To,

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Date: 21/12/18

Submission: Minimize injectables and scale up new drugs in drug-resistant tuberculosis (DR-TB)regimens

Dear Dr. Sachdeva , Mr. Kumar, Prof. Paul and Dr. Gangakhedkar,

We are representing people affected by DR-TB, various health organizations and people living with HIV. With 1.47 lakh citizens affected every year and mortality rates that are amongst the worst in the world, DR-TB continues to pose a major public health challenge in the country. Given this back ground we raise some genuine concerns on access to Bedaquiline (Bdq) and Delamanid (Dlm) and in addition adequate Drug Sensitivity Testing (DST) facilities throughout the country.

Minimizing use ofinjectables and scaling up Bedaquiline (BDQ)

After a gap of 50 years, two new antibiotics – Bdq and Dlm – have been developed that offer fresh hope to DR-TB patients.

In August 2018, the WHO's Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-Resistant Tuberculosis (MDR/RR-TB)noted that "*treatment success for MDR-TB is currently low in many countries and thatthis could be increased by improving access to the highest-ranked medicines for all patients with MDR-TB.*" It also highlighted "*the immediate steps to be taken to ensure that MDR/RR-TB patients receive treatment in accordance with the latest evidence on effectiveness and safety*" and included Bdq inits highest ranked Group A, while they dropped down the injectable amoniglycosideamikacin to Group C (least preferred option).

Further, the Rapid Communication unequivocally states that:

"Medicines no longer recommended are kanamycin and capreomycin, given increased risk of treatment failure and relapse associated with their use in longer MDR-TB regimens."[1]

[1]https://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1

Thus, the clear-cut recommendation is to minimize the use of injectables and at the same time, scale up the use of new DR-TB drugs to help form anefficient treatment regimen that will improve outcomes.

However, in spite of the recommendations by WHO, a mere three months later, in October 2018,the Central TB Division (CTD) in India has floated a tender for the injectable drugs, kanamycin and capreomycin, (Tender No. CMSS/PROC/2018-19/RNTCP/016).

Additionally, although theGuidelines on Programmatic Management of Drug Resistant Tuberculosis (PMDT) have stipulated that patients with any fluoroquinolone(FQ) resistance are eligible for Bdq[2], the DR-TB Scale-Up Treatment Action Team (DR-TB STAT)[3] data shows that only 1607 patients in India have received Bdq till December 2018. However, the first ever Anti TB Drug Resistance Survey of India, released earlier this year,[4]estimates that over 20% of the 1,47,000 MDR-TB patients in India are resistant to FQ. Thus, a mere, 1607of approximately 30,000 patients who are eligible for Bdq have actually received it.

This shows that the number of patients who have received Bdq is abysmally low compared to the need of the country. In fact, going by the precedent set by South Africa and the new WHO recommendations, all patients who have RR-TB should get Bdq as it has clearly been prioritized over several other drugssuch as injectable aminoglycosides to form an effective treatment regimen.

One key reason forthis slow scale up of Bdq is lack of adequate DST facilities in the country. In this context we would like to highlight that under the National Strategic Programme for Tuberculosis 2017–2025 (NSP), although the government intends to perform DST (phenotypic or molecular) on all TB samples, the current universal DST is performed only on samples from 257 of the 712 districts in the country (CTD, India TB report 2018). However, to diagnose the estimated 150, 000 cases of MDR-TB every year, the number of DST laboratories and the number of samples tested in each laboratory will need to be urgently scaled up.[5]

Lessons from South Africa:

Over 15,000 South Africans with DR-TB have already received Bdq, and new recommendations pave the way for many more patients to receive this essential drug.

In South Africa, the National DR-TB directorate, supported by the clinical expert committee have taken all the learnings and clinical progress of patients initiated on Bdq into consideration and therefore recommend that Bdq be incorporated as a core drug in the DR-TB regimen.

This will translate to all DR-TB (RR/MDR/Pre-XDR /XDR-TB) patients receiving Bdq upon diagnosis during the intensive phase of treatment. This recommendation came into effect 1 July 2018.

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[2]Addendum 1: Guidelines for Use of Bedaquiline under RNTCP PMDT – August 2016
[3]http://drtb-stat.org/country-updates/
[4]https://tbcindia.gov.in/showfile.php?lid=3315
[5]http://dx.doi.org/10.1136/bmjgh-2018-000971

Bdq will replace and minimise the injectable aminoglycosides in the standard treatment regimen. The injectables aminoglycosides are associated with a number of serious side effects, including irreversible hearing loss[6].

The South African Department of Health has also started releasing new data on reduction in TB mortality cases from DR - TB in South Africa through use of Bdq[7], [8].

India has a strong case to follow South Africa's lead. The Revised National TB Control Programme (RNTCP) should prioritize forecasting, procurement and scaling up access to Bdq and focus on providing itto DR-TB patients at an early stage when it is proven to be more effective. Time and again, we have lost patientswho could have survived with the help of these newer TB medicines but received the treatment too late.

Increase access to both Bdq and Dlm for DR-TB patients

On 17 August, 2018, the WHO issued a rapid communication[9]that classifies Dlm as an additional drug to help build efficient MDR-TB regimens with the existing core drugs such as Bdq, linezolid, moxifloxacin or levofloxacin, and clofazimine. Clinicians need to make a decision on whether or not to use this crucial drug based on individual patient assessment and well-established considerations for the composition of MDR-TB regimens.

MDR-TB patients with confirmed resistance to FQand/or second-line injectable drugs or who can´t tolerate one of the other drugs (group A or B) present a particular treatment challenge. In such cases, Dlm in combination with Bdq may have a crucial role to play in strengthening a regimen, bringing the number of drugs likely to be effective to a minimum of four, and reducing the risk of acquisition of additional resistance and progression towards XDR-TB.

Dlm also has an approved indication in children and adolescents between 6-18 years old in India, offering an opportunity to reduce the use of injectable aminoglycosidesin children.

While, Bdq has been used in many DR-TB patients with HIV (adjusting the ART treatment), Dlm has less Drug-Drug Interactions (DDIs) with antiretrovirals (ARVs) and can also be provided to people living with HIV/AIDS (PLWHA).

Thus, we strongly recommend that in the Indian context the RNTCP also consider increasing access to Dlm by forecasting and starting the process of procurement and tendering in 2019.

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[6]Reuter A et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? Int J Tuberc Lung Dis. 2017 doi:10.5588/ijtld.17.0468.

- [7]Department of Health, Republic of South Africa, New bedaquiline data shows reduction in TB mortality cases. http://www.health.gov.za/index.php/2014-03-17-09-48-36/2014-03-17-09-49-50?download=2797:media-statement-new-bedaquiline-data-shows-reduction-in-tb-mortality-cases

[8]Schnippel K et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. Lancet Respir Med 2018. http://dx.doi.org/10.1016/S2213-2600(18)30235-2

[9]World Health Organization, "Rapid Communication: Key Changes to Treatment of Multidrug- and Rifampicin-resistant Tuberculosis (MDR/RR-TB)", 17 August 2018. Available at: http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1

Thus, we demand:

- *CTD make greater efforts to scale up universal Drug Susceptibility Testing (DST) as lack of quality assured testing facilities is a major barrier for DR-TB patients to access safer, effective and rational DR-TB regimens.*

- *Injectable kanamycin and capreomycin be totally removed from PMDT guidelines by CTD and a circular regarding the same be sent out urgently.*

- *Technical Expert Group on Treatment of TB of theCTD should expand the PMDT eligibility criteria in line with the current WHO recommendation of expanding the use of Bdq by making it a core drug in standard regimens to treat MDR-TB and should not reserve it only for extensively drug resistant TB (XDR-TB) patients as is the current practice. .*

- *CTD should revise the PMDT eligibility criteria to make Dlm in combination with Bdq available to DR-TB patients with confirmed resistance to fluoroquinolones and/or or intolerance to second-line injectable drugs or other Group A or Group B drugs. Access to Dlm is also needed for PLHIVs co-infected with DR-TB. Children with DR-TB should also benefit from injectable free regimens on the basis of scale-up of Dlm.*

- *CTD phase-out donations from J&J and Otsuka/Mylan that are not sustainable in the long term and streamline procurement by forecasting, budgeting and tendering for Bdqand Dlm.*

- *CTD to ensure that public funded TB research institutions such as* National Institute for Research in Tuberculosis*and* Indian Council of Medical Research(ICMR) *prioritize clinical trials for short-course oral M/XDR-TB regimens that are essential to provide data and guidance to CTD in the coming years to address this public health emergency.*

Sincerely,

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South Indian TB Action Force
Lawyers Collective
ARK Foundation, Nagaland
Global TB Community Advisory Board (TBCAB)
Meghalaya Drug Users Network (MeDuNet)
Kripa Foundation Nagaland
Tamil Nadu Networking People with HIV/AIDS (TNNP+)
Empower India
Nagaland Users' Network
Kohima Users' Network
Mizoram Drug Users' Forum
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