



Report of HIV/TB Research meetings in conjunction with the 2018 Conference on Retroviruses and Opportunistic Infections (CROI 2018)

The World Health Organization organised a meeting on HIV/TB research in conjunction with CROI 2018 in Boston, USA on March 4, 2018. The meeting was chaired by Richard Chaisson of Johns Hopkins Medicine and Constance Benson of University of California, San Diego.

The objective of the 2018 meeting was to review and discuss the latest evidence as well as to stimulate high level scientific debate around the opportunities, challenges, and scientific research implications posed by the latest short-course rifamycin-based TB preventive regimens in the context of scale-up of the latest generation of antiretroviral drugs with particular focus on Dolutegravir.

Haileyesus Getahun of WHO presented the latest updated and consolidated guidelines on the programmatic management of latent TB infection ([link to presentation](#)). He mentioned that the guidelines were necessitated by demand from countries to address challenges caused by the fragmentation of existing recommendations, impacting on simplicity and clarity, as well as offering limited options for high TB burden settings. The new guidelines strongly recommend TB preventive treatment not only for people living with HIV and children under 5 years old who are household contacts of a person with pulmonary TB, but also for patients with silicosis and in those receiving anti-TNF treatment or undergoing dialysis or transplantation in high TB burden settings. Furthermore, TB preventive treatment may be considered for all contacts over 5 years old, in contact with people with pulmonary TB living in high TB burden settings. The guidelines recommend that treatment options may also include a weekly isoniazid and rifapentine combination for 12 weeks (3HP) including for people living with HIV as an alternative to 6 months isoniazid.

Kelly Dooley of Johns Hopkins Medicine presented ([link to presentation](#)) on key opportunities, challenges and knowledge gaps around the use of Dolutegravir and Tenofovir Alafenamide (TAF) with shorter rifapentine based treatment of latent TB in people living with HIV including whether they are safe and could be used without dose adjustment. She also discussed the safety of combined use of 3HP (or 1HP) with Dolutegravir following the study which was terminated after two of the four volunteers developed adverse events. She emphasized the need to collect more data on the issue in individuals with HIV infection, as it is difficult to reach conclusions based on the data from the four volunteers. Her argument was based on the fact that Dolutegravir is well tolerated with daily rifampicin in patients with HIV-associated TB (e.g. in INSPIRING Trial), that 3HP was better-tolerated in HIV-infected than HIV-uninfected persons with lower rates of hypersensitivity events in the large Phase 3 PREVENT-TB trial, and that tolerability of rifamycins has been historically very different in trials involving 'healthy volunteers' who have neither HIV infection nor TB infection than in individuals with HIV and/or TB. Furthermore, the level of isoniazid was high (but concentrations of dolutegravir and rifapentine were not) in the volunteers who developed the reaction. She pointed out that the upcoming result of DOLPHIN trial, part of the IMPAACT4TB effort, will give answers to the safety questions of rifapentine and Dolutegravir in the relevant population.

Francois Venter of University of Witwatersrand ([link to presentation](#)) cautioned that the scale-up of Dolutegravir posed challenges for TB patients living with HIV on top of the logistical problem for programmes. However, he pointed out that the overall toxicity and resistance profile of Dolutegravir is very compelling. In the meantime he emphasized that more studies should be conducted among TB patients and pregnant and non-pregnant women, noting that most of the studies conducted to date are done among men. In addition, he underlined that the scale-up

of isoniazid preventive treatment should also be prioritized, and questioned whether shorter course regimens would be better.

Meeting participants raised several issues including the resistance of programme managers and clinicians in providing TB preventive treatment primarily due to fear of drug resistance, which is not substantiated. Innovative interventions including developing and testing educational programmes for health workers were suggested. In addition, as the pill number needed to be taken by people living with HIV is reducing, the combination of isoniazid with antiretroviral treatment was suggested as one mechanism to boost uptake of TB preventive treatment.

A second round table meeting was organized by the TB and HIV teams of WHO and the Bill and Melinda Gates Foundation to identify critical research and implementation priorities to cut and eliminate TB deaths among people living with HIV in the context of differentiated delivery of the HIV cascade of care. The meeting was held on March 4, 2018 in conjunction with CROI 2018 and was chaired by Peter Ehrenkranz of Bill and Melinda Gates Foundation and Haileyesus Getahun of WHO. The round table will inform the development of a comprehensive framework for research and implementation to cut and eliminate TB deaths among people living with HIV. Research and implementation priorities suggested by participants of the meeting included:

- Development of an effective algorithms and mechanisms (e.g. m-health) that can be used by lower health cadres and community health workers and volunteers to expedite the screening and diagnosis of TB.
- Development of models using community health workers and volunteers to implement TB preventive treatment and triaging of TB suspects at the community level.
- Combination tablets and formulations of ART and TB preventive drugs including financial incentives for generic manufactures, and mechanisms to ensure the adoption by countries of latest policies.
- Studies that explore long acting injectables for TB preventive treatment.
- Studies exploring whether the current TB treatment regimen is effective for people living with HIV with severe illness such as disseminated TB.
- Clinical trials examining same day initiation of TB treatment and ART with steroids.
- Structured operations and programme reviews that systematically promote experience and best practice sharing among programme managers and south-south collaboration, and leveraging existing cross-country networks.
- Well designed studies and good practice models on the integration of TB and HIV services at facility level.
- Identification of critical gaps and challenges (be they supply chain, provider attitudes, patient behaviours, and sample transport).

Several key TB studies were presented on the first day of the Conference including:

- [INSPIRING trial](#) showed that 50mg of Dolutegravir twice daily is effective and well-tolerated in people living with HIV receiving Rifamycin for TB treatment with low rates of IRIS, no new toxicity signals and no discontinuations due to liver events.
- [BRIEF-TB trial](#) showed that one month daily isoniazid and rifapentine (1HP) was non-inferior to 9 months isoniazid, had fewer adverse events and with more completion.
- [STAMP trial](#) showed that systematic use of Urine LAM screening of hospitalised HIV positive patients increased overall TB diagnosis and reduced mortality in those with anaemia, <100 CD4 count and in those suspected with TB at admission.
- [STATIS trial](#) showed no mortality difference between empiric TB treatment and extensive TB screening using Xpert MTB/RIF and urine LAM among ART-naïve adults with CD4<100/μl supporting current WHO recommendations on empiric TB treatment which were formulated based on expert opinion.

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