Treatment Action Group

Transcript: Keynote Remarks by Mark Harrington
at Critical Path to TB Drug Regimens (CPTR) Meeting
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"Thank you for the invitation to speak here. I would like to add my words, my thanks, and praise to Jan Gheuens [TB program officer from the Bill and Melinda Gates Foundation]. It's been a pleasure working with you ever since I met you at the Union Meeting in Cape Town in 2007 and so, at that point Critical Path was just being conceived, but it's really been a pleasure working with you over the years and seeing how your vision moves forward and how much we've all been able to gain from it.

I'm going to do a show and tell. Can you see this? It's part of a regimen. Can you see this? This is an integrase inhibitor called dolutegravir; it was approved by the FDA in 2014 and it's part of my antiretroviral regimen. This product is almost too small to see, it's called Descovy. It was approved last year, and it's a pill from Gilead, which includes two drugs called TAF and FTC. So I'm able to take a new regimen for my HIV treatment, all of which includes drugs that were only approved in the last few years.

And so, that's just a way of showing that this idea of regimen development is not just something that we think is important here in tuberculosis. It's driven enormous innovation and is keeping millions of people alive around the world with HIV. And it's increasingly being used in other infectious disease areas, like hepatitis C, where over five combinations have been approved just in the last three years alone.

So our field is not as richly funded as hepatitis research or HIV research, and the reason is largely because those diseases affect people in both the rich and the poor world, and most people affected by TB live in middle-income countries, which do far too little to invest in their own health and in their own epidemics. I'm going to come back to the issue of research funding in a few minutes, but I'll just note that we're in the most vulnerable place for research funding that we've ever been because of the political situation here in the United States. We've got this situation where the U.S. has been the leading funder of global health for many years. Political support for that has usually been pretty strong, but is amazingly fragile right now in the new administration and the newly proposed budgets for the National Institutes of Health in terms of a proposed 20 percent cut, which would be devastating for everybody, not just for us.

So the U.S. government is the biggest funder of TB R&D, but the second biggest funder is the Bill & Melinda Gates Foundation. I don't think I would be exaggerating to say that not only would we not be here having this meeting, but we also wouldn't be this far along in TB R&D if it wasn't for their joint efforts. But I do have to say that last year in the TAG TB R&D report, which we've been doing since 2006, we noticed global funding for TB research and development had fallen to about $620 million, which was

its lowest level since 2008, the year before the CPTR was founded. What the last decade really describes was that there was five years of an increase from the launch of the second *Global Plan to Stop TB* between 2005 and 2008-2010, and then it stabilized down and then it began to fall and it's been falling. It has fallen a couple of other times, but this is the lowest level since 2008.

The mix of investments also changed. When this group started, there was a lot more investment by the largest pharmaceutical companies. For example, Pfizer was in the TB R&D game. AstraZeneca was involved in TB R&D. Some of the sponsors are beginning to come back in. I believe I heard a rumor that Merck was going to be here at this meeting and that's good; we welcome them. I have to say, coming from the HIV side, having pharma as a partner has really been essential to the progress in HIV. A lot of the compounds—despite the massive investment in basic science that was made by the NIH—a lot of the compounds were only discovered and developed in-house by the pharmaceutical companies. We need their involvement. We need to think about skillful ways to bring them back here. One way that we really can talk about investment, and return on investment with pharma, is to talk about the new End TB strategy, which includes as one of its key elements preventive therapy. The preventive therapy market for TB compounds, which might well be combination compounds, like we use in HIV. So we use Truvada for HIV pre-exposure prophylaxis [PrEP] and that's a two-drug combination. Over the last ten years, we've seen approval by the FDA of a new two-drug combination for the prevention of tuberculosis that is rifapentine and isoniazid taken once a week for twelve weeks. Whenever people say the market isn't big enough for TB, I always tell them about the 2.5 billion people who are infected by TB and how TB prevention is going to be a central part of getting new cases down to below the threshold where TB will continue to be a public health threat. That doesn't mean we also don't need a vaccine and shorter-acting cures, but I think it's a missing piece in the R&D agenda, or until recently it's been a missing piece.

Pharma is only investing about $87 million a year in TB R&D, and that's really not enough for a well-functioning phase I program, let alone a phase I, II, and III program. Overall, the investment that was made in TB R&D over the decade of the *Global Plan* was supposed to be about $10 billion, but it was only $3.3 billion. The global leaders who endorsed that plan in 2005 failed to meet their promises. Just looking at the drug field for 2011 to 2015, the plan called for $810 million in 2015 and $3.7 billion over a five-year period. But in 2015, rather than getting $810 million, funders only gave $232 million to TB drug development. Again, about the size of a decent phase II program. We can actually calibrate the numbers from these TB programs because we've had Otsuka data for every single year they've had delamanid in development. They were, at one-time, the largest funder of TB treatment R&D, including Gates and NIH. But their funding is has fallen by about half, as they are now wrapping up their phase III development program.

Let's talk about the drugs that were in the pipeline when this group was founded. There were five drugs in the 200? TAG *Pipeline Report* at that point that were new. There was TMC207, there was the delamanid, there was PA-824, there was SQ109 from Sequella, and there was a PNU compound, which later turned into sutezolid. And they were all in phase II or I. In the 2016 TAG *Pipeline*, what were the drugs that were listed as being in phase I to III? There was bedaquiline, delamanid, pretomanid, and there was sutezolid. So one big progress that happened between 2008 and 2016 was that the drugs got generic names, which is a good thing. They advanced from I or IIa to II or III.

And then we have a few new drugs, there's a follow up compound from Otsuka; there is a compound from Qurient called Q203, and a compound called PBTZ169. And I'm sure Mel [Spigelman, of the TB Alliance] can talk about other things that are going to enter phase I. But overall what we see is pretty static, slow-moving, kind of like a glacier made out of molasses, where we don't have a lot of forward development. Of course, CPTR is about whole regimens not just drugs, but you can't make regimens without new drugs. I mentioned the new HIV regimen that I'm on. All the elements in it, except for one part of the TAF pill, were developed in the last four years. But the pipeline for them and the other combination regimens that were approved in the last eight years goes back for the whole 25 years of the modern era of HIV drug development.

Now, I don't want to be too depressing or depressed about the progress we've made with the resources that we've got. I'm impressed that actually we have made progress, in spite of being grossly underfunded. I think one of the biggest advances was molecular diagnosis with the GeneXpert, which was launched in 2010. Something that is often not noted is the NIH funding for TB trials grew a lot beginning in 2011 with the AIDS Clinical Trials Group (ACTG)'s TB Transformative Sciences Group (TSG), and now that's the largest group of TB trials in the world. They have to do everything from soup to nuts, so they have to go from phase I to early phase combo studies to really large phase III trials like the trial we're going to launch later this year of delamanid versus INH for the prevention of MDR-TB among household contacts of people with MDR-TB. And that I have to tip my hat off to Otsuka for being willing to contribute drug to that study. That's an example of the kind of innovative thinking that we need in the TB space to get more sponsors out.

Then of course, in 2012, the FDA approved bedaquiline. I just want to point out it took four years between the time when the drug was approved in the phase III study to launch, and that was a gross oversight by the FDA to allow them to take that long to launch their phase III study. They then outsourced the development of it to USAID, which lead to further delays

In 2014, the European Medicines Association provided a conditional recommendation for approval for delamanid, based again on a phase II study, but at least Otsuka actually had a phase III study that was enrolling at the time. And also because the EMA has

more stringent requirements about kids, they have been doing pediatric studies and in fact, are now down to the lowest age cohort of zero or two years. Once we have the data from that age band, one of the things that's exciting about the PHOENIx study is that it's going to enroll people from the age of zero and up. It's going to be one of the first studies that enrolls people at any age who are at risk of MDR-TB, and so that means that the results are going to be very generalizable.

I already mentioned the 3HP regimen (rifapentine and INH) which was approved by the FDA in 2014. The WHO recommended the use of a urine dipstick called LAM in 2015 for hospitalized people with advanced HIV disease with very low CD4 counts who are debilitated. It's a true point-of-care test and it's actually proved to help survival, because in a randomized study, people who received that test were started on TB treatment one day earlier and the one day earlier meant they had a better chance of surviving. The reason I'm mentioning it here is that it's a good example of a tool that works, and that is life-saving, that is affordable, that there's been almost no uptake of. Another question or quandary that haunts our field is when we do get something new and good, like LAM or even like bedaquiline for the first few years, it's not used. It's like people are afraid in the TB community to use new tools. And someone said that wasn't really true of GeneXpert because there's a lot of push behind the roll-out, but GeneXpert is not perfect from the point-of-view of a point-of-care test. It was mostly placed in health district headquarters around South Africa, for example. So it wasn't close enough to the patient to be used as a true a point-of-care test. Now that said, I think there's going to be some good platform to use the GeneXpert technology that will be more accessible, more mobile, and more able to get out in the community where molecular diagnosis is needed. And I also think that we're going to need to have a more mobile form of molecular diagnosis that we're also going to need to be using for drug susceptibility testing.

So in 2016, the phase III trial of bedaquiline was finally launched by USAID. Then last year, in another regimen-related move, the WHO endorsed the modified Bangladesh regimen, which I have to say given the lack of scientific data evaluated on it from well-controlled, randomized studies, rather than good clinical practice, kind of surprised some of us because the data weren't really very compelling, and they weren't really data that was developed to a stringent regulatory authority standard. If those data had gone to HIV department [at WHO], that regimen would never have made it through. But maybe the thought, "well, it's going to be a long time before we get the results from these phase III studies, so we might as well do something, and the current 'standard of care' [in quote marks, because it's never been validated], the 24 month standard of care for MDR-TB, sucks." So maybe they thought, "let's just try this nine-month regimen, it can't hurt. People might be more adherent to it, because it's only nine months long." Like I said, it didn't really meet what I would consider to be a stringent regulatory standard.

It reminds me of an era of desperation in the late 1990s, that happened in the HIV space, where there was a lot of people that had become multidrug-resistant to HIV compounds, because they had started on an AZT-like nucleoside analog. And then when protease inhibitors came out, they added that. And then they became resistant to the nucleoside analogues and the protease inhibitors. So then their doctors switched them to a non-nuke [NNRT]. They were already three-class resistant at the end of the 1990s and it wasn't clear if or when we were going to get new drugs that would overcome that resistance or if they would be from new classes. A French researcher invented this thing called gigaHAART with seven or nine available anti-HIV drugs. And the problem with that was that, not only was it not based on any science, sometimes they were getting two drugs from the same class that had the exact same target but didn't have any synergy because they competed for the same target. In that case, you would really just get overlapping toxicity. Luckily, new compounds came along in the 2000s and we didn't have to keep working on gigaHAART, and it was never recommended by WHO, which I also might point of that in the late 90s, didn't have an HIV program and didn't have any HIV guidance.

Another thing that was launched last year was the 3P initiative, which is an innovative approach which was originally proposed by MSF and is now being worked on by MSF and the Union and others, which attempts to use innovative funding mechanisms to drive the critical path forward for TB products. What I think is needed in that initiative is the resources to actually show that this will work. And because of the resource problem I already mentioned, we have to think about where those resources are going to come from, and whether or not they are going to be from the traditional funders or new funders. And to that end, it's also been promising to notice that there have been some new funders coming into the space like UNITAID, which is funding the endTB study, which is more of an implementation science study of some of the newer TB drugs in programmatic settings.

And then earlier this year, in spite of a welter of new data on the safety of bedaquiline when used in programmatic settings, particularly South Africa, the WHO went through the expense of having a whole guidance meeting and talking about it and putting out a meeting report, but declined to actually update the bedaquiline recommendation because they said there wasn't enough new data. I just want to point out that contradicts what they did last year with the modified Bangladesh regimen. But anyway, we hope that they will update them. The problem is that their bedaquiline recommendation is very conditional based on the phase II study, where there was an excess of deaths in the experimental arm, that was probably due to a statistical blip. So there's been a reluctance to use bedaquiline in the field. Although it's indicated for multidrug-resistant TB, it's mostly only been used for pre-XDR or XDR-TB.

So that means one of our biggest new, innovative compounds is not being used to its greatest potential. And that means that people are suffering and dying because they're

not getting it. And that means that we're failing as a field because of our conservatism and our unwillingness to look at data. The safety data were from this phase II study that was really underpowered, and now it's been used in hundreds of people in South Africa and they're not dropping dead from QTc prolongation, and the drug appears to be safe.

And then this year, we finally have a regimen that includes a new drug, a kind of new drug, and a very new drug, that's being used in XDR-TB and it's actually saving lives. That is the NiX TB study. I would call it a fairly early phase-study that's uncontrolled and used in individuals with pre-XDR and XDR-TB, but it's using a three-drug regimen for a standard treatment of six months, and many of those individuals don't even take one of the drugs for the whole six months, but maybe just two months or until they get a dose-limiting toxicity. And that regimen is bedaquiline, pretomanid, and linezolid regimen. We'll hear about the results, but the takeaway is that the combination seems to be working in the great majority of the individuals who are taking it without having to go off drug prematurely. There were some deaths early on among people who were very ill when they were in the study, but most of the people have been able to finish the study, and most of the people have been able to be followed up without having relapsed or re-infected. We're talking about a disease that most previous historical experiences has been treated unsuccessfully in over 70 percent of patients. I think the NiX TB trial results are kind of giving us a taste of what's possible with new regimen development.

But they also raise some questions that I think this group needs to address and I don't think that we're quite ready to address. What will a regulatory trial even look like for this regimen? Is it enough to approve an indication for XDR-TB being based on historical controls, which are so terrible? I decided to look up the final results from the Clif Barry's study of linezolid in Seoul, and they were published in the *New England Journal* a couple years ago. In that study, there was a 71 percent treatment success rate. So this isn't the only time we've seen good results from an XDR trial. And it may be that it in the linezolid study that was done in South Korea, that people were not actually on the full background regimen until they were hospitalized to take linezolid, so then they received a combination regimen. But in any case, the results were a lot better than I had remembered them as being when I read the earlier results of the paper. So it reminded me: should there be a control arm? How are regulators going to handle this? Would it be acceptable for there to be a control arm?

And it remind me of the debates we used to have in the 1980s about ganciclovir for CMV retinitis, which was one of the most common opportunistic infections in people with advanced HIV. And that was the drug that had been around for several years and there had been expanded access for over 7,000 patients, but there were no randomized data. So the FDA and NIH wanted to do a study where they were going to take people with AIDS that had a condition that they called "non-immediately sight-threatening retinitis," and enrol them into immediate or deferred ganciclovir. We were

ACT UP and we were young and we were naïve and we were arrogant and we were hopeful and we were desperate, and so we demanded that the FDA not require that study, that they approve that drug without a control arm. And it was a pretty unusual decision. But like I said, they had safety data on thousands of patients, there was no control arm. And it did look like the people who did get ganciclovir didn't go blind, and the ones that didn't get it did go blind. So we do have an example from the HIV field of an effective drug that was approved without a control trial. I'm not saying that that's the path we should use with NiX, but I do think that we do need to think about how the regulatory filing is going to look.

Other issues that have almost never come up in the TB space; what does expanded access to a new regimen look like? A clinician might be able to get access to linezolid or bedaquiline, but they're not going to be able to get access to pretomanid. They could take a wild-ass guess and say, "well, delamanid is in the same class, maybe we can get delamanid." We haven't really thought through how we're going to do standard access for the new regimens, when the sponsor of one of the agents is a product development partnership, that doesn't have the type of funding that R&D-based pharma has for expanded access, which for them is actually kind of an early form of marketing, because it's a way of getting their medications in a doctor's office in a more routine programmatic setting rather than in a clinical trial.

I think this group needs to think about these issues. The funding and the mechanism for funding these activities as part of a development package are not yet clear. And yet, if the results are as compelling as they look now, I would expect there to be demand. Certainly if I were affected by XDR-TB, I would want to have a chance to take the all-oral, safe-looking, much more curative regimen. As Francesca Conradie, who is one of the principal investigators (PIs) for that study, said "I'm much more frightened of an aminoglycoside that might make me lose my hearing than I am of bedaquiline."

So I am going to leave you with a bunch of downer thoughts that we need to think about. We don't have enough new molecules. We don't have enough private sector sponsors. I might also add we don't have enough philanthropic sector sponsors. And the public funders we have like the NIH are very threatened right now. We don't have money to rapidly develop compounds once they show promise. I'll never forget being at the K-RITH opening in Durban in 2012 when Jacques Grosset, then at Hopkins, showed me his mouse data on clofazimine when used in combination, and it looked really exciting. And now it's 2017 and we have an ACTG study of clofazimine that's slowly moving forward, but it's taken five years to move from mouse data to that combination. I think that's too long. Certainly in the HIV space, we would say that's too long. Oftentimes, we've had phase II compounds that had been left high and dry without a phase III study. I'm not just mentioning bedaquiline, which is actually on the market in some places, but sutezolid is another example.

I want to call out the role of the priority review voucher, which is intended to help with the development of neglected diseases like tuberculosis. The priority review voucher is something you can trade for the right to get priority review for a drug you think you're going to make money on. They're thought to be worth hundreds of millions of dollars. I contend that the priority review voucher has actually slowed TB R&D because the squabble over who gets the priority review voucher for it, whether it's Pfizer or Sequella or who else, has meant that it's been harder for them to decide how to move the fucking compound forward in phase III. So we've had this promising compound since the first TAG *Pipeline Report* that I mentioned earlier, and we don't know any more about than we did in 2012, or when Pfizer passed it over to a company that didn't have any resources to develop it, which is Sequella. I would contend a priority review is not meeting its goal, and actually should be abolished. But I think there are a lot of other parts of the FDA that are more likely to be abolished under the current administration than the priority review voucher.

We've seen some real progress in molecular drug susceptibility testing, but it's still not available in the field for all relevant compounds, particularly PZA. We still need to develop phenotypic DST for the newer compounds and it needs to get standardized, for drugs such as bedaquiline and delamanid and pretomanid.

But above it all, I think we need a more dynamic and exciting vision for what we're going to be able to accomplish with TB drug development. And that goes back again to the results from NiX, but I think there are also going to be some other exciting results from some other, earlier phase studies, that could drive a lot of innovation in this space and maybe the time for the CPTR to really accelerate what it's doing is going to arrive, because we're going to have several new regimens that need to be advanced. And I hope we could avoid some of the mistakes that have been made.

I welcome the involvement of TB survivors in this meeting, I think that those voices are really important and need to be included. I think we need better alignment within partners, not even between partners but within them. A recent example is that the WHO with great fanfare announced that there are 12 priority drug-resistant pathogens that are going to run around the world with drug resistant disease and kill people and blablabla. And they forgot to include tuberculosis. Then they lamely said, "well, MDR-TB already has a lot of investment, you know, it's got a ton of investment. There's a program; we've been talking about for years, and we really want to bring attention to these others." And then I looked at the compounds and I looked at the pathogens, and what they don't realize is that they really need a series of new classes of antibiotics which are in common between these different resistant organisms, and MDR-TB falls right in the middle of it, because quinolones are one of the classes to which resistance was a big problem. And I thought, you know this is so typical of some of our multilateralism in the current era, where they score an own goal. You have an opportunity to promote this unified anti-microbial resistance development plan, and

instead you put the neglected pathogens over there, and TB over there. So TB again is doubly neglected. It's too prominent to be included in the neglected diseases, but it's too neglected to be in the prominent list. It suffers from under-alignment, poor investment and this is the example of an organization that actually can help alleviate those things, but not alone. I don't know whether the upcoming TB ministerial meeting that's in Moscow in November, or the UNGASS meeting next year—there must be opportunities for us to advance and gain more political will and investment that we need. I'm really impressed that the TB field has done a lot with a little. Just think how much we could do if it had a lot—or at least a lot more. Thanks for letting me share with you my reflections, and thanks again to the Critical Path, and thanks to Jan Gheuens for his leadership at the Gates Foundation.

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The remarks have been edited for clarity.
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