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).

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Thinking about an AIDS end game

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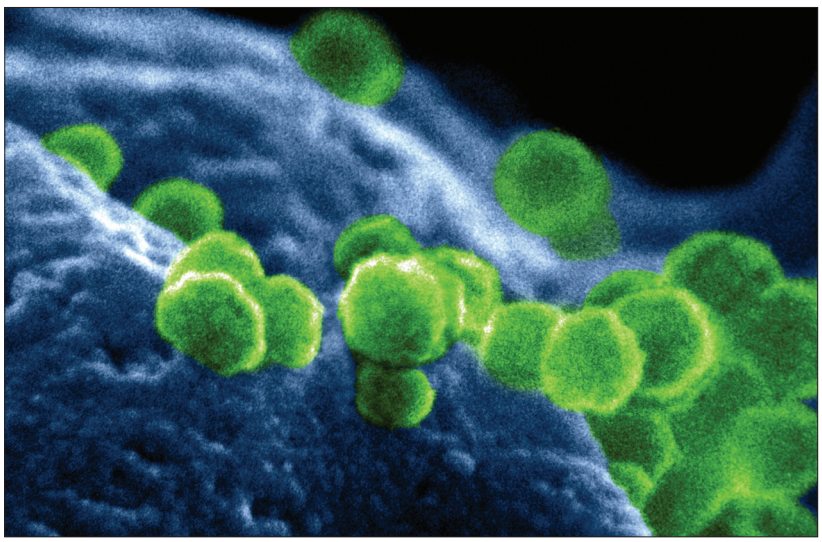
Scientific inquiry can be guided, and misguided, by past experience. When confronted with the emerging AIDS epidemic in the early 1980s, some scientists and clinicians thought of hepatitis B as a model for how to approach understanding and solving the challenges posed by the burgeoning number of immunodeficiency 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 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

the new developments was palpable at the International AIDS Conference in Vancouver, Canada in 1996, with clinicians describing a Lazarus syndrome, as severely ill patients were restored to a functional existence. The lay media took up the hubris, with cover stories in newspapers musing about how communities react when epidemics end.[4]

Unfortunately, the epidemic was far from over. The advent of effective treatment was paralleled by emerging epidemiological insights showing the gravity of the pandemic in southern Africa, with more than 20 million HIV-infected people living there by 2000. At the International AIDS Conference in Durban in 2000, attendees directly faced the stark reality that, despite improvements in management of HIV as a chronic disease, every third resident in that city was likely to die of AIDS because of insufficient access to expensive HAART regimens. Unexpectedly, the mobilisation of political will leading to the creation of the Global Fund and the US President's Emergency Plan for AIDS Relief (PEPFAR), coupled with dramatic decreases in the costs of treatment through scale-up by generic pharmaceutical manufacturers, resulted in treatment of almost 10 million people during the subsequent decade.[5] However, the global economic downturn has since raised questions of sustainability. Moreover, new concerns about the long-term effects of HIV-associated immunodeficiency, inflammation, and chronic HAART have arisen.

Nonetheless, since 2010, a new optimism has begun building, with studies showing the efficacy of chemoprophylaxis[6,7] and earlier initiation of treatment resulting in decreased HIV incidence,[8] suggesting that wider deployment of antiretroviral drugs could stop the epidemic. However, many of these best opportunities for epidemic control are expensive—eg, treating more people with HAART and selective chemoprophylaxis for key populations—and require improved health-care infrastructure in resource-constrained environments. There are also cultural challenges, such as scaling up male circumcision and addressing structural impediments—eg, punitive laws and insensitive health-care systems in settings where male homosexuality or injecting drug use continue to fuel local epidemics. Socially regressive policies (eg, threats of incarceration or violence) could translate into avoidance of testing, decreased engagement in care, and substandard services for those who present for treatment.[9] For countries with generalised epidemics, there is an ongoing need for political will to address the epidemic, but leaders might prioritise competing demands (ie, other communicable diseases, maternal and child health, and increasing burdens of chronic diseases) in view of limited budgets.



Dr Cecil H Fox/Science Photo Library

HIV particles budding from T lymphocyte

But the present optimism is not solely predicated on the expectation that wider deployment of HAART is all that is needed to end the epidemic. The surprising finding in a large Thai study that a combination of two vaccines decreased HIV incidence by 31%,[10] and the description of several adults[11,12] and one baby[13] who have been functionally cured of HIV (ie, no evidence of active viral replication despite months of not receiving HAART) might suggest how to create safe and effective preventive vaccines and HIV cures. Despite the promise of treatment as prevention and chemoprophylaxis in the short term, and vaccines and cures in the longer term, immediate attention to the social, legal, and regulatory environment globally are needed to constrain, and ultimately end, the epidemic. HIV is a wily beast, but recent insights seem to offer tangible clues about how to begin to consign the AIDS pandemic to the dustbin of history.

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Challenges in clinical trial design for HIV-1 cure research

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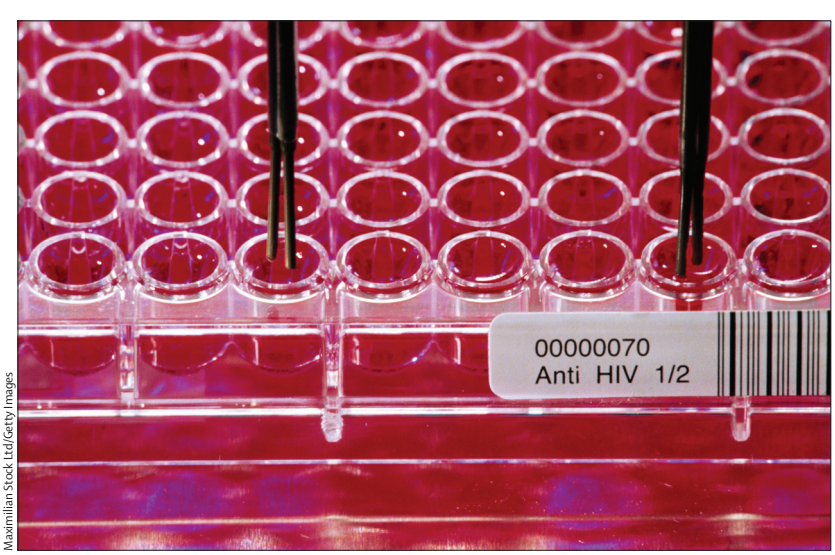
The advent of highly effective, convenient, and well tolerated antiretroviral therapy (ART) for HIV-1 infection has substantially reduced AIDS-related morbidity and mortality. ART does not, however, eliminate HIV-1, which persists as a latent infection in resting memory CD4+ T cells. Treatment must therefore be continued throughout life. Therapeutic approaches that lead to durable drug-free remission or total eradication (cure) of HIV-1 would remove the burdens, costs, toxic effects, and stigma associated with long-term ART, as well as the social costs and risks from development of drug-resistant virus strains. Examples of apparent cure in a recipient of an allogeneic stem-cell transplant from a CCR5-negative donor[1] and in an infected infant who received ART within 30 h of birth[2] have stimulated renewed interest in research towards a cure, which was previously thought to be unattainable.



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The approaches being investigated include drugs to reactivate latent HIV-1 from resting T cells, immune-based therapies to boost HIV-1-specific immune responses, and transplantation of genetically modified CD4+ T cells or autologous stem cells. Several of these approaches are in early-stage clinical trials.[3–5] These trials raise both scientific and ethical challenges.

Scientifically, the design of classic phase 1 studies seeking to establish the pharmacokinetics and preliminary safety of novel therapeutic agents in an HIV-1-infected population is straightforward. But the scientific design of phase 2 proof-of-concept studies is more complex. Should these studies aim to show a biological effect on the proximate target (eg, reactivation of HIV-1 transcription or boosting of HIV-1-specific immune responses)? Or should they show a significant reduction in the viral reservoir, in which case what measure of the reservoir, assayed in which tissue compartment(s), should serve as the primary endpoint? Consensus seems to be emerging that the ultimate test of an intervention targeting the HIV-1 reservoir is an analytical treatment interruption.[6] Specifically, the absence of virological rebound after cessation of ART, although not proof of absence of any residual virus, is generally regarded as an acceptable endpoint to show remission (or so-called functional cure) of HIV-1 infection. However, treatment