Preface: Evolving Ethical Issues Over the Course of the AIDS Pandemic

Anthony S. Fauci, MD[1]

ABSTRACT

In the early years of the AIDS pandemic, one of the major ethical considerations facing frontline AIDS medical researchers was the issue of patient accessibility to clinical trials. This issue loomed large because at the time, there were no licensed antiretroviral drugs to treat people with the disease, there were only experimental drugs being tested in clinical trials.[1] Clearly, the standard approach to the design of clinical trials—that is, rigid eligibility criteria as well as the strict regulatory aspects that attend clinical trial investigations and drug approval—was not well-suited to a novel, largely fatal disease such as this with no effective treatments, and we had many intense discussions about how to make that approach more flexible and ethically sound.

One example, which I and others worked closely with the AIDS activists to develop, was called a parallel track for clinical trials. The parallel track concept, which the United States Food and Drug Administration ultimately came to support, meant that there would be the standard type of highly controlled admission criteria and data collection for the clinical trial of a particular drug. In parallel, however, the drug also could be made available to those who did not meet the trial's strict admission criteria but were still in dire need of any potentially effective intervention, however unproven, for this deadly disease. So that to me was a prevailing ethical issue in the early years of the AIDS pandemic—the need to re-examine the

[1] Dr. Anthony S. Fauci is Director of the National Institute of Allergy and Infectious Diseases (NIAID). Dr. Fauci was appointed Director of NIAID in 1984. He oversees an extensive research portfolio of basic and applied research to prevent, diagnose, and treat infectious diseases such as HIV/AIDS and other sexually transmitted diseases, influenza, tuberculosis, malaria, and illness from potential agents of bioterrorism. NIAID also supports research on transplantation and immune-related illnesses, including autoimmune disorders, asthma, and allergies. Dr. Fauci is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, the Institute of Medicine (Council Member), the American Philosophical Society, and the Royal Danish Academy of Science and Letters, as well as a number of other professional societies. He has received a number of prestigious awards including the Presidential Medal of Freedom, the National Medal of Science, and the Lasker Award for Public Service. He serves on the editorial boards of many scientific journals; as an editor of Harrison's Principles of Internal Medicine; and as author, coauthor, or editor of more than 1,200 scientific publications, including several textbooks.

justification or not of the rigidity and exclusivity of our clinical trial process. The ultimate resolution of the dilemma was to create this parallel track approach where you could be more flexible in letting people have access to experimental drugs.

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HOW I FIRST GOT INVOLVED IN THE AIDS EPIDEMIC

I have been involved in HIV/AIDS since the very first day because I work in the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) and my background is a combination of infectious disease and immunology training. Within weeks of learning of the first AIDS cases that were reported from California and New York in June and July of 1981, I made a decision to change the course of my career and to start studying this devastating and extremely poorly understood disease. So from the summer/early fall of 1981 up to today, I have been actively involved with HIV/AIDS as both a clinician and a researcher, and since 1984, also as an administrator as Director of NIAID.[2]

EVOLVING ETHICAL ISSUES OVER THE COURSE OF THE AIDS PANDEMIC AND LESSONS LEARNED

When a disease has no available therapy, and no previous model exists on which to base your treatment approach, it is important when designing clinical trials for that disease to involve the afflicted community. This enables you to take into consideration the special needs of the constituents who will be involved in those trials in order to make the trials more user-friendly as well as doable. So the lesson we learned is the importance of involving individuals affected by the disease under study in the design and conduct of clinical trials. We also learned that one of the most effective ways to do this is by establishing advisory boards made up of members of the communities where the research is conducted. These community members then can be partners in the trial's design and conduct by working closely with their local trial investigators and research teams.

THE COMPLEX OF INTERVENTIONS THAT TURNED THE EPIDEMIC FROM A HOPELESS TRAGEDY TO A REMARKABLE SUCCESS

After fundamental research on the virus revealed targets that could be vulnerable to therapeutic intervention, basic and clinical researchers, working closely with the pharmaceutical companies, began to develop and test drugs, first separately and later in combination. This effort ultimately led to one of the most important medical breakthroughs in any disease in recent memory: the availability in 1996 of combination anti-HIV therapies.

In 1981, before the availability of any antiretroviral drugs, the median survival after an AIDS diagnosis was about six to eight months. In 2012, if a young person in his or her twenties comes into the clinic with early disease and you start them on appropriate therapy, you can predict using mathematical modeling that he or she could live an additional 50 years, a near-normal lifespan.

This extraordinary advance resulted from step-by-step improvements in our approach to treating HIV disease as well as a very aggressive approach to preventing opportunisitic infections. In classical infectious diseases, it is fairly unusual to have a prophylactic regimen where you treat somebody to prevent an infection. With HIV/AIDS, we now can prophylax against a variety of potentially life-theatening opportunisitic infections like pneumocystic pneumonia, cytomegalovirus, and other diseases to which patients may be vulnerable. Thus, our remarkable success in treating HIV/AIDS has fundamentally come about because of the development of highly effective combination antirerotiviral therapies; in addition, we also have become very skilled and aggressive in prophylactic therapy against opportunistic infections.

THE ROLE OF THE GOVERNMENT, INTERNATIONAL DONORS, AND THE PHARMACEUTICAL INDUSTRY IN THE ACCESS OF ANTIRETROVIRAL DRUGS IN DEVELOPING COUNTRIES

I think all these groups must work together to help make antiretroviral drugs more accessible. I was deeply involved in the development of the President's Emergency Plan for AIDS Relief, or PEPFAR, for the US government. That program demonstrated a pure form of leadership—leadership on the part of the US government, particularly former President George W. Bush. He said it was imperative that we help countries in the developing world, predominantly southern Africa, that do not have as many

resources as the US by creating a program to help those countries treat, prevent , and care for people with HIV disease. PEPFAR, together with the efforts of the multilateral Global Fund to Fight AIDS, Tuberculosis and Malaria, and non-governmental organizations, has been a major success in providing antiretroviral treatment, prevention services, and care to several million people in developing countries, particularly in southern Africa, who are infected with HIV or at risk of infection.

Additionally, the Pretoria Trial in 2001—in which drug companies, in an attempt to protect their patent rights, tried to block a South African law that would enable the country to import inexpensive generic versions of their brand-name medicines—was a good example of constituencies and AIDS activists carefully examining the ethical issues involved in developing life-saving drugs through a lens that was different from that of classic profit-margin incentives. So that was a transforming ethical issue in HIV/AIDS as well. Governments, international donors, and pharmaceutical companies all need to work together when you are dealing with a global health issue of the magnitude of HIV.

PROSPECTS OF A VACCINE FOR AIDS

These past few years have given us the first indication that an HIV vaccine is feasible, beginning with the modest degree of protection found in the RV144 HIV vaccine trial that was announced in 2009. The data are being closely examined to identify any correlates of immunity that might help us to build upon that trial. In addition, very elegant basic science is being done to identify targets, or epitopes, for anti-HIV neutralizing antibodies. A number of groups throughout the world are pursuing this research in order to help develop candidate vaccines that induce these elusive neutralizing antibodies that we know exist in some people but that are rarely induced in response to natural HIV infection, at least not in high quantities and not in time to help protect an individual. So there are major challenges in HIV vaccine research; yet for the first time since the pandemic began, we have begun to see some inkling of hope that we will be able to develop an effective preventive AIDS vaccine. However, I believe that the accomplishment of this goal is still years away.

THE CONTINUING CHALLENGES FOR THE NEXT DECADE IN HIV CONTROL AND WHAT TO EXPECT IN 2020

There are two major challenges: the development of a safe and effective vaccine and the possibility of curing people who are infected with HIV, that is, getting to the point where the virus is suppressed enough that we can take them off therapy. That is a major challenge. I am not certain that it will be widely applicable, but I think we will be successful in certain patients.

Importantly, the big breakthrough in HIV/AIDS science—which *Science* magazine voted as the number one scientific breakthrough of 2011—is the concept of treatment as prevention. There has always been an understandable tension between whether you should put more resources into prevention or into treatment. And now this trial, which is referred to as HPTN 052, found that treatment, in fact, is prevention. In other words, if you treat people early and suppress the viral load to a very low level, below detectable, not only do you save the life of the individual who is infected, but you reduce by more than 95 percent the chance that that treated individual will infect their uninfected heterosexual partner. So now, instead of being something that is competing with prevention, treatment is part of prevention. It helps to avoid an ethical dilema. As articulated by Secretary Hillary Clinton when she gave a speech at the NIH prior to World AIDS Day 2011, we may begin to see a turning around of the trajectory of the pandemic and by 2020, we may see the slope of the pandemic take a sharp downward turn, leading in the long run, we hope, to an AIDS-free generation.

WHAT ETHICAL CONTROVERSIES WILL WE SEE IN THE FUTURE

I think the prevailing ethical controversy we face now and in the forseeable future involves the issue of treatment as prevention. In fact, this may be the major ethical consideration of this entire discussion. Even in the absence of an effective AIDS vaccine, we now have the wherewithal, the scientific data, and the scientific basis to turn around this pandemic by persuading as many people as we can to be voluntarily tested for HIV, linking them to care, and getting those who are infected on therapy. Some people perceive this almost as a moral obligation because you know you can save lives. Moreover, we now know this approach also greatly reduces the likelihood that the treated individuals will transmit the virus to others. A big constraint on aggressively pursuing this approach, however, is the limited availability

of support to implement these programs, particularly in an era of markedly constrained resources like we have today. Thus, it is an extremely difficult situation morally and ethically when you know you can turn around a pandemic and potentially achieve an AIDS-free generation; however, the resources are not readily available to do so. It highlights the moral issue of the obligation of society, particularly wealthy societies, to help people who are both less fortunate and who have life-threatening diseases.

Acronyms List:
NIAID = National Institute of Allergy and Infectious Diseases
NIH = US National Institutes of Health
PEPFAR = President's Emergency Plan for AIDS Relief

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