HIV-AIDS: much accomplished, much to do

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As a result of decades of research-driven breakthroughs in basic and clinical science and recent advances in the broad-scale implementation of interventions for the prevention and treatment of infection with HIV, a turning point has been reached in the global HIV-AIDS pandemic. To end the pandemic and achieve the goal of an AIDS-free generation, researchers and clinicians must follow the dual pathway of optimizing the implementation of existing prevention and treatment interventions and discovering with basic and clinical research new and effective tools in both of these arenas.

The notion that global control of HIV infection and AIDS (HIV-AIDS) may be feasible has gradually evolved over the past 10 years and has been forcefully articulated by many commentators over the past year. Although the world is still in the midst of a global pandemic, with 35.3 million people living with HIV infection and 2.3 million newly HIV-infected people and 1.6 million AIDS-related deaths in 2012 alone, there is reason for optimism[1]. Substantial breakthroughs in the understanding of HIV transmission and advances in the science of the treatment and prevention of infection with HIV have provided strong evidence that a dramatic alteration in the course of the HIV-AIDS pandemic is possible, with movement toward an AIDS-free generation, one in which new HIV infections and deaths from AIDS are rare. While it is clearly too early to declare victory, future success will depend on optimizing and implementing the tools available today for the prevention and treatment of infection with HIV while simultaneously addressing important research questions (**Fig. 1**). This dual path promises movement toward the long-term goal of control and eventual elimination of HIV-AIDS as an important global health threat.

Implementing antiretroviral therapy

The development of antiretroviral therapy (ART) for HIV disease is unquestionably one of the most important biomedical accomplishments of the twentieth century. ART has converted an almost uniformly fatal disease into a chronic, manageable condition. ART substantially diminishes HIV-related morbidity and can extend life expectancy to a nearly normal age regardless of geographic setting, when patients can adhere to daily medication regimens[2].

An estimated 9.7 million HIV-infected people in low- and middle-income countries were receiving ART at the end of 2012, an increase of greater than 30-fold since 2002 (ref. 3). Such substantial expansion in the treatment of HIV-infected people in low- and middle-income countries averted an estimated 4.2 million deaths during that period. Despite those positive results, about 16 million people globally who are eligible for ART under current guidelines of the World Health Organization do not have access to these medications. Thus, ramping up the delivery of ART and other healthcare services for HIV-infected people is an urgent priority. The evaluation of ART-implementation programs must be based not just on the number of people receiving therapy but also on the proportion of patients treated successfully—that is, who remain in care and maintain an undetectable viral load. The steps involved in identifying HIV-infected people, engaging them in care and retaining them on successful ART is often called the 'care cascade'[4]; unfortunately, the rate of retention from step to step in the cascade has been unsatisfactory (**Fig. 2**). Implementation initiatives in the USA and internationally have been undertaken to explore new approaches to address such deficiencies. For example, in the USA, the TLC-Plus study (HPTN 065 of the HIV Prevention Trials Network) is examining the feasibility of an approach of enhanced testing, linkage to care and initiation of treatment in communities at greater-than-average risk of HIV infection[5]. The PopART study (HPTN 071 of the HIV Prevention Trials Network), a randomized three-arm trial in 21 communities involving 1.2 million people in South Africa and Zambia, is comparing the standard of care to two versions of enhanced delivery of treatment and prevention services[6]. The investigators of the PopART study will assess whether the proportion of HIV-infected people in a population who receive ART is increased by enhanced services and if this increased level of service delivery has an effect on HIV incidence in these communities. Other studies under way are looking at approaches to expand the capacity of healthcare systems through 'task shifting' of certain clinical responsibilities from physicians to nurses and other trained healthcare workers and through the use of community engagement to enhance treatment adherence.

Optimizing ART as an intervention

Despite the extraordinary success of ART programs, further research innovations could vastly improve the effectiveness of these therapies. One important goal is the development of improved tools for inexpensive and accurate point-of-care measurements of $CD4^+$ T cell counts and viral loads to improve patient management. In addition, new and improved

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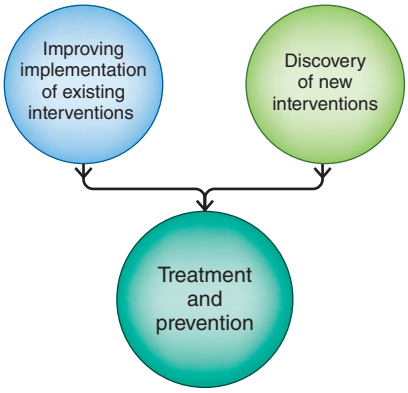

Figure 1 The dual pathway to controlling and ultimately ending the AIDS pandemic.

antiretroviral drugs must be developed with an eye toward greater potency, less toxicity and fewer adverse interactions with other drugs used for the comorbidities commonly observed among HIV-infected people, such as tuberculosis. An additional challenge is the development of antiretroviral agents with a longer duration of action that might be given as a monthly dose or even less frequently. Such drugs could alleviate some of the difficulties in achieving patient adherence to both treatment and prophylactic antiretroviral regimens. Finally social, behavioral and operational research are essential to the development of new ways to increase the number of people being tested for HIV and improve linkage to and retention in care.

Optimizing treatment as prevention

The treatment of HIV-infected people has recently assumed an important place among the combination prevention modalities that are central to the control and ultimately the end of the HIV-AIDS pandemic. The promise of 'treatment as prevention' (TasP) was demonstrated by the results of the groundbreaking HPTN 052 clinical trial (of the HIV Prevention Trials Network)[7]. This study enrolled 1,763 HIV-serodiscordant couples in nine countries and showed a 96% reduction in HIV transmission from the infected partner to the uninfected partner for couples in which the HIV-infected partner with a $CD4^+$ T cell count ranging from 350–550 cells per microliter of blood when ART was started and sustained, relative to that of couples in which the HIV-infected partner had a $CD4^+$ T cell count of 250 cells per microliter or less. This study clearly demonstrated that treatment can also be a highly effective prevention tool, and additional evidence for the effectiveness of TasP is accumulating. For example, a study in KwaZulu-Natal, South Africa, demonstrated a 38% reduction in the risk of HIV acquisition in communities with ART coverage between 30% and 40% compared with that in communities with less than 10% coverage, between 2004 and 2011 (ref. 8).

In the USA, the number of new HIV infections has remained relatively constant over several years at an unacceptable level of approximately 50,000 per year[9]. For TasP to have a clear benefit in reducing the incidence of infection with HIV, it will be essential to increase the proportion of HIV-infected people who are successfully treated. In this context, the most important step in the care cascade is testing for HIV, the entry point for all prevention and treatment services. In the USA, it is estimated that ~50% of HIV transmissions are from the 20% of persons who are infected but unaware of their infection status[10]. Other factors that influence the patterns of new infections in the USA are race, sexual orientation and age. African Americans are nearly nine times more likely to become infected with HIV than are whites. Among all incident HIV infections in the USA in 2010, 62% occurred among men who have sex with men and 26% occurred among young people 13–24 years of age. Nearly 75% of all HIV-infected youth are men who have sex with men (with African Americans disproportionately affected), and nearly 60% of HIV-infected young people are unaware of their infection status[11]. Given such daunting statistics, the US Preventive Services Task Force has published a strong recommendation that testing for HIV infection become part of routine health screening for all people between 15 and 64 years of age[12]. This recommendation promises to help remove barriers to reimbursement for testing and reinforces previous guidance from the US Centers for Disease Control and Prevention on the need for widespread, routine testing for HIV infection and counseling.

Implementing combination prevention

As noted, reaching those who are unaware of their HIV status is a critical step in preventing the further spread of HIV infections. For those who are at risk for infection with HIV, one practical recommendation is that they undergo testing at least twice a year, as is the continued distribution of condoms and clean syringes to at-risk people. Studies of preexposure prophylaxis (PrEP) and antiretroviral drugs have demonstrated that once-daily treatment with Truvada (emtricitabine and tenofovir disoproxil fumarate) can protect men and women from acquiring HIV[13]. However, efficacy in PrEP clinical trials has been seen only in populations with substantial adherence[14]. In this context, PrEP will probably be cost effective as a public health intervention only at levels of high efficacy and in high-incidence settings[15]. Given that the efficacy of PrEP is dependent on adherence, research efforts are critical for the identification and implementation of better means of fostering adherence among people undergoing PrEP as well as those being treated with ART.

Perhaps the most effective and durable HIV-prevention tool currently available globally, particularly in the developing world, is voluntary medical male circumcision (VMMC). In one large cohort, circumcision was >70% effective at preventing infection over nearly 4 years in the Rakai district of Uganda[16], where a substantial population-level impact of VMMC has also been observed[17]. As with other bio-

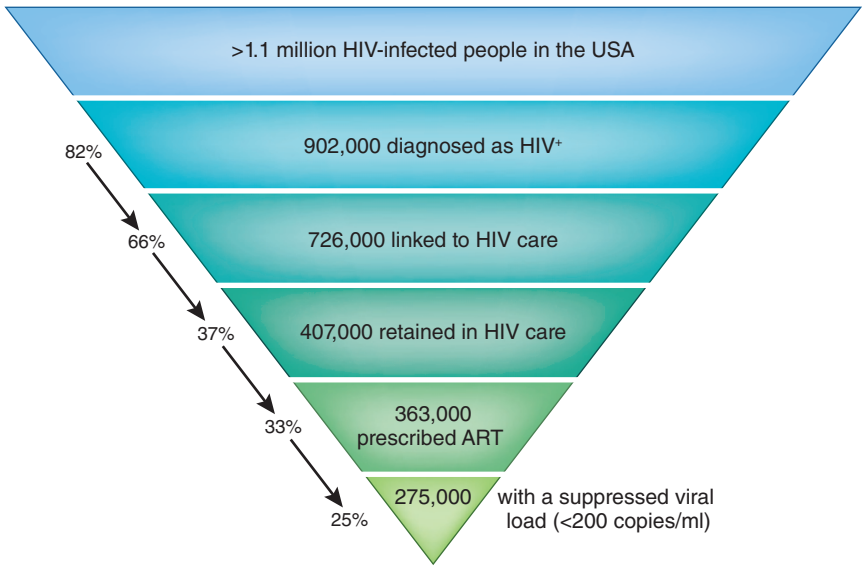

Figure 2 Percentage of HIV-infected people engaged in selected stages of the continuum of HIV care (the 'care cascade') in the USA in 2010 (ref. 27).

medically based HIV-prevention strategies, behavioral and social science research promises to help elucidate the motivations of men seeking VMMC. Such information can then help in efforts to create demand for this highly effective prevention strategy. In addition, several high-prevalence countries with low rates of VMMC have recently begun pilot programs for infant MMC with the goal of creating a generation of men less susceptible to infection with HIV.

Discovering a vaccine against HIV

Research advances that lead to new interventions will be critical for strengthening the likelihood of controlling (and hopefully ending) the HIV-AIDS pandemic. Paramount among such interventions is a safe, effective and durable vaccine to protect against the acquisition of HIV. However, the challenges that confront the development of such a vaccine are formidable, as HIV is unique compared with other viruses for which effective vaccines have been developed (such as smallpox, measles and polio, among others)[18]. While there are variable degrees of morbidity and mortality associated with those other viruses, the vast majority of infected people recover, eliminate the virus from the body and are protected for life against reinfection with the same virus. This has provided proof of the concept that the human immune system is indeed capable of mounting a protective immune response against those viruses and thus has provided a pathway to the development of vaccines. HIV is very different in that infection (with very rare exceptions) is relentlessly progressive, the immune system does not eliminate the virus from body and superinfection with HIV frequently occurs. Although broadly reactive neutralizing antibodies, the 'gold standard' of protection against most other viruses, have been identified in HIV-infected people, these develop in only approximately 20% of such people, they appear late (up to 2 or more years after infection) and they do not control viremia or protect against superinfection with other isolates of HIV.

Despite those challenges, some progress has been made toward the development of a preventive vaccine against HIV. The RV144 trial provided the first sign of efficacy (31%) ever achieved over 26 years of HIV-vaccine trials, and the follow-up and analysis of correlates of risk with the candidate vaccine used in this trial has identified possible immune responses that should be triggered or avoided by subsequent vaccines[19,20]. Moving forward, the prime-boost strategy used in the original RV144 trial will be repeated with modifications aimed at increased efficacy and extended durability of the response. In addition, a range of potent, broadly neutralizing monoclonal antibodies to at least four different epitopes on the HIV envelope protein have been identified[21] (**Fig. 3**). Singly and in combination, those antibodies have activity able to neutralize nearly all the available strains circulating around the globe today. The long-term, formidable challenge is to fashion those neutralizing epitopes on the HIV envelope as immunogens in a manner that will elicit broadly neutralizing antibodies that provide protection against the acquisition of HIV.

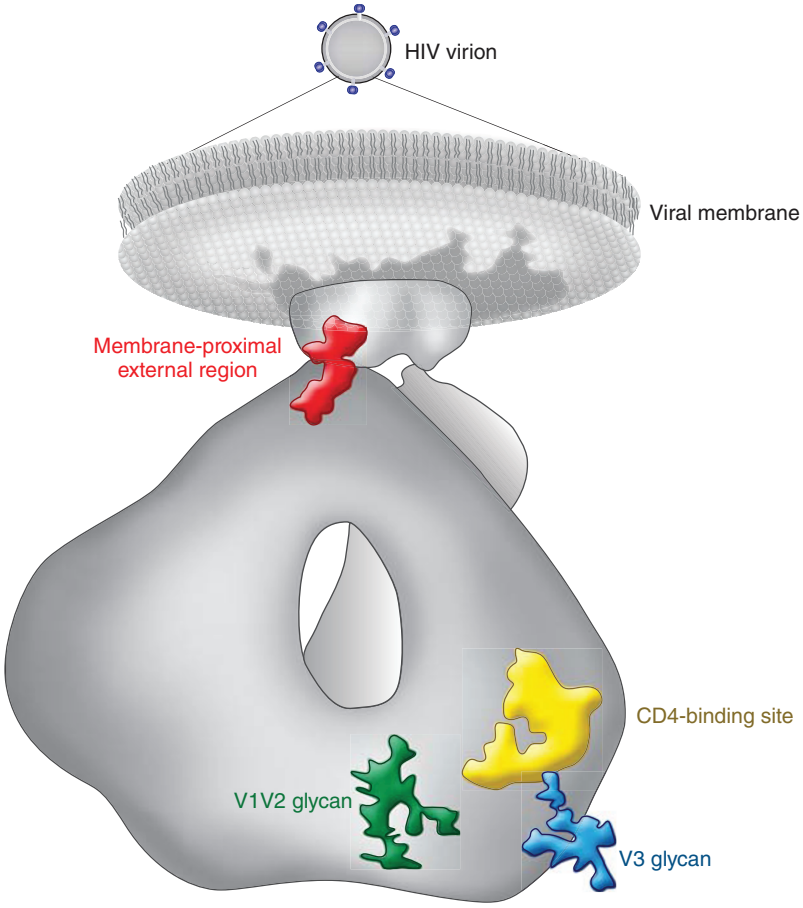

Figure 3 HIV epitopes targeted by broadly neutralizing human antibodies. The colored areas indicate four regions of the HIV envelope spike that are the targets of antibodies that have proven able to neutralize a wide array of virus strains (refs. 18,21).

Discovering a cure for HIV infection

Although the HIV-AIDS pandemic can theoretically be ended without people being cured of their infection (historically, the control of pandemics has not required a cure), the development of a cure remains an important aspirational goal in the HIV-research agenda. Two strategies emerge when the concept of a cure is considered: an eradication cure, in which HIV is no longer present in the body and hence therapy is obviously not required, and a functional cure, in which the virus is still present but is nonetheless controlled long term in the absence of standard therapy[22]. Research suggests that latently infected, resting $CD4^+$ T cells carrying replication-competent, integrated HIV provirus serve as an important component of the 'HIV reservoir' in HIV-infected people; these cells are logical targets to pursue in therapeutics-discovery research[23]. Latently infected, resting $CD4^+$ T cells have been shown to persist in ART-treated patients who have achieved undetectable concentrations of virus in the plasma, and these cells seem to be at least one of the sources of virus that rebounds in patients who discontinue ART[24]. Evidence suggests that the timing of initiation of therapy in an HIV-infected people may have a role in the establishment (or not) of a recalcitrant viral reservoir and thus in the likelihood of a functional cure. The apparent cure of an HIV-infected infant by early initiation of ART suggests that therapy, if initiated early enough in HIV infection, perhaps can preempt formation of the viral reservoir[25]. Furthermore, a

series of patients in France has been identified who started treatment early and later discontinued ART without viral rebound for several years after discontinuation of therapy[26]. Since very early therapeutic intervention is not always feasible, other approaches are being pursued in the quest for a cure, including activating and eliminating latently infected cells, immunotoxic therapy directed at the HIV reservoir, gene therapy and stem-cell transplantation. The quest for a cure is still in the early stages of discovery, but interest in this area remains keen.

Concluding remarks

Much has been accomplished over three decades of HIV research, which has led to the development and implementation of effective interventions for the treatment and prevention of HIV infection. Such accomplishments have made the control and (hopefully) the end of the HIV-AIDS pandemic a feasible goal. However, there is still much to do, both in the arena of the implementation of existing interventions and in the scientific discovery of new and improved interventions, before that goal is actually realized. Now is not the time for a 'victory lap' but the time for racing ahead.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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