90% of all people receiving ART to have viral suppression by 2020 [2]. There is a sizable gap between current rates of viral suppression and the 90% target. Complex interplay of multiple factors contributes to this gap, although pragmatic solutions have been offered and are being implemented [3]. Substandard ARV likely contributes to the suppression gap but could be addressed by improvements in quality control of ARV supplies.

Complete viral suppression is essential to prevent the emergence and spread of HIV-1 drug resistance. In some areas of South Africa, transmitted drug resistance is already at high levels (>10%; [4]), which reduces the efficacy of first-line treatment. In addition, 10%–30% of individuals experience virologic failure on first-line ART [5] and substandard ARV would be expected to increase failures. This undesirable outcome, in turn, would increase the number of individuals requiring more complex and expensive second-line regimens. Substandard ARV formulation could also adversely increase exposure to ARVs, causing toxicities such as renal or liver dysfunction. Greater toxicity could result in poor treatment outcomes and major additional costs to the national health systems that are already stressed.

In closing, we concur with Suthar et al [6] that as transition to country procurement of ARVs increases, it is imperative that country-specific guidelines be developed to monitor the quality of medications being procured. These guidelines should cover both initial and on-going procurement and logistical requirements to ensure that a steady supply of high-quality ARVs is available for individuals on therapy. As countries move to new ARV regimens, these guidelines would also ensure that the transition occurs without loss of quality. A further quality control measure would include sampling of individual ARV levels at primary health care facilities in comparison to expected exposures. Therapeutic drug monitoring has not been a feature of the care of HIV-1-positive individuals and

its main use has been in clinical trials to assess adherence. There are circumstances, however, in which measuring drug concentrations could be useful for individual patient management, including assessment of continued viremia on ART and monitoring ARV exposure during pregnancy to optimize prevention of maternal-to-child transmission, and during preexposure prophylaxis to prevent HIV-1 acquisition. To these ends, there are ongoing efforts to develop point-of-care semiquantitative tests to measure drug levels (particularly tenofovir). Such efforts could help determine if ARVs from new suppliers produce the expected drug levels in blood.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Caution Indicated in Extrapolating Carditis in Rats to Rheumatic Heart Disease in Humans

TO THE EDITOR—The article by Sikder et al [1] demonstrated that repeated injections of killed group G streptococci (GGS) or its purified M protein induced an autoimmune carditis in a rat model. The authors concluded that acute rheumatic fever and

rheumatic heart disease in man “should no longer be described in the scientific literature as a disease solely triggered by group A streptococci”. We contend that this conclusion is a gross oversimplification of the data and cannot be established solely by their results from a Lewis rat model. A direct link between the animal model and human disease is speculative, but not as firmly established as the authors have concluded.

Although some have speculated that GGS may trigger initial or recurrent episodes of acute rheumatic fever (ARF), the data are indirect, at best [1, 2]. GGS are normal human pharyngeal flora, recovered from 1%–23% of healthy individuals. Previous studies have shown that GGS rarely have caused community-wide epidemics of pharyngitis [3], but their role in endemic symptomatic pharyngitis has not yet been clarified [4] and will require large, carefully designed prospective studies. Current RF prevention guidelines do not include diagnostic or treatment recommendations for agents other than group A streptococci (GAS). Thus, proof that ARF is not triggered solely by GAS would necessitate major revisions to the clinical management of the many millions of patients presenting with pharyngitis. Such measures, based solely on the indirect results from one animal model, would not be justified.

We understand and appreciate the potential relevance of animal models to human disease, especially as they relate to mechanisms of pathogenesis and discovery of new therapeutic targets. However, animal models are not a substitute for carefully performed clinical studies to firmly establish cause and effect relationships between pathogens and human disease.

Notes

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Reply to Dale and Shulman

TO THE EDITOR—We appreciate the insightful comments made by Dale and Shulman [1] regarding our article [2]. We found that histological, immunological, electrocardiographic, and echocardiographic changes observed in the cardiac tissue of rats treated with killed *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE or β -hemolytic groups C and G; GCS and GGS) or recombinant GGS M-protein, were indistinguishable from the changes observed in those treated with killed group A streptococci (GAS M5) or rM5 protein, in our Lewis rat autoimmune valvulitis (RAV) model [2]. Furthermore, autoantibody reactivity to cardiac myosin was comparable in both GGS- and GAS-induced RAV, and both GAS and GGS exacerbated valvulitis initiated by the other streptococcal species or M protein [2]. Animal models of disease may provide essential clues to the pathogenesis, diagnosis, and treatment of human diseases, but we strongly agree with Dale and Shulman that animal models are not a substitute for large carefully designed prospective human studies. Nevertheless, the RAV model has afforded us with evidence of similarities to the streptococcal sequelae in human rheumatic heart disease and Sydenham chorea [3–5].

We are aware of the overwhelming epidemiological observations associating GAS throat infection with the development of acute rheumatic fever (ARF) and subsequent rheumatic heart disease (RHD). However, it is also our concern that it has turned out to be a dogma that GAS has become known as the sole agent that initiates and/or exacerbates ARF/RHD, to the extent that additional possibilities are rarely investigated. Our studies were conducted specifically to determine whether the autoimmune process induced and exacerbated by killed GAS and rGAS M protein also could be initiated and or exacerbated by killed GGS or rGGS M protein.

In particular we explored the mechanisms that may be associated with