

The Impact of HIV Antiretroviral Treatments: Evidence for California's Medicaid Population

Very Preliminary and Incomplete – Comments Welcome

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Abstract

In late 1995 and early 1996, the FDA approved four new antiretroviral drugs that were designed to reduce the ability of the HIV virus from replicating in infected patients. Usages rates of these drugs quickly skyrocketed and between 1995 and 1998 the mortality rate for individuals living with AIDS in the U.S. declined by approximately 70 percent. In this paper, we use data for the 1993-2003 period for a sample of more than 10,000 Medicaid recipients from the state of California diagnosed with HIV/AIDS to estimate the contribution of HIV antiretroviral drugs to this decline and the corresponding effect on long-term health care spending. The Medicaid population is a natural one to consider given that over half of AIDS patients in the U.S. are enrolled in this program. Using the detailed information on health care utilization in our Medicaid claims data, we account for the fact that patients taking HIV antiretroviral drugs are significantly less healthy than the average HIV/AIDS patient in our sample. Our findings demonstrate that a rapid increase in the use of Epivir (a nucleoside reverse transcriptase inhibitor) and protease inhibitors was responsible for the entire 70 percent drop in the mortality rate in our sample from 1995 to 1998. Despite the entry of more than a dozen drugs since these four, mortality rates have remained virtually unchanged. Using measures of both actual and simulated long-term health care spending, we find that the use of Epivir and protease inhibitors led to a threefold increase in lifetime Medicaid spending due to their high cost and the sharp increase in life expectancy. Despite this, the new treatments were cost-effective, with the average additional cost in Medicaid spending per life-year saved equal to \$20,256.

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I. Introduction

From 1991 to 1995, HIV/AIDS¹ was the leading cause of death among men between the ages of 25 and 44 in the U.S. and the eighth-leading cause of death overall. Annual mortality rates for individuals diagnosed with this illness stood at nearly 30 percent in 1993, though according to data published by the CDC these rates were trending down at a gradual rate during the early 1990s.² By early November of 1995, four different prescription drugs were available for the treatment of HIV/AIDS. Utilization of these drugs had been declining – perhaps because the drugs were more effective at treating the opportunistic infections resulting from HIV/AIDS rather than attacking the virus itself. Additionally, these drugs were shown to have serious side effects for many patients – leading some to terminate treatment.

In a four-month period from mid-November of 1995 to mid-March of 1996, the U.S. Food and Drug Administration approved four new prescription drugs for the treatment of HIV/AIDS.. Epivir was the first one of these new treatments to be approved for use and belonged to the same class of drugs (nucleoside reverse transcriptase inhibitors or NRTI) as the original four. Invirase, Norvir, and Crixivan were approved next and belonged to an entirely new class of drugs known as protease inhibitors (PI). In June of 1996, a third class of drugs was introduced when Viramune, a non-nucleoside reverse transcriptase inhibitors (NNRTI) was approved for use in patients. Particular drugs from different classes were used in combination form highly active anti-retroviral treatments, also known as HAART therapy.

Early clinical trials of these new drug therapies demonstrated their ability to reduce the viral load in patients and to increase CD4 cell counts, a type of blood cell critical for fighting off infections (Vella, 1994; Danner et al, 1995; Markowitz et al, 1995; Collier et al, 1996). Use of these new therapies spread rapidly, with almost 60 percent of HIV/AIDS patients using protease inhibitors by the end of 1996 (Bozette et al, 2001). As HAART use expanded, mortality rates among AIDS patients dropped sharply. Between 1995 and 1998 annual mortality rates of AIDS patients fell by almost 70 percent.³ As a result

¹ These stand for human immunodeficiency virus and acquired immune deficiency syndrome, respectively.

² <http://www.cdc.gov/hiv/stats.htm>.

³ CDC HIV/AIDS Surveillance Report, 2001.

the life expectancy for individuals with AIDS rose substantially and – despite a decline in infection rates – the number infected with this illness continued to rise.

A large number of later studies, some using randomized research designs (e.g., Hammer *et al*, 1997; Delta Coordinating Committee, 2001), others using observational data on patients (Palella *et al*, 1998; Detels *et al*, 1998; Chaisson *et al*, 1999; Schwarcz *et al*, 2000; Lewden *et al*, 2001; Porter *et al*, 2003; Cohen *et al*, 2002; Eggers *et al*, 2003; and the CASCADE Collaboration, 2003), have investigated the life saving benefits of HAART therapies. Some of these studies also estimate the effect of these new drugs on health care spending (Gebo *et al*, 1999; Keiser *et al*, 2001). All studies show these new drug therapies and/or HAART generates a statistically significant reduction in mortality among HIV/AIDS patients. Although these studies made important contributions, most had important limitations. For example, the typical study had small sample sizes and patients were followed for short periods of time. Additionally, studies varied widely in their efforts to account for endogenous treatment decisions in the non-randomized studies. Studies where treatment was randomly assigned were carefully selected populations, raising the question of whether the drugs would be as effective in real-world settings when patients might not comply with the treatment regimens.

Perhaps most surprising of all, virtually all studies had the same three important limitations. First, nearly all studies assumed HAART use generated a common ‘treatment effect,’ that is, HAART reduce mortality probabilities by the same amount regardless of the stage of the illness. As we outline below, the clinical experience with HAART suggests there should be tremendous heterogeneity in treatment effects with the ‘sicker’ patients receiving the greatest benefit. Therefore, we would expect the impact of HAART to vary with pre-HAART conditions. While most studies control for patient severity in multivariate models, none allow for the treatment effect to vary by these characteristics. Second, no previous work has investigated what fraction of the decline in mortality rates was attributable to HAART therapies versus other factors. As mentioned above, mortality rates among AIDS patients were falling prior to the approval of the new treatments and thus it is possible that other health care treatments, changes in patient behavior, or some other factor was responsible for much of the improvement in health

outcomes. Third, most previous work has focused on estimating the impact of HAART on annualized medical care costs and has not explored the effect of HAART therapy on long term health care spending. Given the significant increases in life expectancy, it is possible that short and long-term health care spending have moved in opposite directions.

In the current study, we aim to build upon previous work by using administrative data for a large sample of individuals diagnosed with HIV/AIDS and eligible for the Medicaid program in the state of California. Given that more than half of U.S. residents diagnosed with AIDS are on Medicaid, the current study's focus on recipients of this program is not as limiting as it might otherwise be. Similarly, the state of California has more AIDS patients than any other state except for New York and is therefore a natural one to focus on if one hopes to obtain large sample sizes.

Our data includes patient demographic characteristics along with detailed information on each individual's health care utilization for the eleven-year period from 1993 to 2003. Using this data, we can follow each person throughout our study period while they are eligible for Medicaid. Additionally, the data has been linked to mortality records maintained by the state of California's Center for Health Statistics, which allows us to investigate the effect of new prescription drugs on mortality. The full data set includes information for a 24 percent random sample of individuals with one or more months of Medicaid eligibility during this period. Of the more than 3.8 million California residents in this sample, approximately 13,000 have two or more claims with a primary or secondary diagnosis of HIV/AIDS between 1993 and 2003. This sample serves as the starting point for our analysis.

We begin by showing that the number of individuals in our sample from one year to the next tracks the number of people living with AIDS reported by the CDC for the entire state of California remarkably well. For example, from the second half of 1994 until the second half of 2001, the number of individuals in our sample diagnosed with HIV/AIDS increased by 58.3 percent, which is almost identical to the 58.2 percent increase for the entire state. We next describe changes in the mortality rate for individuals in our sample, which tracks the statewide trends very closely. From the first quarter of 1996 to the third quarter of 1997, the quarterly mortality rate in our sample falls from 6.9 percent to 1.8

percent. This accounts for the vast majority of the mortality improvement during our study period, with this rate falling somewhat more during the next four years to an average of 1.6 percent in the 2001 calendar year.

The mortality improvements in our sample occurred precisely when utilization of the four drugs described above was growing substantially. In the third quarter of 1995, no individuals in our sample were taking Efavir or a protease inhibitor. Eighteen months later, 56 percent of our sample was taking one or more of these four drugs, and this rate remained fairly constant during the next six years. There was no increase in the use of other drug treatments during this short time interval, strongly suggesting that the driving force behind the sharp decline in mortality rates was the diffusion of the new drug treatments.

To probe more formally on this issue, we next estimate time-series specifications in which we regress changes in the quarterly mortality rate on changes in the use of various drug treatments in our sample. Our findings here demonstrate that the increase in the use of Efavir and protease inhibitors can explain more than ninety percent of the 5.1 percentage point decline in mortality from late 1995 until the middle of 1997. Our point estimate suggests that the average person taking one or more of these drugs reduced their quarterly mortality rate by 8.4 percentage points. Given that this is substantially greater than the average mortality rate of 6.9 percentage points before the drugs were approved, it appears that the 56 percent of patients who took the drug had much higher baseline mortality probabilities than the 44 percent who did not.

We next estimate individual-level specifications to investigate this issue and there are two key facets of our work. First, patients with the highest risk of death are the most likely to be recommended for use of HAART. Subsequently, to account for heterogeneity in health status, we group individuals into one of ten different deciles according to their health care utilization prior to the availability of these new drug treatments. This type of analysis is only possible given the longitudinal nature of our data. Second, the clinical benefits of HAART are correlated with baseline conditions, so we allow for heterogeneity in the treatment effect based on our patient severity index.

The health severity index predicts well not only pre-HAART mortality but also subsequent use of HAART. In the period before the new drugs were introduced, individuals in the top decile were ten times more likely than individuals in the lowest decile to die in the next quarter. Immediately after Epivir and the new protease inhibitors were approved, these same individuals were four times more likely to use the new treatments. The reason for this differential takeup appears to be heterogeneity in the benefits of the treatments – sick patients chose to use the new treatments because they derived a significantly greater benefit than did other patients.

In our final section we investigate the effect of the new treatments on health care spending. While the new drug treatments clearly reduced patient mortality, they also led to substantial increases in spending for the Medicaid program as HIV/AIDS patients now lived much longer. For example from 1994 to 1998 average spending during the next six years increased by more than 80 percent. This is likely much lower than the effect on lifetime health care spending, which for obvious reasons (censoring) cannot be calculated from our data. We therefore simulate the change in lifetime spending resulting from the new treatments and find that the cost per life year saved was approximately \$20,000. Given recent estimates of the value of additional life-years (Cutler and Richardson), our findings suggest that four drugs approved by the FDA in late 1995 and early 1996 were cost-effective. Interestingly while more than a dozen new drugs were approved for the treatment of HIV/AIDS during the remaining six-plus years of our study period, they appear to have done little to reduce mortality still further.

The outline of the paper is as follows. In section II, we provide some background information about HIV/AIDS and the emergence of new drug therapies in the mid 1990s. In section III, we describe how we construct the analysis files from our 24 percent random sample of Medicaid patients in California. In this section, we show our sample reproduces the stylized facts about AIDS mortality and tracks well the aggregate number of HIV/AIDS cases in California over this period. In section IV, we provide some time series evidence on the benefits of new anti-retroviral therapies and demonstrate that the release of Epivir and PIs in the late 1995/early 1996 period is responsible for nearly the entire decline in AIDS mortality over this period. We redo this analysis in Section V using individual-level data,

exploiting the panel nature of our data set to control for severity of illness. In section VI, we use the results from the individual-level regressions to obtain an estimate of the cost per life saved of these new HIV/AIDS therapies. In section VII, we make some concluding remarks.

II. Background on HIV/AIDS

AIDS is a chronic disease that damages, and ultimately destroys, an individual's immune system. AIDS is caused by HIV, an infection that kills the body's "CD4 cells" (also called T-helper cells), a type of white blood cell that helps the body fight off fungal, viral and parasitic infections. HIV is transmitted primarily by having sex with an infected partner, by injections (sharing contaminated needles for drug use or accidental piercing with a contaminated needle), or from an infected mother to child through pregnancy or breast-feeding. HIV is spread within the body when infected cells make copies of themselves. The HIV virus can weaken the immune system to the point where the body has difficulty fighting off certain "opportunistic infections."

Many of the infections usually controlled by a healthy immune system are life-threatening to AIDS patients. According to the CDC, an HIV-infected person progresses to AIDS once his CD4 cell count falls below a certain threshold⁴ or once he is diagnosed with an AIDS defining illness such as AIDS-related cancer, severe wasting, or dementia. Some HIV-infected patients progress to AIDS quickly while others can remain healthy for 10 years or more. Between initial infection with HIV and diagnosis of AIDS, a middle phase called symptomatic HIV infection occurs, which can include symptoms such as weight loss, diarrhea, and swollen lymph glands.

When the AIDS epidemic first appeared, providers could only treat the opportunistic illnesses rather than attack the virus itself. Over the past 15 years however, pharmaceutical advances have produced a number of new drugs that prevent HIV-infected cells from replicating, thereby reducing the progression to AIDS. To understand how these drugs work, it is useful to outline how HIV multiplies

⁴ A reduction in the CD4 cell count below 200 lymphocytes per cubic millimeter triggers an AIDS diagnosis. Healthy people usually have a helper T cell count between 600 and 1,000 cell/mm³.

inside a host. HIV enters a cell by binding both to the host cell's *CD4 receptors* and to a *co-receptor*. Once inside the cell, the virus sheds its protein skin releasing genetic material and enzymes. HIV is a *retrovirus* that has RNA as its nucleic acid and uses the enzyme *reverse transcriptase* to copy its genome into the DNA of the host cells chromosomes. This process is known as *reverse transcription*, and when conversion is completed, the HIV DNA is then integrated into the genetic material of the host cell using another HIV enzyme called *integrase*. Once HIV DNA is integrated into the host cell's genetic material, it directs the production of new HIV proteins. When these new proteins are first produced, they are in the form of long chains called *polyproteins*, which must be cut up into smaller pieces before they can be used to create new viruses. This cutting is done by a third HIV enzyme called *protease*. The newly cut pieces are assembled into new virus particles, which then infect other cells.

The focus of this paper is three classes of AIDS drugs introduced since 1987: nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), and non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI). All these drugs reduce the ability of the virus to replicate inside the host but all work in a different way.⁵ In order for the enzyme *reverse transcriptase* to complete the transcription process, it must first build new chains of nucleotides, the basic building blocks of DNA. NRTIs and NNRTIs work in the early stages of virus replication by preventing the reverse transcription process. NRTIs replace nucleotides with analog nucleosides, creating a defective HIV particle that cannot reproduce itself. In contrast, NNRTIs bind to the *reverse transcriptase* enzyme preventing the reverse transcription process. In the later stages of the HIV virus replication process, protease inhibitors prevent the protease enzyme from dividing the polyprotein strands, producing an HIV particle that is unable to infect other cells. The first NTRI was approved for use in 1987, but more effective types of these drugs were not introduced until late 1995. Soon after that date, the first PIs and NNRTIs were approved for use as well. The drugs introduced during the narrow window from late 1995 through the first half of 1996 that are the focus of this paper.

⁵ A fourth group of drugs - known as fusion inhibitors - was approved by the FDA in 2003. These drugs were however introduced near the end of our sample period and will not be part of our analyses.

Early clinical trials demonstrated that these new therapies were highly effective at reducing viral replication and increasing CD4 T-cell counts in patients with HIV infection (Vella, 1994; Danner *et al*, 1995; Markowitz *et al*, 1995; Collier *et al*, 1996). The success of protease inhibitors in clinical trials led to rapid approval of these drugs by the Food and Drug Administration (FDA). On December 6, 1995, Saquinavir became the first protease inhibitor to be approved for the treatment of AIDS. FDA approval was granted in just 97 days after the application was filed under an accelerated process, a regulatory mechanism through which the agency bases early approval for a product on laboratory markers such as CD4 cell counts, rather than on clinical endpoints such as reduced mortality and morbidity.⁶ Soon after, two other protease inhibitors were approved for use by the FDA: Ritonavir was approved on March 1, 1996 after only 72 days of review,⁷ and Indinavir was approved on March 13, 1996 after only 42 days of review.⁸ A complete list of drugs designed to treat AIDS is provided in Table 1. In the first three columns, we include information about the drug class, the brand name and the FDA approval date. Retrovir is more commonly known as AZT and was the first drug approved to treat AIDS patients. The key dates in this table are however in late 1995 when an incredibly effective NRTI (Epidur) and the first protease inhibitor (Invirase) were released within one month of each other.

The release of these new drugs spawned the use of highly active antiretroviral treatments (HAART), which is the use of three or more antiretroviral drugs to treat HIV. Treatment procedures for HIV patients are outlined in “Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents” developed in 2002 by the panel on Clinical Practices for Treatment of HIV Infection (Department of Health and Human Services) and the Henry J. Kaiser Family Foundation. When initiating therapy in patients who have never been on HAART before, the guidelines recommend patients start with one protease inhibitor in combination with two NRTIs. Other treatment options include mixtures of NNRTIs and NRTIs for patients whose initial regimen was not successful.

⁶ See <http://www.fda.gov/bbs/topics/NEWS/NEW00521.html>.

⁷ See <http://www.fda.gov/bbs/topics/NEWS/NEW00527.html>.

⁸ See <http://www.fda.gov/bbs/topics/NEWS/NEW00528.html>.

The decision of when to initiate therapy is based primarily on CD4 cell counts and HIV viral loads. Current guidelines recommend HAART for all patients with ≤ 200 CD4+ T cells/mm³, and possibly when counts are between 200-350 cells/mm³ (NIH, 2004; Yenni et al, 2003). The NIH notes that there is little evidence of clinical benefits if therapy is initiated when CD4 counts are in excess of 350, although a number of recent studies (Wang et al, 2004; Palella et al, 2004; Sterling et al, 2003) has lead some to re-evaluate this guideline (Schechter 2004). However, studies indicate it is optimal to begin treatment before CD4 counts fall below 200, but or greater than 20,000 copies of HIV RNA/ml of plasma should be offered therapy. However, all patients diagnosed as having advanced HIV disease, which is defined as any condition meeting the 1993 CDC definition of AIDS, should be considered for treatment with antiretroviral agents regardless of plasma viral levels. The ultimate goal of treatment is complete viral suppression, which is defined as less than 500 copies of HIV RNA/ml.

The guidelines note the costs and benefits of an early start of HAART. An aggressive therapy might prevent both the degradation of the immune system and the elevation of viral loads. In contrast, HAART therapy may reduce the quality of life because of severe side effects.⁹ Patients may also develop drug resistance, thereby reducing drug options in the future. In general however, the above guidelines suggest that in a sample of therapeutically naive patients, we should find those who are sicker to be the most likely to begin HAART therapy. A shortcoming of our claims data sets is the lack of clinical information such as viral loads or CD4 counts, but, as we demonstrate below, the pre-treatment intensity of medical care use serves as an effective proxy for those most likely to be enrolled in HAART therapy.

In a short period after the approval of these drugs, HAART became the standard treatment for those infected with HIV. Bozzette et al (2001) found that by the end of 1996, nearly 60 percent of HIV infected patients were using protease inhibitors while estimates for some urban clinics calculated HAART use rates in excess of 80 percent by the late 1990s (Pella et al, 1998; Sackoff, McFarland, and Shin, 2000; Ghani, Donnelly, and Anderson, 2003). Medicaid patients consistently have lower use rates for these new

⁹ Side effects that range from more minor medical conditions such as fatigue, fever, nausea, and headaches, to severe conditions such as liver damage, diabetes, high cholesterol, fat maldistribution, heart attacks and stroke.

drugs than the general population (Bozzette et al, 2001; Shapiro et al, 1999), but estimates for various state indicate that HAART use among HIV positive on Medicaid in 1998 ranged from 37 percent in Texas, to 46 percent in California, to 56 percent in Florida and New York (Kahn et al, 2002), to almost 70 percent in New Jersey (Sambamoorthi, 2001).

As more AIDS patients began HAART therapy, and as mortality detail data for 1996 became available, researchers began to notice a decline in mortality rates from AIDS (Chiasson *et al*, 1997). A February 28, 1997 report in the *Morbidity and Mortality Weekly Reporter* noted that in 1996, for the first time, AIDS-attributable deaths declined from the previous year's total. Between 1995 and 2001 deaths among AIDS patients fell 70 percent. An even more staggering change occurred in the AIDS patient annual mortality rate, calculated as annual deaths divided by the number of AIDS patients alive at the beginning of the year plus those diagnosed during the year, which dropped by 82 percent in the 1995-2001 period. Note however that prior to 1995, unlike AIDS deaths, the death rate was declining, dropping 23 percent between 1991 and 1995.

A number of authors have examined the impact of HAART therapies on medical outcomes and mortality. Using data from a random assignment clinical trial, Hammer *et al* (1997) found that those assigned HAART therapy had a 58 percent lower mortality rate than those in the control group. Survival data on patients in non-experimental settings by Detels et al (1998), Schwarcz *et al* (2000), Porter et al (2003), Cohen et al (2002), Eggers et al (2003) and the CASCADE Collaboration (2003) have all demonstrated that patients using HAART therapy have substantially lower mortality rates than those not using these drugs.

The large number of non-experimental studies, the convincing data from clinical trials, plus the coincidental drop in mortality among AIDS patients in the months just after the introduction of protease inhibitors in 1995 provides powerful evidence of the lifesaving potential of these drugs. Despite this overwhelming evidence, there is no published study that attempts to determine how much of the drop in mortality is attributable to these new drugs or to estimate the extent to which these effects varied across individuals. The strongest statement to date is found in a 2000 report published in the *Lancet* by the

CASCADE Collaboration that notes "HAART itself is likely to be responsible for at least some, and probably most, of this improvement."

Although there is no question that antiretroviral therapies save lives, there is some disagreement about their cost effectiveness. Highly active antiretroviral therapy is expensive.¹⁰ Freedberg *et al* (2001) and Yazdanpanah (2004) put the annual per person costs of antiretroviral therapy anywhere from \$6,000 to \$15,000, with protease inhibitor and NNRTIs providing the higher costs estimates. AT the same time, the large increases in life expectancy generated by these new drugs increases more years of cost per patient. These high costs are however potentially offset by lower hospitalizations and ambulatory care attributed to HAART (Gebo et al, 1999; Keiser, et al, 2001). Some cost effectiveness analyses conducted using utilization data through 1998 suggested that initially, aggregate per person per year costs of medical care were lower with protease inhibitor use (Gebo et al, 1999; Bozzette et al, 2001). However, more recent evaluations suggest that although hospital costs have declined, both the annual and lifetime costs of treating patients with HAART have increased. Freedberg *et al* (2001) develop a mathematical simulation model to analyze the cost-effectiveness of three-drug anti-retroviral regimens. The authors estimate that the three-drug regimen increased per patient lifetime costs from \$45,460 (in 1996 dollars) to \$77,300. Because these drugs increase quality-adjusted life years by 1.38 years, the authors find a treatment cost per quality-adjusted life year of \$13,000 to \$23,000, numbers comparable in cost-effectiveness to other medical interventions for non-AIDS related illnesses. Similar cost per life year save estimates have been obtained for patients from Switzerland, England and Canada (Yazdanpanah, 2004) and for patients treated by the Veteran's Administration (Keiser, 2001).

III. Constructing the Analysis Files

A. The California Medicaid Claims and Eligibility Data

¹⁰ HIV antiviral drugs are more expensive than any other therapeutic category of prescription drugs. A recent study demonstrated that, with an average price of \$404 per prescription, HIV antiviral drugs are more than twice as expensive as any other category (NIHCM, 2002), with antipsychotics the next most expensive at \$168 per prescription.

For this project, we utilize claims and eligibility data for a random sample of Medicaid recipients from the state of California. The Medical Care Statistics Section of the California Department of Health Services has constructed two research data files that include Medicaid claims and eligibility data for 20 and 5 percent of program participants, respectively. Because the two samples partially overlap, using both gives us a 24 percent sample of Medicaid recipients. These files include all Medicaid recipients with particular values in the seventh, eighth, and or ninth digits of their Social Security numbers (SSN), which are scrambled in our data into an individual-specific Medicaid ID. Thus, even if a person has more than one spell of eligibility, the files will include all Medicaid claims and eligibility data for him/her. Our 24 percent sample of Medicaid recipients includes detailed information for 3.7 million people who participated in the program between January of 1993 and December of 2003.

Both Medicaid samples have two research data files that are released annually: an eligibility file and a claims data set. The eligibility file contains some demographic information about sample participants including gender, month and year of birth, race/ethnicity, zip code of residence, monthly eligibility information, plus a monthly “aid code” that indicates whether the person is eligible for Medicaid through AFDC/TANF, SSI, or through some other program. Additionally, there are two variables in each month that indicate whether an individual is eligible for either Part A and/or Part B of Medicare.¹¹ Finally, the eligibility data indicates whether the Medicaid recipient is enrolled in a Medicaid managed care plan and if so, the file lists the plan number.¹²

The claims data includes all fee-for-service payments made from January of 1993 until June of 2004, though because there is often a short lag in processing the claims, we intend to focus on the eleven-year period ending December of 2003. In a typical year, there are approximately 40 million fee-for-service claims in our 24 percent sample of Medicaid recipients.

¹¹ Many SSI recipients are also receiving social security disability (DI) benefits or are over the age of 65 and thus are also eligible for Medicare.

¹² For recipients in Medicaid managed care plans, a third set of files is available that list payment rates by Medicaid eligibility category, plan number, and month (Duggan, 2004). Because we do not consider Medicaid managed care recipients in our analysis we do not use these files.

There are three types of claims in our data. Inpatient claims include detailed information about admissions to hospitals and long-term care facilities including the primary and secondary diagnosis, dates of service, amount paid by Medicaid, procedures performed while in the hospital, and the provider ID. Outpatient and other ambulatory claims have similarly detailed data about all payments to physicians, clinics, hospital outpatient facilities, laboratories, and other health care providers. Finally, prescription drug claims provide information about payments made to pharmacies for drugs covered by Medicaid. Each pharmacy claim includes an eleven-digit National Drug Code (NDC), the number of units of the prescription, the date the prescription was filled, plus other variables. The NDC is unique for a drug and dosage level so coupling this information with the units of the prescription and recommended treatment regimens allows us to estimate the number of days the prescription will cover. Each claim includes the individual's Medicaid ID, which can then be matched to the eligibility file.

Finally, we reached an agreement with both the California Center for Health Statistics and Medical Care Statistics Section that allowed us to merge death records for the 1993 through 2001 period to the Medicaid data. These records identify date and cause of death. Death records could only be matched to Medicaid recipients with valid social security numbers which accounts for roughly 92 percent of the sample.¹³

B. Defining the HIV/AIDS Sample

A number of previous researchers have used Medicaid claims databases to construct samples of HIV/AIDS patients. Typically, patients are identified by using diagnosis codes that indicate HIV/AIDS as the disease being treated and/or identifying patients that have a claim for prescription drugs that are used only for treating HIV/AIDS (Eichner and Kahn, 2001; Kahn et al, 2004; Morin et al, 2002). Since the focus of this project is the impact of new pharmaceutical on AIDS mortality, we do not use drug claims codes to select samples because this would generate a choice-based sample. Instead, we select as

¹³ Approximately 8 percent of Medicaid recipients do not have a valid social security number and we can determine this from the encrypted SSN.

HIV/AIDS patients those with one or more non-prescription drug claims with a primary or secondary diagnosis of HIV/AIDS. California's Medicaid program uses the ICD-9 system of classifying diagnoses, and thus we code a claim as an HIV/AIDS claim if the first three characters are 042, 043, or 044.¹⁴

Patients enter our sample the date of their first HIV claim although they may have been on Medicaid for some time before that point. This algorithm yields a sample of 15,598 individuals who have one or more HIV/AIDS claims, are eligible for Medicaid at some point during our study period, and have consistent age and gender information across years in the eligibility. When we drop the 853 individuals in this group that do not have a valid social security number this reduces our sample by 5.4 percent to 14,745.

The procedure outlined above to identify HIV/AIDS patients depends critically on accurate diagnostic codes. Previous research finds that in the case of hospitalizations, HIV/AIDS codes are very accurate.¹⁵ Even with accurate ICD9 codes however, there will undoubtedly be false positives and negatives in our sample. There will be false positives if providers incorrectly code claims. In our regression models below, we restrict the sample to include patients with two or more non-prescription HIV/AIDS claims, which should reduce the fraction of these false positives but will potentially exclude some true HIV/AIDS patients.¹⁶

False negatives are a more likely concern. There are three primary avenues through which we would not identify HIV/AIDS patients on Medicaid. First, an AIDS patient may not have any claims with

¹⁴ Starting in 1991, there were four ICD-9 codes used to identify HIV/AIDS in claims data. Codes 042, 043 and 044 (and detailed fourth and fifth digits) were defined for AIDS, AIDS related complex, and other HIV diseases, respectively, while code 795.8 was reserved for inconclusive HIV test results. Because of inconsistent coding, the CDC recommended a coding change in 1994 that resulted in three codes including 042 (AIDS and symptomatic HIV) with no subcodes, V08 (asymptomatic HIV) and 795.8 (defined as before). This coding was adopted slowly over the next few years in California but by 1997, virtually all codes were 042.

¹⁵ Rosenblum *et al* (1993) matched hospital and Medicaid claims data to medical records of patients known to be infected with HIV. These authors found hospital records were able to successfully identify 97 percent of HIV patients and Medicaid claims identified 91 percent of the patients.

¹⁶ False positives will also be produced if the only claims we observe are for patients taking HIV tests and the tests consistently come back negative. An article in the *Morbidity and Mortality Weekly Reporter* (1994) notes that ICD-9 codes for asymptomatic HIV and inconclusive HIV test were misused because of lack of clear instructions and guidance, so this may be a problem in the early years in our sample. This should be less of a problem after 1994 when the codes were re-designed to lessen this type of problem. Unfortunately, without data on the universe of HIV/AIDS patients in our sample, we have no way of measuring the false positive rate in this data set. But because mortality rates are higher in our sample than in the California AIDS population as a whole we do not think that this is an important source of bias.

an HIV/AIDS diagnosis because he/she is healthy and thus has no contact with the health care system. Second, a patient may choose not to use medical care despite their illness. These two should not pose a problem for our analysis. Healthy patients and patients not interested in receiving treatment are unlikely to receive HAART therapy so they should not necessarily be included in our sample. Finally, a person may be treated for the illness but have no inpatient or outpatient claims with a primary or secondary diagnosis of HIV/AIDS in our data. For example, there are 1,944 individuals with one or more claims for an HIV antiviral drug but with no inpatient or outpatient HIV/AIDS claims. While we could include these individuals in our sample, we elect not to given that we would then be constructing the sample based on patients' choice of treatment rather than on provider diagnoses.¹⁷

We can use external data to determine the extent of the false negative rate in our sample. An analysis of California death records indicates that between January 1, 1993 and December 31, 2001, there were approximately 31,000 deaths with a primary cause of death listed as HIV/AIDS.¹⁸ Of these, a total of 7,459 deaths have scrambled Social Security numbers that would have placed them in our 24 percent Medicaid sample if they were enrolled in Medicaid sometime over this period. By matching Medicaid records to death certificates, we have identified 4,371 people that were enrolled in Medicaid at some point over this time who died of AIDS. Of this group, our algorithm described above captures 3,617 deaths (almost 83 percent) using just the primary and secondary diagnoses on non-prescription drug claims, leaving. We could identify only an additional 106 patients by using prescription drug claims to identify patients.¹⁹

The 754 Medicaid patients in our full 24 percent sample who died of AIDS but were not identified by our claims algorithm look very different from the 3617 people we captured. Compared to

¹⁷ If the fraction taking an HIV antiviral drug was not changing much over time then it might make sense to include these individuals. But given the sharp increase in the use of these treatments, including individuals with drug claims only raises the risk of composition bias, with individuals included late in the sample while their counterparts from early in the period would not be.

¹⁸ It is important to point out that in most analyses, researchers are interested in the mortality rates of AIDS patients from all causes not just from AIDS. Unfortunately we cannot determine from the mortality data whether non-Medicaid recipients who died from some other cause also had HIV/AIDS.

¹⁹ The fact that less than 6 percent of individuals with only an HIV drug claim die during our study period while approximately 25 percent of those with one or more HIV/AIDS diagnosis claims dies suggests that the first group is much healthier on average.

those decedents identified as having AIDS, the false negative group has one half as many eligible months of service (11.6 versus 22.6) and a much larger fraction of eligible months in managed care (49.1 percent versus 9.7 percent). The first difference suggests that we do not capture some patients simply because they die early in the sample period and thus there is little time over which to obtain information for them. The second difference results from the fact that individuals in Medicaid managed care plans will not have fee-for-service claims (Duggan, 2004) and thus an algorithm that relies on diagnoses on these claims will tend to miss these individuals. Thus we will exclude individuals with one or more months in a Medicaid managed care plan during our study period in our analysis samples below.

Although any claims data set contains a rich set of information, they do have a number of important limitations. First, our data is for just one state. California is however an important state to consider since it has the second highest number of people living with AIDS (behind New York). Second, we do lose patients who temporarily or permanently exit the program. This does not appear to be a severe limitation since permanent and temporary exits per half year are only about 2 percent of the sample and this number has not changed our period of analysis. Third, we do not know when they were first diagnosed, just the date of their first claim. Fourth, for people who enter Medicaid after 1995, we do not know whether they are HAART naive or not. To deal with this limitation, we use the sharp increase in HAART use right after the drugs were first introduced to identify some models and in some cases, we restrict our attention to patients enrolled before HAART became available. Fifth, claims data do not contain important diagnostic information about patients such as CD4 cell counts or HIV viral loads.²⁰ This chart information is important because it indicates who is recommended to receive HAART. As we demonstrate below, we can effectively control for the severity of the patient's condition by using detailed historical data about the patient's prior medical care use. Sixth, we do not have Medicare expenditure data for people dually eligible for that program. Medicare will typically cover most of the hospitalization costs of "dual eligibles." Thus while we can accurately measure utilization, we will understate inpatient

²⁰ Other authors have matched claims data sets to clinical files with this information (e.g., papers from the HIV Cost and Services Utilization Survey, Gebo *et al* (1999), Gebo *et al* (2001), Sambamoorthi *et al* (2001)) but we do not have this capacity in this instance.

expenditures for this group. Finally, we lose claims information on patients who enter a managed care plan at some point during the study period.

Even with these limitations, our data has a number of important benefits over all previous studies. First, it is the largest sample of HIV/AIDS patients generated from one consistent source, which allows us to obtain more precise estimates than virtually any other study on this same topic. Second, our time period of analysis covers an important time period including three full years before and nearly eight years after the introduction of HAART. This period – which is longer than any previous study of HIV/AIDS patients - allows us to investigate the effect on both short and long-term health and spending and to determine precisely which drugs drove the mortality decline. Third, because of the rich set of information in our claims data we can control for individual’s pre-treatment health status and thus account for endogenous treatment decisions. Few previous studies using observational data have done this and thus suffer from the limitation that individuals who take HAART will systematically differ from those who do not. And finally, we can estimate not just the average effect of HAART therapy but also the extent to which this varies across individuals. Recent studies have explored heterogeneous treatment effects for schooling, job training, and welfare programs though we believe that our study provides an important example of this for the Medicaid program.

C. Sample Characteristics

Even with the limitations of Medicaid claims data sets listed in the previous section, our sample tracks well the levels and changes in AIDS patients in the state of California. On the right hand axis in Figure 1, we plot the number of Medicaid recipients with one or more non-prescription drug claims with a primary diagnosis of HIV/AIDS who were alive at the end of half-year periods beginning June 30, 1994. The patients in each half-year cell had their first HIV/AIDS claim by the end of that period although they may have been in Medicaid for some time before that date. The numbers of people represented in this figure include the 15,598 people who had an HIV/AIDS claim regardless of their managed care status and the figure is designed to illustrate how well our selection algorithm does in tracking the size of the

HIV/AIDS population in California. Roughly one third of the sample appears in the first half-year of the time period and the sample grows steadily after that date (though some disappear because of death or because they become ineligible for Medicaid).

On the left-hand axis of the figure, we graph the total number of people living with AIDS in California at the end of each six month period as reported by the CDC in their bi-annual publication *HIV/AIDS Surveillance Report*. These two surveys track incredibly well with the correlation coefficient between the two values being 0.98. Since our Medicaid data is based on numbers are a 24 percent sample, our numbers suggest that roughly 50 percent of people living with AIDS in California are on Medicaid,²¹ a number close to the national average. Given the numerous limitations with claims data sets, our algorithm for identifying HIV/AIDS patients tracks aggregate numbers quite well.

We should note that our sample includes patients with AIDS as well as those who are only HIV+ so we should compare our numbers to the total HIV+ population in the state. Unfortunately, California only reports to the CDC the number of people living with AIDS, not the numbers of people who are HIV+. However, HIV/AIDS patients on Medicaid are not a random sample of all these patients. Given the program rules that qualify these patients for Medicaid, the patients in our sample should be much sicker than the average HIV/AIDS patient in the population. As we document below, the death rates for our sample are much higher than even a sample of all AIDS patients in California. Likewise, Bhattacharya, Goldman and Soon (2003) demonstrate that HIV positive patients on Medicaid have lower CD4 cell counts than both the uninsured and patients with private insurance. Therefore, comparing trends in the number of HIV/AIDS patients on Medicaid to overall trends of AIDS patients seems appropriate.

In Figure 2, we graph half-year mortality rates for the Medicaid patients from Figure 1 over the 1993-2001 period.²² On the second vertical axis of the table, we graph the half-year AIDS mortality rate for California. This rate is calculated as the number of AIDS patients who die in a half year regardless of

²¹ This fraction does not change much over the entire eleven years in our study period.

²² In our sample, mortality rates are defined as the fraction of people alive at the end of a half year period who die in the next 6 months. For California, we define deaths rates as the fraction of people living with AIDS at the end of a six month period who die over the next six months.

cause (obtained from the Office of AIDS from the CDHS) divided by the number of people living with AIDS who were alive at the start of that half-year. There are a number of important results in this table. First, our sample has death rates that are 1.5 – 2.5 percentage points higher than death rates for all AIDS patients in California, indicating that our sample is substantially sicker than the typical AIDS patient in California. Second, the timing and relative change in mortality produced in our sample is strikingly similar to the changes found for California AIDS patients. There is a 75 percent drop in six-month mortality rates in our sample from the first half of 1995 through the second half of 2001. Over the corresponding period, mortality rates fell by 85 percent for all California AIDS patients.

In Table 2, we report some descriptive information about our sample at four points in time: 1994, 1997, 2000 and 2003. In this sample we restrict attention to individuals with two or more claims during our study period to reduce the number of false positives, with this reducing our sample size by 12.3 percent to 12,932. We also drop individuals who live in one of the eight counties that moved its Medicaid recipients into a county organized health system during our study period, with this resulting in an additional 8.2 percent drop in the number of individuals in our sample to 11,869. And finally, we drop the 1802 individuals with one or more months in a Medicaid managed care plan during our eleven-year study period and thus our analysis sample for this table includes data for 10,067 HIV/AIDS patients.

As the final row of Table 2 demonstrates, the sample size grows by more than 50 percent between 1994 and 2003, with much of this increase due to the reduction in mortality among HIV/AIDS patients. Annual mortality fell from 23.0 percent in 1994 to 5.2 percent in 2000. The other striking change generated by the reduced mortality is the almost 7 year increase in average age of patients since 1994. In 1994, 59 percent of the sample was under 40 years of age. By 2003, 72 percent of the sample was 40 years of age or older and just 28 percent was under the age of 40. The fraction Black increased from one fifth to one quarter and the fraction female increased by 7 percentage points as well.

In the bottom half of the table, we report some basic information about health care use in our sample. Patients have high medical care use but some measures are improving over time. Almost half of all patients have an inpatient stay during the year in 1994 and this number falls by 40 percent during the

next nine years. Inpatient spending falls considerably as well. In contrast, annual outpatient spending increases slightly while spending on prescription drugs triples, driven primarily by the increased use of the new drugs and their high cost. Although annual spending on prescription drugs increased by \$8000 over the period, total spending only increased by about \$4,800. The fraction of HIV/AIDS patients dually eligible for Medicare increases by 60 percent, which will understate inpatient costs and is likely responsible for some of the decline in inpatient spending.

The lack of data on patients in managed care is problematic if the composition of this group is changing over time. Although the fraction of HIV/AIDS patients on Medicaid that are enrolled in size of the managed care sample has increased over time,²³ the relative difference in some measures of health between those in fee for service and managed care has not changed much. Much of this change is due to an increase in the number of counties moving wholesale into a managed care plan. The mortality rates of HIV/AIDS patients in managed care have always been substantially lower than similar patients in fee for service Medicaid. The half-year mortality rate for HIV/AIDS patients in Medicaid managed care was 8.2 percent in the first half of 1994. The corresponding number for fee for service patients was 14.6 percent. This difference persisted in all years in our sample, but the relative decline in mortality is similar across the two groups. Between 1994 and 2001, half-year mortality rates fell 82 percent in Medicaid fee for service and 77 percent in Medicaid managed care.

IV. Time Series Evidence of the Benefits of New Anti-retrovirals Therapies

The sharp decline in mortality of HIV/AIDS patients starting in 1996 that is graphed in Figures 1 and 3 coincides closely with the introduction of Epivir (a new NRTI) in the last quarter of 1995 and protease inhibitors in the last quarter of 1995 and the first quarter of 1996. In this section, we estimate more formally the time-series relationship between aggregate mortality rates and the use of these new therapies in our California Medicaid sample over the 1993-2003 period. For this section of the paper, we

²³ In the fourth quarter of 1995, 17.9 percent of individuals in our full sample were in managed plans. This number increased to 22.4 percent by the fourth quarter of 2003.

restrict our attention to the 10,067 HIV/AIDS patients described in the previous section. This excludes individuals with just one HIV/AIDS claim, individuals without a valid social security number, individuals who reside for one or more months in one of the eight COHS counties, and those with one or more months in a Medicaid managed care plan. These changes allow us to more accurately measure changes in drug utilization and in mortality during our eleven-year study period.

For this part of our analysis, we place each patient into quarter of year cells where the first observation for a patient is the first quarter we find an HIV/AIDS claim for him. The person is then in the sample until they die, they exit Medicaid, or until the end of our analysis period. For each person-quarter observation, we determine whether the person filled a prescription for a certain drug and then aggregate these individual-level measures into one average for the quarter. This time series data set has 32 quarterly observations from the fourth quarter of 1993 through the third quarter of 2001 where the key outcome is the fraction of people that dies in the next quarter and the key covariate being the fraction of people taking particular drugs or combinations of drugs. We stop in 2001 because we do not have more recent mortality data.

In Table 1, we report the date that each drug was approved for use by the FDA and also the date we find the first claim for these drugs in our sample. Note that in almost all cases, the first claim appears just days after the drug is approved for use. The rapid increase in use is most clearly illustrated when we graph the fraction of all patients that had a claim for one or more HIV/AIDS drugs in a quarter. These numbers are reported in Figure 3. In the third quarter of 1995, less than 29 percent of patients had a claim for an HIV antiviral drug and the majority of these claims were for Retrovir (more commonly known as AZT). By the second quarter of 1997, useage rates of one or more of these drugs peaks at about 60 percent. This number is very close to estimates for Medicaid patients nationwide and much lower than use rates for the general HIV/AIDS population for the same period. Using data from the HIV Cost and Services Utilization Survey (HCSUS), Shapiro et al (1999) found that nationwide, roughly 56 percent of Medicaid patients with HIV/AIDS had used a protease inhibitor or NRTI by January of 1997.

The sharp rise in HIV/AIDS drug therapies was mainly in the use of one new NRTI (Epivir) and in protease inhibitors. In Figure 4, we graph the fraction of patients that use any protease inhibitor, Epivir, either of these two classes of drugs, and all other HIV drugs.²⁴ By the second quarter of 1997, 43.4 percent of our sample had a claim for a protease inhibitor, 46.3 percent had a claim for Epivir, and 56.0 percent had a claim for either. Most of these people were using these drugs in combination. Notice also that the entrance of Epivir and its combination drugs (Combivir in 1997 and Trizivir in 2000) virtually eliminated the use of all other NRTIs as single prescriptions, with just 3.0 percent of the sample taking one or more HIV drugs in early 1997 but not taking either Epivir or a protease inhibitor. Protease inhibitor use peaked in mid 1998. Some of the decline after that point represented patients failing to respond to treatment and either abandoning the treatment and switching to other drugs.

As we mentioned above, these new drug therapies are very expensive with monthly per patient costs of HAART exceeding \$1,000 in some cases. In Figure 5, we graph the real (in 2003Q4 dollars) quarterly per patient costs of HIV drugs in California Medicaid. This number stood at just \$200 per person-quarter in the third quarter of 1996 but by mid-1997 this had risen to almost \$1570 per person-quarter. Expenditure growth slowed down after that point though was still nearly 40 percent higher at the end of 2003 when it reached \$2170 per person-quarter.

The potential explanatory power of new HIV drug therapies for the rapid decline in mortality among AIDS patients is depicted in Figure 6. On the first vertical axis, we report the fraction of patients that are using either Epivir or protease inhibitors and on the second vertical axis, we report the quarterly mortality rate for the patients. There are three things to highlight in this graph. First, notice that prior to the 1st quarter of 1996, quarterly mortality rates were falling. Taking a simple average of mortality rates over the first three quarters in the sample and comparing them to the first quarter of 1996, quarterly mortality rates fell 20 percent in the two years prior to the introduction of Epivir. These results suggest that there might have been some decline in AIDS mortality rates even if Epivir and protease inhibitors

²⁴ This last group includes only those individuals who take an HIV drug but do not take either Epivir or a protease inhibitor. Individuals who take either Combivir or Trizivir are coded as taking Epivir because these two drugs are combination drugs that include Epivir's ingredient.

had not been introduced. Second, as Efavirenz/protease inhibitor use increased from zero to 56 percent between the fourth quarter of 1995 and the second quarter of 1997, quarterly mortality rates fell by 72 percent, from 6.7 percent to just under 2 percent. As Efavirenz/protease inhibitor use stabilized, so did mortality rates. Between mid 1997 and the end of our sample, quarterly Efavirenz/Protease inhibitor use was steady at 53 to 55 percent of the sample. Over this same period, quarterly mortality rates were originally 1.8 percent, fell to 1.4 percent, and then stabilized at 1.6 percent.

The close correspondence between two series in Figure 6 suggests that a large fraction of the decline in AIDS mortality in the mid 1990s will be explained by the rapid increase in Efavirenz/PI use. In Table 3, we use aggregate data to get a baseline estimate of the likely contribution of Efavirenz/PI use to these trends. In the first column of the table, we run a time series regression in which the outcome is quarterly mortality in the next quarter for the 32 observations in our sample and the only covariate is the fraction of patients with any HIV/AIDS anti-retroviral drug. In all these time series regressions, we estimate models as first differences so the constant term is interpreted as the coefficient on the time trend. These time series models are similar in spirit to those in Lichtenberg (2003) who regressed log nationwide AIDS deaths on the number of drugs approved for use in treating HIV/AIDS by the FDA. The low R^2 in this model is generated by our use of first differences and estimated the model in levels produces similar results but with R^2 close to 0.98 in all models.

In column (1), we find a large and statistically precise coefficient on any HIV drug and the size of the coefficient suggests that rising anti-retroviral use should explain a large drop in quarterly mortality rates over this period. The OLS estimate on the fraction using any HIV drugs is -0.15 with a small standard error of less than .05 suggesting that the 30 percentage point rise in the fraction using an HIV drug between the third quarter of 1995 and the third quarter of 1997 period can explain 4.5 of the 4.7 percentage point drop in quarterly mortality over this period. In column (2) when we replace the coefficient with the fraction of people taking any NRTI, and we get essentially the same results

One limitation of this first specification is that it assumes all of the mortality improvement was attributable to individuals who were not taking an HIV drug in late 1995. However, if those switching

from existing drugs such as AZT and other drugs available in mid-1995 also saw their mortality rates decline, then the point estimate of -0.15 will provide a misleading estimate for the average effect of the new drugs. In columns (3) and (5), we replace the fraction using any HIV drug with the fraction using a Protease Inhibitor and Efavirenz, respectively. The coefficients on these two variables are -0.109 and -0.092 respectively, with small standard errors in both cases. These estimates are much smaller in magnitude than the one from column 2, suggesting that those shifting from the old drugs also benefited. Usage of both of these drugs reaches a maximum of approximately 46 percent in mid 1997 and therefore, these models predict that rising use of these drugs is responsible for 5 and 4.2 percentage point decline in mortality, respectively. Given that the actual decline was 4.7 percentage points, both models suggest that the new drugs were responsible for almost the entire mortality improvement.

Because the increase in the use of Efavirenz and of protease inhibitors was so strongly correlated from late 1995 until mid 1997, reliably disentangling the effect of one from the other with aggregate data is likely to be difficult. Nevertheless in column (6) we include the two utilization measures separately in the regression. While both are essentially the same magnitude, only the coefficient on Efavirenz is statistically significant. In the next column, we group these two treatments together while exploring the relationship between mortality and the fraction of the sample taking either Efavirenz or a protease inhibitor. The point estimate of -.079, coupled with the increase to 56.0 percent in this variable in less than two years, suggests that the diffusion of these two treatments can explain 94 percent of the decline in quarterly mortality rates from late 1995 until mid-1997.

It is interesting to note that our estimate of -.079 for the average effect of Efavirenz and protease inhibitors is substantially greater in magnitude than the average mortality rate in our sample just prior to the approval of these drugs (.067). If this effect is properly estimated, it suggests that individuals taking the new drugs had substantially higher baseline mortality probabilities than did their counterparts who did not take the drugs. Suppose, for example, that the baseline mortality rate among the 44 percent who did not take the new drugs was exactly zero and that this did not change from 1995 to 1997. In that case, the baseline mortality rate for the treated group would have been 12.0 percent per quarter ($= .067 / .56$). The

decline in the overall mortality rate from 6.7 percent to 1.9 percent would imply that quarterly mortality rates fell by 72 percent for the treated group, from 12.0 percent to 3.4 percent. If baseline mortality rates were greater than zero for the untreated group, the mortality improvement for those taking Epivir or protease inhibitors would need to be even larger than 72 percent. If, for example, baseline mortality probabilities in the untreated group were 2.0 percent and this did not change from 1995 to 1997, then the mortality rate in the treated group would have needed to fall by 83 percent (from 10.4 percent to 1.8 percent), suggesting that the treatments were even more effective.

Taken together, the results from this section suggest two key points. First, the four new drugs approved by the FDA in the four months from November of 1995 to March of 1996 were the driving force behind the reduction in HIV/AIDS mortality rates during the past decade. There is little evidence to suggest that the fifteen drugs approved in the years since have led to still further reductions in mortality. Second, individuals who take the drugs appear to be much sicker on average than their counterparts who do not. We probe further on both of these issues in the next section using individual-level analyses.

In the final two columns of Table 3, we highlight some interesting results from the individual-level analysis in the next section by changing the dependent variable in the regression. In columns (9) and (10), we include as outcomes the change in mean quarterly spending and the change in the fraction with any hospital visits. The covariate of interest in these regressions is the change in the fraction of patients using Epivir or PI. In contrast to the pronounced fall in mortality associated with these new treatments, we find little evidence that the rise in use of these drugs changed these two outcomes. Changing Epivir and or PI use is associated with greater changes in mean quarterly spending and a slight drop in the fraction with any hospitalizations. The results for these two models suggests that possibly in a cross section, the drop in expenditures associated with rising health may be more than offset in a cross-sectional basis by higher drug costs for these new therapies. We delve into the point in more detail in the next section.

V. Patient-Level Evidence of the Benefits of New Anti-Retroviral Therapies

In this section, we exploit to a much greater degree the panel nature of our claims data to examine the impact of new HIV drug therapies on mortality and health care utilization. The sample for this section's analysis is an individual-level panel data set similar to the quarterly-level aggregate data we used in the previous section. Initially, we reduce the sample to patients whose first HIV/AIDS claim appears in the 1993-1997 time period, but we delete patients whose first day of enrollment in Medicaid occurs after the introduction of Efavir since we do not want patients in the sample who might have enrolled in the program just to receive coverage for the new drug treatments. We also restrict attention to patients 15 and above since children were not cleared for use of HAART therapy until more recently. To reduce the chance of false positives we only include patients with two or more non-pharmaceutical claims with HIV/AIDS codes in the primary or secondary diagnosis. We also restrict attention to patients with no enrollment period in managed care during our period of analysis or any patient that lived at any time in one of eight counties with a county organized health system for its Medicaid population. Since we need a linkage to death records to measure mortality, we delete those without a valid SSN. We delete a small number of patients who leave Medicaid for at least one quarter, patients who die during their first month of eligibility, or patients who are only in our sample for 1993. We aggregate data to the person-quarter level giving us a sample of 3243 HIV/AIDS patients, aged 15 and above, with valid mortality data and continuous enrollment in non-managed care Medicaid until the end of our analysis period or until they exit the Medicaid program. There are 28,287 person/quarter observations.

Although our data is rich in detail on drug use and total health spending, the evaluation problem is complicated by the nonrandom selection of patients into HAART therapy. As we outlined in Section II, current protocol suggests that patients abstain from HAART therapy until CD4 counts fall below a specified level or until patients obtain an AIDS-defining illness. Low CD4 counts are an excellent predictor of progression to AIDS, higher mortality and higher medical expenses. MacDonell et al (1990) note that in the late 1980s, the four -year cumulative AIDS incidence was 86, 63, and 21 percent for men with entry CD4 counts less than 200, 200 to 399, and 400 or more cells per cubic millimeter (mm^3). Likewise, Enger et al (1996) estimate for the 1989-1993 period 2.5-year survival rates of 54, 71 and 91

percent for HIV patients with CD4 counts of less than 100, 101-200 and 200-350 cells/mm³. For medical care, Bozzette et al (2001), using data from the HCSUS survey finds that total medical expenditures increase dramatically as CD4 counts fall. Comparing patients with CD4 counts of $\geq 500/\text{mm}^3$, 200-499/mm³, 50-199/mm² and $<50/\text{mm}^3$, the authors found monthly expenditures of \$532, \$925, \$1361 and \$2344, respectively.

CD4 counts are also an excellent predictor of morbidity and mortality after the initiation of HAART. In an analysis of over 12,000 patients who started HAART, pooled from 13 Europe and North America cohort studies, Egger et al (2002) find that baseline CD4 counts at commencement of HAART were the 'most strongly prognostic factor (p. 125)' of progression to AIDS and death. Jonathan et al (2003) patients who have the lowest CD4⁺ cell counts when they begin HAART are at the highest risk of progression to AIDS or death and do not experience the same clinical benefit as do patients who begin receiving therapy earlier. These results suggest that we should find that those patients with a priori the poorest health, highest medical care use and highest mortality are those who are the most likely to use HAART.

Unfortunately, claims databases typically do not have clinical markers to use as controls variables. As a consequence, we must construct a surrogate variable that identifies the clinical progression of the disease. After experimenting with a number of different alternatives, we devised a surrogate variable that predicts mortality quite well in the pre-1996 period and the use of the new anti-retroviral therapies once they are introduced. Specifically, we count all claims with a primary or secondary diagnosis of HIV/AIDS that are not for HIV drugs for a person in the four quarters ending in quarter 3, 1995. Next, we rank patients from lowest to highest and place each patient into one of ten different severity deciles. We break the top decile into two groups that include the 90th -95th percentiles and the 96th to 100th percentiles, respectively. Using time varying ranks controls for a changing number of counts over time and ranks each patient in relation to the other HIV/AIDS patients alive at that time. We fix this severity index to the third quarter of 1995 because Efavir becomes available in the next

quarter and patients can potentially move decile rankings based on treatment. Given the rapid spread of new treatments, fixing the severity index at a particular date should not pose much of a problem.

In Table 4, we examine the predictive power of these surrogate variables for a sample of 3243 patients who had at least one HIV claim between the first quarter of 1994 and the 3rd quarter of 1995. We include the last seven quarters in our sample before the introduction of Epivir and protease inhibitors and there are 14,163 observations in total. The first column of numbers in Table 4 reports the average number of claims per quarter for patients in each category. Those in the lowest decile group have little health care use with an average of 0.1 claims during the previous year.²⁵ Moving from one decile group to the next, the percentage change in average claims per quarter is large but even in the fourth decile this average is just 5.8. The average claims per quarter do however increase rapidly past this point, with patients in decile 7 having an average of 22.6 claims during the past year and those in the top 5 percent of the distribution an average of 137 claims.

In the next column, we estimate a linear probability model in which the outcome variable is equal to one if the person died in the next quarter and zero otherwise. The explanatory variables of interest are indicator variables for each decile. The omitted category is the lowest decile. In the next column, we add to the regression some basic demographic characteristics such as indicators for female, Black, eligibility for Medicare, and dummy variables for ages 30-39, 40-49, 50-64, and those 65 and over. In all of these models, we estimate standard errors that allow for an arbitrary correlation in the errors for each person.

The results for models (1) and (2) indicate that the decile rank in the moving average of Medicaid claims is an excellent predictor of future adverse events. The probability that a person will die in the next quarter – conditional on surviving to the end of the current quarter - is monotonically related to the decile rank.²⁶ Looking at the results without covariates, for patients in the top 60 percent of the severity index, the movement from a lower to higher group increases the quarterly death rate by at least one percentage

²⁵ An individual could have zero claims during the past year if – for example – they have multiple HIV/AIDS in the first quarter of 1993 but no subsequent claims during the next four quarters.

²⁶ In the models for Table 5, we suppress the estimation of an intercept so as to obtain estimates for all ten decile dummy variables.

point in all cases except one. Focusing on the results for the final 4 groups, mortality increases rapidly (measured by absolute not relative changes) as patients move up the severity index, from 6.7 percent to 10.2 percent to 12.3 percent to 17.3 percent. Those in the top 5 percent of the severity index have a quarterly mortality rate that is 2.6 times larger than average while those in the bottom group have a mortality rate that less than one-fourth the sample average. Comparing columns (2) and (1), we see that adding covariates does not substantially change, with the coefficients the same out to three decimal places in seven out of ten cases.

In the next two columns, we estimate another set of linear probability models in which the outcome of interest is an indicator that equals one if the patient is hospitalized during the next quarter and zero otherwise. Although there are a number of possible measures of morbidity that can be constructed from a claims data base, we focus only on hospitalizations at this time since hospitalizations are the single largest expenditure category in our sample, representing 44 percent of total Medicaid expenditures in 1994. In this regression, the coefficients on the decile rank dummy variables are nearly monotonic with the only deviations being movement between the first and second deciles and deciles five and six. As with the mortality rate, the impact of the severity index is nonlinear in the severity with the coefficient increasing rapidly in the final five groupings. The coefficient doubles as one moves from decile five to decile eight (from a 6.0 to 11.8 percentage point increase in the hospitalization rate compared to the lowest decile, which had a mean of 15.4 percent). This then doubles again moving to the top five percent in our severity index. As with the mortality equations, adding demographic characteristics to the model has virtually no effect on these coefficient estimates.

In the final two columns of Table 4, we estimate models in which the outcome variable is equal to one if the patient has any claims for an HIV anti-retroviral treatment in the quarter and zero otherwise. During this time period, just four drugs were available and all were NRTIs. Here, the pattern of results on the coefficients for the severity index has an inverted-U shape, with the healthiest and sickest patients having the lowest use. The largest coefficient is for decile eight with patients there having an 18.8 percentage point greater chance of using an HIV drug than those in the lowest decile group. As with the

mortality and hospitalization regressions, adding covariates for demographic variables does not change the coefficients on the decile dummy variables to a significant extent.

As we noted in the time series regressions, the key treatment is not the use of any HIV antiviral treatments but the use of Epivir and protease inhibitors. In Table 5, we examine whether the decile ranking system can accurately predict the use of these new pharmaceuticals after they were approved by the FDA. In the first two columns, the key outcome is a dummy variable that equals 1 if the patient has claims for Epivir or protease inhibitors in the quarter. As in the previous regressions, the key covariates are dummy variables that identify the decile rank of the four-quarter moving average in total Medicaid claims. In the table, we experiment with two samples. First, we examine usage in the ‘transition’ period when these drugs first became available, which is the five quarters starting with the fourth quarter of 1995. This is a period of rapid increase in drug usage. In this time period, there are slightly over 2000 people alive and enrolled in Medicaid for at least one quarter with this generating approximately 8,600 person-quarter observations. A second sample is for the four quarters in 1997, a period when use of HAART stabilized so we consider this to be a representation of the steady state. This sample contains data for 1456 people and almost 5,500 person-quarters. In all regressions, we include the set of dummy variables for demographic characteristics used in Table 5 and allow for an arbitrary correlation in errors for a patient.

In both the transition and steady state periods, the model fits exceedingly well for a cross-section regression with an R^2 of about 0.3 in both cases. During both the transition period and in the steady state, the coefficients on the severity index dummy variables are monotonic. There is a slight drop in use between the final two groups in the steady state and a three percentage point drop in use over the final three groups during the steady state. In the steady state model, usage rates in the 4th decile are about 50 percentage points higher than decile 1, but by decile 9, the difference increases to 73 percentage points. By 1997, usage of protease inhibitors or Epivir by those in the lowest decile was about 15 percent, so the numbers for the steady state suggest that usage rates in the bottom half of patients based on the severity index ranged from 15 to 60 percent, whereas usage rates ranged from 70 to almost 90 percent for those in

the top half of the severity distribution. This heterogeneity in the takeup of the new treatments is clearly illustrated in Figure 7, which shows that patients in the top quintile of claims were almost four times more likely to take the new drugs as were their counterparts in the lowest quintile of claims. This disparity in treatment use contrasts sharply with the “pre” period, when usage rates of the earlier HIV drugs did not differ much between sick and healthy patients (Figure 8).

Having established the power of the four-quarter moving average severity index based on Medicaid claims to predict mortality, morbidity, and the use of the new HIV drug treatments released in late 1995 and early 1996, we next estimate models of the effectiveness of these new drugs in reducing mortality and altering hospitalization rates. The results from the previous two tables indicate that sicker patients as measured by the severity index are both more likely to die and more likely to use Efavirenz and protease inhibitors. Thus we must control for this selection in any statistical model that attempts to measure product efficacy. Likewise, we expect that the benefits of treatment will be highly nonlinear in severity with the sickest patients expected to receive the most benefit (in an absolute sense). To that end, we will control for both the severity index and allow for the treatment effect to vary by the decile dummy variables. The treatment effect is a simply dummy variable that equals 1 if a person is taking PIs or Efavirenz in a quarter and all outcomes are measured next quarter (such as mortality and hospitalization).

The sample for this analysis will be the continuously enrolled Medicaid patients, aged 15 and older who were enrolled in the program from the first quarter of 1994 to the fourth quarter of 1997. This sample contains information on 3243 patients and over 28,000 person/quarter observations. In these models, we control for the personal characteristics listed in Tables 4 and 5, plus a full set of quarterly dummy variables. Again, we allow for arbitrary correlation in errors for each person.

Initially, we consider two outcomes: mortality next quarter and whether or not a patient had a hospitalization next quarter. The results for mortality are reported in the first two columns of Table 6. In the first column, we report the coefficients on the decile rank dummy variables while in the second column, we report the coefficient on the interaction between the any Efavirenz or protease inhibitor use this quarter dummy and the decile rank dummies. The coefficients on these interactions are nearly monotonic

in the decile ranks. Taking Epivir or a protease inhibitor this quarter reduces the probability of death next quarter by a statistically significant 1.2 percentage point for those in 4th decile, by 2.9 percentage points in the 6th decile, by 3.8 percentage points in the 8th decile and by 10.7 percent for the patients in the highest severity group. This heterogeneity in the effect of the treatments is shown in Figure 9, which reveals an almost 12 percentage point drop in quarterly mortality rates from late 1995 until late 1997 for the sickest quintile of patients, which contrasts sharply with the relatively constant mortality rate for the 20 percent of the sample with the lowest number of claims.

To put these results into perspective, consider the following calculation. Between the fourth quarter of 1995 and the third quarter of 1997, quarterly mortality rates among patients in the top quintile of the severity index fell by 9.7 percentage points. Over this same period, usage rates of new anti-retrovirals increased for these patients from zero to almost 80 percent. Taking a weighted average of the coefficients in the final three severity groups from the second column of Table 6, use of PIs or Epivir is estimated to reduce quarterly mortality by 8.6 percentage points. Therefore, rising use of PIs or Epivir is predicted to have reduced mortality in the top quintile of severity by 6.9 percentage points, which is more than 70 percent of the decline in mortality experienced by this group over this time period.

It is worth emphasizing that our estimates are likely to represent a lower bound for the true impact of HIV antiviral drugs. This is because even within a decile it is likely that the sicker patients are the ones taking the drugs. To determine how important this is likely to be, consider the following calculation. In the four quarters before the approval of Epivir and the first protease inhibitors, the quarterly mortality rate among those in the top quintile of claims was 14.6 percent. Two years later this rate had declined to 2.8 percent. But among the 19 percent of this quintile not taking Epivir or a protease inhibitor (who are likely to be the healthiest patients in this quintile) mortality rates at this time were just 11.2 percent. Assuming these mortality rates remained constant during this short period (which seems reasonable given that drug treatments for these patients were not changing) then our estimates imply that quarterly mortality among those taking Epivir and/or a protease inhibitor fell by 12.6 percentage points (from 15.4 percent to 2.8 percent). This is substantially greater than the 8.6 percentage point estimate

from our regression and suggests that the individual-level regressions understate the contribution of the new treatments to improvements in health.

What is clear, however, from this set of individual-level results is that the least healthy patients were the ones most likely to take the new drugs, presumably because the perceived benefit of treatment was greatest for them. This selection effect explains why average mortality rates in our sample fell by more than 70 percent in less than two years despite the fact that the new drugs were used by just 56 percent of our sample once the new equilibrium was reached.

VI. Estimating the Cost per Life-Year Saved

In this section we investigate the effect of protease inhibitors and Efavirenz on long-term Medicaid spending. Most previous studies that have estimated the effect of HAART therapies on health care expenditures have focused on annual rather than lifetime spending. But because the new drugs have increased life expectancy, an annual measure will provide a misleading estimate of the long-term effect and of the eventual costs to the Medicaid program.

The difference between short and long-term measures of Medicaid spending is readily apparent from a comparison of trends in one and six-year Medicaid spending in Tables 2 and 7, respectively. From 1994 until 1997, average Medicaid spending for individuals in our sample increased by less than 4 percent despite the sharp increase in the use of both Efavirenz and protease inhibitors. Spending on prescription drugs almost doubled (from \$4122 to \$7769) during this three-year period, but a similarly large decline in inpatient spending (from \$7125 to \$4309) nearly offset this. Thus the rapid takeup of Efavirenz and protease inhibitor treatments did not lead to large increases in annual Medicaid spending.

But the data summarized in Table 7 yield a very different picture. In this table, we summarize trends in the distribution of Medicaid spending during a six-year period. From 1994 to 1998 average six-year Medicaid spending for individuals in our sample increased by 87 percent and the change for the median person was even larger at 126 percent. Most of this growth in spending was apparently caused by an increase in the number of months that individuals were eligible for the program, which itself was

caused by their lower mortality rate. For example average eligible months during each of the six-year periods increased from 31.5 to 51.3 while the median number of eligible months increased from 21 to 68.

Despite the long time period summarized in Table 7, even these numbers provide an incomplete picture of the effect of Epivir and protease inhibitors on lifetime Medicaid spending for at least three reasons. First, expenditures in year seven and beyond are not included and thus the numbers will substantially understate lifetime expenditures, especially in the more recent period. Second, other factors are changing in the years after Epivir and protease inhibitors diffused and thus these trends will confound the effect of the drug treatments of interest with these other factors. And finally, more than 40 percent of our sample does not take either Epivir or a protease inhibitor at a point in time after these drug treatments have reached their equilibrium (though a much smaller percentage would presumably never take them) and thus a pre-post comparison will combine the effects on the “treated” group with the absence of an effect on those who are not treated.

In an effort to surmount these problems, we next simulate the effect of Epivir and protease inhibitors on long-term Medicaid spending with the following simple algorithm. We group individuals in our sample in the last quarter of 1994 and in the last quarter of 1997 into one of twelve age-gender bins²⁷ and next calculate annual mortality rates and average annual Medicaid spending in each of these bins. We then simulate Medicaid spending over the next 26 years for person j in period t as follows:

$$LTSpend_{jt} = \sum_{\tau=t}^{t+30} Spend_{j\tau} * (1 - Mort_{j\tau})$$

with $Spend_{j\tau}$ equaling average annual Medicaid spending when person j is $t+\tau$ years old and $(1-Mort_{j\tau})$ representing the probability that person j is still alive at that age.

Consider a patient who is HIV positive and, after given the natural progression of the disease, is at a point in treatment where the physician would recommend HAART. Health care costs for the patient up to this point in their disease are assumed to be identical, whether or not HAART has exiCosts up to this point are not altered by the existence of if HAART were available, would be recommended by their

²⁷ The age bins are <18, 18-29, 30-39, 40-49, 50-64, and 65 plus.

physician to begin a treatment regimen. This patient was however This Expected lifetime spending for a patient on Medicaid can be

ES

Table 8 summarizes the results from this simulation, in which we hold fixed the characteristics of the 1994 sample. The data summarized in the first column suggest that – if health care treatment patterns had not changed after the third quarter of 1995 – the fraction of individuals in the sample surviving for five years would have been less than 26 percent and the fraction surviving for ten years would have been just 10 percent. However, if Efavir and protease inhibitors had been available at the time, the results in the second column suggest that those survival probabilities would have been much higher at 69 percent and 51 percent, respectively. Because of this increase in life expectancy, Medicaid spending for individuals in this initial sample is much greater in the later years. For example, while spending in year one is only 13.5 percent higher, in year six it is 222 percent higher and in year fifteen it is 712 percent higher.

Aggregating the (undiscounted) difference in Medicaid spending across all 26 years, the results suggest that Efavir and protease inhibitors increased “lifetime” Medicaid spending for the average person from \$72,777 to \$216,929. Given the corresponding increase in the average number of years alive during this period (from 4.56 to 11.68) for the individuals in our sample, the results suggest that the costs to the Medicaid program for each additional life year were \$20,246. This cost is likely to understate the true increase in health care spending both because we consider just twenty-six years and because a steadily increasing fraction of the sample are dually eligible for the Medicare program and thus an increasing fraction of their health care spending will be covered by another government program. But even with these changes, it is likely that these new treatments would easily pass a cost-benefit test, with recent studies suggesting that the typical person places a value of more than \$100,000 for each additional life-year.

VII. Conclusion

In a six month period starting in November of 1995, six new drug therapies designed to reduce the replication of the HIV virus in infected patients were released. In the two year period after this small window of time, AIDS deaths declined 70 percent. Although dozens of observations studies have shown the lifesaving benefits of these new drugs, no study has isolated the extent to which these new therapies were responsible for this decline in deaths. Using data from a 24 percent random sample of all Medicaid patients in California, we use a variety of techniques to illustrate that virtually all of the decline can be traced to the introduction of Epivir (an NRTI) and three protease inhibitors that were introduced in early 1996.

Our research has uncovered a number of substantive results as well hopefully adding some methodological innovations for the evaluation of these types of medical breakthroughs. Although claims data sets are rich in detailed time series data medical care use, they are devoid of clinical data about important markers such as CD4 counts and viral loads. However, we have devised a simple index of severity that does an excellent job of predicting both pre-HAART mortality as well as subsequent HAART use. This severity index also allowed us to estimate a series of heterogenous treatment effects. The greatest reductions in absolute mortality were found for the most severe cases but in the top decile of the cases, the percent reduction in mortality was similar across groups.

The ability to demonstrate the mortality effect of new medical interventions in an era of HAART outside of a clinical trial is of paramount importance. Because HAART has been so successful at reducing mortality, any intervention that can possibly improve these outcomes would be prohibitive. As Raffi et al (2001) note, given the current one-year death rate among people on HAART, an intervention that could reduce this number by one-third would require 4,600 patients in the treatment sample (Type I error rate of 5 percent and power of 80 percent). Raffi et al conclude that clinical trials in this field with mortality as a clinical outcome are ‘almost not feasible.’ Subsequently, health professionals must increasingly rely on observational data and non-experimental statistical models to evaluate these interventions.

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Figure 1: # with AIDS in CA vs. in CA Medicaid Sample

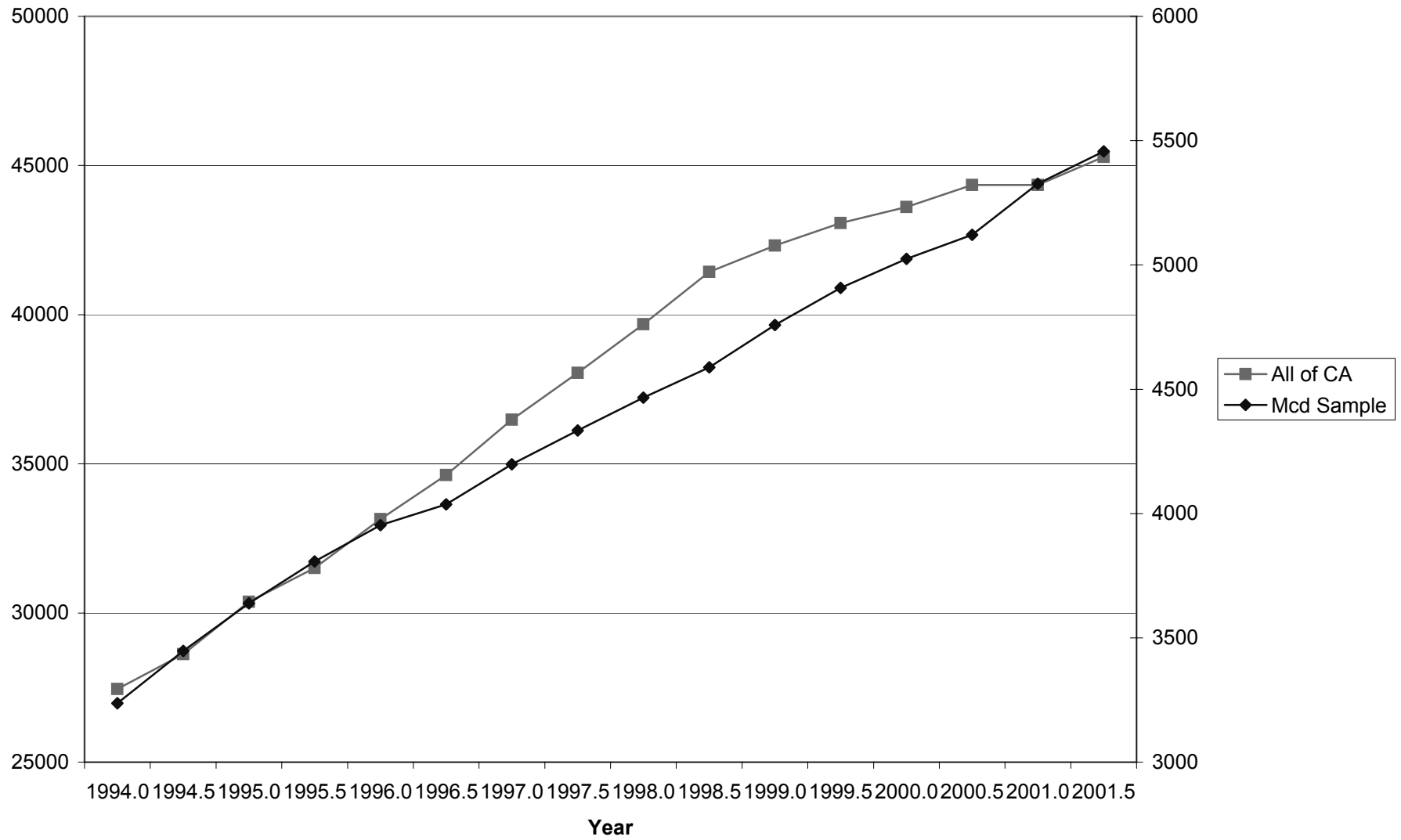


Figure 2: Half-Year Mortality Rate for AIDS Patients

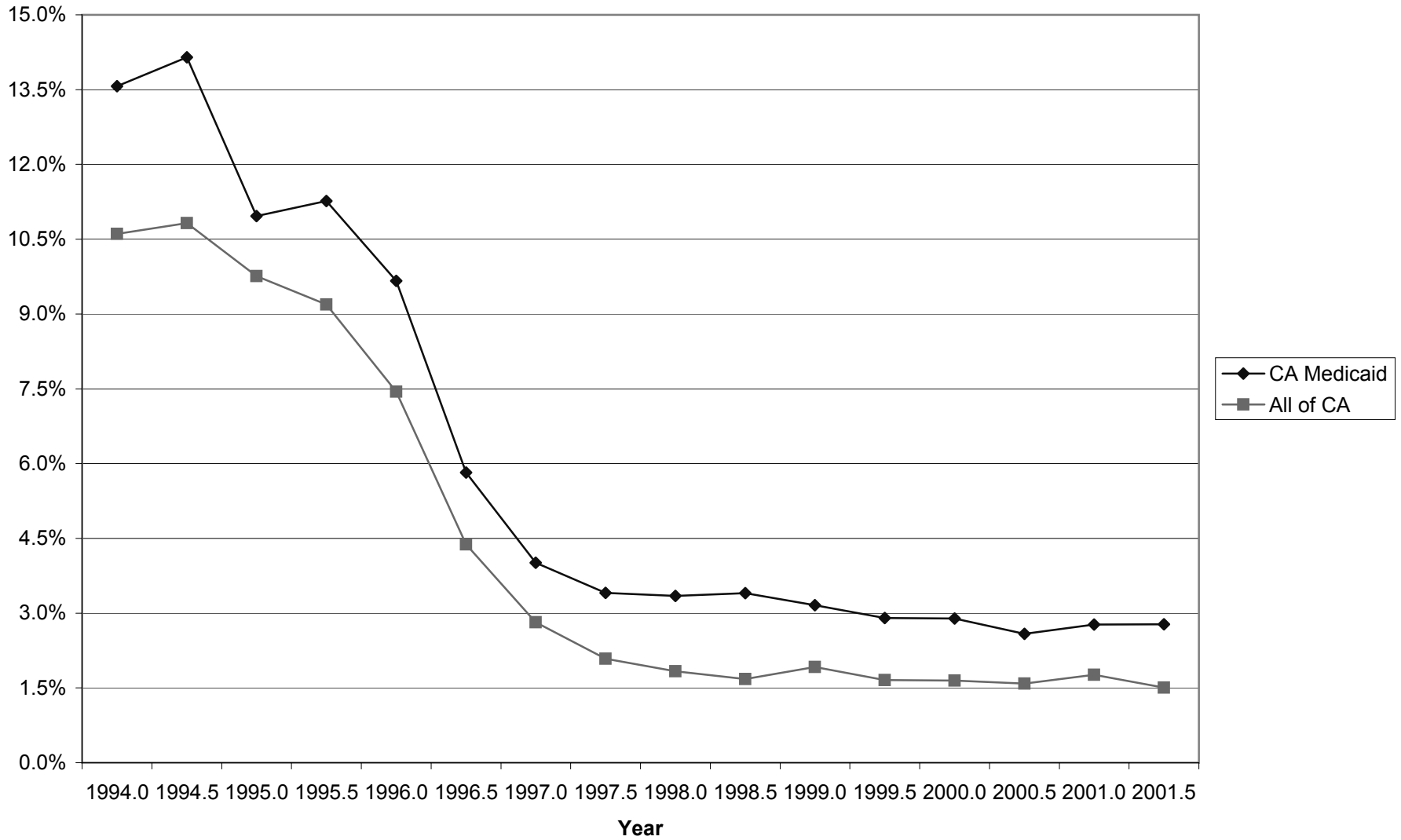


Figure 3: Fraction of CA Medicaid Sample Taking 1+ HIV Drugs in Each Quarter

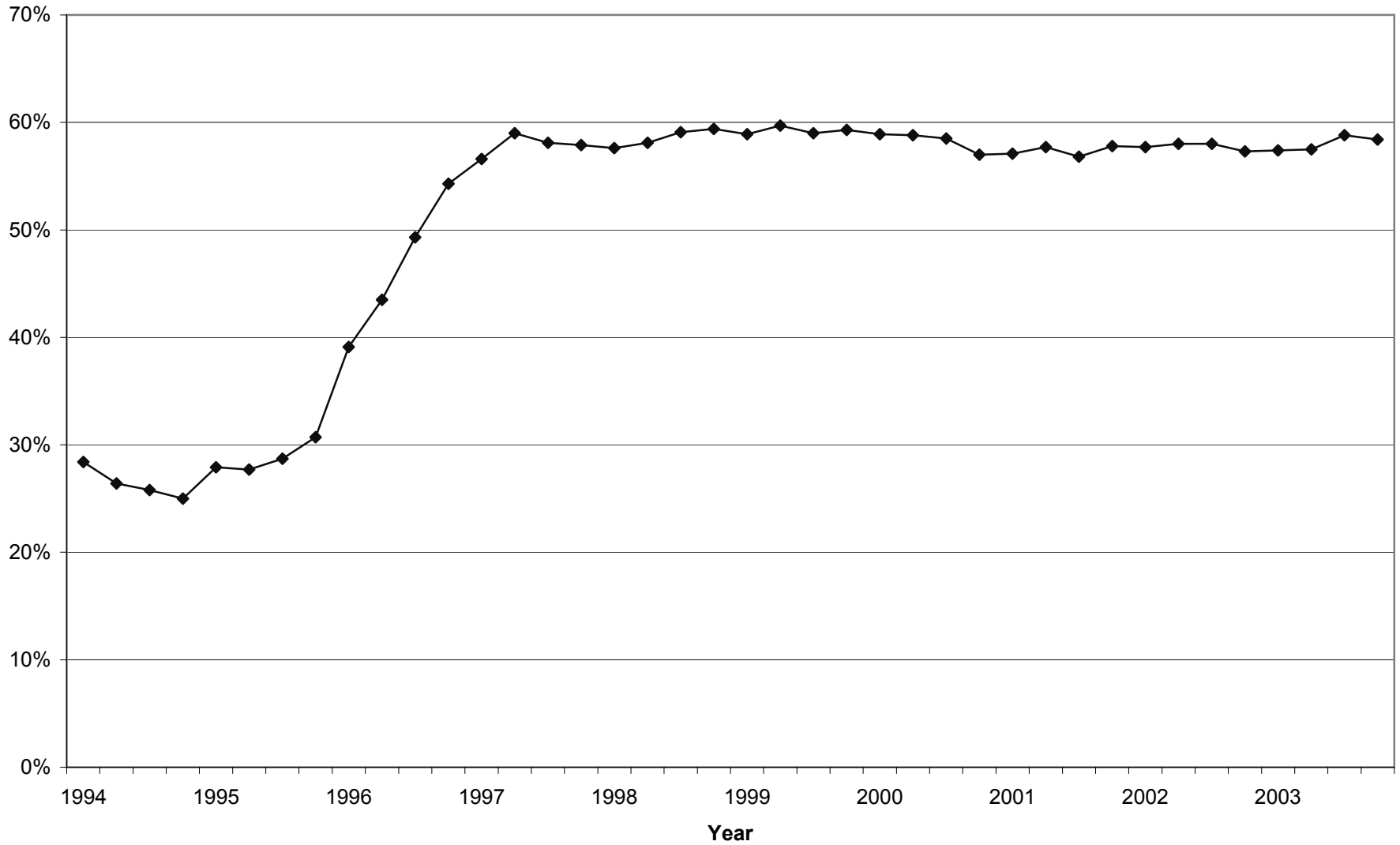


Figure 4: Diffusion of Epivir and Protease Inhibitors: 1994Q1 - 2003Q4

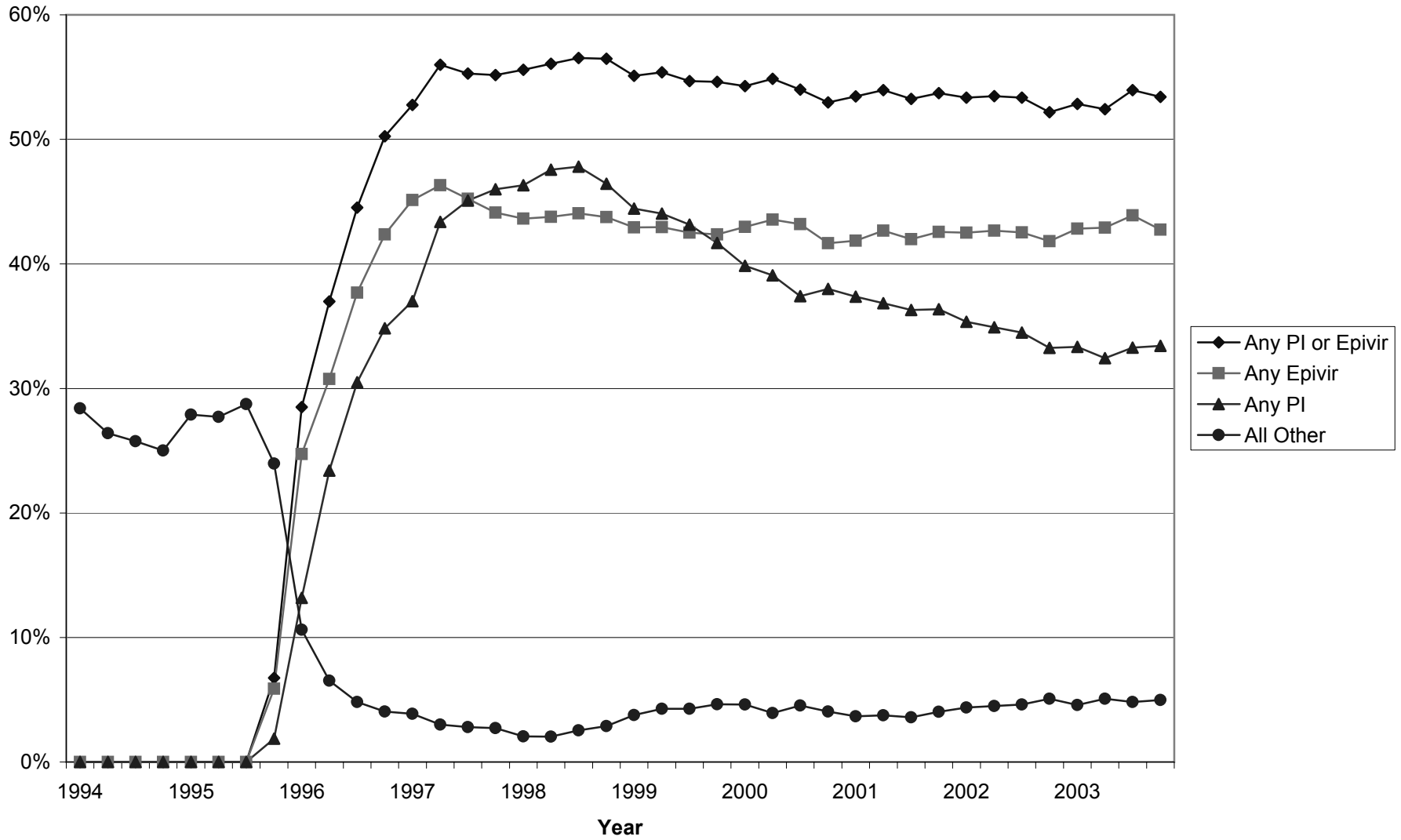


Figure 5: Average Quarterly Spending on HIV Drugs in CA Medicaid Sample

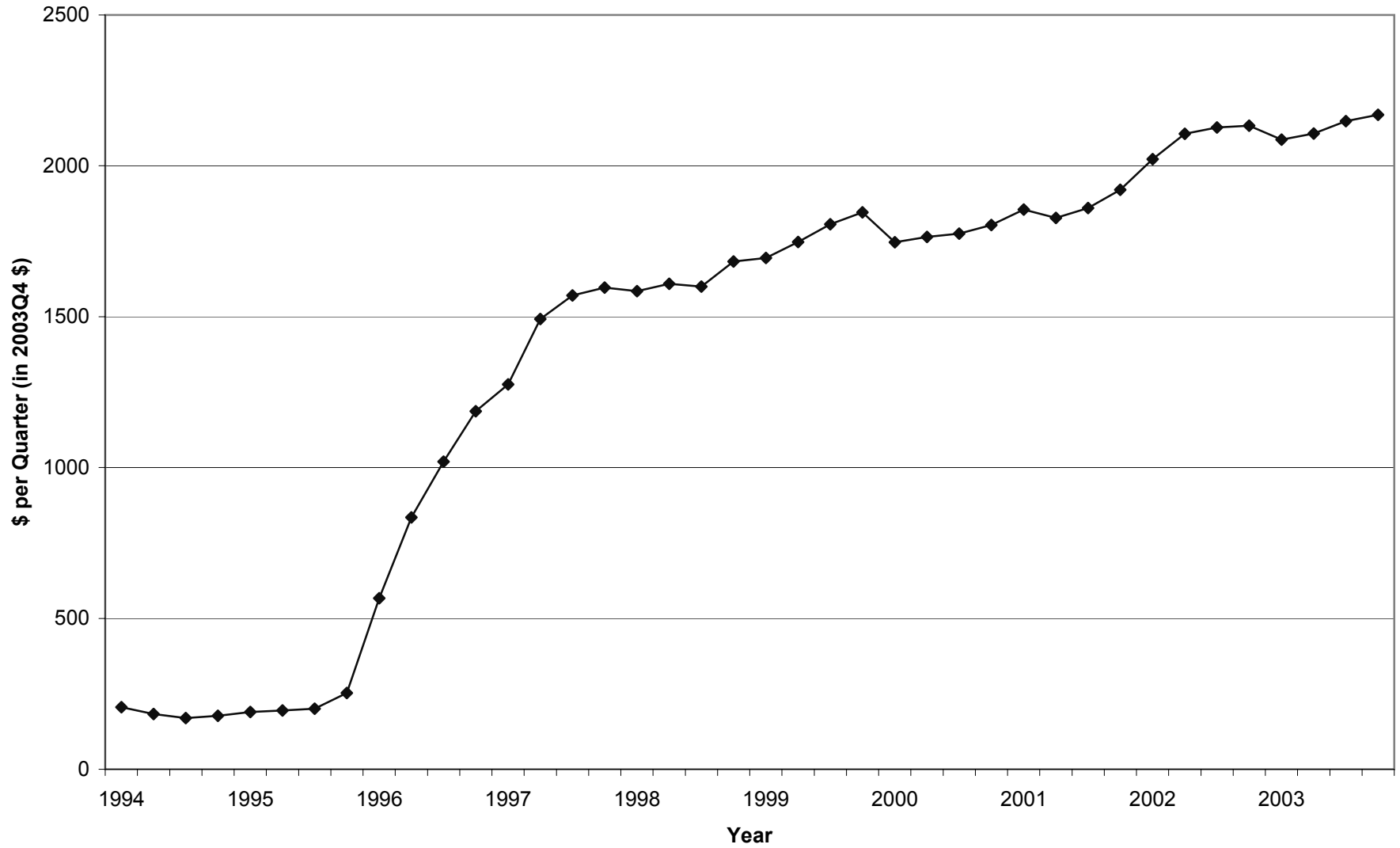


Figure 6: Quarterly Mortality Rate and Use of PI/Epivir

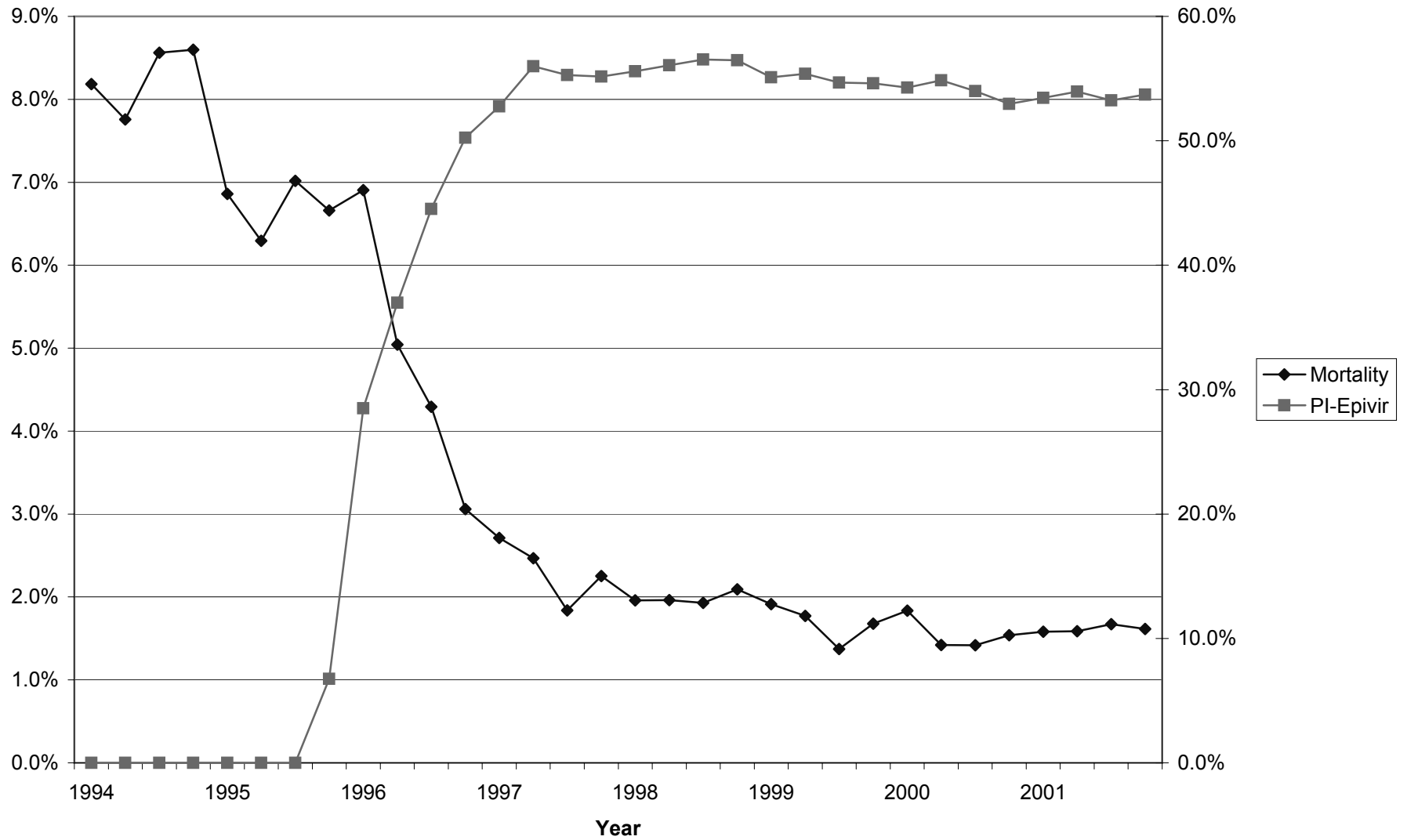


Figure 7: Use of PI and Epivir by Health Status

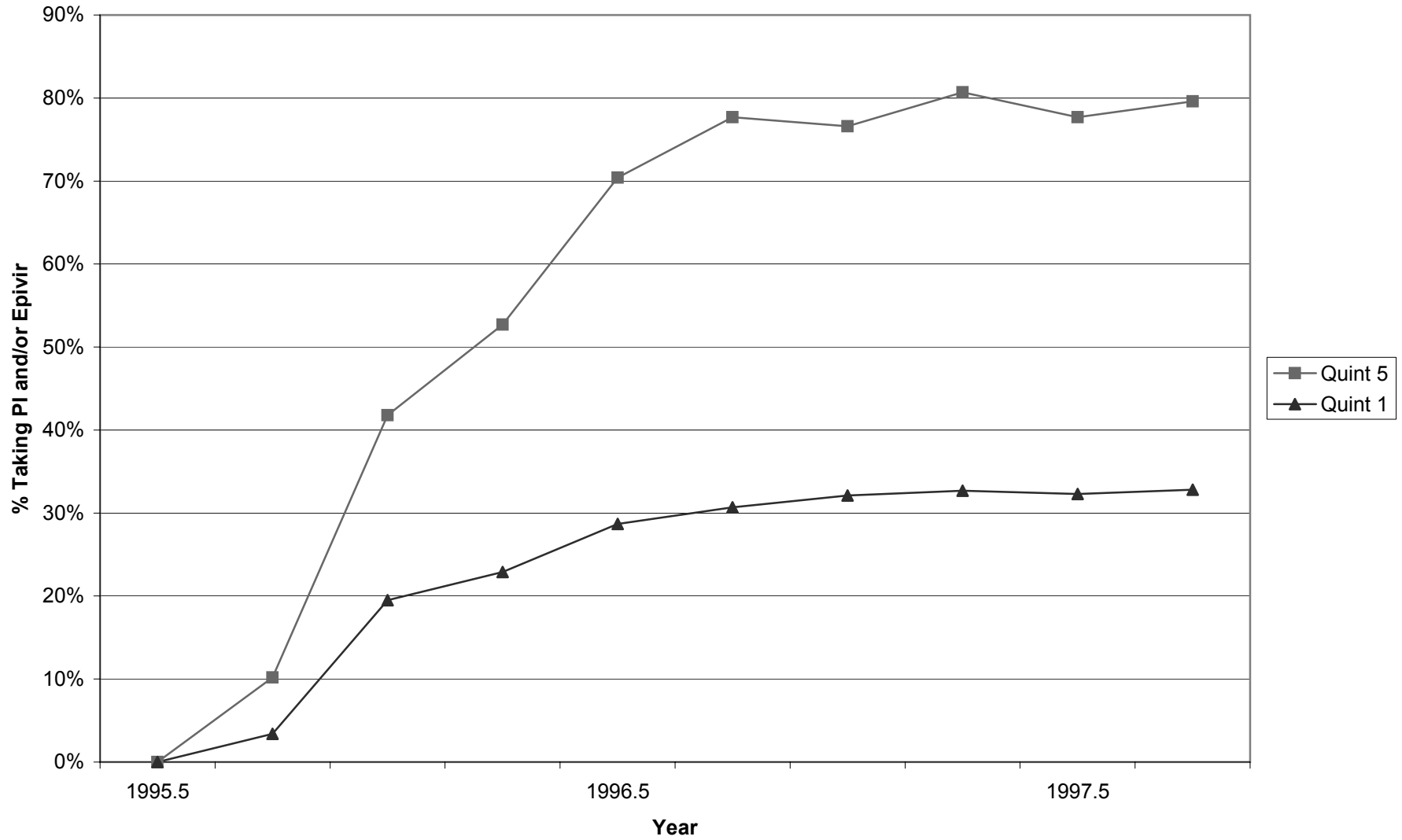


Figure 8: Use of Any HIV Drug by Health Status

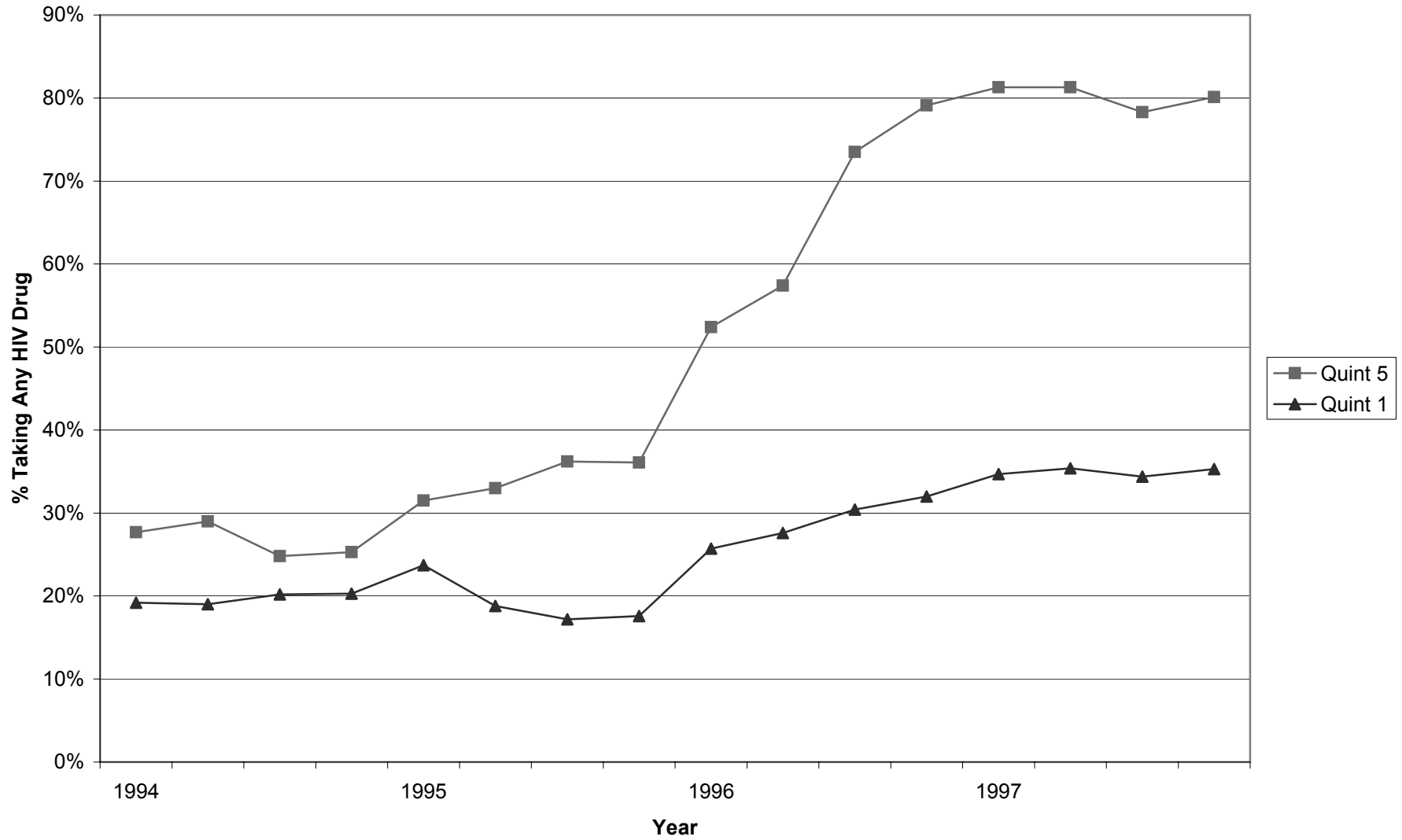


Figure 9: Quarterly Mortality Rate by Health Status



Figure 10: Average Quarterly Medicaid Spending in HIV/AIDS Sample

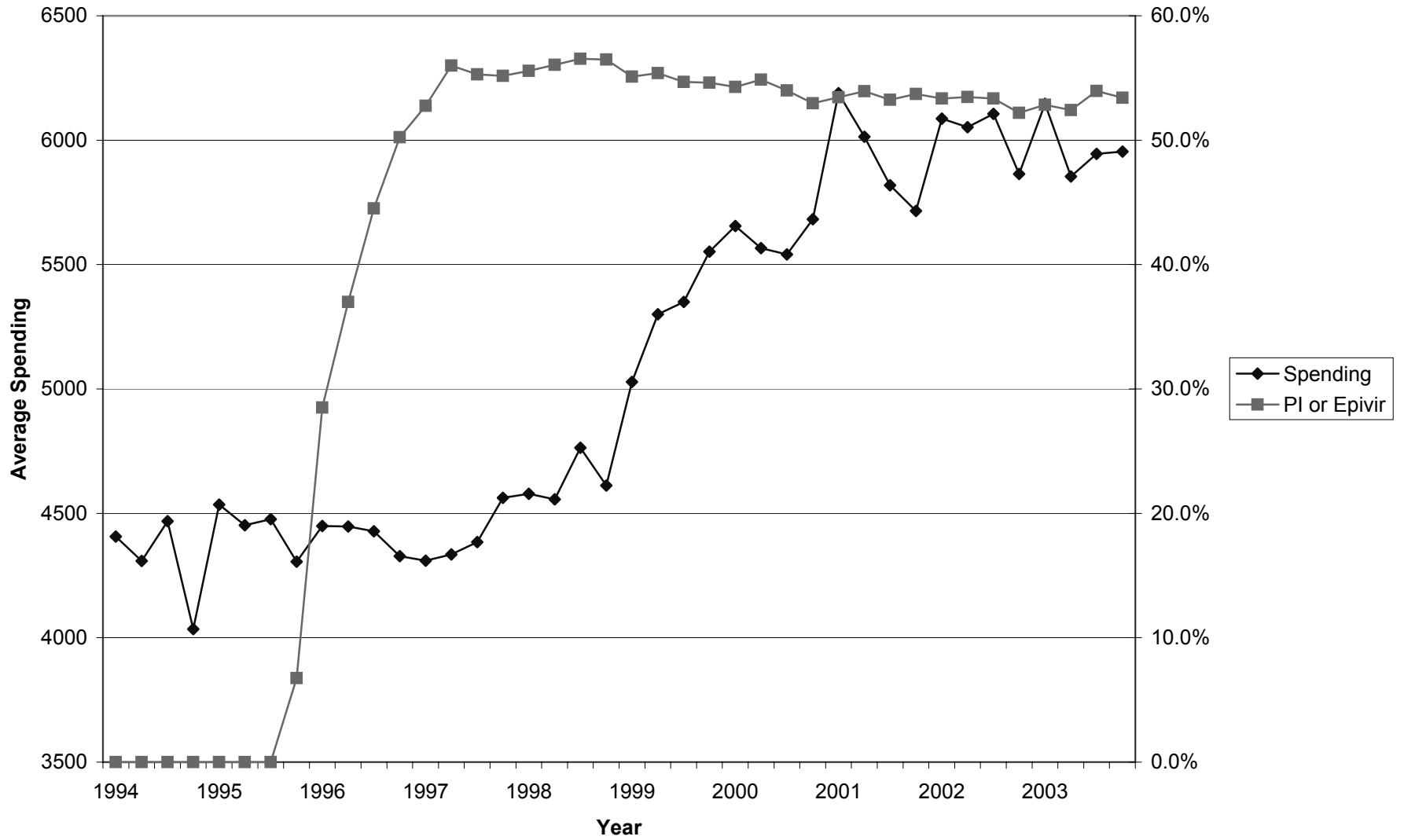


Figure 11: Quarterly Mortality Rates by Gender: 1994-1997

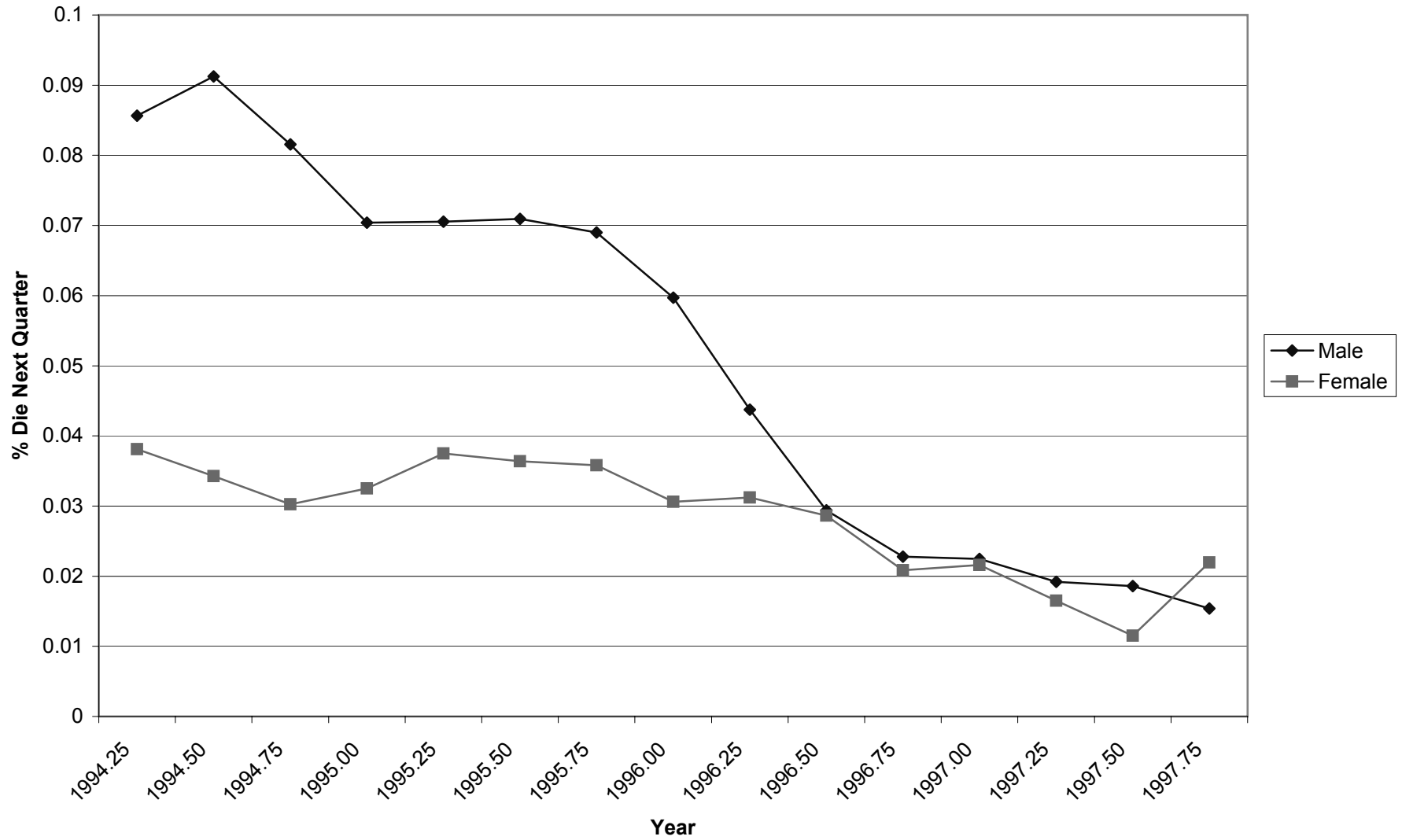


Table 1: Prescription Drugs Used in Treatment of HIV Infection by 12/31/03

Class	Brand Name	FDA Appr. Date	First script in claims data	Ingredients
NRTI	Retrovir	3/19/1987	1/2/1993	zidovudine
NRTI	Videx	10/9/1991	1/4/1993	didanosine
NRTI	Hivid	6/19/1992	1/4/1993	zalcitabine
NRTI	Zerit	6/24/1994	8/6/1994	stavudine
NRTI	Epivir	11/17/1995	11/27/1995	lamivudine
NRTI	Combivir*	9/27/1997	10/17/1997	lamivudine, zidovudine
NRTI	Ziagen	12/17/1998	12/18/1998	abacavir
NRTI	Trizivir**	11/14/2000	12/1/2000	abacavir, zidovudine, lamivudine
NRTI	Viread	10/26/2001	11/1/2001	tenofovir disoproxil fumarate
NRTI	Emtriva	7/2/2003		emtricitabine
PI	Invirase	12/6/1995	12/11/1995	saquinavir mesylate
PI	Norvir	3/1/1996	3/7/1996	ritonavir
PI	Crixivan	3/13/1996	3/26/1996	indinavir
PI	Viracept	3/14/1997	3/19/1997	nelfinavir mesylate
PI	Fortovase	11/7/1997	11/18/1997	saquinavir
PI	Agenerase	4/15/1999	4/26/1999	amprenavir
PI	Kaletra	9/15/2000	9/20/2000	lopinavir and ritonavir
PI	Lexiva	10/20/2003		fosamprenavir calcium
NNRTI	Viramune	6/21/1996	8/10/1996	nevirapine
NNRTI	Rescriptor	4/4/1997	4/25/1997	delavirdine
NNRTI	Sustiva	9/17/1998	9/23/1998	efavirenz
FI	Fuzeon	3/13/2003		enfuvirtide

Source for drug list and approval dates: US FDA at <http://www.fda.gov/oashi/aids/virals.html>

* Combivir is a combination of Epivir and Retrovir

** Trizivir is a combination of Epivir, Retrovir, and Ziagen

Table 2: Summary Statistics for the Medicaid HIV/AIDS Sample

	1994	1997	2000	2003
Average Age	38.4	40.7	43.0	45.1
% Ages 0-17	2.5%	2.6%	2.5%	2.2%
% Ages 18-29	12.0%	8.5%	4.4%	3.8%
% Ages 30-39	44.1%	38.7%	32.0%	21.9%
% Ages 40-49	29.3%	33.1%	37.7%	41.8%
% Ages 50-64	10.0%	13.4%	19.2%	25.3%
% Ages 65+	2.1%	3.8%	4.3%	4.9%
% Black	21.1%	23.4%	24.5%	25.0%
% Female	15.2%	21.3%	21.8%	22.3%
Inpatient Spending	7125	4309	3900	3510
Outpatient Spending	5091	4870	5007	5455
RX Spending	4122	7769	11913	12120
Total Spending	16338	16948	20820	21084
% Die in Year	23.0%	7.5%	5.2%	-
% Any Inpatient	47.8%	39.8%	30.0%	27.9%
Eligible Months	8.9	10.1	10.4	10.8
% Medicare	28.0%	39.2%	43.3%	44.7%
# in Sample	3221	3687	4275	4976

Includes Medicaid-eligible individuals with 1 or more HIV/AIDS claims in current or previous year.
Excludes those with one or more months in a Medicaid managed care plan or in one of the eight counties with a county-organized health system.

Table 3: Time-Series Estimates of the Effect of HAART Therapies

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Δ % Any HIV Drug	-0.1503*** (.0490)									
Δ % Any NRTI		-0.1605*** (.0579)								
Δ % Any PI			-0.1053*** (.0304)			-0.0511 (.0331)				
Δ % Any NNRTI				-0.0026 (.0485)						
Δ % Any Efavir					-0.0919*** (.0172)	-0.0563* (.0278)				
Δ % Any PI or Efavir (t)							-0.0789*** (.0148)	-0.0750*** (.0178)	-262 (641)	-0.0492 (.0374)
Δ % Any PI or Efavir (t-1)								-0.0066 (.0180)		
Constant	-0.0008 (.0011)	-0.0008 (.0011)	-0.0009 (.0009)	-0.0021 (.0014)	-0.0009 (.0009)	-0.0008 (.0010)	-0.0008 (.0009)	-0.0007 (.0010)	51 (42)	-0.0028 (.0029)
# Observations	31	31	31	31	31	31	31	30	31	31
R-squared	0.33	0.301	0.322	0	0.339	0.364	0.336	0.337	0.003	0.023

Dependent variable in specifications 1 through 8 is equal to the change in the fraction of individuals in the HIV/AIDS sample in quarter t and still alive at the end of t who die during quarter t+1. The dependent variables in specifications 9 and 10 are the change in average quarterly spending and in the fraction with some inpatient care. Huber-White standard errors are listed in parentheses.

Table 4: Determinants of Mortality, Hospitalization, and HIV Drug Usage Rates: 1994Q1-95Q3

	Av HIV Clms	Die Next Quarter?		Hosp Next Quarter?		HIV Drug this Quarter?	
		(1)	(2)	(3)	(4)	(5)	(6)
Constant	-	0.014 (.006)	0.003 (.008)	0.154 (.017)	0.151 (.023)	0.172 (.020)	0.172 (.026)
Decile 2	1.4	0.003 (.005)	0.004 (.005)	-0.013 (.017)	-0.007 (.017)	0.066 (.022)	0.057 (.022)
Decile 3	3.5	0.010 (.005)	0.010 (.006)	0.007 (.017)	0.014 (.017)	0.087 (.023)	0.083 (.022)
Decile 4	5.8	0.018 (.006)	0.018 (.006)	0.016 (.018)	0.025 (.018)	0.117 (.024)	0.107 (.023)
Decile 5	9.5	0.032 (.007)	0.032 (.007)	0.060 (.019)	0.069 (.019)	0.179 (.024)	0.173 (.024)
Decile 6	14.4	0.052 (.007)	0.052 (.008)	0.046 (.019)	0.053 (.019)	0.165 (.024)	0.157 (.024)
Decile 7	22.6	0.054 (.008)	0.054 (.008)	0.085 (.019)	0.092 (.019)	0.180 (.025)	0.173 (.025)
Decile 8	33.1	0.067 (.008)	0.067 (.009)	0.118 (.020)	0.126 (.020)	0.188 (.025)	0.189 (.025)
Decile 9	52.9	0.102 (.009)	0.102 (.009)	0.131 (.021)	0.140 (.020)	0.173 (.025)	0.167 (.025)
90th - 95th	79.9	0.123 (.013)	0.124 (.013)	0.192 (.026)	0.201 (.025)	0.112 (.028)	0.116 (.029)
95th - 100th	137.1	0.173 (.015)	0.175 (.015)	0.241 (.027)	0.249 (.027)	0.050 (.028)	0.057 (.028)
Female			-0.021 (.004)		0.008 (.014)		-0.050 (.018)
Black			-0.006 (.005)		0.052 (.013)		-0.035 (.016)
Medicare			0.015 (.005)		-0.018 (.011)		0.084 (.016)
Age 30-39			0.010 (.006)		-0.006 (.017)		-0.013 (.021)
Age 40-49			0.013 (.006)		-0.020 (.017)		0.021 (.022)
Age 50-64			0.025 (.008)		-0.026 (.021)		0.056 (.029)
Age 65 plus			0.013 (.011)		0.086 (.042)		-0.195 (.033)
R-squared		0.036	0.039	0.028	0.033	0.020	0.037
# Observations		14163	14163	13817	13817	14163	14163
# Individuals		3243	3243	3197	3197	3243	3243

Sample in each quarter includes patients with HIV/AIDS claims by or before that quarter. Patients enter the sample in the quarter of their first HIV/AIDS claim and are placed into deciles based on number of claims in current and previous three quarters. Standard errors allow for arbitrary correlation in the error for a particular patient. All specifications include quarter fixed effects.

Table 5: Determinants of the Use of PI and Epivir 1997

	Any PI or Epivir?		Any HIV Drug?	
	1995Q4-96Q4	1997Q1-97Q4	1994Q1-95Q3	1997Q1-97Q4
Constant	0.324 (.032)	0.291 (.050)	0.172 (.026)	0.329 (.051)
Decile 2	0.074 (.030)	0.116 (.043)	0.056 (.022)	0.128 (.045)
Decile 3	0.089 (.030)	0.189 (.043)	0.083 (.022)	0.189 (.045)
Decile 4	0.111 (.030)	0.221 (.046)	0.106 (.023)	0.227 (.047)
Decile 5	0.208 (.033)	0.295 (.045)	0.173 (.024)	0.300 (.046)
Decile 6	0.190 (.031)	0.304 (.045)	0.156 (.024)	0.322 (.046)
Decile 7	0.291 (.032)	0.420 (.044)	0.173 (.025)	0.428 (.044)
Decile 8	0.241 (.032)	0.382 (.045)	0.188 (.025)	0.395 (.045)
Decile 9	0.301 (.032)	0.433 (.045)	0.166 (.025)	0.426 (.046)
90th - 95th	0.271 (.041)	0.495 (.060)	0.116 (.029)	0.496 (.060)
95th - 100th	0.285 (.047)	0.519 (.053)	0.056 (.028)	0.519 (.054)
Female	-0.099 (.018)	-0.133 (.027)	-0.050 (.018)	-0.142 (.023)
Black	-0.097 (.017)	-0.129 (.026)	-0.035 (.016)	-0.116 (.026)
Medicare	0.118 (.016)	0.112 (.022)	0.084 (.016)	0.101 (.022)
Age 30-39	0.036 (.025)	0.011 (.041)	-0.013 (.021)	-0.004 (.042)
Age 40-49	0.066 (.026)	0.062 (.041)	0.021 (.022)	0.045 (.042)
Age 50-64	0.003 (.032)	-0.022 (.049)	0.056 (.029)	-0.046 (.049)
Age 65 plus	-0.165 (.040)	-0.265 (.059)	-0.195 (.033)	-0.298 (.059)
R-squared	0.216	0.178	0.037	0.181
# observations	8627	5497	14163	5497
# people	2002	1456	3243	1456

Sample in each quarter includes patients with HIV/AIDS claims by or before that quarter. Patients enter the sample in the quarter of their first HIV/AIDS claim and are placed into deciles based on number of claims in current and previous three quarters. Standard errors allow for arbitrary correlation in the error for a particular patient. All specifications include quarter fixed effects.

Table 6: The Impact of PI and/or Epivir on Quarterly Mortality & Hosp. Rates

	Die Next Quarter?		Hosp Next Quarter?	
	Main	* PI-Epivir	Main	* PI-Epivir
Decile 1	-	0.008 (.008)	-	0.004 (.037)
Decile 2	0.001 (.004)	0.005 (.006)	-0.018 (.019)	0.057 (.028)
Decile 3	0.005 (.004)	0.010 (.007)	0.021 (.019)	0.011 (.025)
Decile 4	0.014 (.004)	0.001 (.008)	0.031 (.020)	-0.051 (.021)
Decile 5	0.022 (.005)	-0.004 (.008)	0.059 (.021)	0.031 (.030)
Decile 6	0.036 (.005)	-0.025 (.007)	0.035 (.020)	0.006 (.026)
Decile 7	0.048 (.006)	-0.030 (.008)	0.089 (.022)	-0.033 (.029)
Decile 8	0.057 (.006)	-0.047 (.008)	0.119 (.022)	-0.066 (.025)
Decile 9	0.084 (.008)	-0.056 (.010)	0.142 (.021)	-0.008 (.031)
90th - 95th	0.127 (.012)	-0.109 (.016)	0.201 (.026)	-0.079 (.052)
95th - 100th	0.164 (.014)	-0.133 (.018)	0.250 (.028)	-0.089 (.051)
Constant		0.011 (.007)		0.143 (.024)
# Observations		28287		27628
R-squared		0.040		0.032
# Individuals		3243		3197
Age, etc. Controls?		Yes		Yes
Quarter Effects?		Yes		Yes
Quarters Included		94Q1-97Q4		94Q1-97Q4

Sample in each quarter includes patients with HIV/AIDS claims by or before that quarter. Patients enter the sample in the quarter of their first HIV/AIDS claim and are placed into deciles based on number of claims in current and previous three quarters. Standard errors allow for arbitrary correlation in the error for a particular patient. All specifications include quarter fixed effects.

Table 7: Changes in Long-Term Spending and Eligibility for Medicaid HIV/AIDS Patients

Percentile	Medicaid Spending			Medicaid Eligible Months		
	1994-1999	1996-2001	1998-2003	1994-1999	1996-2001	1998-2003
5th	\$594	\$518	\$1,633	2	2	5
10th	\$2,405	\$2,714	\$6,174	3	4	10
25th	\$10,632	\$15,129	\$26,783	8	14	28
50th	\$33,606	\$50,692	\$75,854	21	49	68
75th	\$71,920	\$108,879	\$140,393	62	72	72
90th	\$124,438	\$189,469	\$235,946	72	72	72
95th	\$179,928	\$264,922	\$322,488	72	72	72
Mean	\$57,101	\$83,293	\$106,719	31.5	43.1	51.3
# Observations	2282	2617	2958	2282	2617	2958

The first and fourth columns summarize spending and eligible months from 1994-1999 for individuals with one or more HIV/AIDS claims by or before 1994Q1. The subsequent columns are defined similarly for those with one or more HIV/AIDS claims by 1996Q1 (columns 2 and 5) and by 1998Q1 (columns 3 and 6). Dollar amounts are inflation-adjusted to 2003 values using the CPI-U index.

Table 8: The Cost of PI and Efavir per Life-Year Saved

Year	Number of individuals alive		Yearly spending (million of \$)		Yearly increase in
	No HAART	with HAART	No HAART	with HAART	
1994	3318	3318	56.44	64.07	7.63
1995	2501	3080	43.90	59.29	15.38
1996	1895	2860	31.17	54.86	23.69
1997	1444	2657	23.46	50.84	27.38
1998	1108	2469	17.79	47.11	29.32
1999	857	2294	13.59	43.69	30.10
2000	669	2131	10.46	40.51	30.05
2001	528	1979	8.14	37.55	29.41
2002	421	1837	6.40	34.82	28.42
2003	341	1705	5.10	32.21	27.11
2004	279	1581	4.10	29.74	25.64
2005	233	1465	3.33	27.44	24.12
2006	197	1356	2.73	25.26	22.53
2007	169	1253	2.27	23.21	20.94
2008	148	1156	1.90	21.12	19.22
2009	131	1064	1.61	19.23	17.62
2010	118	977	1.38	17.40	16.03
2011	108	893	1.19	15.67	14.49
2012	100	814	1.05	14.02	12.97
2013	94	740	0.95	12.47	11.52
2014	89	670	0.87	11.07	10.20
2015	85	605	0.81	9.79	8.98
2016	82	544	0.76	8.61	7.85
2017	80	488	0.72	7.55	6.83
2018	78	436	0.69	6.56	5.87
2019	77	389	0.67	5.68	5.01
TOTAL	15146	38758	241.47	719.77	478.30
Total average spending by person (1000s of \$):			72.777	216.929	144.153
% of individuals surviving 5 years			25.8%	69.1%	
% of individuals surviving 10 years			8.4%	47.6%	
% of individuals surviving 25 years			2.3%	11.7%	

Appendix Table 1: Trends in AIDS Mortality in CA and in CA Medicaid Sample

Year	All of CA		CA Medicaid		CA Medicaid Sample		No HIV Diag but HIV Drug	
	All	matchable SSN	Ever eligible	% on Medicaid	In Sample	% in our sample	N	% of total
1993	6129	1502	818	54.5%	625	76.4%	25	3.1%
1994	6551	1619	938	57.9%	774	82.5%	22	2.3%
1995	6278	1526	861	56.4%	714	82.9%	14	1.6%
1996	4082	1031	617	59.8%	529	85.7%	8	1.3%
1997	1780	401	250	62.3%	211	84.4%	5	2.0%
1998	1378	339	226	66.7%	196	86.7%	6	2.7%
1999	1488	368	227	61.7%	187	82.4%	14	6.2%
2000	1400	335	206	61.5%	180	87.4%	5	2.4%
2001	1415	338	228	67.5%	201	88.2%	7	3.1%
Total	30501	7459	4371	58.6%	3617	82.7%	106	2.4%

Appendix Table 2: Number of Claims in Each Quarter for NRTI Drugs

year	Retrovir*	Videx	Hivid	Zerit	Epivir*	Ziagen*	Viread	Emtriva
1993.00	943	446	281	0	0	0	0	0
1993.25	1043	448	327	0	0	0	0	0
1993.50	977	361	322	0	0	0	0	0
1993.75	871	309	307	0	0	0	0	0
1994.00	868	270	314	0	0	0	0	0
1994.25	814	209	307	0	0	0	0	0
1994.50	733	178	286	79	0	0	0	0
1994.75	643	165	286	232	0	0	0	0
1995.00	711	156	282	316	0	0	0	0
1995.25	715	151	262	399	0	0	0	0
1995.50	721	173	267	460	0	0	0	0
1995.75	785	171	285	482	159	0	0	0
1996.00	1022	189	230	517	1103	0	0	0
1996.25	1147	165	170	643	1567	0	0	0
1996.50	1251	203	158	873	1956	0	0	0
1996.75	1297	258	172	1215	2324	0	0	0
1997.00	1338	314	179	1533	2598	0	0	0
1997.25	1413	409	200	1823	2829	0	0	0
1997.50	1426	499	179	1968	2862	0	0	0
1997.75	1375	535	214	2053	2877	0	0	0
1998.00	1422	602	158	2080	2941	0	0	0
1998.25	1362	674	160	2176	2940	0	0	0
1998.50	1367	714	152	2270	3067	0	0	0
1998.75	1411	760	134	2304	3121	2	0	0
1999.00	1401	806	125	2326	3119	325	0	0
1999.25	1516	894	111	2354	3203	608	0	0
1999.50	1571	865	101	2428	3268	750	0	0
1999.75	1605	878	98	2530	3419	845	0	0
2000.00	1607	821	81	2417	3417	891	0	0
2000.25	1660	785	82	2452	3576	999	0	0
2000.50	1701	767	82	2422	3536	1031	0	0
2000.75	1655	782	61	2400	3511	1092	0	0
2001.00	1663	908	63	2439	3542	1194	0	0
2001.25	1604	924	61	2419	3516	1285	0	0
2001.50	1533	956	49	2371	3425	1454	0	0
2001.75	1495	981	46	2336	3460	1545	184	0
2002.00	1428	1002	35	2213	3408	1665	664	0
2002.25	1451	1055	42	2116	3471	1735	1017	0
2002.50	1449	1065	35	2003	3462	1803	1324	0
2002.75	1480	1031	31	1862	3562	1864	1645	0
2003.00	1435	1006	25	1744	3573	1933	1851	0
2003.25	1441	1053	25	1570	3723	1916	2195	0
2003.50	1449	1020	19	1501	3828	1919	2405	55
2003.75	1446	1060	20	1386	3809	1843	2551	165

Appendix Table 3: Number of Claims in Each Quarter for PI Drugs

year	invirase	norvir	crxivian	viracept	fortovase	agenerase	kaletra	lexiva	
1993.00	0	0	0	0	0	0	0	0	0
1993.25	0	0	0	0	0	0	0	0	0
1993.50	0	0	0	0	0	0	0	0	0
1993.75	0	0	0	0	0	0	0	0	0
1994.00	0	0	0	0	0	0	0	0	0
1994.25	0	0	0	0	0	0	0	0	0
1994.50	0	0	0	0	0	0	0	0	0
1994.75	0	0	0	0	0	0	0	0	0
1995.00	0	0	0	0	0	0	0	0	0
1995.25	0	0	0	0	0	0	0	0	0
1995.50	0	0	0	0	0	0	0	0	0
1995.75	49	0	0	0	0	0	0	0	0
1996.00	493	77	5	0	0	0	0	0	0
1996.25	564	268	543	0	0	0	0	0	0
1996.50	638	284	1027	0	0	0	0	0	0
1996.75	670	337	1267	0	0	0	0	0	0
1997.00	709	422	1453	35	0	0	0	0	0
1997.25	817	465	1344	693	0	0	0	0	0
1997.50	820	490	1138	1081	0	0	0	0	0
1997.75	807	541	1146	1224	73	0	0	0	0
1998.00	564	608	1056	1303	428	0	0	0	0
1998.25	426	706	1005	1366	654	0	0	0	0
1998.50	375	749	1064	1382	686	0	0	0	0
1998.75	290	723	1020	1512	779	0	0	0	0
1999.00	233	540	1000	1479	720	0	0	0	0
1999.25	167	517	998	1475	660	188	0	0	0
1999.50	143	718	1005	1434	658	327	0	0	0
1999.75	121	756	1017	1357	597	396	0	0	0
2000.00	94	788	906	1286	549	402	0	0	0
2000.25	82	888	951	1198	531	446	0	0	0
2000.50	83	944	902	1139	500	489	21	0	0
2000.75	62	903	768	1124	462	509	355	0	0
2001.00	60	852	682	1130	447	493	593	0	0
2001.25	46	805	646	1052	418	456	813	0	0
2001.50	58	790	655	1028	403	432	914	0	0
2001.75	49	759	623	1001	390	407	1041	0	0
2002.00	59	693	506	972	363	362	1150	0	0
2002.25	81	652	463	996	333	348	1288	0	0
2002.50	93	581	451	928	303	313	1390	0	0
2002.75	114	568	414	916	267	288	1472	0	0
2003.00	171	580	389	820	234	306	1594	0	0
2003.25	196	563	346	741	206	288	1730		
2003.50	194	678	312	702	198	270	1764		
2003.75	173	843	282	644	176	222	1786		