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Tuberculosis (TB) is one of the most deadly infectious diseases worldwide, yet we still have limited drugs, limited research, no viable vaccines and diagnostics that are old-fashioned or expensive.

The advent of HIV unleashed huge increases in TB, particularly in Sub-Saharan Africa. TREATS was conceived to explore whether a ‘universal test and treat’ intervention for HIV known as PopART could reduce the number of people becoming infected with TB, and the overall amount of TB in urban, high prevalence communities.

It was a unique opportunity to assess an intervention on a massive scale. It was made possible through international collaboration with economists, statisticians, modellers, researchers, technology companies, NGOs, TB experts and our funders – the European & Developing Countries Clinical Trials Partnership (EDCTP).

But above all it was made possible by the locally recruited staff who went door-to-door talking with individual households, and the communities who gave us their trust and support. We are immensely grateful to those communities in Zambia and South Africa for allowing us into their homes and for their willingness to support this valuable work.

TREATS took more than four years from inception to completion, overcoming the suspension of fieldwork caused by the Covid-19 pandemic. Crucially, it included social science elements to help us understand the impact of stigma, poverty and mental health on the experience of TB.

This report explains the aims and design of TREATS, analyses the results and explains the importance of the study to the global fight against TB.

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Tuberculosis (TB) is a major infectious cause of death worldwide. In 2018 10 million people developed TB and 1.5 million lost their lives to it even though it is preventable and treatable.

For people living with HIV, TB is the most significant co-infection.

But there was little impact TB incidence. This is largely attributed to the link between TB and poverty, and the impact of the HIV epidemic.

Southern Africa is the epicentre of the HIV epidemic, and HIV has been driving TB infections in the region since it was first identified in the 1980s. While TB levels there had been high for many decades, they were also stable until the arrival of HIV. The new disease drove a fivefold increase in TB in South Africa and many other countries. In most of the countries hardest hit by HIV, TB levels have plateaued and are gradually coming down, but slowly. In 2019 TB was the leading cause of death in South Africa, taking 58,000 lives. Around 36,000 of these were HIV positive.

The World Health Organization (WHO) End TB Strategy aims to stop the global TB epidemic by 2035. The goals are to reduce global TB incidence (the rate of new cases) by 90% to 10 cases per 100,000 population per year and deaths by 95% compared with 2015 outcomes. In 2021 the WHO warned that the Covid-19 pandemic was putting progress towards this goal at risk.

Between 2000 and 2014 the Millennium Development Goal of halting and beginning to reverse the TB epidemic was achieved, with the WHO estimating 43 million lives were saved by improvements in diagnosis and treatment.

5 WHO. (24 March 2021). World Tuberculosis Day 2021 – the clock is ticking. www.who.int/news-room/events/detail/2021/03/24/default-calendar/world-tuberculosis-day-2021--the-clock-is-ticking
6 WHO. Implementing the end TB strategy: www.who.int/publications/i/item/Implementing-the-end-tb-strategy
THE FOUNDATIONS OF TREATS – THE ZAMSTAR AND HPTN 071 (POPART) TRIALS

From 2004 to 2011 the ZAMSTAR (Zambia South Africa TB and HIV Reduction) trial\(^8\) showed that by working in the community, going into TB patients’ homes and offering a combined package of TB and HIV diagnosis it was possible to make a difference to TB at a community level.

Between 2014 and 2018 the HPTN 071 (PopART)\(^9\) (Population Effects of Antiretroviral Therapy to Reduce HIV Transmission) trial developed the idea of a combined approach to HIV and TB which reached out to a large number of people, mobilising hundreds of community health workers to visit every home in communities in high prevalence urban areas.

PopART was a combination prevention intervention for HIV that included active case finding by screening every member of the population for HIV and TB and referring people for treatment. The randomised controlled trial involved annual house-to-house visits across 14 communities in Zambia and South Africa. Compared with an additional seven control communities, the trial showed the PopART approach was successful, reducing HIV incidence by 20%. Among people with HIV it improved ‘viral suppression’ – reducing the level of HIV sufficiently for someone to remain healthy and prevent transmission to their partners – from 55% at the start of the trial to 70%.

But although PopART encompassed TB case finding, the study was primarily aimed at developing understanding of HIV transmission.

TREATS built on these foundations by measuring whether PopART was similarly successful in reducing TB prevalence (the number of cases present in a population) and TB incidence in the same communities.

If successful, it would enable the ‘universal test and treat’ approach to be adopted in other countries with a high burden of the diseases.

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THE TREATS HYPOTHESIS

The hypothesis was that TB associated with HIV could be reduced by the PopART intervention in two ways. First, screening everybody for TB would identify individuals with the disease who had not yet been diagnosed, and treating them would make them less infectious.

Second, by identifying people living with HIV – who are known to have a high risk of developing TB – and treating them earlier than would have happened without a community HIV screening programme, their risk of developing TB is reduced, so again there are fewer people in the population with TB. Therefore the hypothesis was that the incidence and prevalence of TB could be reduced by a combination of identifying and treating TB and identifying and treating HIV.

The incidence of infection study measured whether the PopART universal test and treat intervention for HIV reduced the number of people becoming infected with TB, while the prevalence survey measured whether PopART had reduced the overall prevalence of active TB (TB disease). Patterns of TB notification data over time would show whether cases had reduced since PopART.

There were three arms to the study with seven communities in each arm. Nine of the 21 communities were in the Western Cape of South Africa and 12 were in Zambia.

The communities in Arm A received the full PopART intervention including immediate antiretroviral therapy for anyone diagnosed with HIV. Arm B had the PopART intervention except that antiretroviral therapy was initiated according to existing national guidelines, which changed over the course of the study. Initially ART initiations were based on a CD4 count threshold that started at 350 and moved to 500, before becoming universal midway through the PopART trial. Arm C acted as the control, and had the standard level of care including antiretroviral therapy initiation according to national guidelines.

The project ran for four years from November 2017 following completion of the PopART intervention. It had 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 (reporting diagnosed TB cases to the health authorities).

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THE IMPACT OF POVERTY

The communities were chosen because they had high levels of TB and HIV. They are vulnerable populations, where the struggle for economic survival greatly increases the difficulty of people engaging in diagnosis and treatment.

TREATS project director Professor Helen Ayles, research director at HIV and TB research organisation Zambart, Zambia, said, “Many of the people living in these communities are unemployed and struggling to survive, so that can undermine the population’s ability to participate. If someone has a choice between finding work or having to queue at the clinic, any of us would try to get food on the table unless we were really sick, and the whole premise of this was that we were trying to pick up individuals before they got really sick, and that’s challenging.”

SECURING COMMUNITY SUPPORT

Community buy-in was critical. Community advisory boards were established to influence the project design, such as shaping the questions households would be asked. The boards, made up of key community figures, helped draw up the approach to informed consent, supported activities such as consultation meetings and helped ensure the communities knew what would be happening, such as the tests that people would be invited to take.

TREATS also worked with faith organisations, neighbourhood health committees and local NGOs.
Dr Musonda Simwinga, deputy research director – qualitative at Zambart, said, “Community engagement is the starting point for informed consent. We need to respect the communities, because they are going to invest so much, and also out of respect for their knowledge, because a lot of things that we did – including deciding what community engagement approaches to use – came from working with the community members.”

The success of the community engagement drive was clear from the “high willingness of people to take part in the study – we met our recruitment targets. In some places recruitment was quite slow at the beginning, but we picked up as we learned how to engage the community and use the lessons learned in one community in another”.

The backbone of the PopART intervention were the community HIV care providers – called CHiPS – who led the door-to-door work. Ayles said, “We recruited CHiPS from the communities themselves, and we specifically encouraged people living with HIV to be part of this, so many of our CHiPS were living with HIV, and many openly.”

TREATS built on this by also recruiting study staff locally, many of whom had been involved in PopART.
ADDRESSING STIGMA

Addressing stigma around TB and HIV was a consistent theme in the project. TB screening was based on people in the community responding to questions about symptoms to decide whether to ask them for a sputum sample, so getting an accurate picture depended on people being open about the symptoms they were experiencing.

“I feel that as the rounds of the intervention went on, the stigma definitely broke down,” Ayles said.

“People were happier to get tested for HIV and to be screened for TB. You can see that the numbers screening positive actually go up over time, which is a reflection of people feeling more confident and saying yes, maybe I am coughing, maybe I could give you a sample.”
TIMELINE

2017
October
- TREATS study advisory group meets in The Hague, the Netherlands
November
- TREATS project begins

2018
July
- Enrolments of participants in the infection cohort begins in Zambia
October
- Prevalence survey dry run to test data management system and questionnaires
November
- Infection cohort enrolment target achieved in Zambia, with 2,655 participants enrolled and blood samples taken
- Enrolment of participants in the infection cohort begins in South Africa

2019
January
- Two members of Zambart begin PhDs at the London School of Hygiene and Tropical Medicine
February
- TB prevalence survey begins in Zambia
March
- Primary results of the HPTN 071 PopART trial reported at the Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, USA
- TB prevalence survey begins in South Africa
- In light of HPTN 071 results, decision taken to seek study advisory board permission to expand the TB prevalence survey to include all 21 communities instead of the 14 in the incidence of infection cohort originally planned

July
- Primary results of the HPTN 071 PopART trial published in New England Journal of Medicine
- Intensive diagnostic phase (IDP) of the TB prevalence survey completed in Luvuyo, South Africa

August
- IDP of the TB prevalence survey completed in Kanyama, Zambia
October
- Qualitative findings on patient and stakeholder perspectives presented to the 50th Union World Conference on Lung Health, Hyderabad, India

2020
February
- DP follow up activities begin in Zambia
March
- Fieldwork suspended as the Covid-19 pandemic hits. Staff develop protocols to keep staff and communities safe from Covid-19 once work resumes
August
- TREATS begins testing for Covid-19 in the Bwacha-Ngungu community of Kabwe, Zambia, using its mobile TB testing facilities
September
- TREATS fieldwork resumes
October
- Early results from the IDP presented to 51st Union World Conference on Lung Health

2021
June
- TREATS fieldwork finishes.
October
- TREATS presents further results to the 52nd Union World Conference on Lung Health and the 10th Annual EDCTP (European and Developing Countries Clinical Trials Partnership) Forum

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IMPACT OF THE COVID-19 PANDEMIC

At the end of March 2020, as the Covid-19 pandemic struck, all field activities were suspended for five months. Both countries were able to restart by September, following consultations with ethics committees and governments. During the suspension, standard operating protocols were developed to control Covid-19 and to comply with government rules.

Other impacts of the pandemic included some staff returning to their usual clinical work to support the Covid response, while others were sick or coping with caring responsibilities or bereavement. Working from home in Zambia and South Africa was not straightforward because the power supply and internet access could be unreliable, affecting the management of fieldwork when it restarted.

Dr Linda Mureithi, senior researcher at the Health Systems Trust in South Africa, said that when they restarted work the communities in the Western Cape had been hard-hit in the first wave of the pandemic: “They had been bruised and traumatised, so empathy and sensitivity were required and we had to take it slowly. It meant a lot of discussions with community stakeholders. They were supportive of restarting.” Staff put themselves at risk by going back into the community, so it was important for both fieldworkers and local people that protocols such as wearing masks were strictly observed: “It was quite taxing emotionally but people really came together.”

In August 2020 TREATS began testing for Covid-19 among the 28,000 people in the Bwacha-Ngungu community in Kabwe, Zambia – one of the PopART and TREATS sites – using the mobile TB testing facilities.12 This began an 18-month study to measure the prevalence and spread of the SARS-CoV-2 virus, contributing to understanding its epidemiology in Sub-Saharan Africa. It was also hoped the study would shed light on the relationship between Covid-19, TB and HIV in disease severity and clinical outcomes.

12 TREATS. (27 August 2020). TREATS will begin testing for covert-19 in Zambia using mobile TB testing facilities treatsproject.org/latest-news
THE TB PREVALENCE SURVEY

The prevalence survey assessed the impact of the PopART universal testing and treatment intervention on the prevalence of bacteriologically confirmed pulmonary TB, using a random sample across all 21 study communities. There were approximately 50,000 participants, aged 15 years and over.

A mobile site was set up at different locations in each community which included stations for symptom screening, sputum collection, blood testing and HIV testing. The infrastructure included mobile testing trucks with a digital X-ray machine and portable laboratory for identifying TB in sputum samples. To recruit participants, TREATS community workers went door-to-door to explain the study and invite people fulfilling the inclusion criteria (aged 15+ years and usually resident) to be tested for HIV and TB at the mobile field sites. All 50,000 participants were X-rayed and those that had TB symptoms or evidence of TB on their X-ray were asked to provide two sputum samples one hour apart, which were tested in the laboratory. Everyone was offered HIV testing.

Frank Vijn, projects director for Delft Imaging Systems, organised the mobile TB analysis trucks, which used software called CAD4TB (computer-aided detection for TB) designed to detect TB on the digital X-rays.

“The novelty of this project was that it didn’t rely on human readings. Chest X-rays were read by artificial intelligence, which produces a score and a heat map. TREATS relied on the score to say ‘this person has an abnormal X-ray and should be asked to provide sputum,’ Vijn said.

Each person who submitted sputum samples was asked to return the following day, when their case was reviewed by a doctor to determine treatment.

Dr Eveline Klinkenberg, independent TB epidemiologist and leader of the prevalence survey, said the study design needed to take account of the latest global developments on defining TB in community surveys, a hotly debated topic. In the first four communities additional research was carried out to investigate whether the Xpert test (which detects Mycobacterium tuberculosis in sputum and resistance to the antibiotic rifampin) needed to be supplemented by growing cultures from samples, which is difficult when working in the field.

The study showed that conducting two Xpert tests increases the chance of finding TB bacilli in a person who has TB, and that performing cultures is only needed for the relatively small number of people where the outcome from Xpert does not produce a definite diagnosis. This has contributed to new WHO guidance for TB prevalence surveys.

Outcome

The key finding of the prevalence study was that the PopART intervention had no impact on the prevalence of TB.

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MEASURING THE RATE OF NEW TB INFECTIONS

TREATS ran the TB incidence study to assess the impact of the PopART intervention on the rate of new TB infections. It followed a cohort of young people aged 15 to 24 years old – known as the ‘infection cohort’ – for two years. They were spread across the communities in Arm A – with the full PopART intervention – and Arm C, with the standard approach to care.

Recruits to the infection cohort were tested using the QuantiFERON Gold Plus (QFT-G+) test for TB infection in the blood. Testing at the beginning of the study revealed a high prevalence of TB infection, with 33% of Zambian participants and 64% of South African participants testing positive.

The baseline findings demonstrated that the prevalence of infection significantly increased with age in both countries, and increased with the presence of a household contact of TB in Zambia, but not in South Africa.

Outcome

The key outcome was that the PopART intervention had no effect on the incidence of TB infection.

ANALYSIS OF THE PREVALENCE AND INCIDENCE OUTCOMES

The research team is in the early stages of analysing the results to identify possible explanations for the unexpected findings that there was no evidence of an impact on either TB prevalence or incidence from the PopART intervention.

PopART had already produced unexpected results, with Arm A – which received the full PopART HIV intervention including immediate ART for anyone diagnosed with HIV – producing less of an impact than Arm B, which had ART initiated according to national guidelines, which changed over the course of the study.

Professor Richard Hayes, professor of epidemiology and international health, at London School of Hygiene and Tropical Medicine (LSHTM), said, “This prepared us for what we are now having to confront with TREATS.”

Hayes said several tentative explanations were being investigated. These included limitations in the case finding, the complexities of the impact of ART on TB prevalence, the delay between completing PopART and TREATS, and random error.
“We have recognised certain limitations of the PopART CHiPS intervention with regard to TB active case finding. It was based on questioning people in the household about whether they have TB symptoms, using a well-developed algorithm that we’ve used previously in Zambia and South Africa on self-reported symptoms, but we know this is an imperfect tool for detecting potential TB cases.

“Other active case finding strategies have used more sensitive tools such as X-ray. So that was a limitation we were always aware of, and the disappointing findings are throwing additional emphasis on that limitation. So one of the key points for future research will be to further explore more intensive and hopefully more sensitive strategies for detecting TB cases.”

But despite the limitations of the active case finding, it was clear the intervention improved ART coverage, and it is known that getting people who are HIV positive onto ART reduces the incidence of TB disease. So further analysis, particular of clinical records, will feed into modelling of the data to see if the expected reduction in incidence can be identified.

But while the impact of ART on TB incidence is understood, “it’s effect on prevalence is less clear, more complex and quite puzzling,” Hayes said.

“HIV definitely increases the incidence of TB, but it’s effect on prevalence is less clear, and that parallels the effect that ART then has on improving the immune status of HIV-positive individuals. The reason it’s complex is because HIV not only increases the incidence of TB, but it also actually reduces the duration of TB and potentially its infectiousness.

So there’s a kind of countervailing tendency with the increase in incidence partly offset by these reductions. The same thing happens more or less when you look at the effect of putting HIV positive people on ART, because that makes them in some ways more like HIV-negative individuals. So that makes their TB incidence lower, but it may also make them have a longer duration of TB and they may be more infectious.

“So putting all those observations together, we could expect that the effect on TB prevalence – which reflects the duration of the disease as well as the incidence – of putting people on ART would be less than the effect on incidence, and taking that to an extreme, you might find no effect on prevalence at all because of those countervailing tendencies.”

The absence of an effect on prevalence to a large extent explains why no effect was found on the incidence of infection, because transmission of TB is driven mostly by prevalence – the number of people at any one point in time with active TB disease: “If you find a negative outcome with one, it’s not really unexpected that you would find it on the other,” Hayes said.

There was a significant delay between PopART and TREATS. The intention had been to carry out the prevalence survey immediately after the PopART intervention, but it took time to secure funding and then work was badly delayed by the Covid-19 pandemic, leading to a gap of approximately three years. And of course the communities have not stood still. In particular, the number of people coming forward for diagnosis and treatment has increased, and in Arm C – the control – the communities have now moved to universal ART: “So it’s highly plausible that any differences between study arms would gradually be declining.”

Another potential factor is that, like any cluster randomised trial, TREATS is susceptible to random error “not least because we only have 21 study communities. That makes it a massive trial, but it means there are only 21 units of randomisation.”

PATHWAY TO IMPACT OF THE POPART COMBINED TB/HIV INTERVENTION

To understand the pathway to impact of the PopART combined TB/HIV intervention on TB the yield of case finding by HIV status, changes in TB notifications at health facilities and self-reported TB incidence were measured. This was researched using a randomly selected cohort of adults across all 21 communities, followed up over 36 months.

Outcome

The outcome was that self-reported TB treatment starts did not follow the hypothesis. There was not the expected initial increase in treatment starts expected from active case finding. Analysis of the data is continuing.
A key element of TREATS was to document how social and structural context intersected with TB illness, and understand if the intervention was flexible enough for people in these communities to seek diagnosis and treatment while meeting the daily demands of their lives.

Professor Virginia Bond, head of the social science unit at Zambart, said it was important to develop a sociological understanding of the reality of TB, because poverty had a major impact on how people responded to the disease: “It significantly affects their decisions around health seeking behaviour, their ability to respond quickly or at all or finish treatment. We have to understand what else is going on in people’s lives and how they experienced that particular intervention, how they experience health services and how they juggle everything in their lives so that they are able to respond to TB symptoms and come forward to services that are able to diagnose and treat them. Understanding the hurdles they face is very important.

“The first hurdle is poverty. In Zambia there is no welfare state and few safety nets, so most people survive by what they do that day. In urban communities where we are working the majority of residents are poor, so being sick with TB, being diagnosed with TB, having the obligation to go to the health centre frequently and not being able to contribute to the household is disruptive to your life. It’s hard to take time off to respond to the symptoms or complete treatment.”
INVESTIGATING MENTAL HEALTH AND STIGMA

There is little understanding of the impact of TB on mental health, and few options for accessing mental health care in the communities most affected by it.

Stigma caused the social isolation associated with TB, such as people not wanting others to know they had it, as well as the fear of infecting their family and others.

The pressure to isolate was greater in Zambia: “It was preached by the health education there. TB nurses would say you must isolate yourself, you must have separate utensils at home, you must stay away from others, sleep in a different room,” Bond said.

People with TB or with the disease in their family would find their social network shrinking, such as not gathering with other people or attending church. There was also an economic impact, such as being unable to sell produce at the market.

The researchers concluded there was more stigma around TB and HIV in Zambia than South Africa: “More stigma in Zambia is linked to a slightly more conservative, less liberal society. There is a bit more judgement and blame,” Bond said. There is also more homophobia in Zambia, partly driven by churches’ moral stances.

One example of the stigma around TB is the concept of it being dirty: “It’s twofold, to do with [the idea that] you get TB in a more dirty environment, but it’s also to do with a kind of moral contagion. It’s assumed that you are culpable for having TB because you’ve done something you shouldn’t have, either smoked or drank too much or had too much sex with too many partners.”

It is still strongly associated with HIV, with around 60 to 70% of TB patients being infected with HIV: “When you are diagnosed with TB you have to deal with the assumption that you may also have HIV and everything that goes with that, the assumption that you’ve done something you shouldn’t have, that’s immoral. So there are many layers and reasons why people might stigmatise you and you might worry that you are going to be stigmatised.

“But we also saw moving examples of social inclusion. People will accompany TB patients to the clinic or invite them in or go to visit them and pray with them. We saw a lot of care from neighbours and families,” Bond said.

Bond said the sociological study showed the need for more mental health services for TB patients, mental health training for staff and a concerted effort to address all forms of stigma: “We need to tackle multiple stigmas because there is the stigma of being poor, of having TB, of having HIV, having mental health issues. There needs to be a more integrated approach to stigma within health facilities and the community.”
IMPACT OF DIFFERENT INTERVENTIONS

Mathematical modelling was used to understand the respective contributions of intervention components – universal test and treat (UTT) for HIV and active case finding (ACF) for TB. The intention was to project the likely outcomes from continuing the PopART intervention to 2030 compared with the control, and estimate the health impacts and cost effectiveness of the intervention, particularly TB active case finding.

Since the PopART intervention did not affect either the incidence or prevalence of TB, it was hoped that modelling would help understand why the expected impact was not found. Dr Pete Dodd, senior research fellow at the School of Health and Related Research at the University of Sheffield, UK, said, “Aim one is to tease out the different aspects of the intervention effect to understand how much of any impact was due to universal test and treatment intervention versus the active case finding.”

Once the different effects have been identified, the modelling allows researchers to, in effect, rewind time to see what would have happened in each community if they had had only one intervention or the other, as well make projections to the end of the decade and translate it into different settings with different epidemiology.
COST EFFECTIVENESS

Modelling is also being used to understand the long-term cost effectiveness of different interventions. This takes into account costs saved in the future by, for example, reducing healthcare spending and people remaining economically active.

Cost effectiveness is judged by the change in cost divided by the gain in health: “It will predict how many people are dying and what age they were, and that’s important because it is telling you how many life years into the future were lost when they died, because it matters if they were a 45-year-old versus a 25-year-old etc,” Dodd says.

Related to this is understanding the economies of scope (the extent to which producing one good reduces the cost of producing another) in having a joint platform delivering HIV and TB services. Dr Ranjeeta Thomas, assistant professor of health economics at the Department of Health Policy, London School of Economics, said, “You potentially have economies of scope because you have shared fixed costs across the different services.

We want to explore that because in this study we have a platform of community healthcare workers who went door to door to every household offering not just HIV testing but also active case finding for TB, and so far there aren’t studies that have looked at this joint platform.”

Thomas stressed that demonstrating economies of scope does not on its own demonstrate that is the best use of the joint platform: “To do that we then need to combine the economies of scope information with the benefit side to look at the cost effectiveness of delivering this in a combined way versus separately. We will be doing that over a time horizon up to 2030, with the idea being that if the prevalence and incidence change in the community, at some point the economies you identify might disappear.”
EVALUATING NEW METHODS FOR MEASURING
THE PUBLIC HEALTH IMPACT

As well as understanding the impact of the public health interventions on TB, an important part of TREATS has been improving the understanding of the best ways to measure that impact, including the use of novel diagnostic technologies.

TESTING FOR TB INFECTION AND ITS PROGRESS TO TB DISEASE

Two members of the TREATS consortium, Qiagen and Zambart, tested a new platform for the ‘QuantiFERON gold plus assay’ — called QIAreach QuantiFERON TB (QIAreach-QFT) — to overcome the infrastructure limitations that this test faces in developing countries. The assay is a semi-automated test that uses nanoparticle technology to measure the level of IFN-γ in plasma released by both CD4 and CD8 T cells using the same TB2 tube of QTF-plus. This enables the detection of TB infection using a single blood collection tube and providing a final positive or negative result within 20 minutes.16 While it yields good results,17 this depends on careful control by laboratory staff and those involved in collecting blood samples, such as ensuring appropriate incubation.18

This study evaluated the performance of the QuantiFERON gold plus assay in the field by assessing whether laboratory staff were adequately trained to perform the test correctly. At five laboratories in Zambia all users completed the test with few difficulties, suggesting the QIAreach-QFT system has the potential to be a scalable solution for detecting TB infection in low resource settings.

The ‘intensive diagnostic phase’ of the prevalence survey, conducted in three communities in Lusaka, Zambia and one community in South Africa, provided an ideal opportunity to analyse a range of tests to see how well different approaches worked.

Traditional TB prevalence survey methods using TB culture with Xpert testing were compared with new tests using mycobacterial load assay (MBLA) and the level of C-reactive protein (CRP), which increases when there is acute inflammation.  

The usefulness of point-of-care-CRP (POC-CRP) testing in improving Xpert diagnostic accuracy to identify ‘active’ TB was evaluated. Although significantly associated with Xpert and culture positive results, the POC-CRP test did not differentiate ‘active’ from ‘inactive’ TB. However, POC-CRP showed a sensitivity of 50% in detecting TB, which was higher than symptom screening. The combination of POC-CRP testing and symptom screening, in parallel, resulted in a higher sensitivity than POC-CRP or symptom screening alone, so it may have a role in future TB screening algorithms in high burden countries, where tools such as X-ray might be inaccessible.

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BUILDING CAPACITY

TREATS helped to build the capacity of TB research leadership in Africa by supporting individuals to undertake study programmes and research, in collaboration with LSHTM.

Two candidates from Zambart – Modupe Amofa-Sekyi and Tila Mainga – began PhDs at LSHTM. Jacob Busang from South Africa, and Hudson Mumbole from Zambia, both completed an MSc in medical statistics. Chali Wapanesa and Chepela Ngulube began distance learning MSc programmes. Among others to benefit, LSHTM student Johaness Kusters had a one-month internship with Zambart.

Dr Kwame Shanaube, Zambart deputy director of research – quantitative, said, “The objective of the training and capacity building was threefold: to strengthen the capacity for Zambart to carry out research, including clinical trials; to increase research capacity in Zambia through provision of PhDs and Masters degrees, and to build the capacity of the Zambart central laboratory with the aim of accreditation for it to work as a TB research lab.”

Mainga was Zambart’s study manager for research on stigma when the PhD opportunity arose. “I decided it would be good to understand the toll of TB on people’s mental health.”

The research included interviews with people who were diagnosed with TB during PopART, as well as healthcare workers. In one community a mental health screening tool was embedded in the prevalence survey to provide quantitative data.

Her research revealed “there is a strong need to acknowledge the mental health implications of a TB episode. People talk about it being really challenging, especially when they were initially diagnosed. The TB stigma that they had to deal with, the fact that TB is a disease of poverty, that having this diagnosis put their income on hold. The biggest takeaway for me is the role of poverty. We had individuals who had contemplated suicide.”

Mainga said international collaboration to support capacity building in Africa is important because “it’s vital that people develop skills to research the problem that they have lived with and understand. That means you create solutions that are sustainable and respectful, because they’re not being imported”.

Amofa-Sekyi, a clinical doctor, assessed whether the QuantiFERON gold plus assay could be used in young people to predict who will progress to TB disease. “We were working with young people and young adults who would, if you compare with older adults, have fairly recent TB infection. We followed them up over two years to see how many of them would go on to develop TB and see if the assay could pick up that they were recently infected.”

Busang worked closely with Zambart’s data management team: “I was exposed to working in multidisciplinary research teams and had the advantage of working with numerous scientists from Africa.”

Mureithi from the Health Systems Trust in South Africa highlighted the capacity building from delivering the trial: “That has been one of the most valuable aspects of this project. It’s been fantastic in terms of understanding all the different aspects that go into running a trial, and doing all that from scratch. It’s been a steep learning curve.”

Dr Alwyn Mwinga, executive director of Zambart, said the importance of capacity building “is that it serves as a launching pad and ensures that the impact of this grant lasts through generations, because you are training the scientists who in turn can help younger people.”
INFORMING GLOBAL POLICY AND RAISING AWARENESS OF COMBINED TB/HIV INTERVENTIONS

The ultimate goal of TREATS is to raise awareness among researchers, funders and civil society of the impact of a combined TB/HIV intervention to inform future approaches to TB and HIV.

Awareness raising and policy engagement has taken place throughout TREATS, including with the WHO, UNAIDS, EDCTP, the Ministry of Health in Zambia and Department of Health in South Africa.

The study design and initial findings were presented at international conferences, including The Union’s World Conference on Lung Health in 2019, 2020 and 2021 and the 10th EDCTP Forum in 2021.

Following the 2019 conference, the WHO invited the TREATS consortium to participate in meetings discussing the challenges of measuring the prevalence of TB at population level using new technologies. As a result TREATS conducted additional testing in the TB prevalence survey to inform the WHO’s guidelines on measuring the prevalence of TB.
CONCLUSION

Despite the unexpected outcomes of the prevalence and incidence research, TREATS has made an important contribution to the global fight against TB.

It has shed light on the evolving relationship between HIV and TB now that access to antiretroviral therapy has opened up to far more communities, notably in Sub-Saharan Africa. PopART and TREATS have shown how to carry out clinical trials and interventions at scale among urban populations, building relationships with communities that have sustained over several years.

The evaluation of new methods for measuring the public health impact of TB interventions has important implications for future fieldwork. African leadership in clinical research has been strengthened. Further research will be vital in building on the lessons of TREATS to find the best ways to fight this devastating disease.

THERE IS A STUBBORNLY HIGH TB BURDEN

The burden of TB in urban communities in Zambia and the Western Cape remains extremely high, especially among people living with HIV. TREATS taught us how hard it will be to achieve the WHO target of stopping the TB epidemic across the world by 2035. It will need more intensive control measures and more structural changes such as improved housing and addressing issues such as alcohol use.

WE NEED MORE THAN UNIVERSAL TESTING AND TREATMENT FOR HIV TO REDUCE TB

TREATS has shown that improvements in the diagnosis and treatment of HIV do not easily translate into greater success against TB.

UTT reduced HIV incidence in the communities in the study and there is some evidence that universal testing and treatment for HIV can reduce the incidence of TB disease and mortality, but it does not reduce the prevalence or transmission of TB at a community level.

However, for a modest additional cost, it did find undiagnosed cases of TB and reduced the rate of self-reported TB.

MORE SENSITIVE STRATEGIES FOR TB CASE FINDING ARE NEEDED URGENTLY

The active case finding strategy tested in PopART relied on screening for TB symptoms, but it was not sensitive enough to reduce TB transmission. More sensitive strategies for TB case finding could include more appropriate screening tools and new technologies such as mobile digital X-ray.

STIGMA AND THE MENTAL HEALTH BURDEN OF TB NEED TO BE ADDRESSED

TREATS has highlighted the central importance of addressing stigma around TB and HIV in encouraging people to come forward for diagnosis and treatment, and has underscored the impact of TB on mental health, driven by stigma and poverty.

COMMUNITY-LED APPROACHES TO TB ARE CRUCIAL

Communities have to be an integral part of TB services. The services provided in PopART were delivered by community health workers who were mostly local residents. This approach proved highly acceptable to the community, and reduced HIV incidence. This type of platform can be built on to provide a wider range of health services to capture economies of scope and support the drive for universal health coverage.

Community services need to be developed and implemented through close partnership with community members. We learned that community advisory boards, community health workers, local health facilities and other local relationships play a crucial role in successful delivery of health services.