
# Saving Lives Today And Tomorrow

## Ensuring ongoing research into HIV/AIDS medicines

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## Abstract

This paper analyses trends in drug development using data from the drug industry association, the Pharmaceutical Research and Manufacturers of America (PhRMA). Worryingly, the findings suggest that far fewer AIDS drugs are in development compared to several years ago, and at a time when drug development for other communicable diseases is increasing. There are several probable explanations for this phenomenon, but the least benign is the likelihood that continual pressure group and media attacks on the industry over pricing of drugs in Africa has reduced incentives for development of new AIDS medicines.



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## Overall Trends in non-AIDS infectious diseases medicine development

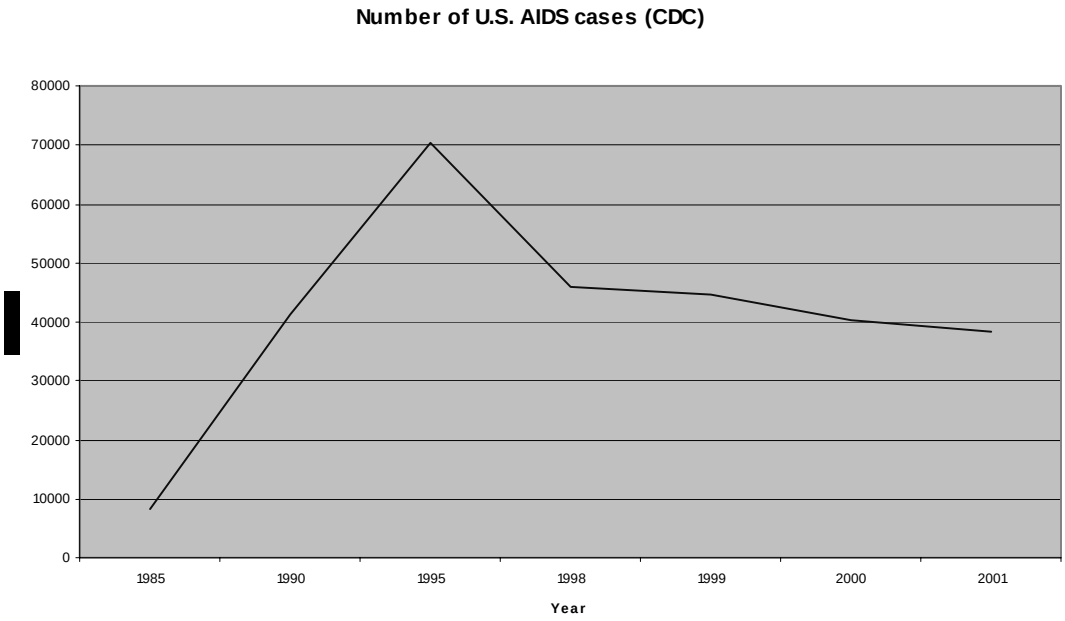
Background: Infectious diseases, such as pneumonia, influenza and even tuberculosis, are a significant problem in developed countries, with millions of people suffering from serious infectious disease in America every year. Although infectious disease causes relatively few deaths in wealthy countries, it is the biggest killer world-wide. Of some 50 millions global deaths that occurred every year in the 1990s, one third was due to infectious disease, of which 9 million were children. Diseases such as pneumonia, cholera, dysentery, tuberculosis, and newer threats like West Nile virus and Ebola mean there is a need for the development of drugs to combat these dangers.

According to data compiled by PhRMA[1], there has been a consistent increase in the number of medicines developed for infectious diseases over the past decade. The numbers of new antibiotics, anti-fungals, vaccines, anti-virals and other biologics in development have increased by over 100% in the past 9 years. And if one includes responses to bio-terrorism threats, the increase is even greater. At the end of 2002, 256 medicines were in development, 187 were in clinical trials or awaiting approval by the Food and Drug Administration, and 69 were in pre-clinical development.

## Overall Trends in AIDS medicine development

Background: HIV/AIDS used to be a death sentence. In the mid-1980s few sufferers survived, but by the late 1980s drugs, such as AZT, developed by the research-based industry delayed the onset of symptoms of the disease. Incredible advances in new treatments, such as anti-retrovirals, can now help delay, perhaps indefinitely, the onset of symptoms, allowing HIV positive individuals to live normal lives. Since the early 1990s, medicines have helped reduce mother to child transmission of HIV by two thirds in America. As can be seen from the graph below, the number of new AIDS cases in America peaked in 1995 and has declined annually since then.

[1] PhRMA Annual Surveys: 'New Medicines In Development for Infectious Diseases', 1994, 1996, 1998, 2000, 2002

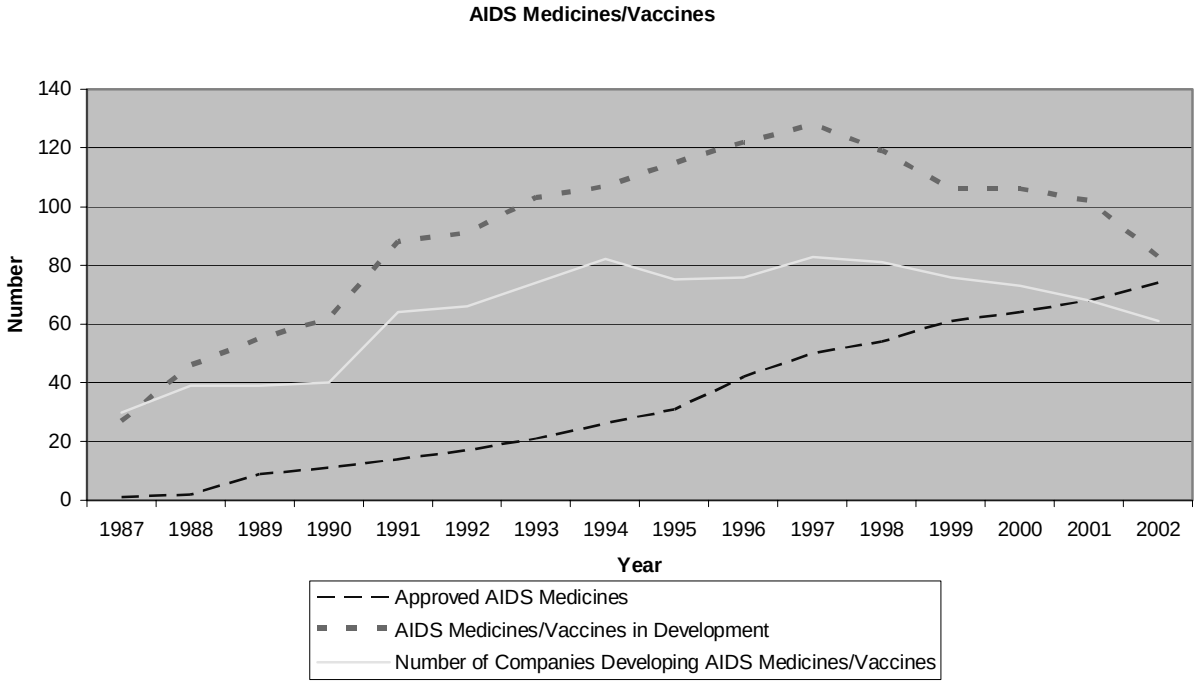



However, the situation has worsened globally each year. According to UNAIDS, at the of end 2002, there were at least 40 million people world-wide with AIDS, over 26 million of whom are in the most impoverished part of the world – Sub-Saharan Africa. Of these 40 million people, far fewer than a million are receiving treatment. And even though many poor countries are pursuing education programmes against the disease, UNAIDS predicts that the number of cases will increase substantially over the coming years. Perhaps as many as 25,000 new cases will occur each day – over 7 million new cases in 2003 alone.

As can be seen from the graph below, the approval of AIDS medicines[2] has gradually increased over time and each year the total number of drugs approved is higher than the year before – over 75 at the end of 2002. However, the number of AIDS drugs in development and the number of companies developing the AIDS drugs both reached a peak in 1997 and has declined ever since. In 2001, for the first time, the number of approved AIDS medicines was greater than the number of companies developing the medicines themselves. The trend of declining company interest, which is causing fewer new drugs to be developed, looks set to continue in 2003.

This recent decline in AIDS drug development should be contrasted with the significant increase in development of drugs for infectious diseases. This is important because it appears that drug research and development is increasing in general for communicable disease, while declining for AIDS.

[2] PhRMA Annual AIDS Drug Development Reports 1988-2002 inclusive.




It is important to note that the decline in company interest is not manifested within the major companies, such as Merck, Bristol-Myers Squibb and GSK. It is smaller, usually younger companies, often biotech start-ups, which are no longer developing drugs, and enduring the risk of clinical trials in this area. Small companies such as VIMRx Pharmaceuticals, which were working on AIDS anti-cancer and anti-infective drugs in the late 1990s, are no longer engaged in such research.

The decline in small company interest is a worrying trend, because, according to Frank Lichtenburg of Colombia University, there has been a reduction of 6,100 AIDS deaths in America for each new drug developed[3]. New drugs have reduced the number of AIDS deaths in America from 51,670 in 1995 to 15,603 in 2001.

The trend is especially worrying since 'resistance remains a formidable problem' according to Dr Richard Colonno of Bristol-Myers Squibb. As Dr Michael Rogers, head of HIV Clinical Development at GSK said in 2001 'We are constantly looking for new drugs that can defeat these mutated viruses'. This means that some of the currently used drugs will probably become ineffective in the near future.

[3] Lichtenburg, Frank (2002), The contribution of New Drugs to Health and Economic Growth in the United States (November 18th 2002). www.aei.org/doclib/20021229_conf021118c.pdf

## Analysis

### Why the decline

For drugs developed by the private sector it is essential for the company developing the drug to be able to recover its Research and Development costs through sales.

### The Drug Development Process

The Tufts University Project on Drug Development[4] has noted that both increasingly high research and development costs and pressure from politicians have forced pharmaceutical firms to speed up the drug development process.

To offset the increasing cost of developing drugs, estimated in their most recent study[5] as $802 million per drug, the U.S. Congress has attempted to cut the time taken by the FDA to approve new drugs. This figure is undoubtedly at the upper end of cost estimations, and many have claimed that it is inflated. However it is probably impossible to get a completely realistic estimate of cost of drug development as it involves so many different factors and because drug companies are, understandably, loath to reveal their true cost structures. What is certain however, is that drug development is both enormously costly and very time consuming, and much of this cost has been imposed by government.

The U.S. approval phase for pharmaceuticals (from filing to submission) for the 1960s, 1970s, 1980s and 1990s averaged 2.4, 2.1, 2.8 and 1.8 years, respectively. The approval rate for 1999 was 1.1 years. However, the total time from discovery to U.S. marketing approval increased 75% from the 1960s to the 1990s. The PhRMA data itself states that total development time has risen from 10 years in 1990 to 15 years in 2002.

It is not only the US government that imposes lengthy delays and costs on drug developers. Many poor countries also have their own regulatory regimes that can delay the sale of a new drug for many years, even if it is already approved in the US, Japan or EU. The demands for cheap medicines by many African governments ring hollow when they often impose unreasonable demands and costs on the drug developers. In one case of note, the Namibian government recently required all drugs registered in the country prior to 1990 to be re-registered. In 1990, Namibia achieved its independence from South Africa and therefore formed its own Medicines Control Council. Re-registering drugs that were already accepted for use in Namibia and in dozens of other countries worldwide, not only places burdensome costs on drug companies, and ultimately patients, but sends a message to the drug developers, that the government is more interested in building its bureaucracy than in ensuring more people have access to essential medicines.

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[4] Dimasi et al (1995) R&D Costs, Innovative Output and Firm Size in the Pharmaceutical Industry, International Journal of the Economics of Business Vol 2, No.2

[5] (November 2001) Backgrounder: A methodology for Counting Costs for Pharmaceutical Research and Development. http//csdd.tufts.edu/newsevents/recentevents.asp?newsid=5

Tufts University has determined that approximately half of clinical research failures occur early. The drug is likely to succeed, however, once it has been through the first two phases of clinical trails. Drugs are likely to be abandoned before phase two due to a combination of a lack of therapeutic efficiency, and high cost.

According to Scott Gottlieb of the American Enterprise Institute, 70% of the cost of drug development was pre-clinical in the 1970s, 20 years later the majority (at least 60%) of the cost is in clinical trials. This explains why pharmaceutical firms abandon unsuccessful compounds more quickly, 'throwing out good drugs as well as the bad,' as Gottlieb puts it. But even if drugs make it through the trials at massive expense to the companies, some problems may just be beginning.

As CEO of Pfizer Hank McKinnell explains that several drugs were recalled in the late 1990s for concerns about potential liver toxicity, and today "companies may decide not to file an application for new drug approval even though they found a medication to be effective in their trials."

**Price Discrimination**

For those drugs that make it through the approval process and on to the market, it is essential for industry to be able to cover the massive research and development costs of the drug and all those that failed before it. Upfront costs must also be recovered in a way that is equitable and economically efficient. Given that the first pill may cost millions of dollars and the second a dollar or less, it makes sense to price discriminate in different markets, both domestically and internationally. Clearly, the usual economic mantra of marginal cost pricing cannot work in this instance because the marginal cost is close to zero. Consequently, wealthy Americans will pay far more than middle income Mexicans for the same medication.

This approach is true for all drugs, but for AIDS drugs there is an added problem. Since the majority of AIDS cases are in the poorest regions of the world, even marginal cost pricing puts the drugs out of reach for most people. The discrepancy between a reasonable price differential in rich and poor countries and the income in the poorest countries is still huge. The lowest price for AIDS drugs, diagnostics and delivery per person is at least $400 a year, which is far more than any but the richest African is capable of spending.

Unsurprisingly, because of the usual model of price discrimination, all companies initially refused to massively lower their AIDS drug prices in Africa. However, various companies undertook pilot projects and more substantial humanitarian campaigns.[6]. But many companies only lowered prices after activist claims that high drug pricing was killing Africans received widespread attention and South Africa, Brazil and other countries threatened the patents of drug companies with compulsory licensing demands.

[6] For an up to date list see www.ifpma.org From 1998 to the present, the global industry has contributed $2 billion to poor countries via partnerships.

**Patents not the problem**

Ironically, pricing, and especially patents do not block access in the poorest nations. Most African countries have no patents on AIDS drugs; only 13% of potential patents exist in Africa[7]. Of course, lower drug prices help, but in many African countries there are few doctors capable of correctly diagnosing AIDS, often because they have no diagnostic equipment with which to test viral loads, and hence cannot know what drug regimes to follow.

However, although patents were not blocking access in Africa, attacks on patents were reducing the incentive to develop new AIDS drugs for fear that patents would be further attenuated. The reduction in incentive may be contributing to companies' decreased research on new AIDS treatments.

Dr Des Martin, President of the South African HIV Clinicians Society, has his suspicions as to the cause. 'Among several reasons, the threat of generic competition and attacks on multinational companies could be behind the recent decline in HIV anti-retroviral compounds' he says. The latter point is one that the pharma industry does not want discussed widely. According to Ruth Rabinowitz, an MP with the South African Inkatha Freedom Party, "Industry has been numbed into silence" by the activist and media attacks in South Africa and in the west.

And I could find no industry executives to go on the record when I started analysing this problem in Summer 2002[8]. One of the rare industry executives who would actually discuss the topic, but did not wish to be identified, agreed that although he didn't like to admit it, "we have lost the battle with the activists, and now the market is less profitable. The result is that we are spending less R&D time on anti-retrovirals. Why bother to innovate these products when any advance will not be profitable?" he said.

An additional explanation is that the number of AIDS patients in western countries, where patients can afford treatment, has declined over the past few years from a high of 70,000 new cases a year in the mid 1990s down to only 40,000 in 2002.

**Other explanations?**

There may be several relatively benign reasons for having fewer products in development.

The switch from developing new drugs through traditional chemistry to cutting-edge biotechnology may also be partially responsible for the drug development slowdown. Furthermore, when scientists and researchers undertake new approaches to combating a

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[7] Attaran A and L Gillespie-White (2001) Do Patents for Anti-Retroviral Drugs Constrain Access to AIDS Treatment, JAMA 17/10/2001, vol.286 # 15.

[8] However, in the very recent past drug company executives have started to make the point about lack of incentive for research if patents and prices are constantly attacked. See Geoff Dyer, How do you price AIDS treatment?, Financial Times, 26th March 2003

disease, they may find that some of their research is ultimately fruitless. Thus, it is quite possible that the drug development drop off reflects the failure of recent research projects. Those anti-AIDS drugs that remain in development today are of higher quality, and are more likely to succeed in clinical trials. This would mean that the data could be slightly misleading and the picture is rosier than imagined.

This is the opinion of some industry experts, such as Trevor Jones, Director of the Association of British Pharmaceutical Associations. But it seems more likely that the lack of potential profitability is driving industry away from research. After all, a decrease in AIDS research would be consistent with drug companies' general message that patent protection is an essential incentive for research.

## Discussion

### What to do?

Into this void came the welcome announcement from President Bush that he wanted to try and treat 2 million African AIDS victims, offering to spend $2billion a year to make it possible. This should have been seen as a boost to the research-based industry, but Mr Bush said something in his State of the Union speech that probably sent shudders through the research-based industry. He implied that generics companies, those that copy western company patents, and do no original research, should be used to supply drugs. He did this by quoting the price of an annual cost of AIDS drugs as $300, which is below what even the cheapest generics companies can offer. His error was compounded by Dr Anthony Fauci, director of the US National Institute for Allergy and Infectious Diseases who claimed that the US would work with Cipla, the patent-breaking Indian generics company[9].

Nevertheless, President Bush's initiative should be welcomed. But as the above analysis suggests, no amount of drug buying from generic companies, or pressure on western companies is going to develop new drugs. The vast majority of AIDS drugs that have reached the market have been developed by the private sector, a successful system dependent on patent enforcement and intellectual property rights. However, the status quo is not enough.

If President Bush truly plans to combat AIDS, then his humanitarian assistance programme will require a pro-technology and pro-market agenda.

The US is the center for most drug research in the world, a recent development directly related to America's longstanding commitment to the institutions of a free society. In the 1970s and 1980s, Germany, Switzerland and Britain were arguably more important in drug development than the US, but many researchers operating in these countries (especially Germany) have fled to the more benign market of America. While the US Government has provided valuable direct assistance, such as through National Institutes of Health grants to researchers, far more important has been America's ability to create

[9] Bush AIDS Plan www.bbc.co.uk/2/hi/americas/2708089.stm 30/1/03

and maintain an environment where private enterprise can flourish (based on respect for intellectual property rights, the rule of law and contract, a well-educated workforce and low taxation). This must continue and furthermore the Government must:

1. Reduce the time it takes for drugs to be approved by FDA. Many doctors, including 60% of oncologists believe that FDA approval rates are far too slow[10]. $800 million is the **most** powerful disincentive to risk bringing new products into uncertain markets. Why should any company bring anything to the market if it can never recover the costs of R&D? To help with this problem the approach taken by The Orphan Drug Act of 1983 could be copied, to help with AIDS drug development. This Act provides incentives for pharmaceutical manufacturers to develop drugs, biotechnology products and medical devices for the treatment of rare diseases and conditions. Incentives for orphan product development include marketing exclusivity, tax incentives, and research grants. From 1983 to July 2001 the FDA has approved 183 new orphan products. The Act has been very successful in finding new treatments for rare diseases and conditions.
2. Poor country governments that require new drugs to tackle age old diseases can and should reform their medical bureaucracies so that new drugs are registered more easily and at lower cost to the drug company. In addition, greater progress should be made towards common registration within, for example, Southern African countries.
3. Provide incentives for drug companies to research solutions to important diseases, such as malaria, AIDS and tuberculosis, where markets are uncertain. They can do this in several ways, such as by providing cash prizes (in the form of tax breaks) to companies that make breakthroughs, or by providing patent extensions on valuable drugs in western markets for any breakthrough in a treating a disease of poverty[11].
4. Provide tax incentives to venture capital firms to fund small nanotechnology, or biotechnology companies that want to enter the AIDS research field. At the moment, all the incentives are to invest in companies working on valuable western lifestyle problems such as erectile dysfunction and baldness.
5. Maintain a consistent position in international meetings, such as at the World Trade Organisation, on the vital importance of patents, independent company pricing, and free markets in general.

[10] See A National Survey of Oncologists Regarding the FDA, April 30th 2002 www.cei.org
[11] See Morris et al (2002), Ideal Matter: Center for the New Europe, Brussels, for a fuller discussion