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IN RESPONSE: Dr. Flandre raises important points regarding the ACTG Study A5202 results; however, the abstract's conclusion does not stand alone. The Results section of the abstract and the Results and Discussion sections of the manuscript state that the equivalence boundary was not met. We do believe that the similarity in response rates is relevant to clinicians considering these treatment options. Differences in baseline HIV-1 RNA values have been addressed in a secondary analysis adjusting for this as continuous and categorical variables (<50 000 copies/mL, 50 000 to <100 000 copies/mL, 100 000 to <500 000 copies/mL, or ≥500 000 copies/mL), with the treatment effect estimate showing similar results to the primary analysis. The HRs and 95% CIs when baseline HIV-1 RNA was analyzed as continuous and categorical variables were 1.11 (0.81 to 1.54) and 1.06 (0.77 to 1.47) for abacavir–lamivudine and 1.01 (0.70 to 1.46) and 1.04 (0.72 to 1.51) for tenofovir disoproxil fumarate–emtricitabine, respectively.

Prespecified equivalence boundaries were based on the relative treatment difference of the HR (specified as 0.71 to 1.40). The paper's Statistical Analysis section states that an HR of 1.40 with a 32% event rate would represent a 96-week difference in probability of VF of approximately 10%. The VF rate makes the current equivalence definition very strict. With the observed rate of approximately 15%, an HR of 1.40 would correspond to an approximately 5% absolute difference, and a 10% difference would correspond to HR boundaries of 0.56 to 1.77.

Dr. Kuchenbecker and colleagues are correct that the drugs compared in this study were open-label; however, blinding protease and nonnucleoside reverse transcriptase inhibitors is challenging and rarely done in recent HIV treatment trials—we acknowledged this in the manuscript as a limitation of the study. We stand by our statement that A5202 was different in design and results from A5142 (1). Unlike the A5142 study, the A5202 study randomly assigned patients to commonly used NRTIs in a blinded fashion and also used atazanavir–ritonavir, which is a preferred agent; this is no longer true for the lopinavir–ritonavir used in A5142 (2). Although the A5202 study was unable to declare equivalence, response rates by all other measures were similar between the 2 regimens. Compared with efavirenz in the A5142 study, the time to VF was significantly shorter with lopinavir–ritonavir (HR, 0.63 [CI 0.45 to 0.87]; $P = 0.0006$).

We agree with the commentators and acknowledged the relatively high loss to follow-up in the manuscript. We did several sensitivity analyses to address potential attrition bias (Appendix Table 2 in the article), including as-treated analyses in which time to VF failure was censored at modification of the third drug that showed results similar to those of the primary intention-to-treat analysis.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1780.

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A Transmission Model of the 2010 Cholera Epidemic in Haiti

TO THE EDITOR: The article by Tuite and colleagues (1) proposed a spatially explicit scheme reproducing the sequence and the timing of regional cholera epidemics through waterborne and person-to-person transmission of cholera. Two additional modeling studies of the ongoing Haiti cholera outbreak and its controls were independently and almost simultaneously published (2, 3). In particular, a similar transmission model, based on a finer spatial detail of the affected communities and on alternative descriptions of hydrologic and human mobility drivers of pathogen dispersal (4, 5), has been likewise applied to the unfolding Haiti epidemic (3). Despite differences in the assumptions, the results regarding the effect of control strategies, such as vaccination and sanitation, are similar. However, the article by Bertuzzo and colleagues (3) pointed out that larger intervention efforts involve nontrivial effects, with sanitation exhibiting a threshold-like behavior in effectiveness.

From a modeling standpoint, the main difference between the approaches is that Tuite and colleagues (1) neglect the role of asymptomatic patients who do not report to a hospital, which is suggested to be a critical factor in cholera epidemics, particularly those in Haiti (2, 3). Asymptomatic patients acquire immunity, thus reducing the number of persons in a region who are susceptible to the disease. Figure 4 in Tuite and colleagues' article shows that their model with realistic values of the basic reproductive number ($R_0 = 2.78$ or 2.90) fits the initial phases of the epidemic but would predict an excessive number of reported cases at later stages. To overcome this, they propose that the effective reproductive number decreases from 3 to

0.5 in the first 3 months of the epidemic, owing to disease-control interventions that would have effectively prevented thousands of cases. A 6-fold decrease of the reproductive number—if asymptomatic patients are not accounted for and the compartment of susceptibles is not depleted—implies a 6-fold decrease of transmission rates.

These figures seem unrealistic, especially compared with the sanitation intervention that Tuite and colleagues analyzed (1): Providing vaccines or clean water to 500 000 persons clearly represents a major effort largely exceeding the disease-control interventions adopted in the first 3 months of cholera insurgence in Haiti, yet it would lead to a much smaller decrease in the transmission rate. This apparent paradox is solved by adopting a model in which asymptomatic infections are accounted for (2, 3). This does not require reproductive numbers to decrease with time because of unspecified disease-control measures to prevent an excess of persons who were calculated to be infected, which is an artifact of neglecting asymptomatic patients (2, 3).

Despite differences in methods, a comparative study on the limits and validity of modeling large-scale epidemic management suggests that such tools should be seen as essential components of future control of cholera epidemics.

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IN RESPONSE: We welcome the opportunity to clarify our analysis for Dr. Rinaldo and colleagues. We modeled a pool of infective patients that included both hospitalized and nonhospitalized individuals, but calibrated the model to reproduce hospitalized cases that were accurately measured. Our analysis of vaccines and water was not intended to represent the massive and far more robust multiagency public health response to the Haitian cholera epidemic; rather, it was intended to explore the projected relative effects of low levels of vaccination and water distribution. We did not distinguish symptomatic and asymptomatic cases in our model.

Dr. Rinaldo and colleagues suggest that the marked decline in the rate of growth of Haiti's cholera epidemic resulted from asymptomatic infection of large numbers of individuals in the population, and that the epidemic effectively stopped by itself. They suggest that our empirical reduction in effective reproductive number (which they misstate as reduction in R_0) is problematic and fails to capture the degree to which population immunity resulted in transient control of the epidemic. Recent events in Haiti show this thesis to be implausible, and our modeling approach has unfortunately been somewhat validated by the recent large surge in cholera cases in Haiti since early May 2011. This surge has been particularly marked in the capital region and in the south of the country, as our model projected (1).

It is important to distinguish the basic reproductive number of a disease (R_0), which is the average number of secondary cases of infection created by a primary case introduced into a totally susceptible population in the absence of intervention (2), from the *effective* reproductive number, which is the reproductive number in the presence of immunity or intervention (often denoted R_e). Dr. Rinaldo and colleagues confuse these concepts. For R_e to decline from around 3 to around 0.5 solely on the basis of immunity, approximately 85% of the Haitian population would have had to be infected in a 3-month period (2). This would require implausibly short "serial intervals" between cases for a disease with an R_0 of 3 (3) and would also have resulted in sufficient herd immunity to make the recent epidemic surge in cholera cases impossible (2). Better data are needed for the modeling and control of cholera in Haiti, but to be credible, modelers need to consider the important and hard-to-measure effects of public health responders in the successful control of epidemics.

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