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Passive immunization and the quest for an HIV vaccine

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Successful vaccines often depend on the stimulation of pathogen-specific neutralizing antibodies[1]. Evidence suggests that this may also be true for an HIV vaccine although current vaccine candidates are not able to elicit such antibodies with sufficient breadth. Studies in animals with passively administered HIV monoclonal antibodies (mAbs) have shown them to be effective in preventing and treating infection[2–6] but these findings need to be confirmed and extended in humans. In the last 5 years, a large number of extremely potent and broad neutralizing mAbs have been isolated from HIV-infected donors[7]. This has opened up the possibility for directly assessing whether neutralizing antibodies are able to protect humans from HIV infection.

Passive administration of polyclonal antibodies to prevent or treat infectious diseases has been done successfully for more than 100 years[8]. Technological advances have enabled the isolation and large-scale production of mAbs with well-defined functional specificities suitable for clinical application. Today, passive immunization (polyclonal or monoclonal) has a role in a number of infectious diseases including rabies, RSV, anthrax, SARS, *Clostridium difficile* colitis, Ebola and hepatitis B. Passive immunization is also being actively explored for prevention, treatment, and cure of HIV[9]. Currently new generation anti-HIV antibodies are being tested for safety in healthy people and in infected subjects on HAART [10] with efficacy trials planned, including studies in populations with a high incidence of sexual HIV transmission.

While the primary objective of preventive passive immunization trials is to assess the ability of *pre-formed* antibody to block HIV acquisition relative to a placebo, advancing HIV vaccine research has been cited as an important secondary objective[11]. The assumption that antibodies neutralizing HIV in the current in vitro assays are able to protect against HIV infection underpins much of the research on broadly neutralizing antibodies and envelope immunogen design. Passive administration of mAbs can test this assumption directly and may determine the minimal level of neutralization in plasma and at mucosal surfaces that is sufficient to confer protection. Such levels could be used as a benchmark for vaccine candidates, allowing down-selection of candidates at earlier stages of the clinical trials process, thereby accelerating vaccine discovery. Testing mAbs with different specificities and assessing how the level of protective efficacy varies with the sequences of the breakthrough viruses could help to reveal the critical sites on the HIV envelope that should be targeted by a vaccine[12]. Finally, preventive trials have the potential to shed light on the role of antibody isotype and Fc effector functions in protection and facilitate important discoveries on the role of other functional properties of antibodies.

Gathering all this useful information, however, will not be trivial. A correlation analysis to identify a level of neutralization as minimally sufficient for protection will require variability both in the level of neutralization and in the protective efficacy. Variability in antibody levels occurs naturally due to decreases in the mAb concentration after each administration and to differences among individuals, and can be enhanced by administering the mAb at multiple schedules or doses to different groups (Fig 1.). Variability in the protective efficacy needs to be obtained in an ethical manner without breaking equipoise or putting participants at risk. In order to better interpret the trial outcome, it will be important to study the distribution of mAb between serum, mucosal tissue, and mucosal secretions at the entry site for sexual HIV transmission, as well as to sequence the breakthrough viruses and test them for resistance to mAb. The trial would also require frequent visits for diagnosis to more accurately define timing of infection.

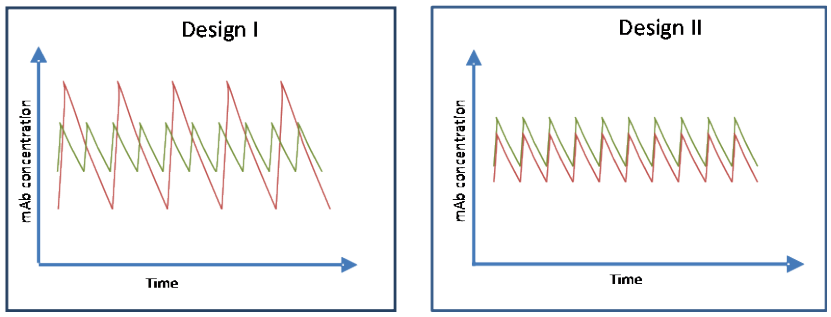

Figure 1: Two potential trial designs that may help define the minimal level of neutralization required for protection. Design I: In Arm A, participants receive larger doses of the antibody at less frequent intervals, while in Arm B, participants receive more frequent but smaller doses of the same antibody. Design II: In Arms A and B, participants receive different doses of the antibody at the same schedule.

Information from passive immunization trials will come with certain caveats for HIV vaccines. First, these trials measure short-term protection by a single mAb specificity (or a combination of several mAbs), while a vaccine will generate a polyclonal response, ideally with long-lasting immune memory. Polyclonal and monoclonal responses may result in different levels of efficacy even if the observed neutralization levels are similar. Secondly, passive immunization delivers antibody in the absence of other immune responses, while a vaccine stimulates complex innate and cellular responses. T-cell responses may provide additional protection, but they may also have negative effects if, as many researchers argue, HIV-specific CD4 T cells serve as preferred targets for HIV replication.

The enthusiasm and support for conducting passive immunization trials to prevent HIV infection provides a unique opportunity to advance the HIV vaccine agenda. Data generated by passive immunization may tell us exactly what a vaccine needs to do to prevent HIV infection. Ideally, the field would be able to evaluate mAbs with different specificities and functional properties to best inform benchmarks needed for active immunization. As such, passive protection trials should be designed to maximize what can be learned and with the intended aim of benefiting HIV vaccine development.

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