

comes and making quality more transparent to the public, providers, and policymakers. Making greater use of e-health tools — especially electronic medical records — is also high on the political agenda.

Overall, the Swiss health care system is costly and has room for improvement, particularly in terms of accountability for the quality, appropriateness, and cost of health care services. Yet by and large, it has served the Swiss population very well. The combination of “liberalism,” in the

classic European sense, and solidarity — of respecting choice, autonomy, and individual responsibility while not letting anyone in need of health care suffer or die for lack of financial resources — seems to work, at least for Switzerland.

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

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Ending the HIV–AIDS Pandemic — Follow the Science

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

Related article, p. 2237

In July 1996, researchers, policymakers, and activists involved in the fight against HIV–AIDS met in Vancouver, Canada, for the 11th International Conference on AIDS. During that historic meeting, practitioners and patients heard evidence regarding a powerful weapon to stop the relentless onslaught of the human immunodeficiency virus (HIV): combination antiretroviral therapy (ART), with a protease inhibitor as the centerpiece of the regimen. In the nearly 20 years since that watershed meeting, the early promise of durable effects from combination therapy has been realized for many patients: between 2000 and 2014, the rollout of ART saved an estimated 7.8 million lives worldwide.

Despite this success, the timing of ART initiation has remained the subject of intense debate. As with any therapy, clinicians and their patients weighed ART's ben-

efits against its risks, and the results of that calculus seemed to depend on the patient's stage of illness. Specifically, evidence supporting treatment later in the course of HIV infection, when the CD4+ T-cell count fell below a certain critical level, seemed far stronger than that supporting early treatment (particularly given the toxic effects associated with the first approved antiretroviral drugs). Today, a series of well-designed efficacy studies conducted over a period of more than a decade has fundamentally changed this discussion.

In addition, researchers continue to accrue promising data on the concept of using ART for HIV prevention in HIV-negative persons — preexposure prophylaxis (PrEP). Findings from the landmark Intervention Préventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study, now reported in the *Journal* (pages 2237–2246), demonstrate the safe-

ty and efficacy of “on-demand” PrEP for men who have sex with men and transgender women (persons who are born male but identify as female), who are at high risk for HIV infection. In this study, persons who took PrEP in an event-driven manner around the time of sexual activity were 86% less likely to acquire HIV infection than those taking placebo.

Taken together, these studies have shown definitively that the benefits of prompt initiation of ART — regardless of the CD4+ T-cell count — outweigh the risks, for both the infected person and uninfected sexual partners and that PrEP can be implemented in a way that is both acceptable to patients and safe and effective in blocking HIV transmission.

With regard to ART initiation, three critical questions were asked and answered by a “trifecta” of large international randomized, controlled trials over the course

of a decade. First, practitioners, including ourselves, and patients had worried about the risks of toxic effects of long-term ART, particularly on the cardiovascular system, and wondered whether long-term treatment was worse than the virus itself for some patients. Moreover, practical concerns about the cost and inconvenience of ART loomed large, as did the related risks of poor adherence and the potential emergence of resistant virus.

The **first** of the relevant seminal studies, the Strategies for Management of Antiretroviral Therapy (SMART) study published in 2006,¹ was designed to answer the clinical question about toxic effects. Researchers randomly assigned 5472 HIV-infected participants in 33 countries with initial CD4+ counts above 350 cells per cubic millimeter to receive continuous therapy (viral-suppression group) or episodic therapy (drug-conservation group); treatment was initiated when CD4+ T-cell counts fell below 250 per cubic millimeter and stopped when counts rose above 350 per cubic millimeter. The study's primary analysis found a 160% higher risk of death, opportunistic illness, or both in the drug-conservation group ($P < 0.001$). Moreover, the risk of grade 4 toxic drug effects did not differ significantly between groups, and cardiovascular events were actually more common in the drug-conservation group. The SMART study thus demonstrated that the benefits of therapy far outweighed the risks of toxic effects.¹ The virus was worse than the drugs.

A **second critical** question was whether viral suppression could prevent forward transmission. If so, the benefits of treatment would extend beyond the infect-

ed person to his or her uninfected sexual partners (and in the case of people who inject drugs, potentially to those with whom they shared needles). Observational cohort studies among serodiscordant couples strongly suggested that lower viral loads were associated with a reduced likelihood of forward transmission.² At the same time, surveillance studies demonstrated that the majority of transmissions could be traced to persons with uncontrolled viremia. So the question arose whether therapy that suppressed the plasma viral load would also result in lower transmission.

This question was definitively answered by a controlled, prospective clinical trial, the HIV Prevention Trials Network (HPTN) 052 study, published in 2011.² Its investigators enrolled 1763 HIV-serodiscordant, predominantly heterosexual couples in nine countries with CD4+ T-cell counts between 350 and 550 per cubic millimeter, assigning half the infected volunteers to immediate ART and half to deferred therapy (delayed until the CD4+ T-cell count fell below 250 per cubic millimeter, or until development of an AIDS-related illness). Uninfected partners were tested quarterly for seroconversion. The study documented a 96% reduction in HIV transmission in the immediate-therapy group as compared with the deferred-therapy group.² Combined with PrEP, taken regularly or possibly in an event-driven manner by certain high-risk persons (as reported in the IPERGAY study), treatment as prevention could dramatically reduce the incidence of HIV infection.

Although these findings regarding treatment as prevention **clearly demonstrated the public health benefit of early treat-**

ment, a third critical question was whether initiating treatment at normal or near-normal CD4+ T-cell counts actually benefited the person being treated. It is true that many practitioners and a variety of treatment guidelines, particularly in higher-resource environments, suggested consideration of treatment at higher CD4+ T-cell counts. However, conclusive scientific evidence in the form of results from randomized, controlled clinical trials was limited. The answer to this third question was therefore eagerly awaited.

In July 2015, the international AIDS community convened once again in Vancouver for another watershed moment during which they heard the answer. In the Strategic Timing of Antiretroviral Treatment (START) study, which opened in March 2011 in 35 countries, investigators randomly assigned 4685 patients with CD4+ T-cell counts of more than 500 per cubic millimeter to therapy initiated immediately or deferred until their CD4+ T-cell count fell below 350 per cubic millimeter (or until AIDS-defining illness emerged).³ The study revealed that patients in the immediate-initiation group were 57% less likely to develop serious illness (AIDS-related or otherwise) or die than those in the deferred-initiation group. Risks of grade 4 toxic drug effects did not differ significantly between groups. Patients receiving immediate therapy were more than 70% less likely to develop an AIDS-related illness and 40% less likely to develop severe non-AIDS-related illness (e.g., myocardial infarction). The TEMPRANO study conducted in Ivory Coast added weight to these findings, also demonstrating the benefits of early treatment.⁴

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An audio interview with Dr. Fauci is available at NEJM.org

trials, SMART, HPTN 052, and START settle the debate concerning early initiation of ART. Clinicians and patients can now be assured that ART's benefits outweigh the risks for the infected person, regardless of CD4+ T-cell count. Public health officials can confidently support early treatment, recognizing the spillover public health benefits for HIV prevention. Moreover, IPERGAY provides important new data that support the use of PrEP for preventing HIV infection in high-risk populations.

Taken together, these studies

provide an evidence-based blueprint for effective treatment and prevention of HIV infection and will serve as critical tools in the fight to end the HIV-AIDS pandemic. However, in order to realize that promise, the political will must be mobilized to match the scientific evidence and provide the financial and human resources necessary to dramatically scale up HIV testing and treatment around the world. The science has spoken. There can now be no excuse for inaction.

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Tenuous Tether

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In 1816, René Laennec was confronted with a young woman “laboring under general symptoms of diseased heart, and in whose case percussion and the application of the hand were of little avail on account of the great degree of fatness.”¹ Physical examination required “immediate auscultation” — placement of the ear to the chest. Laennec engaged in immediate contact with patients often, but in this case, he could not do so: “In the case of females it is not only indelicate but often impracticable; and in that class of person found in the hospital it is disgusting.”

In a move that has become legendary, he “rolled a quire of paper into a kind of cylinder and applied one end of it to the region of the heart and the other to my ear . . . and could thereby perceive the action of the heart in a manner much more clear and distinct than I had ever been

able to do by the immediate application of my ear.” Calling on his training as a flutist, he coined the terms we still associate with auscultation today, publishing his findings in 1819.¹ Laennec thus invented “mediate auscultation,” which eliminated, for almost two centuries, yet another direct interaction between physicians and their patients — but also improved diagnosis and understanding of diseases.

Movement away from patients was not removal altogether, and in some respects, the distance introduced was beneficial. It was moderate, and physicians remained tethered to their patients, shifting from an ear-to-chest posture to a face-to-face interaction.

Today, however, the tether is fraying, and the auditory stethoscope is all but obsolete. Auscultation is a fading art. Physicians who hear murmurs call for an echocardiogram with little addi-

tional effort at sound differentiation — falling prey not only to the loss of physical examination acumen and the allure of images, but also to a belief in the physical exam's futility.

Echocardiography can discern disease better than humans can — but at what price? The ordering physician doesn't do the imaging, is rarely present when the examination is done, and often reads the report without viewing the images. Masterful technicians perform echocardiography but rarely engage in patient care. A hand-held echocardiography device may one day displace the stethoscope in the clinician's pocket.² But even if it does, special skills will be required to perform a study oneself, and physicians may find it easier to defer to dedicated technicians.

Innovation has made us better physicians and changed the face of medicine. Our hospital has