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THE EFFECT OF NEW DRUGS ON MORTALITY FROM RARE DISEASES AND HIV

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ABSTRACT

I investigate the effect of large increases in the number of drugs available to treat rare diseases and HIV on mortality associated with them. Mortality from both diseases declined dramatically following increases in drug approvals.

Before the Orphan Drug Act went into effect (between 1979 and 1984), mortality from rare diseases grew at the same rate as mortality from other diseases. In contrast, during the next five years, mortality from rare diseases grew more slowly than mortality from other diseases. I estimate that one additional orphan drug approval in year t prevents 211 deaths in year t+1 and ultimately prevents 499 deaths, and that about 108 thousand deaths from rare diseases will ultimately be prevented by all of the 216 orphan drugs tha t have been approved since 1983. Deaths are more closely related to the number of orphan product designations (which include experimental drugs) than they are to the number of approvals.

Consistent with previous patient- level studies of HIV, I find that new drugs played a key role in the post-1995 decline in HIV mortality. I estimate that one additional HIV drug approval in year t prevents 5986 HIV deaths in year t+1 and ultimately prevents 33,819 HIV deaths. HIV drug approvals have reduced mortality both directly and indirectly (via increased drug consumption). HIV mortality depends on both the quality and the quantity of medications consumed, and new drug approvals have a sizeable impact on drug consumption: one additional HIV drug approval in year t results in 1.2 million additional HIV drug units consumed in year t+1 and ultimately result in 3.6 million additional HIV drug units consumed.

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During the last two decades, there have been large, sudden increases in the number of drugs available to treat two kinds of diseases: "orphan" (rare) diseases, and Human Immunodeficiency Virus (HIV). As Figure 1 indicates, the average annual number of drugs for rare diseases brought to market during 1983-1999 was twelve times as great as it was during 1973-1982[1], and the average annual number of HIV drugs brought to market during 1994-1998 was three times as great as it was during 1987-1993.

These increases occurred for different reasons and under different circumstances. The increase in drugs for rare diseases occurred because Congress passed the Orphan Drug Act in January 1983. The increase in drugs for HIV occurred because AIDS was first reported in 1981, was identified as being caused by HIV in 1984[2], and (in the 1990s) the average length of time required to develop a drug was about 15 years.[3]

Both increases provide a good opportunity to investigate the effect of pharmaceutical innovation on mortality. In this paper I investigate the effect of increases in the number of drugs available to treat these diseases on mortality associated with them.

Econometric framework

I hypothesize that mortality in year t is inversely (and linearly) related to the stock of drugs available by the end of year t-1:

$$MORT_t = \alpha - \beta\ DRUG\_STK_{t-1} \qquad (1)$$

where $MORT_t$ is a measure of mortality (the number of deaths or life-years lost) in year t and DRUG_STK is the stock of drugs available by the end of year t-1.[4] I consider two alternative hypotheses about DRUG_STK.

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[1] "More than 200 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten such products come to market." (Source: http://www.fda.gov/orphan/History.htm)

[2] http://www.fda.gov/oashi/aids/miles81.html

[3] DiMasi, J.A., "New Drug Development: Cost, Risk, and Complexity," *Drug Information Journal*, May 1995, cited in *PhRMA Industry Profile 2000*, Chapter 2, http://www.phrma.org/publications/publications/profile00/index.phtml

[4] β is the effect of changes in the stock of drugs on mortality. The variance of the least-squares estimator of β is inversely related to the variance of DRUG_STK: the greater the variability of DRUG_STK, the more

The first is that it is simply the sum of the number of drugs approved by the FDA for the disease in all previous years:

$$DRUG\_STK_{t-1} = FDA_{t-1} + FDA_{t-2} + \ldots \quad (2)$$

where FDA_{t-1} is the number of drugs approved by the FDA in year t-1, etc. Equations (1) and (2) imply that

$$MORT_t - MORT_{t-1} = -\beta\,(DRUG\_STK_{t-1} - DRUG\_STK_{t-2})$$

or

$$\Delta\, MORT_t = -\beta\, FDA_{t-1}$$

where $\Delta\, MORT_t$ $(= MORT_t - MORT_{t-1})$ is the increase in mortality between year t-1 and year t. Multiplying both sides by –1,

$$-\Delta\, MORT_t = \beta\, FDA_{t-1} \quad (3)$$

The reduction in mortality $(-\Delta\, MORT_t)$ is proportional to the number of drugs approved in the previous year.

The second, more general, model of the stock of drugs is

$$DRUG\_STK_{t-1} = FDA_{t-1} + (1-\delta)\, FDA_{t-2} + (1-\delta)^2\, FDA_{t-3} + \ldots \quad (4)$$

where δ $(0 \leq \delta < 1)$ represents the depreciation (or obsolescence) rate of drugs. If $\delta = 0$, this reduces to the previous model (2). If $\delta > 0$, recent FDA approvals have a larger impact on the current stock of drugs than approvals in the distant past. Substituting (4) into (1), and subtracting $(1 - \delta)$ times the lagged value of the resulting equation from itself,

$$MORT_t = \alpha\delta - \beta\, FDA_{t-1} + (1-\delta)\, MORT_{t-1} \quad (5)$$

The regression of mortality on FDA approvals in the previous year and its own lagged value will yield estimates of the parameters β, δ, and α.[5] From these one can estimate

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precise (reliable) the estimate of β. Since there were large changes (increases) in the stocks of drugs for both diseases, it should be feasible to obtain precise estimates of β.

[5] A statistically significant β implies that FDA approvals "Granger-cause" mortality.

both the short-run and long-run impacts on mortality of changes in the number of FDA approvals: the short-run impact is β and the long-run (cumulative) impact is (β / δ).

Orphan diseases

The Orphan Drug Act (P.L. 97-414) amended the Federal Food, Drug and Cosmetic Act as of January 4, 1983, and additional orphan drug amendments were passed by Congress in 1984, 1985 and 1988. The 1983 Orphan Drug Act guaranteed the developer of an orphan product seven years of market exclusivity following the approval of the product by the FDA. It also provided a tax credit, and established a clinical research grants program, whereby researchers may compete for funding to conduct clinical trials to support the approval of drugs for rare diseases.

Congress passed the Act because it found that

(1) there are many diseases and conditions, such as Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome, and muscular dystrophy which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States
(2) adequate drugs for many of these diseases and conditions have not been developed
(3) drugs for these diseases and conditions are commonly referred to as "orphan drugs"
(4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss
(5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs
(6) it is in the public interest to provide such changes and incentives for the development of orphan drugs.

The original definition of "rare disease or condition" in the Orphan Drug Act was amended in October 1984 by P.L. 98-551 to add a numeric prevalence threshold to the definition:

> "...the term rare disease or condition means any disease or condition which (a) affects less than 200,000 persons in the U.S. or (b) affects more than 200,000 persons in the U.S. but for which there is no reasonable expectation that the cost of developing and making available in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug."

The FDA publishes a list of products that are currently designated as orphans by the Office of Orphan Products Development (http://www.fda.gov/orphan/designat/list.htm). The list includes the generic and trade names of the drug, its sponsor and indication(s), the date it was designated, and, for those products that have also been approved for marketing, a marketing approval date. As of 6/18/01, the list included 1089 designated products, 216 of which had been approved for marketing.[6] Orphan drugs (and biologicals) that have been designated but not yet approved are considered experimental. Insurance companies will generally reimburse for orphan products that have been approved for marketing, but may not reimburse for products that are considered experimental.[7]

Figure 2 displays the number of orphan designations and approvals, by year. The mortality data I will examine begin a few years before the Orphan Drug Act (in 1979), but 1983 is the first year in which any designations or approvals were recorded. I therefore imputed the values of designations and approvals shown for the years 1979-1982. According to the FDA, fewer than one orphan drug came to market per year in the decade prior to the Act, so I assumed there was one approval per year during 1979-1982. Since the ratio of designations to approvals after 1983 is about 5, I assumed there were five designations per year during 1979-1982.

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[6] There is a separate designation (and marketing approval) for each indication of a drug. Aldesleukin, for example, has five designations and two marketing approvals. Thus, the frequencies of designations and approvals we will analyze may be viewed as drug frequencies, *weighted* by the number of indications for which a drug is designated or approved.

[7] "Office of Orphan Products Development Frequently Asked Questions," http://www.fda.gov/orphan/faq/index.htm

I obtained data on mortality from rare and other diseases from the Center for Disease Control's 1979-1998 Compressed Mortality File (CMF) (http://wonder.cdc.gov/mortsql.shtml). This file contains data on the number of deaths, by cause (ICD9 code), age (and other characteristics) and year. Perhaps the theoretically ideal procedure would be to link the drug data to the mortality data at the individual disease level. For example, Gaucher disease is a listed indication of some of the drugs in the orphan products database, and the term "Gaucher" occurs within two ICD9 codes (272.7 and 330.2) of the "ICD9 Finder" of the CMF. However in many cases it is difficult or impossible to determine the ICD9 codes to which orphan products correspond. Moreover, the cause of death recorded on death certificates—the underlying basis for the CMF—is known to be subject to error, and presumably, at lower (more detailed) levels of classification, the probability of error is greater.

I therefore pursued an alternative approach: analysis of all rare diseases combined. Data on drugs for all rare diseases combined were shown in Table 2. I calculate deaths from all rare diseases combined by calculating the total number of deaths in each year from all of the (approximately) "2-digit" ICD9 diseases that caused less than 2000 deaths in that year.[8] 2000 deaths appears to be a reasonable threshold since rare diseases are defined as diseases that affect less than 200,000 persons in the U.S., and the overall U.S. morality rate is approximately 1%.

Figure 3 presents annual data for 1979-1998 on the number of deaths from rare diseases (based on this definition) and from all other diseases. Between 1979 and 1984, the number of deaths from rare diseases increased at a faster rate than the number of deaths from other diseases: 2.0% vs. 1.3% per year. However in the following decade, the number of deaths from rare diseases *declined* at a rate of 3.1% per year, while the number of deaths from other diseases increased at 1.2% per year. Deaths from rare diseases increased slightly from 1994-1998. Data on

[8] There are 108 "2-digit" diseases; about half of these diseases cause fewer than 2000 deaths per year.

orphan drug designations and rare disease deaths (plotted on an inverted scale) are superimposed in Figure 4.

Although I don't have *annual* mortality data for rare vs. other diseases for years prior to 1979, I thought it would be useful to examine relative mortality over a longer period, and using an alternative definition of rare diseases. Figure 5 shows the number of deaths from rare diseases and other diseases in 1970, 1980, and 1995 (computed from the Vital Statistics--Mortality Detail files for those years); in this figure, rare diseases are defined as diseases causing fewer than 5000 deaths per year. Consistent with the findings above, mortality from rare diseases increased between 1970 and 1980 (albeit more slowly than mortality from other diseases), but declined about 20 percent from 1980 to 1995.

One can perform a simple, formal test of the hypothesis that the relationship across diseases between initial mortality and subsequent growth in mortality changed in 1984, by estimating the following regressions[9]:

$$\ln N_{i,1984} - \ln N_{i,1979} = \alpha_{PRE} + \beta_{PRE} \ln N_{i,1979}$$

$$\ln N_{i,1989} - \ln N_{i,1984} = \alpha_{POST} + \beta_{POST} \ln N_{i,1984}$$

where $N_{i,1984}$ represents the number of deaths caused by disease i in 1984, etc. The estimate of β_{PRE} is not significantly different from zero, indicating that, between 1979 and 1984, mortality from (initially) rare diseases grew at the same rate as mortality from other diseases. In contrast, the estimate of β_{POST} is positive and significant, indicating that, between 1984 and 1989, mortality from (initially) rare diseases grew more slowly than mortality from other diseases. This finding seems particularly noteworthy, since growth is often *inversely* related to initial size due to "regression towards the mean".

Estimates of models of mortality from rare diseases are presented in Table 1. Column 1 shows the regression of the number of deaths on current orphan drug

[9] Moreover, this test does not rely on the accuracy of a specific size cutoff, such as 2000 deaths.

approvals and the lagged number of deaths. Column 2 shows the regression of the number of deaths on lagged orphan drug approvals and the lagged number of deaths. This corresponds to eq. (5) derived earlier. As one might expect, the second equation fits better than the first: deaths in the current year depend on the number of approvals by the end of the previous year. The coefficient is negative and significant at the 5% level. The estimates imply that one additional orphan drug approval this year will prevent 211 deaths next year and ultimately prevent 499 deaths. I estimate that about 108 thousand (216 drugs * -499 deaths/drug) deaths from rare diseases will ultimately be prevented by all of the 216 orphan drugs that have been approved since 1983.

Column 3 shows the regression of the number of deaths on the lagged number of orphan product *designations*, as opposed to approvals. As discussed above, products that are designated but not approved are considered experimental, and are presumably available to fewer patients. Deaths are more closely related to the number of designations than they are to the number of approvals: the coefficient on lagged designations is significant at the 1 percent level. One additional designation this year will prevent 40 deaths next year and ultimately prevent 130 deaths. Although deaths prevented per designation are smaller than deaths prevented per approval, the estimated number of deaths ultimately prevented by all designations since 1983 (141 thousand = 1089 designations * -40 deaths /designation) is about one-third greater than the estimated number of deaths ultimately prevented by all approvals since 1983 (108 thousand).

Column 4 shows the regression of the number of deaths on the lagged number of designations and a time trend. While there is no clear theoretical justification for including a time trend in the mortality model, I report this equation to show that the coefficient on lagged designations remains highly significant when a time trend is included; the inverse relationship between deaths and designations is not a “spurious correlation”.

Both approvals and designations are included in the regression in column 5. Due to the reasonably high positive correlation between these variables (evident in Table 2), distinguishing between their effects is difficult. But the estimates of this equation lend further support to these conclusions: both approvals and designations have a negative impact on mortality, and the marginal effect of approvals is larger, but less reliably estimated.

The equations in columns 6 through 10 are similar to those in columns 1 through 5, but instead of the number of deaths, the dependent variable is the number of life-years lost before age 75. If a person dies from a rare disease at age 50, for example, then he has lost 25 years of life.[10] The overall pattern of these estimates is similar to that of the earlier estimates, although the implied reduction in mortality is greater. For example, column 8 implies that one additional designation this year will save 748 life-years next year and ultimately save 3689 life-years. Life-years ultimately saved per death ultimately prevented is 28.4 (= 3689 life-years / 130 deaths), which is much greater than 15.8 (= 75 – mean age at death from rare diseases). Evidently, this is because designations increase age at death as well as reduce the number of deaths, although the former effect is not statistically significant.

HIV

Several excellent studies have examined the impact of new drugs on HIV mortality at the patient level. For example, Palella et al (1998) analyzed data on 1255 patients who were seen at nine clinics specializing in the treatment of HIV infection in eight U.S. cities from January 1994 through June 1997. They found that mortality among the patients declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in the second quarter of 1997, and that this decline was attributable to the use of more intensive antiretroviral therapies. Mocroft et al (1998) analysed data from a prospective, observational, European, multicentre cohort of 4270 HIV-1-infected patients. They found that death rates at the

[10] During the period 1979-1998, mean age at death from rare diseases was 59.2, and from other diseases was 70.8.

beginning of 1998 were less than a fifth of their September, 1995 level, and that a large proportion of the reduction in mortality could be explained by new treatments or combinations of treatments.

Here I will re-examine the impact of new drugs on HIV mortality at the aggregate level during the period 1987-1998. It is interesting to know whether the effects identified from painstaking analysis of large micro datasets can be detected from aggregate data. Also, my analysis, unlike the micro studies cited, will include the period of rapidly increasing HIV mortality as well as the period of declining HIV mortality. In addition, I will investigate the interrelationships between drug approvals, drug consumption, and mortality.

My objective is to estimate eqs. (3) and (5), using data on HIV mortality and HIV drug approvals. I obtained annual data on the number of U.S. deaths caused by HIV (ICD9 code 042) for the period 1987-1998 from the Compressed Mortality File.[11] These data are displayed in Figure 6. Between 1987 and 1995, the number of HIV deaths more than tripled, from 13,151 to 41,388. Fortunately, however, this eight-year increase was completely reversed in the following three years: the number of HIV deaths in the U.S. fell to 12,459 in 1998.

To compute the number of HIV drugs approved by the FDA, by year, I needed (1) to identify all drugs that have HIV as an indication, and (2) to determine the FDA approval dates of those drugs. I used the Drug Indications Master Table in First DataBank's National Drug Data File (http://www.firstdatabank.com/drug/index.html) to identify drugs that have HIV as an indication. I obtained FDA approval dates from the FDA Orange Book (http://www.fda.gov/cder/ob/default.htm) and unpublished FDA data. The drugs are listed in order of date of FDA approval in Table 2.

[11] 1987 is the first year in which any HIV deaths are recorded in the Compressed Mortality File.

The number of HIV drugs approved, by year during the period 1987-1999, is shown in Figure 7. During 1987-1993, only 4 HIV drugs (0.57 drugs/year) were approved. During 1994-1998, 10 drugs (2 drugs/year) were approved.

Recall that the simplest mortality model (based on the assumption of zero depreciation) implied that the reduction in mortality is proportional to the number of drugs approved in the previous year. Annual time-series data on the reduction in HIV deaths and the number of HIV drugs approved in the previous year are plotted in Figure 8. There appears to be remarkably strong correlation. Both series were essentially constant from 1988 to 1993; both increased significantly from 1993 to 1996; and both declined from 1996 to 1997.

Estimates of eq. (3) confirm the existence of a strong direct correlation between mortality reduction and lagged FDA approvals. The estimated relationship is (t-statistics in parentheses):

$$-\Delta \text{MORT}_t = \underset{(3.40)}{-6328} + \underset{(4.74)}{6093}\ \text{FDA}_{t-1} \qquad R^2 = .7378$$

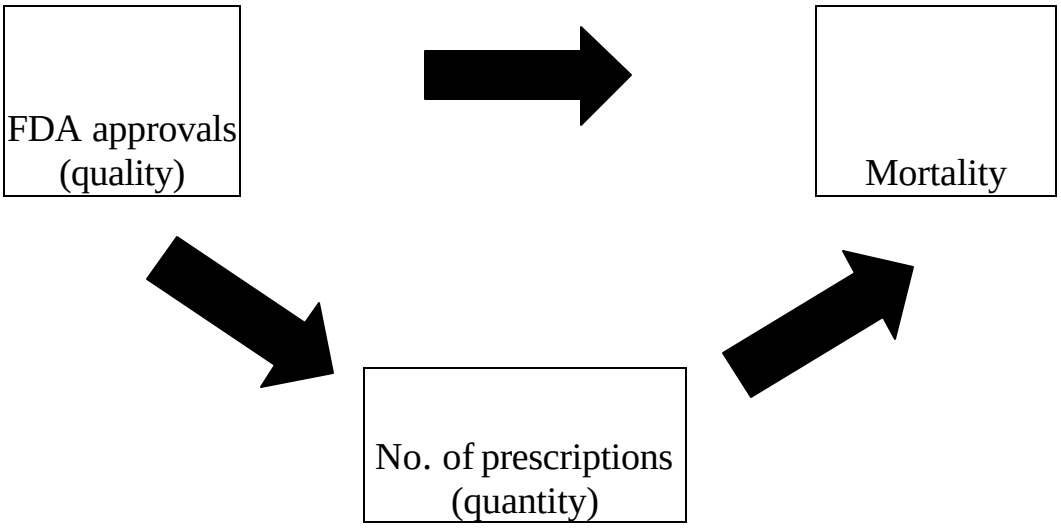
The probability value associated with the FDA_{t-1} coefficient is .0015, indicating that we can reject the null hypothesis of no relationship at the 99.85% level of significance. The R^2 value indicates that the number of FDA approvals explains almost three-fourths of the annual fluctuations in the reduction in HIV mortality. The point estimate of the FDA_{t-1} coefficient indicates that the annual number of HIV deaths is reduced by 6093, on average, by one additional HIV drug approval.

Estimates of other, more general, models of HIV mortality are presented in Table 2. Column 1 shows the estimate of eq. (5), in which the depreciation rate is not constrained to equal zero. The estimated FDA_{t-1} coefficient is similar to its value in the restricted equation, which is not surprising since the restriction cannot be rejected. The equation implies that one additional HIV drug approval this year will prevent 5986 HIV deaths next year and ultimately prevent 33,819 HIV deaths. Column 2 includes a time

trend; its inclusion has essentially no effect on the estimates. In column 3 the dependent variable is the log rather than the level of the number of deaths.[12] The estimated FDA_{t-1} coefficient is also highly significant in this version, but the implied short-run and long-run marginal effects of FDA approvals on mortality (evaluated at the sample mean values of MORT and FDA) are slightly smaller than they are in column 1.

Data provided by IMS Health Global Services (http://www.ims-global.com/) on the total number of units of HIV antivirals sold in the U.S. enable me to analyze the interrelationships among quantity of drugs (number of units), "quality" of drugs (assumed to be an increasing function of DRUG_STK), and mortality. Column 4 includes the log of the number of HIV prescriptions (n_rx) but excludes FDA_{t-1}. The coefficient on ln(n_rx) is negative and highly significant: HIV mortality is strongly inversely related to the quantity of HIV drugs consumed. Column 5 includes both drug quantity and drug quality variables. The coefficient on drug quantity declines more than 50 percent in magnitude, and is no longer significant. The drug quality variable (FDA_{t-1}) declines too, but by less than a third, and remains significant at the 7 percent level. This suggests that mortality depends to a greater extent on drug quality than it does on drug quantity, and also that quality and quantity are positively correlated. The relationship between quality and quantity—the impact of approvals on drug consumption—is examined in column 6. The dependent variable is the log of the number of prescriptions (in thousands of units). The regression indicates that new drug approvals have a sizeable impact on drug consumption. One additional HIV drug approval this year will result in 1.2 million additional HIV drug units consumed next year and ultimately result in 3.6 million additional HIV drug units consumed. The regressions in columns 4-6 jointly indicate that drug approvals reduce mortality both directly and indirectly (via increased drug consumption), as depicted in the following diagram:

[12] Because FDA_{t-1} is 0 in some years (see Figure 5), we cannot also take the log of FDA_{t-1}.



Summary and conclusions

I have investigated the effect of large increases in the number of drugs available to treat rare diseases and HIV on mortality associated with them. Figure 9 indicates that mortality from both diseases declined dramatically following increases in drug approvals.

Before the Orphan Drug Act went into effect (between 1979 and 1984), mortality from (initially) rare diseases grew at the same rate as mortality from other diseases. In contrast, during the next five years, mortality from (initially) rare diseases grew more slowly than mortality from other diseases. I estimate that one additional orphan drug approval in year t prevents 211 deaths in year t+1 and ultimately prevents 499 deaths, and that about 108 thousand deaths from rare diseases will ultimately be prevented by all of the 216 orphan drugs that have been approved since 1983. Deaths are more closely related to the number of orphan product designations than they are to the number of approvals.

Consistent with previous patient-level studies of HIV, I find that new drugs played a key role in the post-1995 decline in HIV mortality. I estimate that one additional HIV drug approval in year t will prevent 5986 HIV deaths in year t+1 and ultimately prevent 33,819 HIV deaths. HIV drug approvals have reduced mortality both directly and indirectly (via increased drug consumption). HIV mortality depends on both

the quality and the quantity of medications consumed, and new drug approvals have a sizeable impact on drug consumption: one additional HIV drug approval in year t results in 1.2 million additional HIV drug units consumed in year t+1 and ultimately result in 3.6 million additional HIV drug units consumed.

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Figure 1
Average annual number of drugs brought to market

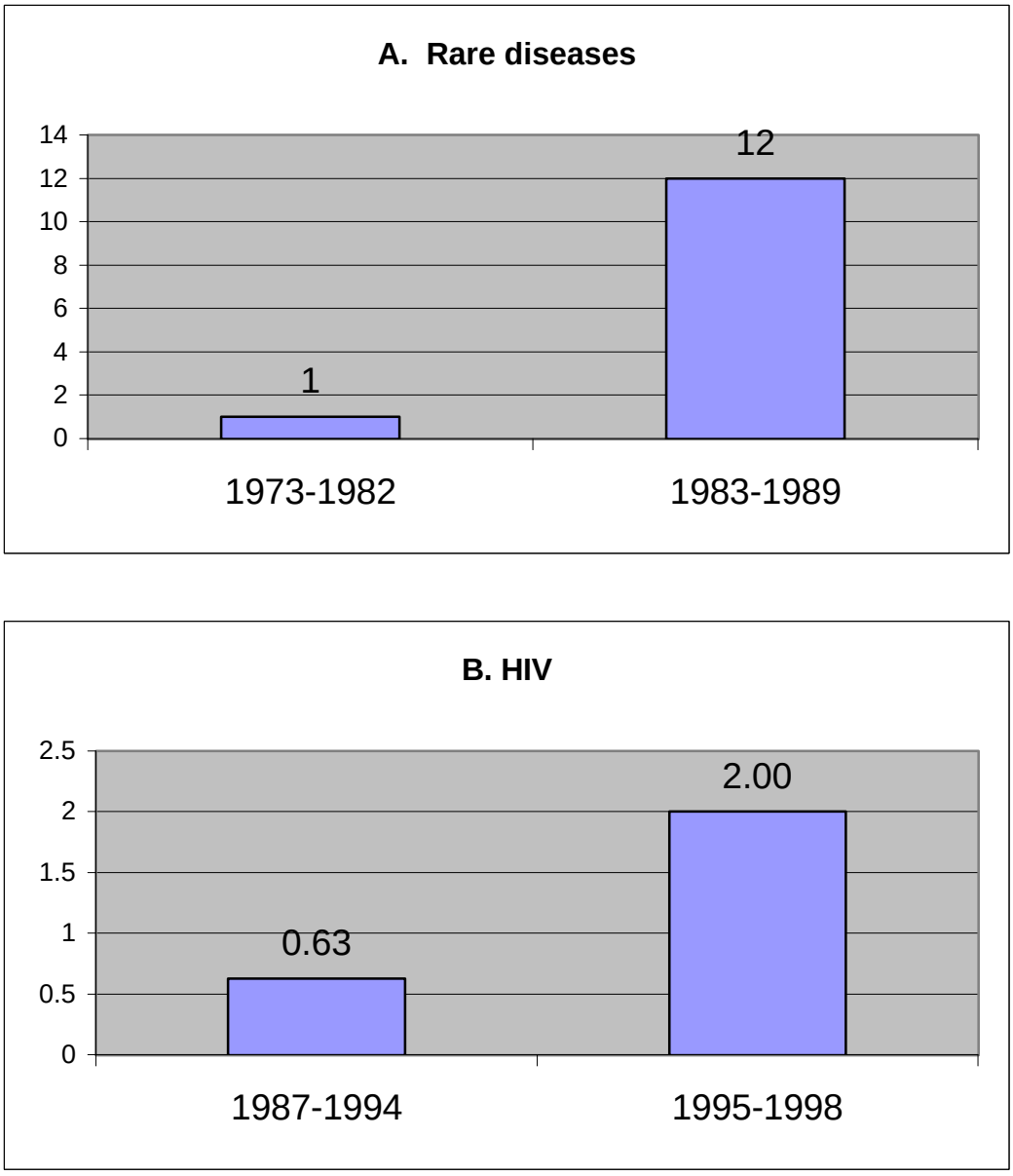


Figure 2
Number of orphan drug designations and approvals

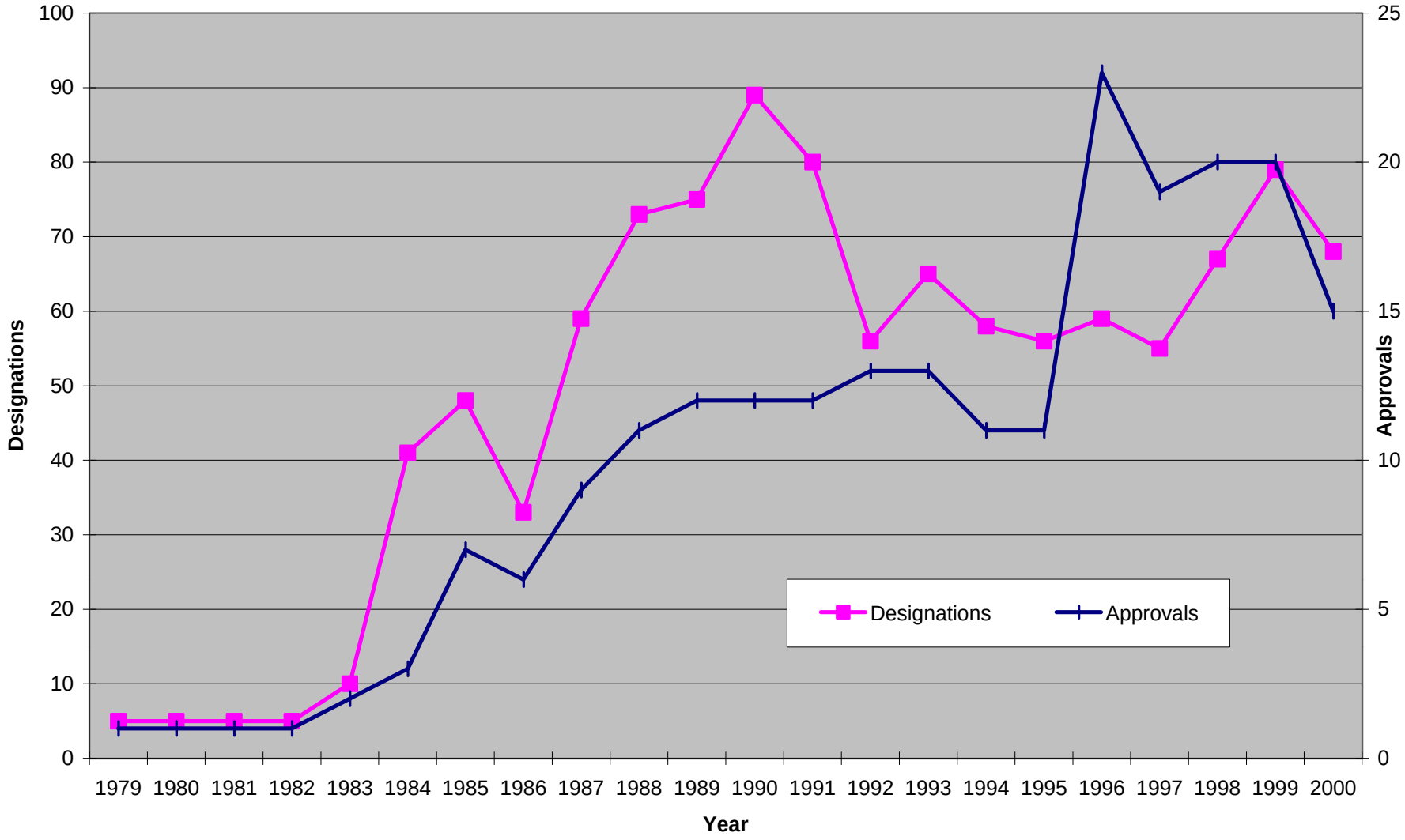


Figure 3
Number of deaths from rare diseases and other diseases, 1979-1998

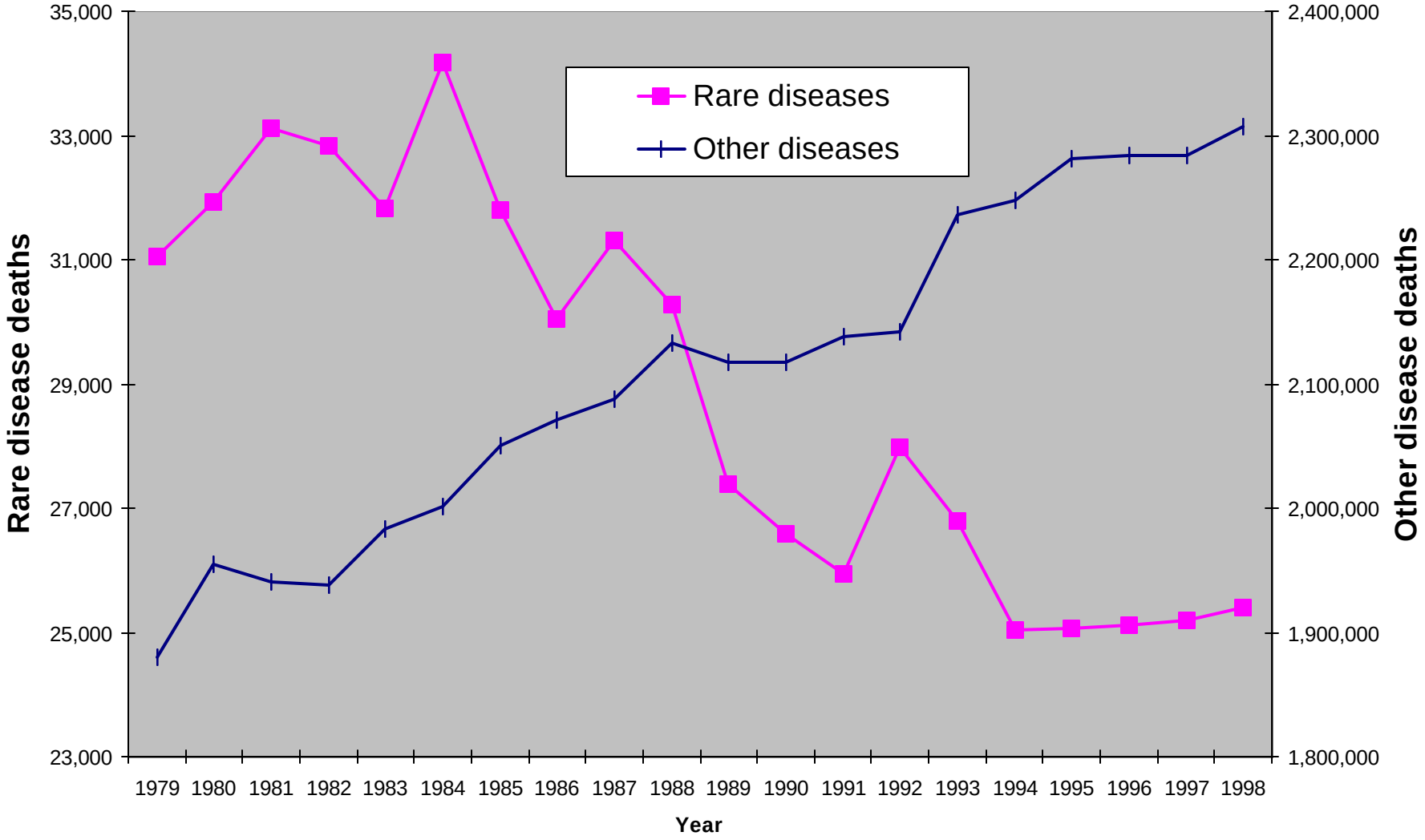


Figure 4
Orphan Drug Designations and Rare Disease Deaths, 1979-1998

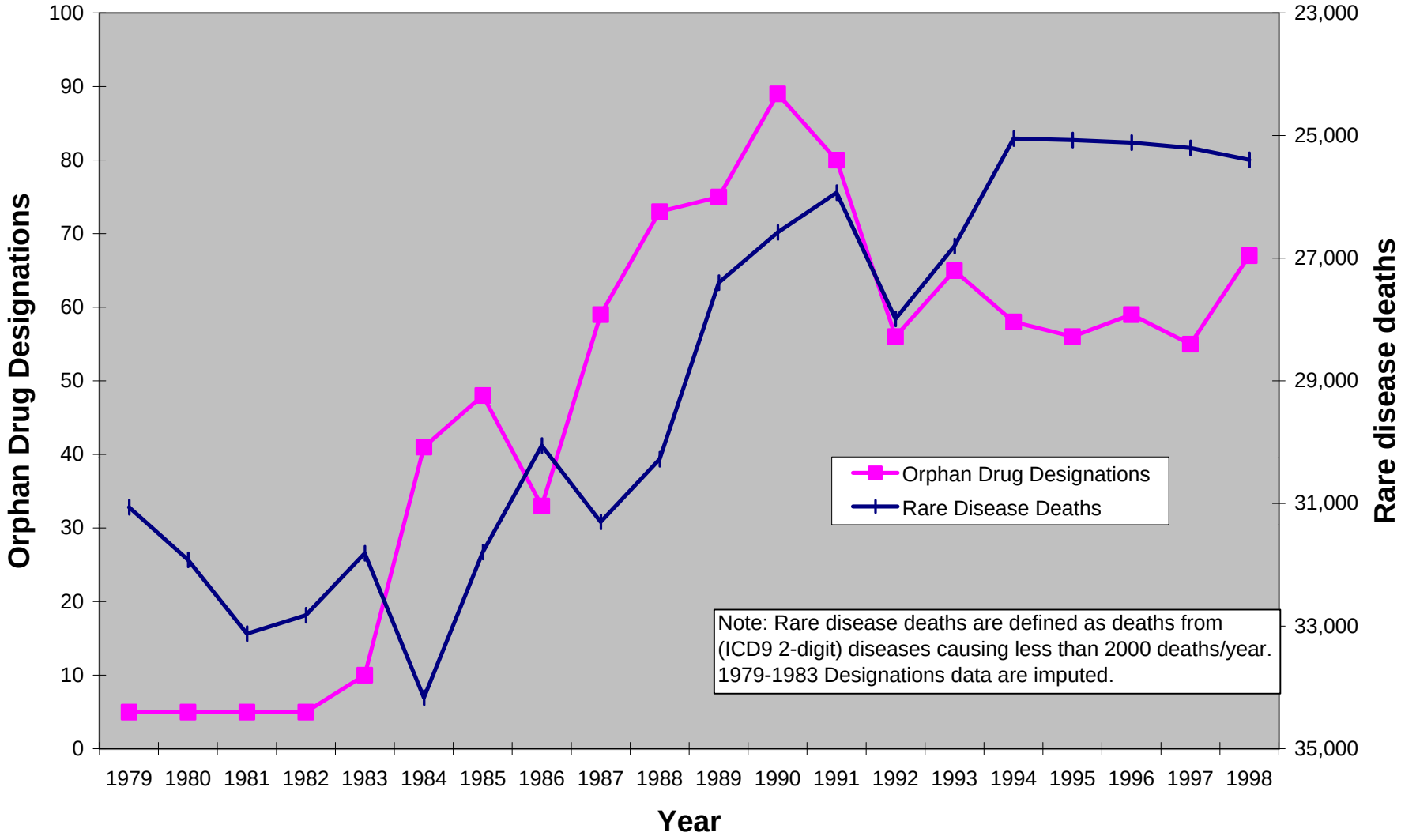
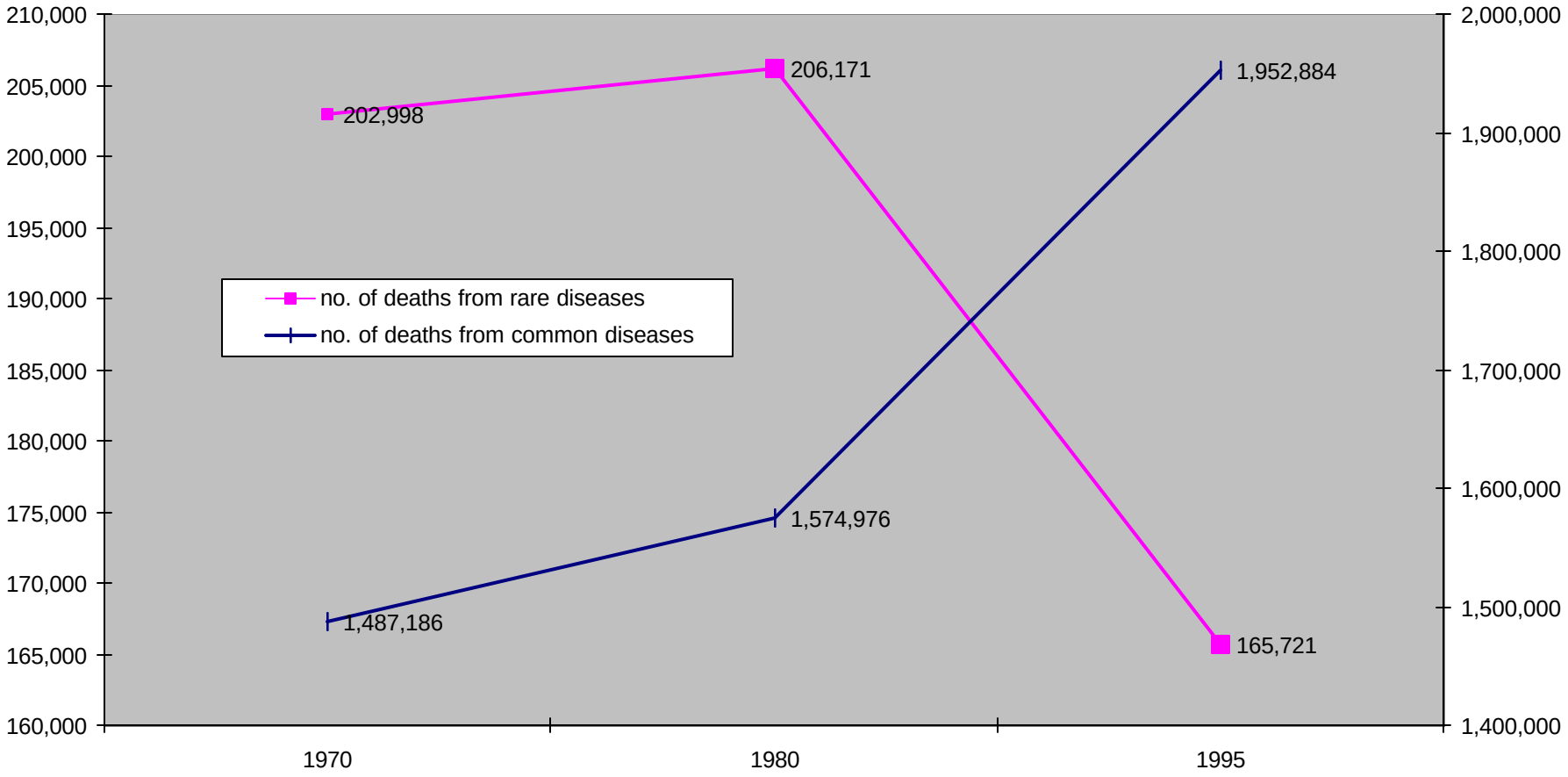


Figure 5
Number of deaths from rare diseases and other diseases, 1970, 1980, & 1995:
Alternative definition of rare disease (< 5000 deaths)



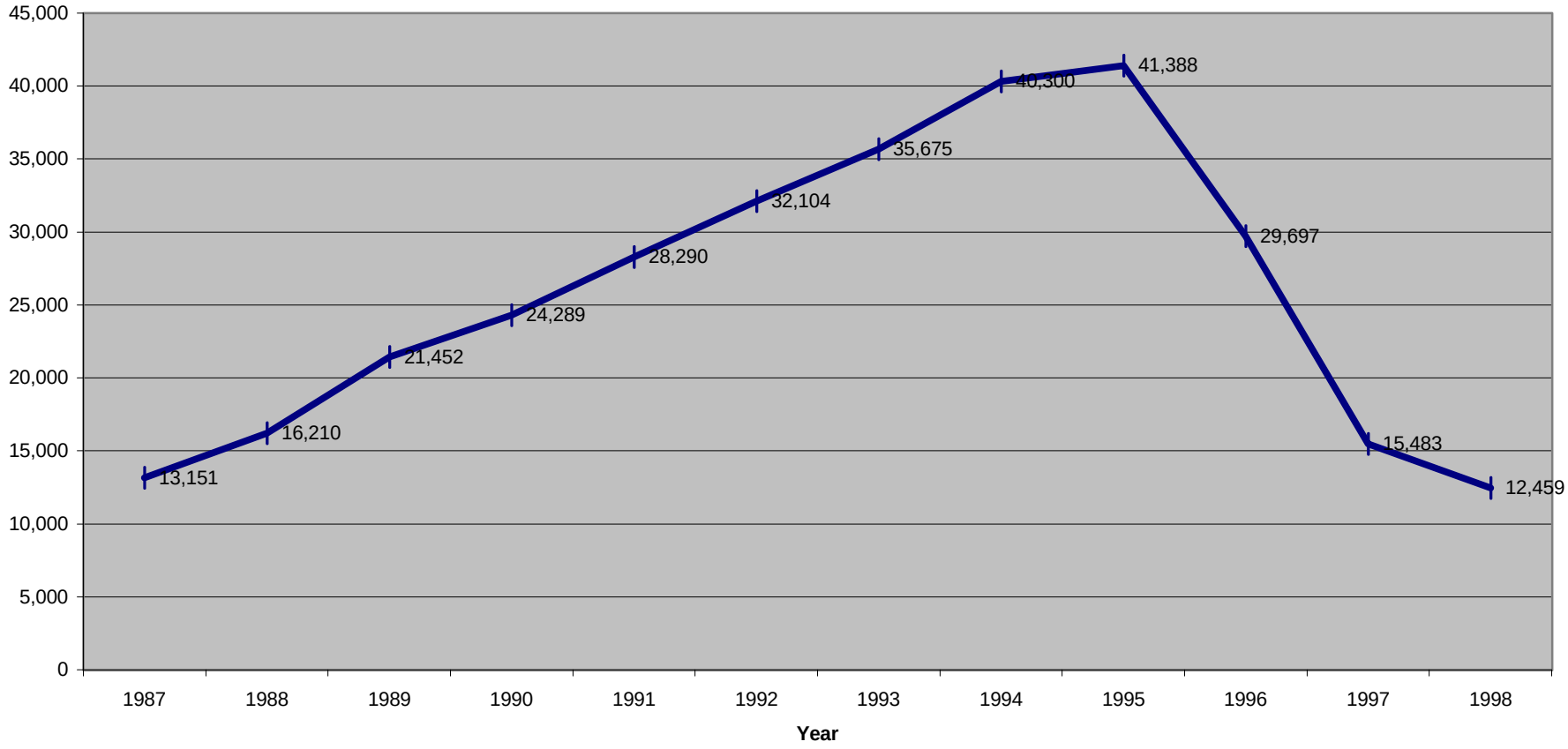
Source: Author's calculations based on 1970, 1980, and 1995 Vital Statistics--Mortality Detail files. Rare diseases are defined as diseases causing fewer than 5000 deaths per year.

Table 1
Estimates of models of mortality from rare diseases
(t-statistics in parentheses; p-values in brackets)

Column	1	2	3	4	5	6	7	8	9	10
Dependent variable*	deaths	deaths	deaths	deaths	deaths	lyl	lyl	lyl	lyl	lyl
apps	-172.9					-5486				
	(2.04)					(2.15)				
	[0.0599]					[0.0472]				
$apps_{-1}$		-211.232			-114.649		-4847			-3489
		(2.36)			(1.26)		(1.96)			(1.48)
		[0.0321]			[0.2268]		[0.0685]			[0.1605]
des_{-1}			-40.478	-29.7861	-31.5802			-747.795	-702.85	-625.478
			(3.11)	(2.35)	(2.17)			(2.42)	(3.77)	(1.99)
			[0.0072]	[0.034]	[0.048]			[0.0286]	[0.0021]	[0.0667]
year				-231.879					-11814	
				(2.11)					(4.89)	
				[0.0532]					[0.0002]	
lagged dependent variable	0.6366	0.5766	0.6883	0.3776	0.5485	0.6027	0.6631	0.7973	0.0676	0.5965
	(3.65)	(3.25)	(5.98)	(2.09)	(3.47)	(3.24)	(3.76)	(8.03)	(0.42)	(3.62)
	[0.0024]	[0.0054]	[<.0001]	[0.0552]	[0.0038]	[0.0051]	[0.0019]	[<.0001]	[0.6844]	[0.0028]
Long-run effect effect	-476	-499	-130			-13,808	-14,387	-3,689		

* deaths =no. of deaths; lyl= life-years lost before age 75

Figure 6
HIV mortality, 1987-1998



Source: Compressed Mortality File, a county-level national mortality and population database spanning the years 1968-1997. Data for 1979-199 available on CDC WONDER (http://wonder.cdc.gov/mortsql.shtml). 1987 is the first year in which any HIV deaths are recorded in the Compres Mortality File.

Table 2
Drugs with HIV indication, by FDA approval date

FDA approval date	Drug	Indication
19-Mar-87	ZIDOVUDINE	HIV INFECTION
21-Oct-88	OCTREOTIDE	AIDS-ASSOCIATED DIARRHEA
9-Oct-91	DIDANOSINE	HIV INFECTION
19-Jun-92	ZALCITABINE	HIV INFECTION
24-Jun-94	STAVUDINE	HIV INFECTION
17-Nov-95	LAMIVUDINE	HIV INFECTION
6-Dec-95	SAQUINAVIR	HIV INFECTION
1-Mar-96	RITONAVIR	HIV INFECTION
13-Mar-96	INDINAVIR	HIV INFECTION
21-Jun-96	NEVIRAPINE	HIV INFECTION
14-Mar-97	NELFINAVIR	HIV INFECTION
4-Apr-97	DELAVIRADINE	HIV (IN COMBO WITH NUCLEOSIDE ANALOGUES)
17-Sep-98	EFAVIRENZ	HIV (IN COMBO W/ANTIRETROVIRAL AGENTS)
17-Dec-98	ABACAVIR	HIV (IN COMBO W/ANTIRETROVIRAL AGENTS)
15-Apr-99	AMPRENAVIR	HIV (IN COMBO W/ANTIRETROVIRAL AGENTS)

Sources: National Drug Data File (indications); FDA Orange Book and unpublished FDA data (approval dates).

Figure 7
Number of drugs with HIV indication approved

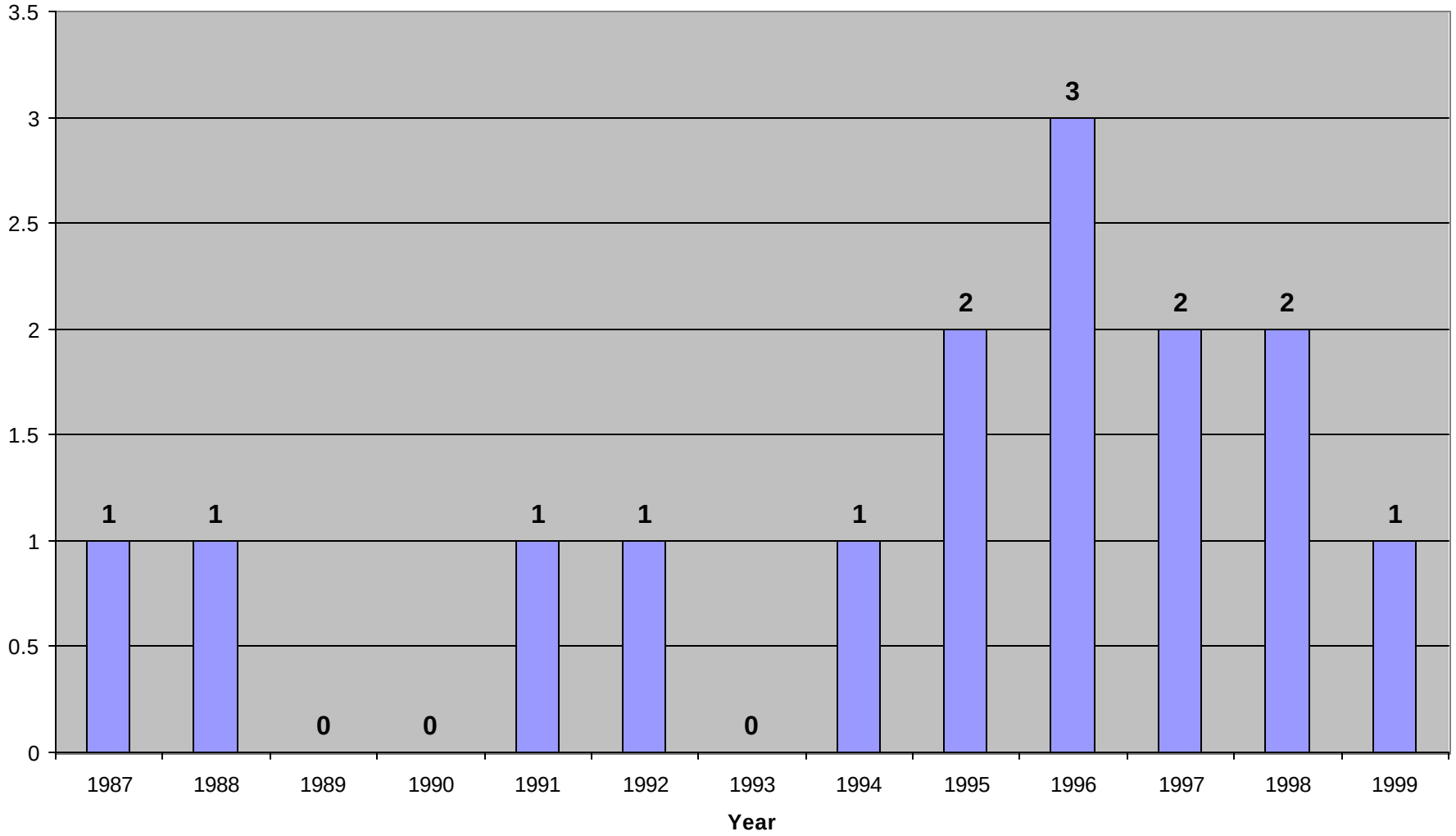


Figure 8
HIV drug approvals and HIV mortality reduction

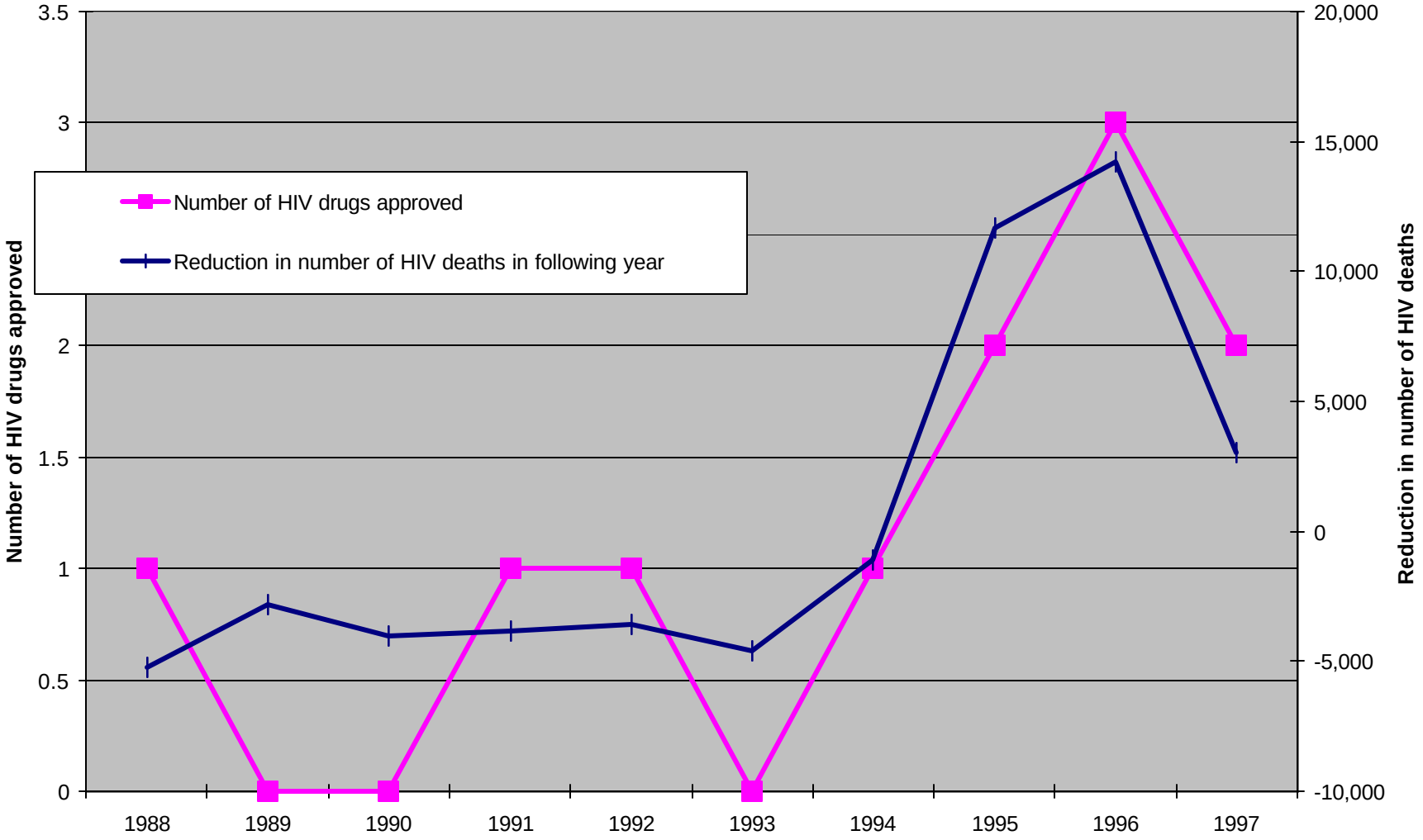


Table 3
Estimates of models of mortality from HIV
(t-statistics in parentheses; p-values in brackets)

Column	1	2	3	4	5	6
dependent variable	deaths	deaths	log(deaths)	log(deaths)	log(deaths)	log(n_rx)
FDA_{t-1}	-5986	-5574	-0.2493		-0.1661	0.3626
	(4.89)	(3.04)	(5.01)		(2.22)	(5.68)
	[0.0018]	[0.0227]	[0.0015]		[0.0679]	[0.0003]
log(n_rx)				-0.2887	-0.1325	
				(4.37)	(1.48)	
				[0.0033]	[0.1886]	
year		-191.1728				
		(0.32)				
		[0.7613]				
lagged dependent variable	0.823	0.852	0.8025	0.9806	0.8936	0.6746
	(7.03)	(5.47)	(6.76)	(6.96)	(7.55)	(13.36)
	[0.0002]	[0.0016]	[0.0003]	[0.0002]	[0.0003]	[<.0001]
short-run effect of FDA	-5986	-5574	-5,160			1182.093
long-run effect of FDA	-33,819	-37,662	-26,129			3,633

Figure 9
Average annual change in number of deaths