

Antierens agrees that such trials may not detect small effects of a drug, but says the goal is to determine whether an intervention is worthless or clearly works. “We are not interested in whether some liver enzymes are a little bit higher,” she says. “We are looking for a significant change in survival.” For the brincidofovir trial, for example, the researchers have agreed to define survival below 50% as “failure” and above 80% “success.” If the data are ambiguous, an RCT could be considered, she adds.

The horrific nature of the epidemic has led to other arrangements rarely seen in clinical studies. The researchers conducting the favipiravir study initially wanted to target adults within the first 2 days of their illness. MSF asked for the design to be changed so no one would be refused the drug—including people who have been sick longer and children. “People from the field said, ‘What are we going to do when a family arrives? We treat the parents and not the child?’” says Xavier de Lamballerie of Aix-Marseille University in France, who is leading the study. The brincidofovir study will enroll up to 140 people, and at MSF’s request it will continue offering the drug while data from the trial are being analyzed to make sure that no patient misses out on a potentially effective treatment.

**PROPOSERS OF RCTS** are aggressively pushing ahead with trial plans, too. Luciana Borio of the U.S. Food and Drug Administration in Silver Spring, Maryland, who attended the WHO meeting; NIAID’s Lane; and others have developed a protocol that would test multiple interventions—including ZMapp and TKM-Ebola—in a single large RCT, using sophisticated Bayesian statistics to get an answer as fast as possible. Lane is now negotiating with the Liberian government about setting up several of these studies. Liberia is not opposed to RCTs, says Stephen Kennedy, an investigator at the University of Liberia-Pacific Institute for Research and Evaluation Africa Center in Monrovia, who advises the country’s ministry of health about its oversight of Ebola clinical research. “We have to use the gold standard,” Kennedy says. “We understand the issues and know what is appropriate for Liberia.”

Borio well understands the concerns about randomization, but says that not getting a clear answer would be worse. The nonrandomized trials announced last week have a “significant risk of not generating interpretable data,” Borio says. “It is so important to get this right. It’s important for patients who will become affected during this epidemic, and also for generations to come, since future outbreaks will surely occur.” ■



A room reserved for Ebola patients at the University Medical Center Groningen in the Netherlands.

## Saving lives without new drugs *By Jon Cohen*

**W**hen people from the United States and Europe working in West Africa have developed Ebola, time and again the first thing they wanted to take was not an experimental drug. It was an airplane that would cart them home.

Care for Ebola patients in Liberia, Sierra Leone, and Guinea varies greatly at different clinics, but it never matches what wealthy countries provide. This partly explains why the Ebola epidemic has had a case fatality rate (CFR) of 70%, according to World Health Organization calculations. Too few Ebola patients have been treated outside Africa to make scientifically valid comparisons—and they may have been healthier before falling ill—but only five out of 20 to date have died, a CFR of 25%.

Now, there’s a push to improve care in West Africa. Just a handful of basic interventions to fight the killer effects of Ebola, including dehydration and secondary infections, could dramatically lower the CFR there, says Michael Callahan, an infectious disease specialist at Massachusetts General Hospital in Boston. A case in point appeared online on 5 November in *The New England Journal of Medicine (NEJM)*: Relatively intensive care in Conakry led to a CFR of 43%.

With so much room for improvement in supportive care, the current international focus on drugs is “misguided,” says Callahan, who has recently worked in Monrovia and provided care in four previous Ebola outbreaks. “While we wait for months for forthcoming experimental therapies, many lives can be saved, certainly hundreds and possibly thousands, using inexpensive and simple therapies,” he says.

Callahan is helping an international team develop guidelines dubbed Maximum Use of Supportive Therapy (MUST), aimed at keeping more patients alive. It includes intravenous (IV) drips to replace massive fluid loss from diarrhea and vomiting, a risk factor for shock; balancing of electrolytes such as calcium or potassium, which prevents kidney and heart failure; nasogastric tubes for feeding; and testing and treatment of secondary infections such as malaria. Introducing MUST will also make it easier to study new treatments, Callahan says: Randomized controlled trials—ethically fraught because only some patients get the novel treatment (see main story, p. 908)—will be much more acceptable if everyone receives high-level care. In addition, MUST might reveal side effects of new drugs that would otherwise be masked by Ebola symptoms, and it could reduce the rate of complications that might be incorrectly blamed on a drug.

It’s an important proposal, but Ebola clinics will need more resources to offer MUST, says John Fankhauser, an American clinician who has worked at the ELWA hospital in Monrovia since before the outbreak surfaced. Overwhelmed by patients and logistical challenges, many clinics have provided minimal supportive care. “We are able to give IV hydration, but the testing is limited to malaria and Ebola,” Fankhauser says. Tests for electrolytes and other types of monitoring MUST calls for are simply beyond reach, he says. Callahan says the additional measures cost less than \$600 extra per patient at a Monrovia clinic in August.

Armand Sprecher of Doctors Without Borders (MSF) in Brussels, who co-authored the *NEJM* report, concedes that the standard of care dropped when Ebola exploded this summer. But Sprecher, who is “very supportive of supportive care,” says MSF clinics have corrected several problems and now doubts that MUST can save many more lives. “I’m less optimistic than some people about how much of an effect we’re going to have,” he says. “I hope I’m wrong.” ■

# Science

## Saving lives without new drugs

Jon Cohen

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