People who recovered from Ebola place handprints on a "survivor wall."

INFECTIOUS DISEASES

Surviving Ebola survival

After recovering from Ebola, some patients are struggling with other health problems

By **Kai Kupferschmidt**

The Ebola outbreak in West Africa is far from over. That is true for those still battling the deadly disease in Sierra Leone and in Guinea, where 24 new cases were confirmed last week, up from 12 cases 4 weeks ago. And it is true for the thousands who survived the infection but are reeling from the shock of their experiences and, in many instances, still suffering symptoms long after being declared free of the virus. Now, large studies have begun to catalog these sequelae and to help make sense of this "post-Ebola syndrome."

Foday Gallah, a 37-year-old Liberian ambulance worker, fell ill in August after picking up an Ebola-stricken child. He survived the disease but today suffers from memory problems and a chronic headache. His left knee hurts, his eyes burn, and he sometimes gets double vision.

Gallah's story is not unusual, says Mosoka Fallah, the principal investigator of the PREVAIL III study launched last week by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and the Liberian ministry of health. (PREVAIL I is an Ebola vaccine study; PREVAIL II is testing potential Ebola drugs.) Fallah hopes to enroll 1500 Ebola survivors and 6000 close contacts in the study.

> ***"Some of them have lost their jobs, they have been driven from their homes, relatives have abandoned them."***
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> **Mosoka Fallah**, principal investigator of PREVAIL III

The group will examine not only the long-term health effects of contracting Ebola, but also whether survivors are protected from future infections and whether some may still be able to pass the virus on to others.

Several Ebola outbreaks have occurred in recent decades, and hundreds of infected people beat the virus. But more people have survived the current outbreak than all previous others combined. At least 16,000 people survived an infection in West Africa, the World Health Organization (WHO) estimates.

Earlier research has shown that Ebola survivors can have health problems even years after defeating the virus. One study, published earlier this year in *The Lancet Infectious Diseases*, examined survivors of a 2007 Ebola outbreak in Uganda that was caused by a less deadly species of the virus called Bundibugyo. In 2010, scientists went back to the area and compared 49 survivors with more than 200 uninfected contacts. They found that survivors were more likely to suffer from hearing loss, eye pain, blurred vision, difficulty sleeping, and other symptoms.

The same seems to be happening in West Africa. Fallah says that a survey among Ebola survivors found that one-third suffered from fatigue and one-fifth from hearing impairments, for instance. Doctors who treated infected health care workers flown

to Europe or the United States report the same. Anthony Fauci, who heads NIAID, has helped treat two Ebola patients in the United States. Both showed some symptoms even after they had fully recovered from the acute infection, he says. "When I call up colleagues and ask if they are running into the same problems, they say, 'Yes.'"

At least three explanations are possible, says Danielle Clark, an epidemiologist at the Naval Medical Research Center in Fort Detrick, Maryland, who headed the Bundibugyo study. The lingering symptoms may stem from cells and organs damaged by the virus before it was brought under control. They could be a side effect of the immune system battling the virus, or a sign the immune system has subsequently turned on its own body. In that scenario, the immune system does its job, recognizing certain structures on the virus and fighting off the invader, but then trains its weapons on noncombatants. "If there are structurally similar host molecules, the immune system gets confused and starts fighting that," Clark says.

The eye seems to be affected frequently, possibly because the immune system's reach does not normally extend to the organ. U.S. doctor and survivor Ian Crozier was found to have Ebola virus in his eye more than 2 months after the virus had disappeared from his blood.

Other viruses haunt people after they have recovered. Lassa virus infections can cause hearing loss, for instance, and dengue fever, chikungunya, and Rift Valley fever can all lead to chronic problems after the acute infection. "By studying Ebola, we may get insight into these other infections as well," Clark says, including who is particularly at risk for lingering symptoms.

The PREVAIL III study will follow participants for 5 years with a physical exam every 6 months. Investigators will collect blood as well as sweat, tears, and semen or cervical secretions from some survivors and from close contacts. INSERM, the French biomedical research agency, has already started a similar study in Guinea, called Postebogui, which aims to follow 450 patients for a year, checking them every 3 months. "We will also check contacts to see if there may have been silent infections and to understand when antibodies arise and for how long," says study coleader Eric Delaporte.

Indeed, one of the most pressing questions is whether the virus still lurks in some survivors and, if it does, whether that poses a risk to others. Ebola virus can persist in the seminal fluid of men who have cleared the virus from their blood. Before the outbreak in West Africa, the longest reported time was 82 days after symptom onset. But in one recent case, genetic material from Ebola virus was isolated from the semen of a survivor 199 days after symptom onset, prompting WHO to change its advice on sexual transmission. It now recommends that survivors use condoms until their semen has twice tested negative or for at least 6 months after symptom onset. If sexual transmission occurs, it is infrequent, says Dan Bausch, an infectious disease specialist at WHO in Geneva, Switzerland. Still, even a single case could lead to a new outbreak, he says. "I don't think we need to panic over that, but we need to recognize it."

Many survivors not only have to deal with the sequelae of the disease, but also with the psychological fallout of their traumatic experiences, Bausch says. "There is post-traumatic stress disorder, anxiety, depression. Those things are much harder for us to measure." Then there is stigmatization. "Some of them have lost their jobs, they have been driven from their homes, relatives have abandoned them," Fallah says. He hopes that studies such as PREVAIL III will increase knowledge about survivors and so help overcome unfounded fears. "Imagine you survive this terrible disease, then you come home and may have five or six family members dead and you are fighting with the consequences of Ebola and then the stigmatization as well," Bausch says.

The uncertainty is hard to bear, Gallah says. "We don't know what our life is going to be like for the next 5 or 6 or 10 years." He hopes he will be able to go back to work soon. "At least when I'm busy doing something, I feel OK. When I sit by myself, my mind just goes back to the terrible things I went through." ■

Ebola's lingering legacy

Some survivors are reporting symptoms long after the acute infection. Several studies are underway to assess how common this is and whether these people still harbor the virus.

- Eye inflammation, pressure, pain, blurred vision
- Hearing loss
- Headache, attention difficulties, memory problems
- Joint pain and stiffness, muscle weakness
- Erectile dysfunction
- Fatigue, difficulty sleeping

GENETICS

An enhanced view of gene control

Chromosomal loops and domains help enhancers turn on genes

By **Elizabeth Pennisi**, *in Cold Spring Harbor, New York*

Genes may be the stars in a cell's nucleus, but they would never shine without a strong supporting cast. Take the stretches of regulatory DNA called enhancers, which help turn genes on at the right times and places. Although researchers have scrutinized genes as closely as the paparazzi track Hollywood celebrities, enhancers have largely stayed in the background, their workings a mystery. A recent genetics meeting here signaled a change: In talk after talk, researchers described where and how these quiet fixers exert their influence.

One group showed how enhancers maintain the right level of sensitivity to other signals, so that they switch genes on only at the right times and places. Others explored how cells package genes and their enhancers so that they can work together properly, and how DNA forms loops that bring enhancers right to the target gene. The advances even point to strategies for exploiting these regulatory elements to treat disease, by switching off disease genes and turning up the activity of healthy ones.

"We've been talking about [enhancers] for a long time," says Susan Gasser, director of the Friedrich Miescher Institute for Biomedical Research in Basel, Switzerland. "But now we are really beginning to understand them."

One revelation is that it doesn't pay for an enhancer to be too good at its job. Enhancers switch on genes when transcription factors and other proteins bind to specific segments in the enhancer DNA. By tinkering with one enhancer's sequence, Michael Levine from the University of California, Berkeley, and his colleagues found that, in principle, enhancers could be more sensitive to the signals that activate them. They focused on the enhancer for *Otx*, a gene that plays a role in nervous system development.

The *Otx* enhancer attracts two proteins, each of which uses a different four-base