Report of HIV/TB Research meeting in conjunction with the 21st conference on retroviruses and opportunistic infections (CROI 2014)

The 8th meeting on HIV/TB research in conjunction with CROI 2014 was organised by the World Health Organisation in Boston, USA on March 3, 2014. The objective of the meeting was to discuss latency in TB and HIV, to explore the alignment of approaches and synergies, and to identify priority questions to advance basic and molecular HIV and TB research. The meeting was attended by HIV and TB researchers, public health policy makers and programme managers. The meeting was convened by Haileyesus Getahun of WHO and Richard Chaisson of John Hopkins University, USA and chaired by Eric Goosby and Diane Havlir of the University of California San Francisco, USA.

Sarah Fortune of Harvard School of Public Health presented (link to presentation) on the latency of TB and discussed the challenges and opportunities for synergised approach to molecular TB and HIV research. She highlighted the conceptual similarities between HIV and TB infection including progression to disease as characterized by replication and expansion of the pathogen population, the fact that both immunity and therapy control but do not fully eradicate the infection and that patients are without evidence of clinical symptoms and signs. She also mentioned that lessons can be derived from the research and programmatic experiences of latent TB for advancing the HIV latency agenda, including recent studies that demonstrate the importance of transmission as well as reactivation of latent reservoirs in driving disease. She also summarized the findings from the nonhuman primate models that present the best animal model to study the pathogenesis of TB latency and that both latent and active disease are characterized by a spectrum of lesions with variability even in a single host. She also suggested where isoniazid succeeds in treating latent infection, that there are important bacterial states in latently infected individuals beyond non-replicating persistent bacteria. She emphasized the need to identify the bacteria in latently infected individuals that will actually go on to reactivate. She concluded by identifying the following areas for possible TB and HIV latency research convergence: synergistic efforts to define the force of ongoing transmission, efforts to develop experimental animal models of the latent reservoirs relevant to reactivation and quantitative frameworks to define the threshold for cure and the effects of protective immunity.

A commentary was conveyed by Henry Boom of Case Western University, USA (link to presentation) particularly discussing latency in TB from the host's perspective and highlighting the presence of numerous dogma in its understanding. He posed many questions that need better understanding of the pathogenesis of TB latency including the reasons why the very extensive and diverse T cell response can not eliminate latent mycobacteria, better understanding of the role and mechanism of human genetics in TB susceptibility and the likely natural resistance to Mycobacterium tuberculosis infection which may provide insight into innate immune mechanisms of resistance. He concluded his commentary by highlighting areas that can further be explored to seek for synergy between TB and HIV research including investigating key T cell antigens and functions that could potentially control latent MTB, identification of biomarkers for progression from latent TB to active disease given the higher
rates of progression in HIV infection and deriving lessons from HIV "cure" approaches and exploring the effects of immune activation of latent and active TB on HIV in macrophages and Ag-specific T cells in lymph node and lung.

Mike McCune of University of California San Francisco, USA presented (link to presentation) the progression of thinking about the HIV latency and cure agenda including a historical perspective. He mentioned even with the presence of effective antiretroviral treatment and long duration of treatment, more than 80% of people living with HIV will continue to have low level HIV viraemia. This is mostly due to the presence of long-lived CD4 reservoir cells with latent HIV genomes and the interaction of myeloid and T cells leading to viral replication and persistence. He also pointed out that eradication of HIV is likely to require multiple therapies targeting these cells and would probably be preferable than putting patients on life-long treatment. He acknowledged that collaborative efforts between research groups have been the mainstay for advancing the HIV cure agenda. He expressed concern that much of the ongoing HIV cure research is limited to the US, Europe, and Australia and does not cover diverse population groups, and that this current limitation poses a challenge in the broader and long term impact of the research. He underlined the importance of better understanding the impact of TB upon the size and composition of HIV reservoir and the impact of selected HIV eradication interventions on HIV-associated TB. He further reiterated the need for comprehensive tissue-based research, including the evaluation of availability of drugs in HIV-associated TB.

Meeting participants debated on the use of the term “latent Mycobacterium tuberculosis infection”. David Cohn of University Colorado, USA reminded that the term was coined in early 90s by public health practitioners attending US CDC’s guidelines development meeting without much consideration for the pathological complexity and input from biologists and questioned if the use of the term is still valid. However, participants reiterated the importance of retaining the terminology for its clinical significance as it helps to differentiate latent TB from active TB disease.

The meeting was concluded with a general consensus on the value of intensifying efforts to align research between TB and HIV latency and seek for synergies including defining the force of ongoing TB and HIV transmission, development of experimental animal models of the latent reservoirs and better understanding of the immunopathological impact of TB in the HIV cure research agenda. Similarly efforts are needed to expand the HIV cure research both geographically and in diversity of the population groups covered.