follow-up study is designed to provide much-needed safety data on potential late effects of ART in both mothers and children in Africa.

Mary G. Fowler, M.D., M.P.H.
Johns Hopkins University School of Medicine
Baltimore, MD
mgfowler@mujhu.org

Lynne M. Mofenson, M.D.
Elizabeth Glaser Pediatric AIDS Foundation
Washington, DC

Taha E. Taha, M.D., Ph.D.
Johns Hopkins University Bloomberg School of Public Health
Baltimore, MD

Since publication of their article, the authors report no further potential conflict of interest.

1. Mofenson LM. New challenges in the elimination of pediatric HIV infection: the expanding population of HIV-exposed but uninfected children. Clin Infect Dis 2015;60:1357-60.
2. Prevention gap report. Geneva: Joint United Nations Programme on HIV/AIDS, 2016 (http://www.unaids.org/en/resources/documents/2016/prevention-gap).
3. The gap report. Geneva: Joint United Nations Programme on HIV/AIDS, 2014 (http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf).
4. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach — second edition. Geneva: World Health Organization, 2016 (http://www.who.int/hiv/pub/arv/arv-2016/en/).

Trial of ZMapp for Ebola Virus Infection

TO THE EDITOR: Davey and colleagues (Oct. 13 issue)[1] are to be commended for completing the ZMapp trial under challenging circumstances. However, in order to determine whether ZMapp represented the only difference across study groups, more detail should have been provided for the between-group comparisons. The ZMapp infusion protocol describes monitoring every 15 to 30 minutes during early dose escalation[1]; however, no description exists for similar monitoring of the patients who received the standard of care. Frequent monitoring of patients receiving ZMapp may have resulted in earlier identification of serious adverse events and improved care delivery, an effect observed in other trials involving severe illness in similar settings.[2] Elevated baseline creatinine levels are associated with Ebola virus disease mortality.[3,4] In the JIKI trial, the elevated baseline creatinine level was lethal in virtually all enrolled patients (97%) with a low cycle-threshold value for the virus (<20).[5] In the ZMapp trial, patients receiving the standard of care appear to have had slightly higher baseline creatinine levels; it was not reported whether there was a significant between-group difference. It is conceivable that such differences between study groups contributed to the improved survival trend attributed to the ZMapp intervention.

Shevin T. Jacob, M.D., M.P.H.
University of Washington
Seattle, WA
sjacob2@uw.edu

Thomas E. Fletcher, M.D.
Liverpool School of Tropical Medicine
Liverpool, United Kingdom

No potential conflict of interest relevant to this letter was reported.

1. The PREVAIL II Writing Group. A randomized, controlled trial of ZMapp for Ebola virus infection. N Engl J Med 2016;375:1448-56.
2. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483-95.
3. Schieffelin JS, Shaffer JG, Goba A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. N Engl J Med 2014;371:2092-100.
4. Hunt L, Gupta-Wright A, Simms V, et al. Clinical presentation, biochemical, and haematological parameters and their association with outcome in patients with Ebola virus disease: an observational cohort study. Lancet Infect Dis 2015;15:1292-9.
5. Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med 2016;13(3):e1001967.

THE AUTHORS REPLY: Jacob and Fletcher raise important issues of potential bias in assessments of survival between the study groups, specifically citing differences in monitoring during follow-up and the possibility of chance imbalances in baseline creatinine levels. As acknowledged in the Discussion section of the article, one limitation of the trial was its open-label strategy (rather than a double-blind, placebo-controlled strategy), which may have influenced bedside monitoring during infusions. Accordingly, we cannot say whether the additional bedside monitoring provided some benefit to ZMapp recipients that was independent of any effect of ZMapp itself. If so, however, it did not translate objectively into any differen-

tial provision of daily measures of supportive care between groups (see Table S3 in the Supplementary Appendix, available with the full text of the article at NEJM.org). Consonant with prevailing recommendations,[1-3] P values for baseline comparisons were not reported (Table 1 of our article). Consistent with other reports, higher baseline creatinine levels (>2 mg per deciliter vs. ≤2 mg per deciliter) were associated with an overall increased risk of death (crude odds ratio, 15.0; P=0.004) in our trial. However, the inclusion of baseline creatinine levels (available for only 44 of 71 patients) as a covariate with location and polymerase-chain-reaction cycle threshold did not alter the odds ratio for mortality with ZMapp versus control (odds ratio, 0.21; 95% confidence interval [CI], 0.03 to 1.48) from that without the inclusion of creatinine levels (odds ratio, 0.24; 95% CI, 0.04 to 1.33).

Richard T. Davey, Jr., M.D.
National Institute of Allergy and Infectious Diseases
Bethesda, MD
rdavey@niaid.nih.gov

Jacquie Nordwall, M.S.
University of Minnesota
Minneapolis, MN

Michael A. Proschan, Ph.D.
National Institute of Allergy and Infectious Diseases
Bethesda, MD

for the Prevail II Study Team

Since publication of their article, the authors report no further potential conflict of interest.

1. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63(8):e1-e37.
2. Senn S. Controversies concerning randomization and additivity in clinical trials. Stat Med 2004;23:3729-53.
3. Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med 2002;21:2917-30.

Von Willebrand's Disease

TO THE EDITOR: In their review article on von Willebrand's disease, Leebeek and Eikenboom (Nov. 24 issue)[1] state that it is reasonable to measure both levels of factor VIII and ristocetin cofactor activities during surgery in order to monitor the patient's hemostatic response to replacement therapy with concentrates containing both von Willebrand factor and factor VIII. We think that levels of factor VIII alone should be measured because they are the best predictor of hemostasis in patients undergoing surgery.

Patients with alloantibodies to von Willebrand factor[2] have safely undergone surgery with the use of recombinant factor VIII that is devoid of von Willebrand factor.[3,4] This indicates that the control of soft-tissue and surgical bleeding depends on factor VIII rather than on ristocetin cofactor levels, which remain unmeasurable in plasma throughout the postinfusion period because of the neutralizing action of alloantibodies.[3,4] Furthermore, levels of factor VIII increase more than would be predicted from the administered dose, owing to its endogenous stabilization by the infused von Willebrand factor and accumulation of the factor VIII contained in concentrates. Thus, since evidence that surgical hemostasis depends on ristocetin cofactor levels is lacking, it is important to monitor levels of factor VIII after surgery.

Pier M. Mannucci, M.D.
Maggiore Policlinico Hospital
Milan, Italy
pm.mannucci@policlinico.mi.it

Massimo Franchini, M.D.
Carlo Poma Hospital
Mantova, Italy

Dr. Mannucci reports receiving lecture fees from Alexion Pharmaceuticals, Baxalta, Bayer, Grifols, Kedrion Biopharma, and Novo Nordisk. No other potential conflict of interest relevant to this letter was reported.

1. Leebeek FWG, Eikenboom JCJ. Von Willebrand's disease. N Engl J Med 2016;375:2067-80.
2. James PD, Lillicrap D, Mannucci PM. Alloantibodies in von Willebrand disease. Blood 2013;122:636-40.
3. Bergamaschini L, Mannucci PM, Federici AB, Coppola R, Guzzoni S, Agostoni A. Posttransfusion anaphylactic reactions in a patient with severe von Willebrand disease: role of complement and alloantibodies to von Willebrand factor. J Lab Clin Med 1995;125:348-55.
4. Franchini M, Gandini G, Giuffrida A, De Gironcoli M, Federici AB. Treatment for patients with type 3 von Willebrand disease and alloantibodies: a case report. Haemophilia 2008;14:645-6.

THE AUTHORS REPLY: Mannucci and Franchini suggest that monitoring patients with von Willebrand's disease during surgery should involve