fractional volumes and routes of administration.

Use of fractional-dose vaccination in mass vaccination campaigns presents an opportunity to compare the safety of fractional-dose and full-dose yellow fever vaccines — particularly rates of rare, serious adverse events such as vaccine-associated neurotropic and viscerotropic disease. Preliminary data from routine safety monitoring during campaigns involving more than 5 million people in Brazil who received a fractional-dose vaccine are reassuring.

The 2016 outbreak in central and southern Africa was a reminder of the delicate supply-and-demand situation for yellow fever vaccines. Beyond the WHO vaccine stockpile, there is limited capacity to respond to demand peaks during larger outbreaks. Limited market incentives and a long manufacturing process requiring embryonated chicken eggs have created barriers to market entry and manufacturing surge capacity.

Recently, another vaccine shortage has prompted fractional-dose vaccination campaigns in large cities in Brazil, including areas not previously recognized as being at risk for yellow fever and thus with largely susceptible populations. Although the yellow fever vaccine stockpile is in place to address peaks in demand, it is less suited to cover the surge capacity needed for major urban vaccination campaigns. During the 2016 outbreak, the stockpile was depleted three times. Compounding this problem is the fact that global vaccine coverage is well below the 80% target that is expected to maintain a sufficiently high level of population immunity to eliminate outbreak risk: a recent study estimated that at least 393.7 million people living in high-risk settings (43%) remain unvaccinated.[5] International air travel may introduce yellow fever virus to new cities suitable for transmission. The best defense against future vaccine shortages is to achieve adequate routine vaccine coverage in all affected areas.

Other countries have considered a broader application of fractional-dose yellow fever vaccination outside emergency shortages. However, core questions remain. Although available evidence supports the use of fractional-dose vaccination when needed, a larger evidence base will be important to ensure optimal use and protection. Ongoing studies will provide much-needed information about specific products, target populations, and duration of protection to strengthen vaccination policies.

Continued dialogue and coordination among the policy, research, and funding communities are critical to ensure that when public health emergencies arise, there is sufficient evidence to make robust policy decisions quickly. Policy-driven research agendas are important tools for facilitating such coordination.

The views expressed in this article are those of the authors and do not necessarily represent the decisions or policies of the World Health Organization. Dr. Vannice was on staff at the WHO during the development of its policy on fractional-dose vaccination.

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Ibalizumab in Multidrug-Resistant HIV — Accepting Uncertainty

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The Food and Drug Administration (FDA) has long recognized that physicians and patients are generally willing to accept greater risks from drugs used to treat life-threatening illnesses than they would from drugs used for less serious illnesses. The agency has therefore exercised broad flexibility in cases of life-threatening disease, while ensuring that statutory standards for safety and effectiveness are met.

Patients with multidrug-resistant (MDR) human immunodefi-

ciency virus (HIV) infection are at risk for illness and death because of their limited remaining treatment options. Recognizing the need for more streamlined clinical trial designs for these patients, FDA representatives consulted with interested parties including clinicians and patient advocates to discuss ideas for acceptable approaches to drug development for extensively treated patients with MDR HIV infection.[1] After these discussions, the agency recommended a streamlined trial design for this population in a 2013 draft guidance document, which was finalized after public comment in 2015.[2] Emu et al. now report in the *Journal* the results of a clinical trial of ibalizumab, which was designed following these recommendations (pages 645–654). Although the streamlined trial design permits assessment of safety and efficacy in the target patient population, clinicians and patients should be aware that it has important limitations.

The streamlined trial design is recommended for extensively treated patients with MDR HIV, which is defined by resistance to multiple classes of drugs and the absence of available treatment regimens that can effectively suppress the patient's plasma HIV RNA. Four design elements distinguish such streamlined trials from HIV drug registration trials for new molecular entities in patients without MDR HIV infection. First, because the patients being targeted are rare in the United States, a sample size commensurate with the population with MDR HIV in the United States is acceptable. Second, the primary virologic efficacy assessment occurs 7 to 14 days after initiation of treatment with the investigational drug or placebo (added to a failing background regimen). In the case of ibalizumab, patients served as their own controls, with a 7-day period of continued use of the failing background regimen preceding the addition of ibalizumab. Third, immediately after the primary efficacy time point, participants begin receiving an individualized optimized background regimen, which is tailored on the basis of resistance testing. Finally, durability and safety analyses are conducted after 24 weeks of treatment, rather than 48 weeks. These design elements facilitate an efficient assessment of safety and efficacy in extensively treated patients with MDR HIV and minimize the risks associated with trial participation, such as emerging viral resistance and disease progression.

The ibalizumab trial provided information to assess the virologic activity and safety profile of ibalizumab in this population. Researchers enrolled 40 patients with extensive antiretroviral drug exposure at baseline: more than half of participants had been treated with more than 10 drugs in the past, and two thirds of them carried viral substitutions conferring resistance to integrase strand transfer inhibitors. Seven days after ibalizumab was added to the failing background regimen, 33 patients (82.5%) had at least a 0.5 $\log_{10}$ reduction in HIV RNA, as compared with 1 patient with such a reduction during the control period. Because a reduction of this magnitude is associated with a reduced risk of disease progression, it is considered a clinically meaningful end point for this patient population.[3] In addition, the safety and side-effect data generated in the trial were reassuring; the adverse events that occurred, regardless of severity or causality, were generally consistent with events expected in patients with advanced HIV/AIDS. These data provided evidence that ibalizumab could provide benefit to extensively treated patients with MDR HIV infection and that the benefits likely outweigh the risks. However, the complexity of the patient population, the small trial size, and limitations of the trial design resulted in uncertainty about ibalizumab's safety profile and the durability of treatment response.

Although the 24-week viral response results were consistent with those seen in previous trials of new antiretroviral drugs in similar patient populations, the absence of a control group limits researchers' ability to define ibalizumab's role in longer-term virologic response. In addition, individually tailored optimized background regimens were necessary for this patient population, and the variability in these regimens posed another challenge. Even among patients following the same background regimen, the effectiveness of the background drugs may have varied owing to unique resistance profiles and variable adherence to the regimens. Although the use of a control group might have improved researchers' ability to assess ibalizumab's contribution to the durability of response, longer-term placebo-controlled comparisons in this population would not have been acceptable to clinicians or patients because of concern about the emergence of new drug-resistant substitutions. Given these issues and the high risk of disease progression and death in this patient population, we concluded that some degree of uncertainty regarding ibalizumab's contribution to durability of re-

sponse is acceptable, and probably inevitable.

For rare conditions, the FDA determines the necessary size of a drug's safety database on a case-by-case basis.[4] Including the 40 patients who participated in the trial, 292 patients received at least one dose of ibalizumab during drug development. Because extensively treated patients with MDR HIV are rare in the United States and face a high risk of illness and death without access to new antiretroviral drugs, we decided that ibalizumab's safety database, although small, was adequate to provide evidence of the drug's safety. The small database, however, limits our ability to detect less common safety signals and increases reliance on postmarketing pharmacovigilance. In addition, the complexity of the enrolled population and the absence of a control group affected our ability to assess causality. The study participants had advanced HIV disease, as evidenced by the median CD4 T-cell count of 73 cells per microliter. Mortality during the study was high (4 patients [10%]), and 9 patients (23%) had serious adverse events. Although it was relatively straightforward to attribute the most serious events to the underlying disease (3 of the patients who died had CD4 T-cell counts below 5 cells per microliter at baseline), determinations of the causes of mild-to-moderate events were less definitive. Because extensively treated patients need access to new treatment options, we decided that uncertainty regarding infrequent safety events and attribution of causality was acceptable.

The trial design for the study of new drugs for extensively treated patients with MDR HIV had substantial limitations, but it allowed for an informative assessment of ibalizumab's safety and efficacy in a population that needs new treatment options. Post-marketing pharmacovigilance will be important in better defining the efficacy and safety profile of ibalizumab.

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Lessons from an Angry Patient

Emmet Hirsch, M.D.

She bore a scowl and a combative attitude from the moment I walked into the room. In response to my hopeful "How can I help you?" she unleashed a tirade that seemed to pick up where some prior conversation had left off. Though she was new to my practice, she seemed to have already concluded that she would get no satisfaction from me.

And I experienced an uneasy feeling: she was probably right.

I took a history. The patient had had a terrible outcome to her pregnancy nearly a decade earlier. Her premature baby, delivered by emergency cesarean section, had died, and she herself had nearly died from sepsis. Since that time, she reported, she'd had an abnormal vaginal discharge. A different doctor had validated her suspicion that there was a persistent bacterial infection, the same one that had caused her septic pregnancy. That other doctor had treated her with antibiotics, but the discharge had remained. Her boyfriend complained about it. She believed it was responsible for her failure to conceive a second time. For years, she had gone to practitioner after practitioner. All were either unable or unwilling to help her.

On physical exam, I found her discharge to be normal in all respects. I examined it under a microscope. Again, completely normal. I sent a Gram stain and culture and some DNA screens to the laboratory; the results were all negative. I told her I could find no abnormality and that therefore I had no diagnosis to