Passive Immunization Trials to Inform Vaccine Design

Points for Consideration

from deliberations held at the August 8, 2014 workshop

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I. Introduction

A number of research groups are working on passive immunization as an approach to prevent, treat, or cure HIV infection. It is often stated that these studies will inform preventive HIV vaccine research and development by 1) establishing a proof of principle that bNAbs can prevent HIV infection; 2) setting minimal levels of neutralization required to prevent HIV infection; 3) providing additional correlates or other relevant information for vaccine design and testing. The Enterprise organized a workshop to review the current research plans in this area and to discuss what specific information relevant to the preventive HIV vaccine field can be gathered from such studies. This document summarizes the main points of discussion from that meeting.

II. Types of trials

1. Therapeutic and cure applications

There was a general agreement that therapeutic and cure efforts set a much higher bar for the effectiveness of passive immunization than would be required for prevention of infection. To treat or cure infection, antibodies should effectively suppress large numbers of virions already present in the body, while typically only one to two viruses establish infection. Antibody present at levels sufficient for 90% neutralization in vitro can be expected to translate into 60-70% efficacy in preventing transmission. Therefore, therapeutic applications may benefit from antibodies that are highly potent against the specific virus being treated, while prevention may be better accomplished with antibodies that have the broadest coverage.

Using antibodies in combination with antiviral drug therapy, an approach proposed by some groups, would make it difficult to extrapolate how effective an antibody can be on its own. Moreover, the use of antibodies in therapeutic or cure settings may require different specificity and/or functionality of antibodies than those required for prevention, also calling into question whether information from such trials can be informative for preventive vaccine research.

Most participants felt that demonstrating an efficacy of a bNAb in an infected human would provide additional line of evidence that neutralization or effector functions observed in vivo are translatable to in vivo settings.

2. Prevention trials

a. Prevention of MTCT

Due to the well-defined period of infection risk and the small doses needed to establish the desired concentration of Ab per kg of weight in an infant, MTCT settings present a unique opportunity to use the small-scale manufacturing batches of Ab to study the efficacy of passive immunization in preventing HIV transmission. As a result, these studies are likely to be the first to provide efficacy data, which may happen as soon as 2018. Nevertheless, the confounding factors for applying information obtained from this approach to vaccine research are as follows:

1) passive immunization would not be used on its own, but in addition to the existing standard of care; and

2) the biology of MTCT transmission is different from the predominantly sexual transmission in adults and may require different (lower or higher) antibody levels for protection.

b. Prevention studies in adults

At the moment, clinical studies in adults are limited to Phase I trials that aim to investigate safety and pharmacokinetic properties of Abs in healthy or infected adults. These studies, while critical for future clinical development of antibodies, are not very informative for the HIV vaccine field. Prevention efficacy studies in high-risk adults are being considered, but the data will likely not be available until at least 2020. On the positive side, long timelines mean that the field still has the opportunity to plan ahead and consider how such studies can be performed to better inform HIV vaccine research.

3. Preclinical studies

Because bNAbs are specific for HIV Env, they have to be tested in preclinical models that use HIV or SHIV, which have been limited in the diversity of available viruses or in how well they approximate human transmission and disease. Infection of humanized mice with HIV has been instrumental in early-stage studies to evaluate and down-select antibody candidates for further development. New SHIV models are being actively developed that hold promise for studying effects of bNAbs in vivo, although (just like the current models) they will still be limited to a single antibody administration due to anti-antibody responses by the animal's immune system. Nevertheless, these models will be critical for downselecting candidates from the wide variety of available individual antibodies and their combinations – they can be used to detect large differences in efficacy, evaluate PK/PD properties, and detect synergistic effects within combinations.

III. Expected information

1. Proof of principle

For many existing vaccines it is believed that neutralizing antibodies are responsible for protection, but it is not known whether this belief can be extrapolated to HIV. A definitive proof that neutralizing antibodies can provide protection against HIV in the absence of any other anti-HIV responses would be valuable. However, data from animal models already strongly suggest that bNAbs can protect against infection and most researchers agree that if bNAbs were elicited via vaccination in humans, they would prove efficacious. Therefore, while such proof of principle will be valuable, many participants felt that it would not have a dramatic impact on the field.

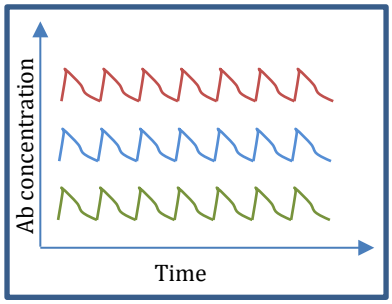
Moreover, some argued that findings from passive immunization studies cannot be directly translated to vaccine research because these studies depend upon high titers of neutralizing antibodies established in the absence of any other anti-viral immune response in the body, which is not possible to accomplish via vaccination. Additional anti-viral immune responses may either contribute to protection, or they may reduce protection if, as some researchers argue, HIV-specific CD4 cells serve as effective target cells for the virus and promote infection.

It was also pointed out that passive immunization studies may reveal some unexpected information about antibody activity *in vivo*. For example, if it's found that antibodies protect *in vivo* at levels that are substantially lower than those required to suppress the virus *in vitro*, it may help identify some alternative mechanisms of protection beyond those measure in in vitro neutralization assays.

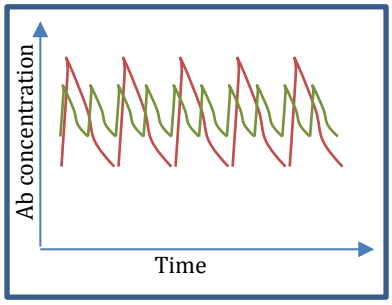
2. Establishing minimal level of neutralization needed for protection

Passive immunization trials could help define the quantitative relationship between the levels of neutralization observed in sera and the efficacy of protection, thus perhaps establishing goalposts for bNAb-based vaccines. However, this simple concept requires careful consideration and planning if it is to be accomplished effectively. In order to define a specific level of neutralization as a correlate of protection, one needs to have measurable variability in both antibody levels and in efficacy of protection. As a result, the search for correlates in some cases may be at odds with product development goals. The objective of an efficacy trial is to maximize overall treatment efficacy, but to maximize the chances of defining a correlate, the trial should maximize the variability of treatment efficacy, while retaining reasonably high overall protection (50-70% is ideal). Correlates analysis also requires establishment of low-noise assays for measuring functions that one may expect to vary in the trial and planning for appropriate sample collection. Finally, trial design needs to be evaluated for statistical power needed to conduct the appropriate correlate analysis.

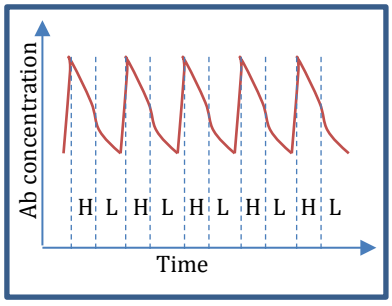
Probably the most straightforward way to establish antibody concentration as a correlate of protection would be to administer antibodies in different doses and measure the resulting efficacy (see Fig on the right). However, several meeting participants raised the concern that administering antibodies in suboptimal concentration would be unethical. The issue was not extensively discussed at the meeting.



Maintaining equipoise may be accomplished by comparing study arms with hard to predict relative efficacies. For example, as shown on the right, group A may receive large doses at longer intervals, while group B may receive smaller doses more frequently, both providing the same average antibody concentration, but group A having both higher or lower concentrations at certain times. Higher efficacy in group A would indicate that highest concentrations of Ab achieved in group B are less effective than the highest concentrations of Ab in group A. Alternatively, higher efficacy in group B would indicate that the lowest concentrations in group A are less effective than the lowest concentrations in group B. Other creative administration schedule variations may also help address this question, while preserving investigators' equipoise.

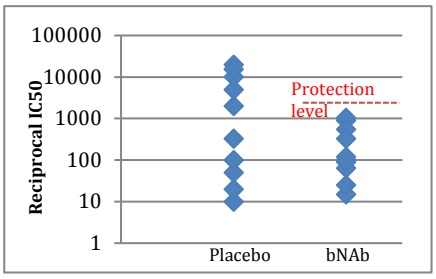


It was pointed out that even within a single arm antibody concentrations will vary over time and this variation may help determine the concentration required for protection. For example, dividing each administration period into "High" and "Low" periods, as shown on the right, may allow one to correlate average concentrations with observed efficacy during these periods. One challenge for this approach is that timing of HIV diagnosis should be sufficiently frequent and accurate to place each infection into one of the two periods, which may be as short as 1 week.



Finally, the information on correlation between neutralization levels and transmission rates may come from analysis of the sensitivity of transmitted viruses to neutralization

by the tested antibody. Comparing phenotypes of transmitter/founder viruses isolated from volunteers in placebo and bNAb arms may reveal a neutralization threshold below which sensitive viruses are not found in the bNAb arm (but are still found in the placebo arm). The approach is in line with the "neutralization sieve" analysis proposed recently by David Montefiori. One caveat to this approach is the need to plan in advance for labor-intensive T/F virus reconstruction and neutralization assays. Another caveat is that for some of the bNAbs, resistance of most viruses to neutralization can be described as "all or nothing", while this analysis requires a continuous spectrum of sensitivities. Therefore, to inform vaccine design it may be useful to test bNAbs that have a more gradual resistance profile in viral panels. In addition, a more classical sieve analysis may also identify viral signatures associated with breakthrough infections.



To summarize, passive immunization studies may help establish the minimal level of neutralization required for protection, but this information will not be readily available unless researchers proactively plan for appropriate study design, necessary sampling, assays, and statistical power.

3. Other correlates of protection and information useful for vaccine design

a. Breadth vs Potency

Newly discovered bNAbs vary both in the potency of viral inhibition and in the breadth of diversity of affected viruses. It may be informative to test whether an antibody with lower potency but wider breadth (such as PGT121 or 10-1074) will be more (or less) effective in vivo than a highly-potent antibody with a narrower breadth (such as VRC01 or 3BNC117). This information may help focus future efforts in bNAb-based vaccine research. While the antibodies that are now going into the clinic do differ in these properties, that difference was not specifically considered in selecting the candidates for testing and there are no plans for head-to-head comparisons.

b. Fab considerations

It is conceivable that bNAbs targeting different sites of the Env protein may have different protection efficacy in vivo even when they have similar neutralization potency and breadth in vitro. Such information would help guide immunogen selection for future vaccines. Among the current candidates going into the clinic, VRC01 and 3BNC117 target the CD4 binding site, while PG9 targets the glycan on the V1/V2 loops. In addition, comparing single antibodies to antibody combinations may provide information on synergistic effects of targeting multiple sites on Env.

c. Fc considerations

All three of the current candidates in clinical trials are of IgG1 subtype, although the exact sequences of the Fc portions are not identical. Fc-mediated functions may play an important role in protection via a variety of mechanisms such as ADCC, ADCVI and others, which are not well understood. However, for proper comparison and understanding of the role these functions may play in protection, it would be necessary to construct and compare antibodies that are specifically designed to answer these questions, e.g. by introducing targeted mutations that improve or abrogate these functions. Additional studies in animal models may be appropriate to generate and test hypotheses on the importance of Fc functions before clinical studies would be justified. Indeed, Nussenzweig's group observed that antibodies with mutations in Fc resulted in

virus escape while the virus remained sensitive to the antibody *in vitro*. This work may help identify new mechanisms (or correlates) of protection.

IV. Gene-based Ab delivery

Overall, the same considerations described above apply to gene-based antibody delivery platforms as to the direct protein delivery. The biggest difference is that gene-based platforms provide more stable antibody concentrations. As a result, antibody concentration at the time of infection is much easier to measure in these settings. However, this can also be a downside because correlate analysis requires variability in antibody concentration in order to define the minimal required levels for protection. Thus, different dosing will be required for such analysis with gene-based platforms.

V. Acknowledgements

We thank all participants of the 2014 workshop "Passive Immunization Trials to Inform Vaccine Design"; the full list of attendees can be found at http://www.vaccineenterprise.org/timely-topics/passive-immunization-trials-inform-hiv-vaccine-design

The report was developed by Yegor Voronin with contributions by Peter Gilbert, Barney Graham, Nancy Haigwood, and Lynn Morris.