HIV: dark and light, then and now

"...there should be a new, intense effort for a preventive HIV vaccine, involving both eastern and western hemispheres of the world, based on sound scientific principles, driven by scientists..."

A ‘return’ of epidemics & pandemics?
By approximately the mid-1970s much of the medical science community became confident that serious epidemics were no longer significant problems for developed nations. There was also a strong prevailing view that retroviruses did not infect humans. Such sentiments led to the closures of microbiology departments in some medical schools and the termination of the US Virus Cancer Program. Yet, within a span of a few years human retroviruses were discovered. Some were shown to cause certain types of leukemia as well as neurologic disease (human T-cell leukemia virus [HTLV]-1); and several old epidemics re-emerged while new epidemics emerged including perhaps the greatest pandemic in medical history, AIDS, caused by the HIV retrovirus.

What lessons should be learnt?
Firstly, we have been reminded that microbes, including viruses, will always be with us. Secondly, they may disappear for long periods but can abruptly return or new ones emerge with societal changes. Some recent prominent examples include:

- Lyme disease
- Legionnaire’s disease
- The re-emergence of tuberculosis
- AIDS
- Severe acute respiratory syndrome
- West Nile fever
- Avian flu

It can be convincingly argued that most, if not all, of these came about in part because of societal change. Thirdly, humans are not microbiologically special; like animals there is no particular class of microbe we can be assured will not infect us.

What is the status of the HIV/AIDS epidemic today, & what of the future?
Suffice it to say that HIV is one of, if not the most important epidemic in history. The future remains unpredictable because of the development of HIV variants, the unpredictability of human habits and the uncertainty of long-term public and governmental support among both more economically developed countries (MEDCs) and less economically developed countries (LEDCs).

What are the major needs?
Although educational programs are vital, it seems clear that the tragic advance of HIV/AIDS must chiefly be halted by scientific advances.

There are three great needs in the treatment and prevention of HIV/AIDS. The first is to obtain effective anti-HIV therapy for LEDCs. The second need is the continued research and development for new forms of therapy, needed for both MEDCs and LEDCs. Due to drug resistance, basic research on the biology of HIV will continue to be a high priority in order to find new approaches to therapy: science must ‘keep up’ with the virus. Such research is also needed for LEDCs. The distribution of available anti-HIV drugs has been problematic, and a debate has ensued among well-meaning people with the same ultimate goal. Some simply want the drugs ‘poured’ into these nations. Others believe this must be accompanied by the close involvement of clinicians and medical scientists from developed nations for training in the proper use of the drugs in order to avoid multi drug-resistant mutants. A still highly controversial position, but one I also believe in, is that we require novel therapeutic approaches that might lead to treatments which are less toxic, less complex to administer, less likely to yield drug resistance and less expensive.

The third great need is, of course, the development of an effective preventive vaccine against HIV.
How can we develop a successful HIV preventive vaccine?

Three frequently mentioned key obstacles are:

- The lack of small animal models
- The lack of information on what kind of immune response is needed (i.e., the immune correlate of protection)
- The great variability of HIV

However, I do not believe these are great obstacles, and certainly not the greatest ones. We have relevant primate models, but research is handicapped by the limitations of monkeys to scientists within primate centers, their close collaborators, or some drug companies, which have purchased them in great numbers. Although some agencies do provide primates for wider use by funded investigators, these are invariably extremely limited. This problem could be solved with money and policy; namely, making these primates far more available to a wider number of scientists. As to correlates of protection, I fail to see the problem, since many successful vaccines of the past were made without this knowledge being available. Moreover, it is known that the administration of the right kinds of antibodies can protect against HIV infection; we need to know how to induce these antibodies with a vaccine. Finally, as to the variability of HIV, work at the Institute of Human Virology (IHV), MD, USA, over the past 5 years indicates that this is a solvable problem.

In my view, the real problem is that HIV is a retrovirus. As such, it integrates its genes into the chromosomal DNA of the cells it infects. To prevent HIV infection, we may not have time to wait for an immune response to be recalled. Rather, the immune response may need to be maintained after the vaccine ‘takes’, and we believe that we must approach ‘sterilizing immunity’ (i.e., complete or almost complete protection against infection from the start), something that to my knowledge has not been achieved by any prior vaccine. For previous successful vaccines, cell infection is not prevented but later the specific immune response (induced by a prior vaccine) is recalled as a result of new stimulation by the infecting virus. However, such viruses do not integrate their genes, ‘recall’ can lead to their complete elimination. We may not have this luxury with HIV.

Almost all current HIV vaccines focus on induction of cellular immune responses, namely the Cytotoxic T-Lymphocyte (CTL) response. Although this is a beneficial goal, and any vaccine should include approaches that include promoting CTL responses, this alone cannot prevent infection. We know of only two ways to prevent HIV infection: firstly, by promoting production of molecules known as β-chemokines, which block infection by preventing HIV from binding to its key receptor, the cell surface receptor called CCR5. How to induce β-chemokines and either maintain their levels or be certain they are rapidly made upon exposure to HIV is not easy to do but is being explored. In my view this merits more attention.

The second is more conventional: it is a vaccine method that induces neutralizing antibodies reactive with a broad range of HIV variants. These neutralizing antibodies block HIV cell entry. Their induction requires an immune response to the HIV envelope (Env) protein, because it is Env that interacts with the specific surface molecules of the targeted cell – first CD4 and then CCR5. This would typically require using whole attenuated but ‘live’ HIV or ‘killed’ HIV particles, but due to biohazard problems their use would be prohibited by regulatory agencies. These approaches never demonstrated that they could induce such antibodies. This leaves us requiring some or all of the HIV Env. However, early attempts in this direction led to the induction of antibodies that only neutralized the HIV strain used to make the Env vaccine (i.e., the immune response was too narrow.) In recent years we have learned how to broaden the immune response so that we are now able to neutralize a broad range of HIV variants.

At the IHV, we have achieved this using appropriately folded glycoprotein (gp)120 bound to the D1D2 region of CD4. Driven by Devico and Lewis, this approach employed an expression system for gp120 of an R5 strain of HIV, a linker sequence, and the CD4 binding region. The resulting complex has a fixed configuration, one we believe is in transition to bind with the coreceptor, CCR5. This appears to generate complex specific antibodies, which interfere with HIV–CCR5 binding. Since the vast majority of HIV strains infect CCR5 tropic variants (R5 ‘strains’), in theory it is possible to completely block HIV infection. In this context, our results showing cross-clad neutralization of primary HIV isolates are an exciting first step. Now we must learn how to increase the levels (titer) of these antibodies and to keep them sustained by testing various adjuvants.
Specific recommendations related to HIV vaccine development

- A science- and scientist-driven program
- An inspired leader or a few such leaders without ‘an axe to grind,’ (Professor Gus Nossal is one who comes to mind)
- Unencumbered and adequate funding for 6–8 years, and if unsuccessful the funding should move elsewhere (eg., the new National Institutes of Health Center for HIV/AIDS Vaccine Immunology program and Gates Enterprise program, but I believe it is a mistake to put competing scientists in charge of dispersing funds to their selected colleagues)
- Far more availability of primates, this problem is solvable by funding and policy change
- A research push to solve the problem of the lack of sustainability of responses to HIV proteins, especially the envelope. I believe this must be solved as HIV integrates its genes, thereby establishing infection straight away, leaving little or no time for recall

Overall recommendation

Firstly, several international institutes or centers of human virology should be created, and a base of government funding should be provided. A sufficient number of such centers could provide expertise on all viral classes. These centers would be responsible for assisting in the detection of new epidemics, providing the evidence for their cause and developing diagnostics, therapy (when needed), and preventive vaccines. At the onset of the HIV pandemic no such place with such responsibilities existed except perhaps the US Center for Disease Control and Prevention (CDC); however, the CDC cannot be expected to have detailed expertise on every class of virus and indeed did not with retroviruses. We might also expect that such centers be collaborative with at least a few centers in LEDCs. This would serve two functions: enabling more economically developed countries to help LEDCs, and help monitor emerging and re-emerging epidemics.

Secondly there should be a new, intense effort for a preventive HIV vaccine, involving both eastern and western hemispheres of the world, based on sound scientific principles, driven by scientists, and bringing together the best people to solve the obvious scientific problems that urgently need to be solved.

Affiliation

- Robert C Gallo, MD
  Director, Institute of Human Virology,
  University of Maryland Biotechnology Institute,
  Baltimore, MD, USA
  and,
  Professor, Department of Medicine and Department of
  Microbiology and Immunology, School of Medicine,
  University of Maryland Baltimore, School of Medicine,
  Baltimore, MD, USA
  Tel.: +1 410 706 8614;
  Fax: +1 410 706 1952;
  galo@umbi.umd.edu