The AMP Trials — A Glass Half Full

Bruce D. Walker, M.D.

Induction of broadly neutralizing antibodies (bnAbs) is considered the holy grail for a preventive human immunodeficiency virus (HIV) vaccine, but four decades into the HIV pandemic, this goal has still not been achieved. Success will probably require multiple sequential immunogens to guide the affinity maturation needed for the induction of antibodies that can target well-concealed neutralization epitopes on the heavily glycosylated, highly variable HIV envelope protein[1] — a formidable task.

In contrast, in some persons with HIV infection, nature has achieved what vaccines have not: the gradual generation of potent bnAbs that have been cloned and have shown antiviral efficacy in early clinical trials.[2] The Antibody Mediated Protection (AMP) trials (HIV Vaccine Trials Network [HVTN] 704/HIV Prevention Trials Network [HPTN] 085 and HVTN 703/HPTN 081), reported in this issue of the *Journal*,[3] took these findings a step further. These parallel trials involving participants in the Americas, Europe, and Africa tested the protective efficacy of a single bnAb, VRC01. The good news is that this strategy can indeed prevent HIV type 1 (HIV-1) acquisition, but the caveat is that in the majority of participants it did not, and these findings have important implications for future prevention efforts.

VRC01 was derived from a person with HIV-1 infection and targets the CD4 binding site on the HIV-1 envelope protein. The trials were designed to answer two major questions: whether passive immunization with VRC01 would prevent HIV-1 acquisition and whether neutralizing antibody levels in plasma would be predictive of protection. On the basis of pretrial studies, it was estimated that between 65% and 81% of isolates from the trial sites would be sensitive to VRC01, which provided a rationale for the single-antibody proof-of-concept trials.

In an organizational and implementational tour de force, the HVTN and the HPTN working together infused VRC01 every 8 weeks for 20 months in the two concurrent international trials, which involved 4623 participants in total. One trial involved at-risk cisgender men and transgender persons in the United States, Switzerland, and South America, and the other involved at-risk women in seven countries in sub-Saharan Africa.

Antibody was infused intravenously at one of two randomly assigned doses and was compared with a saline placebo. Participants were monitored for acquisition of HIV every 4 weeks, and in vitro neutralization sensitivity testing was conducted for each transmitted HIV-1 strain with the use of a standardized TZM-bl neutralization assay. Preexposure prophylaxis was offered to all participants throughout the trials, but usage was low, particularly in Africa, where less than 4% of participants had detectable drug levels and less than 1% had therapeutic levels.

The disappointing result of these logistically complex and impressively conducted trials was that neither trial showed significant VRC01-mediated protection overall. However, when viruses were stratified according to prespecified criteria into sensitive, intermediate, and resistant categories, a different picture emerged from the pooled data. The frequency of transmission of VRC01-sensitive viruses, defined as those with an 80% inhibitory concentration of less than 1 μg per milliliter, was 0.20 per 100 person-years among participants receiving VRC01, significantly lower than the 0.86 per 100 person-years in the placebo group. Thus, for sensitive viruses, which represented only 30% of isolates, the protective efficacy of the single monoclonal antibody was 75%. In contrast, for viruses in the intermediate and resistant categories, there was no significant effect.

Despite the overall lack of efficacy of VRC01, the trials answered two important questions they sought to address. Passive immunization with VRC01 indeed protected against acquisition of HIV-1, but only against viruses that were highly sensitive to the antibody. And even for these sensitive viruses, the protection was not absolute, and it was less effective than oral preexposure prophylaxis when taken as prescribed.[4] The trials also showed that serum neutralization

titer, as measured with a standardized high-throughput assay, may be predictive of protection, thereby providing an important metric for future trials.

These trials represent an important step forward as proof of concept, and there is plenty of room to improve on these results. Trials of combinations of three antibodies are already under way, in which more potent and more broadly neutralizing antibodies are used, but these combinations may still not be sufficient for the ever-evolving global diversity of HIV. Antibody engineering can render antibodies even more potent, increase tissue levels, and extend the half-life such that they may require administration only every 4 to 6 months. However, the use of bnAbs as a mainstream method of prevention will have to compete with other emerging methods, particularly long-acting injectable formulations of antiretroviral drug cocktails, which are showing durable protection in early clinical trials and are likely to be less logistically challenging.[5]

Finally, the results of these trials have important implications for HIV vaccine development aimed at induction of bnAbs. Although they show that bnAbs can protect against some HIV infections, this protection was limited to highly neutralization-sensitive viruses. These results strongly suggest that vaccine-mediated protection will require induction not only of high antibody titers but also of antibodies of multiple specificities, both of which will be challenging. However, the AMP trials make the goal much clearer and provide important metrics to guide the path forward.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard University, Cambridge, MA.

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