DR-TB STAT - March 2017 call

16 March 2017

Attendees: Vivian Cox (DR-TB STAT); Jennifer Furin (SWIFT); Erica Lessem (TAG); Khairunisa Suleiman (South Africa); Christian Lienhardt (WHO); Medea Gegia (WHO); Tsu Zhao (WHO intern); Ramon Crespo (GDF); Heather Stone (FDA); Lice Gonzales (WHO); Edmund Rutta (USAID); Brian Kaiser (GDF); Jane Coyne (UCSF); Laura Vaughan (PIH); Nataliya Morozova (PIH); Sonya Soni (PIH); Fraser Wares (KNCV); Dennis Falzon (WHO); Erica Lessem (TAG).

Agenda:

1. General update and global numbers for new drugs (10 minutes)
2. Report on WHO GDG evidence assessment and recommendations for BDQ – Christian Lienhardt, WHO (20 minutes)
3. Union conference planning (10 minutes)
4. Wrap up and date for April call (10 minutes)

Minutes: Nataliya Morozova

General Update

- Many of the numbers for BDQ and DLM are the same for March as for February, as some programs only update their enrollment numbers quarterly. South Africa is still leading the rollout of BDQ (account for 60% of BDQ use globally)
- Current use of BDQ - 8,195 patients on the program use. DLM - 496 patients, almost all in the PIH/MSF/IRD endTB project
- GDF Orders:
    - BDQ orders from GDF: 7,285
    - DLM orders from GDF: 1,676
- Some countries don't order from GDF (i.e. South Africa, Russia), so the numbers of orders versus patients do not match.
- Estimated global need for new drugs is 74,000 - this comes from an estimated **cumulative number of patients started on DR-TB treatment**. In 2015/2016, we reporting ~33,000 patients that needed BDQ/DLM. In 2017 it has grown to 41,000. If we calculate the cumulative need, that is **33,000 + 41,000 = over 70,000 patients estimated to need new drugs**. This is a conservative estimate based on the number of persons started on DR-TB treatment and NOT the estimated number of cases.
    - See graph 2 in the global summary
- Shorter regimen: Fraser Wares - Challenges for collecting data on the shorter regimen—we know these numbers are not representative as there are no patients listed for

Bangladesh. This shows we clearly have a problem with how we are collecting data on the shorter regimen. How can we best collect and capture data? According to KNCV, the projected numbers for shorter regimen should overtake the numbers for bedaquiline. It's important we find a way to collect and update this data.

- Jennifer Furin – DR-TB STAT completely agrees. Until recently, it was unclear if STAT would take leadership on this or work with another group, and STAT has not received updated numbers from countries on the shorter regimen for several months It now appears that STAT will take the primary leadership on this. As such, STAT will coordinate with other groups—especially the Union working in the Francophone African countries but also with KNCV, MSF, Damien Foundation—who are collecting data on the shorter regimen, so as to improve our data accuracy. We can also check in with MSF in terms of their "Out of Step" report to see how we can coordinate. We hope to get better numbers in April.

<u>Report on WHO GDG evidence assessment and Meeting Report for BDQ - Christian Lienhardt</u>

- Background and work of the Guideline Development Group (GDG)
- Decided to review the cumulative evidence because there was limited data in 2013 available for BDQ (Phase IIB trial)
- Based on phase IIB data decided to issue interim guidance because of limited data and also concerns for cardiotoxicity and hepatotoxicity
    - Interim guidance was issued in 2013, with very clear conditional statements on how to use the drugs and who can get them
    - Included in this interim guidance was the request to review guidance after 2 or 3 years in view of the evidence that was accumulating
- WHO review of evidence: started with looking at published report or reports presented at conferences. Five studies were identified that could be used to evaluate the interim guidance for the use of BDQ
    - South African BDQ Clinical Access Programme
    - BDQ as part of compassionate use in France
    - Two MSF cohorts of compassionate use of BDQ (Armenia and Georgia)
    - A study from the drug manufacturer from 11 countries
    - A total 537 MDR-TB cases that could be considered in the database. Details of cohorts presented in GDG report
- Effectiveness of BDQ (sputum conversion at 6 months): success rate of about 80% when measured as total effect from the 5 cohorts
- Outcome of treatment (at least 12 months follow-up after the end of treatment; total 18 months of treatment):
    - Cure: ~64%
    - Treatment success (cure+ completed treatment): ~67%
    - Failure: ~8% (fixed effect)
    - Death: ~10%
    - Treatment success rate was higher than the global success rate as reported in Global TB Report (which is about 50%). Death rate is comparable.

- Be aware that summary figures presented here had high heterogeneity; heterogeneity index was 65%. Various cohorts in various settings with various methods. Important to keep this in mind in terms of the judgment of the GDG on the quality of the evidence
- Safety:
    - 520 pts(90%) had at least one AE
    - 180 (1/5th) of patients had severe AE
    - 42 pts (7-8%) had serious AE
    - Three most frequent serious AEs: 1) respiratory/thoracic/mediastinal disorders; 2) cardiotoxicity, QTc prolongation; 3) laboratory signs of hepatitis
    - 10% patients had QTcF interval > 480ms ; 30% had QT interval > 450ms: give both numbers here because there is still disagreement between cardiologists about what is a long QTcF interval
    - 15% of patients had a QTcF interval that grew by 60ms (compared to baseline)

- Duration of BDQ: there was very uncertain data; some cohorts had more than 6 months of BDQ but some of this included people who had to stop BDQ for some period of time. Only cohort of France clearly mentioned the cohort who received more than 6 months of BDQ. GDG looked at the data and there was no specific trend in terms of more or less important cardiotoxicity in people who received more than 6 months of BDQ compared with those who had less than 6 months

- Mortality: overall mortality rate as an outcome of the 5 cohorts together was about 10%. At the GDG review in June, the experts present were uneasy about the data because it was from observational cohort and there was no comparator. Wanted to try and find a comparison group. Tried to look at the individual patient database or the PETS study but it didn't work out because of the complexity of getting access to the data and because of the fact that safety data were not reported consistently in this cohort.

- During the June GDG review, WHO became aware of a study done in South Africa about mortality. Had a strong data source for comparator group based on Electronic Drug-Resistant Tuberculosis Register and looked back at people who received BDQ versus those who didn't. They had a total 25,000 patients, out of them 1556 had received BDQ. This study looked at mortality among BDQ patients versus those who did not. It was retrospective so needed to be controlled for bias. Did propensity score matching to control for confounding and analyzed using Cox method. Overall, patients with BDQ had a decreased risk of death by 50%. When we used logistic regression, this was down to 40%. There were some other differences in terms of HIV versus non-HIV, MDR or MDR+SLD resistance. But overall a reduction in mortality. This was shown to GDG in September because WHO was informed very late, so this meeting took place via webinar.

- The GDG committee used the GRADE system to assess the quality and certainty of evidence:

    - The data is based on observational data, not an RCT. Biases and confounders could be present. So although these data may reflect the "real life conditions" there was concern about biases and confounders since there were no control groups. This could lead to an overestimation or underestimation of endpoints.
    - The 5 cohorts studied had substantial heterogeneity, in background treatment, in different settings, some are trial-like, different patient selection, difference in follow-up, difference in background therapy, etc.
    - On the whole the GDG concluded that the certainty they could have in the estimate of effect was to remain "very low"
    - They judged that the observed effects of BDQ on culture conversion and treatment success were good enough to outweigh the harms they noted for most of the patients
    - The mortality data they reviewed are in the reverse direction of what was seen in 2013 and this was appreciated by the experts, but there were still concerns on the potential confounders and such a bias could limit the generalizability of the data arising from this retrospective cohort
    - On the whole the GDG concluded that the data and methods used were subject to a number of biases and therefore the initial concerns about increased mortality could not be allayed fully
    - On that account the group decided that they could downgrade the undesirable effects from "large" to "moderate". This means that the group looked at each of the endpoints from 2013 and then decided whether they should keep the initial assessment or not. By downgrading the undesirable effects from large to moderate, the expert group showed they were reassured that the concern was less.
- These are the overall conclusions of the GDG experts and on the basis of that, they made the recommendation that the initial guidelines that were outlined in 2013 should remain valid and was to be prolonged until additional evidence like phase III trial data is available.

- Questions:
    - Why did WHO only issue a meeting report about this? Did the Guidelines Review Committee see this?
        - Answer (Christian Leinhardt): What I have given you is the GDG recommendation. Now we have to consider that the update of the MDRTB treatment guideline in May 2016 which is very different from the situation in 2013. In 2013 there was recommendation for conventional treatment. What WHO was saying then is that we should give BDQ on top of this regimen. Since in 2016 we made the recommendation clearly that the shorter regimen should be done following the studies done by the Union, Damien Foundation, etc. This 2016 guidelines stressed the fact that the shorter regimen is being proposed under specific conditions and we have to take this into account. We have no evidence on how we should give BDQ on top of the shorter regimen. So it was difficult to issue

guidance since we knew it would not be possible to say how BDQ should be used in patients on the shorter regimen. Therefore for BDQ it is the same as what was being said in 2013, it is a prolongation of the recommendation from then.

- Second, we have received from the Guidelines Review Committee (GRC) at WHO the recommendation to start consolidating our guidelines. There are increasing concerns that we issue guidance on different aspects and on specific drugs in specific populations. There were concerns that this additional issuance of guidelines might lead to more confusion. There is a trend here in the Global TB Program of WHO to start moving to consolidating guidelines. In this view it did not appear to us to be appropriate to do a new guidance to fully repeat what was there before in the 2013 interim guidance just to differentiate we are speaking about MDR-TB patients treated with a shorter regimen and those treated with a longer regimen. We thought it would be better to wait until the time of the consolidated MDR-TB guidance and the full TB guidelines, and until then, continue with the present interim guidance. But in order to show that work has been carried out, that evidence has been assessed, that an expert group has been meeting, and has been giving evidence to WHO, we thought it would be better to issue that as a "newsflash" with a meeting report so that people know exactly what was assessed, the conclusion of the report so that people understand exactly how we are recommending the use of BDQ and then frequently asked questions so that people could more into depth on the practical aspects. This is what has been guiding us not to have new guidance which would not have brought drastically new aspects but to prolong the guidance but with clear indications of the new aspects are coming from the evidence assessed.

- How were unpublished cohorts considered, and how can DR-TB STAT help connect the WHO to the additional cohorts of patients receiving treatment. More than 5,000 people on BDQ in June 2016 when this meeting happened. So how can we better put WHO and the GDG in touch with those countries so their information can be included (as happened with the shorter regimen)?

    - Answer (Christian Lienhardt): WHO did a thorough assessment of what is there starting in 2015. It is important that we look at evidence that is tangible, so should be presented as an abstract or published. Three cohorts were found this way. Then the GDG looked at supplementary sources to ensure they would not miss data. That is how they found the 2 MSF cohorts. WHO has selection criteria that were applied - safety and mortality. Cohort must be established in such a way thatBDQ was being used and data collected as was recommended by the WHO. And need evidence on effectiveness, efficacy, safety and mortality. We knew South Africa had the biggest project so we contacted them and got 195 patients.

Then we found out about the unpublished mortality data, so this data was included. Now in 2017 we have more data, and in the future there will be a revision of evidence and information will be welcomed. We welcome that DR-TB STAT is collecting data from a wide array of partners. But WHO must follow criteria on quality of data.

- DR-TB STAT emphasized need to include more countries and offered to collaborate with WHO to find these cohorts in the future.

- Why was there no update/comment on adolescent use, especially considering previous recommendations on the shorter regimen in this population that were based on more limited evidence?
  - Answer (Christian Leinhardt): The response is straightforward. We wanted to look at this group, but unfortunately, only 39 patients in these cohorts who were adolescents, and very few had outcome data. So that limited what WHO could evaluate. So due to this small sample size and final outcome data being limited, the expert group and WHO was not able to make a recommendation on this data.
  - But GDG did not say it is not forbidden to treat adolescents with BDQ - it is up to clinicians to decide. And here WHO is very clear that we are not meant to be prescribers of what has to be done and then as examiners of who is not doing whatever we are saying. We are giving the larger frame based on evidence we think is important and the guideline it then for the world. Every clinician in terms of the patient may take the decision that he or she estimates is necessary to treat the patient. So we did mention that BDQ has been used in adolescents because that is what the evidence is that the experts have seen but there are limitations of the data and the rest is up to the clinicians to take the responsibility. And we never say that if you don't do what we are doing then something terrible will happen. All we can say is we don't have the evidence to say yes or no.
  - Jennifer Furin: clinicians' hands are tied based on what the program tells them they can and cannot do. But can you explain why the different approaches to the 9 month regimen versus bedaquiline in adolescents. Especially given the mortality benefit seen in the adolescents from South Africa.
  - Dennis Falzon: The basic difference is the experience with the use of the drug. BDQ is still very new and even if the initial benefits being reported are quite substantial and allow for the avoidance of other drugs that can cause side effects, which is another reason people are using BDQ, is still very limited data. But clinicians should feel free to use the drug. There are no negative recommendations on the use of BDQ, instead there are areas in which no recommendation could be made. Same with the use of BDQ with DLM. Programs should use them and not feel constrained on the use of them

        - The difference with the shorter regimen, is that the composite drugs used in the shorter regimen are well-known and safety profiles are well-known. Even though the drugs are not well tolerated, they are well known and it is less likely there will be things coming out about which the clinicians are not aware. With BDQ and DLM, there are more unknowns.
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    - Erica Lessem (TAG, technical resource person for the GDG): Wants to highlight what was been changed in the meeting report compared with the 2013 guidance. Since not everyone has read the full meeting report, could WHO spend a couple of minutes and go over what is different in some of the language in the meeting report versus what is in the 2013 guidance? Although the overall recommendation hasn't changed there are some important updates and nuances in the language and we were wondering if you could highlight those for the people on the call.

    - Christian Leinhardt: Overall this is very important because you are really asking us to be on the positive side which is really important. In the situation we are in presently the use of BDQ is really being made larger in the sense that we are really saying use the drug for whoever is not eligible for the shorter regimen. And that is very important in the sense that the GDG report, there is a long list of the situation in which MDR-TB patients should receive the drugs. That is:
        - WHO is recommending BDQ for whomever is not eligible for shorter regimen
        - BDQ should be added in situations where 5 effective drugs cannot be found. So the idea of BDQ being an optimal drug is somehow dropped in the sense that BDQ really becomes one of the key drugs in the situation where patients cannot be treated with the 5 effective drugs
        - Update on DDI - WHO issued advice on caution with use of BDQ with antiretrovirals (such as efavirenz), or other QT-prolonging ART drugs (such as lopinavir and ritonavir)
        - As said before, the GDG noted that BDQ has been used in adolescents but that there is insufficient data to make recommendations
        - We are changing the request from strong "pharmacovigilance" to the new notion of "active drug safety monitoring" which is more pragmatically friendly
        - I mentioned the duration of 6 months. We again noted no change in recommendation based on lack of data
        - We are looking for evidence. What I would like to say to this group here is that if there is information that is being collected which could lead us to revise the guidance more widely, I would encourage this with the proviso that it is being done under very strict and rigorous research conditions, then WHO will be willing to consider these data. This also means there is an ethical approach, a data safety monitoring board and appropriate

surveillance and monitoring of the patients. If this is in place then we would consider reviewing this evidence.

- Additional comment (Erica Lessem): I think this was a good overview of what changed. Did you mention the different language around informed consent? I can help you summarize that language if you want.
  - The language changed slightly but this could have a big impact in programs. Original guidelines required signed consent, and now it is updated to match how the wording is phrased in the DLM guidelines, which says “local policies around informed consent in line with MDR-TB policy”. CL confirmed this change in language.

Next DR-TB STAT call: **April 13 2017, agenda to follow**