical analysis, which will allow rigorous analysis and triangulation of the data which will also be used in mathematical and economic modelling to predict the impact of the PopART intervention on the burden of TB and to estimate the cost-effectiveness of the intervention.

Spanning all of the studies will be capacity development to enhance the capacity of organisations to conduct TB trials, to develop African research leadership and to improve the capacity to conduct epidemiological assessments of TB across the globe.
KEY ACHIEVEMENTS IN THE FIRST YEAR

The TREATS project began on 14-15 November 2017, with the first official meeting of the TREATS consortium.

In the first year of such a complex research project, with multiple partners and delivered across two countries, Zambia and South Africa, it is vital to establish the best practice protocols, processes and procedures in order to ensure the highest quality results possible. This has been a priority for the TREATS project team in this first year.

As well as building the foundations for a strong research project that looks to support the global ambition to ‘End TB’, there have been several key achievements in the first year.

Below are some of these achievements.

THE STUDY ADVISORY GROUP

The TREATS Study Advisory Group was constituted and the first face-to-face meeting took place on 29 October in The Hague. The group oversees study processes and findings and advises on challenges, as well as supporting communication of findings and advocacy. The study advisory board members and affiliations include:

- Dr Wafaa el Sadr, University of Columbia
- Dr Peter Godfrey-Faussett, UNAIDS
- Dr Alasdair Reid, UNAIDS
- Mr Kenly Sikwese, African Community Advisory Board (AfroCAB)
- Dr Andrew Silumesii, Ministry of Health, Zambia
- Dr Gail Andrews, National Department of Health, South Africa
- Dr Beth Engelbrecht, Western Cape Department of Health
ETHICAL APPROVAL

The TREATS protocol achieved ethics approval from national competent authorities and ethics committees in Zambia and South Africa and the London School of Hygiene & Tropical Medicine Research Ethics Committee.

DATA CAPTURE

The data management system for the prevalence of TB survey was successfully designed and tested, enabling data to be effectively captured, synchronised and analysed. The survey participant flows were also finalised and ready for piloting in January 2019. The electronic data capture system was developed and successfully used for the incidence of infection cohort participant recruitment in Zambia and South Africa.
COMMUNITY ENGAGEMENT

In Zambia and South Africa, Community Advisory Boards were established to provide them with an active voice in the TREATS project design and the sharing of its findings. The boards, made up of key community figures, have supported the revision of the informed consent form and communities outreach activities for the infection cohort. The activities include:

• Consultation Meetings
• Door-to-door Sensitisation
• Health Talks
• Community Announcements
INITIAL QUALITATIVE FINDINGS

One key element of the TREATS project is to evaluate the uptake and effect of the PopART intervention on routine TB case notifications and its effect on changing individual, health worker and community behaviours and values towards TB. The qualitative research performed in 2018 has already revealed initial findings.

CLEARER UNDERSTANDING OF BIO-MEDICAL TREATMENT

In all of the study sites, TB is now experienced as more manageable than it was in the recent past. There are fewer explicit links with HIV and death. There is also a clearer understanding of the bio-medical treatment pathway and more optimism about treatment outcomes.

STIGMA OF TB PERSISTS BUT HAS CHANGED

Stigma of TB persists but has changed. There is less of an association with HIV and more links with smoking, alcohol consumption and multiple sexual partners; the risk of casual transmission; poverty; physical frailty; and being identified by others as having TB when accessing care at the health facility.

IMPROVING THE MANAGEMENT OF TB

Encouragingly the PopART study was perceived as galvanising and improving the management of TB across two communities. However, there is little awareness of the impact of TB on mental health and there are very few options for mental health referrals if needed.

ALTERNATIVE TREATMENT OPTIONS

Alternative treatment options were still listed and utilised as TB treatment options in all communities. This included herbal and spiritual traditional medicine and Christian faith healing linked to Pentecostal churches. This was sometimes parallel or alternate to bio-medical treatment.
ENROLMENT SUCCESS IN THE INFECTION COHORT

In Zambia, the enrolment of participants started on 11 July 2018 and the target was achieved in all eight sites by November. As at 31 December 2018, 4,111 households have been enumerated and 2,655 participants (aged 15-24 years) have been enrolled and completed a baseline questionnaire and provided blood samples.

Enrolment in South Africa also started on 25 November and is still ongoing, with 1,462 households enumerated and 322 participants enrolled. This cohort will be followed up for 24 months.

EVIDENCING OPTIMAL DIAGNOSTICS

The TREATS project team held discussions with the World Health Organization Global Task Force regarding the best diagnostic algorithm for the prevalence survey. An intensive diagnostic phase was conducted to retrieve more insight into what the best diagnostic algorithm for prevalence surveys would be.
A member of the mathematical modelling and economics project team received an MRC Career Development Award fellowship for the duration of the project.

Two PhD candidates were selected and registered at the London School of Hygiene & Tropical Medicine to start in January 2019.

One candidate was selected for and registered for an MSc in Medical Statistics at the London School of Hygiene & Tropical Medicine, which began in 2018.

FUNDING AWARD

Additional funding was awarded by Medical Research Council UK Confidence in Concept Scheme, in collaboration with King’s College London, to investigate if extracellular vesicles in the blood (sacs released from cells into blood) can differentiate between individuals with M. tuberculosis infection, active TB disease and healthy controls. The ultimate aim is to develop a diagnostic test to identify individuals at risk of progressing from infection to disease.
THE TREATS CONSORTIUM IS MADE UP OF A PARTNERSHIP INCLUDING:

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