How to get There From There

Dr. Steve has nothing good to say about AIDS research and activism. He also has a map to the end of the epidemic.

October 1, 1999 By Mike Barr

“Right now, in 1999, we should be able to figure out this disease,” researcher-provocateur Steven Miles, MD, says flatly in this interview, serving up both a scathing attack on current “groupthink” and his own bold vision for new directions. Miles, an associate professor of medicine and director of the CARE Clinic at the UCLA AIDS Institute, argues that advocates and scientists alike are corralled in a therapeutic paradigm that guarantees failure. Bought off by pharmaceutical largesse, community reps no longer act “outside the box”; drug development languishes not due to tech-no--logical or intellectual limitations, but for the lack of free thought and free will. The protease revolution, Miles charges, set research back years, as drug firms shelved development programs once AIDS was declared virtually cured. Among other reforms, Miles would have the FDA turn off the fast-track spigot for antiretroviral “me too”s, forcing industry to re-evaluate its cynical approach to research. But more than anything, Miles’ keen observations could challenge a lackadaisical activist movement to rise again. --MB

Mike Barr: *Many see this as the best of times in AIDS research. But you’re very critical of current directions. Why?*
Steven Miles: First, let me say that despite all my criticisms, what I want to communicate is excitement about the current moment. The protease revolution, which has saved so many lives, has presented us with unprecedented opportunities and challenges. This is a great time to make enormous strides in research very quickly if we all work together and keep our minds open.

Now for the bad news: Over the past three years we’ve lost sight of one essential thing: It’s not “the virus, stupid”—as some leading voices argue. Our myopic focus on eradicating HIV has had a destructive effect on other research—especially immune-based therapies. There’s no question that the virus destroys the immune system, and because of this people get sick. But they get sick not because they have billions of particles of virus in their blood—they get sick because they no longer have an immune system producing CD4 cells. There are plenty of people with 600 CD4s and 1 million copies of virus who are asymptomatic and healthy. And yet somebody with 1 million viral copies and 10 CD4s is at serious risk for PCP, crypto, CMV and other life-threatening infections. So while it’s true that the virus gets you down to 10 CD4s, if there were a way to restore the lost cells, it’s irrelevant how much virus is floating around in your blood. That’s the fundamental fact that has been shunted aside by our virus obsession.

MB: *So the race to eradication was a wrong turn?*
SM: Researchers have been operating on the assumption that if we focus on suppressing the virus, then the immune system will get better on its own. And while the body does have remarkable reparative powers, that may not be true. What we're actually seeing are many people undetectable for two, three, even four years who seem to plateau in terms of immunologic recovery. If you look at our current ability to stop HIV, you come to one of two conclusions: Either we're nowhere near suppressing viral replication completely and that's why we're seeing only partial immune restoration, or we're very close to completely suppressing viral replication but there's some other defect and that's why we're not seeing immune restoration. I argue that it's the former.

I'd like to see researchers operate on this assumption: If we could give you back enough immune cells or prevent their loss in the first place, then you wouldn't need to take multiple-drug regimens for the rest of your life because the amount of virus in your blood is irrelevant. So what we need to say is, "What research do we need to do to get you back to 600 CD4 cells?" And the answer is a radically different track of research than the one we're currently embarked upon.

MB: *So right now we should be pouring money and energy into immune-based research.*
SM: Yes. Of course, work is already being done, and advances have been made, but I don't think IL-2—which most of the excitement is about—is the answer. But overall I see very little investment by the pharmaceutical industry in this question of how to rebuild the immune system. Look at the number of companies now entering the market with yet another "me too" drug in the same class, and you'll realize that the likelihood of a company striking out in a new area of study is quite low. The closest thing to novelty we're getting is "Well, my drug works against virus X, Y or Z that has this extra mutation." And what they fail to say is that the virus will develop resistance to their drug soon enough.

The enormously frustrating thing is that right now, in 1999, we should be able to figure out this disease. We have all the biotechnology to search for and find the X factors: either the things that cause key immune cells to grow, and so must be developed, or the things that suppress cell growth, and so must be blocked. This is not rocket science—it's a technical engineering task, and directed grants and reasonable budgets for specific, focused areas should give us very solid leads in a short time.

MB: *So the structure is in place to identify these growth or suppressive factors. What's the problem?*
SM: You know, we lost two to three years' worth of drug development with the protease gold rush and all the hype about a cure following the 1996 International AIDS Conference in Vancouver.A lot of companies left the field.If you're a drug-firm executive with a $200 million development project and one group over here says they might be curing AIDS and another group over there says there's no end in sight to diabetes, you're going to put the money in diabetes!

MB: *So Vancouver cost us…*

SM: Two or three years of drug development.

MB: *You're the first person I've heard say that.*
SM: It's not a popular view. AIDS was the great new area for drugs from 1993 to 1995. Many small companies saw it as their way to the big time: Find a drug, make sure it has an AIDS indication so it gets fast-track approval, and make millions as the market explodes. Look at Agouron and Vertex. Then in 1996, AIDS was virtually cured. "Why develop a second-generation protease inhibitor when your first one lasts forever?" was the view. Many companies stopped dead in their tracks. Roche quit, Boehringer dropped out. All these protease inhibitors underway were sold or shelved. Some came back to life as smarter folks at the bigger firms picked them up. But we lost time. And now, three years later, suddenly it's "Oh my god! We've got resistance! Let's develop the next generation of drugs."

Look, from a drug developer's standpoint, AIDS is now the most attractive disease on the earth. For four obvious reasons: The drugs are very expensive; many patients are privately insured because they are healthy and working; thanks to advocacy, the government pays for drugs for many people who can't afford them; and the drugs don't cure anybody. So where in 1996 you had 52,000 new infections and 48,000 deaths, you now have 52,000 new infections and 25,000 deaths—that's 23,000 new candidates for your drug this year alone. And every year you just keep adding 23,000 to this stable population paying for multiple drugs for the rest of their lives. There's no disease where the number of drug consumers is going up as fast as it is in AIDS. Why wouldn't you develop a drug for this disease?

MB: *Especially if your drug is…*
SM: A "me too," already proven knockoff.

MB: *It'll fly through the FDA-approval process…*
SM: And all the drug company exec has to worry about is marketing—which he's a pro at.

MB: *So the drug companies are responsible for this.*
SM: It's not just the drug companies—it's the activists, the doctors, the government, all of us. What's happened is there's a lot of groupthink going on. And it's very difficult to reverse the trend, but we have to do it. One thing that would definitely make everyone at least stop and think is for the FDA to crack down on accelerated approval. To say, "Hey, no longer do you get a fast-track exemption for a 'me too' drug. We're not giving you early licensure for 48-week data based on the fact that there's a need for new drugs. You have to demonstrate how this nuke, NNRTI or protease inhibitor is different from what's already out there."

MB: *You've proposed a plan to refocus research: First, focus on identifying factors responsible for either encouraging or suppressing an effective immune response; second, fund targeted grants for development of new drugs that destroy HIV-infected cells; third, make changes at the FDA to squelch the explosion of me-toos. It sounds like an agenda for activism.*
SM: The reality is, many activists have been co-opted. They like flying all over the world to the company-sponsored conferences at the fancy resorts just like anybody else.

You have pharmaceutical firms that, before their drug is even on the market, target the activist groups. It's absurd, though it's no different from what goes on with the doctors. We're all very reluctant to bite the hand that feeds us. The drug companies have programs of co-opting the activists!

Agouron hired someone to reach out and stroke the community even when it still had only two or three people doing drug development.

The truth is, there's very little objectivity among activists to begin with. The drug du jour is Abbott's [protease inhibitor] ABT-378. Now, I look at ABT-378's resistance pattern and I can't tell the difference between that and amprenavir (Agenerase). So why is everybody so hot to suddenly have ABT-378? Just go take amprenavir, is the best I can tell. But taking their cue from industry, activists have created the buzz that you have try 378.

MB: *But if industry's not willing to push the research envelope, who does that leave? The government? What's happening there?*
SM: At the National Institutes of Health, the study sections responsible for grant approvals are also guilty of groupthink. Basically, you can't apply for money now unless you have already done the experiments and know the results. And if your project doesn't go along the path of what everybody expects, then the likelihood of being funded is near zero. I just saw a review where the study section said the peptide therapies for HIV were impractical. Well, tell that to all the patients taking T-20 with their viral load drops! But this groupthink is based on ignorance of the new data. If Trimeris [the maker of T-20] succeeds in nothing other than showing you can successfully give a peptide as an inhibitor of HIV, that in and of itself will be valuable. It will change the thinking in the field to, "Oh, peptides can work in some circumstances."

Many scientists who have novel and promising research won't even put in a grant because they know, first, it won't get funded because it doesn't fit current thinking and, second, the people reviewing it will steal the idea.

So why risk having somebody else take your idea if it's a good one and if you're not going to get funded, either?

MB: *So the truly innovative ideas are being buried? How would you change that?*
SM: I would focus on the professional administrators—very senior people who have overseen these study sections now for 10 or 12 years. We need to give them the capacity to award money for research outside the mainstream—things that the study sections didn't like but that the administrators, who have years of experience and perspective on the disease, think may work. We need to start holding those folks accountable for what's in their portfolio—to motivate them to get good research through their committees, rather than funding the same thing over and over again.

Wall Street likes sure bets, and new areas of research are high risk. So we have to recognize that industry is risk averse, and take advantage of that fact—by putting the government to work. The National Cancer Institute has a very strong program in drug screening and development. It can do

the initial research to identify the lead compounds that might work against the target in question, and then either license them out to pharmaceuticals or put them in the public domain and let companies develop them. Pay them to do something they should be doing anyway. Otherwise, the companies aren't going to undertake either new approaches or the development of new drugs when they can put $20 million into making a slight modification of an existing protease inhibitor and come up with another $1.2 billion product.

We also need to motivate industry to bring more novelty to the types of drugs under development. What we are trying to do with AIDS has never been done before. In every other infectious disease, if you use suppressive therapy, you almost always fail. Our drugs are suppressive drugs.

They don't kill the target—the proviral DNA inside the infected cell. What they do is roughly akin to having a police officer round up gang members and tell them to sit nicely on the curb and behave themselves. They do that as long as the cop is there, but the minute the cop turns his back, they go back to being gang members.

MB: *Is there a precedent for eradicating viruses with drug therapy?*
SM: I believe there are ways of doing that. What we need is a series of drugs that are both highly selective and destroy infected cells. To take one example, we would be more effective if we exploited the NNRTIs' amazing ability to bind to HIV's reverse transcriptase by somehow getting the drugs not only to stop the virus from replicating but kill the entire cell. In the best case, you now have one set of uninfected, healthy immune cells that responds to the immune stimulant that you are developing, and another set that is infected, unresponsive and can be killed off. Think of the control that gives you. You can grow uninfected cells while selectively eliminating infected ones. That's the beauty of this approach: It's no longer necessary to quote-unquote eradicate the virus. Consider the example I used early on: The person who has 600 CD4 cells and 1 million copies of virus doesn't have to have her virus eradicated—as far as she's concerned, everything's fine.

We don't have to hit a home run. The slope is so slow, with the average person taking 10 to 12 years to get sick, that if you change that slope by 2 percent per year, your patient will have a normal lifespan and good quality of life.

MB: *What does the future hold for people now on therapy? In her controversial Esquire piece last spring, "The Virus at the End of the World," Laurie Garrett wrote that everyone will develop multidrug-resistant HIV and get sick at the same time—when services and resources are way down.*
SM: Garrett is right about multidrug-resistant virus [MDR]—it's a very real problem—but she's wrong about the timing. MDR is all I see in my clinic now. My typical new patient has 18 mutations, and it's unlikely that his virus will be vulnerable to any drugs. But I don't think the picture is the doomsday scenario that Garrett describes because the time frame for clinical failure is much further down the road than where we are right now. Our current regimens suppress below the limit of detection for two, three, even four years. Now, if we get 18 months for 12 weeks' suppression,

as the early AZT studies indicated, how long do we get for four years'? If we get many years' worth of benefit, that gives people with HIV and the rest of us time for additional drug development—the agenda we talked about earlier—to get done. So even if in a year 25 percent of patients have drug failure, I don't think we'll see a disaster, the re-emergence of hospitalizations and deaths.

MB: *How do you treat patients with resistance? Is there an argument for keeping them on therapy endlessly?*
SM: There are three important factors. First, many of them have virus that is still below the level that it would be at their baseline, even if the drugs aren't fully suppressing the virus. So they're still deriving some clinical benefit. Second, the drugs may be suppressing things other than HIV that we have yet to identify. This is very likely, because we're seeing so many people with undetectable virus whose immune systems are far from completely recovered. The third thing, of course, is the sheer clinical toll these toxic drugs take on patients. So with each patient, I try to balance what's happening with their viral load, how they're feeling clinically and what drug toxicities they're facing. It's a very individual decision.

MB: *Is there a future for such radical treatment strategies as pulsed therapy—going on and off a drug regimen to maximize effect and minimize toxicity?*
SM: Look at how we treat chronic lymphocytic leukemia, which is a genetic disease like HIV: We treat people intermittently until they get better clinically, and then we stop therapy. And then we treat them again when they deteriorate. It's a completely different approach from what's currently done with HIV. And it shows a great deal of promise.

MB: *TAG, Project Inform and others are proposing studies of structured treatment interruptions—similar to pulsed therapy—and the opposition from doctors has been incredible. Plus, industry's not happy at the prospect of people taking half as much medicine in a year.*
SM: That's another example of groupthink. You know, in oncology we do this all the time—treat patients when they're symptomatic, and when they're not, don't treat them. So it's not so revolutionary. You structure a clinical trial and you try it.

I learned a long time ago that the patients who do best are the ones who live long enough to remember that my previous statement was wrong. I'm always reminded of the things that I've done wrong in the past. I've given Tumor Necrosis Factor to block TNF, and I've given soluble TNF receptors to make it grow!

Now, one of those two is very wrong. But a patient comes to me and says, "I want to do this." And I have to say, "Well, the last time I looked, I didn't have the cure for this disease, so it looks reasonable to me. Let's try it." So why are we closing off potential avenues for research? That makes no sense to me.
