triple-drug therapy does not seem to select significant escape mutation, unlike single- or double-drug therapy; part of the protection must be due to the drug-induced low level of virus replication. This gives some hope that if the immune response is activated very early in infection, there is a chance that the virus could be controlled by a response to at least three epitopes before high-level virus replication occurs. Given the above arguments about pre-existing virus variability, this could mean inducing CTL responses to ten or more epitopes.

Breadth of the immune response

A remarkable feature of the natural T-cell response to acute or chronic virus infection is that the CD8+ T-cell response can be focused on a very small number of epitopes[77,78]. In the CD8+ T-cell response to acute EBV infection, as many as 40% of blood CD8+ T cells can respond to a single epitope[13], despite the fact that this herpes virus expresses hundreds of proteins. This type of CTL response could be disastrous for a vaccine, as it offers an easy escape route. It is not clear how to broaden a vaccine response, and the obvious possibility of adding more virus proteins to the vaccine might not work (as for EBV). It might be better to mix several small vaccine constructs together, fooling the immune system into responding to several 'invaders', each requiring a strong T-cell response. For a DNA prime and recombinant virus boost schedule, it might only be necessary to do this for the DNA priming component.

Duration of the immune response

In macaques that were immunized with non-replicating MVA, the half life of tetramer-stained CD8+ T cells seems to be around seven days[68]. The memory T-cell response that remains is at a much lower level. This is probably typical of the response to a non-persisting antigen. If a high level of mature effectors is required for protection, continuous or repeated antigenic stimulation will be required. The evidence from the Nairobi sex workers indicates that this will be needed, at least for complete protection; in several cases, susceptibility to HIV infection was restored when they ceased prostitution[109]. However, their concentration of antigen-specific CD8+ T cells while they were protected was less than that which can be induced in humans by a vaccine, so the situation might not be exactly comparable. Amara *et al.*[64] found that their macaques were protected against SHIV-89.6P disease when challenged seven months after the last immunization. By contrast, there was little or no protection in macaques challenged at the peak of the tetramer response to a single epitope[68] (T. M. Allen, T. Hanke and D. Watkins, unpublished observations).

The SHIV-89.6P-challenge studies indicate that useful but incomplete protection can be obtained by long-lasting memory T cells; complete protection might need higher levels of fully activated effectors. Only phase III efficacy trials will show whether CTL memory that is induced by current vaccines will work. If non-persisting vaccines do not protect, persisting antigen vaccines will have to be tested. The regulatory authorities will have to confront this need.

Why the idea might be right but fail

The animal studies that have been discussed show that the CTL-vaccine approach can work. However, for HIV, conditions will have to be exactly right. There is a danger that one or two negative trials could kill the whole idea of a CTL vaccine. Therefore, it is vital that conditions for the first efficacy trials are optimal. The reasons that a vaccine might fail have been discussed: the vaccine-induced T cells might have to be in an activated state that cannot be maintained by the vaccine, the immune response might be too weak, the T cells might not see enough epitopes to cope with virus variability, the virus might escape from the T-cell response or the duration of protection might only be brief. Even at best, a CTL-inducing vaccine might be only half a vaccine — that is, it might only really protect in combination with neutralizing antibody.

These concerns combine to produce a formidable challenge, but one that cannot be avoided. There is now a CTL-vaccine bandwagon, with several teams gearing up to test the same hypothesis. One bad trial could ruin the whole lot, although a good trial that gives a clear negative answer would be scientifically very important. A positive protective effect would open the door to a vaccine and could be within our grasp soon.

Glossary

CLADE
A subgroup of HIV variants with a greater degree of genome homology.

LICENSING
The activation of dendritic cells by CD4+ T cells through CD40–CD40L interaction.

PRIME-BOOST
When a single application of a vaccine is insufficient, repeated immunizations are performed using the same vaccine preparation (homologous prime boost) or using different vaccine preparations (heterologous prime boost) to sequentially stimulate a better immune response.

TETRAMER
A reagent composed of four MHC–peptide complexes linked by biotin and streptavidin, which can be fluorescently labelled and used to track antigen-specific T cells by flow cytometry.

Trials: ethical and political issues

The need for an HIV vaccine is desperate in developing countries. Apart from a few exceptional sites, only these countries have a high enough incidence of HIV infection to conduct phase III efficacy trials. Therefore, it is essential to establish strong collaborations well in advance of such trials. Matching of clades between vaccine and the most prevalent virus has been used as a political argument to ensure that such collaborations are truly in the interests of the African or Asian partner. In fact, there are stronger scientific arguments as to why the clades should be matched in any phase III efficacy trial. It is also important to have an outline plan for further vaccine development to ensure that, if the vaccine works, it will be made available in the partner country at the earliest opportunity. The medical, scientific and regulatory authorities are well aware of these issues, and trials need at least two years of preparation to deal with these issues before the trial itself. The associated infrastructure development needs similar forward planning.

Thought also has to be given to serious ethical issues. The trials will only give answers if some control volunteers become infected with HIV. If the vaccine only partly protects, or does not work, vaccine recipients will also be infected. The level of treatment that they should be offered — for life — needs very careful discussion, which must involve the community to which the trial participant belongs. For these and more commercial reasons, vaccines that are targeted at developing countries are not attractive to the pharmaceutical industry. Alternative funding streams have been created and need continued support (for further discussion of these issues, see http://www.iavi.org).

Conclusions

HIV presents an unprecedented challenge to vaccine design and conduct of trials. Virus variability is a particularly serious problem. It must not be assumed that 90% similarity between HIV clades means that a vaccine that is based on one clade will give 90% protection against another clade; it is more likely that such cross protection would be as little as 33%. Efforts must be made, therefore, to ensure that the vaccine stimulates a broad response. This is difficult to ensure, given the tendency of the immune response to focus on only a few

epitopes — sometimes only one. These issues present formidable challenges, but if these problems are properly addressed, the animal models indicate that the vaccine will work.

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Ethical issues for vaccines and immunization

Jeffrey B. Ulmer and Margaret A. Liu

Vaccination is the only type of medical intervention that has eliminated a disease successfully. However, both in countries with high immunization rates and in countries that are too impoverished to protect their citizens, many dilemmas and controversies surround immunization. This article describes some of the ethical issues involved, and presents some challenges and concepts for the global community.

Vaccines stand out as being among the most efficacious and cost-effective of global medical interventions[1] (BOX 1). Vaccines have saved millions of lives, prevented significant morbidity and suffering, and even eradicated a disease. This last accomplishment, the eradication of smallpox, highlights what can be achieved by vaccination. However, unfortunately, the inequalities in the distribution and use of vaccines are also striking. If vaccines