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PRESS RELEASE

A BLOOD TEST TO FIND THOSE AT HIGH RISK OF TUBERCULOSIS IN PEOPLE LIVING WITH HIV.

The *Lancet Global Health* journal reports the findings of a study of a host blood test that can find those at high risk of tuberculosis in people living with HIV. The blood mRNA biomarker differentiated between people living with HIV who had active tuberculosis from those without TB and predicted which individuals would develop TB within 15 months.

14 April 2021: Researchers from the **South African Tuberculosis Vaccine Initiative** at the University of Cape Town, the **Aurum Institute**, the **Centre for the AIDS Programme of Research in South Africa**, **Stellenbosch University**, the **London School of Hygiene and Tropical Medicine** and the **Fred Hutchinson Cancer Research Center** have published the results from a study of a blood-based RNA biomarker which tested diagnostic and prognostic performance for tuberculosis (TB) in people living with HIV in *The Lancet Global Health* journal.

Almost a quarter of the world's population is estimated to be infected with the bacterium (*M. tuberculosis*) responsible for TB disease. Importantly, only 5-10% of people with the infection are at risk of progression to TB disease and would benefit from antibiotic treatment. Existing tests for *M. tuberculosis* infection (the tuberculin skin test [TST] or interferon gamma release assay [IGRA]) would result in considerable over-treatment with preventive therapy. Traditional TB symptom screening would miss the majority of undiagnosed TB in people living with HIV in community settings, as the majority of early TB is asymptomatic. The repercussions of a missed TB diagnosis in people living with HIV are potentially catastrophic: severe illness, hospitalisation, long-term lung damage, and death. A delayed diagnosis could also potentially allow onward transmission of TB to family members and close contacts.

This publication advances the development of a point-of care blood test with which health practitioners could accurately identify people at risk of TB disease, who would then require confirmatory diagnostic testing and treatment, or others who are likely to progress from *M. tuberculosis* infection to active TB disease and make it possible to apply available TB preventive antibiotic regimens selectively to those who are most likely to benefit in communities.

The research team set out to test the diagnostic and prognostic performance of a blood-based RNA biomarker of TB risk (RISK11) in people living with HIV. The study was conducted between 2017 and 2019 across five distinct geographic communities across South Africa.

Results

A total of 861 adults living with HIV from communities in Worcester, Ravensmead, Durban, Klerksdorp, and Rustenberg were screened for participation. All participants were intensively tested for TB at baseline, if symptomatic during the 15-months of follow up, and again at the end of the study. More than 70% of detected TB cases did not have any symptom compatible with TB disease and would not have been detected by current TB screening strategies, which require symptoms as the entry point to investigation. The RISK11 blood test differentiated between individuals with current TB disease or those who would progress to incident TB within 15 months after testing, and individuals who remained healthy, with excellent performance. The risk of current TB was 13-times higher in those with a positive RISK11 test versus a negative RISK11 test, and the risk of developing TB within 15 months of testing was 16-times higher in those with a positive RISK11 test versus a negative RISK11 test.

The recorded performance of RISK11 as a screening test for active disease in people living with HIV with TB symptoms exceeds the World Health Organisation requirements for a triage test. Diagnostic performance in asymptomatic participants also approached these requirements. The RISK11 signature was able to predict TB disease progression within 15 months of testing in this trial population with prognostic performance approaching, but not meeting, the World Health Organisation requirements for a TB prognostic test.

Current South African guidelines advocate 12 months of universal isoniazid preventive therapy for people living with HIV who have not yet received TB preventive therapy, irrespective of *M. tuberculosis* infection status. This study suggests that an RNA biomarker of TB risk, such as RISK11, might be more specific in determining need for targeted preventive therapy for people living with HIV. Two-thirds of the 38 million people living with HIV worldwide are on antiretroviral therapy and, with the advent of well tolerated and effective short-course TB preventive regimens, annual or semi-annual community-based testing of people living with HIV might be useful to monitor risk of progression to TB and target those likely to benefit from repeat courses of preventive therapy.

This study was funded by the **Bill & Melinda Gates Foundation** and the **South African Medical Research Council**.

Comments from research study leaders

Prof. **Mark Hatherill**, Principal Investigator of the study, said “These results bring us one step closer to a TB blood test for use at point of care to guide curative and preventive TB therapy for people living with HIV”.

Prof. **Tom Scriba**, Laboratory Director of the South African Tuberculosis Vaccine Initiative, where the test was developed, commented that, “These promising results are similar to those seen in a trial of the RISK11 biomarker in HIV-uninfected persons. They highlight the importance of finding people with undiagnosed, subclinical TB.”

Prof. **Gavin Churchyard**, Group CEO, The Aurum Institute said that “The ability to identify people living with HIV that are at high risk of developing active TB disease that may benefit from TB preventive treatment is a major scientific advance.”

Prof **Kogie Naidoo**, study co-investigator at the CAPRISA site, said “TB remains the leading cause of death among people living with HIV/AIDS. These results bring hope for more efficient diagnosis of current active TB, and for detection of those at heightened risk of progression to active TB disease, thereby enabling effective patient triage to TB treatment or prevention.”

About the participating research groups

About SATVI.

The South African Tuberculosis Vaccine Initiative (SATVI) is a TB research group based at the Faculty of Health Sciences of the University of Cape Town. SATVI has conducted 30 Phase I–IV trials of BCG and 9 different TB vaccine candidates since 2005. SATVI's research also seeks to understand the risk for, and protection against, *M. tuberculosis* infection and disease, in order to develop more effective vaccines and preventive strategies for global impact on the TB epidemic. Read more at: www.satvi.uct.ac.za

About the Aurum Institute.

Established in 1998, the Aurum Institute is an African Public Benefit Organisation whose mission is to improve the health of people and communities living in poverty through innovation in global health research, systems and delivery. It is rooted in Africa is dedicated to researching, supporting and implementing innovative, integrated approaches to Global Health with their headquarters in South Africa with offices in the USA, Ghana and Mozambique. The Aurum Institute has developed itself into a leading player, bridging the worlds of research, policy and implementation for impact.

Read more at: www.auruminstitute.org

About the Centre for the AIDS Programme of Research in South Africa (CAPRISA).

CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy and hosts a DSI-NRF Centre of Excellence in HIV Prevention and a MRC HIV-TB Pathogenesis and Treatment Research Unit. The primary goal is to undertake globally relevant and locally responsive research that contributes to understanding HIV Pathogenesis, Prevention and Epidemiology, as well as the links between Tuberculosis and AIDS care. CAPRISA has diverse expertise in basic and molecular epidemiology, virology, immunology, infectious disease medicine, bioinformatics, statistics, ethics and health policy.

Read more at www.caprisa.org.

About the Stellenbosch University, Immunology Research Group.

The Stellenbosch University Immunology Research Group is part of the Division of Molecular Biology and Human Genetics at the Faculty of Medicine and Health Sciences, Stellenbosch University. The group focuses on the immunology of *M. tuberculosis* infection and disease and has a strong interest in host-based biomarker discovery and validation to aid the development of urgently needed tools in the fight against TB, particularly in resource constraint settings with high caseloads.

Read more at:

http://www.sun.ac.za/english/faculty/healthsciences/Molecular_Biology_Human_Genetics/Immunology_Research_Group

About the London School of Hygiene and Tropical Medicine.

The London School of Hygiene and Tropical Medicine (LSHTM) TB Centre established in 2012, supports cross disciplinary research to develop tools and interventions for the prevention and treatment of TB. As part of these efforts the TB Modelling Group (<https://tbmodelling.lshtm.ac.uk/>) uses mathematical and statistical models to understand the natural history and epidemiology of TB and to improve the contribution of TB modelling to policy decisions and implementation.

Read more at: www.lshtm.ac.uk/research/centres/tb-centre

About the Fred Hutchinson Cancer Research Center

At Fred Hutchinson Cancer Research Center, home to three Nobel laureates, interdisciplinary teams of world-renowned scientists seek new and innovative ways to prevent, diagnose and treat cancer, HIV/AIDS and other life-threatening diseases. Fred Hutch's pioneering work in bone marrow transplantation led to the development of immunotherapy, which harnesses the power of the immune system to treat cancer. An independent, non-profit research institute based in Seattle, Fred Hutch houses the nation's first National Cancer Institute-funded cancer prevention research program, as well as the Clinical Coordinating Center of the Women's Health Initiative and the international headquarters of the HIV Vaccine Trials Network.

Read more at: www.fredhutch.org.

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