Videx® Expanding Possibilities: A Case Study

Acquired Immune Deficiency Syndrome (AIDS) has devastated millions of lives worldwide. The virus that causes AIDS, the human immunodeficiency virus (HIV), attacks immune system cells, leaving the body vulnerable to illnesses that would otherwise pose little threat. In the worldwide AIDS pandemic, there are 5 million new HIV infections and over 3 million deaths each year. [i] By 1993, AIDS was the leading cause of death among persons 25 - 44 years old in the United States. The hope brought by the first drug approved by the Food and Drug Administration (FDA) to attack the HIV, zidovudine, dissolved as patients rapidly developed resistance to its therapeutic effect.

The second anti-HIV drug approved by the FDA, Videx® (didanosine, ddI), developed by Bristol-Myers Squibb in collaboration with the NIH, offered hope for people when zidovudine was not effective. It also helped usher in a new way of thinking about suppressing HIV infection as it became possible to test whether and how anti-viral drugs could be combined to obtain lasting benefits.

As additional anti-HIV drugs became available, clinicians discovered how to design drug combination regimens that can control HIV infection well enough to allow patients' immune systems to recover. These combination regimens -- called Highly Active Anti-retroviral Therapy (HAART) -- can transform HIV from a sure killer to a chronic illness. Today, there are four classes of anti-HIV drugs and nineteen different drugs that can be used. Videx® is an important option in the drug combinations used in HAART.

Epidemiological Features of HIV Disease

Epidemiologic Measure, 2002	Statistics in US[ii]
Persons Infected With HIV	850,000 - 950,000
Annual Deaths from AIDS	16,371
New HIV Infections	42,136

Management of HIV Infection

HAART is the current standard of care for people with symptomatic HIV infection. It is also often offered to HIV-infected people with no symptoms but with severely impaired immune systems. No one knows how long HAART can keep the HIV at bay.

Videx® is one of a class of drugs called Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs) that interfere with the activity of an enzyme necessary for HIV to reproduce. Today, the most common foundation for a HAART combination involves two NRTIs. The third drug may be another NRTI or a drug from another class. Videx® is a long-standing and effective choice for building the dual-NRTI foundation.

Development of Videx®

Role of NIH

A well-established research program at the National Cancer Institute (NCI) gave it a unique capacity to screen compounds for anti-viral activity. The use of ddI to treat AIDS was discovered by NCI scientists Drs. Robert Yarchoan, Hiroaki Mitsuya, and Sam Broder, who also spearheaded the early clinical development of ddI. Using capacities developed in the "War on Cancer," the NCI was able to do preclinical and toxicology research and move ddI rapidly to the clinic to perform some of the early tests in patients. The NIH patented these discoveries.

The National Institute of Allergy and Infectious Diseases (NIAID) AIDS Clinical Trials Groups (ACTGs), consisting of clinical research centers from across the country, were instrumental in the rapid testing of Videx®. NIAID set up the ACTGs to provide a unique clinical trial network ready and waiting for testing new anti-HIV compounds. The ACTG conducted many clinical trials in partnership with industry, including the early testing of Videx® and three other NRTIs.

The technology transfer challenge was to negotiate a license that would provide a strong incentive for a drug company to make the significant investment necessary for the rapid development of a new drug while ensuring the long-term public health benefits. This balance was struck by offering a license that was initially exclusive, but which could became non-exclusive early, prior to the expiration of the NIH patents. Several companies competed for the license. Criteria for selecting the licensee included the company's technical ability to develop this compound into a drug and manufacture it in large quantities, its willingness to work cooperatively with the NIH, and its willingness to make development of this compound a priority. The Bristol-Myers Squibb plan was judged superior by the selection panel, and the license was signed in January 1988. NIH

R & D TIMELINE

Synthesis of ddA Reported -- 1964

Conversion of ddA to ddI Reported -- 1980

NCI Scientists Identify Activity of ddI Against HIV -- 1985

NIH Patents Filed 8/85 - 4/93

First Meeting of NIAID AIDS Clinical Trials Group -- 1987

Bristol-Myers Squibb License to Develop ddI Signed -- 1/88

Clinical Trials Begin
Phase I/II 7/88
Phase II/III 10/89

NIH Patents #4,861,759 #5,026,687 #5,254,539 #5,376,642 and #5,616,566 Issued 8/89 - 4/97

FDA Approves Videx® 10/91

First Commercial Sale Last Quarter/91

License for NCI Patents Becomes Non-Exclusive 10/01

exercised its prerogative to have the license become nonexclusive in October 2001.

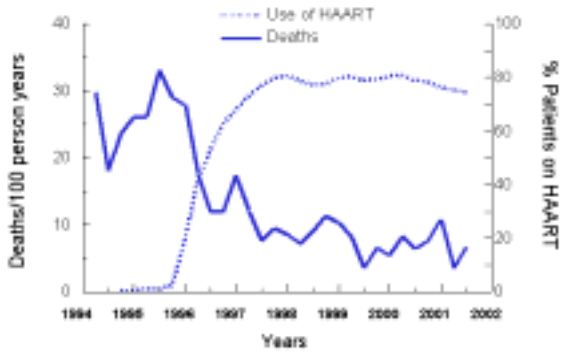
Role of Bristol-Myers Squibb

Videx® was a difficult drug to develop, in part because the active ingredient is destroyed by acid in the stomach. Bristol-Myers Squibb did substantial work to develop a tablet formulation that protects the active ingredient without causing excessive side effects. Bristol-Myers Squibb continued to work on this drug after initial FDA approval and made additional discoveries, including the development of an extended release formulation, Videx® EC, that is effective when taken only once a day. Videx® EC was the first one capsule, once-a-day HIV medication used in combination HIV therapy.[iii] Bristol-Myers Squibb independently patented its discoveries.

In addition to this formulation research, Bristol-Myers Squibb (BMS) coordinated several early clinical trails of ddI with the ACTG, and devoted considerable resources to speed this drug to market. BMS also provided supplemental funds for the key clinical trials used for FDA approval. Bristol-Myers Squibb also operated an expanded access program that, outside standard clinical trials, provided free drug to over 23,000 people prior to FDA approval.[iv] The safety data collected from the expanded access program helped speed FDA approval.

Public Health Benefits

Initially, Videx® was the only way to delay disease progression and death in patients who could not tolerate or who were no longer helped by zidovudine.[v] With the discovery of additional anti-HIV drugs, Videx® became part of the backbone of many life-saving HAART regimens. With HAART, the incidence of AIDS in the United States dropped dramatically from 33.4 per 100,000 population in 1994 to 17.2 in 2000,[vi] and the number of deaths each year fell dramatically.



The years of potential life lost due to HIV disease per 100,000 population dropped from 383.8 in 1990 to 175.4 in 1998. [vii]

The public health benefits from the NIH investments in Videx® and other anti-HIV compounds includes advances in other areas that stem from HIV research. Methods used to design drugs that target different phases of the HIV life cycle are being applied to the development of drugs to treat other viral diseases such as hepatitis C, influenza, and Cytomegalovirus. Techniques developed for diagnosis and monitoring of HIV infection are now being used for TB and herpes simplex.

The commitment of NIH and Bristol-Myers Squibb to rapid development and approval of this drug included early pediatric testing. Videx® was simultaneously approved and launched with both adult and pediatric indications and dosing. In addition, Videx® was an important test case for a new FDA approval process for speeding drugs to market in urgent circumstances. The FDA accepted early evidence of the effectiveness of Videx®, without the full data set that the FDA normally required, and approved Videx® before the clinical studies were complete. The Videx® approval process was successful and served as a model for the FDA's "accelerated approval" regulation, published the year after Videx® was approved. Drugs for many life-threatening conditions, including cancer, have been approved under this rule.

References

[i] AIDS Epidemic Update, December 2002. UNAIDS/World Health Organization.

[ii] "HIV Cases Climb Among Gay, Bisexual Men in US." National News, The CDC HIV, STD, TB Prevention News Update, July 28, 2003.

[iii] Videx ®EC, www.videxec.com, accessed 9/15/03.

[iv] Bristol-Myers Squibb Company, Annual Report 1991, p. 2.

[v] HIV Trialists' Collaborative Group, "Zidovudine, didanosine, and zalcitabine in the treatment of HIV infection: meta-analyses of the randomized evidence." Lancet 353:2014-2025, June 12, 1999.

[vi] CDC Divisions of AIDS/HIV Prevention, Surveillance Supplement Report Vol.9, No.1, Table 3.

[vii] Health, Unites States, 2002, Table 31. DHHS, CDC, NCHS.

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