The World Health Organization convened a meeting on HIV/TB research in conjunction with CROI 2019 in Seattle, USA on 4th March 2019. The meeting was chaired by Richard Chaisson of Johns Hopkins Medicine and Diane Havlir of the University of California, San Francisco.

The objective of the 2019 meeting was to review the longer-term prospects for TB prevention among people living with HIV and to stimulate high level scientific debate on the opportunities, challenges and research implications for developing a more durable and acceptable method of TB prevention.

**Longer Acting medications for TB Prevention:** Nicole Ammerman from Johns Hopkins University School of Medicine presented on the potential for long-acting injectable formulations, including the benefits of reduced toxicity, and ease of administration, and potential for greater adherence (link to presentation). In particular, she highlighted the case for bedaquiline in which studies have already demonstrated that plasma concentrations and exposures can be maintained using long-acting formulations. Dr Ammerman shared findings of a recent study, using a paucibacillary mouse model of LTBI treatment to evaluate the *in vivo* bacteriocidal activity of a long-acting bedaquiline formulation, compared with that found in untreated mice, mice treated with daily rifampicin, once weekly high-dose isoniazid and rifapentine, and daily oral bedaquiline. The findings showed that over 12 weeks, once-monthly dosing of long acting bedaquiline demonstrated superior or equivalent activity to daily oral administration or the same total bedaquiline oral dose; a single dose of long acting bedaquiline demonstrated bactericidal activity for up to 12 weeks post-administration at plasma concentrations above the MIC (7H11) for *M. tuberculosis*.

In his commentary, Gary Maartens from the University of Cape Town, pointed out that although drug-drug interactions are reduced by long-acting injectables, clinically significant interactions still occur. (link to presentation). For example, studies on the interaction between antiretroviral drugs and long-acting progesterone-only contraception demonstrated that lower plasma concentrations of progesterone are achieved when co-administered with efavirenz – this interaction has resulted in unintended pregnancies. Dr Maartens also cautioned that, once administered, long-acting formulations cannot be interrupted in the event of toxicity occurring. The possibility of emergence of drug resistance as a result of gradually declining concentrations of mono-therapy should be carefully ruled out in clinical studies.
Vaccines for TB prevention: Ann Ginsberg of IAVI shared recent data from two trials published in 2018 and stressed that now is the time to accelerate TB vaccine development after a year of unprecedented progress (link to presentation). The proof of concept Phase 2 prevention of infection study evaluated safety, efficacy and immunogenicity of H4:IC31 and BCG revaccination among QuantiFERON negative adolescents in the Western Cape in South Africa, in whom risk of infection is approximately 10% per year. Results from this trial found that both H4:IC31 and BCG revaccination appeared safe and immunogenic, neither showed statistical significance in preventing initial infection (measured by initial QuantiFERON conversion), BCG revaccination resulted in statistically significant prevention of sustained control of infection (measured by sustained QuantiFERON conversion), lasting at least six months, whereas H4:IC31 did not show statistical significant prevention at 95% confidence level.

Results from the primary analysis of the M72/AS02 Phase IIb prevention of disease trial were also presented. Conclusions from early phase trials, two of which had been among people living with HIV, showed that this vaccine was generally well tolerated, with a high seroconversion rate and long lasting humoral response, strong poly-functional CD4 Th1 cells responses, and low levels of CD8 cells responses and of IL-17-expressing CD4 T cells. The presented double-blinded, randomized 1:1 study compared M72/AS02 with placebo among HIV-negative healthy adults (18-50) years who were sputum Xpert MTB/RIF negative but Mtb-infected (measured by QuantiFERON). Results showed that M72/AS02 prevented TB disease in Mtb-infected adults with an efficacy of 54% (CI90% 14-75%, p=0.04), and had an acceptable safety profile. Dr Ginsberg emphasised the need for further research on these vaccines and the implications and feasibility of mass vaccination campaigns, as well as the need to establish safety and efficacy in people living with HIV.

In his commentary, Mark Harrington from Treatment Action Group highlighted the insufficient levels of investment in TB vaccine development and the need both to increase investment from existing investors and expand the pool of investors within both industry and public sectors, looking also at middle income countries that have potential for domestic investment in R&D. He argued that stronger collaboration and engagement with a broader range of stakeholders including civil society, the public health community, occupation and labour community, health workers and people who work in prisons would be critical for advancing the vaccine development agenda. He pointed out that the landscape of TB prevention clinical trials design will become more complex with new advances in both preventive therapy and promising candidate vaccines, and emphasized the need for studies including people with HIV, adolescents, and older adults. He concluded that we are at an exciting phase in vaccine research and development but we need now to galvanise resources and political will to get us to where we want to be within the next five to ten years.

During the main CROI conference notable highlights included:

- A presentation from the IMPAACT4TB network DOLPHIN study (abstract 80LB) that co-administration of dolutegravir and 3 months of rifapentine and INH as TB preventive treatment was well tolerated (no grade>3 adverse events) and no dose adjustment was needed.
- A prospective cohort study on 2nd/3rd trimester initiated INH prophylaxis for latent TB among HIV positive pregnant women from the Tshepiso cohort (abstract 77) in Soweto South Africa found no association with poor maternal and infant outcomes. The result differs from TB APPRISE results presented at CROI in 2018.
- Data from the DELIBERATE trial (abstract 84) demonstrated that in 74 participants receiving an MDR-TB regimen including both bedaquiline and delamanid, (and not including other MDR TB drugs with significant QT prolongation effects such as clofazimine and moxifloxacin), there were no grade 3 or 4 QT interval prolongation events.
- The DO ART study (abstract 723), an ongoing RCT of ART service delivery approaches in KwaZulu Natal South Africa, showed that TB preventive treatment provision is feasible and acceptable with community ART delivery.