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Rapidly Progressing Hepatitis C in New York Gay Men New Surveillance Networks Needed

By Tracy Swan

Recent outbreaks of acute hepatitis C virus (HCV) among HIV-positive men who have sex with men (MSM) have been reported in England, France, Germany, Holland, and the United States. Many of these cases were sexually transmitted, which is unusual because HCV is typically transmitted via injection drug use. Furthermore, many of these men were HIV-positive before they acquired HCV.

Now, researchers in New York report a worrisome new finding: significant liver damage in HIV-positive MSM within months of HCV infection. Acute HCV may be a “whole different level of worry” for HIV-positive people, says Dr. Daniel Fierer of New

Accelerated pace of liver damage seen in HIV-positive men.

York’s Mount Sinai Medical Center. At this year’s 14th Conference on Retroviruses and Opportunistic Infections, Fierer and colleagues presented disturbing data from liver biopsies of five HIV-positive men. Within months of acute HCV infection, four already had developed stage-two liver fibrosis (on a scale of four). Alcohol, recreational drugs, and antiretroviral therapy were eliminated as causing the damage; acute HCV was the sole culprit among all four men.

Significant liver damage has never been reported in otherwise healthy people with acute HCV. Fierer went to medical literature from the pre-HAART era, finding a few reports of rapid HCV progression in people who were already HIV-positive or may have been infected with both viruses at once. In one report, three patients had liver failure within three years; in another, the patient died from liver failure in less than three years. “These cases seem to have been considered ‘zebras’ [medical oddballs]. In retrospect, they may have been the first reports of the same rapid liver disease progression that we are seeing now in HIV-positive men with acute HCV. I’m concerned that this accelerated pace of liver damage may actually be the usual course, not the ‘zebra,’” says Fierer.

Acute HCV is difficult to diagnose—there are usually no symptoms. Most cases are detected by chance, during routine liver enzyme testing. “This is a new clinical syndrome.

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Providers need to be aware that HIV-positive men are getting acute HCV, and many of them do not have traditional risk factors [injection drug use]," says Fierer. He has been talking with HIV specialists around the city, asking them to join the New York Acute HCV Surveillance Network, which he set up to facilitate patient care and research. Surveillance Network providers perform routine liver testing every three months, as well as yearly HCV antibody testing, and repeat these tests when patients acquire sexually transmitted infections, which may pave the way for HCV infection. "We need to get all New York providers involved," Fierer says. "So far we've seen only the tip of the iceberg; for every case we have, there are probably 10 more that we haven't found."

Detecting acute HCV is important, because treating it may prevent progression to chronic infection. "It is one thing to miss acute HCV in an HIV-negative person, who has a good chance of curing it later on and a low risk of getting sick in the meantime. When you miss acute HCV in someone who is HIV-positive, the chance for curing it later is much worse," says Fierer. "Given our recent findings, there may already be significant liver damage, and it may continue to progress rapidly. But the good news is

Detecting acute HCV in HIV-positive people improves chance of cure.

that acute HCV is much easier to treat than chronic HCV, even in HIV-positive patients."

Treatment issues are not necessarily straightforward. HCV therapy has serious side effects. Not everyone with acute HCV needs treatment, regardless of HIV status, since some people are cured by their own immune systems. "Diagnosing acute HCV is not clear-cut, and there are no guidelines or 'standard treatment approach' for acute HCV. When acute HCV is suspected, immediate referral to a specialist is recommended," Fierer cautions.

Fierer admits, "As worrisome as our findings are, these five biopsies many not be representative of all cases. I hope we are wrong in the end, but our findings are too serious to ignore."

More research is clearly needed to understand how HCV is spreading in these men and how the accelerated liver damage is occurring. "We have important science left to do," says Fierer.

Tracy Swan is HCV/HIV Coinfection Project Director for the Treatment Action Group (TAG).

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Fierer D, Uriel AJ, Carriero DC, et al. (abstract 889). Portal fibrosis During Acute HCV Infection of HIV-infected Men. 14th Conference on Retroviruses and Opportunistic Infections. Feb 25-28, 2007. Los Angeles, CA.

The Sitges Statement on HCV Drug Development

In March 2007, a group of community activists, many living with HIV and hepatitis C virus (HCV), gathered with researchers, doctors, regulators, and representatives from Abbott, Roche, Schering, and Tibotec, in Sitges, Spain, at a meeting held by the European AIDS Treatment Group (EATG).

The meeting addressed a critical issue: the clinical development of novel HCV therapies for HIV/HCV coinfecting people, who have urgent need for new treatments. It was a unique opportunity for stakeholders to discuss how coinfecting people will gain access to experimental HCV therapies through well-designed clinical trials.

Hepatitis C is highly prevalent, progresses more rapidly, and causes significant morbidity and mortality among HIV-positive people. In Western Europe, an estimated 500,000 people are HIV-positive; 30% are coinfecting with hepatitis C. In the United States, more than a million people are living with HIV, and 25-30% (250,000 to 300,000) also have hepatitis C.

HCV-associated end-stage liver disease is now a leading cause of death among HIV-positive people in Europe and the United States. HIV accelerates hepatitis C progression; coinfecting people may develop serious liver damage within a decade. The risk for cirrhosis is twice as great, and the risk for

liver failure is six times greater for coinfecting people vs. those with HCV mono-infection. Although some centers in Europe and the United States are performing liver transplants in HIV-positive candidates, medical management of transplant recipients is complex, and access to transplantation remains limited.

HCV is treatable, regardless of HIV status, but there are serious limitations to the current standard of care. Coinfecting people are less likely to respond to treatment, and more likely to experience severe, potentially treatment-limiting side effects than their HCV mono-infected counterparts.

Several promising HCV therapies are currently in the pipeline; some have already entered phase III. HIV/HCV coinfecting people are excluded from participation in these studies. Companies often cite safety issues—such as uncharacterized pharmacokinetic profiles, and potential drug-drug interactions—as the rationale for excluding HIV-positive people. HCV treatment trials in coinfecting people are launched only after agents have been approved for HCV mono-infection.

Currently, there are no regulatory requirements or recommendations for studying novel HCV therapies in HIV-positive people prior to their approval for treatment of HCV mono-infection, but guidelines may be coming soon.

Since the Sitges Meeting, the European Agency for the Evaluation of Medicinal Products (EMA) has begun work on draft guidelines on HCV drug development. In the United States, a dialogue between industry, regulators, clinicians, researchers and community members began in October 2006, when the Food and Drug Administration (FDA) Antiviral Advisory Committee met to address development of products for the treatment of hepatitis C infection. The agency has not yet released their recommendations.

The Sitges Statement was created at the end of the meet-

Sitges Statement

Community activists, doctors, researchers, company representatives and members of regulatory agencies, concerned about the life expectancy and the quality of life of people living with HIV and HCV, hereby declare that:

Collaboration between the community, regulatory agencies and industry is a crucial part of the HCV drug development process. The community is an important stakeholder, and must be given the opportunity to provide input into HCV drug development. We want to participate in:

The development of regulatory guidance for HCV drug development

- We believe that regulators with experience in HIV drug development and treatment need to be involved in the development of regulatory guidance for new HCV drugs.

The development of industry-sponsored clinical trials

- We ask to meet regularly with sponsors of novel HCV therapies, and to participate in designing clinical trials, and oversight of these trials via Data Monitoring and Safety Boards (DSMBs) of these trials.

The development of research networks

- We support building additional research networks, public-private partnerships, investigator-initiated studies and registries of data from multi-center collaborations to bring HCV therapies forward quickly and explore new therapeutic paradigms before and after their approval.
- We encourage creating networks of investigators with expertise in treating HCV coinfection to study novel HCV therapies in coinfecting people.

We believe that the health care needs of different populations and the patient perspective must be considered part of the HCV drug development process. Studies should include people with the most urgent need for new HCV therapies.

Trials of novel HCV therapies in HIV/HCV coinfecting people should begin before approval is granted for their use in HCV monoinfection, once results from Phase 2B studies are known,

when all participants were asked to state their primary concerns about HCV drug development, trial designs, and access for coinfecting people. A draft was circulated to all participants for comments; these were incorporated and then a final document, as follows, was approved by the signatories. Signatories and their affiliations are listed at the end of the Statement.

The meeting was co-planned by Joan Tallada, Director of El Grupo de Trabajo sobre Tratamientos del VIH (GTT) and Tracy Swan, Coinfection Project Director at Treatment Action Group (TAG).

and there are indications from earlier toxicology, pharmacokinetic and drug-drug interaction studies that the specific agent, or agents, under investigation will not have the potential for significant drug-drug interactions, or other toxicities relevant to HIV.

It is clear that combination therapy will be necessary to avoid HCV drug resistance. We need to consider the most expeditious methods for co-developing drugs; this may depend on the outcome of early monotherapy studies of each agent. Since safety is paramount, we believe that in vitro and in vivo drug interaction studies must be conducted early, to facilitate pre-approval multi-agent trials and studies in persons likely to be using other medication, such as coinfecting persons, and transplant recipients.

We support trials that look at methods to delay, or reverse fibrosis progression as well as trials to eradicate HCV. It is important that trials in different populations consider different outcomes for different patient populations (SVR vs. histological improvement or averting/delaying transplantation). We also support investigation into alternative and complementary therapies for HCV.

We ask that all possibilities are explored for conducting pre-approval studies of HCV therapies in the highest prevalence population, people who use drugs. We encourage studies in people using methadone, buprenorphine, naltrexone and heroin substitution prior to approval.

In addition, we ask that sponsors design studies that:

- Enroll sufficient numbers of women to yield information on potential gender-specific side effects of new HCV treatments,
- Include TDM [therapeutic drug monitoring] in studies of persons with advanced liver disease
- Accelerate pediatric research

When possible, trials should include:

- Characterization of resistance
- Non-invasive assessments of liver damage, to see if they can be validated as an alternative to biopsy
- Assay standardization

Research to optimize the current standard of care must continue. Studies on management of side effects and models of care, especially those that will continue to explore the use of multidisciplinary care, are a priority. Interferon will still be part of HCV treatment for the next few years, but it may be possible to find a less toxic alternative to ribavirin.

We have seen high rates of liver-related mortality in the last few years. Since it will take time for new drugs to become available, we must raise awareness of the need for donor organs, promote policies to increase organ donation, and remove obstacles to transplantation for HIV-positive and coinfecting people. Organ transplantation, and access to the highest quality care and treatment, must be provided to HIV-positive and coinfecting people throughout Europe.

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Studying New Drugs for HCV Excerpts from the FDA hearings

By Bob Huff

There are a large number of experimental drugs now being developed to treat hepatitis C virus (HCV) infection. A race is on to find new HCV drugs because millions of people may one day require treatment, and the current generation of drugs are difficult to tolerate and do not reliably cure this potentially deadly liver infection (unlike HIV, HCV infection can sometimes be cured). The outcome for untreated HCV can be decompensated cirrhosis requiring transplantation—or, if no donor liver is available, death. The outlook for people infected with both HIV and HCV is worse, and in the US, blacks typically have poorer treatment outcomes than whites.

Because different patient groups have such varied outcomes from treatment, researchers are grappling with novel

challenges over the best way to test these new drugs and bring them to market.

The US Food and Drug Administration (FDA) convened a two-day meeting of its antiviral advisory committee in October 2006 to discuss drug development issues for new HCV agents. The panel was composed of clinicians, researchers, industry representatives, and community advocates.

The following is an adaptation of the panel's deliberations on the question of how much data should be known about certain challenging populations—people with advanced liver disease, people with HIV, and African Americans—at the time the drug is approved for sale in the US. The original, full transcripts may be viewed at www.fda.gov/ohrms/dockets/ac/cder06.html#AntiviralDrugs.

Patient Populations

Dr. Sherman: What patient populations should have been studied at the time of initial approval of a new HCV agent?

Dr. Seef: The question is: who should be treated in order to get approval as quickly as possible so we can get this drug into the market and, if possible, move on to secondary studies? My initial impression is that the groups that really warrant treatment are the non-responders, true non-responders. These are the people at highest imminent risk of ending up with serious disease.

I think we have to include African Americans in this. Almost a third of the people in this country who are infected with hepatitis C are African Americans and we know from studies that African Americans do not respond as well to treatment. Therefore to talk about an overall 40-50 percent response rate does not reflect reality because response rates are somewhere between 30 and 80 percent, depending on race, depending on genotype.

However, I would not involve people with decompensated liver disease in this first series of studies. I think their treatment is too complicated, and I think we need to first know whether these drugs are going to be effective in compensated patients.

Dr. Sherman: But would you start with compensated patients with cirrhosis?

Dr. Seef: Yes, I would include patients with cirrhosis. While they respond less frequently, they are appropriate to be treated.

Ms. Swan: I would reframe the question as: how much do we need to know about a drug's safety before it goes into a person with decompensated cirrhosis?

Dr. Vierling: I would like to see selected studies in decompensated patients who are listed for transplantation in specific regions of the country where, were they to have deterioration due to the natural process of their disease or unforeseen severe adverse events, they would have the rescue potential of transplantation. I think that we have a way to protect the patient, to do the study, and to obtain the evidence of potential benefit in those who are decompensated. There is no way, short of studying them, to know whether we are advancing a therapy that could be of benefit.

Dr. Haubrich: My bias is toward what is going to get the drug approved in the most efficient manner. With that in mind, for each of these categories of patient I would like to see safety data or at least pharmacokinetic data to some extent. But if involving a particular patient category could actually hinder the drug's development by introducing toxicity complications that delay studies in, say, a naïve population, then I would probably set the studies up but not necessarily require that they be done at the time of approval.

Dr. Chung: I think it has been an industry concern that an adverse event will arise and put the kibosh on a drug devel-

opment program in treatment-naïve patients. I think that has created a concern with treating certain high-risk treatment populations. I think it is important for the FDA to perhaps allow a little bit of a leeway.

Dr. Birnkrant: We are in agreement with Dr. Chung. That is, if we did find a problem in a more advanced population, obviously it would raise concerns for us, but then we could take what we learned from that population and perhaps increase monitoring in a naïve study.

Dr. Alter: I am concerned that our assumption is that, we get the drugs to the market as soon as possible so that there is the greatest access for the most patients, but in fact they may not be appropriate for these groups. Yes, they are going to be licensed therapies, and therefore physicians can use them as they choose and with whoever they choose, but maybe they won't be useful in that group of patients. I honestly don't know what the forecast is and how generalizable these treatment regimens are going to be between these different patients. Certainly current therapies aren't very generalizable.

On the other hand, if you had a group of patients with decompensated cirrhosis who were going to die because they couldn't get a liver, would you offer them an experimental therapy that could be potentially dangerous? How did we do the first transplants? How did we do a lot of things that are actually life-saving? It is either that or death. So, maybe they are the group that should be right up front. How many people die every year waiting for a liver?

Dr. Sherman: Thousands.

Dr. Alter: With hepatitis C?

Dr. Sherman: Yes.

Dr. Alter: So, that is the group I am talking about, and therefore there may be an ethical obligation to initiate a study up front on those individuals.

Dr. Birnkrant: We do have means of making investigational therapies available to patients who desperately need them. So, if that were the situation, clearly they would be made available as long as the company agreed to provide it. If we received multiple requests for that type of population, at that point we would ask the company to develop some sort of protocol to actually actively collect the data.

HIV Coinfection

Dr. Sherman: What data on people coinfecting with HIV should be required at the time of initial approval of a new HCV drug?

Dr. Fish: We know that HIV is a factor for progression, so we would want to have early treatment data for this group. There is the concern that Ms. Swan raised earlier about drug-drug interactions and cytochrome P450 interactions, so we would have to be careful and thoughtful about the patients that we would have enter those trials. For those on antiretroviral therapy we would need pharmacokinetic data to look at

drug-drug interactions and make sure that the nonnucleosides and the protease inhibitors for HIV maintain adequate blood levels, and that the hepatitis C therapy maintains adequate blood levels. Since those requirements would probably delay a trial, I would not see them as necessary for approval. So, we would like to have data on HIV but I don't know if it is realistic to expect that all of that information be available at the time of the approval process.

Dr. Sherman: Tracy Swan?

Ms. Swan: I would like to say first that drug-drug interaction studies with antiretrovirals and also other drugs commonly used by people who are living with HIV need to be done very early in the drug development process so that the lack of data can't be used as a rationale for not using the drugs in co-infected people who are taking antiretroviral agents and other drugs. I can't stress the importance of interaction studies enough. There was a life-threatening interaction between an antiretroviral drug, didanosine and the HCV drug, ribavirin. I don't know off the top of my head how many deaths resulted but they were all unnecessary, and if better studies had been done to characterize that interaction those lives would have been saved. If we can bring these treatments into a population with such urgent need we are going to save more lives. So, I would say at the barest minimum what I would find an acceptable amount of data would be the interaction studies and at least 12-week efficacy data in co-infected people.

Dr. Chung: I would amplify on both what Dr. Fish and Ms. Swan said and say that now is the time to start those PK studies and cytochrome P450 studies so that the groundwork can be laid to do parallel trials in both mono-infection and co-infection. One plausible scenario could be an initiation of a naïve trial in HCV/HIV co-infection at the same time you are doing a naïve trial in HCV mono-infection. That would be a treatment group that had a reasonable likelihood of success, of superior responsiveness to the add-on therapy to the standard of care, and could allow licensing and immediate implementation within the HIV co-infected population and likely extension into more difficult-to-treat populations within the HIV co-infected group. So, I would argue for parallel trials in both mono-infection and co-infection. But that requires, as Tracy suggested, early up-front work on the part of pharma to do the interaction studies.

Dr. Haubrich: I will take an intermediate stance. The expectation of having PK studies completed with 22 approved antiretroviral drugs is probably not realistic. So, that work has to be targeted. And exactly what data is needed to have a full parallel registrational trial in HIV? I think that is also unrealistic and would probably slow down the process. So, I would be satisfied with pilot data over 12 weeks.

Ms. Swan: From my understanding, there is a large group of co-infected people who have both advanced HIV and advanced hepatitis C. That is where I would see the greatest

clinical need and the greatest urgency to move these therapies forward, although I also think stratification by HAART or no HAART or other parameters is a very good idea. The other thing is that some of the new drugs in development might be good candidates for pharmacokinetic boosting with ritonavir, which is given with a lot of other HIV protease inhibitors. So, it sort of begs the question: if you have a three-times-a-day regimen (which are notorious for poor adherence, risk of resistance, etc.), and it could be improved by boosting with a commonly used HIV drug, wouldn't you want to examine that scenario and make sure we are getting the data we need?

Dr. Sherman: Remember, one of the features of the population of HCV/HIV co-infected is a tendency towards very high viral loads, which is probably one of the factors that affects efficacy but, again, may be an issue in terms of resistance. So, I would argue that some understanding of resistance emerging in the setting of very high viral load be evaluated before a drug is released and used in that population

I think the feeling here is that prior to initial approval efforts should be made to initiate early stage studies at least in co-infected patients; that those studies should include analysis of major drug interactions and pharmacokinetics.

This is very similar to what we agreed upon earlier for decompensated cirrhotic patients, that there should be studies initiated and under way. They don't have to be pivotal trials taken to completion, but we shouldn't wait until Phase IV.

African-Americans

Dr. Sherman: Should groups, such as African Americans where response rates are lower, be included in the main efficacy studies or would there any reason for separate trials? Should their inclusion be required?

Dr. Alter: In my opinion we at least have to include the two major racial ethnic groups in the U.S., if not three. It should be a requirement that there be a sufficient sample size to address efficacy in the three major racial ethnic groups in the United States.

I just want to make sure this isn't one of these situations where we say, "Yeah, we can have some PK data in these groups when we go for approval" but that there would actually be sufficient data for approval in these populations.

Ms. Swan: We really need to get population-specific PK data during Phase II to see if there is any signal of difference before we move into Phase III with diversely populated studies. Also, it is not a question of whether you can enroll diverse populations, it is a question of how. There are studies that have done it. Many of the sponsors of these products have done studies in HIV that have enrolled people of color without a problem, so it can definitely be done.

Dr. Seef: I cannot believe that we are even thinking about this. This has to be a reflex I believe in doing this. We must have whites and blacks in the study, absolutely.

Dr. Chung: When you are planning the studies, especially in African Americans, given what we know about their high frequency of null responses or at least non-responses from VIRAHEP-C and other studies, we ought to plan to look carefully at biologic endpoints including resistance.

Dr. Sherman: I think the issue of the barriers to enrollment in clinical trials needs to be raised. In the major pivotal trials ongoing today, African American have exceedingly low enrollment relative to their risk and prevalence in the population. I think this committee should encourage the FDA to look at barriers that appear in trial designs that then lead to enrollment of primarily upper middle class white populations that are not representative of the disease as a whole in this country.

Dr. Alter: These trials take a lot of work to begin with,

granted. And it takes a lot more work to get difficult-to-reach populations. But that doesn't mean it can't be done. It just takes more work. I think that there are a lot of people experienced in getting to hard-to-reach populations and there are a lot of ways to do it.

Dr. Sherman: I would point out two salient points in ACTG 5071, which was a co-infection study. There was 33 percent African American enrollment, and the overall dropout rate in the study was 13 percent, which was no different than what was seen in the pivotal trials in HCV mono-infection.

Dr. Seef: Also, compliance was not an issue. There was no less compliance among the African Americans, at least in the VIRAHEP-C trial, than there was among the whites. So, I don't think that is an issue either.

Worldwide Antiretroviral Drug Sales 2006*

Drug	Company	\$ Million	Change from 2005	Notes
Truvada	Gilead	1,194	+210%	
Kaletra	Abbott	1,135	+13%	
Combivir	GlaxoSmithKline	977	-8%	
Reyataz	Bristol-Myers Squibb	931	+34%	
Sustiva	Bristol-Myers Squibb	791	+16%	Includes \$76 million related to Atripla sales
Viread	Gilead	689	-12%	
Trizivir	GlaxoSmithKline	496	-10%	
Epzicom	GlaxoSmithKline	446	+207%	
Epivir	GlaxoSmithKline	374	-21%	
Viramune	Boehringer-Ingelheim	353	-4%	Estimate, based on 276 Euros
Crixivan	Merck	327	-6%	
Fuzeon	Roche	250	+19%	Estimate, based on 312 Swiss Francs
Lexiva/Agenerase	GlaxoSmithKline	242	+19%	
Ziagen	GlaxoSmithKline	216	-23%	
Atripla	Gilead	206	—	Gilead recorded 100% of Atripla sales, then paid BMS \$76 million for the efavirenz
Zerit	Bristol-Myers Squibb	155	-28%	
Invirase/Fortovase	Roche	145	+28%	Estimate, based on 182 Swiss Francs
Aptivus	Boehringer-Ingelheim	67	—	Estimate, based on 53 Euros
Emtriva	Gilead	36	-23%	
TOTAL		9,030	+14%	

*Does not include unreported drugs (Videx, Norvir, Viracept, Rescriptor, Retrovir)

Source: AIDSMeds.com based on SEC filings

Faster TB Test for Resource-limited Settings

By Theo Smart

Published Feb 2, 2007 on AIDSmap.com

A large multicenter study conducted in Honduras and Brazil has shown that a new and relatively simple technique to detect active tuberculosis (TB), the microscopic observation drug susceptibility (MODS) test, is just as sensitive but about three times faster than conventional solid culture, the gold standard for confirming a diagnosis of active TB. MODS yields clear results in a median of seven days, compared to three weeks for solid culture.

In addition, in a smaller subset of patients, MODS performance was similar to that of the automated liquid culture system, the MGIT 960, which is now widely used in industrialized countries. However, MODS' "low cost, relative to other liquid culture methods, may make it feasible for use in resource-limited countries," wrote the authors of the study, published in the March 1, 2007 edition of *Clinical Infectious Diseases*.

Also, although capacity in most peripheral laboratories would need to be upgraded in order to perform MODS, in contrast to concerns expressed in an editorial published with an earlier major study of MODS—which worried about the hazards to laboratory staff handling liquid cultures containing live and infectious micro-organisms—the authors of the current study believe that MODS could be made safer "without complex or expensive measures."

Background on TB Diagnostics

TB, a generally curable illness, continues to be the leading killer of people with HIV in resource-limited settings. One of the primary reasons for the failure to control the disease is that its diagnosis is dependant upon slow or insensitive techniques that are over 100 years old.

The first laboratory test that a person with suspected TB is likely to have is the smear microscopy test (also called the acid fast bacilli or AFB test). In this test, a biological sample (usually sputum) is smeared onto a glass slide and stained with dyes that specifically bind to the cell wall of *Mycobacteria tuberculosis* (MTB), the organism that causes TB. When this is magnified under a simple light microscope, the lab technician ought to be able to see the stained microbes on the slide.

However, the method is far from exact, depending upon the relative quantity of the sputum in the specimen and the training, eye, and motivation of the lab technician performing this task day after day. As a result, smear microscopy is notoriously insensitive, and in order reach a diagnosis, a person with suspected TB needs to provide at least two or three specimens (usually on successive

days provided the patient can make it back to the laboratory).

Although some researchers are investigating techniques for improving the speed and sensitivity of smear microscopy, in practice it misses about half the cases when performed in resource-limited settings. Among people with HIV, it may miss up to 80 percent of the cases later confirmed to be TB cases by culture. (Such cases are referred to as smear-negative TB).

The insensitivity of smear microscopy has led some activists in resource-limited settings to call for wider access to culture, which essentially involves trying to grow mycobacteria (if there are any in the specimen) in a solid gelatin-like substance (the

most commonly used type is called Löwenstein-Jensen [LJ] medium). This can usually only be done at reference laboratories—and in most countries, few laboratories perform culture on any meaningful scale.

Even if a specimen is sent off for culturing, the process takes a few weeks, usually longer in smear-negative cases, and diagnosis often comes too late to save a person's life.

However, a number of new culturing techniques have been devised which speed the growth of MTB, using new liquid media. Most of these methods are technically sophisticated, automated, and proprietary—increasing the cost of culturing by at least ten fold. For example, the cost of the machine used in the *Mycobacterial Growth Indicator Tube* (MGIT) 960 system is at least 50,000 euros, and twice as much once transported to Africa or Asia (or if the cost of maintenance is included). Furthermore, preliminary studies in resource-limited settings suggest a much greater susceptibility to bacterial contamination using this system.

MODS is a much simpler, manual, liquid culturing technique that relies on basic laboratory equipment and microscopy skills similar to those used for smear microscopy—and the only aspect of the process that is proprietary is the liquid medium (Middlebrook 7H9). To perform a test (start a culture), enriched liquid medium is placed into a well of a tissue culture plate, which is then inoculated with a patient's specimen (after it has been decontaminated for other micro-organisms). Once a culture has had a chance to grow, MTB should be easily identifiable when examined under a light microscope because it grows in very distinctive cord-like shapes.

A proof-of-concept study by Caviedes et al. had already shown that the MODS assay was highly sensitive for TB. And a recent study in Lima, Peru with a large number of samples demonstrated that MODS had a similar sensitivity and specificity for TB as LJ culture and the MGIT system—and can also be used for faster drug susceptibility testing (Moore et al.).

**“Activists are calling for wider access
to TB culture diagnosis.”**

MODS Study in Honduras and Brazil

The current prospective study demonstrates that the MODS test can be successfully performed in laboratories in two other resource-limited settings: Rio de Janeiro, Brazil and Tegucigalpa, Honduras. The study analyzed data from 1,639 routinely collected respiratory specimens from 854 study participants; 559 from Brazil and 295 from Honduras. The two groups included 102 individuals with HIV.

In this trial, a participant was considered to have TB if at least one culture on LJ medium was positive for MTB. If a specimen was only positive on MODS, the participant from whom it was collected was deemed to have TB, if after 90 days of follow-up, one of their subsequent specimens was positive on LJ culture, or if they had a clear clinical response to anti-TB treatment (without an alternative diagnosis), or if they died of TB.

A total of 357 participants (41.8%) received a final diagnosis of TB. Of these, 348 participants were positive on the MODS test, while 28 participants who were positive on MODS were diagnosed as negative by LJ. The sensitivity, specificity, positive predictive value, and negative predictive value of the MODS assay were 97.5% (95% CI, 95.7%–98.6%), 94.4% (95% CI, 93.1%–95.2%), 92.6% (95% CI, 90.9%–93.6%), and 98.1% (95% CI, 96.8%–98.9%), respectively.

Not all of the 28 MODS-positive, LJ-negative participants were false positives however: four were later determined to have TB by response to anti-TB treatment. Of the remainder, four were given an alternative diagnosis and eleven were determined to have non-tubercular mycobacteria (NTM) (by biochemical techniques performed on the LJ cultures), while nine were categorized as not-TB because they were lost to follow-up. There is a good chance, however, that some of these were indeed TB because the authors noted, “the clinical suspicion for TB was high.”

Per specimen, there was concordance between MODS and LJ culture in 94.2% (95% CI, 93.1–95.1%). MODS tests were also less prone to contamination than LJ cultures, 62 [3.8%] vs. 95 [5.8%] of 1,639 samples, respectively ($P \leq 0.01$). Of note, a significantly greater proportion of the LJ cultures were contaminated in the Honduras lab. The performance of the MODS test, however, was consistent across study sites.

The MODS test was also dramatically faster than LJ culture, with a median time to growth of 7 days (interquartile range [IQR] 5–10 days) compared to 21 days (IQR 17–25 days) for LJ cultures ($P < 0.01$). Similarly, a subset of 64 specimens evaluated by the MGIT 960 system had a median time to growth of 8 days [IQR, 6–11.5 days; ($P = 0.16$)]. MODS detected 90.4% of the positive samples within two weeks, compared to just 16.6% by LJ culture ($P < 0.01$).

A total of 83 individuals were determined to have smear-negative TB. The MODS assay detected 75 of these cases, although the time to detection was slightly longer than for smear-positive patients: a median of ten days for the MODS assay versus 26 days for LJ culture. Nevertheless, MODS com-

pared well to culture—only 2.2% of these were culture positive on LJ medium within two weeks, while the MODS assay detected 73.1% of the positive cultures within two weeks ($P < 0.01$).

The Promise of MODS

The earlier the diagnosis, the sooner treatment can begin, which is particularly important for people with HIV and smear-negative TB.

One possible drawback, however, could be the inability of laboratory technicians to distinguish between TB and some NTM. This could potentially have clinical impact in settings where NTM prevalence is high and not all mycobacteria respond to anti-TB treatment. This is a problem for other liquid culture techniques as well, so a number of laboratory tests (some based on molecular techniques) are currently in development to improve and speed the identification of NTM.

Another issue is that although the technique can probably be performed in any lab that can currently perform culture, MODS is technically more challenging than smear microscopy. In addition to training technicians, most laboratories would need to upgrade capacity and establish supply chains for reagents and supplies that may not be readily accessible. The process is still manual and requires motivated lab techs. In middle-income countries with a heavy burden of TB (where laboratories must analyze a high number of specimens), it may still be more cost-effective to use an automated system—particularly if countries are receiving assistance from bi- or multilateral funding partners.

And then there is the safety issue—most laboratories where smear microscopy is performed do not have functioning biosafety hoods that are necessary to safely examine live cultures. In this case, the liquid cultures are in plates that must be transported from an incubator to a microscope—and there is a serious risk of spillage and exposure to TB (possibly even MDR- or XDR-TB). However, the authors of the current study suggest that “modification of the current plate platform into a more secure platform (e.g., the use of a tight-fitting lid to reduce the possibility of spills) would be advantageous and is likely to be feasible.”

Finally, even though this is a low-tech and more rapid way to culture, resource constraints will create logistical problems with transportation of specimens and getting the results back to the clinic. In practice many people will still not receive their diagnosis in time to receive life-saving treatment. Simple, low cost, same-day TB tests that can generate an accurate diagnosis when and where the patient first presents for care are still urgently needed.

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Basic Research is a Government Responsibility

By Robert Siliciano, M.D., Ph.D.

Johns Hopkins University School of Medicine.

Excerpts from testimony before the US Senate Committee on Appropriations, March 19, 2007.

The United States has long been the world leader in scientific discovery, thanks largely to government policies that encourage innovation, improve education, and facilitate the transfer of knowledge from the laboratory to the marketplace. Today we face serious threats to this preeminence. Other nations bring to the table strong educational systems, focused government policies, and low-cost workers.

Basic research is essential to our ability to meet this challenge. William R. Brody, president of The Johns Hopkins University and co-chair of a national committee on competitiveness, puts it this way: "Knowledge drives innovation. Innovation drives productivity. Productivity drives economic growth." Our ability to compete in the global economy depends, first and foremost, on our ability to continue making new discoveries. The more we learn about how things work—the principles of basic biology, chemistry, physics, and mathematics—the more opportunity we have to put that knowledge to work. When we know more, we can use that knowledge to make our world better, to build new businesses, devise new products, and to improve our standard of living.

America's most innovative industries are built on decades of basic research, research that had no discernable practical application at the time it was undertaken. For example, the highly theoretical world of quantum mechanics spawned the

semiconductor industry and the information revolution. Johns Hopkins scientists thinking about the principle of physics, called the Doppler effect, used it to invent what became today's Global Positioning System. Two Johns Hopkins biologists shared a Nobel Prize in 1978 for using restriction enzymes to cut DNA into fragments that created today's thriving biotechnology industry, which is based on genetics.

In the United States, funding basic research has long been a governmental function. Why? Because it takes a long time to do it, because there is always a risk that any single project will come to nothing, and because it is difficult to capture an immediate return on investment for an idea that has not yet been developed to the stage of a marketable invention.

Despite a societal consensus that basic research is a government responsibility, US federal research and development spending, as a percentage of Gross Domestic Product (GDP), peaked 40 years ago in 1965, at just below 2 percent of GDP. In the past 40 years, that percentage has diminished by more than half, to about 0.8 percent of GDP. Overall R&D spending, especially in basic sciences, continues to decline. We must reverse this trend now, by strengthening the nation's commitment to science related federal agencies and departments.

The life sciences research funded by the NIH is a key component of our overall national science agenda. For example, Johns Hopkins University is the nation's leading recipient of federal research grants. In FY2005, our researchers attracted nearly \$1.3 billion in federal R&D funding and \$1.4 billion in overall R&D funding, a category in which Johns Hopkins has led all US institutions for 27 consecutive years. This support enables us to improve medical care worldwide, advance human knowledge, and train new generations of innovative researchers.

While the President and Congress have embraced the notion that funding for basic research in the physical sciences is essential to strengthening America's competitive standing in the world..., we remain concerned that funding for biomedical research has not kept pace with this commitment. Aggressive, stable, and sustained federal spending on the NIH and biomedical research must be understood and embraced as a critical component of America's competitiveness.

On January 15, 2007, President Bush signed the National Institutes of Health Reform Act of 2006. While the law calls for a 6% increase for FY2007 and an 8% increase for FY2008, the reality is that this funding commitment has not fully materialized. For FY2006, the NIH budget was cut in both nominal

AIDS Research Suffers

Everyone I know has had to scale back research efforts because of flat NIH budgets. In my own lab we are now finding it difficult to take on new staff and begin new projects. Typically, in the past, I would spend about 30 percent of my time applying for grants; now about 60 percent of my time is spent preparing applications. Furthermore, some prominent investigators are getting out of research. Few scientists want to tackle high-risk problems...because research of this type is more difficult to fund. In fact, a very good colleague of mine has made a major discovery on a unique group of patients who control HIV without medication. He has not been able to get funding even though the potential savings is more than \$14,000 annually per patient. Additionally, a mentor of mine, and one of the most respected people in the field, is thinking of getting out of research because he has no funding.

An anonymous AIDS researcher

and real terms. For FY2007, the NIH received a modest yet important increase of approximately \$620 million. Despite this increase, however, FY2007 marks the fourth year in a row, when adjusting for inflation, that NIH funding has been cut.

At Johns Hopkins, we have annually led the nation in NIH research dollars and we have seen a marked decline in grants awarded to our School of Medicine. Fewer projects are being funded and NIH support of on-going investigations is being cut. Recent figures suggest that the number of grants and overall funding levels have declined. In FY2002, the average funding level per grant was \$142,210 for the School of Medicine. By FY2006, the funding level dropped nearly \$50,000 per grant to \$92,683, a decline of 34.8 percent. Hardest hit are America's young researchers. I fear that we may lose a generation of enthusiastic, inquisitive scientists if they conclude that NIH grants are out of reach.

Flat Funding Threatens Our Young Investigators

One of the first and earliest victims of declining NIH funding has been the young investigator. You have heard...often over the past several years...that we are discouraging and potentially sacrificing an entire generation of young scientists. This situation is compounded by the fact that not only is our country producing a shrinking number of researchers in the life and physical sciences, but the best and brightest of foreign-born U.S. trained scientists are increasingly returning to their home country as opportunities expand overseas.

Quite simply, we have to do more to support and encourage our young investigators. Most ideas that turn into Nobel Prizes come from investigators before they reach the age of 40. As a country, then, shouldn't we be supporting these scientists when they are in their professional prime? Unfortunately, the statistics tell an entirely different story. In the case of initial R01/R29 awards, between 1970 and 2004, the average age by which an investigator with a Ph.D gains his or her first award has gone from 34.3 years of age to 41.7. In the case of MDs, during this same period, that age has gone from 36.7 years to 43.3 (AAMC 12 July, 2006). With diminished NIH funding, our young scientists are witnessing firsthand the decline in overall success rates for grant applications. In 1998, the first year of the doubling, success rates were over 50 percent for grant submissions. For 2007, the success rate is projected to drop to only about 18 percent. Left unaddressed, there is no question that the current decline in NIH funding places an entire generation of young scientists at risk.

Even at my own institution, where we have many of the best and brightest among the current generation of young scientists, we are seeing many of these men and women unable to gain funding support. Without sustainable and predictable increases in NIH funding, this nation is at risk of losing an entire generation of scientists.

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Immune Activation in HIV Infection More than Just Markers

By Richard Jefferys

At the recent International AIDS Society conference in Sydney, Mike Lederman reminded attendees that abnormally high levels of immune activation were described in the first case reports of gay men with AIDS in 1981. The authors of those reports, led by Michael Gottlieb, specifically noted the “increased percentage of cells bearing the thymocyte-associated antigen T10.” This antigen is now known as CD38, and an extensive literature—particularly the work of the late Janis Giorgi, an immunologist at UCLA—demonstrates that CD38 expression on CD8 T cells correlates strongly with the rate of disease progression in people with HIV infection (in many instances, more strongly than viral load and peripheral blood CD4 T cell counts). It has also become clear that immune activation is a broader phenomenon than just CD38 expression on CD8 T cells. CD4 T cells are also over-activated and additional T cell activation markers—such as HLA-DR—are elevated along with levels of pro-inflammatory cytokines including TNF-alpha, IL-6 and IL-1beta.

The role of immune activation in HIV infection has generally received less attention than HIV-associated immune deficiency. But recently, immune activation has received renewed attention for a number of important reasons:

- Immune activation—but not viral load—has emerged as the critical factor distinguishing pathogenic immunodeficiency virus infections—such as HIV infection in humans and SIV infection in rhesus macaques—from non-pathogenic infections, such as SIV infection in sooty mangabeys and African green monkeys.
- Results from the large SMART trial, which evaluated the strategy of interrupting ART in a large population of more than 5,000 HIV-infected individuals, clearly showed that the relative risk of clinical events not normally considered to be AIDS-related was higher in people who interrupted therapy. Many of the events—such as cardiovascular, liver and kidney disease—are associated with inflammation and immune activation, and recent analyses of the SMART results are suggesting that levels of biological markers known to predict an increased risk of these events were raised by treatment interruption.
- The effectiveness of ART in restoring immune responses to opportunistic pathogens has greatly reduced the inci-

dence of opportunistic infections, but even individuals on long-term ART with well-suppressed viral load typically show elevated levels of T cell activation compared to uninfected controls as well as markers of incomplete immune restoration (e.g. persistently skewed CD4/CD8 ratios). This suggests that these individuals may remain at increased risk for conditions associated with inflammation and/or perturbed T cell homeostasis (e.g. the cardiovascular events mentioned above and autoimmune-like phenomena).

- Studies have demonstrated variations in background levels of immune activation based on geographical location and an impact of immune activation on susceptibility to HIV infection; these results suggest immune activation also contributes to geographic variability in HIV transmission risk and the speed of progression from HIV infection to AIDS.

**“...no longer solely of interest to
academic immunologists...”**

Taken together, these findings argue strongly for a renewed focus on unraveling the causes and consequences of immune activation and inflammation in HIV infection. The intimate correlation between viral load levels and immune activation markers and the precipitous decline in activation that occurs on ART are compelling evidence that HIV is driving the phenomenon. But exactly how this is occurring—particularly the extent to which HIV antigens are involved versus other potential sources of activation such as bacteria leaking across the gut mucosa—remains unresolved. Even the exact types of CD4 and CD8 T cell that are expressing high levels of CD38 in HIV is still uncertain; are they naïve T cells that have been activated, memory T cells that have been activated, or some mix of both? What antigens are these T cells specific for?

These questions are no longer solely of interest to academic immunologists, they are now increasingly recognized to have a vital relation to the transmission and pathogenesis of HIV infection and AIDS. Obtaining answers will require a multi-pronged approach involving studies addressing clinical questions—such as the best time to start ART—and translational research to evaluate therapies that might both ameliorate immune activation and shed light on its causes, such as toll-like receptor antagonists, CCR5 inhibitors and anti-inflammatory approaches. HIV research has come a long way in addressing immune deficiency; it’s now time to take on immune activation.