South African HIV-patients with Low Level Viremia are at Risk for therapy Failure.

Johannesburg, November 8th 2017. In a large South African cohort study, a team of researchers from the University of the Witwatersrand (Johannesburg, Gauteng, South Africa), the Ndlovu Research Consortium (Groblersdal, Limpopo, SA), the National Health Laboratory Service (SA), the University of California San Diego (USA), and the University Medical Center Utrecht (The Netherlands) found that low level viremia in treated HIV-patients is an important risk factor for treatment failure.

The goal of antiretroviral therapy (ART) in HIV positive patients is to suppress the amount of HIV in the blood (also known as viral load) to undetectable levels. An undetectable viral load protects the patients' immune system and lowers the risk of transmission of the virus to others. In low- and middle-income countries the trigger to change ART in HIV positive patients happens at higher viral loads than in high income countries.

In the current World Health Organisation (WHO) guidelines for antiretroviral therapy (ART), which are applied in low- and middle-income countries, therapy failure is defined as a viral load of 1000 copies/mL blood despite continuous ART, while virological suppression is defined as less than 50 copies/mL. In high income settings guidelines cut-offs for therapy failure are lower and clinical intervention is already required above 50 copies/mL.

The researchers conducted a large cohort study in South Africa that aimed to investigate the fate of patients with viral loads between these different cut-offs, also known as low-level viremia (LLV). Dr. Lucas Hermans, the junior investigator performing the analysis studied 69 454 HIV positive patients from 57 urban and rural clinics that had been "successfully treated" with ART. All participants had access to routine viral load monitoring and were treated in accordance with the South African ART guidelines which follow WHO recommendations.

A quarter of the patients in this cohort on first-line ART experienced one or more episodes of LLV. Compared to patients with virological suppression, that is with <50 copies/ml, patients with LLV were threefold more prone to develop failure of ART. In patients with LLV of the highest range (400-999 copies/mL) this risk increased to nearly fivefold.

Important conclusions can be drawn from this study. The findings indicate that the current WHO-defined threshold for virological failure fails to identify a large subset of patients who are at increased risk of poor outcomes of ART.

Results from this study will be published in *Lancet Infectious Diseases* next week.

Comments from the principal investigators of this large study:

Dr. Hugo Tempelman, CEO of Ndlovu Care Group
Because African treatment programmes are based on the WHO guidelines defining failure at >1000 copies/mL, no actions are taken if HIV-patients in these settings show persistent LLV. It is unacceptable that criteria for failure and whether action is taken differ based on where you are in the world.

Dr. Francois Venter, WHRI, Witwatersrand University, Johannesburg
Sustainable virological suppression is an important part of the 90-90-90 targets defined by UNAIDS. This study shows that patients with LLV are at risk for therapy failure. A strong message from WHO regarding the risk of virological failure after LLV could motivate clinicians to act when LLV is encountered.

Dr. Annemarie Wensing, University Medical Center Utrecht

The programmatic treatment supplied in low-middle income countries allows for rapid selection of resistance, a lenient strategy towards detectable viremia is not justified in this context.

Dr. Sergio Carmona, National Health Laboratory Services - Witwatersrand University, Johannesburg
Viral load monitoring remains key to determining ART success, this study provides clear evidence that clinical interventions should take place at lower viral loads than those proposed by the current WHO guidelines. We need to support the scale-up of viral load testing in low- and middle-income countries and proactive clinical response to viral load results.