DR. SHARON LEWIN: "..the biggest hurdle will be getting rid of latently infected cells."

PLOTTING A STRATEGY

INTERVIEW BY JEFF BERRY

***PA* SAT DOWN IN VIENNA WITH AUSTRALIAN RESEARCHER** and physician Sharon Lewin to get her thoughts on some of the emerging strategies for a cure, and what work may still lie ahead.

JB: Could you summarize for us some of the highlights from the talk you gave at the opening plenary of the conference?

SL: The main areas I wanted to cover in my talk were why we need a cure, why we don't have one, and what strategies we're going to need to get there. Why we need one is that HAART is not perfect. HAART is great—it's changed people's lives, and it's been fantastic, but life expectancy is still reduced and there are ongoing treatment related toxicities. And then the argument is the sustainability of long-term treatment for everyone. It's not a problem if you live in the U.S. or Australia, but it's still a threat if you're living in a lower income country. I think we know a lot more now about why HAART doesn't cure HIV and what the causes of viral persistence are, and I explained the difference between persistent infected cells, which we measure by DNA, and persistent low-level viremia. There's really no such thing as an undetectable viral load—there's always low-level viremia and persistent infected cells. There's a lot of debate and argument amongst scientists about what's contributing to low-level viremia. Is it latently infected cells, residual viral replication or anatomical reservoirs? I don't think that's the fight we need to have. I think they all probably play a role, but the biggest hurdle will be getting rid of latently infected cells.

Latency is when the virus enters into a resting cell, integrates, and then sits there and doesn't do anything unless the cell gets activated. What we now know is that latency can be established in lots of resting cells including memory cells. We now know there are a whole lot of other cells including stem cells where latency can be established. And that's going to be pretty tricky, first of all understanding if latency is the same in all those cells and whether you can target all of those cells with the same strategy.

Latently infected cells have a very long half-life and they also can probably proliferate and divide. Then what's called daughter cells will contain a latent virus as well, so there's probably a source that's replacing these latently infected cells all the time.

JB: So what happens is you suppress the virus for a long time and then suddenly these other latent cells become activated?

SL: When you're on treatment you can suppress the virus for a long, long time, or you'll have low-level viremia (meaning detectable virus of less than 50 copies/ml in blood). In most people low level viremia sits at around 3-5 copies/ml. But the minute you take away antiretroviral therapy the virus takes off again. That's because latently infected cells can be activated, release virus, and then go on to infect new cells. I think anatomical reservoirs are also going to be important because you have very high levels of virus replication in some of these sites, specifically the gut—and in the CNS and genital tract there are specialized, long-lived infected cells. The evidence for brain and genital tract reservoirs in patients on HAART is not really great, they're very hard areas to access. But in the gut there are lots of studies now showing that there's probably about 10 times as much virus there than in blood, even in people who have been on treatment for years.

I talked about the difference between functional cure and sterilizing cure—maybe simpler words for these are "cure" or "remission" so that cure means eliminating every single infected cell. To achieve a "cure" you would give HAART plus a certain treatment for a number of years and have no virus detectable, and that's what scientists are now calling sterilizing cure. The other strategy [functional cure] may be just

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to induce remission, meaning that you lower the virus to a level less than 50 copies per ml in the absence of treatment. That's what I'd call the cancer model—the virus is always there, but you can control it, not have any immune damage, and not be taking HAART.

I also talked about what strategies we're going to be able to use, and those include optimizing HAART, which could be with intensification or starting early. I've reviewed some of the intensification studies that show no difference in persistent DNA and low-level viremia if you're adding T-20 [Fuzeon], or more protease inhibitors, or adding raltegravir [Isentress]. In other words, all of these studies showed no change in the measures of persistent reservoir. But in one very good study from Spain, probably the largest intensification study so far, they gave patients raltegravir and a third of them had an increase in 2-LTR circles [another marker of virus replication] and that was really proof that there must be ongoing virus replication in at least some patients on treatment. That doesn't mean that's the explanation for the fact that we can't cure HIV, it just means that there's still some residual replication, and that has to be addressed with any kind of purging strategy.

The other interesting data concerning treatment is that if you do treat early, during acute infection, the size of the reservoir is much smaller than if you treat late. There's some pooled data from a large French cohort that if you treat very early, the number of latently infected cells is about 1 to 2 logs less than if you treat someone who's got a chronic, established infection. So the optimal way to really crunch the reservoir down to its smallest size would be treating early and treating with maximal therapy to turn off any replication. That still doesn't get rid of the reservoir—it just makes it as small as possible.

And then I think that even if we do all of that, all the evidence says that we still haven't eliminated the reservoir, and the next strategy that people are thinking about is trying to push virus out of these latently infected cells. They're trying to "reverse" latency, or what some call "purge the reservoir" or wake up the virus so it starts to replicate.

JB: It's almost counter-intuitive.

SL: Yes, it's counter-intuitive because you're causing the virus to replicate, but the basis of why people think that this might work is if you cause the virus to replicate and it can't get into new cells, then the latently infected cells will die. Once the virus comes out of a latently infected cell, it destroys the cell it was in. For this to work, HAART has to block 100% of any new rounds of replication. That's the idea behind purging the reservoir, or pushing the virus out.

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And the last thing I talked about is that there may be ways that you can make cells resistant to HIV using gene therapy. The gene that is the most attractive target is the CCR5 gene and there are now mouse models that have shown it is possible to introduce a gene that knocks out CCR5.

None of these strategies will replace HAART. All of these strategies are designed to be used after several years of HAART. We don't really know how long, but maybe three to five years, and the aim is to get people off HAART, but it'll never replace HAART. So, therefore universal access still has to be number one.

I also talked a little about community engagement because I think this is really complex science, and the community hasn't come along in understanding what people are thinking. I think clinical trials with people taking antiretroviral therapy and having a really good quality of life, that then introduce something that's potentially unknown or toxic, is one of the challenges in designing those studies. And then if we can achieve an effective cure, when will we feel comfortable interrupting treatment knowing that interrupting treatment is unsafe? So there are lots of issues to explore in how best to design clinical trials.

JB: So, what are the implications of the Berlin patient? Obviously it's not something you'd want to try in everyone.

SL: I think that case is really interesting. We have to absolutely know everything about that patient and what happened to him, and why they got that result of basically a sterilizing cure. No HIV in the blood, the gut, or the cerebral spinal fluid (CSF)—it shows that you can eventually get rid of these latently-infected cells. You can also get rid of anatomical reservoirs, and it's possible to have no replication when off HAART. The next question is, what's done it? Is it the transplant, so that you've made every cell resistant to HIV? The Berlin patient received a transplant of bone marrow from a donor that contained a delta 32 mutation in the CCR5 gene so that there was no CCR5 expressed on the donor bone marrow cells. The strategy to mimic this would be to knock out CCR5 by gene therapy. But I'm not sure it was just the transplant that "cured" this man—I wonder if there are other factors at play. Another theory could be that he had total body irradiation which knocked out all of his T-cells in the very earliest phase in bone marrow and it got completely replaced by new T-cells so any reservoirs in the bone marrow would have been knocked out. He had chemotherapy, and whenever you give someone a transplant, you have something called graft versus host disease, so the cells in the new bone marrow get rid of any cells from the patient that are lurking around. I agree that you're never going to be able to use this as a strategy, but we have to try and pick out what might have worked. I think that's the basis for thinking that maybe gene therapy and altering CCR5 expression may be one strategy.

JB: Is there anything you'd like to add?

SL: I think we shouldn't be embarrassed to talk about a cure. With cancer, which is far more diverse and likely to be more challenging to cure, people proudly say they're "aiming for a cure." So I think it should just be part of the language, a goal that we need to strive for. We shouldn't be timid about using the word.

To view a webcast of Dr. Lewin's opening plenary talk visit www.aids2010.org.