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tagline

TAG
Treatment Action Group

NEWS ON THE FIGHT FOR BETTER TREATMENT, A VACCINE, AND A CURE FOR AIDS

Merck HIV Vaccine Trial Results: Hopes Dim for Struggling Field

Immunizations in a trial of Merck's HIV vaccine were stopped when it was determined that the vaccine was not working. There are now concerns that the vaccine may have increased the risk of HIV infection in some participants.

BY RICHARD JEFFERYS

On September 18, 2007, the world of HIV vaccine research was dealt a dismaying and unanticipated blow: immunizations in an ongoing efficacy trial of Merck's HIV vaccine candidate were stopped when the Data Safety Monitoring Board (DSMB) conducted a planned interim analysis of the results and concluded that the vaccine was ineffective, both at preventing HIV infection and reducing viral loads in immunized individuals who became HIV infected. Results from the trial were not anticipated until 2009 and, while there was certainly some skepticism about whether the approach would work, nobody predicted that the vaccine would fail so quickly and unequivocally.

After the DSMB's decision was announced publicly, concern began to mount that the vaccine had not only failed to work but also somehow increased susceptibility to HIV infection among a subset of the trial participants. The basis for this concern was finally revealed when the trial data were presented at a meeting of the HIV Vaccine Trials Network (HVTN) in Seattle on November 7. The results indicate that vaccine recipients with high levels of antibodies against the virus used as a vector in the Merck trial—a weakened form of a cold-causing virus called adenovirus serotype 5 (Ad5, for short)—were more likely to acquire HIV infection than those who got a placebo shot. Ad5 vectors are being used in a number of vaccine studies for diseases such as malaria, TB, and Ebola, and the next large HIV vaccine efficacy trial is slated to also include an Ad5-based vaccine as a booster shot following a series of DNA immunizations. The Merck results have caused all Ad5 vaccine trials to be placed on hold while researchers attempt to figure out what happened.

To follow the unfolding story of the Merck trial—a collaborative effort between Merck and the HVTN called STEP or HVTN 502—it's important to know the background to both the vaccine construct and the design of the clinical trial. Merck initially made a prototype Ad5 vaccine that expressed a single protein (Gag) from HIV-1 subtype B and used this version to conduct preliminary studies. These studies showed that the vaccine triggered the development of CD4 and CD8 T-cell responses against the HIV Gag protein in the majority (~ 60–70%) of recipients; this was something of a breakthrough as previous vaccine candidates had induced CD8 T-cell responses in only around a third of recipients (at best). However, the studies also showed that the Merck vaccine was far less effective at inducing Gag-specific T-cell responses in people who had been exposed to the natural form of Ad5 and had high levels of anti-Ad5 antibodies.

The Merck results have caused all Ad5 vaccine trials to be placed on hold while researchers attempt to figure out what happened.

As a result of these initial data, Merck and the HVTN designed a "test of concept" efficacy trial, STEP/HVTN 502. The idea was to try and test whether the HIV-specific T-cell responses induced by the vaccine could offer benefit—either in terms of preventing infection or reducing viral loads—to individuals at a high risk of acquiring

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HIV infection. But because idea was to test the efficacy of vaccine-induced HIV-specific T-cell responses, a decision was made to limit the trial to individuals who responded best to the vaccine: those with low levels of antibodies against Ad5 (defined as an antibody titer <1:200). The target sample size for the trial was 1,500 and it began enrolling in December of 2004. To increase the number of parts of HIV being targeted, the final version of the Merck Ad5 vaccine used in the trial was a "trivalent" mixture of three Ad5 vectors, one that encoded Gag and two additional vectors encoding the HIV-1 Nef and Pol proteins.

Shortly after STEP began enrolling, new data from phase I studies of the trivalent version of the Merck Ad5 vaccine suggested—for reasons that are still unclear—that it was less affected by the presence of anti-Ad5 antibodies than the prototype Gag-only vaccine. In other words, even among people with relatively high levels of anti-Ad5 antibodies, the majority of recipients developed T-cell responses to the three HIV proteins produced by the vaccine. What turned out to be a fateful decision was made: to enroll another 1,500 people in STEP without regard to their anti-Ad5 antibody titer. Enrollment of this second cohort began around September of 2005.

Participants in the trial included men and women aged 18–45 at risk for HIV infection due to sexual activity; injection drug users were not excluded but needed to have additional sexual risk factors. Study sites were located in the US, Puerto Rico, Canada, Haiti, Brazil, Peru, Jamaica, the Dominican Republic and Australia. Overall, STEP had two goals, called coprimary endpoints: to assess whether (1) the vaccine could prevent HIV infection and/or (2) reduce viral load in vaccine recipients who became infected during the trial. Interim analyses of the data by the DSMB were built into the study design; the trigger for the first such analysis was the occurrence of 30

Participants in the trial included men and women aged 18–45 at risk for HIV infection due to sexual activity.

HIV infections in the initial low anti-Ad5 antibody titer cohort.

It was reaching this trigger point that prompted a meeting of the DSMB on September 18. The DSMB reviewed data from the first 1,500-person cohort enrolled in the trial and found that of the 45 infections that had occurred, 24 were in the vaccine group and 21 in the placebo (dummy vaccine) group. Among these infected participants, viral load levels measured 8–12 weeks after infection were similar; approximately 40,000 copies in the vaccine group and 37,000 copies in the placebo group. Additionally, there was a worrying difference in the number of infections between vaccine and placebo recipients when the analysis was restricted to individuals who had received at least two shots of either vaccine or placebo; in this subgroup, there were 19 infections in the vaccine group compared to 11 in the placebo group. In line with the original study design, the DSMB stopped further immunizations in the trial because of what researchers call "futility"—even if the study were to continue, there was no possibility of the vaccine showing any efficacy.

The news provoked widespread disappointment. Although there was very little evidence to suggest that vaccine-induced T-cell responses could fully protect against HIV infection, data from animal studies offered reason to hope that the vaccine might reduce viral loads in study participants who became infected. This hope was clearly not borne out.

But worse news was to come. Another recently initiated HVTN trial in South Africa of the same Merck Ad5 vaccine—the Phambili/HVTN 503 trial—was placed on hold due to the STEP results. When the Phambili DSMB subsequently reviewed the STEP data, they not only permanently halted the Phambili trial but also recommended counseling participants that the vaccine might have enhanced susceptibility to HIV infection.

The basis for these recommendations became clear on November 7 at the HVTN

Table 1: STEP Trial Results—Number of infections and post-infection viral load levels

Trial Cohort	Vaccine: Infections	Placebo: Infections	Vaccine: Post infection viral loads	Placebo: Post infection viral loads	Vaccine: Infections (men)	Placebo: Infections (men)	Vaccine: Infections (women)	Placebo: Infections (women)
First 1,500 person cohort, anti-Ad5 antibody levels <1:200	28	25	41,527 (n=25)*	26,696 (n=21)*	28 (n=522)	24 (n=536)	0	1
Second 1,500 person cohort, anti-Ad5 antibody levels >1:200	21	9	19,070 (n=21)	89,810 (n=9)	21 (n=392)	9 (n=386)	0	0
All 3,000 persons	49	34	29,109 (n=46)*	38,416 (n=30)*	49 (n=914)	33 (n=922)	0	1

**viral load data from seven of the infected participants is not yet available*

meeting. In the second 1,500-person STEP cohort (involving individuals with anti-Ad5 antibody titers > 1:200), the skewing of infections between vaccine and placebo groups was even more notable: there 21 infections among vaccine recipients and 9 in the placebo group. Taking into account an additional eight infections in the initial cohort that occurred after the September 18 DSMB review (evenly split between vaccine and placebo groups), the totals became 49 infections in the vaccine group and 34 in the placebo group. The infections were almost entirely among the 1,825 male trial participants; only one of the 1,185 women in the study became infected—in the placebo group.

Due to the relatively small size of the study and the fact that subanalyses of the results among the second STEP cohort and men versus women were not planned in advance, the difference in infections between the vaccine and placebo groups does not quite attain statistical significance. But there is a complete consensus among the researchers involved that it is an extremely strong trend that demands investigation and explanation. Adding to the concern is an apparent association with baseline levels of anti-Ad5 antibody levels: the higher the baseline titer, the greater the imbalance of infections between the vaccine and placebo groups (see Table 2).

This finding was completely unanticipated and there was no indication from any prior studies—in the laboratory, in animals, or in people—that the presence of anti-Ad5 antibodies could somehow cause the vaccine to increase susceptibility to HIV infection. Much of the focus at the HVTN meeting was on plans to evaluate every potential explanation for the results. The principal investigator for STEP, Susan Buchbinder, is heading efforts to look at baseline and behavioral differences among study participants that might have confounded the study outcome. Buchbinder noted that while the incidence of HIV infection in the study was around 4% overall, it was lower in placebo recipients with higher anti-Ad5 antibody titers (see Table 3).

Since these data were presented, antibody expert John Moore from Cornell University has suggested that anti-Ad5 antibody levels may not solely reflect prior exposure to Ad5 but also the ability of an individual's immune system to mount a vigorous immune response against any pathogen. In other words, people who generate high levels of antibodies against Ad5 may be less susceptible to HIV infection than people who mount weak antibody responses. There is a precedent for this notion: in a prior efficacy trial of an HIV vaccine candidate called AIDSVAX, similar numbers of people in the vaccine and placebo groups became infected because the vaccine did not work. However, when researchers looked at the magnitude of the antibody responses participants generated against the vaccine, an interesting finding emerged: people who mounted the highest antibody responses were significantly less likely to acquire HIV infection during the trial when compared to the placebo group overall. Conversely, people who mounted weak antibody responses were more likely to acquire HIV infection than the placebo group. This analysis was published in the *Journal of Infectious Diseases* in 2005 (http://www.journals.uchicago.edu/doi/full/10.1086/428405). The study authors' conclusion was that antibody levels were offering a rough gauge of the quality of an individual's immune response such that people capable of mounting high magnitude responses were inherently also more likely to be able to resist HIV infection.

It seems very possible that, in STEP, the levels of anti-Ad5 antibodies also correlated with susceptibility to HIV

Table 2: Number of infections dependent on baseline anti-Ad5 antibody titers

Anti-Ad5 antibody titer	Infections, vaccine	Infections, placebo
less than 1:18	20	20
1:18–1:200	8	4
1:200–1:1000	14	7
over 1:1000	7	2

Adenovirus-Specific T-Cell Immunity

One of the yawning information gaps highlighted by the Merck HIV vaccine trial is the absence of data regarding the impact of vaccination on adenovirus-specific T-cell immune responses. Although it was logical for researchers to focus on the HIV-specific T-cell responses induced by the vaccine, in retrospect it was an oversight to not pay attention to the effect of the vector on adenovirus-specific T cells—particularly CD4 T cells, which are potential targets for HIV infection.

The literature on adenovirus-specific T-cell immunity is relatively sparse, but the published data indicates:

Adenovirus-specific T-cell responses are detectable in the majority of individuals studied.

Responses are biased toward CD4 T cells with an effector memory phenotype.

Adenovirus-specific CD4 T-cell responses are generally of a high magnitude but wane with age.

Adenovirus-specific CD4 T cells recognize epitopes that are conserved across adenovirus serotypes, including epitopes that are present even in Ad5 vectors with multiple gene deletions.

Taken together, the published data certainly suggests that studies of the impact of Merck's Ad5 vector on adenovirus-specific CD4 T cells should be a priority in the ongoing effort to understand the outcome of the Merck HIV vaccine trial.

infection; this would explain why placebo recipients with high anti-Ad5 titers had a lower incidence of HIV infection. If true, however, there is still a need to explain why receipt of the Merck vaccine appeared to override the reduced susceptibility to HIV infection associated with high anti-Ad5 titers.

Buchbinder's initial evaluation of study participants uncovered some significant differences between the first and second STEP cohorts, but no indications of any important differences between vaccine and placebo recipients in either cohort. Buchbinder emphasized that because of the small size of the study and the concentration of the infections among an even smaller subset of the overall population (the 1,825 men) it remains possible that the results reflect the play of chance. But given the serious implications if the Ad5 vector did enhance susceptibility in people with high anti-Ad5 antibody levels, Buchbinder argued that chance must be considered as an explanation only when all other potential factors have been evaluated and ruled out.

Juliana McElrath from the HVTN and Danny Casimiro from Merck are taking the lead on evaluating biological mechanisms that could account for the STEP results. At the Seattle meeting, McElrath reviewed the current status of these efforts. In terms of why the vaccine failed, McElrath and colleagues are looking particularly at the breadth and functional capabilities of the vaccine-induced HIV-specific T-cell responses. Results to date indicate that, on average, vaccine recipients developed CD8 T-cell responses to just one epitope from each HIV protein in the vaccine (Gag, Pol, and Nef). Preliminary data indicates that the responses were functional but additional analyses are being conducted to look at a number of potentially important features of the HIV-specific T cells, including their phenotype (effector memory vs. central memory, two slightly different types of memory T cells), ability to proliferate (copy themselves), ability to produce multiple cytokines and chemokines (sometimes referred to as polyfunctionality) and ability to kill HIV-infected cells in vitro (in a lab dish).

Shifting to the evidence of enhanced susceptibility, McElrath outlined the leading hypotheses that might explain the data: generalized immune activation as a result of immunization, immune responses to the Ad5 vector, and/or immune responses to the HIV proteins produced by the vaccine. McElrath also highlighted the importance of studying whether repeated doses of the vaccine impacted the outcome, since the Ad5 vector itself would have led to the development of anti-Ad5 antibodies in individuals who had low titers at baseline. McElrath showed data indicating that Ad5 immunization does increase immune activation as measured by levels of the cytokines IL-6, IL-10, TNF-alpha and IP-10, but levels return to baseline by seven days after immunization. Further studies are being performed, but the presence of anti-Ad5 antibodies would be expected to reduce this immune-activating effect rather than enhance it. Another key question is whether the vaccine boosted the number of potential target cells for HIV by increasing the numbers of activated, CCR5-expressing CD4 T cells (particularly Ad-specific CD4 T cells, which would be stimulated by the vaccine). McElrath reported that individuals with anti-Ad5 antibody titers above 1:200 did have significantly more activated, CCR5-expressing CD4 T cells but there were no apparent differences between vaccine and placebo recipients at week 30 of the trial (four weeks after the last immunization). More detailed analyses involving additional timepoints are underway. McElrath listed other priority areas for future studies:

- Defining Ad5-specific immune responses (T cells and neutralizing antibodies) and possible association with increased acquisition (Ad5-specific CD4 T-cell responses would be activated by the vaccine, and some researchers have speculated that these Ad5-specific CD4 T cells may have provided additional targets for HIV infection)

Results Among Women

The sponsors of STEP made a laudable effort to ensure that at least a third of study participants were women (who represented 38% of the total study population). However, the occurrence of only one infection among women (in the placebo group) leaves questions about sex-specific efficacy—or harmful effects—of the vaccine unanswered. The results suggests that women in the trial were not as frequently exposed to HIV as the researchers had predicted, and/or that behavioral prevention interventions that were part of the study protocol were particularly effective in reducing the risk behaviors of women trial participants. It will be important for researchers and advocates to delve further into the STEP results among women in order to ensure that future trials can adequately answer questions about the sex-specific effects of vaccine candidates.

Table 3: HIV incidence declined with increased anti-Ad5 antibody titers in the placebo group

Anti-Ad5 antibody titer	HIV incidence vaccine (95% CI)	HIV incidence placebo (95% CI)	Relative incidence (vaccine:placebo)
less than 1:18	4% (2.5–6.3)	4% (2.5–6.2)	1.0
1:18–1:200	4.4% (1.9–8.8)	2.2% (0.6–5.5)	2.0
1:200–1:1000	6.1% (3.3–10.2)	3% (1.2–6.2)	2.0
over 1:1000	4.4% (1.8–9.1)	1.2% (0.2–4.5)	3.5

• Examining the potential effect of repeated vaccine doses

• Examining the effect of immunization on CD4 T-cell numbers, activation state and CCR5 expression in the rectum and lower genital tract

• Exploring the relationship of specific Ad5 gene deletions with increased CD4+ T cell activation

• Assessing in vitro susceptibility of CD4 T cells, dendritic cells, and macrophages in participants with low versus high anti-Ad5 antibody titers

An expanded version of the HVTN's Laboratory Science Committee, chaired by Bruce Walker, will be responsible for developing the complete agenda for follow-up studies pertaining to STEP. The HVTN will also use their website to solicit applications from outside investigators who may be able to contribute to the analysis effort.

After the November 7 HVTN meeting, the decision was made to unblind STEP and inform all participants whether they received vaccine or placebo; participants will also be informed of their baseline anti-Ad5 antibody titer and counseled about the possibility that the vaccine may have enhanced susceptibility to HIV infection in individuals with high titers. Participants will continue to be followed in the hopes of evaluating the long-term effects of the vaccine. So far, of the infections in the study that occurred after week 52, seven were in vaccine recipients and six in placebo, perhaps providing some reason to hope that any enhancing effect—if real—was transient.

The worst-case scenario raised by the STEP results is that the HIV-specific T-cell responses induced by the vaccine were somehow harmful. But if that were the case, then the worst outcomes in the trial would have been among participants with the highest levels of HIV-specific T cells (i.e., individuals with low titers of anti-Ad5 antibodies). The fact that the trend toward enhanced susceptibility was only seen in individuals with anti-Ad5 antibodies suggests that immune responses to the Ad5 vector itself—or some interaction between the vector, vector-specific immunity, and potential target cells for HIV (such as CD4 T cells and dendritic cells)—are more likely culprits.

Another key question is whether the vaccine boosted the number of potential target cells for HIV.

On December 12, the AIDS Vaccine Research Subcommittee (AVRS) of the National Institute of Allergy and Infectious Disease (NIAID) met to discuss the implications of the STEP trial for the next planned NIAID-sponsored HIV vaccine efficacy trial, dubbed PAVE100. This trial involves two candidates designed by the Vaccine Research Center (VRC) at the National Institutes of Health, a DNA vaccine (given three times) followed by a single shot of an Ad5 vector as a boost. The vaccines contain additional HIV antigens not used in the Merck trial (Env proteins from clades A, B, and C) and the Ad5 vector also has additional genes deleted (the Merck construct is missing a gene called E1 and part of E3; the VRC's also has the E1, E3, and E4 genes removed) which is intended to reduce the magnitude of the immune response against the Ad5 vector.

However, it remains possible that the VRC's Ad5 vector could have a similarly detrimental effect on susceptibility to that seen in the Merck trial. One means to reduce this risk—apparently already adopted by PAVE100 proponents—is to limit enrollment to individuals with zero antibody titers against Ad5. However, to do so would be to ignore the evidence that the magnitude of antibody responses is an indicator of the quality of an individuals immune response; in effect, the trial would be limiting enrollment to people with the highest susceptibility to HIV infection because of their qualitatively poorer immune response (in other words, a population least likely to benefit from a vaccine, even if it was efficacious). This presents a catch-22 from which PAVE100 may not be able to escape, because unless a convincing explanation for the STEP results which exonerates Ad5 is eventually forthcoming, it would certainly not be appropriate or ethical to give an Ad5 vector to a representative population of individuals without regard to anti-Ad5 antibody titers, because of the risk of enhancement. Another AVRS meeting and discussion is planned in order to offer a formal recommendations regarding PAVE100, and it will be important for these issues to be explored and discussed in more detail.

TAG will continue to monitor and report on developments as analysis of the STEP data continues. ●

Links

Data presentations from the HVTN Meeting:
http://www.hvtn.org/science/1107.html

News and commentary from TAG's Basic Science, Vaccines & Prevention Project Weblog:
http://tagbasicscienceproject.typepad.com

Information, links and Q&As from the AIDS Vaccine Advocacy Coalition:
http://www.avac.org/pr_step_study.htm

Special bulletins from the *IAVI Report*:

November 13, 2007
http://www.iavireport.org/Issues/Issue11-4/Iavireport_volume11Number4-SpecialEdition2.asp

October 5, 2007
http://www.iavireport.org/Issues/Issue11-4/Iavireport_volume11Number4-SpecialEdition.asp

Palm Project Interviews:
A Talk with Steven Deeks

Dr. Deeks's focus is on research that aims to translate advances in basic science into clinically relevant therapies and treatment strategies.

BY RICHARD JEFFERYS

Steven G. Deeks, MD, is a highly respected clinician and scientist whose work encompasses both clinical care and research into the pathogenesis of HIV infection. Deeks became widely known among treatment activists for his work on individuals with multidrug resistant HIV who remain clinically and immunologically healthy despite the fact that their antiretroviral therapies fail to fully control HIV replication. Deeks is now involved in many different projects and collaborations but maintains a particular focus on research that aims to translate advances in basic science into clinically relevant therapies and treatment strategies.

What are your research priorities right now?

In the last ten years, I've focused in on trying to understand the pathogenesis of drug resistance; focusing on the virus host interactions, and how reductions in viral fitness can lead to improved immunologic outcomes. We are still working on these issues, focusing on antigen-specific T-cell responses, HIV-specific T-cell immunity; T-cell activation; T-cell turnover; T-cell trafficking, and so forth.

But in the past few years, it's become quite clear to us that we really can't fully understand how drug resistance and viral fitness impact outcome without a complete understanding of the normal response to HIV; and since there is no clear consensus on the immunologic correlates of virus control, and as there are no really validated standard assays to measure this stuff, we have become very interested in the study of untreated people.

In particular we became very interested in studying a rare subset of individuals who we think are completely controlling the virus due to their immune responses; we call them elite controllers. About two years ago we began to aggressively recruit these individuals who have no measurable virus in the absence of therapy. And so while we're all still focusing on drug-resistance and viral fitness, we're devoting more and more time to characterizing these elite controllers, and we're doing this in collaboration with a number of investigators across the country.

Ultimately, what we'd like to do—and what we're starting to do—is to use lessons learned from this type of work to perform immune-based therapeutic studies. Our ultimate goals with those studies are to, one, confirm what we understand about pathogenesis; and two, to come up with novel strategies for individuals who really cannot respond to or don't want to go on therapy.

We became very interested in studying a rare subset of individuals who we think are completely controlling the virus due to their immune responses.

Have you seen research questions come up based on your direct involvement with the pressing clinical issues that people face?

Yes, it's a two-way street, right? The lab informs the clinic, and the clinic needs to inform the lab. One of the things that we're really becoming interested in is these individuals who have been on long-term therapy, with viral load undetectable for many years, but their T cells have remained well below normal, and there's a sense that they are suffering consequences—either accelerated atherosclerosis or other types of complications. We haven't confirmed that, but others have the same sense.

As a consequence, we are now using our cohort to support two lines of investigation: one, the impact of aging on the immune system; and two, the impact of abnormal persistent inflammatory responses in the face of suppressive therapy on cardiovascular function, and so forth.

So these types of observations definitely feed some of our pathogenesis work—I think, actually, it's one of our strengths.

In terms of immune-based therapies, are there any particular approaches that you're excited about right now?

Yes, we're very interested in a lot of work that's being done regarding the critical role—the absolute key role—that CCR5 plays in pathogenesis. For example, monkey experiments by Guido Silvestri really suggest that CCR5 is key and genetics work by Sunil Ahuja suggest that CCR5 is key.

And then there are some recent clinical trials data with maraviroc, a

About the Palm Project Interviews

TAG has conducted a series of interviews with leading scientists about the underlying pathogenesis of AIDS to gain insights into emerging lines of research and observations about the current research funding environment.

A longer version of this interview with Dr. Deeks may be found on TAG's website. Go to www.treatmentaction-group.org.

Also online: an interview with immunologist Doug Nixon.

CCR5 antagonist, suggesting that these drugs have an effect on the immune system independent of its effect on the virus. So we're very interested in CCR5 inhibition as an immune-based therapeutic.

And based on the work of Danny Douek and our colleagues regarding the loss of mucosal integrity in the gut and the potential impact on long-term outcomes, we are very interested in a series of toll-like receptor [TLR] antagonists.

And I keep my eye very closely on what's happening in rheumatoid arthritis and the various different autoimmune disorders, because there's a tremendous number of very focused biologics that can be used to manipulate the immune system in presumably a safe way; and I think that the people doing research on transplant biology and autoimmunity might actually be the ones to come up with the next great thing that can really push the field forward in HIV.

Do you think it might be time to have some kind of collaborative discussion between researchers in those two fields?

I would love to see some kind of connection between the very successful, NIH-funded, Immune Tolerance Network and pathogenesis-oriented clinical investigators in HIV. Actually, I think that the Immune Tolerance Network should be a model for the future for individuals trying to figure out [HIV] immunopathogenesis issues.

And I see that you're involved in the NA-ACCORD, the North American AIDS Cohort Collaboration on Research and Design.

Yes. I think one of the best ways to move the pathogenesis field forward is to access information regarding what's happening in the clinics worldwide, or at least in the United States and so forth. And NIH has done, I think, a very nice thing by funding this NA-ACCORD multicohort collaborative approach, which is now getting up and going; which essentially is going to try to link all the cohorts in the states. I think that these kinds of database can uncover trends, like early mortality or new cardiovascular events, which can be important for clinical management or public policy. But I also think they can be important for pathogenesis research.

Was that something that you had a sense was happening in your clinic before you saw results from the SMART study?

You know, we had a sense—a growing sense—before the SMART data came out that HIV itself is causing lots of the complications that we used to blame on treatment.

I'm somewhat optimistic that a cure might be feasible; and I'm happy that people are now willing to at least talk about it again.

I've had this growing sense that HIV itself is causing progressive neurologic damage; loss of mental acuity; perhaps cardiovascular stuff; perhaps renal stuff. And in a large part, based on that, I am becoming a bigger and bigger fan of early therapy, and think that—essentially—everyone with HIV needs to be on meds unless there's a reason not to be. That's been my sense, because I do spend a fair amount of my time in the clinic.

And in terms of advocacy groups like Project Inform and TAG, are there specific things you think we can be doing that would be helpful?

I actually was at a Project Inform town hall meeting recently, and I went there to talk about the Merck integrase inhibitor, which I think is an incredibly effective, fairly potent drug; and it's going have a huge impact on my patients with drug resistance. So I figured we would talk for a couple of hours about integrase inhibitors.

But I wish certain people had been at that meeting, because it was just amazing. It was packed, and it was primarily people that had been on long-term therapy; and all people wanted to talk about were these issues which, at the end of the day, it seemed to me always came back to chronic inflammation—joint pain, weight loss, persistently low CD4 T-cell counts, various complications, despite having an undetectable viral load.

It really wasn't a discussion about drug toxicity. It certainly wasn't a discussion about getting viral load undetectable. It was really about quality of life issues after being on therapy for 10 to 15 years. And it really struck me that, at the end of the day, there we were talking mainly about what sounded like inflammation-related, autoimmune-type symptoms.

I actually thought that was a great success because it linked, via Project Inform, investigators with this broad cross-section of individuals struggling with the disease, and my only regret was that people who fund this type of research were not there. You could see what the next series of research questions is going to be.

One question that often comes up is whether you're optimistic about the possibility of getting beyond antiretroviral therapy at some point; whether the body might be able to be persuaded to do a better job of controlling HIV.

I'm actually very optimistic but—I gotta tell ya—I'm a bit dubious about whether we're going to come up with an immune-based therapeutic that prevents disease progression such that people never need antiretroviral therapy. But I think we can delay it, and we can probably improve the immune system in people on therapy.

But I actually think that immunopathogenesis-oriented work and immune-based therapeutics will lead to a cure, and actually, we're really focused on these elite controllers as a potential first step in that direction.

You know, maybe I'm naïve—I don't understand the viral latency stuff as well as I probably should—but I'm somewhat optimistic that a cure might be feasible; and I'm happy that people are now willing to at least talk about it again.

Action Needed Against TB/HIV and the MDR- and XDR-TB Crisis

A TAG-sponsored forum in South Africa brought together scientists, policy makers, and community activists to discuss multidrug resistant and extensively drug resistant TB and HIV and to identify steps to address the growing crisis.

BY THEO SMART AND JAVID SYED

"Now that we know that multiple drug resistant tuberculosis [MDR-TB] exists and is a problem in our countries, what are we going to do about it?" asked Olayide Akanni, of Journalists Against AIDS, an advocacy organization based in Nigeria, at the close of a workshop held before the World Lung Health Conference in Cape Town, South Africa, and organized by the Treatment Action Group (TAG) and Stop TB Partnership (STP). The meeting brought together scientists, policy makers, and community activists to review recent data on MDR- and extensively drug resistant- (XDR) TB, to discuss critical issues, and identify steps to address those issues.

The day was organized into three panels: Emergence and Prevention of MDR- and XDR-TB, Scaling up M/XDR Diagnostics and Treatment: Addressing the Bottlenecks, and TB Research and Development: Strategies to Move Forward.

Introduction

MDR-TB is TB resistant to at least the two cornerstone TB drugs, isoniazid and rifampicin. These difficult-to-treat infections have traditionally been regarded as a problem in the countries of the former Soviet Bloc, in Peru, and in parts of Asia.

XDR-TB is resistant to not only isoniazid and rifampicin (MDR-TB), but also to any fluoroquinolone drug (such as ofloxacin, ciprofloxacin) and to at least one of a group of injectable antibiotics. Without any of these key drugs, it is very difficult to cure TB, and especially so when delayed diagnosis delays appropriate treatment.

The emergence of XDR-TB in Tugela Ferry, South Africa, last year demonstrated what a threat TB drug resistance becomes when combined with HIV, as fatality rates among people with HIV and XDR-TB approached 100%. This outbreak, plus new research documenting the worldwide emergence of XDR-TB released in March 2007, caused TB experts and policy makers to state that targets for treating people with MDR-TB should be doubled.

The revised Global Plan to Stop TB: 2006–2015 now targets treating close to 1.6 million people with MDR-TB by 2015—at an estimated cost of US $14.4 billion. But getting from targets to implementation will require a massive and well-orchestrated effort to mobilize sufficient human, laboratory, organizational, and financial resources. With only 30,000 people put onto second-line TB treatment so far, "we are a long way from achieving the targets," noted Akanni.

"Now that we know that multiple drug resistant tuberculosis exists, what are we going to do about it?"

The Growing Threat of MDR in the Context of HIV

TB is the leading opportunistic infection and cause of death among people with HIV. If treated soon enough, TB is curable. But MDR- and XDR-TB are now on the increase in countries with a high burden of HIV; and when MDR- and XDR-TB occur among people living with HIV, many die quickly before they are appropriately diagnosed.

"Nearly half the people with HIV and either MDR- or XDR-TB die within the first 40 days—the time it typically takes to receive a culture and drug susceptibility results," said Dr. Neel Gandhi, of the Albert Einstein College of Medicine and the Church of Scotland Hospital in Tugela Ferry. It's been over a year and a half since the Tugela Ferry report, and yet the number of XDR-TB cases continues to increase. XDR-TB is now more common than MDR-TB in Tugela Ferry. "Mathematical modeling projects the epidemic will continue to grow rather than dying out," Dr. Gandhi said.

XDR-TB cases have now been reported in all nine provinces of South Africa, but the country has still not conducted another systematic drug resistance survey, and few countries in Africa have a clear idea about their burden of MDR-TB.

Similarly, Dr. Carmelia Basri of the National TB Program (NTP) in Indonesia—which has the third highest burden of TB in the world—worries that there are many risk factors for an increase in of MDR-TB in her country. Only 40% of hospitals and under 5% of the private providers currently participate in the NTP's directly observed therapy (DOTS) program; laboratory systems aren't standardized; second-line TB drugs are readily available and misused; poor history taking results in the underdetection cases that have failed standard treatment. Furthermore, HIV incidence is increasing in some areas. Without aggressive action, Dr. Basri believes Indonesia could have a serious MDR-TB problem on its hands, and many resource-limited countries share this recipe for disaster.

Challenges in Africa

"In Africa, less than 40% of countries include MDR-TB treatment as part of their routine program activities," said Dr. Haileyesus Getahun of the World Health Organization's (WHO's) Stop TB Department. "Only 4% of those patients who were estimated to have MDR-TB are able to be detected and get services from national programs."

Confronting the dual epidemic of TB and HIV is difficult in resource-limited settings, according to Dr. Rhehab Chimzizi of Malawi's National TB Program. Despite being a very poor country with a high HIV burden, Malawi has been a model for the region, with a relatively strong TB program with one of the highest TB treatment success rates (between 70 and 80%). Although within four years HIV testing increased among TB patients from 8% to 64%, Dr. Chimzizi worries that "we're only detecting 46% of all TB cases in the country." They are having trouble getting those who need antiretroviral therapy (ART) on treatment and there is also a

high rate of attrition among health care workers in the country—with 44% of the attrition due to death. Added Dr. Chimzizi, "We will not have the staff to deal with all the issues."

Trouble Accessing Second-Line Medications

Dr. Chimizizi said the country would like to address MDR-TB, but with only one laboratory that can perform culture and drug sensitivity testing (DST) for 12.8 million people, developing adequate laboratory infrastructure capacity is difficult. The lack of laboratory infrastructure has caused problems for Malawi and other countries trying to access treatment for MDR-TB, since building a strong laboratory is key to getting Green Light Committee (GLC) approval to access high-quality second-line drugs (which are not widely available).

The GLC is a technical review panel that makes certain that countries needing second-line anti-TB drugs get them from the Global Drug Facility, the Stop TB procurement mechanism, and use the treatments effectively and safely. There is no third-line regimen to cure TB, so it is critical to use drug sensitivity testing (DST) to identify the best drugs for each TB case; establish good infection control practices to stop TB transmission; provide adherence support through strong community-based care programs; and develop guidelines, training programs, and good supervision in partnership with the national TB program.

Due to political pressure in Malawi to begin treating people with MDR-TB the drugs were procured directly from other suppliers and people were started people on MDR-TB treatment. But it's expensive: "The prices of second-line drugs range anywhere from US$1,500 to $4,000 for a course of treatment," said Dr. Robert Matiru, manager of the Global Drug Facility. And the drug quality is suspect: "We may even be complicating the issue—increasing the number of XDR cases," said Dr. Chimzizi.

Indeed, the GLC could fail in its mandate to limit the development of more XDR-TB if countries (or individual patients) find it easier to get the drugs themselves. At present in Africa, the GLC is only making drugs available to small projects in Burkino Faso, the Democratic Republic of Congo, Uganda, and Lesotho.

"So, can the GLC respond quickly enough and at the scale that's being demanded?" Mark Harrington, executive director of TAG, asked Dr. Salmaan Keshavjee of Harvard Medical School, who acts as chair of the GLC, and Dr. Ernesto Jaramillo, of the MDR working group at the WHO. "Because you've been doing pilot projects for 5 or 10 years and now suddenly it's going to be going to scale involving 1.6 million people. Do the times demand a change in structure?"

"One of the solutions is to improve the way that we're providing technical assistance to countries," said Dr. Keshavjee. As a technical review panel, this is not the GLC's role. "Where there's a gap—and this is something we all have to work on—is in getting the projects to the stage that they can implement DOTS Plus projects or MDR-TB projects appropriately without putting patients at danger and without actually risking having an increase in XDR-TB."

"We need to seriously expand advocacy . . . and identify and address all bottlenecks."

It's the WHO's job (and that of other partners) to provide that technical assistance. Dr. Jaramillo agreed that better coordination of efforts and identification of potential partners are needed. "We need to work collaboratively to seriously expand advocacy, coordinate all efforts, to approach all possible supporters, and identify and address all bottlenecks," he said, adding that there has been progress at recent meetings on how to tackle some of these bottlenecks.

Lesotho's Success

Lesotho—a very remote and poor country—was presented as the model for how to successfully apply to the GLC. Despite its limitations, Lesotho got help, according to a presentation by Dr. Hind E. Satti of Partners in Health (PIH). The process began when Lesotho identified its MDR-TB problem and asked the WHO for technical assistance. PIH helped to devise a plan and prepare the GLC application.

In addition, the Foundation for Innovative New Diagnostics (FIND) set up a national reference lab (NRL) capable of performing culture and DST on solid media, training local staff. The NRL is now introducing the Mycobacteria Growth Indicator Tube (MGIT) automated liquid culture system to perform more rapid DST and culture.

The Open Society Institute helped upgrade TB facilities, complete with a state-of-the-art ventilation system (for infection control).

Dr. Keshavjee said, "It's not just a matter of putting in the right technical assistance and getting the systems in place on a global level—there have to be a lot of resources for health systems development. In Lesotho, we had to build the infrastructure that makes the system capable to deliver this type of care."

The country submitted its application to the GLC in November 2006 and the drugs arrived in July 2007. Within two months, the country had put its first year's target of 40 patients on second-line drugs.

Lesotho did things the right way, according to Dr. Jaramillo: "You don't want to have second-line drugs available where conditions are not ready, but to start piloting treating patients in those areas where patients can receive the best treatment and where the health care worker can develop the skills and the managerial capacity to replicate that treatment, that capacity, to the rest of the country."

These partners deserve praise; however, it is unfair to suggest that every country in Africa can easily duplicate this success. "The amazing progress in Lesotho is not because the GLC was nice," said Harrington. "It was because PIH, the Open Society Institute, and all these donors were there helping to set it up. But there aren't cadres of Partners in Health who are able to go all around the world and treat 1.6 million cases of MDR-TB." So additional partners must be identified and resources leveraged for other countries.

"We hear from the Global Fund that TB programs aren't asking for enough money," said Harrington. "So TB programs should ask for enough money to do the MDR scale-up that they need, to build the labs and to ensure the purchases and supply chain management of the drugs and the

training of the people that will be providing the services."

"We need to be ambitious," said Dr. Alasdair Reid of UNAIDS. "The TB community has always done what it can with the resources it has. We need to say that these are the resources that we need, and without it, we will fail."

Scaling Up Laboratory Capacity

"Increasing lab capacity is essential to the management of MDR-TB, and it's also critical for improved surveillance," said Carole Mitnick of PIH. "It has become clear that the estimates suffer from a lack of data from sub-Saharan Africa."

"Less than 3 to 5% of MDR cases are currently being diagnosed," said Dr. Abigail Wright of the WHO—and this clearly complicates the goal of putting close to 1.6 million cases of MDR-TB on treatment by 2015. "We can't put patients on treatment until we can find them," she said. "Right now, we don't even have the ability to find these patients in most countries. So as far as I'm concerned, until we start seriously dealing with labs, the targets are kind of a joke."

Another development that could increase the capacity to perform cultures and diagnose drug-resistant TB is the rollout of MGIT 960 systems in several countries. FIND has negotiated a new cost structure with the manufacturer, Becton, Dickinson and Company, for low-income countries that reduces costs to under US$3 per test—comparable to solid culture costs. Also, PEPFAR has announced a commitment to funding the rollout of MGIT systems in several countries.

This will occur in stages, based upon FIND's experience in Lesotho. In most settings, laboratories first need to renovate and upgrade their infrastructure, train technicians, and establish the basics before attempting liquid culture. Additionally, safety, transporting and rapid results reporting systems must be established.

But Dr. Ruth McNerney of the London School of Hygiene and Tropical Medicine cautioned against "airlifting" such complex machinery—which will require ongoing maintenance—into lower-resourced settings. "We haven't yet seen any data on the impact of MGIT and the liquid culture systems on patient care," she said. "No one even knows if it's going to make an impact. Two weeks is still quite a long time to get your results. Is that going to make a difference to your patients or will you already have them on treatment? If they're not on treatment, will you ever see them again?"

Where Best to Treat People with Drug-Resistant TB—Addressing Stigma

Another important discussion topic at the meeting was how to care for people with drug-resistant TB in the context of stigma, and concerns around transmission.

In Southern Africa, drug-resistant TB is usually treated in a hospital (in some cases, behind barbed wire fencing) so patients do not transmit infection to other members of the community. This has led to demonstrations by some people with MDR-TB who feel that they are "not being treated like human beings," said Dr. Eric Goemare, from the Médecins Sans Frontières (MSF) clinic in Khayelitsha.

"We can't put patients on treatment until we can find them."

The irony is that there aren't enough beds in the MDR-TB units for everyone with MDR-TB in South Africa, so while some are virtual prisoners in these facilities, most must wait for months for admittance and treatment (if they survive); in the meantime they are potentially transmitting drug-resistant TB within their communities.

"Hospital-based management of MDR-TB is not really the answer at this point in time," said Dr. Pheello Lethola of MSF-Lesotho. "We don't really have the resources and capacity. We have to decentralize TB treatment to the communities, to the district hospitals, and to the clinics."

"The way to treat patient is in the community—a big relief in terms of human resources and time," said Dr. Jaime Bayona of Socios en Salud, which has pioneered community-based care of MDR-TB in Peru. "However, one of the challenges is the high default rate due to poor tolerance to many patients, stigma, lack of follow-up, and ineffective DOTS programs."

In Peru, community members were invited to take part in the program to control MDR-TB and were trained to supervise treatment. A similar opportunity exists for community-based support in South Africa, according to Boniswa Seti, of the Treatment Action Campaign (TAC) in Khayelitsha.

"Directly observed therapy doesn't work in this setting because people feel that health workers are policing" them, Ms. Seti said. But a peer support system provides a "way of encouraging people and making sure that they adhere to their treatment."

It worked in Peru. "Peer supporters provided the moral support and helped the doctors to identify, on time, the problems that may arise. The community health worker helps MDR-TB program managers identify and put in practice potential solutions," said Dr. Bayona. "We used the same strategy with HIV. Since community health workers were familiar with the health system, they helped identify more HIV patients and put them on ARV treatment right away."

But in Southern Africa, people with HIV are more likely to be called on to be treatment supporters—and are at a much greater risk of contracting and dying from TB.

Dr. Goemaere worried that MDR-TB is so stigmatized in South Africa that treatment advocates are afraid to work with people with MDR-TB. But even Harrington admitted that he would be concerned about that. "I don't hear enough about the support and training that's going to be necessary for these so-called treatment supporters," he said. "I mean, I'm HIV-positive, I've been doing HIV work for over 20 years, and I would be frightened to be a treatment supporter for an MDR-TB patient. I would first want to know about how you do it."

"What is the real risk for a layperson with HIV in South Africa?" said Javid Syed of TAG. "We don't only need education and understanding, but also aggressive efforts for infection control and intensified case finding, detection, and appropriate treatment." Detecting and treating cases sooner is critical to prevent transmission.

Infection Control in Lesotho

Good infection control is essential to reduce the risk of TB transmission—and to reduce stigma.

"We first started treating patients with MDR-TB in the private wards," said Dr. Lethola. "The nurses and the workers who learned that these were MDR cases did not want to have anything to do with them. No one wanted to go into the room," she said.

So they performed trainings at the hospital and community clinics on MDR-TB, infection control, and how to care for these patients.

Infection control measures include:

- keeping the windows wide open, especially on opposite sides of the room (with heaters to keep the patient warm in cold weather)
- providing respirator masks for the staff and education on how to use them
- teaching cough etiquette for the patient
- creating outside waiting rooms
- providing triage for suspected TB carriers

"The stigma came down," added Dr. Lethola. "I cannot say that there is no stigma, but people have become more willing to work with these patients."

Dr. Bayona said that successful treatment also reduces stigma: "With the first culture-negative patient, hope began to spread to health workers and to people in the community." Cured patients now participate in their trainings.

The Need for TB Research and Development

Safety is also essential for lab technicians and is another reason Dr. McNerney worries about rolling out culture-based diagnoses into new areas. "We're pushing out culture facilities to people who haven't got many resources—and these new labs are expensive to maintain. What happens when the [biosafety] filter blocks or you run out of masks? It is dangerous," she said.

She believes some of other newer technologies, such as rapid molecular tests for drug resistance would be much safer for technicians. The molecular techniques—with a turnaround time of two days or less—would also speed the detection of drug-resistance in smear-positive infectious cases. "Molecular testing in the next couple years has the potential to make obsolete growth-based detection methods for MDR-TB," said Dr. O'Brien.

FIND is currently demonstrating one such system, the HAIN MTBDR Plus Assay, in South Africa. Even though this test must be performed in a well-equipped laboratory by very well trained technicians, it could be introduced into the laboratories that currently do HIV molecular tests.

FIND is also working on a rapid rifampicin resistance test from Cepheid that could be introduced to peripheral laboratories, with some electricity, where microscopy is done.

Dr. Elsa Villarino of the Centers for Disease Control and Prevention believes such tests could be used for a much more aggressive treatment algorithm, with a positive test as a cue to starting a second-line MDR-TB regimen (culture-based DST results could be used later to optimize the regimen). "With rapid detection of drug resistance, there are improved cure rates. People get to live long enough to get treatment, if they start soon enough."

"The U.S. government's investment in TB research actually went down last year."

A point-of-care dipstick test that could reliably detect TB without any laboratory infrastructure could have an even greater impact on speeding access to TB treatment. But Dr. O'Brien believes that such a test may still be 10 years away.

New drugs that could improve the treatment of MDR-TB also seem to be years away, according to Dr. Mel Spigelman of the TB Alliance and Dr. David McNeeley of Tibotec Pharmaceuticals. However, at least two compounds could get to market faster by first being evaluated against MDR-TB—according to an article in the recent issue of *PloS Medicine* (Mitnick, et al., *PLoS Med* 4, 11 (2007): e292; doi: 10.1371/journal.pmed.0040292).

Yet the rather meager pipeline is evidence that the small market for second-line TB treatment and diagnosis is not incentive enough to stimulate commercial interest in research and development, said Dr. Tido von Schoen-Angerer of MSF—and that alternate incentivies are needed.

One idea: a sort of Kyoto Treaty among countries to invest in care and treatment for diseases of high public health importance. But countries are currently showing little inclination toward making such investments on their own accord. "Some of the biggest and most powerful institutions and organizations in the world did not step up to the challenge," said Harrington. "The U.S. government's investment in TB research actually went down last year—indeed, they gave less in the first year of the Global Plan than they gave in the year before the Global Plan!"

Strategies for Moving Forward

"We have to work with the health workers; the scientists have to be on board; community activists have a key role to play," Akanni said in her conclusion. "And one of the key ways is to speed up and scale up treatment literacy efforts."

"The community has to become more involved in research and development," said Ezio Santos Filho, an activist from Brazil. But he also stressed the need to strengthen existing health systems: "We need new drug sensitivity tests, but how can we do that when the systems are broken and the laboratories don't work? We cannot detach research and development from the health systems problems."

"Nothing is going to translate into practical changes on the ground within the next two years," said Dr. Umesh Lalloo of the Nelson Mandela School of Medicine. "In the interim, we should strengthen the current technologies and facilities we have."

Activists will have to work together to get TB programs and research plans, as outlined in the Global Plan to Stop TB, 2006–2015, fully funded and supported by political leaders to ensure the prevention of drug-resistant TB.

One action already taking place is that PIH and TAG are organizing a meeting to discuss how the GLC will not be able to resolve the need for country level capacity and that activists need to advocate more with the STP to address this gap.

"We really need a multidisciplinary approach and the engagement of all the aspects—the laboratory, clinical, research, and the community are critical," said Dr. Villarino. "Because if one of the parts doesn't work, really, none of the parts work."

"Cure for AIDS" Finds New Life Among Scientists and Activists

Scientists at conference examine barriers to curing HIV infection. TAG proposes workshop in 2008 to move these efforts forward.

The HIV persistence workshop is a biannual event held on the small Caribbean island of St. Maarten. The goal of the workshop is to bring together scientists working on issues relating to the persistence of HIV despite treatment and potential strategies for curing HIV (either by eradicating the virus or rendering it unable to cause disease without the need for lifelong drug therapy).

There is continued controversy over a number of aspects of HIV persistence and potential barriers to a cure, such as:

- Does HIV continue to replicate in most people on ART despite viral loads below the detection limit?
- What is the most important factor maintaining the reservoir of HIV-infected cells despite ART?
- Which types of cells are the most important reservoirs of HIV infection?
- What is the best way of measuring HIV DNA that is integrated into a cell's genome versus DNA that is not integrated?
- Can intensification of ART (e.g., with integrase inhibitors) reduce the HIV reservoir?

Does HIV continue to replicate in most people on ART despite viral loads below the detection limit?

During the workshop, representatives from TAG, Project Inform, the FAIR Foundation and amfAR stressed their support for more coordinated efforts to resolve these issues and strengthen and accelerate research on a cure for HIV infection.

Toward this end, plans are underway to sponsor a 2008 workshop on these specific topics that will bring together researchers, activists, policy makers, and funders.

TAG BE INVOLVED

About TAG

Treatment Action Group is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action by all affected communities, scientists, and policy makers to end AIDS.

Program areas include antiretroviral treatments, basic science, vaccines, prevention, hepatitis C, and tuberculosis.

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TAG is a not-for-profit organization founded in 1992 and based in New York City.

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