World Health
Organization

Position statement
on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results

April 2018

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This position statement by the World Health Organization (WHO) has been issued in response to the release of preliminary results of the STREAM Stage 1 trial at the 48th UNION World Conference on Lung Health in Mexico in October 2017[1], as well as additional details about deaths and the study protocol made available to WHO by the trial investigators in January 2018. The position statement is released in response to queries from multiple stakeholders, including national TB Programmes, donors and civil society.

The STREAM Stage 1 study is a phase III, multicentre, open-label, randomized controlled clinical trial that was conducted to evaluate the safety and efficacy of a standardised "shorter" regimen (40-48 weeks; study arm) for multidrug-resistant tuberculosis (MDR-TB) compared to a "longer" regimen (18-24 months; control arm)[2]. The findings of this first-ever trial of the shorter MDR-TB regimen are relevant to the conditional recommendation on its use issued by WHO in 2016 which was based on observational study data[3]. The conclusions in this document should be read in conjunction with the 2016 guidelines.

Background

- In 2010, the first publication on the outcomes of shorter MDR-TB regimens in selected patients in Bangladesh reported relapse-free cure in 88% of those treated[4]. At the time, WHO advised that the introduction of such regimens needed to be done under operational research conditions. Similar outcomes were reported subsequently from patients treated with shorter regimens in Cameroon and Niger[5,6].

- In 2016 WHO issued evidence-based conditional recommendations on the use of a standardised shorter regimen for the treatment of patients with multidrug- or rifampicin-resistant TB (MDR/RR-TB)[3]. This policy guidance was developed in accordance with WHO requirements, using the GRADE approach[7,8]. The development of the 2016 policy was informed by evidence from observational

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[1] Preliminary results from STREAM trial provide insight into shorter treatment for multidrug-resistant tuberculosis. Available from: http://www.ctu.mrc.ac.uk/news/2017/preliminary_results_from_stream_trial_provide_insight_into_shorter_treatment_for_multidrug_resistant_tuberculosis

[2] Nunn AJ, Rusen ID, Van Deun A, Torrea G, Phillips PPJ, Chiang C-Y, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials. 2014;15:353.

[3] WHO treatment guidelines for drug-resistant tuberculosis, 2016 update (WHO/HTM/TB/2016.4). Available from: http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf. Geneva: World Health Organization; 2016.

[4] Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010 Sep 1;182(5):684–92.

[5] Kuaban C, Noeske J, Rieder HL, Aït-Khaled N, Abena Foe JL, Trébucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis. 2015 May;19(5):517–24.

[6] Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis. 2014 Oct;18(10):1188–94.

[7] WHO Handbook for Guideline Development – 2nd ed. Available from: http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf. Geneva: World Health Organization; 2014.

[8] GRADE Home. http://www.gradeworkinggroup.org/.

studies conducted in Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Democratic Republic of Congo, Niger, Uzbekistan and Swaziland.

- A meta-analysis compared treatment outcomes from 1,205 participants in these observational studies to those from a pooled cohort of MDR-TB cases without previous exposure to second-line TB agents and who were treated with longer regimens[3]. The certainty in the estimates of effect was considered *very low* based on the GRADE evidence assessment.

- The 2016 WHO conditional recommendation indicated that a shorter MDR-TB regimen of 9–12 months may be used instead of longer MDR-TB regimens in selected patients with MDR/RR-TB who were not previously treated with second-line TB medicines and in whom resistance to fluoroquinolones and second-line injectable agents is excluded or is considered highly unlikely. Specifically the recommendation is limited to MDR-TB patients to whom the following exclusion criteria do not apply:
    - Confirmed resistance or suspected ineffectiveness to any medicine in the shorter MDR-TB regimen (except isoniazid);
    - Exposure to one or more second-line medicines in the shorter MDR-TB regimen for one or more months;
    - Intolerance to one or more medicines in the shorter MDR-TB regimen or at increased risk of toxicity from such medication (e.g. drug-drug interactions, pre-existing QT-interval prolongation);
    - Pregnancy;
    - Extrapulmonary disease; and
    - Unavailability of one or more medicines of the shorter regimen.

- The 2016 conditional recommendations included children and HIV-positive individuals based on inferences drawn from observational data available at the time. Use of the standardised shorter regimen under programmatic conditions and outside of operational research settings is also conditional upon active TB drug-safety monitoring and management (aDSM)[9].

- In late January 2018, the STREAM trial investigators provided WHO with preliminary results on effectiveness, death, safety and health economic impact from Stage 1 of the study. At the time of the expedited review, all patients had completed treatment but 50 patients were still being followed-up and the data were complete for 87% of enrolled cases. The results from this first-ever randomized controlled trial for a shorter MDR-TB regimen were long-awaited and anticipated to improve the quality of available evidence for the outcomes of interest. The findings were reported as a set of tabulations, graphics and narratives (not as individual patient data). Additional information to the results presented in Mexico in October 2017 was provided to WHO, but all data referred to the same database lock-down of 19 September 2017 (Stage 1 is expected to be completed in July 2018). Anonymized reports were provided containing clinical details for the 33 study participants who had died. The study protocol was also made available[10].

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[9] Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. (WHO/HTM/TB/2015.28). http://apps.who.int/iris/bitstream/10665/204465/1/WHO_HTM_TB_2015.28_eng.pdf. Geneva: World Health Organization; 2015.
[10] STREAM. The evaluation of a standard treatment regimen of anti-tuberculosis drugs for patients with MDR-TB. ISRCTN 78372190. Protocol Version 6.2. 2015.

Expedited review process

- In agreement with the WHO Guideline Review Committee, a group of external experts conversant in clinical trials, pharmacology, microbiology, therapeutics and clinical management of MDR-TB was convened by the WHO Global TB Programme to: i) review the preliminary results of the STREAM Stage 1 trial; ii) assess the quality of the evidence and remark on other issues related to the STREAM Stage 1 trial design and execution; and iii) advise WHO whether the 2016 policy on the use of the shorter MDR-TB regimen should be retained, modified or withdrawn. The same experts were involved in a similar expedited review of the Phase III trial of delamanid for MDR-TB in December 2017[11].

- The review was comprised of a detailed GRADE evidence assessment in compliance with established WHO procedures[7]. To ensure procedural and methodological consistency, preliminary outcomes of the STREAM Stage 1 trial were assessed according to the same PICO[12] question and outcomes that had informed the 2016 WHO policy guidance, i.e. whether a treatment regimen lasting up to 12 months was as likely to lead to cure and other outcomes[13] in MDR-TB patients when compared with longer MDR-TB regimens recommended in the WHO guidelines of 2011[14].

- The GRADE evidence summaries and evidence-to-decision tables created in this expedited review are expected to be updated with the final results of STREAM Stage 1 trial ahead of a comprehensive update of WHO MDR-TB treatment policy planned later in 2018. At that time additional data from observational studies of the shorter regimen in different settings are also expected to become available for analysis.

Trial design and characteristics

- The sample size of the STREAM Stage 1 trial was powered to assess non-inferiority of the shorter regimen against longer regimens based on WHO recommendations (80% power, assuming 20% of patients could not be assessed). The basic premise was that the shorter regimen would achieve a "favourable outcome" in 75% of patients and the longer regimens in 70%. These thresholds were based on the reported performance of comparable regimens under programmatic conditions at the time the trial started, and assumptions for a better performance of the control and lower efficacy of the study regimen than those in published reports[15].

- Non inferiority trials are intended to show that a novel medicine or regimen is not worse than the usual treatment recommended (control)[16]. The STREAM Stage 1 trial protocol stipulated that non-inferiority would be accepted if the upper level of the 95% confidence limit for the difference in

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[11] WHO position statement on the use of delamanid for multidrug-resistant tuberculosis (WHO/CDS/TB/2018.1). Available from: http://www.who.int/tb/publications/2018/WHOPositionStatementDelamanidUse.pdf. Geneva: World Health Organization; 2018.

[12] An acronym for **P**opulation, **I**ntervention, **C**omparator and **O**utcomes, referring to the method used to formulate a clinical question in a systematic manner to guide the collection and summarization of relevant evidence when using GRADE.

[13] Other outcomes in addition to cure were: completed, culture conversion by 6 months, failure, relapse, survival (or death), adverse reactions, acquisition (amplification) of additional drug resistance, adherence to treatment (or treatment interruption due to non-adherence)

[14] Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 Update. (WHO/HTM/TB/2011.6). http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf. Geneva: World Health Organization: 2011.

[15] Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

[16] US FDA. Non-Inferiority Clinical Trials to Establish Effectiveness. Guidance for Industry. 2016. https://www.fda.gov/downloads/Drugs/Guidances/UCM202140.pdf

efficacy between the shorter and the longer regimen was **no more than 10%**; thus, if this limit was not exceeded then non-inferiority would have been demonstrated.

- The study regimen was based on the regimen described by Van Deun *et al* 2010[4], consisting of clofazimine, ethambutol, high-dose moxifloxacin (in place of gatifloxacin), and pyrazinamide given for 40-48 weeks, supplemented in the first 16-24 weeks (intensive phase) by high-dose isoniazid, kanamycin, and prothionamide. The control arm was the locally-used longer MDR-TB regimen based on WHO recommendations[14].

- Patients in both arms were followed up until 132 weeks post-randomization. Direct observation of treatment was conducted by health care workers or family members during the trial. Local and reference laboratory assessments, including microbiological tests used to assign patient outcome, were conducted blindly. However, the patients, study coordinators, health care workers and data managers were not blinded to the treatment arm.

- Trial outcomes were specified in the protocol as follows:

  - "Favourable outcome" was the primary study endpoint, defined as being culture negative at 132 weeks post-randomization and at the previous occasion that the patient was seen, unless the patient's outcome had already been classified as unfavourable;

  - "Unfavourable outcome" was defined as not satisfying the favourable outcome criteria because of (i) start of two or more additional medicines (including a change of regimen); or (ii) treatment extension beyond the permitted duration; or (iii) death at any point up to 132 weeks post-randomization; or (iv) a positive culture result at 132 weeks post-randomization or when last seen; or (v) not having been seen at 76 weeks or later.

- Safety monitoring during the STREAM Stage 1 trial was done by serial monitoring of clinical and laboratory testing according to a schedule defined in the protocol. The QT-interval duration was corrected using the Fridericia method (QTcF), by means of an automated measurement on the electrocardiogram.

- A health economic impact analysis was done in Ethiopia and South Africa as part of the STREAM Stage 1 trial, evaluating both patient and health service costs. Patient-related costs (inclusive of socioeconomic and income data, and supporter costs) were captured at baseline and during treatment. Staff interviews were also performed to gather information on clinical management, tests, examinations and durations. Not all data had been analysed at the time of the review; therefore, the health economic findings are considered preliminary. Data on direct patient costs were available only for Ethiopia (there were insufficient data available from South Africa for this review). Moreover, given that both economic assessments were performed in African countries, the findings may not be widely generalizable outside this setting. A full cost-effectiveness analysis is planned upon completion of the STREAM trial.

- STREAM Stage 1 enrolled patients between July 2012 and June 2015 at seven sites located in Ethiopia, Mongolia, South Africa and Viet Nam. Eligible patients were adults with rifampicin-resistant strains and without *in vitro* resistance to fluoroquinolones or aminoglycosides on line probe assay. Patients who were pregnant, who were breast feeding, or who had pre-existing QT-interval prolongation (QTcF ≥500 ms) or evidence of liver abnormality (aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal) were excluded.

- STREAM Stage 1 randomized 424 participants in a 2:1 ratio, into either the short regimen (study arm, 282 participants) or the longer regimen (control arm, 142 participants). One patient did not start treatment and therefore 423 participants constituted the "intention to treat" (ITT) population, used for assessment of safety. The "modified intention to treat (mITT)" population included all randomized participants who had bacteriological results and could thus be assessed for efficacy (383/424 cases). Overall, 254 study arm participants (90% of ITT individuals) and 129 control arm (91%) participants were included in the mITT analysis. Most of the 41 exclusions from the ITT were due to negative cultures at the point of randomisation (28 cases) or rifampicin susceptibility (8 cases).

- Additional exclusions from the expedited review were necessary: 50 patients lacked full follow-up information at the time of the review, nine participants had not been seen at week 132, and six participants had been confirmed to be re-infected rather than having relapsed (through DNA fingerprinting). Thus, 318 participants (210 in the study arm and 108 in the control arm) were retained for the assessment of efficacy (representing 83% of the mITT population, and 75% of those randomized).

- Annex 1 shows the main efficacy and safety outcomes in the two arms assessed during this review. Time-to-culture-conversion by week 20, deaths, adverse events and QT-interval prolongation were assessed using the ITT population. "Favourable outcome", lack of culture conversion or culture reversion during therapy, or relapse after end of therapy were assessed using the available mITT population. No information about the acquisition of additional resistance was available at the time of this review.

Main findings

- The external experts acknowledged that the overall conduct of the STREAM Stage 1 trial met high scientific standards; that the trial was guided by an extensive and detailed study protocol, and had broad geographic distribution of recruitment (seven sites in four countries).

- The GRADE assessment rated the overall certainty of the evidence as _moderate_[8]. Certainty was lowered one level from _high_, largely because of imprecision, given that results were still interim and the number of patients in each arm was relatively small resulting in wide confidence intervals around the estimates (see column on Effects in Annex 1). No information was available about possible selection of patients prior to randomization.

- For the two mortality outcomes (see Annex 1), imprecision led to further downgrading of the certainty in the evidence by one level, from _moderate_ to _low_, because the wide confidence intervals implied substantial uncertainty on risk of death or likelihood of survival.

- Amongst the mITT population, 58% were aged 18-34 years, 61% were males, 46% weighed less than 50kg at start and 33% were HIV-positive. Overall, 99% of trial participants tested at the time of analysis were susceptible to both fluoroquinolones and second-line injectable agents and 6% were susceptible to isoniazid (no information was available for pyrazinamide resistance at the time of this review). These baseline characteristics were comparable between the two arms.

Efficacy

- "Favourable outcome" by 132 weeks in patients treated with longer regimens in the control arm was **marginally higher than in those receiving the shorter regimen** although **not statistically significantly different** (80.6% vs. 78.1% respectively; relative risk (RR) 0.970, 95%CI 0.862 - 1.090; P=0.60; risk difference +2.5%, 95%CI -6.9% to +11.8%[all values unadjusted]).

- When adjusted for study site and HIV status (a pre-specified analysis accounting for stratified randomization on these factors), the difference was 2.1% in favour of the control arm regimen (95%CI -6.9% to +11.2%). The study thus **did not satisfy the non-inferiority criterion** (as per the protocol); the upper limit of the 95% confidence interval exceeded the pre-specified threshold of 10%. However, there was uncertainty about the true risk difference because the confidence interval of the estimated risk difference extended on both sides of zero (see *Conclusions*).

- The observed **proportion of patients in whom sputum culture failed to convert to negative or reverted to positive during therapy, or who relapsed after therapy, was higher in the study arm** than the control arm (9% vs. 3.7% respectively), although this difference in risk was **not statistically significant** (RR 2.443; 95%CI 0.852-7.002).

- **No statistically significant difference in patient retention** was observed between the two arms, but fewer patients were not seen at 76 weeks or later in the study arm than among the controls (2.9% vs. 6.5% respectively; RR 0.441; 95%CI 0.152-1.279).

- Overall, there was **not a clinically-relevant or statistically significant difference in all-cause mortality** between the two arms: at 132 weeks 8.5% of the study arm participants had died compared to 6.4% of the control participants (RR 1.333; 95%CI 0.637-2.792). Deaths occurred at different time points, up to 128 weeks after randomization (mean: 47 weeks; median: 28 weeks); 7 of them occurred after treatment was completed among patients in both arms.

- In the subgroup of **patients with HIV, the number of observed deaths was higher in the study arm** (18/103; 17.5%) compared to the control arm (4/50; 8.0%); however, the number of observations was small and the difference in risk was not statistically significant (RR 2.185; 95%CI 0.780 – 6.115; P=0.14). Details on the composition and timing of antiretroviral therapy in the HIV-infected participants were not available for this expedited review.

- There was **no clinically relevant or statistically significant difference** between the two arms in **time-to-culture-conversion** as assessed at 20 weeks (Hazard ratio (HR) 1.14; 95%CI 0.93 - 1.40).

Safety

- There was **no statistical difference in the proportion of patients with adverse events** of Grade 3 to 5 severity (DAIDS scale, 2009[17]) between the study and control arm (45.7% vs 44.7% respectively; RR 1.024 (95%CI 0.819 – 1.280)).

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[17] Division of AIDS (DAIDS). Table for grading the severity of adult and pediatric adverse events. Version 1.0, Dec 2004; Clarification August 2009. http://rsc.tech-res.com/docs/default-source/safety/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf

- The proportion of study participants with an AE of Grade 3 to 5 severity did not differ substantially by arm in HIV-positive participants (49.5% in study arm vs. 44% in control arm; RR 1.125 (95%CI:0.778-1.627)), nor in HIV-negative individuals (44% in study arm vs. 45% in control arm).

- New-onset **prolongation of the Fridericia-corrected QT interval (QTcF)** to 500ms or longer was more often observed in patients in the study arm (9.9%) than in the control arm (5.0%), although the difference did not achieve statistical significance (RR 2.000, 95%CI 0.896 – 4.465).

- Besides QT-interval prolongation, **other Grade 3 to 5 AEs** reported at a frequency >3% in the study arm were: decreased weight (10% in study arm vs. 11% in control arm), deafness/ototoxicity (5% vs. 4%), hepatic events (6% vs. 5%) and anaemia (4% vs. 0%). The investigators noted that hearing loss was assessed using audiometry in South African sites only, and with a whisper test elsewhere. This may have under-estimated ototoxicity in both study arms in other sites.

- Twice as many patients in the study arm (8% by 56 weeks) compared to the control arm (4%) had a significant increase of the ALT; time to reach this level was also shorter in the study arm[18] (HR 5.62; 95%CI: 1.30 – 24.30). However, this was not correlated with clinically important hepatic events.

- No previously unrecognized toxicities or possible drug-drug interactions (e.g. with antiretroviral therapy) were reported.

Health economic impact

- In Ethiopia, the preliminary analysis showed that the shorter regimen reduced direct costs to the patient associated with transport and food, as it required fewer visits to health facilities. The reduction in cost per patient during the course of treatment was approximately 18USD. Patients also had reduced expenditure on supplementary food in the study arm, particularly in weeks 12 to 84. This reduction in supplemental food costs was approximately 120USD per patient. The shorter regimen also allowed patients to return to work sooner.

- The shorter regimen reduced the cost of treatment for the health system by an average of 2,879USD per patient in Ethiopia (34% reduction) and 4,916USD in South Africa (46% reduction).

Conclusions

- The STREAM Stage 1 trial is the first-ever phase III, randomized controlled clinical trial testing a standardised shorter MDR-TB treatment regimen. Once completed and with final results reported, it will represent an important addition to the knowledge base on treatment of MDR-TB. WHO commends the efforts of everyone involved, including those MDR-TB patients who consented to participate.

- The preliminary Stage 1 results heighten the interest in Stage 2 of the trial, in which the injectable agent will be replaced by bedaquiline, and other modifications to reduce toxicity, pill burden and treatment duration will also be studied[19].

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[18] comparing the length of time needed until levels of ALT - an indicator of liver function – reached five times the upper limit of normal, a deviation that is considered a Grade 3 AE. Tests for ALT and AST were repeated routinely until week 56, following which they were only performed upon clinical indication.

- The preliminary results of the trial show that "favourable outcome" in patients treated with longer regimens was marginally higher than in those receiving the shorter regimen (80.6% vs. 78.1% respectively; +2.1% (95%CI -6.9% to +11.2%) after adjustment). The upper limit of 11.2% thus exceeded the 10% non-inferiority margin specified in the study protocol.The study investigators do not expect substantive changes to these preliminary estimates of the main trial outcomes once the remaining participant follow-up is completed.

- As a result, the trial's preliminary data could not confirm non-inferiority of the shorter regimen when compared with the longer regimen. The implications of this outcome may differ from the perspective of patients, clinicians, policy makers and trial investigators. In this respect the following considerations apply:

  − There remains uncertainty about the overall performance of the shorter regimen when compared to the longer regimens given that (i) the difference in the point estimates for "favourable outcome" is small (2%); and (ii) the confidence interval of the difference extends well above and below zero (the "no-difference-in-effect"), and thus the performance of the shorter regimen in terms of "favourable outcome" could vary from being 11% inferior to the longer regimen to being 7% better;

  − The sample size aimed for in Stage 1 limited the statistical power of the study to show non-inferiority for the particular margin chosen. When compared to other, contemporary data on MDR-TB patient outcomes at the time the trial started, a higher proportion of patients than expected had a successful outcome in the control arm. This improved performance of the longer regimen in the trial narrowed the difference in "favourable outcome" between the arms, and made it more difficult to meet the non-inferiority requirements in the study protocol;

  − The results suggest an overall tendency for a lower proportion of bacteriological cure, with a higher proportion of treatment failure or relapse – key determinants of "unfavourable outcome" - among patients treated with the shorter regimen compared with the longer one (9% vs. 3.7% by week 132 respectively). Conversely, loss to follow-up was higher in the control than the study arm (6.5% vs. 2.9% respectively), stressing the need for patient support and adherence monitoring, especially when the shorter regimen is applied under programmatic conditions;

  − The trial endpoints do not directly reflect the relative benefits of reducing treatment duration by at least half when the shorter regimen is used. As a result, this clear advantage to both patients and disease programmes may be understated by focusing attention exclusively on whether the study met its non-inferiority criterion or not; and

  − This expedited review of evidence relied on trial outcomes as defined in the study protocol. Trial endpoints have not yet been mapped to the WHO definitions that are widely used to assign cohort outcomes in programme settings.

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[19] The Evaluation of a Standard Treatment Regimen of Anti-Tuberculosis Drugs for Patients With MDR-TB - Full Text View - ClinicalTrials.Gov N.d. https://clinicaltrials.gov/ct2/show/NCT02409290.

- Notwithstanding the robust design and conduct of the Stage 1 trial, a number of factors may limit its external validity and the translation of its findings to programmatic settings:

    - Firstly, the study could not be fully blinded, a limitation that was anticipated in the study protocol and in part mitigated by the requirement that changes to treatment be discussed with a member of the central clinical team;

    - Secondly, a consequence of the exclusion criteria (e.g., resistance to fluoroquinolone or second-line injectable) is that the regimen was only applicable to selected MDR-TB patients;

    - Thirdly, potential for additional bias from selection of study participants prior to randomization could not be excluded as patients included in the trial were from amongst those presenting for TB treatment at the facilities in the study sites;

    - Fourthly, there were some inter-site variations in the duration (18-24 months) and composition (e.g., use of later generation fluoroquinolones) of the longer regimen used in the control arm. Some of these variations may have occurred during treatment in response to individual patient condition;

    - The control regimen performed better than anticipated from use of longer treatment regimens in many programmatic settings. This may also have been influenced by the level of care provided to ensure good retention, particularly the careful design and implementation of the trial (e.g. appointment of trial investigators; careful selection of sites and participants after sample size calculations, excluding highest-risk individuals; and ensuring high standards of care including comprehensive patient support ; and probably also to improved MDR-TB management at country level over time (facilitated by earlier detection with rapid molecular diagnostics and improved treatment regimen composition);

    - Finally, other factors such as the effectiveness of concomitant treatment for HIV and other co-morbidities and the absence of audiometry to measure hearing loss in all sites may also have varied between sites and modified the reported estimates.

- Based on these findings, **the 2016 WHO recommendation on the use of the shorter MDR-TB remains in place**. The recommendation remains conditional, based on moderate certainty on the estimates of effects.

- The current conditions for use of the shorter regimen also remain unchanged (see page 2). Adults and children with pulmonary MDR/RR-TB who were not previously treated with second-line TB medicines and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely may receive a shorter regimen instead of longer MDR-TB regimens.

- No changes to country-level guidelines, essential medicine lists or procurement mechanisms are envisaged at this point.

- At the time of the expedited review, information on the impact of measures taken to achieve the high levels of patient retention seen in the trial was not available. Nonetheless, patient-centred care to support adherence to treatment, either through in-person direct observation of treatment or through other recommended means (such as psychosocial support, enablers and digital

technologies) is considered important for both shorter and longer regimens[20]. Informing patients about the relative benefits and risks of the shorter regimen with respect to effectiveness, safety, quality of life and duration is also very important.

- Active TB drug-safety monitoring and management (aDSM) continues to be recommended in all patients on the shorter regimen[9]. Clinical and laboratory testing schedules may need to be adapted for patients with pre-existing conditions or risks (e.g. QT-interval prolongation, liver disease).

- The higher proportion of patients with HIV who died in the study arm may have been confounded by the presence of more advanced HIV-associated disease in that arm, and by site of recruitment. This is a patient group in whom medication adherence support and closer monitoring for clinical response and adverse events is particularly advised. Importantly, antiretroviral treatment regimens need to be optimised, and should be initiated early in accordance with WHO recommendations[14].

- In the STREAM Stage 1 trial the shorter MDR-TB regimen has been studied as a standardized intervention. The results provide no information on the effect of any changes to this regimen, such as varying the duration of the intensive and continuation phases; a lowering of the dose of moxifloxacin, or its replacement by levofloxacin or gatifloxacin; the withdrawal of ethionamide because of intolerance or presumed ineffectiveness, or conversely its use throughout treatment[21]. Neither could this preliminary review of the trial answer questions on the performance of the shorter regimen when there is resistance to pyrazinamide, or in the presence of specific mutations (particularly *kat*G, *inh*A and *eth*A). Resistance to fluoroquinolones or second-line injectable agents were exclusion criteria for the trial and therefore the final results will not provide information about the performance of the shorter regimen in patients with such forms of MDR-TB.

- Further clinical trials and operational research on the shorter regimen are still very much needed. Outstanding questions for which more information would be useful include variations to optimize further the composition and duration of the regimen; effect of the regimen in HIV-positive patients (especially drug-drug interactions with antiretroviral agents); effectiveness and safety in subgroups who have been excluded from the trial and other studies (e.g. children, extrapulmonary disease); and performance in settings where background resistance to medicines other than fluoroquinolones and second-line injectable agents is high.

Next steps

- Further to this expedited review, WHO will conduct an extensive revision of its MDR/RR-TB treatment guidelines in mid-2018. This will include updates on the use of the WHO-recommended shorter MDR-TB regimen, alongside other topical matters relating to longer regimens such as the role of bedaquiline and delamanid, the value of injectable second-line medicines and a review of the positioning of other second-line agents in MDR-TB regimen composition.

- For this review the STREAM Stage 1 trial endpoints will have to be matched to the definitions used by WHO for treatment outcome monitoring to harmonise the analyses. In addition, details on the

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[20] Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update. (WHO/HTM/TB/2017.05). http://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf. Geneva: World Health Organization; 2017.
[21] WHO | Frequently asked questions (FAQ) about the shorter MDR-TB regimen (Dec 2016). http://www.who.int/entity/tb/areas-of-work/drug-resistant-tb/treatment/FAQshorter_MDR_regimen.pdf

composition of regimens (including choice of fluoroquinolones), the composition and initiation of antiretroviral therapy and adherence to treatment will be required.

- In preparation for the 2018 guidelines revision WHO has issued a public call to the pharmaceutical industry, researchers, national TB programmes and other implementers to submit suitable data from patient cohorts treated with longer or shorter MDR-TB regimens[22]. For more information, please contact the WHO Global Tuberculosis Programme at ldr.policies@who.int.

Acknowledgements

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[22] WHO | Public Call for Individual Patient Data on Treatment of Rifampicin and Multidrug-Resistant (MDR/RR-TB) Tuberculosis. http://www.who.int/tb/features_archive/public_call_treatment_RR_MDR_TB/en/

ANNEX 1: SUMMARY OUTCOMES, STREAM STAGE 1 TRIAL[a]

Outcomes	№ of patients		Effect[b]	
	Shorter regimen (study arm)	Longer regimen (control arm)	Relative (95% CI)	Absolute (95% CI)
Time-to-culture-conversion by week 20 (ITT population)	271[c]	138[c]	**HR 1.14** (0.93 to 1.40)	-
Favourable outcome at 132 weeks (follow up: 132 weeks; mITT efficacy population)[d]	164/210 (78.1%)	87/108 (80.6%)	**RR 0.970** (0.862 to 1.090)	**24 fewer per 1,000** (from 73 more to 111 fewer)
Died from any cause during treatment or follow-up, among all cases (follow up: 132 weeks; ITT population)[e]	24/282 (8.5%)	9/141 (6.4%)	**RR 1.333** (0.637 to 2.792)	**21 more per 1,000** (from 23 fewer to 114 more)
Died from any cause during treatment or follow-up, among only people living with HIV (follow up: 132 weeks; ITT population)[f]	18/103 (17.5%)	4/50 (8.0%)	**RR 2.185** (0.780 to 6.115)	**95 more per 1,000** (from 18 fewer to 409 more)
Lack of culture conversion, culture reversion or relapse (follow up: 132 weeks; mITT efficacy population)	19/210 (9.0%)	4/108 (3.7%)	**RR 2.443** (0.852 to 7.002)	**53 more per 1,000** (from 5 fewer to 222 more)
New onset QTcF interval prolongation to 500ms or more on electrocardiogram (ITT population)	28/282 (9.9%)	7/141 (5.0%)	**RR 2.000** (0.896 to 4.465)	**50 more per 1,000** (from 5 fewer to 172 more)
Adverse event of GRADE 3 to 5 severity (follow up: 132 weeks; assessed with ITT population)[g]	129/282 (45.7%)	63/141 (44.7%)	**RR 1.024** (0.819 to 1.280)	**11 more per 1,000** (from 81 fewer to 125 more)

CI: Confidence interval; **HR:** Hazard Ratio; **ITT:** intention to treat; **mITT:** modified intention to treat; **RR:** Risk ratio

Notes to Annex 1

a. Results shown as per interim data provided by the STREAM Trial investigators on 24 January 2018 (database extract 19 September 2017).
b. Risk ratios were unadjusted.
c. The number of individuals in the ITT population with culture conversion by week 20.
d. "Favourable outcome" is defined as culture negative at 132 weeks post-randomization and at the previous occasion that the patient was seen, unless the patient outcome had already been classified as unfavourable. "Unfavourable outcome" is defined as not satisfying the favourable outcome criteria because of (i) start of 2 or more additional medicines (including a change of regimen); or (ii) treatment extended beyond the permitted duration; or (iii) death at any point up to 132 weeks post-randomization; or (iv) positive culture result at 132 weeks post-randomization or when last seen; or (v) not seen at 76 weeks or later. The "favourable outcome" status at 132 weeks, when ignoring changes or extensions of treatment - a secondary outcome as per the statistical analysis plan - was 181/210 (86.2%) in the study arm and 93/108 (86.1%) in the control arm (+0.1% difference; RR 1.001 (95%CI: 0.912 to 1.099)).
e. In the mITT population the difference in mortality between the arms was also not statistically significant (5.7% vs 6.5% respectively; RR 1.029 (95%CI: 0.397 to 2.665)). N=423 because one person did not receive treatment.
f. The outcome in this subgroup analysis is considered exploratory, being a population that was not pre-specified in the protocol.
g. Grade of severity was defined by the criteria of the Division of AIDS (DAIDS) (see footnote 17). Hearing loss was not assessed using audiometry in all centres. The proportion of patients with any GRADE 3-5 AE did not differ substantially by arm in HIV negative individuals (44-45%) but was slightly higher among HIV-positive patients in the study arm than in the control arm (49.5% vs. 44% respectively; RR 1.125 (95%CI:0.778-1.627))