STEVEN P SPIELBERG MD, PhD DISCUSSES THE EVOLUTION OF THERAPEUTIC INTERVENTIONS THAT HAVE STEMMED FROM THE AIDS EPIDEMIC

Therapeutic evolution

February, 2013, marked the 60th anniversary of the announcement of the structure of DNA by Watson and Crick. On the basis of this discovery, our understanding of the basis of heredity and of biology as a whole was forever changed. In 1981, only 28 years after that landmark, reports of a new type of 'acquired immune deficiency' emerged. The scientific and social responses to the new epidemic continue to evolve, and the lessons learned in both spheres have impacted the discovery, development, and evaluation of therapeutic interventions for all human disease.

The first lesson of the AIDS epidemic is the recognition that advocacy for cures in the absence of sufficient scientific understanding of a disease process can be futile and even counterproductive. Imagine that the AIDS epidemic began in 1951. We lacked knowledge of molecular biology, DNA and RNA function, and retroviruses.

Contrast this to leprosy, clinically described thousands of years ago and attributed to a variety of causes based on superstition and prejudice until we began understanding infectious diseases. The organism was discovered barely a hundred years ago, and no useful intervention was developed until much later.

Even in 1981, at the outset of the AIDS epidemic, the etiology and pathogenesis were obscure; was the syndrome caused by a toxin or by an infectious agent? It was only possible in the context of the science developed from 1953 to 1981 to figure out that we were facing a retrovirus. That recognition and understanding of the biology of these agents, defining the cause of the disease rapidly led to the translation of that knowledge into a potential drug target – reverse transcriptase.

While we look back as though the rest was scientifically obvious, both defining the organism and target were unimaginable only 30 years prior. Thus, the basic science of the mid-20th Century primed the pump to move from disease recognition to potential drug targets (including multiple targets – including reverse transcriptase, protease, integrase to address the emergence of resistance), to multiple effective therapies in less than a decade.

Base science

With crucial basic science and technology in place, the process of translation and conversion of knowledge into therapies was driven pivotally by patient advocacy. The perspective of patient-organised advocacy for science, and, for the rapid development of medical products, set the stage for a change in pharmaceutical and regulatory science.

Open discourse of benefit risk for a fatal condition without therapy at the outset, of rapid validation of biomarkers that could serve as early indications of efficacy, and accelerated, but scientifically rigorous, approaches to approval of drugs all benefitted from strong interaction with the advocacy community, physicians, drug companies and the regulatory community. Recognition of rapid emergence of resistance drove increasingly basic and applied science to seek different targets and drug combinations.

As compounds that prolonged life became available, the advocacy community wisely began emphasising the need for greater consideration of the quality of life, number of medicines and regimens, and decreased side effects. New drugs and regimens were developed in time frames not thought possible before.

Strikingly, while some of those medicines have been supplanted by newer, more effective and less toxic drugs, none were withdrawn. Biomarkers were validated for patient relevant outcomes, and new models for scientific translation were defined.

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False starts

None of this happened without false starts, without examples of scientific hubris, without considered suffering and pain; this was a complex human undertaking with all the foibles of the human condition. Yet, the experience represents a human triumph beyond reckoning only a very few years ago.

Patient compliance

According to Aidsmap.com – certified by The Information Standard as a producer of reliable health and social care information – having a daily timetable for taking medication, and taking all doses exactly as prescribed, is the traditional definition of adherence, also known as 'compliance'.

This may sound simple, but in the case of highly active antiretroviral treatment (HAART), it is not. The challenge only increases as people who are infected and able to access therapy face life-long treatment and side effect management.

If some medications are not taken at the correct time interval, the drug level can either be too high (causing unnecessary toxicities or side effects) or too low (encouraging viral resistance). From a public health standpoint, suboptimal adherence also increases both the risk of transmission and the risk of transmitting drug-resistant virus to others.

For those who want an effective response to HAART, daily, near-perfect adherence (>95%) to a dosing schedule is required. This includes adhering to instructions as to whether a drug is taken on an empty stomach or with food, taking all drugs as prescribed, and taking each drug at the correct dosing time. This calls for a high level of precision, consistency, and commitment on the part of the patient.

Predictors of successful adherence include a level of trust between the patient and caregiver and a shared belief in the efficacy of the regimen selected. Clinician qualities found to encourage adherence were skill, knowledge, and experience as well as the willingness and ability to educate and support patients on an on-going basis.

The benefits of correct adherence to therapy include an improved quality of life through reduction in the number of illnesses, hospitalisation events, rate of disease progression, and mortality. Because of these factors, adherence has been intensely studied since the advent of protease inhibitor therapy. Results of this research have altered, to some degree, how drugs are formulated and the scope of the patient/caregiver relationship. Pharmaceutical companies were urged to develop drugs with simpler dosing schedules (optimally, once-daily dosing with no food restrictions) and a longer half-life (referring to the amount of time the drug is active in the body).

Predictors of adherence success include the commitment, motivation, and preparation of the person starting on therapy and on-going information, simplified dosing, a consistent and convenient source for medication, and support from the healthcare team.

The number of heroes in this story is too numerous to count, but we should step back and celebrate just how remarkable an achievement this is in our history. It also represents a fundamental shift in our view of how science can be translated, and how drug development and regulatory science and practice can be aligned in real-time.

As scientific insight in human biology changes ever more rapidly, it challenges us all to assure that therapeutic innovation is matched by regulatory innovation. The good news is that the better the science, the more open and collaborative the scientific environment, the more confident we can be in advancing regulatory science.

The recent development of a drug targeted against one mutation responsible for cystic fibrosis, the basic and translational science driven by patient advocacy, the clinical trials optimised by detailed understanding of the disease, its pathogenesis, and clinical outcomes owes so much to our experience with HIV. Reviewed and approved in barely three months at FDA (following a discovery and development programme of barely six years), the primacy of outstanding basic, translational, and regulatory science has been validated yet again.

A final thought

Recently, Dr C Everett Koop died at the age of 96. He became Surgeon General of the US at the outset of the AIDS epidemic. Based on medical and epidemiologic data, it quickly became apparent that the disease could be sexually transmitted. Even before medical interventions were available, Dr Koop took a strong, scientifically and ethically-driven stance on behalf of prevention, talking forthrightly about sex education and condoms.

Equally critical was his stance on behalf of the fundamental humanity of all afflicted by the disease, regardless of the origins of their disease. He lived his view that he was Surgeon General for all people in need.

Contrast again the stigmatisation and isolation of those afflicted by leprosy for so many centuries. So, too, with AIDS, so many patients were (and continue to be) stigmatised and shunned internationally.

We often lack the courage that Dr Koop had in framing the discussion. There are so many throughout the world still becoming infected, and still untreated for AIDS. One of the miracles of the HIV epidemic has been prevention of 'vertical transmission' of the disease from mothers to infants by HIV drugs, nearly wiping out neonatal AIDS in the US.

Yet, in so much of the world, despite knowing how to prevent the disease, the epidemic continues, and babies continue to be born with a preventable disease.

The AIDS epidemic has been crucial in driving a new era of therapeutic innovation and regulatory science. That innovation will yield therapeutic interventions beyond our current imagination. The final translation of our science into maximum health and wellbeing for all requires a new level of commitment and courage; we struggle yet to align basic, translational, and regulatory science together with social systems recognising, respecting, and celebrating the humanity in us all.

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Steven P Spielberg MD, PhD
Editor-in-Chief
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