An anniversary without celebration?

To the Editor:

A child born in Zambia today has an average life expectancy of 32.4 years and a one in three chance of being orphaned by 2010. This is the human face of the retrovirus human immunodeficiency virus (HIV), whose syndrome was described a quarter of a century ago. It has been 25 years since the US Centers for Disease Control reported the first cases of AIDS (http://www.cdc.gov/mmwr/preview/mmwrhtml/00001114.htm), which was subsequently published in the *Lancet*. The United Nations has called for annual global spending of at least US$10 billion on HIV and AIDS in developing countries, where more than 25 million people are now infected with HIV-1 and around 12,000 people are becoming infected every day. Although that seems like an enormous amount of money, it represents only 1.25% of global military spending (http://www.unaids.org/en/HIV_data/2006GlobalReport/default.asp).

The immunodeficiency syndrome caused by HIV-1 is a disease of poverty and inequality. For the most part this is true for the developing world; however, even in the West there are distinct communities with high rates of infection that correlate with poverty and lack of education. Infection is more likely for people who cannot attend school and learn about HIV-1; for people who cannot afford condoms; and if poverty encourages people into sex work. At present there is no preventive vaccine, and palliative drugs are still out of reach for most infected Africans.

There is, however, some cause for optimism. Even in the presence of poverty, the effects of HIV-1 can be controlled. An enormous amount of scientific endeavor has led to understanding of the viral life cycle and has enabled the development of acceptable 'cocktails' of highly effective antiretroviral drugs whose price is now dropping and that are becoming more accessible, thanks mainly to substantial philanthropic funding. Carefully designed educational programs have also had success. For example, it seems certain that wide social communication and education leading to a decrease in casual sex has been an important factor in the steep decrease in HIV-1 prevalence seen in Uganda. Advances in basic science have uncovered new targets for the development of new classes of HIV-1 therapeutic drugs that, rather than targeting specific viral enzymes, stop viral factors from interacting with host proteins and prevent entry of the virus into the cell. HIV-1 entry can be targeted during attachment, subsequent coreceptor interaction and fusion of the virion to the cell[1]. Therapies undergoing immediate development include integrase inhibitors and maturation inhibitors. After 10 years of research, two investigational, orally administered, HIV-1 integrase inhibitor drug candidates have reached clinical trials (http://www.retroconference.org/2006/Abstracts/27911.HTM; and http://www.retroconference.org/2006/Abstracts/27977.HTM). These drugs show potent activity in treatment-naive patients and may also be useful as 'salvage therapy' in highly drug-experienced patients. In addition, maturation of the virus can be inhibited by promising new maturation inhibitors such as PA-457. Other promising drug targets are endogenous innate antiviral factors present in the host cell: the restriction factors APOBEC3G and TRIM5α[1,2]. As HIV-1 actually targets those restriction factors, new therapeutic strategies must be developed to protect APOBEC3G and TRIM5α, thereby allowing them to interfere during the next round of HIV-1 reverse transcription.

The promise of immune-based therapy in conjunction with highly active antiretroviral therapy builds on observations made in HIV-1-infected patients who do not develop profound immunosuppression or develop AIDS—the so-called 'long-term nonprogressors'. Any imperfections in the management of HIV-1 disease with new drugs can be modified by the use of optimized immune-based therapy based on several modalities such as vaccines, cytokines and hormones with the potential to induce balanced immune responses that control viral rebound after the cessation of highly active antiretroviral therapy[2,3].

However, the 'Holy Grail' remains an effective prophylactic vaccine to halt the pandemic[2]. Here, perhaps strategies must be reconsidered and the focus redirected from vaccine induction of single entities such as T cells or antibodies or the innate response. Although some virological, immunological and genetic correlates with protection to infection have been suggested, work in nonhuman primates and in exposed seronegative people is far from conclusive. There is still insufficient knowledge of how to manipulate the immune system to induce responses of the desired quality, specificity and vigor. Perhaps the methods should now become more empirical, based on experience or observation rather than on imperfect theories. It must be recognized that prophylactic vaccines, which do not have the ability to induce sterilizing immunity at mucosal surfaces, may nevertheless rapidly limit the effect of early viral infection, leading to lower viral set points, thus substantially delaying the necessity for highly active antiretroviral therapy and the development of AIDS and also reducing viral transmission. Mathematical modeling suggests that a single 'log reduction' in the viral set point would reduce HIV-1-associated mortality for 20 years after vaccination and would have a profound effect on the pandemic[4]. Small pilot studies with high-risk HIV-1-negative people and with well characterized HIV-1-positive people using in-depth, well validated immunogenicity and new *in vitro* infectability assays should hasten the day when all people at risk of infection become 'exposed seronegatives' and all infected people become 'long-term nonprogressors'.

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