times intense. Within Maryland, hospitals, payers, physician organizations, consumer groups, and others contributed ideas — and eventually their support — in dozens of meetings and through public commenting. Maryland health officials met with CMS representatives for more than a year, sharing ideas on how the all-payer system could be aligned with the goals that CMS has set for the country in terms of lower cost and improved outcomes in health care. Although CMS has a long history of working with states through the Medicaid program and already collaborates with states on multiple innovative reforms, this model is unique in its all-payer approach. The two parties were able to reach agreement because they concentrated on areas of mutual benefit and shared goals.

CMS and Maryland have a strong shared interest in the success of this model. If it proves successful, Marylanders, including both Medicare and Medicaid beneficiaries, will benefit from improved health at lower cost, and the experience will offer an important proof of concept for other states. If it's unsuccessful, Maryland will transition to the national Medicare hospital-payment system over the course of 2 years — abandoning an approach to hospital financing that has served the state well for more than three decades.

The new model addresses two challenges in health care in ways that should provoke thoughtful examination. First, a critical challenge for national delivery-system reform is to align payment incentives across multiple payers. Maryland's all-payer system can be a laboratory for rapid innovation in delivery-system reform, because the state can bring all payers to the table in order to create consistent and aligned incentives for providers. Second, implementing this model throughout a state with more than 5.8 million people living in urban, suburban, and rural settings will test these reforms in many different environments.

With this new foundation, we believe that Maryland has taken an important step forward. Its model heralds a new opportunity to emphasize partnerships between federal and state governments and between the public and private sectors to support delivery-system reform. CMS will continue to seek other state partners that want to transform care delivery by focusing on care improvement, better health, and a more efficient health system.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Centers for Medicare and Medicaid Services (R.R., A.P., K.M., J.D.B., P.H.C.), the Maryland Health Services Cost Review Commission (J.M.C.), Johns Hopkins Medicine (J.M.C.), and the Maryland Department of Health and Mental Hygiene (J.M.S.) — all in Baltimore; Brigham and Women's Hospital, Boston (R.R.); and Cincinnati Children's Hospital Medical Center, Cincinnati (P.H.C.).

This article was published on January 10, 2014, at NEJM.org.

1. Murray R. Setting hospital rates to control costs and boost quality: the Maryland experience. Health Aff (Millwood) 2009;28:1395-405.
2. Porter E. Lessons in Maryland for costs at hospitals. New York Times. August 28, 2013: B1.

DOI: 10.1056/NEJMp1314868
Copyright © 2014 Massachusetts Medical Society.

Ending AIDS — Is an HIV Vaccine Necessary?

Anthony S. Fauci, M.D., and Hilary D. Marston, M.D., M.P.H.

In the past decade, according to the 2013 Global Report of the Joint United Nations Program on HIV/AIDS (UNAIDS), the numbers of AIDS-related deaths and new human immunodeficiency virus (HIV) infections have fallen by about one third from their peaks — accomplishments made possible by the accelerated implementation of effective prevention and treatment tools.

Of particular note, the scale-up of antiretroviral therapy (ART) averted 5.4 million deaths in low- and middle-income countries between 1995 and 2012. HIV prevention efforts have expanded from a narrow agenda of providing condoms and clean needles to use of a comprehensive toolkit of preventive interventions that have had a profoundly positive effect on the pandemic. For example, improved approaches to the prevention of mother-to-child transmission have averted the deaths of more than 1 million children worldwide. The rate of male acquisition of HIV can be diminished by two thirds through voluntary medical male circumcision. Preexposure prophylaxis with antiretroviral medication, when adhered to, significantly reduces the risk of HIV infection. Finally,

The New England Journal of Medicine
Downloaded from nejm.org at NIH on February 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

treating infected persons with combination ART dramatically reduces their likelihood of transmitting HIV to an uninfected partner. By combining these methods and deploying them strategically, we will most likely continue to reduce HIV incidence.

The reduction in incidence has occurred without a vaccine, raising the question of whether a vaccine is necessary to end the pandemic. In considering this question, it is important to appreciate that substantial barriers to nonvaccine HIV prevention will hinder public health efforts. The most challenging of these relate to human behavior. Prevention of HIV infection necessitates individual action, usually requiring people to continually make positive health choices. Social context affects individual behavior and often negatively influences the effectiveness of biomedically based preventive interventions. For example, cultural factors have probably slowed adoption of male circumcision — less than one quarter of the targeted 20 million African men have undergone the procedure. Legal factors also slow progress, since homosexuality remains illegal in more than 70 countries. Treatment as prevention is similarly complex, given that only one quarter of HIV-infected people in the United States have successfully navigated the care continuum to achieve an undetectable viral load with ART. Thus, health interventions are failing 75% of infected persons in this country and larger percentages in other countries — a situation that cannot be allowed to continue.

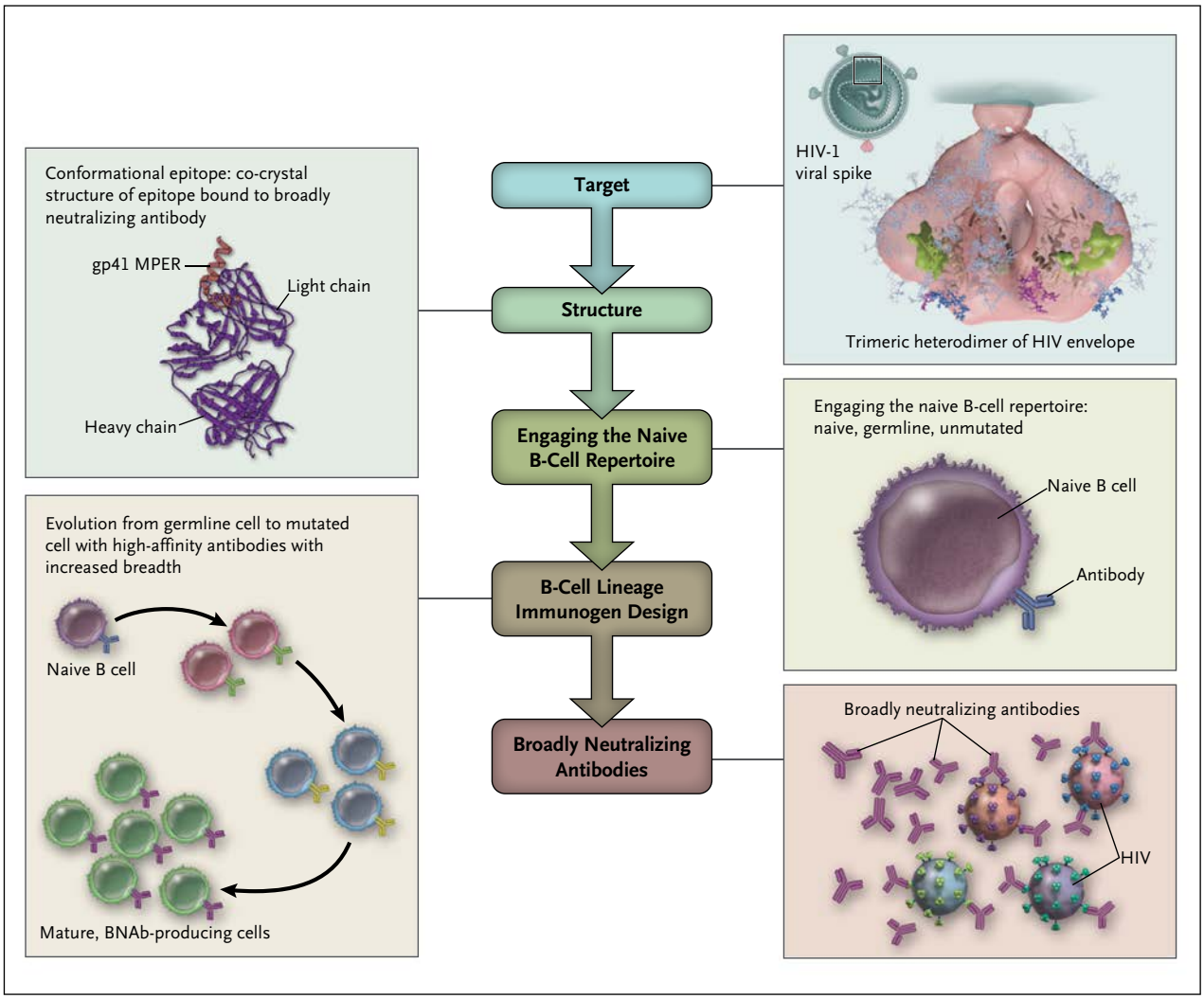
Even if HIV prevention efforts were optimally implemented to achieve a new infection rate of near zero, recidivism could threaten this success. Historically, for instance, health officials and funders often responded to impressive reductions in malaria infections by cutting funding and attention paid to control programs. After the island of Zanzibar, for example, used indoor residual spraying to reduce the prevalence of malaria parasites from 76% to less than 5% between 1957 and 1967, victory was declared prematurely, the program was defunded, and the parasite population resurged. Success carries the same threat for HIV programs, particularly in the absence of a sustainable solution like a vaccine. Therefore, although it might be possible to control and even end the HIV–AIDS pandemic using existing interventions, in order to reach this goal more quickly and to sustain the success, we believe that a safe and at least moderately effective HIV vaccine is essential.

Even if HIV prevention efforts were optimally implemented to achieve a new infection rate of near zero, recidivism could threaten this success.

However, the road to an HIV vaccine has not been and will not be an easy one. Despite global commitment, the first decades of scientific effort brought disappointment. In small trials in humans, beginning in 1987, vaccines failed to induce an immune response that would predict protection. Two larger trials aimed at inducing protective antibodies failed as well. Subsequently, investigators turned their attention to T-cell vaccines, hoping to induce CD8+ lymphocytes to control viral replication after infection. Between 2007 and 2013, three major T-cell vaccine trials, including the recently published HVTN 505 trial,[1] failed to demonstrate efficacy. In 2012, an unexpected success occurred in a vaccine trial (RV 144) conducted in Thailand. The RV-144 vaccine regimen had modest efficacy of 31%, most likely because it produced nonneutralizing or weakly neutralizing antibodies.[2] In this regard, the gold standard for most successful viral vaccines is the induction of broadly neutralizing antibodies (BNAbs) that protect against multiple pathogenic strains.

Generating BNAbs against HIV, however, presents a major challenge. Unlike most other viruses, HIV elicits such antibodies in a minority of infected persons and only after several years of infection. Furthermore, by the time these antibodies are produced, HIV's genetic material has long since been integrated into the chromosomes of an infected person's cells, establishing recalcitrant, latent reservoirs of virus. Thus, intense investigations are under way to elucidate how these BNAbs develop and the characteristics of the virus that drive their production. For example, researchers have examined serial blood samples from a newly infected patient and documented the coevolution of the virus and antibodies.[3] The analysis demon-

The New England Journal of Medicine
Downloaded from nejm.org at NIH on February 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.



The B-Cell Pathway to an HIV Vaccine.

The target immunogens to which antibodies will bind are regions of the trimeric heterodimer of the HIV envelope. The conformation of the envelope epitope — in this case, the gp41 membrane-proximal external region (MPER) as it is bound to the broadly neutralizing antibody (BNAb) — represents the structure of the target. The naive B-cell repertoire, residing in bone marrow and secondary lymphoid tissues, must be engaged by the vaccine. That engagement would occur using a process called B-cell lineage immunogen design, ultimately yielding broadly neutralizing antibodies in the vaccinee. (Pathway elaborated by Kwong et al. Broadly neutralizing antibodies and the search for an HIV-1 vaccine: the end of the beginning. Nat Rev Immunol 2013;13:693-701.)

strated the evasive changes that HIV undergoes to escape the host immune response and the ensuing hypermutation of B-cell genes, which produces antibodies that bind targets on the HIV envelope with progressively greater affinity. The work defined an essential paradox in the interaction between HIV and its human host: as the virus mutates to evade HIV-specific antibodies, it ultimately stimulates production of antibodies with much greater breadth — that is, BNAbs. The iterative design of sequential immunogens that mimic the mutational evolution of the virus during natural infection — immunogens that could be used as a constituent of a vaccine — represents a critical challenge for HIV science.

A pathway to that end has now been proposed (see diagram). The targets to which these antibodies bind have been delineated: regions of the trimeric heterodimer of the HIV envelope. The conformational structure of the specific envelope epitope

The New England Journal of Medicine
Downloaded from nejm.org at NIH on February 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.

bound to the BNAb has been characterized using x-ray crystallography and cryo-electron microscopy.[4] Next, the naive B-cell repertoire residing in bone marrow and secondary lymphoid tissue must be engaged. That engagement will probably need to be accomplished through a process referred to as B-cell lineage immunogen design. Specifically, one or more clonally related BNAbs must be isolated and, using next-generation sequencing, an antibody lineage constructed through inference that links the mutated BNAb-producing cell to its naive, germline ancestor. Next, recombinant antibody technology would express members of that BNAb lineage in order to select HIV-envelope constructs that optimally bind them. Finally, those envelope constructs would be used as immunogens in a prime–boost fashion to engage the naive B cell in vivo and iteratively stimulate B-cell "evolution" until BNAb-producing cells are elicited.

Just as B-cell vaccine science is advancing, so, too, are T-cell approaches. These models could enhance B-cell responses by providing broad help to the B cells and eliciting immune-stimulating cytokines. Furthermore, it has been discovered that levels of T-follicular cells in the blood of HIV-infected persons correlate with the creation of BNAbs, probably because these cells enhance hypermutation of B-cell genes. In addition, in experiments using a virus related to HIV, the simian immunodeficiency virus (SIV), a vaccine constructed by inserting SIV genes into a cytomegalovirus vector induced potent CD8+ T-cell responses that controlled SIV replication and resulted in viral clearance in roughly half the nonhuman primates studied.[5]

These advances demonstrate the dynamic nature of HIV vaccine discovery and the promise of impending breakthroughs. Therefore, while continuing to scale up the delivery of ART and deploying nonvaccine prevention methods, the HIV prevention community should hold fast to its commitment to vaccine science. Ultimately, we believe, the only guarantee of a sustained end of the AIDS pandemic lies in a combination of nonvaccine prevention methods and the development and deployment of a safe and sufficiently effective HIV vaccine.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Office of the Director, National Institute of Allergy and Infectious Diseases, Bethesda, MD.

1. Hammer SM, Sobieszczyk ME, Janes H, et al. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med 2013;369:2083-92.
2. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med 2009;361:2209-20.
3. Liao HX, Lynch R, Zhou T, et al. Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. Nature 2013;496:469-76.
4. Cohen J. HIV surface proteins finally caught going au naturel. Science 2013;342:546-7.
5. Hansen SG, Piatak M Jr, Ventura AB, et al. Immune clearance of highly pathogenic SIV infection. Nature 2013;502:100-4.

DOI: 10.1056/NEJMp1313771
Copyright © 2014 Massachusetts Medical Society.

Transforming Lives, Enhancing Communities — Innovations in Global Mental Health

Vikram Patel, F.Med.Sci., and Shekhar Saxena, M.D.

Mr. K. spent nearly a year and a half bound to a log in his home village in northeastern Ghana. His crime? He had a psychotic disorder, and his family could not afford the $17 for antipsychotic medication that would have stabilized his condition. Instead, they consulted a traditional healer, who pinned Mr. K.'s right leg inside a hole in the log and warned his family not to free him lest the wrath of the gods be visited on them.

At least 10% of the world's population is affected by one of a wide range of mental disorders; as many as 700 million people had a mental disorder in 2010. The 2010 Global Burden of Disease Study showed that mental disorders account for 7.4% of the world's burden of health conditions in terms of disability-adjusted life-years[1] and nearly a quarter of all years lived with disability — more than cardiovascular diseases or cancer (see pie chart for the contribution of different mental disorders to this burden). Incredibly, these numbers probably underestimate the true burden, since they do not include the effects of mental disorders on other high-priority health conditions — for example, the effect of maternal depression

The New England Journal of Medicine
Downloaded from nejm.org at NIH on February 10, 2014. For personal use only. No other uses without permission.
Copyright © 2014 Massachusetts Medical Society. All rights reserved.