romosozumab than with alendronate, whereas in FRAME, the incidence of such events was balanced in the romosozumab and placebo groups. One possible mechanism underlying such events could be a role for sclerostin in vascular smooth muscle, a concept that comes from studies showing that *SOST* is expressed in other tissues, including aortic vascular smooth muscle. Thus, inhibition of sclerostin by romosozumab could potentially alter vascular remodeling that is normally induced by the Wnt signaling pathway.[6] In addition, sclerostin is up-regulated at sites of vascular calcification, although its pathogenic role there is not defined. Another possibility, albeit remote, is that the comparison drug, alendronate, is cardioprotective, and therefore the rate of cardiovascular events in the romosozumab group appears relatively higher than expected. However, several meta-analyses of randomized, controlled trials of alendronate have not shown a decrease in cardiovascular events. Finally, the number of adverse events was small, leading to the possibility of a type I error, since the trial was not powered to test noninferiority versus alendronate for safety.

What can we learn from this trial, which is unique as a fracture efficacy trial comparing a new bone-active drug with a long-established therapy — a true comparative-effectiveness trial? Romosozumab is very effective in preventing fractures among high-risk postmenopausal women, particularly when taken for 1 year followed by alendronate. Romosozumab has strong antiresorptive properties, although it is unclear whether the sequence of romosozumab followed by alendronate increases the risk of atypical femoral fractures. Finally, the cardiovascular signal for romosozumab is particularly troubling. Although it may be surprising that a bone-specific drug has off-target cardiovascular effects, this finding is very consistent with our recent understanding of the skeleton as an endocrine tissue that modulates whole-body homeostasis by secreting peptides such as sclerostin, fibroblast growth factor 23 (FGF-23), and osteocalcin. Moreover, other bone-targeted therapies, including estrogen and odanacatib, have adverse cardiovascular effects.

In sum, ARCH revealed that romosozumab has great potential as a short-term anabolic treatment for osteoporosis. However, until the cardiovascular and endocrine effects of this antibody are clarified, romosozumab will remain more a part of our expectations than our armamentarium.

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Handle Survivors with Care

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In 1967, a woman became ill after exposure to a newly discovered pathogen that we now call Marburg virus, a member of the family Filoviridae (filoviruses), to which Ebola virus also belongs.[1] Testing of the semen of her husband, who had recovered from the disease 6 weeks previously, determined that her exposure was through sexual intercourse. This was the first confirmed case of sexual transmission of filovirus disease from a convalescent man. It was also the last . . . until the West African outbreak.

In March 2015, Ebola virus disease (EVD) developed in a Liberian woman after the country had been free from EVD for 30 days.[2] This woman had no identifiable risk factors for EVD other than sexual contact with a male survivor of the disease. This survivor's semen tested positive for Ebola virus RNA, which suggested sexual trans-

mission. Mate and colleagues presented in the *Journal* the results of a genomic analysis that provided support for the development of EVD in this woman through sexual transmission from a male survivor 6 months after his recovery.[3] Before this case, the furthest into convalescence that Ebola virus had been isolated from semen was 82 days.[4]

This case raised the question of how late into convalescence male survivors are capable of infecting their sexual contacts. Deen and colleagues address this concern in a study whose final results now appear in the *Journal*.[5] They examined semen specimens from male survivors of EVD and were able to detect Ebola virus RNA in a surprisingly large proportion, with RNA present in semen as late as 470 days (15.7 months) into convalescence. As Deen et al. acknowledge, finding Ebola virus RNA in semen does not imply that it is infectious. Further testing of semen specimens with viral culture is necessary to determine whether active virus is present. Regardless of the results of such study, sexual transmission clearly occurs, but it appears to be a rare event.

There are more than 17,000 survivors of the West African EVD outbreak, approximately half of whom are male.[6] Most of these male survivors are now more than 2 years into their convalescence. If sexual transmission from survivors were an important means of disease propagation, we would have seen a number of cases by now. As Deen and colleagues noted in their preliminary report in 2015, fewer than 20 suspected sexually transmitted infections had been reported, and there have been only two well-documented cases of probable sexual transmission since then.[7,8]

The challenge with sexual transmission is not that it is a source of many new EVD cases but that it is a source of late EVD cases, such as those that sparked the resurgence of EVD in Sierra Leone in January 2016 and in Guinea in March 2016.[7,8] The World Health Organization (WHO) usually declares an outbreak in a given location to be finished 42 days after the resolution of the "last" case.[9] However, the possibility of cases arising from sexual transmission as late as 500 days after the survivor's onset of symptoms[8] creates an atmosphere of uncertainty as to when an outbreak is truly over.

We cannot ask a country emerging from an EVD outbreak to be alert for late presentation of new cases without calling attention to the risk posed by male survivors, even if this risk can be managed somewhat by providing them with condoms and counseling. Communities within and beyond western Africa have not dealt kindly with perceived risks when it comes to Ebola. Survivors have been isolated from their communities, have been evicted from their homes, and have lost their jobs.[10] Male survivors have been involuntarily quarantined[11] and even, reportedly, have been jailed[12] by governmental authorities who are afraid these survivors may transmit EVD.

Their treatment raises a practical concern. If we want to be able to detect the next case of EVD that might emerge from late sexual transmission, we must consider that the people who may one day become the next patient will see how survivors are treated. If they find that being identified as a patient with EVD has but two outcomes — death in a frightening treatment unit or survival to return as a social outcast — they have a considerable disincentive to be identified. This prospect may drive persons with new cases of EVD into hiding and defeat the objective of the surveillance system. When Médecins sans Frontières (MSF) was compelled by the government of Guinea to share the results of semen testing in survivors of EVD who came to our clinic, we disclosed this fact to our patients. The rate of presentations of survivors for testing subsequently fell by 50% (MSF internal data). Failing to exert extreme caution in the way we communicate the risk that survivors of EVD pose to the public might have devastating effects both on the well-being of the survivors and on the effectiveness of the surveillance we need to end outbreaks. Treating survivors with discretion and coupling survivor surveillance with communication programs that reduce stigma and facilitate the social reintegration of survivors will be more effective at motivating them to participate in surveillance programs.

Some survivors consent to semen testing in order to know the risk they pose to their loved ones, and some participate in research because they are financially compensated, but for many these are insufficient inducement. Survivors of EVD have needs, care for both the medical and psychological consequences of their illness, as well as a desire to be reintegrated into their communities. Coupling surveillance with services that address their needs may be the most effective way to ensure the well-being of survivors and their communities.

To the extent that the unfortunate situation of male survivors of EVD stems from their being

seen as a continued threat to their communities, perhaps some hope is offered by the prospect of effective vaccines. The results of the Partnership for Research on Ebola Virus in Liberia (PREVAIL) I trial that are now presented in the *Journal* by Kennedy and colleagues[13] show the safety and immunogenicity of the chimpanzee adenovirus 3 vaccine (ChAd3-EBO-Z) and add to our understanding of the recombinant vesicular stomatitis virus vaccine (rVSVΔG-ZEBOV-GP), the efficacy of which was shown in a ring vaccination trial conducted in Guinea.[14] Vaccines against EVD have been traditionally thought of as countermeasures that might be used in the context of a bioterrorism event, as protection for front-line workers during EVD outbreaks, and as a means to control outbreaks by stopping transmission. To this list we might add the protection of the contacts of survivors of EVD. If such protection allows communities and public health agencies some measure of certainty that the end of an outbreak is truly the end, perhaps the survivors of EVD can be granted some peace and the opportunity to resume their lives beyond Ebola.

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From Médecins sans Frontières, Brussels.

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We Can Do Better — Improving Outcomes in the Midst of an Emergency

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On August 8, 2014, the World Health Organization declared the third Public Health Emergency of International Concern in response to the emerging Ebola crisis in Guinea, Liberia, and Sierra Leone. Approximately 20 months later, on March 29, 2016, this emergency was declared over, although many issues remain. After a slow initial response and limited health care resources, traditional epidemic-control measures — in particular, infection-control strategies — were finally able to limit the spread of the disease. But infection control has its limits as well, particularly when there is public mistrust at the epicenter of the epidemic; we should not forget that thousands of people died before the outbreak ended.

Early in the epidemic, much was learned through traditional epidemiology, including modes of transmission, incubation periods, and reproductive number. For example, the finding that Ebola virus was present in semen raised new challenges,