Passive Immune Therapy in Acquired Immunodeficiency Syndrome

To the Editor:

We read with concern the article on passive hyperimmune therapy in the treatment of acquired immunodeficiency syndrome (AIDS). In this report, the investigators attempted to show the efficacy of plasma taken from asymptomatic human immunodeficiency virus (HIV)-positive donors with antibody to HIV on the clinical course of AIDS patients. The investigators set up four requirements to establish efficacy: decreased mortality, improved length of survival, decreased number of opportunistic infections, and positive changes in CD4 count. Overall, there was no efficacy, i.e., no statistically significant changes during the study period!

The concept of passive immune modulation of HIV infection is attractive; however, in general, with viral diseases antibody is useful in preventing primary infection, but usually requires cell-mediated immunity and/or other antiviral responses for eradication. Levy et al. misstate the findings of the reference they cite when they note that "Hyperimmune plasma... [is] useful in the treatment..."; in their references, hyperimmune plasma or immunoglobulin preparations provided effective prophylaxis (prevention, not modification of ongoing infection).

In the Levy et al. study, only a minority of patients (72 of the original 220) were reported to have some "benefit"; in these, three of the stated criteria for efficacy (mortality, survival, and infections) were not significantly different from controls. The fourth, a change in the level of CD4 cells, was "statistically significant" only in a subpopulation of 32 patients among the 72, and then with a wide standard deviation. Considering that the majority of the patients studied did not meet even this criterion, the data must be viewed with caution.

A previous study of such therapy indicated that the level of neutralizing antibody in the passively transfused plasma was important in producing a reduction in cultured virus in recipients. Neutralizing antibody was determined in two separate laboratories in the Levy et al. study, but no data are given about the infused material other than it was active against a broad strain of isolates. In the baseline data of Table 2, the full-dose group antibody to p24 data excludes 5 "outliers" with antibody titers of greater than 1:5,000. What was the fate of such individuals? Did their elevated titers contribute to the alleged improvement in this group?

The Levy et al. report is littered with such phrases as "near statistical significance," "suggested benefit," or "favorable trend," which are only useful in obfuscating the lack of rigor of the data. They found that the number of opportunistic infections was not different for the three groups as well as the number of deaths in each group. No data were provided about the nature of any of the deaths. Were they infectious or due to other AIDS complications? Two deaths were not AIDS related; how was that determined? It is stated that there were no instances of viral transmission from donor plasma but there are no studies to prove this finding, nor appropriate techniques detailed in the Materials and Methods. Such statements and omissions are troubling.

In experimental systems in primates, passive immunization is only successful using material from animals shown to be immune when administered to prevent retroviral infection. Studies in animals already infected and using plasma from animals also infected but asymptomatic (as is done in this study) were unsuccessful and may have accelerated the disease. Finally, it appears the study by Levy et al. was completed in 1992. Are there follow-up data on the fate of the three groups? Specifically, is there any evidence of rebound or accelerated disease in the treated groups over the controls in the years after the study and the submission of this report in June of 1994? In the Vittecoq et al. study, stopping the anti-HIV infusions resulted in a "rebound" effect with 7 of 9 in the treatment group dying, versus only 1 of 9 in the control group. In a larger study by this same French group, they also found no survival benefit with hyperimmune plasma but have continued to give it for fear of this "rebound" effect. We believe that the results of the Levy et al. report do not support a move to a phase 3 study.

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REFERENCES
3. Gardner MB, Rosenthal A, Jennings M, Yee JA, Antipa L,
Response

The letter by MacKenzie and Holland regarding our recent publication in Blood shows more subjective than scientifically objective criticism.

The issues raised such as the preliminary nature of our work and the limitation of interpretation possible due to small numbers of subjects we ourselves bring out clearly in the report. Additionally, the authors report our patient numbers incorrectly and even incorrectly represent the information in some of our tables.

Addressing specific issues raised by these authors, I would like to make the following points.

(1) With regards to the statement "overall there was no efficacy," we made a special point in our report to define the subset of patients who did and did not respond to passive hyperimmune therapy. We made the point that drug effect could only be observed in the subset of subjects with baseline CD4 cell counts greater than 50 and that when patients with less than 50 CD4 cells at baseline are included in the analysis no efficacy can be seen. What new information are MacKenzie and Holland bringing to the discussion?

(2) With regard to the references of past use of hyperimmune antibodies, although the references cited in the text were primarily related to prophylaxis applications, the use of hyperimmune antibodies to herpes zoster in disseminated herpes zoster infection and anti-Hepatitis B antibody in chronic Hepatitis B infection have all been reported in the past as modalities for treatments.

MacKenzie and Holland confuse HIV treatment with cure or an absolute response as shown by prevention of disease after prophylaxis. The use of hyperimmune antibodies as treatment in the past and in our current application is as an adjunct to other therapy to induce a reduction in viral burden. At no time did we even suggest in our report that we eliminated the HIV virus from the subjects. It is also of some interest that reduction of HIV viral burden is an important predictor of improved survival and is becoming an important surrogate marker.

(3) With regard to the size of the treatment group, it is important to note that this was a 3-arm study and in the groups of patients with CD4 cell counts between 50 and 200 at baseline only 21 subjects were treated with full-strength drug. I therefore fail to understand the comment that a "change in the level of CD4 cells was statistically significant only in a subset of 32 (should be 21) among the 72." These 21 patients were the full-strength arm of the patients with baseline CD4 cell counts between 50 and 200.

(4) The authors raise the issue of in vitro neutralizing antibody assays of our plasma. Although we have assayed the neutralizing titer of HIV of our hyperimmune plasma, we reported the anti-HIV antibody as p24 antibody. The thrust of our paper was a clinical report and a detailed discussion of in vitro characteristics of our hyperimmune plasma will be the basis of another report.

(5) With regards to their comments on Table 2, they indicated that the full-dose group contained 5 outliers with regard to p24 antibody. This is a misreading of the table. In fact, the 5 outliers were distributed between all 3 groups and had no impact on the analysis.

(6) The author's criticism of our terminology (ie, "near statistical significance" or a "favorable trend") seems more a question of semantics than science. The full data are presented and the exact P values are given in the report and there is no attempt to misrepresent the data. A "favorable trend" or "near significance" means that, if the trend observed (1 death out of 21 for full-strength drug, 3 out of 21 for half-strength, and 6 out of 30 for placebo, giving a P value of .065) was continued with larger numbers of patients, statistical significance would be reached.

(7) With regard to viral transmission by donor plasma, our comment in the report that there was no evidence of viral transmission is based on no seroconversions for Hepatitis B or Hepatitis C during the study.

(8) The authors make a statement regarding studies in primates that do not appear to be relevant to our study. The primate studies mentioned looked at the ability of hyperimmune plasma to protect or "cure" infection as opposed to our goal of reducing viral burden.

(9) The authors comments regarding follow-up data on the 3 groups hardly seem relevant to the 12-month double-blind controlled study and to the results. In fact, the regulatory agency overseeing the study allowed the crossover of placebo and half-strength drug recipients to full-strength drug; therefore, we have no experience with large-scale discontinuation of the treatment. We are summarizing the data of passive hyperimmune therapy relating to long-term treatment for a future publication.

(10) The letter's last sentence, "we believe that the results of the Levy et al report do not support a move to a phase III study," suggests some bias on the part of these authors. Nowhere in our report do we make any mention of a phase III study. This remark by the authors therefore seems entirely inappropriate.

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REFERENCES

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[letter; comment]

MR MacKenzie and PV Holland