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20 years on: Donald Francis discusses advances in the fight against HIV

Interviewed by Rebecca N. Lawrence

Donald P. Francis, President and Cofounder, VaxGen

When you were at the Centers for Disease Control (CDC) and the CDC published the first reports of AIDS 20 years ago, did you realize what a devastating impact this disease was going to have?

I think we knew. My background is in dangerous viral infections such as smallpox and Ebola and, early on, we knew that HIV was a major league virus. I remember when I was mixing up the material for inoculation in our initial primate studies, I treated this just as I would a really dangerous viral agent so we knew it was going to be bad. But did I expect that 30% of Southern African adults would be infected? No – I am still amazed by this organism. And at that time, did we know that it would be essentially a 100% fatal virus? No – even Ebola does not kill everyone it infects. So the combination of the invasiveness and the high mortality of HIV makes it a very different infectious disease from any we had ever dealt with before.

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What were the first key steps taken by the CDC when these reports first came out?

We first did what is typical in epidemiology – the who, what, where and why of the disease. We had been controlling and doing research on infectious diseases in gay men for years at that time and we knew very well the capability of gay sexual activity to spread infectious diseases. We published the first *Morbidity Mortality Weekly Report* (MMWR) when there were only five cases so we recognized at that point that a disease in gay men that was highly fatal and that might be sexually transmitted could be a major threat.

The first thing was to determine what the disease was, make a case definition, set up surveillance systems, and contact health departments and local doctors. As reports of the next generation of cases came in from intravenous drug users, we started to think that this could be a blood-borne and sexually transmitted infection. Soon the list was expanded to include haemophiliacs and transfusion recipients.

When the pattern of the disease became clear, the next challenge was growing the virus. In these situations, the usual steps are to inoculate laboratory animals with the virus. However, all of our small animals did just fine. Even with a huge effort early on, we could not get laboratory animals and our standard cultures infected. We were doing many cultures such as of primary lymphocytes but we were looking for the long-term retroviral expression. Then came the early work from the Institut Pasteur (France). Once they called us and told us how to culture the virus, it did not take long before we had antibody tests. Then we really started to understand the epidemiology of the virus. It then became very scary because we went back to the hepatitis B bloods from our hepatitis B studies and found that 20–50% of the volunteers for that study were already infected with HIV. By now it was 1984 and we had thousands of cases, and the African CDC team had already been over to Zaire and seen hospitalized patients suffering. The epidemic started taking form extremely rapidly. This was of great concern to the CDC.

Why do you think it has been so difficult to find a successful treatment/prevention for HIV in particular?

Well, if you think about it, there have been both successes and failures. I am actually very impressed at the successes in therapy – they are not perfect but look at how we do with the common cold or other common viral infections – our armentarium against viruses is still relatively limited because of their simplicity. When there are only 10–12 genes, there are not many proteins to target and so to treat these infections is extremely difficult.

On the prevention side, I think there are successes in behaviour-change prevention, especially in gay men around the world. There have been impressive results. My feeling is that you really need to 'visualize' the disease before taking action. There are not really many cases in society where behaviour change really occurs. Blood prevention programmes and behaviour change really have been successful here. Needle exchange programmes in some very forward-looking countries have been successful. But the politics that are involved are very difficult to deal with. It has only really been successful in a few places such as Switzerland.

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As far as the vaccines go, it has been a slow process. There are challenges scientifically but I think the greater challenge is economic and political. Vaccines, like all types of prevention, tend to get secondary support and, therefore, the value given to vaccines is low. Going back a few years when we were using the vaccine that was made at Genentech (South San Francisco, CA, USA) for chimpanzees, it was not looking very promising, probably because of the challenges of manufacturing it. We thought we were making a protein but we were actually probably damaging it during the manufacturing process. When Tim Gregory at Genentech finally saw that this was the problem, it really opened up a new arena for the vaccine. There are still challenges without doubt, and still discussions about how much antibody and cytotoxic lymphocytes will provide protection, but I think the current generation of vaccines is very promising. The major challenge I see is not in making the vaccine but in addressing the subtype variation of the virus, which we still do not understand particularly well.

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What do you think are the most promising approaches at the moment towards the treatment of HIV?

Obviously, the protease inhibitors markedly reduce viral replication and, therefore, affect the progression of the disease. In the short-term, prolonging life with the antiviral agents is terrific if you can afford the treatment, which some parts of the world can. But the highest-infected areas cannot. These treatments are, therefore, not going to make a significant dent on the HIV epidemic worldwide. For these types of viral diseases, you really have to interrupt the infection with vaccines and so for the long-term, vaccines are going to be the key.

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How does the HIV vaccine (AIDSVAX) from VaxGen work?

AIDSVAX follows along the model of modern vaccines. With recombinant technology, one can make any part of the virus required. Early studies with HIV-1 showed that the neutralizing antibodies were directed to the envelope glycoprotein (gp). The challenge was to snip out the part of the gene that encodes for the envelope glycoprotein and produce it in some system that could be used as a vaccine. The early attempts used non-mammalian systems (e.g. baculovirus insect cell lines and *Escherichia coli*) but they just did not produce an accurate replica of gp120 (it has a molecular weight of 120,000 but half of it is sugar). That requires a mammalian system and, fortunately with Genentech's skill, we were able to produce this, ultimately leading to studies showing protection from HIV in chimpanzees.

How are the two current Phase III studies going?

The Phase III trials are going fine. We have 5400 people in trials in North America and Europe with the B/B vaccine and 2500 individuals in Thailand with the B/E vaccine. We can say that the vaccine is doing just what we want. That is, it is safe and everyone who receives it develops a strong immune response. However, we do not yet know how effective it is, as the trial is double-blind and placebo-controlled. We will look at the end of the year when we can break the codes for the first time. We have also retained 95% of the people who volunteered for the trials and I think that is quite remarkable.

Are there any moves to develop vaccines against the other subtypes of HIV?

Yes, we have started to work with subtypes C and D because we think we are going to need vaccines against different subtypes. There are also other groups sponsored by the International AIDS Vaccine Initiative (New York, NY, USA) with other products. There is a group in Oxford (UK) working on different systems that specifically address the African viruses. We too hope to look at these subtypes but it is more of a challenge because of the problems of financing this work. Unfortunately, much like for the drugs, the private sector is driven by profit and we are essentially totally sponsored by investors. Until the world really wants to drive this, and the individuals that have concerns over health and security in Africa really come forward, we are going to have a hard time making vaccines for this area.

How successful do you think vaccines will be for preventing HIV considering the ability of the virus to mutate so rapidly?

I think that is a key issue. It is different for vaccines though – we tend to stress viral mutation in drug discovery. Antiviral drugs are a poison to the virus and there is a clear survival benefit to mutating around that poison. That is not really true for vaccines as they act more as a barrier. If the barrier has holes in it, the virus gets through but the virus does not look at the barrier and then neutralize the antibody or mutate to get around it. For example, the polio virus mutates at about the same rate as HIV. There are three subtypes, but we have been able to almost eradicate polio.

What we have to address is the differences in HIV that have taken place during its evolution initially in chimpanzees and then in humans. I do think that the major risk to a vaccine is biological variation, but I would not call it a mutation. The job of viruses is to survive, so they will keep coming back to the most effective arrangement of proteins that will aid transmission. Although they will continue to evolve, they will tend to stay within a certain range. How many strains there are remains to be seen. We are just developing assays at the moment to try to quantitate that. The real quantitation will be the Phase III trials, where we can determine what viruses break through and what viruses are protected, but we've also been pleased with recent results from our lab. Phil Berman, our Senior VP of Research and Development, recently reported on some new assays in which he found laboratory evidence that a vaccine that induces HIV-C antibodies might be effective at preventing infection not only by HIV-C, but the HIV-B subtype as well. So the development of a worldwide vaccine for HIV might not be quite as tough as we expected.

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What other vaccines are being developed against HIV and which do you think are the most promising?

I think the approach that one really hopes will work is ours. The issues of safety have already been answered at this stage and a purified protein that induces a high level of antibody that could be made against all strains would be ideal. There is a second hypothesis that is very reasonable to test and this is that a cytotoxic (cellular) response is needed in addition to an antibody response. Hence, the next generation, if they are needed, will be vaccines that deliver HIV genes into cells and onto the surface of cells and, through the major histocompatiblity complex (MHC) system, induce cytotoxic lymphocytes. This is being developed by Aventis Pasteur (Lyon, France) in collaboration with VaxGen and, therefore, induces a combination of cytotoxic lymphocytes and the antibody. If all goes well in the current Phase II trials, Phase III studies should start in late 2002–early 2003, by which time we will have the final results of our trials.

Next, there are other delivery systems, either using naked DNA or other viral vectors that are being studied in a variety of small-scale studies. Some of these raise potential safety issues especially when recipients are immunosuppressed. When you start giving HIV genes to people, there are concerns that are very different to those of administering proteins, but given the dangers of HIV, I think the risk is certainly worth taking.

Other than viral mutation, what are the other particularly difficult hurdles that stand in the way of a vaccine for HIV?
The big issue with vaccines is a very simple one – it is social value. I think the science and the technology can be mastered; the question is, do we as humans desire it and are we going to put the resources forward to do it? I think we will, but the question is also 'how long are we going to have to wait?' These vaccines do not come fast or cheap. For our vaccine, so far it has been a 15-year effort and each vaccine costs ~$200 million to develop, so you have got to make a major commitment to do it. Vaccines are not priority products in the pharmaceutical industry for the investment and development decision makers.

I am optimistic that there will be purchasing power for the HIV vaccine and ultimately a delivery system.

If your vaccine does produce successful results in trials and is approved, how will your company go about trying to ensure that the vaccine gets to those desperately in need, especially in poorer countries?
We have a whole section of our company devoted to this, that is looking at markets, i.e. what the demand will be and who will pay for it. Our mission is to develop vaccines for the entire world. It is clearly not our responsibility to get them there, but I think it is our responsibility to maximize the chance of them getting there.

I think we are seeing changes now. When we started this company, there was not the understanding nor the priority given to vaccines, especially for the third world. I think you have to admire the Bill and Melinda Gates Foundation and then the Ted Turner Foundation and now the EU. They really started something by saying that vaccines in general are a high priority for the entire world, especially for the lesser-developed countries, and that HIV is one of the highest priorities within the vaccine arena. I think there will be a market for vaccines for the third world driven by the purchasers for such third parties, for example, the World Bank, foundations and bilateral organizations. I think people will see what has been done for smallpox, polio, and childhood immunizations generally. The challenge is making the vaccine and getting the R&D up-front to do it so that one is ready to produce it as fast as possible. What the world vaccine community is saying is that we do not want a repeat of the hepatitis B vaccine story: that is, we do not want to have a highly priced vaccine for industrialized countries when there is great need in lesser-developed countries. I hear the sounds, I think they are good sounds, and I think we are going forward. I am optimistic that there will be purchasing power for the HIV vaccine and, ultimately, a delivery system.

What do you think are the reasons behind the increasing prevalence of HIV now being reported in developed countries such as the UK and the US and how should we best try to prevent this?
There were lots of AIDS cases in the early 1980s. Many people saw their friends dying and it was clear that they needed to change their own behaviour. We have seen a remarkable change in homosexual and heterosexual youth behaviour. However, there are limits to behavioural changes and we might have reached the threshold.

In San Francisco, we have very good data to show that in 1982–1983, 10% of gay men were infected every year and this has now dropped to 2.0–2.5%, so behaviour change programmes have worked as a very effective 'vaccine'. To keep that figure down will require continued reinforcement, continued vigilance and the delivery of programmes that support and stimulate this behavioural change.

The other need is to take a very radical change in our approach to intravenous drug use. We need to take better care of addiction problems, otherwise things such as crime and AIDS will continue to spread. However, I think the general political feeling is against this: many see every addict as a junky who should be thrown in jail without care or treatment. This is a big mistake for both crime and for HIV. Again, it is a measure of the lack of social maturity – I have yet to see proper provision of care, needle exchange, really intensive methadone treatment and the prescription of drugs to get them off these addictive drugs. I think this is going to take a while, but we do see some very exciting things in some places such as Switzerland, which is really a leader in this area.

Do you envisage a future society that is free from HIV and, if so, what do you think will be mainly responsible for this?
I do have that vision and I think a vaccine will be the force that is responsible for it in large part, of course, with behavioural change on top of that. However, I think it will take a long time to completely eradicate HIV. Even if we had a 100%-effective vaccine delivered to 100% of at-risk people, the disease will continue to surface in the infected people over the next 10–20 years. So it is not going to be eradicated until after my lifetime.

Are you and your company working/going to start working on vaccines for other severe infectious diseases, such as Ebola?
We would love to, but the AIDS vaccine is such a huge endeavour that we have decided to focus exclusively on it, which could itself be many viruses. For a company of 80 people, trying to make an AIDS vaccine for the world is enough for us to chew on for a while. Certainly, the technology is readily applicable to many other disease entities.

What would you like to have achieved by the end of your career?
All I want to do in my career is feel like I have done the job in front of me, be it smallpox eradication or an HIV vaccine, and to have done the best I can – that is all I can ask. If we have an HIV vaccine, or have even moved a step towards an HIV vaccine, I figure I will have done my job.

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