

**Press release****Kommunikation und Medien**  
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med.uni-muenchen.de[www.lmu-klinikum.de](http://www.lmu-klinikum.de)**A view to the inside: Blood-based biomarkers as a promising tool for early detection of incipient Tuberculosis in people living with HIV**

**Findings of the LMU University Hospital Munich, the German Center for Infection Research (DZIF) and the U.S. Military HIV Research Program in collaboration with the African Cohort Study (AFRICOS) Group suggest that blood-based biomarkers can often detect incipient Tuberculosis (TB) between six to twelve months earlier in people living with HIV before a sputum-based TB diagnosis is possible. The detection of TB disease activity within the body using sputum-independent biomarkers could provide a window of opportunity to identify active TB earlier. This would allow to directly start medical treatment and thus to prevent progression and transmission of the disease. The outcomes of this longitudinal study on TB have been published in the journal eClinicalMedicine by The Lancet.**

According to the World Health Organization (WHO), one quarter of the world's population is estimated to be infected by TB bacteria, Mycobacterium tuberculosis (MTB), which can cause Tuberculosis (TB). Although it is preventable and curable, 1.5 million people die from the infectious lung disease each year. TB is also a leading cause of death for people living with HIV. Most people infected with TB bacteria remain in a stage of latent TB and never develop TB disease. However, about five to 15 percent of people with latent TB may develop active TB disease in the future and potentially spread it to others. As X-ray and CT diagnostics are too unspecific for early and accurate detection of subclinical TB disease, there are to date no diagnostic tools to assess TB disease activity in living patients during clinically latent TB or during a HIV/TB coinfection.

In collaboration with the AFRICOS Study Group\*, a research team led by the DZIF scientists Director Michael Hoelscher, Christof Geldmacher and Inge Kroidl from the Division of Infectious Diseases and Tropical Medicine at the LMU University Hospital Munich and Col. Julie Ake from the U.S. Military HIV Research Program (MHRP), Walter Reed Army Institute of Research, decided to tackle this problem and to understand the dynamics of TB



disease activity. Within the AFRICOS cohort, the researchers assessed TB disease activity over five years in people living with HIV who are co-infected with MTB. The study team used a blood-based biomarker throughout multi-year follow up, combined with a yearly assessment of MTB occurrence in sputum.

### **AFRICOS - a systematic longitudinal cohort study**

Established by MHRP in 2013, AFRICOS is a systematic longitudinal cohort study of people living with HIV and of HIV-uninfected adults. The study is conducted at eleven clinics across five geographically distinct HIV treatment and care programs, which are supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) in Kenya, Tanzania, Uganda, and Nigeria.

"AFRICOS, a 15-year longitudinal study, is helping us capture the broader picture of the overall health of our HIV-infected patients, including outcomes data on co-infections such as TB." said Col. Julie Ake, M.D., the director of MHRP and the AFRICOS lead investigator. "The progression of latent TB to active disease can be life-threatening to people living with HIV, so an early biomarker for active TB disease could be a critical tool to profoundly improve clinical outcomes for patients with this co-infection."

For this study, HIV-infected AFRICOS participants were randomly selected from existing clinical patient lists or new enrollees at the clinics. Between January 2013 and August 2018, the participating African clinics screened 2,014 people with HIV annually for active TB using the Xpert MTB/RIF diagnostic assay. In addition, the scientific team examined longitudinal blood mononuclear cell samples from HIV-infected participants before, during and after diagnosis of microbiologically confirmed active TB and TB recurrence, as well as patients with a clinically latent TB infection over up to five years.

Based on these samples, the researchers analyzed the activation status of MTB-specific CD4 T cells as a surrogate biomarker to diagnose TB disease in HIV-positive patients. Christof Geldmacher explains: "Activated MTB-specific CD4 T cells in blood are a sputum-independent surrogate biomarker, which has been shown to differentiate between latent and active TB disease with high accuracy and hence mirrors in vivo TB disease activity. Assessment of these over time is possible and does not require repeated exposure of patients to Xray/CT related radiation."

### **Blood-based biomarker could facilitate the early detection of incipient TB**

The laboratory analysis showed that the MTB-specific CD4+ T cell activation differentiated active TB (Xpert MTB/RIF positive result) from latent TB with a sensitivity and specificity of 86 percent in study participants living with HIV. In many cases, the progression to active TB disease, characterized by activated MTB-specific T-cells, started six to twelve months before the diagnosis by clinical symptoms and sputum occurrence of bacilli. This

provides evidence for the onset of disease active TB long before a sputum-based TB diagnosis. The findings suggest that using a blood-based biomarker, like the activation status of MTB-specific CD4+ T cells, could facilitate the early detection of incipient TB. Once a diagnostic product based on the principle described in this basic research becomes available in the future, this could improve clinical outcomes, reduce the transmission of MTB, and potentially save lives.

### The Research Group

- Division of Infectious Diseases and Tropical Medicine, LMU University Hospital Munich (LMU), Munich, Germany
- German Center for Infection Research (DZIF), partner site Munich, Germany
- U.S. Military HIV Research Program, Walter Reed Army Institute of Research, Silver Spring, MD, USA
- Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD, USA
- Makerere University Walter Reed Project, Kampala, Uganda
- HJF Medical Research International, Kericho, Kenya
- U.S. Army Medical Research Directorate – Africa, Kisumu, Kenya
- HJF Medical Research International, Kisumu, Kenya

Further information including all members of the AFRICOS Study Group and the local implementation partners is available in the original publication.\*

### \*Original publication

#### Assessment of tuberculosis disease activity in people infected with *Mycobacterium tuberculosis* and living with HIV: A longitudinal cohort study.

Kroidl I, Ahmed M, Horn S, Polyak C, Esber A, Parikh A, Eller L A, Kibuuka H, Semwogerere M, Mwesigwa B, Naluyima P, Kasumba J M, Maswai J, Owuoth J, Sing'oei V, Rono E, Loose R, Hoelscher M, Ake J, Geldmacher C, on behalf of the AFRICOS Study Group. *eClinicalMedicine* 2022;00: 101470. doi: <https://doi.org/10.1016/j.eclinm.2022.101470>

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*The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army, the Department of Defense, or HJF.*

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***Images are available on request.***

**LMU Klinikum**

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Outstanding facilities of the LMU University Hospital include the oncological center CCC M and Bavaria's largest transplant center TxM.

The LMU University Hospital is represented in all German centers of health research.

The Medical Faculty of Ludwig Maximilians-University Munich and the LMU University Hospital make a significant contribution to the excellence strategy of the Ludwig Maximilians University in Munich.

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