

Achieving an AIDS-free world: science and implementation



When AIDS was first recognised in 1981, health professionals were ill-equipped to address the emerging pandemic. Opportunistic infections were treated and supportive care was provided in accordance with the regional availability of health care; however, even after HIV was recognised as the causative agent of AIDS, truly effective therapy would not be available for more than a decade. Prevention methods were similarly insufficient, as messages about safe sex and condoms often proved weaker than human impulse.

But helplessness has now given way to hope. Basic and clinical scientific advances have yielded powerful therapeutic and preventive interventions. **By the end of 2012, 9.7 million HIV-infected individuals worldwide were receiving antiretroviral therapy (ART) and some 4.2 million deaths had been averted during the previous decade in low-income and middle-income countries.** These feats were accomplished through the joint efforts of the US President's Emergency Plan for AIDS Relief; the Global Fund to Fight AIDS, Tuberculosis and Malaria (among other multilateral and bilateral organisations); health practitioners in endemic countries; and community activists worldwide. Combination prevention methods have been applied with striking results.¹ For example, programmes aimed at the prevention of mother-to-child transmission have proven highly successful.² Voluntary male medical circumcision for the prevention of HIV acquisition shows considerable promise.³ Pre-exposure antiretroviral prophylaxis lowers the risk of infection, particularly if adherence to treatment is high.⁴ Treatment of an HIV-infected individual with ART benefits that person and substantially reduces the likelihood of transmitting HIV to his or her uninfected sexual partner;⁵ additionally, it can significantly reduce community-level HIV incidence.⁶ Research into the social and behavioural factors governing acceptance and uptake of these interventions will guide effective deployment. Thus, for the first time since AIDS was recognised, the goal to control and even end the HIV/AIDS pandemic has become part of the global health dialogue.⁷

Despite these accomplishments, there is much unfinished business. While expanding availability of existing interventions, new prevention and treatment methods must be developed. An HIV vaccine is a

crucial goal for prevention, and several strategies are being pursued. Although an effective vaccine has proven elusive **so far, a trial (RV144) undertaken in Thailand showed a modest 31% reduction in infection in people given the vaccine.**⁸ Traditionally, induction of neutralising antibodies against the targeted pathogen is the hallmark of a successful vaccine. So far, HIV vaccines, including the RV144 candidate, have been unable to generate broadly neutralising antibodies or cytotoxic T-cell responses capable of preventing HIV infection in human trials. In fact, natural infection with HIV elicits detectable broadly neutralising antibodies in about 20% of infected individuals—a process that takes 2 years or longer. On the basis of this finding, several groups of investigators have pursued an alternative B-cell vaccine strategy: broadly neutralising antibodies derived from infected individuals have been used to identify epitopes on the HIV envelope trimer that could be used as immunogens to induce broadly reactive antibodies.^{9–11} This B-cell pathway towards an HIV vaccine will likely need to be combined with an additional strategy involving the induction of T cells that enhance B-lymphocyte responses, produce anti-HIV cytokines, or provide cytolytic activity against HIV-infected cells. Finally, harnessing the innate immune response as part of a vaccine strategy is being actively pursued.

In addition to preventing HIV infection, prevention and treatment of disease progression in the 35.3 million HIV-infected people worldwide is an enormous challenge, which will require efficient delivery of existing therapies and the discovery of improved interventions. Where ART is available, improved implementation will need to address deficiencies in the care continuum—

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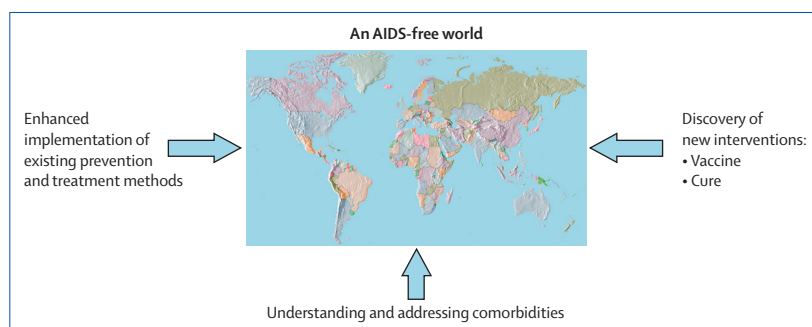


Figure: A three-pronged strategy to achieve an AIDS-free world, defined as very few new infections, and minimum morbidity and premature death from existing infections

the steps from diagnosis to retention in care and successful treatment. In some regions, discrimination, stigma, and legal barriers impede the realisation of optimum care. These impediments must be addressed. Furthermore, longer-acting therapies could improve adherence to pre-exposure prophylaxis and treatment. Understanding of co-infections such as tuberculosis and hepatitis B and C; chronic comorbidities including atherosclerosis, some cancers, liver and kidney disease, and neurocognitive problems; and the ageing process—is also crucial.

Finally, a cure for HIV infection is no longer beyond the imagination, and efforts are aimed at either eradication of HIV in infected individuals or indefinite control of viral replication in the absence of ART, referred to as a functional cure.¹² To realise the potential of these efforts, along with those directed at vaccine development and new treatments, translation of concepts into interventions will prove essential.

A range of highly effective HIV treatment and prevention methods is available, and others are under intensive investigation through basic and translational research. By combining effective implementation of existing methods with the discovery and eventual introduction of new interventions, achieving an AIDS-free world is no longer an idealistic aspiration—it is an achievable goal (figure).

Thinking about an AIDS end game

Scientific inquiry can be guided, and misguided, by past experience. When confronted with the emerging AIDS epidemic in the early 1980s, some scientists and clinicians thought of hepatitis B as a model for how to approach understanding and solving the challenges posed by the burgeoning number of immunodeficiency cases.¹ Hepatitis B was transmissible by blood and anogenital secretions, similar to the patterns of spread noted with the yet-to-be-defined pathogen. In the previous decade, researchers had identified hepatitis B's epidemiology, found that surface antibody titres correlated with protection, learned how to diagnose different stages of infection, and developed a highly protective vaccine. Thus, when Jerome Groopman and I sent a panel of blood specimens from asymptomatic men who have sex with men who were partners of patients with AIDS to Robert

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Gallo's laboratory in late 1983, and were subsequently informed that 21% tested positive for HTLV-III,² we were left with the quandary of what we would tell those who tested positive. At the time, our counselling messages included the hope that some of the men might have developed immunity and would not get sick. Subsequent follow-up showed a disease with a savage natural history, with most men who were infected with the renamed virus HIV getting sick and dying.

The grim reality of the first 15 years of the epidemic was replaced by new-found therapeutic optimism once partially effective drugs were tested in combination, and treatment responses could be monitored by recently developed nucleic acid amplification technology, creating a new regimen of highly active antiretroviral therapy (HAART) to suppress plasma viraemia.³ Excitement about

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