BMJ

BMJ 2013;346:f2947 doi: 10.1136/bmj.f2947 (Published 13 May 2013)

FEATURE

INTERVIEW

Functional HIV cure is no pipe dream, says codiscoverer of the virus

Geoff Watts talks to French virologist and Nobel prize winner Françoise Barré-Sinoussi about HIV and the prospects of a cure

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Rounding off the autobiographical statement she issued on receiving the 2008 Nobel prize for her part in discovering the human immunodeficiency virus, Françoise Barré-Sinoussi wrote: "I anticipate continuing my professional endeavours largely unchanged." Indeed she has.

To a British ear, long accustomed to hearing winners of the UK's national lottery similarly deny that their good fortune will change their lives, that sentence strikes an oddly familiar albeit incongruous chord. But while any comparison between the luck of a lottery draw and the intellectual labour underpinning a Nobel award is ludicrous, the two events do have one thing in common: their consequences are not always as you might predict.

When I confidently suggested to Barré-Sinoussi that her Laureate status would have guaranteed her easier access to research funds, her response was immediate. "Not at all." Her laboratory, she says, has to apply for research grants—sometimes without success—exactly as before she won the prize. Paradoxically, it can even make things harder; some grant awarding bodies are less inclined to be generous, wrongly believing that any lab run by a Nobel holder is bound to be awash with money.

I was more on target in suggesting that the Nobel prize has made it easier to get a hearing for her ideas. But for winners whose concern with their work is more than intellectual—and Barré-Sinoussi's certainly is—even this carries a penalty. "I have tried to be a voice for scientists and a voice for people living with HIV. So I feel even more responsibility on my shoulders than before."

Moving targets

The focus of research into HIV has shifted in response to knowledge and experience. In the early years it was simply to pin down the causative agent. Then came the ultimately successful attempt to devise drugs to keep the virus in check, followed by notably less productive efforts to develop a vaccine. Most recently, the search for a cure has moved on to the agenda. And it's this ambition to which Barré-Sinoussi has been giving vocal support. But in view of the efficacy of current antiretrovirals, is it really worth the effort?

"When I speak with patients who are on treatment and doing well," she says, "I ask them, 'What are you expecting from us as scientists?' In the vast majority of cases they say they would like a treatment that they can eventually stop." It's hard being on a medicine for life, and drug resistance does eventually become a problem for some. Then there's the risk of complications. She might also have added that the cost of ongoing treatment comes out at some $50bn (£32bn; €38bn) annually.

The obstacle to a cure is clear enough. "The virus is hidden in the host's genome," says Barré-Sinoussi. "When antiviral treatment is stopped the virus activates and starts to replicate again." Consequently, she explains, the therapeutic strategy is to reactivate latent virus so that drugs can get at it. "But we need to understand more about the mechanism of latency," she adds. "And we need a combination of treatments. Not only a drug to reactivate the virus, but another to eliminate it if the patient's own immune system cannot cope."

Barré-Sinoussi is confident it can be done so long as we set a realistic goal. "I believe we should be able to achieve a functional cure, which is different from total elimination of the virus from the body. These patients will be in remission after they've been treated and the virus will remain under control without further treatment. Why do I believe this? Because we already have proof of concept." There is, for example, the Berlin patient whose viral load disappeared after a bone marrow transplant for leukaemia.

Another of these proofs is the existence of "elite controllers": individuals who've been infected for many years, had no antiviral treatment, and yet remain disease-free. "We also know that a proportion of patients treated very early during the active

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phase of the infection become what we call post-treatment controllers. They've stopped their antiviral treatment, but years later are still free of the disease."

Barré-Sinoussi insists that a functional cure is no pipe dream. "There are compounds and molecules that have been used in cancer research that have been shown to reactivate other viruses from latently infected cells." A majority of scientists now agree with her that a functional cure is achievable. Interest in the possibility is intense and growing. But it will take a lot more basic research into the mechanism of latency.

In the meantime, where does this leave the search for a vaccine? Barré-Sinoussi admits that the task has proved far harder than she'd originally imagined. "In the 1980s we were quite naive. We thought that once the virus was isolated we would have a vaccine quite rapidly." As the work proceeded it became clear that this wouldn't be so. We started to understand the complexity, she says. Of the trials so far reported only one shows even moderate efficacy.

Given this difficulty, should we divert resources from vaccine development into research directed at a cure? "No, because you cannot separate vaccine research and cure research. You need to have both." An effective cure will require either a drug or a strong immune response to eliminate the cells with reactivated virus.

Lifelong interest

Now in her mid-60s, Barré-Sinoussi has said that even as a child she was fascinated by the living world. But when it came to choosing a university course she was undecided whether to opt for a biomedical science or medicine. She chose the former, simply because the course was shorter and would therefore be financially less burdensome for her family. Her attraction to research was confirmed towards the end of her time at the University of Paris when a friend happened to put her in touch with the virologist Jean-Claude Chermann at the Institut Pasteur.

Having started work in his lab as a volunteer she was soon taken on to do a PhD. A post-doctoral fellowship at the US National Cancer Institute preceded her return to Chermann's lab, by then part of the unit run by Luc Montagnier. In late 1982 Montagnier invited Barré-Sinoussi to join him in work on a newly described illness that had appeared in homosexual American men. The aim was to find out if a retrovirus might be involved. At the beginning of the following year, using material from a lymph node biopsy specimen and after some initial technical difficulty, they isolated what they called lymphadenopathy associated virus or LAV, later to be renamed HIV.

Barré-Sinoussi is now director of the Institut Pasteur's regulation of retroviral infections division. The current projects in her laboratory include a study of elite controllers to fathom what mechanisms need to be stimulated to emulate their success in keeping the virus at bay, and an attempt to understand why early treatment is most effective.

Optimistic outlook

The global picture presented by HIV is nothing like as gloomy as it was towards the end of the 1990s. Most people in developed countries have access to antiretroviral drugs. "Now it's not a question of access to treatment but of early access," says Barré-Sinoussi. "But we still have a proportion of people—in France it's around 30 000—who are living with HIV, don't know they're carrying the virus, and so can transmit it to others."

While the picture in developing countries differs from nation to nation and continent to continent, it is overall less encouraging. Of the 34 million people globally with HIV, the highest proportion is in Africa. But as Barré-Sinoussi points out, even here you have different patterns. "In Senegal the prevalence of infection is less than 1%, which is lower than in Washington, DC."

Asia too harbours great variations. In central Asia there is little political willingness to fight the infection and few programmes of prevention. South East Asia is more encouraging. "I like to give the example of Cambodia, a country where I've been collaborating for more than 15 years," says Barré-Sinoussi. "They have a very strong national HIV programme. As a result the prevalence is dropping to less than 1%. Most people who need treatment are on treatment"—an impressive achievement in such a poor country. "If there's a strong political will—and that means that the local authorities are submitting applications to get international funding for a network of centres for care, prevention, and treatment—you can get good results."

Barré-Sinoussi keeps emphasising the central importance of political will. "In Eastern Europe, in a country like Russia, you have no political will at all. They feel that the people who are affected by HIV do not need any consideration because they are intravenous drug users or homosexuals and not a priority."

Many scientists who spend their working lives researching disease have no more than fleeting or occasional contact with patients, and fewer still adopt a campaigning role in relation to the illness. Barré-Sinoussi by contrast takes a close interest not only in HIV but in those infected by it. She feels a responsibility to look beyond the laboratory.

Her motivation, she explains, stems from what she describe as the "terrible period" of the 1980s when the disease first emerged. "Before HIV/AIDS I was working in my lab doing cancer research but without any contact with patients." Starting to work on AIDS and successfully isolating the virus changed that. She began to meet patients.

"People began coming to us as scientists asking what we were going to do about the virus to help them live. At that time we had nothing to propose. But we knew they hadn't got time to wait. It was really dramatic. The community of scientists and physicians working in the 1980s were all strongly affected." She felt compelled to work in collaboration with organisations representing people with HIV.

It is three decades since Barré-Sinoussi published her *Science* report identifying the virus responsible for AIDS. Wisely, and despite all her experience, she declines to make predictions of where we'll be in another 30 years.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2013;346:f2947