

**Open Forum II: Key Issues in TB Drug Development – Day 2:  
Opportunities and Challenges For an M(X)DR Clinical  
Development Program  
TB Alliance  
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[START RECORDING - TBALLIANCE SESSION 3]

**RICHARD CHAISSON, MD:** Okay, we're going to begin this afternoon with two presentations on very pertinent and worrisome and challenging problems, MDR and XTR-TB. The first presentation is going to be on the extent of the problem and then the second will be on proposal for how to deal with MDR and XTR-TB in clinical development and then we'll have a panel discussion prior to our break. So, to set the stage and describe the extent of the problem, Ernesto Jaramillo from the World Health Organization is going to scare us to death [laughter].

**ERNESTO JARAMILLO:** Thank you Richard. Well, I hope that is going to be a productive scaring [laughter]. Well, I'd like to do is, in the next 15, 20 minutes or so, is to give you a quick overview of all the most recent information we have about the extent of MDR-TB and also the emerging issue of XTR-TB and the current response from WHO and partners.

First of all, it's important to realize that the data we have to determine the extent provides - comes from the Nervous System Service [misspelled?] that, having conducted since 1994 by - in a joint project of WHO and the International Union Against Tuberculosis and Lung Diseases, and although there has been a lot of progress, you can see

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from this map, there are still plenty of areas where we still have no data whatsoever, particularly from the biggest countries like China, India and Russia. We are expecting that by mid-2007, WHO and the Union will be releasing the full report with now some addition information on the resistance patterns to second-line drugs, and therefore, a better understanding about what is going on with XTR-TB.

This year, we have published in the "Journal of Infectious Diseases" an analysis on the resource from the drug - from the thorough report and, basically what we have found, is that the Globalistic name for 2004 is this figure, 400,000 cases of MDR-TB, both in new cases and in previously treated cases, which makes it a overall of point, 4.3-percent of the global notification of TB.

All these leads us segregated data when it comes to a country level analysis, you can see that in some countries, the situation is worrisome, Baltic countries has been very well-known for several years, that MDR-TB is a major issue in country like Estonia and Latvia, but those things sent to Elatia [misspelled?], where Kazakhstan, we would include also those re-treatment cases are really making huge proportion of the total number of patients.

So, those are countries in which the DOTS strategy alone cannot make any serious difference unless MDR-TB

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treatment is provided under proper conditions. A very important feature of this analysis is that those areas where MDR-TB has an important number of cases, precisely those where HIV is rapidly emerging as a major public health issue and talking specifically of countries like Russia, China and India and we know very well that HIV has been the driving force of the epidemic in sub-Saharan Africa, so we could speculate about the impact that HIV can do on MDR-TB epidemiology in countries like China, Russia and India, where we know already that second-line drugs are being widely used and not exactly under proper management conditions.

During the last six years, WHO and partners have started the process of developing a strategy for management of MDR-TB. You may have heard about something called the Green Light Committee mechanism; that was a sort of compromise between those who were pushing strongly in favor of treating MDR-TB and those strongly against using second-line drugs in low and middle-income countries.

Out of that compromise, it has been possible to pilot in low-income countries management of MDR-TB and the results are very clear, it is feasible, it is effective and it is cost-effective to manage MDR-TB in low and middle-income countries.

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Now, there are around 42 countries that are using the GLC mechanism in order to have access to low price, quality issue of drugs and they are benefiting as well of a monitoring mechanism that is external and promotes technical assistance in order to improve the standards of a complex public health intervention. The Global Fund has endorsed the GLC, the Green Light Committee mechanism, as a mandatory way in order to release funding for second-line drugs and there are ongoing projects now in China, Russia and India, which are the three countries making around 62-percent of the total estimate of the burden of MDR-TB.

However, they are still small pilot projects and they are not treating even more than 10-percent of the globalist - or the country estimate. Another recent important development is the increasing number of consultants properly trained on management of MDR-TB. We are not - no - not very far away from the situation where we were in the mid-90s, where the DOTS strategy was launched and there was a dire need of a properly trained consultants able to provide the technical assistance of countries are in need.

During the last year, we have affiliated that process and through the GLC's, becoming more easily available to have properly trained people who can deliver the assistance that countries need. The Supranational Reference Laboratory

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Network is a powerful tool, not only to conduct the surveys, but also to help countries to improve the capacity to do drug susceptibility testing.

As it was mentioned this morning in one of the sessions, lab capacity to make diagnosis of MDR-TB is one of the major bottlenecks to scale up proper management of MDR-TB and the Supranational Reference Lab are contributing in that respect. When the MDR-TB initiative of WHO and partners, through the GLC, started six years ago, the best treatment outcomes achieved by the first projects were around 62-percent, 60-percent.

It has been very interesting to observe a sort of matching processing, which as long as they, management in the field and the projects are mature enough, developing better skills and better coordination and better tools, the treatment outcomes are improving and now you can see data measuring in projects in Philippines, in Peru, in Tonsk and Russia, where cure rates are now getting around 80-percent.

This is still the beginning of what we can foresee as a major result of proper management, proper use of second-line drugs. One of the key bottlenecks, one of the limiting factors for scaling up management of MDR-TB is the small market of second-line drugs, particularly the small size of the market of quality issue second-line drugs.

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WHO has launched a pre-qualification program of antiretrovirals, anti-malarials and anti-tuberculosis drugs in 1994, it included second-line drugs as part of the portfolio and thanks to the involvement of Global Fund, and now this year, with the involvement of Unidata, a new initiative from the French Government, Norway, Chile and Brazil, it has been possible to identify a sustainable way to promote, to obtain resources to purchase second-line drugs.

And we are expecting that this is going to introduce a new dynamic in the market of second-line drugs, like we continue to, not only would use the price, but also to become a powerful incentive for manufacture of second-line drugs to meet the quality standard that are required in order to have access to the market created by these two founding mechanism.

Finally, the Drug Assistance Service, as I mentioned before, are now including drug susceptibility testing for some of the second-line drugs for which reliable data can be obtained with the current tools, so we are expecting that by mid - by next year, we can have a better picture of the situation.

XTR-TB was a turning point for the very first time in the paper published in the MMWR in March of this year in the occasion of the World TB Day and XTR-TB, for those who are more familiar with clinical management of TB, is really

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nothing new. In the first GLC approved projects in the year 2000, it was very clear that, in small proportion of patient who were suffering of a particularly serious form of MDR-TB in which there were several second-line drugs already compromised, so that was not new.

However, in May in Atlanta this year, during the making of the Working Group on MDR-TB, it was presented in that paper, were the preliminary results of a study being conducted in KwaZulu-Natal in South Africa and the results were extremely worrying. Basically, what that presentation was telling us, was that XTR-TB in communities heavily, seriously affected by HIV, was becoming a highly lethal disease.

Ninety-percent of patients will die, some of them before having even the result of the lower artery test and as a result of that, there was a massive malarization [misspelled?] of WHO and partners in order to get better understanding of the situation and development - developing a plan of action. One of the key factors to understand the situation is to agree in basic concepts. One of them was what is exactly XTR-TB? In this paper, the definition was including three different kinds of second-line drugs, after the six kinds of second types of second-line drugs.

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However, considering that laboratory is not perfect when it comes to reliability and predict the value for second-line drugs, it was agreed that it was a definition that would not be very helpful, that WHO commission convene a Global Task Force on XTR-TB that met last October in Geneva, and one of the specific outcomes of that Task Force was to agree on a definition of XTR-TB, which is basically MDR-TB, resistance to Refampicine and it's on the aside [misspelled?], plus Fluoroquinolone, which is one of the most effective second-line drugs, plus resistance to any of the three injectables, either Annamycin or Amnicussin [misspelled?] or Acupromyosin [misspelled?] and under this definition, we have produced a map, which is not exactly a representative sample, it was not a representative sample that the data presented and then WR [misspelled?], but this data indicating that XTR-TB is basically everywhere.

The proportion of cases varies from country to country and to some extent, reflects the conditions under which second-line drugs are used. The treatment outcomes in people with XTR-TB varies, depending on how severe the pattern of resistance is our preliminary results on this study to be sub - to be published very soon from the GLC-approved project of Latvia, lead by Vidal Legmonaire [misspelled?] and colleagues and it shows very clearly that

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the most serious the resistance pattern is, the lower cure rates.

So, for those patients that are having MDR-TB resistance to Fluoroquinolones and aminoglycosides, the cure rate is around 25-percent, which is not really different to the natural history of the disease. In conclusion, we can say so far, that the XTR-TB is definitely serious [inaudible], to the control is basically presenting all regions, the size of the presence is unknown, because we still don't have representative samples that allow us to make any sales estimate.

It's a problem with a high fatality rate, particularly in communities where HIV is highly prevalent. In the best hands, in the best conditions, like in Latvia for example, cure rate is not going beyond 60-percent and the data that so far has been obtained from KwaZulu-Natal from the outbreak, if I can say so, though I would prefer to say the epidemic, of XTR-TB in that province, suggests that it's not only a single strain, but at least four different strains, which is indicating that the problem is far more complex than what originally thought.

Capacity to detect XTR-TB is definitely a limiting factor because only a few of our laboratories, particularly the Supranational Labs, they are in the capacity to conduct a

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proper test of isolates and finally, there is no doubt that if this goes beyond control, the goals of the Millennium Development Goals project and the goals of the global plan to stop TB are, might be in jeopardy, might be in trouble if we want to really make a difference.

There are plenty of questions to be addressed, plenty of questions that require answering, in order to get a better understand about what XTR-TB and what is - how it is affecting, this is not by all means an exhaustive list of the result questions, but the WHO Task Force on XTR-TB has come out with a sort of recommendations which includes, amongst other factors, two isolate efforts to produce new drugs and only question is what for to produce new drugs if they are not delivered under proper conditions.

So, this is definitely one of the key elements in order to prevent and control XTR-TB and talking about strengthening basic TB control, but all dose can't [misspelled?] basically control is always be the first priority should require also that those patients who are suffering from XTR-TB also receive a proper treatment or have access to the best tools and the best resources that are available in the world.

Some of recommendations were produced out of the Global Task Force meeting, not only the definition, but also

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the need to update the WHO guidelines under the resistant TB management, were particularly the chapter on HIV, the realities that the resource that we are, that colleagues in South Africa are producing, requires careful thought and review many of the elements that are included in the guidelines, though they do not require a major change on the fundamental principles when it comes to management and treatment design.

Advocacy and communication definitely places an important role. We know very well how stigmatized has been HIV and TB and now XTR-TB can - means - can result in a reinforcement of the stigma, so involving our community in serious efforts to prevent further stigmatization is part of the agenda to be consider within the next months and years.

Within the last six months, there has been important progress in addressing XTR-TB. The first one has been to produce a budget that has been submitted already to several donors with relatively positive response. One of the bottom in excess you can see, you can imagine, is that social capacity of country level, it does interfere from these things anticipation [misspelled?] of the Global Fund.

Consist [misspelled?] of those areas where we predict the dissipation is particularly serious are our South African countries like South Africa; Lesotho; Mozambique; Swaziland;

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Namibia; Malawi; Zimbabwe and I'll submit into WHO plans of action that includes a request for technical assistance, which in practical terms, open the walls for WHO and partners to get more closing role with countries in the delivering and coordination of the measures that are necessary.

Rapid surveys, a protocol for developing of a rapid survey has been agreed and two rapid surveys have been conducted at the moment in South African in Lesotho and contracts and utilizations are on their way to start very soon, perhaps early in January. Rapid surveys on XTR-TB in three or they're four, four, five other countries. Twenty-nine MDR-TB management has been already conducted first round in Tanzania in October, but further training is planned for first quarter of 2007, with the support of a Medical Research Counsel of South Africa.

The Foundation for Novel [misspelled?] Diagnostics that has been working in producing and testing new clues for diagnosis of TB and resistance to Refampicine has agreed to start demonstration sites in some of these countries. At least in two of them; there has been major progress in Lesotho and South Africa.

So we are expecting that we think the next 12 months, there will be an escalation of the capacity - local capacity to conduct rapid surveys for Refampicine. An update of the

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Infection Control Guidelines, which has emerged as a very, very important element in key controlling the context of the XTR-TB epidemic is now on the website and the further training and further worldwide creation of a sub-group, we think the world can grow up on TB and HIV, will result in isolation as well of the efforts at country level. So, that's basically in a nutshell an update and a summary of the current situation in MDR-TB and XTR-TB, the extent of the problem, but also the progress that we have achieved so far, thanks to the support and commitment of partners and governments. Thank you. [Applause].

**MARTIN BOKTOFKEIN [misspelled?]:** Thank you very much for this overview. You presented the plans for and the activities for Southern Africa and I was wondering about the plans and activities in Eastern Europe, because it's quite likely that XTR-TB is an even bigger problem in that part of the world.

**ERNESTO JARAMILLO:** Thank you, Martin. Well, this is not exactly South Africa, but Southern African countries including all those surrounding South Africa. Definitely, the first immediate reaction has focused on sub-Saharan Africa, but in Eastern Europe, in country like for instance Ukraine Vuelos, we know very well that MDR-TB and XTR-TB is

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an issue and with the WHO regional office in Copenhagen, we are having already working in the local reaction.

Lack of capacity again is a major bottleneck there, so we are already plan for training activity and improving of lab capacity for DSD [misspelled?] for second-line drugs working with some Supranational Reference Labs in Germany and in Stockholm and London, that can vastly [misspelled?] take to conduct surveys in areas like Donetz in Ukraine, but also in Russia.

By all means, second-line drugs, wherever second-line drugs are being used, are the places where we can expect that in our - in the XTR-TB has emerged, or will be emerging if the treatment is not delivered under proper conditions. I cannot share with you at the moment what are the details of that reaction of that response to Eastern Europe, because it is still a work in progress. Thank you.

**RICHARD CHAISSON, MD:** We'll take one more quick question in the back.

**BANEM JUSTEFINIKA [misspelled?]:** From the decision points that was right at the Global, that Global Task Force, perhaps my recollection is not that great, but I thought that more investment into the development in R&D of new drugs as well as diagnostics were part of that decision?

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**ERNESTO JARAMILLO:** Absolutely, that's one of the concrete recommendations to isolate efforts in Research and Development for diagnostics and treatment. In fact, one of the specific action that are going to take place within the next months is a meeting that is, I think is finally convened to take place in Cape Town in South Africa in for ready next year in order to focus exclusively on whether the next steps and what are the ways to isolate, enforce [misspelled?] on that regard, definitely.

**BANEM JUSTEFINIKA:** Okay, thank you.

**MALE SPEAKER:** Thank you Dick and thank you to the organizers for inviting me. I have the advantage of going late in the program, and therefore, a lot of discussion has already occurred about potential ways to investigate new drugs in the context of M and XTR, but I will try to put these in, in context without repeating a lot of things that have previously been said. Is there a pointer, I thought there was a point ...

**MALE SPEAKER:** [Inaudible].

**MALE SPEAKER:** Okay, I don't need it right this second. Alright, so what I'll do is, first I'll talk a little bit about what we know the treatment of MDR and XTR and how we learned it and then I'll talk about the potential endpoints for MDR Clinical Trials. Following that, I'll go

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over how we might control off our other predictors of these endpoints and then propose a couple of MDR trial designs that might move a drug towards licensure and then talk a little bit about MDR trial designs with a goal of optimizing treatment effectiveness.

So, what we know about the treatment of MDR and XTR and how we learned it in the very first drug trial, the Streptomycin trial in 1947, we learned that drug resistance can emerge when you treat with a single agent and this is obviously something we don't want to learn again. The - as we move forward looking at drug resistance, we figure out how to produce it and fortunately, there were some Clinical Trials done to understand better how to treat INH monoresistant TB and those done before they [inaudible] the Androphampen [misspelled?] can give us some idea of how to treat disease that's resistant to INH Androphampen.

And what we see here is that in a nice series of trials done in East Africa in the late 1960s, we first learned that Streptomycin plus PZA alone for six months didn't really do a very good job with culture conversion of only 58-percent at the end of course. When you lengthen the course to 12 months, we got better conversion and when you lengthen it even further to 18 months, we got up to sort of an acceptable level and then by using three drugs together,

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we were able to reduce the duration of therapy down to 12 months.

So, we went through a process whereby we developed a regimen that we thought was adequate and then shortened the course as best we could. Unfortunately, these are the last systematic trials that have been done to determine how to treat MDR-TB and since then, we've had mostly observational studies. We can learn something from the observational studies.

The first thing we can learn is, and this is a compilation of the various published observational studies done over the last 15 years, and as we all know, things have changed a bit over the last 15 years, so it's hard to make these completely comparable. I limited these to inpatient studies, but what this one shows is, that when you look at culture conversion as an endpoint, the more drugs that you're resistant to, the less well you do, not a counter-intuitive discovery.

I would point out that those numbers down at the far end there, where the isolates were resistant to four or five or six drugs, are effectively MDR-TB, now they keep changing exactly what's MDR-TB, but I'm going to sort of make the assumption that those isolates - those studies who had the median number of isolates resistant to five or six drugs,

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were essentially treating XTR-TB and, in fact, as one of those studies is one that we published, I know that that is, in fact, true that the people are on the far end of the MDR spectrum are, in fact, the XTR patients.

So, let me just here, okay - we also know that as the number of drugs that Gehrig you are resistant to goes up, the survival goes down. We, in fact, do see at the far end of the spectrum the XTR equivalent cases, that there is a substantial death rate in the population and this goes along with what Ernesto just pointed out to us, that this is - these kind of death rates are similar to what's seen in or what is seen in untreated TB prior to the advent of effective drugs.

So, the current recommendations for treatment of MDR-TB, which I'll summarize here, are, in fact, that if you have resistant Dyazinazid and Rifampin and the third drug, you need to use four drugs to which the isolate is susceptible and treat for 18 to 24 months. If you have one more drug that you're resistant to, you add a fifth drug, hopefully having five drugs to add and treat to culture conversion plus 24 months, and when you have HR and three more drugs, you try to find five more drugs and add - and treat for another 24 months.

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These recommendations are based on clinical experience and, as I said, some of the observations in observational studies, but really have not been effectively evaluated and I think the challenge to us is to move past this and do a better job when we have some more drugs available to us. To sort of go through the process, I want to compare this just briefly, and I'll apologize now for summarizing 50 years of work at the DM, VR, VMRC into three slides.

But if we started out doing a trial in which the major endpoints were death and radiologic improvement and in a rather small trial with slightly over 50 patients per arm, and I apologize, I don't have a pointer here, so we were able to demonstrate quite effectively that death was reduced and that culture negativity was increased and radiographic improvement was straightforward. We didn't have to go through a lot of regulatory hurdles in those days, but I think it was pretty easy to come to the conclusion that this was an effective drug and we should move forward. We then moved to another endpoint, now we're trying to figure out how to treat with combinations of drugs and because we've done a good job at preventing death and having clinical improvement, we have to move to another endpoint.

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So, now we're going to look at the number of negative cultures at three months and we see INH alone doesn't do a very good job, with only 37-percent, when you do a combination therapies, you can get that up to 55 and optimally 67-percent, and then, once we were able to get to the point of achieving high rates of culture conversion, we moved onto studying regimens and looking at the relapse rate, because now everyone is achieving culture conversion and relapse becomes the endpoint of interest and we have, we can do studies in looking at the duration.

And then, as was already presented, and I won't repeat it, we then run onto short course regimens using the same endpoint, but shortening the duration of therapy and maintaining the relapse rate at only 4-percent. So, to kind of summarize how this goes, and it's important to keep this in mind, the proper endpoint for a trial evolves over the course of time, and in the early trials, the endpoints were death and clinical radial - radiologic improvement and once we did a good job at evaluating those, we moved to bacteriologic conversion and then to relapse.

Now, I want to sidestep that for a minute, because I think we will want to revisit that, in terms of deciding what are the best endpoints to use in a Clinical Trial of MDR/XTR-TB and talk a little bit about how we control it for other

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predictors of the outcome of interest in Clinical Trials and there are sort of four methods that we use.

Restriction and stratification are an important way of controlling variability in a trial and, in fact, restriction was one of the things that was done in the Streptomycin trial, only certain patients were enrolled, not far advanced patients, not patients with chronic disease who were thought possibly might not respond as well to the drug and I mean, doing that, they were able to achieve the smaller sample size.

Stratification is also an important method of controlling for other predictors and it was mentioned earlier, HIV infection is one, is a big predictor that we worry about and it does have a major effect on the outcomes of treatment, and therefore, stratification is usually warranted for HIV status. Matching I'm not going to deal with so much, it's not really something we do in clinical trials. Randomization, of course, is the other important feature that we use to control for other predictors of outcome in clinical trials and when we don't do as good a job as we would like in controlling by randomization, we can use multivariate analysis afterwards to try to control for those things that didn't come out to be comparable in the randomization.

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In MDR-TB, the retrospective studies have suggested that all of these variables are ones that may be associated with our clinical endpoints and therefore, we might want to try to control for all of these. A daunting task and I think this is one of the things that makes us be concerned that we have sort of too much to do in trying to develop regimens for MDR-TB, because all of these other things might relate to the outcome of interest and, therefore, how are we possibly going to be able to control for them all, and I would suggest there are a number of ways we can do it.

Certainly, we can use restriction and stratification to control for those predictors that we know upfront, that we know ahead of time and here we have the five probably most powerful predictors, but the first three are actually all, I believe, the same - essentially the same thing. I know in doing multivariate analysis of our own observational cohort, we easily found that, if you put in the number of drugs received, then the number of drugs resistant dropped out of the analysis and if you put number of drugs resistant in, number of previous drugs received dropped out and for the previous treatment in, the other two dropped out, because they're really all markers of the same thing.

They may measure it less well, or more well, but if you can use one of those to restrict your population, and in

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this case, you might want to restrict your population to people who had resistance to at least five drugs, that would be effectively an XTR trial or resist, or people who had previous treatment.

And since previous treatment is something that you can know upfront, and drug resistance you might not know until you were a bit into the trial, restricting a trial to people who've had previously failed, been treated and failed, would be a good way to ensure that you were looking at the population you thought you were looking at.

Extent of disease is another thing that you can either stratify by or just, as was done the Streptomycin trial, restrict to a particular stratum, say cavitary disease or non-cavitary disease, HIV infection is also a good one to stratify on, the TBTC trials have in fact done that. It has importance for sample size, because you basically have to develop your sample size for each stratum independently, but it is a way to ensure that you, your results are not confounded by that variable.

The other things, age; sex; BMI; background regimen; and surgery, are all things that you - it's more difficult to do restriction stratification for it and you generally are able to successfully randomize on most of those, and

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therefore, don't have to worry about controlling them in the multivariate analysis.

The issue of background regimen is something that can be randomized to either arm was discussed this morning, but I just want to point out that it really does allow the opportunity to avoid having to try to have a standard regimen for everyone if, in fact, the background regimen is best available treatment, or if it is what the physician using drug susceptibility testing decides to do, you can, in a large enough trial, assume that will be randomly distributed equally between the two arms.

And therefore, you can look at the effect of the study drug independent of or controlling for that background regimen, and this is the concept that has been used in the HIV trials and I want to just go through a little, in a little detail, one of them, there have now been three different HIV drugs that have used this design as a way to bring a drug to market.

And in fact, the Enfuvirtide was the first one and this was a trial for drug-resistant HIV, not similar to, not dissimilar from what we're looking at. The people in this trial had resistance to several antiretroviral agents and they were on sort of the best available regimen that the

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clinicians could find, their HIV was not completely suppressed.

So we know it wasn't a completely active regimen and they were - the subjects were randomized to either the best available anti - to the best available antiretroviral regimen with or without the new drug of interest and the outcome in this case was a surrogate marker, the HIV titer in serum. The results were quite straightforward; the Enfuvirtide group had quite remarkable and highly statistically significant differences in viral load.

No matter how you sliced it, mean didn't change from baseline percent of persons who had less than 50 copies per center [misspelled?] persons with less than 400 copies, percent with greater than the law of reduction. In addition, the second surrogate marker, the CD4 count, was also markedly increased, so you had a very straight forward difference here that was quite remarkable.

And I think this, these kinds of data can be very effective, although the point of my talk is not to talk about surrogate markers specifically, but I want to digress a little bit, because I was actually on the FDA Antiviral Advisory Committee when we made the decision to go to surrogate markers, and we did it at the time that very good drugs became available, and so that you weren't talking about

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a surrogate marker going from 34 CD - 35 CD4 cells to 40 CD4 cells.

You were talking about it going from 35 to 70 or 35 to 200 and I think my experience would suggest that the FDA Advisory Committees will, in fact, be much more eager to accept surrogate marker data when they're this strong and I think that we can at least hope that some of our new TB drugs will, in fact, have such marked effects on markers such as time to conversion, or percent of patients that convert, that we may, in fact, be able to make the argument convincingly that those surrogate markers are associated with clinical benefit and, therefore, would be acceptable endpoints.

So, let's talk a little bit about specific trial designs. The first thing that I want to talk about is trial designs that would get licensure for new anti-Tuberculosis agents and the goals would be to demonstrate that the agent itself was clinically effective, to demonstrate that the toxicity was acceptable and to minimize the time and resources spent in demonstrating those two.

So, here's my first proposal, and this would be a trial to decrease the death rate, because we know that in XTR-TB, the death rate is quite high and it's clearly a clinical endpoint, so you won't have too much difficulty

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convincing is a panel that you've had a - an important clinical effect, if in fact you can decrease the death rate. So, if the study population was previously treated patients who had failed and the design was to randomize to the best available regimen plus a new drug or placebo stratified by HIV status, you probably would not have to do the kind of large equivalence trial that we've been talking about.

In fact, you're doing a superiority trial and the sample size would be between 50 and 100 patients per arm. The outcome would be death or clinical deterioration and the follow-up would probably not be terribly long. The disadvantages are that, once you demonstrate that you have a really good drug, and that drug becomes available, you then will have that one to compete against, but I'm skeptical that that will happen very quickly.

And I also think that there are enough patients with XTR and Ernesto showed us that they're in a lot of countries, that it might be possible to do a number of trials simultaneously or at least concurrently, in which you could demonstrate the effects using this design. I'd also like to point out that, although we - the best available regimen that these patients are receiving, is not a very good regimen and we know that.

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The second-line agents are not particularly good at achieving cure. I personally believe they would be very adequate at protecting against the emergence of resistance, and that, of course, is something you don't want to have happen in a trial of this design, so you're using a single agent, plus a background, but I believe the background would, in fact, prevent against emergence of resistance, so you would not be doing Streptomycin trial all over again, you would be doing a sort of an updated version of it.

Once you did sort of demonstrate that you had an agent that reduced death, and hopefully reduced death down to a point where you could no longer use it as an endpoint, you could do a trial to increase culture conversion. Our observational studies, in fact, I think it's a question of whether the glass is half empty or half full.

Ernesto pointed out it's really great we now actually can achieve 75 and some cases even 80-percent culture conversion in our MDR-TB observational studies, but in fact, that's not very good and, therefore, we could do a study in which that was the endpoint that we were trying to improve on and if we enrolled previously treated patients who were smear positive and stratified by cavetary status, again, randomized to best available regimen plus new drug or placebo, with the outcome being bacteriologic conversion, you still would be

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able to do a superiority trial with a reasonable sample size, probably between the order of 100 and 200 patients per arm, depending on what the baseline rate of bacterial logic conversion was, you could, in fact, examine conversion at two months, when we know it's less than 50-percent in the patients that we're seeing now and that would allow rapid assessment.

And as I said before, if you could get it from 50-percent to 80-percent, I think that would, in itself, would be an impressive demonstration of clinical effectiveness and the surrogate marker, as you were, that would likely be acceptable for licensure, although I can't speak for the regulatory agencies. I had the advantage with not being associated with one of them.

So I can say what I feel like. The disadvantages, obviously we need to understand and say upfront that that's what we're trying to do and this is what we hope will be acceptable as an endpoint, but my understanding is that, this is these - is something that would be considered. Once we've done that, we've got a couple of drugs available, we really need to move on to optimize MDR-TB treatment efficiency and the goals of these studies would be to achieve a high rate of cure and then to minimize the duration of therapy and minimize toxicity.

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After that, we can move towards developing intermittent regimens and all along, we want to keep in mind the issue of whether HIV infected patients respond similarly to HIV uninfected patients, since a high burden - a high percentage of the burden of the problem is in HIV infected populations, and we need to know early if they respond differently to the regimens, in which case we need to do different studies to address those issues. So, I want to just conclude by repeating the observation that a systematic series of clinical trials over 50 years defined and continues to define optimal treatment for drug-susceptible TB and that trial endpoints evolve as the regimens improve.

The goals of an MDR-TB clinical trials will also evolve over time from reducing deaths, to shortening regimens, but I would argue that we're at the beginning of that and not at the end. As one of these goals is achieved, we'll need to then address the next until we've optimally shortened regimens that achieve less than 5-percent failure relapses in cases of MDR-TB and as additional new drugs become available for treatment of MDR-TB, we'll need to refine this process to determine the simplest and most effective regimens. Thanks. [Applause].

[END RECORDING - TBALLIANCE SESSION 3]

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