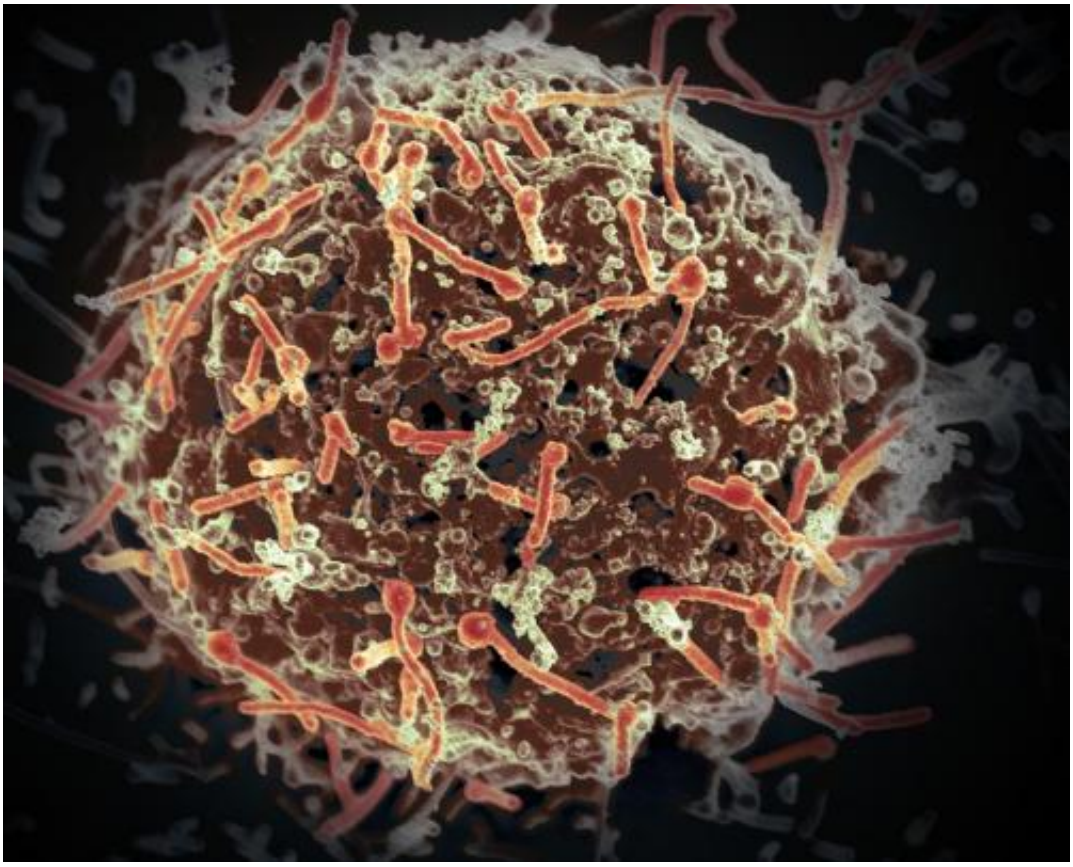
# Researchers explore effectiveness of statins against Ebola

June 29 2015, by David Orenstein



The Ebola virus, isolated in November 2014 from patient blood samples obtained in Mali. The virus was isolated on Vero cells in a BSL-4 suite at Rocky Mountain Laboratories. Credit: NIAID

There is scientific reason to believe that statins, the ubiquitous and cheap drugs prescribed to hold down cholesterol levels, could help patients

endure Ebola virus disease. Last summer, Dr. Steven Opal, professor of medicine in the Alpert Medical School and a physician at the Memorial Hospital of Rhode Island, and Dr. David Fedson, a retired physician in France, argued in a New York Times op-ed that the idea deserved a shot as the often-fatal virus rampaged around Guinea, Liberia, and Sierra Leone.

The argument, however, did not win the support of major health organizations. Still, Opal and Fedson were eager to help patients and to test the idea. Starting in September, without any funding or experimental infrastructure but with the permission of the Sierra Leone government, they and two colleagues were able provide about 100 patients in two hospitals with a 10-day combination of the generic drugs atorvastatin and irbesartan, a medication known as an angiotension receptor blocker (ARB). The Norwegian doctor Ole Martin Rordam was in Sierra Leone to ensure treatment delivery.

In a new paper labeled as an "Opinion/Hypothesis" in the journal mBio, the small team also including Jeffrey Jacobson of the University of Illinois, reports on the outcome. Of the 100 patients, all but two reportedly survived, but Opal readily points out that these "stories" are poorly documented. Rather than hailing the results, he calls the experience "disappointing." He hopes that research into the idea, which he said remains promising and compatible with more mainstream antiviral approaches, will continue. He spoke to David Orenstein about the new paper.

## Why was it important to try statins and ARBs?

The attraction of using statins [and ARBs] in Ebola is that statins have a very long safety record and are given out to tens of millions of people daily throughout the world and have been so for the last 20 years. All these drugs have potential problems but it's a very well-tolerated drug.

It's available orally and can be taken once a day. Last but not least, it's already gone through its product life span as a trade name and at least some of them are available generically, so they are very inexpensive.

From a mechanistic perspective, they preserve the function of the endothelial cells that line the blood vessels. They help prevent them from dying. The reason why this is at least theoretically important for Ebola virus is that it's very clear now in animal studies that the major determinant of living or dying when you expose animals to Ebola is how well you can tolerate the initial onslaught of the virus. The virus invades cells including endothelial cells. Mice than can protect themselves by holding the virus at bay in endothelial cells are those that are resistant to Ebola. Mice strains that can't do that, where the virus destroys the endothelial cells and then invades the organs when the endothelial barrier is breached, wind up dying.

Mice whose endothelial cells survive for a longer time than those of susceptible mice can stay alive long enough until the immune response kicks in. The virus is cleared by the immune response very readily if you can survive the initial exposure. This is true in mice but is it true in humans? Nobody knows. It hasn't been studied.

## How did your attempt to try this come together?

We were never able to convince enough people on the ground in West Africa or funding agencies in various parts of the globe to put money into at least studying this treatment strategy. That's why in the end, if you look at the top of the page of our paper it says "Opinion." It seemed like a good idea back in September but we really haven't been able to prove or disprove this because we could never get enough people on the ground interested enough in the idea to do a formal study, which is a great lament of ours.

The whole idea that we proposed was that this would be a simple, pragmatic clinical trial that could be done in West Africa by West African doctors with their own patients. We were not going to suggest anything terribly complicated, we weren't going to ask for a whole lot of blood work. The idea was a simple trial where you give one pill a day of the two drugs (for 10 days). You'd go with the combination of the statin and the ABR and for a control you could do just statins or just the ABR or the "placebo," which would be standard care. Then we would look to see what the mortality rate was at two weeks or a month.

But we never got a satisfactory study going. Ole Martin Rordam was actually there on the ground and he was able to supervise some of this to show that it was administered. People were treated. But we had all kinds of problems getting results.

## How would you describe your findings?

We had reports about 100 patients who received this combination, and we got glowing preliminary reports but we never got final data. In all candor I do not know how effective this is or not. We're still hoping we will get a final report. This is hugely disappointing. The data may still be sitting there but we don't have that information. I don't wish to imply that we're confident with the results. It shows the difficulties, if you are not physically there, and are relying on other people who have other priorities, and we didn't have any money. It was incredibly frustrating.

We're left with the idea. It seemed like a good idea in September and we still think is a good idea—and there is some animal data to support it. But that's basically it.

## Why has the idea been controversial?

People thought it was logical, but the criticism we got was that it is an indirect mechanism. We should be focusing on antivirals, not wasting our time focusing on something like this, which is an indirect therapy.

We also had people saying if it doesn't work people would really get depressed because you wasted this time doing a clinical trial and it didn't work. We said yeah, that's true but how depressing is it now in Africa and there's no treatment at all? We bristled a little bit at that response. But it's natural to think that if you have a virus, give an antiviral. We totally agree with that. Our thought was let's also give a host-stabilizing response at the same time.

Also, one of the side effects of statins is hepatitis, but the incidence with statins is less than 1 in 100.

On the priority list of what's important, this got relegated to lesser importance. But this is a low-cost, low-risk, easily administered agent. Why not try it?

## What could the next steps be?

Number one is we'd like to have a simple, clinical trial: a head-to-head comparator study with a placebo group. You'd have to do informed consent.

Secondly we should go back and look at the genetics of patients who lived and patients who died to see if a similar situation to what we see in mice is true in humans: that endothelial defense proteins were protective. If what's been found in mice is true in humans, that would be a strong argument to say let's worry about the host tolerability to the virus.

The third thing is people want to see animal studies, so let's do animal studies. These [drugs] have never been studied formally in a large animal

model of Ebola. Those should be done. If people are convinced by those studies, then maybe they'd be more convinced to do a clinical trial.

**More information:** "Treating the Host Response to Ebola Virus Disease with Generic Statins and Angiotensin Receptor Blockers." DOI: 10.1128/mBio.00716-15

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