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ESTIMATING THE IMPACT OF MEDICAL INNOVATION: THE CASE OF HIV ANTIRETROVIRAL TREATMENTS

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ABSTRACT

In 1995 AIDS was the eighth-leading cause of death in the U.S. and the leading cause among men between the ages of 25 and 44. During the next three years the number of deaths among individuals with HIV/AIDS in the U.S. declined by nearly 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 and diagnosed with HIV/AIDS to estimate the contribution of HIV antiretroviral treatments (ARVs) to this decline and their corresponding effect on long-term health care spending. The Medicaid population is a natural one to consider given that approximately half of all AIDS patients in the U.S. are enrolled in this program. Using the detailed information on health care utilization in our claims data, we account for the fact that patients taking ARVs are significantly less healthy than the average patient in our sample. Our findings demonstrate that the increase in the use of four drugs approved by the FDA in late 1995 and early 1996 was responsible for more than 90 percent of the drop in the mortality rate from 1995 to 1998. Despite the entry of more than a dozen drugs since these four, mortality rates have remained virtually unchanged. We find that the use of the new drugs led to a threefold increase in lifetime Medicaid spending due to their high cost and the resulting increase in life expectancy. Despite this, the new treatments were costeffective, with the average additional cost in Medicaid spending per life-year saved equal to $23,000.

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I. Introduction

From 1991 to 1995, HIV/AIDS[1] 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 these rates were trending down at a gradual rate during the early 1990s. By October of 1995, four different prescription drugs were available for the treatment of HIV/AIDS, but because of limited clinical benefits and serious side effects, utilization of these drugs had been declining during the preceding two years.

In a seven-month period from November of 1995 to June of 1996, the U.S. Food and Drug Administration (FDA) approved five new prescription drugs for the treatment of HIV/AIDS. Epivir was the first one of these 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 a new class of drugs known as protease inhibitors (PI). In June of 1996, a third class was introduced when Viramune, a non-nucleoside reverse transcriptase inhibitor (NNRTI), received FDA approval. Many patients took more than one of these antiretroviral treatments (ARVs) simultaneously, with the combination of two or more often referred to as highly active antiretroviral therapy (HAART).

Early clinical trials of the new treatments demonstrated their ability to reduce the viral load in patients and to increase the concentration of CD4 cells, a type of blood cell critical for fighting off infections. Use of them spread rapidly, with almost 60 percent of HIV/AIDS patients using protease inhibitors by the end of 1996 and mortality among AIDS patients falling by 70 percent from 1995 to 1998.[2] Despite a decline in infection rates, the number of individuals living with this illness continued to rise because of the increase in life expectancy. A large number of studies, some using randomized research designs and others using observational data on patients investigated the effect of the new treatments on mortality, with virtually all of them finding that the new therapies led to significant reductions in mortality among HIV/AIDS patients. Another strand of the literature estimated the effect of

[1] These stand for human immunodeficiency virus and acquired immune deficiency syndrome, respectively.
[2] CDC HIV/AIDS Surveillance Report, 2001.

the new drugs on health care spending with these studies finding that the drugs reduced spending on hospital care and on other health care services.

Although these studies made important contributions to knowledge, most had significant limitations. For example, the typical study had small sample sizes and patients were followed for just a short period of time. Additionally, non-experimental studies varied widely in their efforts to account for the non-random selection of patients into treatment, with some using regression-based methods while others used a case/control method. Studies where treatment was randomly assigned contained carefully selected patients, raising the question of whether the drugs would have the same effect when used by a more diverse set of patients. Similarly, participants in these studies were tightly monitored and thus it is not obvious that patients in the real world would comply as closely with the recommended treatment regimen.

Another important limitation of most previous studies was the assumption of a "common treatment effect," which implied that ARVs reduced mortality probabilities by the same amount regardless of the characteristics of the patient. Heterogeneity in the treatment effect of ARVs was noted by the National Institutes of Health (2004) in their clinical guidelines for the use of these drugs but most studies do not investigate this.[3] A further limitation of the previous literature is that no study investigated what fraction of the decline in mortality rates was attributable to new ARV treatments versus other factors. As mentioned above, mortality rates among AIDS patients were falling prior to 1995 and thus it is possible that other factors (e.g. changes in the composition of patients, in the behavior of patients, or in the treatment of opportunistic infections) was responsible for some of the improvement. A final limitation is that most studies estimating the impact of ARVs on health care spending focused on short

[3] NIH notes that there is limited evidence of a clinical benefit when CD4 counts are above a certain threshold. Some studies selected patients with low CD4 counts, thus reducing the need for modeling this heterogeneity. Other studies have examined how the progression to AIDS and death varies based on initial CD4 and viral load counts, but almost all of them examine cohorts of individuals on ARVs and do not compare outcomes for similarly defined people not taking ARVs.

time periods of one year or less.[4] Given the substantial increases in life expectancy, it is indeed plausible that short and long-term 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 approximately 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.[5] 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 death records maintained by the state that allows us to investigate the effect of new drug treatments 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 4.0 million California residents in our full Medicaid 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 and it is worth emphasizing that no prior study has examined as large a sample of patients for as long a period as the one studied here.[6] We begin by showing that the number of patients in our sample from one year to the next tracks the number of people living with AIDS reported by the U.S. Centers for Disease Control and Prevention (CDC) for the entire state of California quite closely. We next demonstrate that the implied fraction of California residents living with HIV/AIDS who are on Medicaid is close to 50 percent. We then show that changes in the mortality rate for the individuals in our sample track the statewide trends very closely. These three

[4] Those that estimated the effects over longer periods (Freedberg *et al.*, 2001) used estimates of lifesaving potential and costs from many different sources.

[5] 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.

[6] The HIV Cost and Services Utilization Consortium (Shapiro *et al.,* 1999) followed a cohort of 2,864 HIV+ patients for January of 1996 through January of 1998. The CASCADE Collaboration (2003) pooled data from 22 cohorts of HIV+ patients from European, Canadian and Australian studies to construct a sample of 7740 HIV patients covering the pre-1997 through 2001 period. The ART Cohort Collaboration (Egger at al, 2002) pooled data from 13 cohort studies of patients starting ARVs from Europe and North American to generate a sample of 12,574 patients.

findings suggest that our algorithm for determining which of the 4.03 million individuals in the full Medicaid sample was infected with HIV/AIDS during our study period is quite accurate.

The mortality improvements in our sample occurred precisely when utilization of Epivir and protease inhibitors was growing rapidly. In the third quarter of 1995, no individuals in our sample were taking Epivir 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 similarly large 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 these new antiretroviral treatments.

To probe more formally on this issue, we next estimate aggregate time-series models in which we regress changes in the quarterly mortality rate on changes in the use of various drug treatments in our sample. Our findings demonstrate that the increase in the use of Epivir and protease inhibitors can explain more than ninety percent of the 5.1 percentage point decline in quarterly mortality rates from late 1995 until the middle of 1997.

In the second empirical section, we use individual-level data to examine the impact of ARVs on a variety of outcomes. There are two key facets of this section. First, patients with the highest risk of death are the most likely to be recommended for use of these new ARVs. 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 because of the detailed information available in our data and its longitudinal nature. Second, the clinical benefits of new ARVS are correlated with baseline conditions, so we allow for heterogeneity in the treatment effect based on our patient severity index.

Our health severity index predicts well both the pre-1996 mortality and the use of the new ARVs released in late 1995 and early 1996. 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

three times more likely to use these new therapies than those in the lowest decile. In regression models with individual-level data, we find that use of Epivir and/or protease inhibitors in a quarter reduced next quarter mortality for those in the top half of the severity index. Measured in percentage point terms, the benefit of treatment is increasing in the severity index, though the decline is proportionally similar for all of the top five deciles.

In the final section of our paper, we investigate the effect of Epivir and protease inhibitors on long-term health care spending. While the new drug treatments reduced inpatient costs, there was little change in annual spending given the substantial increase in expenditures on prescription drugs. But given the significant decline in mortality rates, our estimates suggest that Epivir and protease inihibitors increased lifetime spending for individuals with HIV/AIDS by more than a factor of three. Our findings also suggest that the cost per life year saved was approximately $22,000, a number that is on the low end of estimates of other important medical interventions, indicating that Epivir and protease inhibitors are cost effective.[7] This appears not to be true for the 15 drugs approved since early 1996, as prescription drug spending has continued to rise but there has been little further decline in patient mortality.

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

[7] See Cutler (2003) for a review of previous studies of the cost per life year saved of various health care treatments. Studies of changes to the Medicaid program (rather than of specific treatments) include Currie and Gruber (1997) and Baicker and Staiger (forthcoming), whose findings suggest that expansions of Medicaid eligibility and increased Medicaid reimbursement rates for safety net hospitals, respectively, led to significant improvements in health.

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 their CD4 cell count falls below a certain threshold[8] or once they are 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 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 slowing the progression to AIDS.[9] The focus of this paper is on the three classes of prescription drugs introduced since 1987 for the treatment of HIV/AIDS: nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), and non-nucleoside reverse transcriptase inhibitors (NNRTI). All three reduce the ability of the virus to replicate inside the host but all work in a different way.[10] The first NRTI was approved for use in 1987,

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[8] 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/mm^3 .

[9] To understand how these drugs work, it is useful to outline how HIV multiplies 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.

[10] 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.

though use of these drugs was declining among AIDS patients until the release of Epivir in late 1995. Soon after that, the first PIs and NNRTIs were approved for use.[11]

Early clinical trials demonstrated that these new therapies were very 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 these new therapies in clinical trials led to expedited approval 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.[12] Soon after, two other protease inhibitors were approved for use by the FDA: Ritonivir was approved on March 1, 1996 after only 72 days of review,[13] and Indinavir was approved on March 13, 1996 after only 42 days of review.[14] A complete list of drugs approved to treat HIV/AIDS by the end of 2003 is provided in Table 1. In the first three columns, we include each drug's class, its brand name, and its FDA approval date.

The release of Epivir and protease inhibitors in late 1995 and early 1996 spawned the use of highly active antiretroviral therapies (HAART), which is the use of two or more antiretroviral drugs to treat HIV. When initiating therapy in patients who have never been on ARVs, the guidelines recommend patients start with one protease inhibitor in combination with two NRTIs. Other treatment options include mixtures of NRTIs and NNRTIs or NRTIs only for patients whose initial regimen was not successful. The decision of when to initiate therapy is based both on the strength of the patient's immune system (measured by CD4 cell counts) and by the concentration of HIV in the patient's blood (also known as the viral load). Current guidelines recommend HAART for all patients with less than 200 CD4+ cells per cubic millimeter of blood (mm^3), and all patients with CD4 cell counts between 200-350

[11] 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 a part of our main analyses.
[12] See http://www.fda.gov/bbs/topics/NEWS/NEW00521.html.
[13] See http://www.fda.gov/bbs/topics/NEWS/NEW00527.html.
[14] See http://www.fda.gov/bbs/topics/NEWS/NEW00528.html.

cells/mm^3 should be offered treatment (National Institutes of Health, 2004; Yeni *et al.,* 2003). The National Institutes of Health (NIH) notes that there is little evidence of clinical benefits if therapy is initiated when CD4 counts are in excess of 350/mm^3, but they recognize that some clinicians may consider treatment in these patients when viral loads are in excess of 100,000 HIV/RNA copies per milliliter (mL). Results from a number of recent studies (Wang *et al.,* 2004; Palella *et al.,* 2003; Sterling *et al.,* 2003) have led some to re-evaluate these guidelines (Schechter 2004) and to consider starting ARV treatment when CD4 counts are in excess of 350. The ultimate goal of treatment is complete viral suppression, which is defined as less than 50 copies of HIV/RNA/mL.

The guidelines note the costs and benefits of an early start of HAART therapy. 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.[15] 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 HIV-positive patients, we should find those who are sicker to be the most likely to be taking antiretroviral drugs.[16]

In a short period after the approval of Epivir and protease inhibitors, HAART became the standard treatment for those infected with HIV. Bozzette *et al.,* (1998 and 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 (Palella *et al..,* 1998; Sackoff, McFarland, and Shin, 2000; Ghani, Donnelly, and Anderson, 2003). Medicaid patients typically have lower use rates for these new drugs than the general population (Bozzette *et al.,* 2001; Shapiro *et al.,* 1999) with the estimated utilization rates varying to some extent across states.[17]

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[15] 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.

[16] 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.

[17] For example, HAART use among HIV-positive patients on Medicaid in the late 1990s 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, *et al.,* 2001).

As more AIDS patients initiated HAART therapy, and as mortality detail data for 1996 became available, researchers began to notice a decline in mortality rates from AIDS. A February 28, 1997 report in the *Morbidity and Mortality Weekly Reporter* noted that in 1996, for the first time, deaths among AIDS patients declined from the previous year's total.[18] Between 1995 and 2001 deaths among AIDS patients fell 70 percent.[19] An even more staggering change occurred in the annual mortality rate of AIDS patients, 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 from 1995 to 2001. Note however that prior to 1995, unlike AIDS deaths, the death rate was declining, dropping 23 percent between 1991 and 1995.

A large number of later studies, some using randomized research designs (e.g., Hammer *et al.,* 1997; Delta Coordinating Committee, 2001; Floridia *et al*., 2002) and others using observational data on patients (Palella *et al.,* 1998; Detels *et al.,* 1998; Schwarcz *et al.,* 2000; Lewden *et al.,* 2001; Egger *et al.,* 2002; and the CASCADE Collaboration, 2003; Messeri *et al.,* 2003) investigated the life saving benefits of new ARVs. Virtually all of the studies find that the new drug therapies generated statistically significant reductions in mortality among HIV/AIDS patients. A number of other studies estimated the effect of the new drugs on health care spending (Gebo *et al.,* 1999; Gebo, Keiser *et al.,* 2001) with most finding that the drugs offset spending on hospital care and on other health care services.

Although these studies made important contributions to knowledge, most had significant limitations. For example, a typical study had small sample sizes (e.g., Hammer *et al.,* 1997; Palella *et al.,* 1998; Vittinghoff, *et al.,*1999; Wong *et al.*, 2000; Hogg *et al.,* 2001; Messeri *ey al.,* 2003) and patients were followed for just a short period of time (Raffi *et al.,* 2001; Wong *et al.,* 2000; Floridia, *et al.,* 2002). Additionally, non-experimental studies varied widely in their efforts to account for the non-random selection of patients into treatment, with some using regression-based methods (Schwarcz *et al.,* 2000;

[18] "Update: Trends in AIDS Incidence, Deaths, and Prevalence – United States, 1996," *Morbidity and Mortality Weekly Reporter,* Fenruary 28, 1997, Vol. 46, No. 8, 165-173.
[19] CDC HIV/AIDS Surveillance Report, 2001, Table 31.

Vittinghoff *et al.,* 1999) while others used a case/control method (Palella *et al.,* 1998; Wong *et al.*, 2000). Studies where treatment was randomly assigned contained carefully selected patients, raising the question of whether the drugs would be as effective when used by a more diverse set of individuals with HIV/AIDS. Similarly, participants in these studies were tightly monitored and thus it is not obvious that patients in the real world would comply as closely with the recommended treatment regimen.

Another important limitation of many previous studies was the assumption of a "common treatment effect," which implied that ARVs reduced mortality probabilities by the same amount regardless of the characteristics of the patient (Hammer *et al.,* 1997; Raffi *et al.,* 2001; Palella *et al.,* 1998; Vittinghoff, *et al.,* 1999; Schwarcz *et al.,* 2000; Messeri *et al.,* 2003). Heterogeneity in the treatment effect of ARVs is noted in the National Institutes of Health (2004) in their clinical guidelines for use these drugs when they note that there is limited evidence of a clinical benefit for these drugs when CD4 counts are above a particular threshold. Some studies selected samples based on particular characteristics (e.g., Palella *et al.,* 1998; and Miller *et al.,* 2000; only included patients with low CD4 counts) eliminating the need for heterogeneous treatment effects. In contrast, other studies have examined how the progression to AIDS and death varies based on initial CD4 and viral load counts, but almost all of these studies examine cohorts of individuals on ARVs and they do not compare outcomes for similarly defined people not taking ARVs (e.g., Hogg *et al.,* 2001; Egger *et al.* 2002; Cascade Collaboration, 2003, Palella *et al.,* 2003).

The large number of non-experimental studies, the findings from clinical trials, plus the coincidental drop in mortality among AIDS patients in the months just after the introduction of Epivir and protease inhibitors in 1995 provides powerful evidence of the lifesaving benefit of these drugs. Despite this, no previous study has attempted to isolate how much of the drop in mortality is attributable to antiretroviral treatments, to determine precisely which drugs drove the decline, or to estimate the extent to which the effects of the treatments varied across individuals. The strongest statement to date on the first of these can be found in a 2003 report published in the *Lancet* by the CASCADE Collaboration, which

noted that "HAART itself is likely to be responsible for at least some, and probably most, of this improvement" in health.

III. Constructing the Analysis Files

A. The California Medicaid Claims and Eligibility Data

We utilize claims and eligibility data for a random sample of Medicaid recipients from the state of California to estimate the causal effect of HIV antiretroviral drugs. The Medical Care Statistics Section of the California Department of Health Services has constructed two sets of 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 ninth digits of their Social Security numbers (SSN), which are scrambled in our data into an individual-specific Medicaid identifier. Thus, even if a person has more than one spell of eligibility, the files will include all Medicaid claims and eligibility data for her during our study period. Our 24 percent sample of Medicaid recipients includes detailed information for 4.03 million people who were eligible for the program in at least one month between January of 1993 and December of 2003.

Our Medicaid eligibility files contains demographic information for program 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 some other program. Additionally, there are two variables that allow us to determine whether an individual is dually eligible for health insurance through Medicare in each month.[20] Finally, the eligibility file indicates whether the Medicaid recipient is enrolled in a Medicaid managed care plan in each month and if so, lists the plan number.

The claims data includes all fee-for-service payments made from January of 1993 until June of 2004, though because there is often a lag of a few months in processing the claims, we focus on the

[20] Many SSI recipients are also receiving OASDI benefits and thus are also eligible for Medicare.

eleven-year period ending in December of 2003. In a typical year, there are more than 45 million fee-for-service claims in our 24 percent sample of Medicaid recipients.

There are three types of claims in our data. Inpatient claims are for admissions to hospitals and long-term care facilities and these records include information about the patient's primary and secondary diagnosis, the dates of service, the amount paid by Medicaid, the procedures performed while in the hospital, and a provider identifier. Outpatient and other ambulatory claims have similarly-detailed data about payments to physicians, clinics, hospital outpatient facilities, laboratories, and other health care providers. Finally, prescription drug claims provide data on payments made to pharmacies and similar health care providers for drugs covered by Medicaid. Each pharmacy claim includes an eleven-digit National Drug Code (NDC), the number of units of the prescription, and the date that the prescription was filled. The NDC is unique for each drug and dosage amount, which allows us to estimate the drug treatment(s) that each patient is consuming at any point in time.[21] Every claim includes the patient's Medicaid identifier, which can then be matched to the eligibility files.

Finally, we reached an agreement with both the California Center for Health Statistics and the 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 for all residents of the state of California. Death records could only be matched to Medicaid recipients with valid SSNs, which accounts for roughly 92 percent of the full Medicaid sample.[22]

B. Defining the HIV/AIDS Sample

A number of previous researchers have used Medicaid claims data to construct samples of HIV/AIDS patients (Eichner and Kahn, 2001; Kahn *et al.,* 2002; Morin *et al.,* 2002). Typically, patients are identified by using diagnosis codes that indicate HIV/AIDS as the disease being treated or by

[21] One obvious concern is that a patient may fill the prescription but not take the drug. This would understate the effectiveness of ARVs on outcomes such as mortality and hospitalizations.
[22] This is not a data error but instead simply reflects the fact that approximately 8 percent of Medicaid recipients in the state of California do not have a SSN.

identifying patients that have a claim for one or more prescription drugs that are used only for treating this illness. Because the focus of this project is on the impact of antiretroviral drugs and we do not want to generate a choice-based sample, we do not use prescription drug claims to determine whether a Medicaid recipient in our sample has HIV/AIDS. Instead, we use the primary and secondary diagnosis codes on the inpatient and outpatient claims. 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.[23] Patients enter our sample on 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 eleven-year study period, and have consistent age and gender information across years in the eligibility files. We then drop individuals without a valid SSN because we do not have mortality information for them. After this change, the number of individuals in our sample declines by 5.5 percent to 14,745.

Our procedure 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.[24] Even with accurate ICD-9 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 analyses below, we restrict the sample to include patients with two or more non-prescription HIV/AIDS claims, which reduces the number of individuals in our sample by 12.3 percent to 12,932. This should reduce the fraction of these false positives but will potentially exclude some true HIV/AIDS patients.[25]

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[23] 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 (*Morbidity and Mortality Weekly Reporter,*September 30, 1994, vol. 43, no. RR-12) 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.

[24] 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.

[25] 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. The CDC notes that ICD-9 codes for asymptomatic HIV and inconclusive HIV tests were misused because of lack of clear instructions and guidance, so this may be a problem in the earliest years

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 infected person may have no claims with an HIV/AIDS diagnosis because he/she is healthy and thus has limited contact with the health care system. Second, a patient may choose not to use medical care despite their illness. These two types of errors should not pose a problem for our analysis. Healthy patients and patients not interested in receiving treatment are unlikely to be prescribed antiretroviral drugs so they should not necessarily be included in our sample. Third, 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 antiretroviral drug but with no inpatient or outpatient HIV/AIDS claims during our eleven-year study period. 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.[26]

We can use external data to gauge the potential importance of false negatives for our sample. Our 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.[27] Of these, a total of 7,459 deaths have SSNs that would have placed them in our 24 percent Medicaid sample if they were enrolled in Medicaid at some point during our study period. A match of the eligibility files to this death data indicate that 4,371 of these 7,459 (58.6 percent) individuals who died with a primary cause of HIV/AIDS were on Medicaid at some point between 1993 and 2001. Of this group, our algorithm captures 3,617 of the individuals who died (almost 83 percent) using just the primary and secondary

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in our sample (*Morbidity and Mortality Weekly Reporter*, September 31, 1994, vol. 43, no. RR-12). This should be less of a problem after 1994 when the codes were redesigned. But given that 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.

[26] If the fraction taking an HIV antiretroviral 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 certain individuals included late in the sample while their counterparts from early in the period would not be.

[27] 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.

diagnoses on inpatient and outpatient claims. We could identify only an additional 106 patients by using claims for antiretroviral treatments as well to identify patients.[28]

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 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 main analyses below.

Although our claims data contain a rich set of information, it does have some important limitations. First, our data is for just one state. California is however an important state to consider given that it has the second highest number of people living with AIDS.[29] Second, we lose patients who temporarily or permanently exit because they become ineligible for Medicaid. This does not appear to be a severe limitation since less than 2 percent of the sample exits the sample per quarter and this number has not changed substantially during our period of analysis (Appendix Figure 1). Third, we do not know when patients were first diagnosed with HIV or AIDS but instead only the date of their first Medicaid HIV/AIDS claim during our study period. Fourth, claims data do not contain important diagnostic information about patients such as CD4 cell counts or HIV viral loads.[30] This information is important because it indicates who is recommended to receive ARVs. As we demonstrate below, we can to some

[28] 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.
[29] Only New York has a larger number. See the CDC HIV/AIDS Surveillance Report, 2003, Table 12.
[30] 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, Diener-West, and Moore (2001), Sambamoorthi *et al.,* (2001)) but we do not have this capacity in this instance.

extent control for the severity of the patient's condition by using claims data about the patient's prior medical care use. Fifth, 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 total expenditures by the government on both inpatient and outpatient care for this group.[31] Finally, we have very little utilization data for patients who are enrolled in a Medicaid managed care plan and thus will exclude them from our analyses.

Even with these limitations, our data has a number of important benefits over the data sets used in all previous research. First, it is the largest sample of HIV/AIDS patients generated from one consistent source, which allows us to obtain more precise estimates than other studies on this same topic. Second, our period of analysis covers an important time including three full years before and nearly eight years after the introduction of Epivir and protease inhibitors. This period – which is substantially longer than any previous study of HIV/AIDS patients has considered - allows us to investigate the effect of the treatments 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 antiretroviral drugs will systematically differ from their counterparts who do not. And finally, we can estimate not just the average effect of antiretroviral treatments but also the extent to which this varies across individuals. Recent studies have explored heterogeneous treatment effects for education, job training, and welfare programs though we believe that our study provides one of the first such estimates for the second largest government program in the U.S.[32]

[31] Medicare did not cover prescription drug costs during our study period and thus we observe the full cost to the government of ARVs and other drug treatments for dual eligibles.

[32] Only Social Security (OASDI) is larger in terms of total spending. Medicaid accounted for $280 billion in federal and state government spending in 2003 (compared with Medicare at $250 billion). Nearly 50 million people were eligible for Medicaid for one or more months during the year and thus Medicaid is even larger than Social Security in terms of the number of recipients.

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 left-hand axis in Figure 1, we plot the number of Medicaid recipients in our sample who were alive at the beginning of half-year periods starting in January of 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 data summarized in this figure includes information for the 12,932 people who had two or more HIV/AIDS claims during our study period and have a valid SSN. Roughly one-fourth 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 right-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 well with the correlation coefficient between the two at a statistically significant 0.98. Since our Medicaid data is based on a 24 percent sample, our numbers suggest that roughly 52 percent of people living with AIDS in California are on Medicaid,[33] a number close to the national average. Similarly the number of individuals in our sample grows at an almost identical rate to the statewide average. From the second half of 1994 until the second half of 2001 the number of individuals in the state of California reportedly living with HIV/AIDS rose by 58.3 percent. The corresponding increase in our sample was an almost identical 58.2 percent. Given the possible limitations with using claims data, our algorithm for identifying Medicaid recipients with HIV/AIDS appears to work quite well.

[33] Consider the first half of 1994 when there are 3237 individuals in our sample. To estimate the number on Medicaid with HIV/AIDS one must multiply this by (1/.24) as this is just a 24% sample. Additionally we must multiply by 1.058 to account for the fact that we are excluding individuals with an invalid SSN. This yields 14,270, which is 52.0% of the statewide total of 27,454. The actual fraction may be even higher given that we are excluding individuals with just one HIV/AIDS claim or with prescription drug claims only during the study period. On the other hand, some of the individuals in our sample have not yet progressed to AIDS and thus our fraction will to some extent overstate the Medicaid fraction.

We should note that our sample includes not only patients with AIDS but also some who are just HIV-positive so it would be more appropriate to compare our numbers to the total HIV-positive population in the state. Unfortunately, in most years California only reported to the CDC the number of people living with AIDS, not the number with HIV. Thus in one respect it is plausible that the patients in our sample would be healthier than the typical AIDS patient in California. However, the individuals in our sample are not a random sample of California residents with HIV. Most of the individuals in our sample qualify for Medicaid through the means-tested Supplemental Security Income (SSI) program. Thus they must be in relatively poor health to meet SSI's medical eligibility criteria. It is therefore plausible that the patients in our sample will be sicker than the average AIDS patient in California.[34] As we document below, the death rates for our sample are substantially higher than for non-Medicaid AIDS patients in California. Therefore, comparing trends in the number of HIV/AIDS patients on Medicaid to overall trends of AIDS patients seems a reasonable compromise given the available data.

In Figure 2, we graph half-year mortality rates for the Medicaid recipients in our sample of 12,932 patients during the 1994-2001 period.[35] 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 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 deaths rates for all AIDS patients in California, indicating that our sample is substantially sicker than the typical AIDS patient. 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 69 percent drop in six-month mortality rates in our sample from the first half of 1995 through the second half of 1997. Over the corresponding period, mortality rates fell by 79 percent for all California AIDS patients.

[34] Consistent with this, Bhattacharya, Goldman and Sood (forthcoming) demonstrate that HIV-positive patients on Medicaid have lower CD4 cell counts than both the uninsured and patients with private insurance.
[35] 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.

In Table 2, we report descriptive information about our sample at four points in time: 1994, 1997, 2000 and 2003. In this sample we still restrict attention to individuals with two or more claims during our study period and with a valid SSN. 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[36] 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 that is to some extent generated by the reduced mortality is the almost 7 year increase in average age of patients since 1994.[37] 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 thus the fraction under the age of 40 fell by more than half. The fraction Black increased from 21 percent to 25 percent and the fraction female increased by more than 7 percentage points from 15 to 22 percent.

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. Annual inpatient spending falls by an even larger percentage from $7125 to $3510.[38] In contrast, annual outpatient spending increases slightly while spending on prescription drugs triples, driven

[36] The lack of data for patients in managed care could be problematic if it leads to changes in the composition of our sample over time. The fraction of all Medicaid recipients in a managed care plan does increase substantially during our study period, though as Duggan (2004) notes these changes differentially affected AFDC/TANF recipients who account for a small share of our sample. SSI recipients, who account for nearly 70% of the patients in our sample, were not required to enroll in managed care in any counties except those moving to a county-organized health system and it is for this reason that we drop COHS counties. The fact that the number of individuals in our sample tracks the number statewide with AIDS quite closely (Figure 1) suggests that this issue is not too problematic.

[37] Some of this is likely also caused by changes in the age distribution in the U.S., with baby boomers aging into their forties and fifties during this nine-year period.

[38] All dollar values reported here and elsewhere in the paper are adjusted to 2003 dollars using the CPI.

primarily by the increased use of antiretroviral drugs and their high cost. Although annual spending on prescription drugs increased by $8000 over the period, total spending increased by just $4,800. The fraction of HIV/AIDS patients dually eligible for Medicare increases from 28 to 45 percent. This change is likely responsible for some of the decline in Medicaid spending on inpatient care.

IV. Time Series Evidence of the Effect of HIV Antiretroviral Treatments

The sharp decline in mortality of HIV/AIDS patients starting in 1996 that is graphed in Figure 2 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 and other drug treatments in our California Medicaid sample over the 1993-2003 period. For this section of the analysis, we 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 SSN, 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 sample inclusion criteria allow us to more accurately measure changes in both drug utilization and mortality during our eleven-year study period.

At the individual level, one can model the effect of drug treatment Z on outcome Y for individual j in period t as follows:

$$Y_{jt} = \alpha + \beta X_{jt} + \gamma Z_{jt} + \varepsilon_{jt}$$

with the X vector including j's demographic characteristics, observable measures of her health in the previous period, and other factors that could influence the outcome of interest Y. In this equation, the parameter of interest is γ, which represents the causal effect of the treatment Z on outcome Y. This effect could of course vary across individuals or within a person over time and thus one could index it by both j and t. Reliable estimation of this at the individual level is complicated by the fact that patients who take the drug may differ substantially from their observably similar counterparts who do not. For example, as

noted above, treatment guidelines encourage people to initiate treatment once their health deteriorates to a certain point. Thus a simple cross-sectional estimate of γ would suffer from possible omitted variable bias – with unobservably sicker individuals selecting into the treatment. The direction of this bias for the average effect of the drug on an outcome such as mortality is not obvious, as high γ individuals would be more likely to take the drugs but they might also be in worse health.

In an effort to surmount this obstacle to identification, we begin by estimating models at the aggregate level that exploit the sharp changes in the use of HIV antiretroviral drugs during our study period. Our unit of observation is the person-quarter and the first observation for a patient is the first quarter that we have 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 an average for the quarter. This time series data set has 32 quarterly observations from the fourth quarter of 1993 though the third quarter of 2001[39] and the key outcome variable that we focus on is the fraction of people in the sample and alive at the end of the current quarter who die in the next quarter. The key covariate is the fraction of people taking particular antiretroviral treatments.

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 antiretroviral treatments 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 antiretroviral drug and the majority of these claims were for Retrovir (more commonly

[39] We stop in 2001 because we do not have more recent mortality data and we begin in the fourth quarter of 1993 to give at least one year for individuals to have accumulated an HIV/AIDS claim.

known as AZT).[40] By the second quarter of 1997, the fraction of individuals in our sample taking one or more of these drugs had reached almost 60 percent.[41]

The sharp rise in HIV/AIDS drug therapies was mainly in the use of Epivir and in protease inhibitors. In Figure 4, we graph the fraction of patients that use any protease inhibitor, Epivir, either of these two treatments, or any other HIV antiretroviral drug.[42] 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 one or both.[43] Notice also that the entrance of Epivir 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, with much of the subsequent decline resulting from the failure of certain patients to respond to treatment and switching to other antiretroviral drugs as a result.

As we mentioned above, the new antiretroviral treatments were very expensive. From the first quarter of 1994 until the third quarter of 1995, spending on HIV antiretroviral drugs remained roughly constant, and stood at an average of $158 per quarter. But by the third quarter of 1997, average spending on ARVs in our sample increased to $1311 per quarter, representing a 730 percent increase in expenditures from just two years earlier. Expenditure growth slowed down after that point but expenditures still rose by 45 percent from the end of 1997 to the end of 2003 when per person-quarter spending reached $1900.

The potential explanatory power of Epivir and protease inhibitors for the rapid decline in mortality among AIDS patients is depicted in Figure 5. On the left vertical axis, we report the fraction of

[40] See Appendix Tables 1 and 2.
[41] 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.
[42] 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.
[43] Virtually all of the patients taking Epivir or a protease inhibitor in a quarter during our study period were taking two or more drugs, with 87% taking three or more during the quarter and 2.6% taking only one. These averages account for the fact that combivir combines two different drugs (epivir and retrovir) while trizivir combines three (ziagen, retrovir, and epivir).

patients that are using either Epivir or protease inhibitors and on the right 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 first quarter of 1996, quarterly mortality rates had been falling, with all of the drop occurring from the fourth quarter of 1994 to the first quarter of 1995. Taking a simple average of quarterly mortality rates in 1994 and comparing them with the corresponding average for 1995, mortality fell by 19 percent. This suggests that there might have been some decline in AIDS mortality rates from late 1995 to late 1997 even if Epivir and protease inhibitors had not been introduced. Second, as Epivir and 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 Epivir and protease inhibitor use stabilized, so did mortality rates. Between mid 1997 and the end of our sample, quarterly Epivir / protease inhibitor use was steady at 53 to 55 percent. Over this same period, quarterly mortality rates were originally 1.8 percent, fell as low as 1.4 percent, and ended up at 1.6 percent.

The close correspondence between the two series in Figure 6 suggests that a large fraction of the decline in AIDS mortality in the mid 1990s was caused by the rapid increase in the utilization of Epivir and protease inhibitors. In the first eight columns of Table 3, we summarize the results from first-difference specifications in which the outcome variable of interest is the change in the quarterly mortality rate in our sample. The mortality rate in quarter t is defined to be equal to the fraction of individuals alive and in the sample at the end of quarter t-1 who die during quarter t. We explore the relationship of this variable with changes in the fraction of the sample with one or more prescriptions for HIV antiretroviral drugs in period t-1.[44] Given that we are estimating a series of first-difference specifications, the constant term will control for trends in mortality during our study period.

In column (1), we obtain a large and statistically precise estimate for the coefficient on the change in the fraction taking an antiretroviral drug. The magnitude of the coefficient suggests that rising antiretroviral use can explain a large drop in quarterly mortality rates over this period. The OLS estimate

[44] These time series models are similar in spirit to those in Lichtenberg (2003) who regressed the log of nationwide AIDS deaths on the number of drugs approved to treat HIV/AIDS by the FDA. One advantage of our analysis is that we can allow for heterogeneity across drugs both in utilization and in the effect on mortality.

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 morality over this period. In column (2) when we replace the coefficient with the change in the fraction of people taking an NRTI we get essentially the same results.[45]

One limitation of the first two specifications is that they essentially attribute all of the mortality improvement since 1995 to individuals who started taking ARVs for the first time after late 1995. However, if those switching from existing, less effective drugs to new ARVs also experienced mortality rates declines, then the point estimate of -0.15 will provide a misleading estimate for the average effect of new drugs. In columns (3) and (5), we replace the fraction using any HIV drug with the fraction using a Protease Inhibitor and Epivir, respectively. The coefficients on these two variables are -0.105 and -0.092, respectively, and both estimates are statistically significant at the one percent level. These estimates are much smaller in magnitude than the ones in the first two specifications, 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 over this period. The coefficient estimate in column (4) for the change in the use of NNRTIs suggests that these drugs had virtually no effect on mortality rates.

Because the time-series growth in the use of Epivir and of protease inhibitors is so strongly correlated, we cannot reliably disentangle the effect of one from the other with aggregate data. 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 Epivir is statistically significant. In column (7), we group these two treatments and include the fraction of the sample taking either Epivir or a

[45] Estimating the model in levels produces similar results but with much greater precision. For example in most cases the R-squared is greater than 0.97 and the t-statistics are typically greater than 10.0.

protease inhibitor and obtain a statistically significant point estimate of -.079. Coupled with the increase to 56.0 percent in this variable in less than two years, this suggests that the diffusion of the 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 Epivir 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.

In the ninth column of Table 3, we investigate the relationship between the change in PI / Epivir use and the change in average Medicaid spending. An examination of the trend in average Medicaid spending in Figure 6 shows that, during the period when Epivir and protease inhibitors were diffusing rapidly, average spending was actually declining. For example, from the third quarter of 1995 to the third quarter of 1997, average spending in the sample fell by almost 7 percent from $5401 to $5030. Once PI / Epivir use reached its equilibrium level, Medicaid spending began to increase, rising by 18 percent from the third quarter of 1997 to the third quarter of 1999. Given these trends, it is not surprising that the estimate for the effect of PI-Epivir use on costs is negative. The (insignificant) point estimate of –262 in

column (9) suggests that the new treatments had a much smaller effect on average quarterly spending than on quarterly mortality rates, as this implies less than a 5 percent reduction in spending.

In column (10) we explore the relationship between changes in PI / Epivir use and changes in the fraction of individuals with one or more days of inpatient care (either hospitals or nursing homes). As expected, our findings suggest that the new treatments reduced the use of inpatient care. The point estimate suggests that an average effect of approximately five percentage points (off of a mean of 24 percent), though it is not statistically significant.

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 in the U.S. during the past decade. There is little evidence to suggest that the fourteen 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.

V. Individual-Level Evidence of the Effect of HIV Antiretroviral Treatments

In this section, we exploit to a much greater extent the panel nature of our Medicaid claims data to examine the impact of Epivir and protease inhibitors on mortality and on health care utilization. The sample for this section's analysis is similar to the one used in the previous section, though we restrict attention to patients whose first HIV/AIDS claim appears during the five year period from 1993 to 1997. We focus on this period in order to disentangle the effect of the rapid diffusion of Epivir and protease inhibitors from other changes in health care treatments occurring in the latter part of our study period. We also delete patients whose first HIV/AIDS claim occurs after the introduction of Epivir and protease inhibitors since we want baseline measures of health for individuals when the treatments are first released. We also restrict attention to patients ages 15 and above since children were not cleared for use of

antiretroviral drugs until more recently.[46] We delete patients who leave Medicaid for one or more quarters, patients who die during their first quarter of eligibility, or patients who exit our sample in the first quarter of 1994 or earlier. We aggregate data to the person-quarter level giving us a sample of 3243 HIV/AIDS patients ages 15 and above with valid mortality data and continuous enrollment in Medicaid until the end of 1997 or until they exit the Medicaid program. We consider the sixteen quarters from early 1994 until late 1997 and this generates a data set with 28,287 person/quarter observations.

Although our data is rich in detail on health care utilization, total Medicaid spending, and mortality, the evaluation problem is complicated by the nonrandom selection of patients into antiretroviral treatments. As we outlined in Section II, current protocol suggests that patients abstain from antiretroviral drugs until CD4 counts fall below a specified level or until patients obtain an AIDS-defining illness. The results from previous studies indicate that low CD4 counts are an excellent predictor of progression to AIDS, higher mortality and higher medical expenses.[47] This suggests that we should find that those patients in the poorest health, with the highest medical care use, and with the highest baseline mortality probabilities when Epivir and protease inhibitors were released were the ones most likely to use these new treatments.

Unfortunately, our Medicaid claims data does not have clinical markers such as CD4 counts and viral loads to use as control variables. As a consequence, we must construct a surrogate variable that identifies the clinical progression of the disease. To do this, we use our claims data to devise a simple proxy for health status that predicts mortality quite well in the pre-1996 period and the use of the new

[46] As before 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 in managed care during our period of analysis and with no months in one of eight counties with a county organized health system. Since we need a linkage to death records to measure mortality, we delete those without a valid SSN.

[47] 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/mm^3. 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/mm^3, 200-499/mm^3, 50-199/mm^2 and <50/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.

antiretroviral therapies once they are introduced. Specifically, we count all inpatient and outpatient claims with a primary or secondary diagnosis of HIV/AIDS for a person in the current quarter and in the previous three quarters.[48] 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 90^{th} -95^{th} percentiles and the 96^{th} to 100^{th} percentiles, respectively. Using time varying ranks in this fashion controls for the changing number of claims over time and ranks each patient in relation to the other HIV/AIDS patients alive in that quarter.

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 by the third quarter of 1995 and were still alive in the second quarter of 1994. We include the last seven quarters in our sample before the introduction of Epivir and protease inhibitors and there are 14,163 person/quarter observations in total. The first column of numbers in Table 4 reports the average number of claims during the past four quarters for patients in each category. Those in the lowest decile group have little health care use with an average of just 0.1 HIV/AIDS claims during the previous year.[49] Moving from one decile group to the next, the percentage change in average claims is large but even in the fourth decile is just 5.8. The average number of claims does 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.[50] 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 these specifications and all subsequent ones, we include a full set of year-quarter interactions and estimate

[48] We experimented with alternative measures by, for example, using a different number of quarters and weighting inpatient more than outpatient claims but obtained qualitatively similar results in our analyses below.
[49] 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.
[50] Individuals are included in this regression only if they are alive at the end of the current quarter.

standard errors that allow for an arbitrary correlation in the error terms in the multiple observations for each person.

The results for specifications (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.[51] Looking at the results without covariates, for patients in the top 60 percent of the severity index, the movement to the next highest group increases the quarterly death rate by at least one percentage 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 the sample average while those in the bottom group have a mortality rate less than one-fourth the sample average. Comparing columns (2) and (1), we see that adding covariates does not substantially change the coefficient estimates for the decile indicator variables, 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 has some inpatient care (either in a hospital or in a nursing home) during the next quarter and zero otherwise. Although there are a number of possible measures of morbidity that can be constructed from our data, we focus on inpatient care since it is 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, and then doubles again moving to the top five percent in our severity index. As

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

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 antiretroviral drug 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 in a meaningful way.

The results from our time-series analyses and the sharp drop in mortality from late 1995 to 1997 suggest that the key explanatory variable is not the use of any antiretroviral treatments but the use of Epivir and protease inhibitors specifically. In Table 5, we examine whether our proxy for health status can accurately predict the use of these new treatments after they received FDA approval.[52] In the first two columns, the outcome is an indicator variable that equals one if the patient has any claims for Epivir or protease inhibitors in the quarter and zero otherwise. As in the previous regressions, the key covariates are dummy variables that identify the decile rank of the four-quarter average in Medicaid claims with a primary or secondary diagnosis of HIV/AIDS. Because Epivir and protease inhibitors may influence a person's health and thus their number of inpatient and outpatient claims, we use each person's decile rank in the third quarter of 1995 as their rank in all subsequent quarters.[53]

In the table, we consider two separate time periods. First, we examine usage in the 'transition' period when these drugs first became available, which are the five quarters starting with the fourth quarter of 1995. In this time period, there are slightly more than 2000 people alive and enrolled in Medicaid for at least one quarter, generating 8,627 person-quarter observations. A second sample is for the four

[52] Here the decile is the one for the patient in the third quarter of 1995. The results look quite similar if we instead allow individuals to move from one decile to another after the release of Epivir and protease inhibitors.
[53] Our results are qualitatively similar if we instead allow a person's rank to change from one quarter to the next.

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 1,456 people and 5,497 person-quarters.[54] In all regressions, we include the same demographic control variables that we used in Table 4 and allow for an arbitrary correlation in errors for each patient.

In both the transition and steady state periods, the model fits well for a cross-section regression with an R^2 of approximately 0.2 in both cases. During both the transition period and in the steady state, the coefficients on the severity index dummy variables are monotonic, except for a slight drop in use from decile seven to decile eight. In the steady state specification, usage rates in the fourth decile are about 22 percentage points higher than in decile one, but by decile ten the difference increases to 50 percentage points. By 1997, usage of protease inhibitors or Epivir by those in the lowest decile was about 29 percent, suggesting that utilization was approximately 2.7 times higher for the sickest 10 percent of patients than for the healthiest 10 percent.[55] 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 approximately 2.5 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).[56]

This heterogeneity in treatment of new ARVs is further illustrated in Figure 9, which demonstrates that men in our sample were approximately 1.5 times more likely than women to take Epivir or protease inhibitors soon after they were released. Perhaps not surprisingly, men in our sample in 1995 had mortality rates that were 80 percent higher than those for women. For example during the second half of 1995, 13.3 percent of the men in our sample died while just 7.2 percent of women died in the same six-month period.

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[54] The number of individuals is declining because of our requirement that individuals have their first HIV/AIDS claim by the third quarter of 1995. Thus there are no new entrants to this sample after that point in time.

[55] By requiring individuals to have entered our sample by the third quarter of 1995, we actually understate the heterogeneity in treatment utilization. For example the ratio between PI / Epivir utilization in the top 20% versus the bottom 20% in this sample is 2.2 while in a sample that allows new entrants this ratio is closer to 4.0.

[56] The corresponding ratio was 2.0 in the third quarter of 1995. More importantly, the percentage point difference in the use of ARVs increased from 19 percent in the third quarter of 1995 to 47 percent by the first quarter of 1997.

Having established the power of our severity index 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 Epivir and protease inhibitors. Thus we must control for this selection in any model that attempts to measure product efficacy. Likewise, we expect that the benefits of treatment will be 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 across deciles. The treatment variable is simply an indicator variable that equals one if a person is taking Epivir or protease inhibitors in a quarter and zero otherwise. We interact this variable with each of the decile variables to explore the extent to which the effect of the treatment varied with severity. All outcomes (such as mortality and hospitalization) are measured in the next quarter and individuals are included in the regression only if they survive to the end of the current quarter. The sample for this analysis will be the same one used in the preceding specifications. In these models, we control for the personal characteristics listed in Tables 4 and 5 and continue to include a full set of quarter-year interactions. Again, we allow for arbitrary correlation in errors for each person.

We focus on two outcome variables of interest: 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 PI-Epivir variable and the decile rank dummies. The coefficient estimates on these interactions suggest that the effect of the drug treatments is statistically insignificant for the healthiest half of the sample but is increasing in severity for the less healthy patients. Taking Epivir or a protease inhibitor this quarter is estimated to reduce the probability of death next quarter by a statistically significant 2.5 percentage points for those in sixth decile, by 4.7 percentage points in the eighth decile, and by more than 12 percentage points for the sickest decile of patients. This heterogeneity in the effect of the treatments is shown in Figure 10, 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.

Further evidence of the differential benefit of Epivir and protease inhibitors is provided in Figure 11, which plots half-year mortality rates for men and women in our sample from 1995 through 2001. In the year before the release of Epivir and protease inhibitors, the average half-year mortality rate for men was 13.0 percent whereas for women it was much lower at 7.2 percent. But just two years later after the rapid diffusion of Epivir and protease inhibitors, these mortality rates were almost equal at 4.4 percent and 3.8 percent, respectively.[57]

It is worth emphasizing that our estimates in Table 6 are likely to represent a lower bound for the true impact of HIV antiretroviral 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[58] 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 benefit of the treatment was

[57] A difference-in-differences estimator here would not be appropriate given the likelihood that the distribution of treatment effects – even among those taking the drugs – likely differs substantially by gender.
[58] This is calculated by taking a weighted average of the estimates for the top two deciles.

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. Additionally, our findings suggest that four drugs released approximately nine years ago were responsible for virtually all of the decline in mortality rates during the past decade, suggesting that the twelve treatments approved since then have not been nearly as effective at improving patient health.

VI. Estimating the Effect of Antiretroviral Treatments on Long-Term Health Care Spending

In this section we investigate the impact of Epivir and protease inhibitors on long-term health care spending by the Medicaid program. There are three factors that impact this calculation. The first is the average effect on spending per quarter when a patient initiates treatment with an ARV. As described above, average spending on HIV antiretroviral drugs increased by 730 percent from late 1995 until late 1997 [59] but the results summarized in Section IV suggest that this additional spending was largely offset by a fall in spending on inpatient care.[60] The second factor is the growth rate of spending. If treatments influence the rate at which a person's health decays then this will also influence the growth rate of spending. Finally, the large reduction in mortality generated by Epivir and protease inhibitor use increased life expectancy, and hence the amount of time that individuals were eligible for Medicaid.[61]

There have been some attempts to estimate the cost per life year saved of new antiretroviral treatments. Freedberg *et al.,* (2001) develop a mathematical simulation model to analyze the cost-effectiveness of three-drug anti-retroviral regimens. The authors estimate that a three-drug regimen costs an average of $13,000 to $23,000 per quality adjusted life year, numbers comparable in cost-effectiveness

[59] Freedberg *et al.,* (2001) and Yazdanpanah (2004) put the annual per person costs of ARVs anywhere from $6,000 to $15,000 depending on the treatment regimen used.
[60] This finding is consistent with the results of previous research (Gebo *et al*., (1999) and Keiser *et al*., (2001)).
[61] As Meltzer (1997) outlines, there is some controversy about whether future medical costs should be considered in medical cost-effectiveness studies. Meltzer argues that for cost-effectiveness studies to be consistent with utility maximization, they must include all future lifetime costs, including non-medical expenses. At the other extreme, others argue that only future medical costs directly related to the illness should be included in these calculations. Given available data, we examine all future medical costs but do not include non-medical expenses.

to other medical interventions for non-AIDS related illnesses. Similar estimates of the cost per life year saved have been obtained for patients from Switzerland, England and Canada (Yazdanpanah, 2004) and for patients treated by the Veteran's Administration (Keiser *et al.,* 2001).

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 Epivir 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 Epivir and protease inhibitor treatments did not lead to large increases in annual Medicaid spending.

But the data reported 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 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.

The way that the three factors listed above can potentially impact the marginal lifetime costs of treatment by ARVs can be illustrated in the following exercise. Consider an HIV positive patient that has progressed in their illness to the point that physicians would recommend ARV therapy. We assume that up to this point in their treatment, the presence or absence of ARVs would not change costs, so we only consider the change in expenditures for patients after the point they become clinically eligible for ARV treatment, which we label as quarter 0. Suppose in the absence of ARVs, a patient will have medical expenditures of M_0 in period 0, and for simplicity, assume this amount grows at a rate of (p) per quarter. Patients are assumed to die at a rate of δ in each quarter and this rate is assumed to be constant over time. The expected lifetime costs for this patient in the absence of antiretroviral treatments are therefore,

$$\text{COSTS} = \sum_{\tau=0}^{\infty} M_0(1+p)^t\ (1-\delta)^t$$

If $p/(1+p)<\delta$, which is certainly the case in the mid 1990s when quarterly mortality rates were in the 7 to 9 percent range, then COSTS reduces to $M_0/(\delta+\delta p-p)$.

Further assume that when Epivir and protease inhibitors were introduced, baseline costs, the cost growth rate, and mortality rates changed to M^a_0, p^a and δ^a respectively. As a result of this change, costs would now be equal to $M^a_0/(\delta^a+\delta^a p^a - p^a)$. If this is lower than the initial value then the new treatments reduce lifetime costs, but given the substantial increase in life expectancy generated by Epivir and protease inhibitors, a more likely outcome is that lifetime Medicaid spending increased and we therefore must consider the cost-effectiveness of the drug in life years saved. The increase in life expectancy in quarters is simply $[1/\delta^a - 1/\delta]$ and therefore, the marginal change in costs is $[M^a_0/(\delta_a+\delta^a p^a-p) - M_0/(\delta+\delta p-p)]$. Dividing this number by $[1/\delta^a - 1/\delta]$ produces the cost per life year saved. Given our assumptions, this calculation requires just six parameters.

Looking at all patients in our sample from the previous section, we see that average spending per quarter from 1994 through 1999 (in real 2003 dollars) are $5,356 (1994); $5,377 (1995); $5,191 (1996); $5,056 (1997); $5,237 (1998); $5,882 (1999). Notice that there is a clear break in the spending pattern as real quarterly expenses drop by $321 between 1995 and 1997 as new ARV use is diffusing. By the end of 1997, 54.8 percent of all patients are using Epivir or PIs. If we attribute all of the decline in spending to the diffusion of these new treatments, then the $321 drop is spread over 54.8 percent of patients. This implies that on a quarterly basis, Epivir / PI use reduces spending by $586 per quarter. Patients taking either Epivir or PIs in 1997 are spending an average of $6323 per quarter so we will use this estimate for M^a_0, and use $6323+$586=$6,909 as M_0.

To obtain an estimate for δ, we use data for the seven quarters just prior to the release of new ARVs (1994:1 through 1995:3), and we restrict our attention to a group likely to take ARVs if they were available. From the previous section, we see that 80 percent of patients in the top half of the severity index will take Epivir or PIs before the end of 1997 so we examine that group. Running a regression of

average spending per quarter in individual fixed-effects plus a quarterly time trend (and allowing the standard errors to be correlated across observations for a person), we find that costs are increasing at a statistically significant $231 per quarter which is 3 percent of the 1994:1 average of $7602 for this population. Therefore, we set p=0.03. Corresponding numbers for the 1997:1 through 1998:2 period show that spending increases by a statistically insignificant $71 per quarter which is 1.1 percent of the sample mean. Given the imprecision of this estimate, we assume p^a=0. The sharp drop in the growth rate of spending is to be expected since ARVs reduce the progression of the disease. Finally, quarterly mortality rates of patients on Epivir/PI in 1997 were 2 percent (δ^a) and estimates from Table 3 indicate that taking Epivir/PI reduces mortality by an average of 7.9 percentage points yielding δ=.099.

Using these six parameters, we calculate that once a person becomes medically eligible for antiretroviral treatments, taking these drugs will increase life expectancy by almost 10 years (40 quarters), increase the lifetime costs of treatment by $220,000. This implies that the cost per life year saved is approximately $22,000. So, although the use of Epivir and protease inhibitors increased the lifetime costs of treating HIV/AIDS patients on Medicaid, the cost per life year saved is actually somewhat modest. Tengs et al., (1995) catalog 587 cost per life saved estimates for different life saving interventions and find a median value of $48,000 for all interventions and $19,000 for medical ones.

We should note that we make a number of strong assumptions, including a constant mortality rate and a constant growth rate in spending. The marginal cost per life year saved calculation is not particularly sensitive to the assumed values of M_0 and M^a_0. If we assume there is no change in spending associated with ARVs then the cost per life year saved increases to roughly $25,000 and if ARVs increase spending by $600 per quarter, the cost per life year saved only increases to $27,000. Likewise, the results are not very sensitive to the assumed drop in mortality produced by ARVs. Notice that the numerator and denominator in the marginal cost calculation both contain $1/\delta^a$ so the rise in lifetime costs associated with living longer is functionally proportional to additional life expectancy costs. The key variables in the calculation are the difference in the quarterly growth in spending with and without ARVs. If costs are

increasing at 1 percent per quarter as a result of the new treatments, then the cost per life year more than doubles to $53,000.

VII. Conclusion

In a four-month period starting in November of 1995, four new drug treatments 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 many previous studies have shown the lifesaving benefits of the new treatments, no study has isolated the fraction of this decline attributable to the new treatments nor which drugs drove the decline. 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. The twelve drugs introduced in the last nine years have done little to reduce the mortality rate still further.

Our research has uncovered a number of substantive results as well as 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-1995 mortality as well as subsequent use of antiretroviral treatments. This severity index also allowed us to estimate the heterogeneity in the effect of the treatments by health status. The greatest reductions in absolute mortality were found for the most severe cases, though the percentage reduction in mortality was similar across groups.

While our study examines the efficacy of one particular medical intervention, our work contributes to two more general strands of literature. First, our study is part of a growing body of research that attempts to evaluate the effect of health care treatments on both expenditures and on health

outcomes in non-experimental settings.[62] Although random assignment clinical trials are still considered the gold standard for determining causal relationships, not all questions about new treatments can be analyzed through experiments because of cost considerations or other factors (Raffi et al., 2001). The recent Vioxx controversy highlights the possible benefits of using observational data to examine the post-release effect of new health care treatments. Thus, researchers must increasingly rely on observational data and non-experimental statistical models to evaluate the benefits of new health care treatments. Given the current strains on government budgets and the fact that Medicaid and Medicare account for almost $600 billion in state and federal expenditures, more work on this issue is clearly warranted.

Our paper also provides an example of how administrative data for a government healthcare program can be used as a motivation for estimating heterogeneity in treatment effects. In recent years, a number of authors including Heckman, Smith and Clements (1997), Abadie, Angrist, Imbems (2002), and Bitler, Gelbach, and Hoynes (2003) have developed econometric techniques to estimate heterogeneity in the effect of education, job training, and welfare programs. While few would expect any treatment to have uniform effects across all subjects, in many situations, there is no definitive prediction about how the treatment effect should vary across these people.[63] In the case we consider, the receipt of treatment and the benefits of treatment should both vary monotonically with patient severity, which is exactly what we find.

[62] See, for example, McClellan, McNeil, and Newhouse (1994), Cutler (2003), and Duggan (2005).
[63] An exception is the work of Bitler, Gelbach and Hoynes (2003) who use quantile treatment effects to evaluate the impact of a random assignment welfare reform experiment in Connecticut.

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Figure 1: HIV/AIDS Cases 24% Medicaid Sample and Living with AIDS in CA

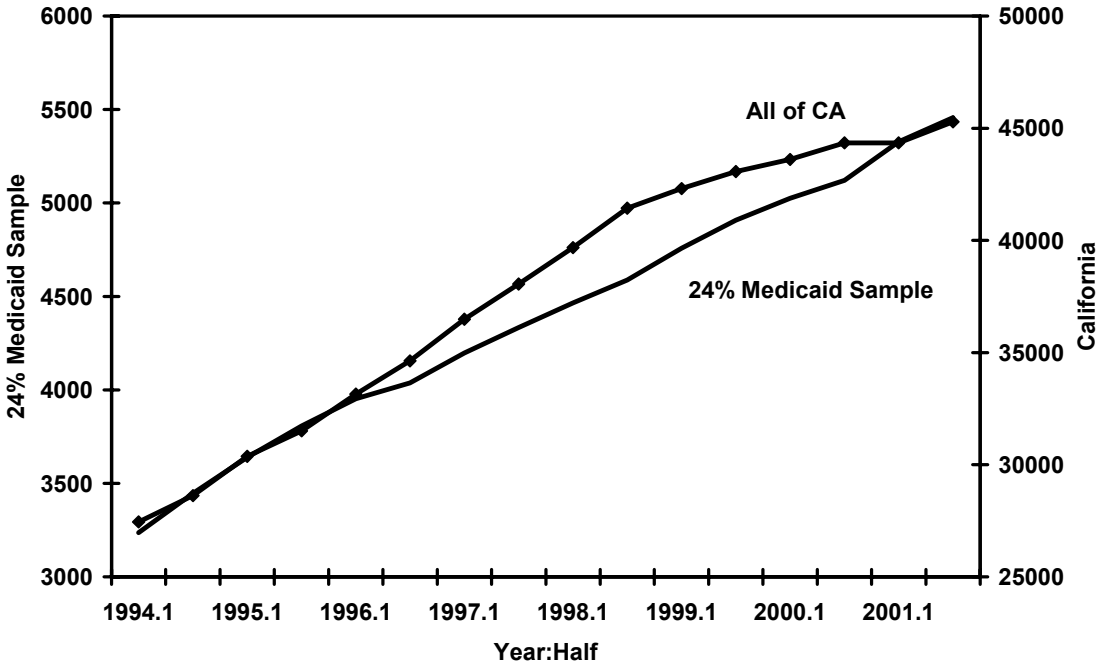


Figure 2: Half-Year Mortality Rate for AIDS Patients

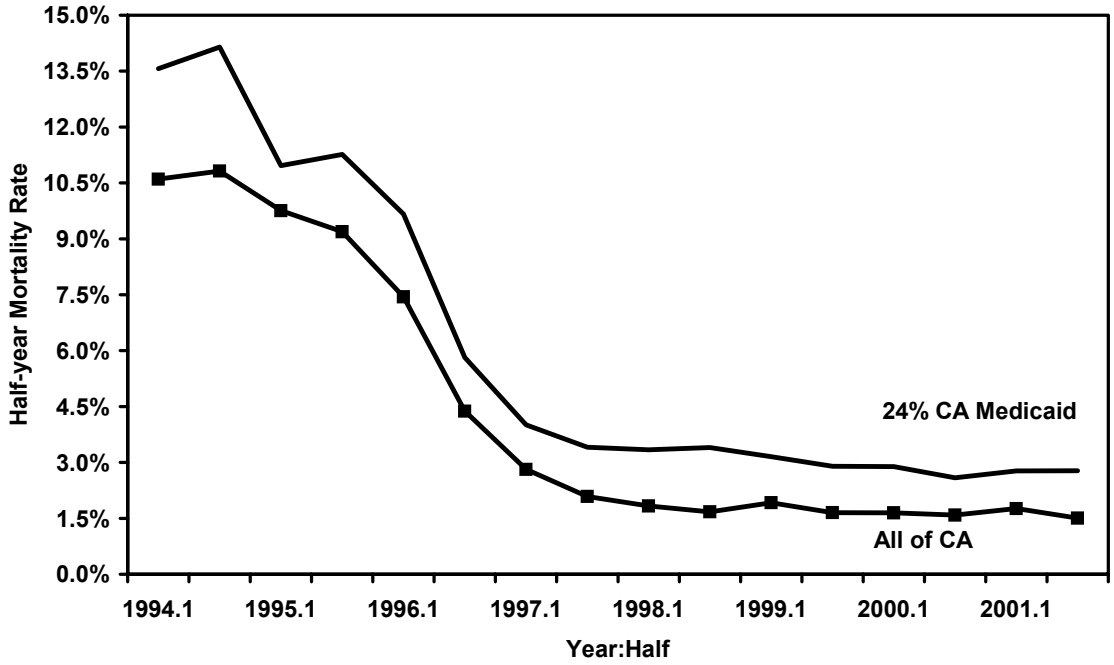


Figure 3: Fraction of CA Medicaid Sample Taking 1+ HIV Drugs in Each Quarter

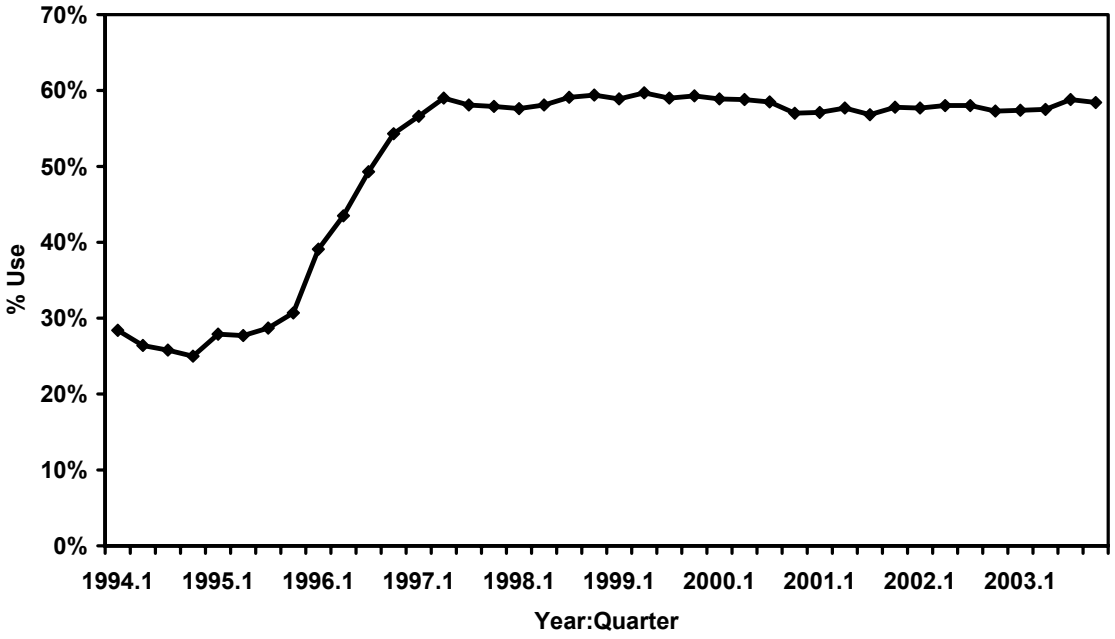


Figure 4: Diffusion of Epivir and Protease Inhibitors: 1994Q1 - 2003Q4

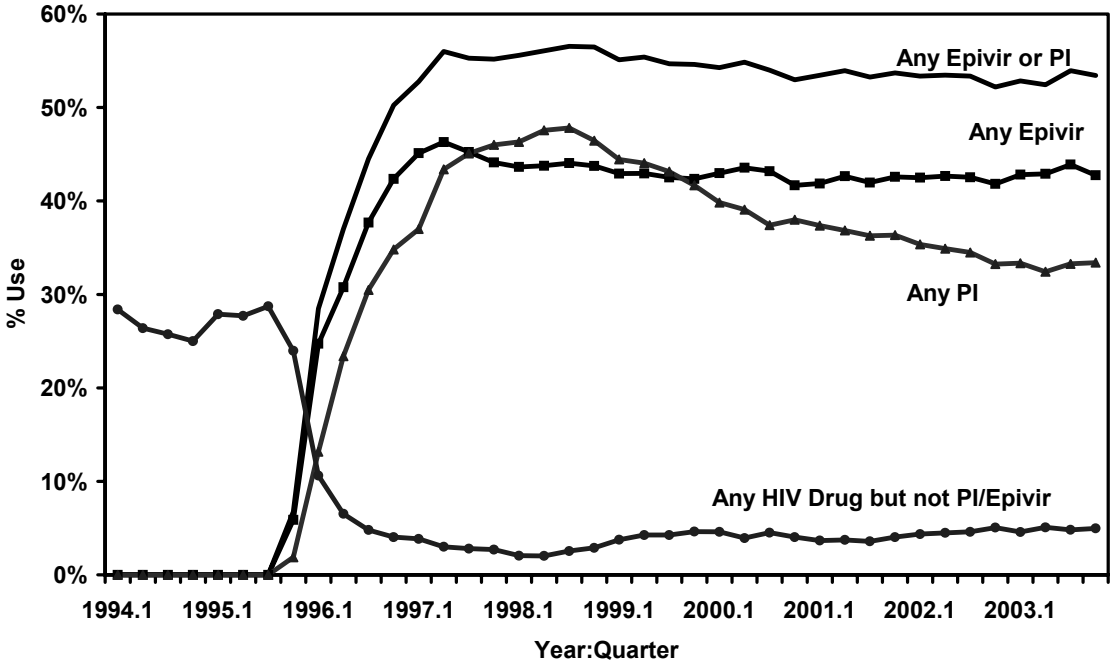


Figure 5: Quarterly Mortality Rate and Use of PI/Epivir

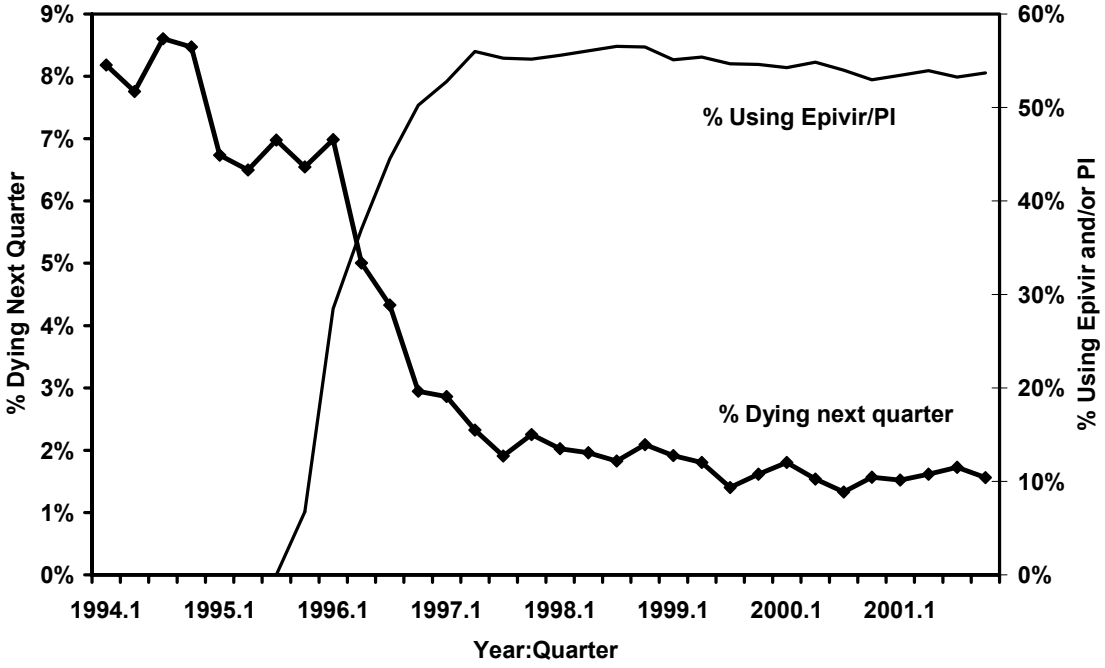


Figure 6: Average Quarterly Spending in the Medicaid HIV/AIDS Sample

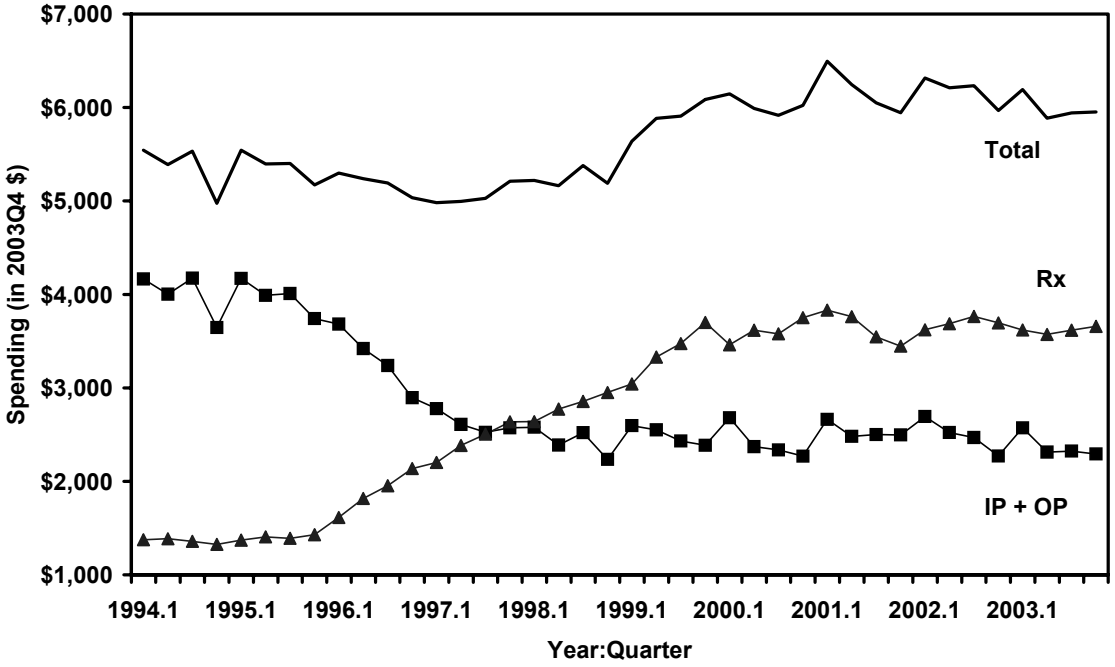


Figure 7: Use of PI and Epivir by Health Status

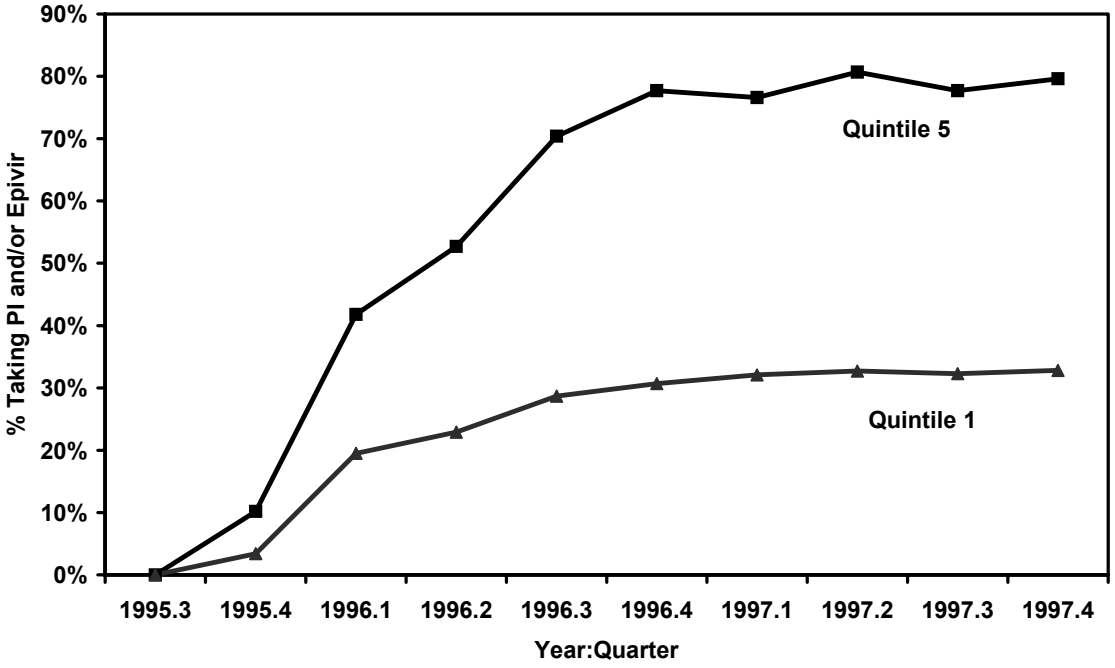


Figure 8: Use of Any HIV Drug by Health Status

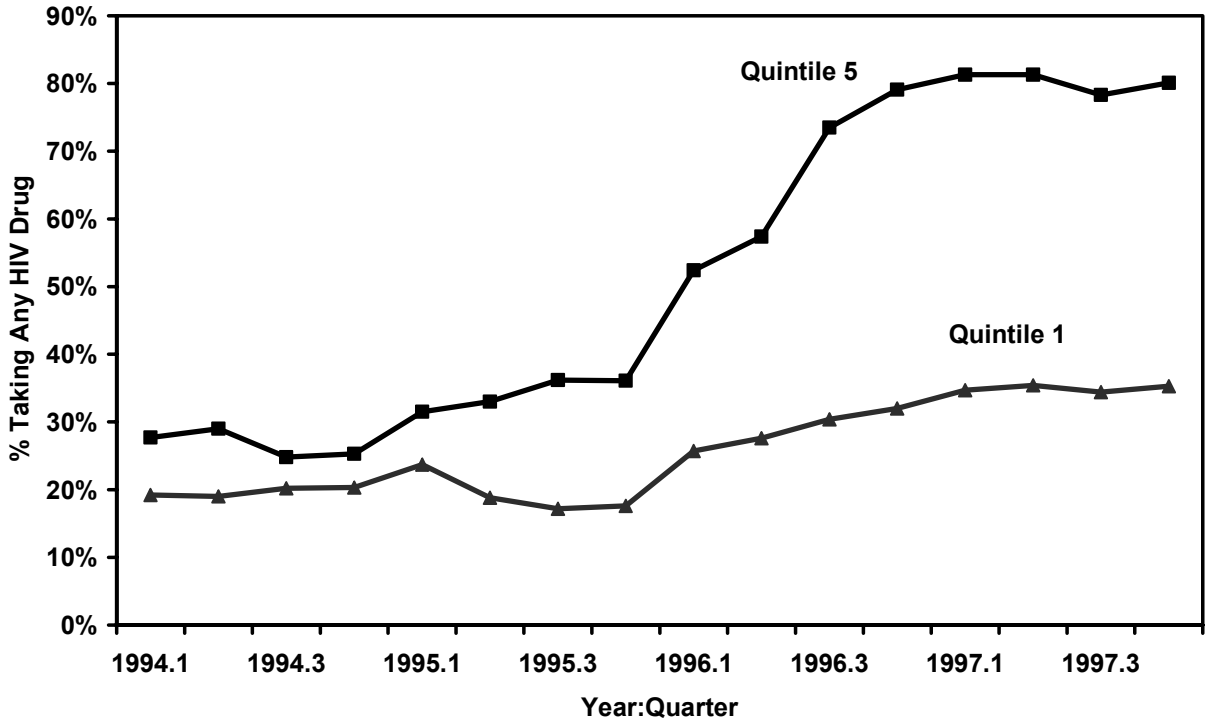


Figure 9: Use of PI and/or Epivir by Gender in the Medicaid HIV/AIDS Sample

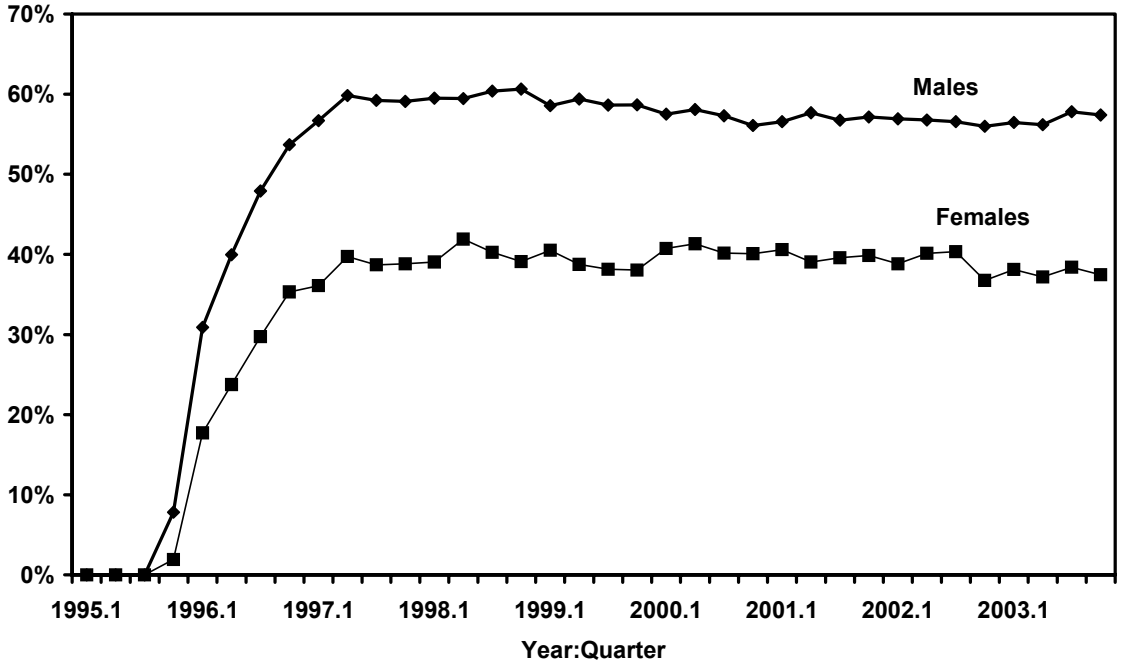


Figure 10: Quarterly Mortality Rate by Health Status

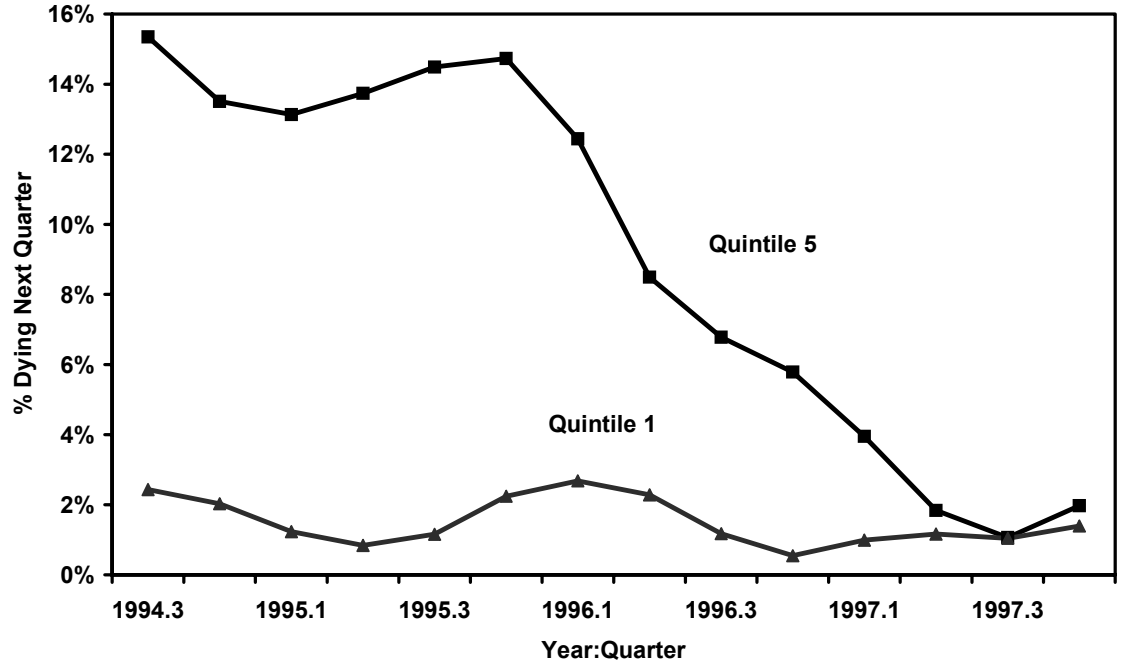


Figure 11: Half-Year Mortality Rates in the Medicaid HIV/AIDS Sample

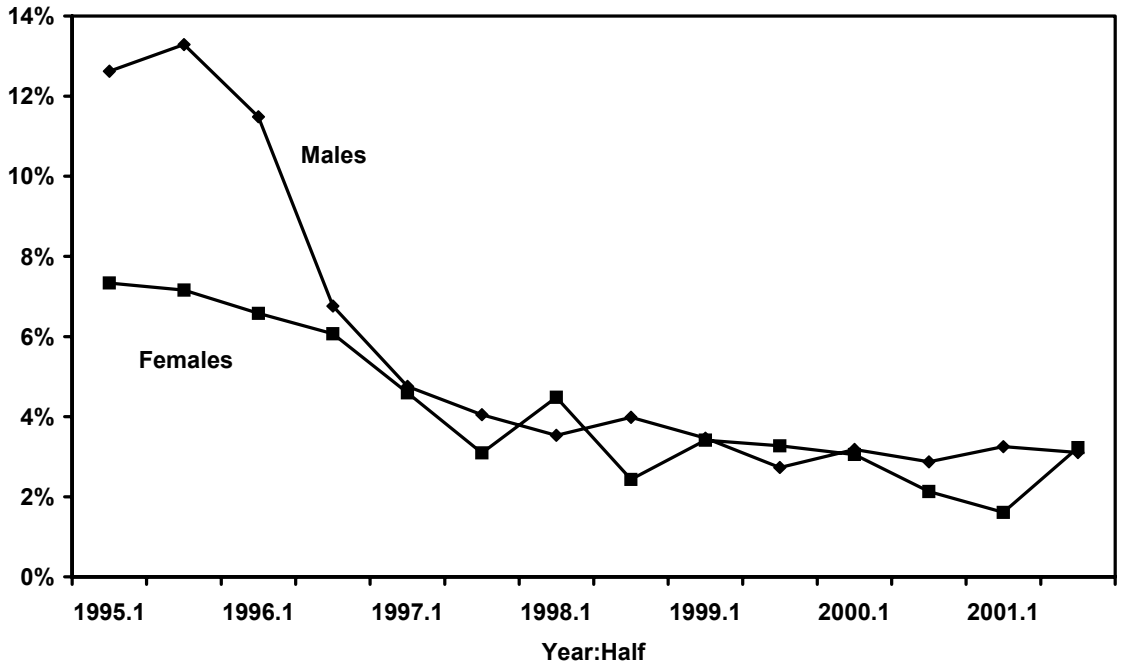


Table 1: Prescription Drugs Used in Treatment of HIV/AIDS by 12/31/2003

Class	Brand Name	FDA Appr. Date	First script in claims data	Ingredients
Nucleoside Reverse Transcriptase Inhibitors (NRTI)				
	Retrovir	3/19/1987	1/2/1993	Zidovudine
	Videx	10/9/1991	1/4/1993	Didanosine
	Hivid	6/19/1992	1/4/1993	Zalcitabine
	Zerit	6/24/1994	8/6/1994	Stavudine
	Epivir	11/17/1995	11/27/1995	Lamivudine
	Combivir*	9/27/1997	10/17/1997	Lamivudine, zidovudine
	Ziagen	12/17/1998	12/18/1998	Abacavir
	Trizivir**	11/14/2000	12/1/2000	abacavir, zidovudine, lamivudine
	Viread	10/26/2001	11/1/2001	tenofovir disoproxil fumarate
	Emtriva	7/2/2003	7/16/2003	emtricitabine
Protease Inhibitors (PI)				
	Invirase	12/6/1995	12/11/1995	saquinavir mesylate
	Norvir	3/1/1996	3/7/1996	ritonavir
	Crixivan	3/13/1996	3/26/1996	indinavir
	Viracept	3/14/1997	3/19/1997	nelfinavir mesylate
	Fortovase	11/7/1997	11/18/1997	saquinavir
	Agenerase	4/15/1999	4/26/1999	amprenavir
	Kaletra	9/15/2000	9/20/2000	lopinavir and ritonavir
	Lexiva	10/20/2003	11/11/2003	fosamprenavir calcium
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)				
	Viramune	6/21/1996	8/10/1996	nevirapine
	Rescriptor	4/4/1997	4/25/1997	delavirdine
	Sustiva	9/17/1998	9/23/1998	efavirenz
Fusion Inhibitors (HI)				
	Fuzeon	3/13/2003	4/8/2003	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 Antiretroviral Drugs

	Δ Quarterly Mortality Rate								Δ Costs	Δ % Hosp.
Independent Variable	(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			-0.0511				
			(.0304)			(.0331)				
Δ % Any NNRTI				-0.0026						
				(.0485)						
Δ % Any Epivir					-0.0919	-0.0563				
					(.0172)	(.0278)				
Δ % Any PI or Epivir (t)							-0.0789	-0.0750	-262	-0.0492
							(.0148)	(.0178)	(641)	(.0374)
Δ % Any PI or Epivir (t-1)								-0.0066		
								(.0180)		
Constant	-0.0008	-0.0008	-0.0009	-0.0021	-0.0009	-0.0008	-0.0008	-0.0007	51	-0.0028
	(.0011)	(.0011)	(.0009)	(.0014)	(.0009)	(.0010)	(.0009)	(.0010)	(42)	(.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

	Avg. HIV Claims	Die Next Quarter?		Hosp Next Quarter?		HIV Drug this Quarter?	
	4 Quarters	(1)	(2)	(3)	(4)	(5)	(6)
Constant	-	0.014	0.003	0.154	0.151	0.172	0.172
		(.006)	(.008)	(.017)	(.023)	(.020)	(.026)
Decile 2	1.4	0.003	0.004	-0.013	-0.007	0.066	0.057
		(.005)	(.005)	(.017)	(.017)	(.022)	(.022)
Decile 3	3.5	0.010	0.010	0.007	0.014	0.087	0.083
		(.005)	(.006)	(.017)	(.017)	(.023)	(.022)
Decile 4	5.8	0.018	0.018	0.016	0.025	0.117	0.107
		(.006)	(.006)	(.018)	(.018)	(.024)	(.023)
Decile 5	9.5	0.032	0.032	0.060	0.069	0.179	0.173
		(.007)	(.007)	(.019)	(.019)	(.024)	(.024)
Decile 6	14.4	0.052	0.052	0.046	0.053	0.165	0.157
		(.007)	(.008)	(.019)	(.019)	(.024)	(.024)
Decile 7	22.6	0.054	0.054	0.085	0.092	0.180	0.173
		(.008)	(.008)	(.019)	(.019)	(.025)	(.025)
Decile 8	33.1	0.067	0.067	0.118	0.126	0.188	0.189
		(.008)	(.009)	(.020)	(.020)	(.025)	(.025)
Decile 9	52.9	0.102	0.102	0.131	0.140	0.173	0.167
		(.009)	(.009)	(.021)	(.020)	(.025)	(.025)
90th - 95th	79.9	0.123	0.124	0.192	0.201	0.112	0.116
		(.013)	(.013)	(.026)	(.025)	(.028)	(.029)
95th - 100th	137.1	0.173	0.175	0.241	0.249	0.050	0.057
		(.015)	(.015)	(.027)	(.027)	(.028)	(.028)
Female			-0.021		0.008		-0.050
			(.004)		(.014)		(.018)
Black			-0.006		0.052		-0.035
			(.005)		(.013)		(.016)
Medicare			0.015		-0.018		0.084
			(.005)		(.011)		(.016)
Age 30-39			0.010		-0.006		-0.013
			(.006)		(.017)		(.021)
Age 40-49			0.013		-0.020		0.021
			(.006)		(.017)		(.022)
Age 50-64			0.025		-0.026		0.056
			(.008)		(.021)		(.029)
Age 65 plus			0.013		0.086		-0.195
			(.011)		(.042)		(.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 year*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	0.291	0.172	0.329
	(.032)	(.050)	(.026)	(.051)
Decile 2	0.074	0.116	0.056	0.128
	(.030)	(.043)	(.022)	(.045)
Decile 3	0.089	0.189	0.083	0.189
	(.030)	(.043)	(.022)	(.045)
Decile 4	0.111	0.221	0.106	0.227
	(.030)	(.046)	(.023)	(.047)
Decile 5	0.208	0.295	0.173	0.300
	(.033)	(.045)	(.024)	(.046)
Decile 6	0.190	0.304	0.156	0.322
	(.031)	(.045)	(.024)	(.046)
Decile 7	0.291	0.420	0.173	0.428
	(.032)	(.044)	(.025)	(.044)
Decile 8	0.241	0.382	0.188	0.395
	(.032)	(.045)	(.025)	(.045)
Decile 9	0.301	0.433	0.166	0.426
	(.032)	(.045)	(.025)	(.046)
90th - 95th	0.271	0.495	0.116	0.496
	(.041)	(.060)	(.029)	(.060)
95th - 100th	0.285	0.519	0.056	0.519
	(.047)	(.053)	(.028)	(.054)
Female	-0.099	-0.133	-0.050	-0.142
	(.018)	(.027)	(.018)	(.023)
Black	-0.097	-0.129	-0.035	-0.116
	(.017)	(.026)	(.016)	(.026)
Medicare	0.118	0.112	0.084	0.101
	(.016)	(.022)	(.016)	(.022)
Age 30-39	0.036	0.011	-0.013	-0.004
	(.025)	(.041)	(.021)	(.042)
Age 40-49	0.066	0.062	0.021	0.045
	(.026)	(.041)	(.022)	(.042)
Age 50-64	0.003	-0.022	0.056	-0.046
	(.032)	(.049)	(.029)	(.049)
Age 65 plus	-0.165	-0.265	-0.195	-0.298
	(.040)	(.059)	(.033)	(.059)
R-squared	.216	.178	.037	.181
# Obs	8627	5497	14163	5497
# Patients	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 year*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	-	0.004
		(.008)		(.037)
Decile 2	0.001	0.005	-0.018	0.057
	(.004)	(.006)	(.019)	(.028)
Decile 3	0.005	0.010	0.021	0.011
	(.004)	(.007)	(.019)	(.025)
Decile 4	0.014	0.001	0.031	-0.051
	(.004)	(.008)	(.020)	(.021)
Decile 5	0.022	-0.004	0.059	0.031
	(.005)	(.008)	(.021)	(.030)
Decile 6	0.036	-0.025	0.035	0.006
	(.005)	(.007)	(.020)	(.026)
Decile 7	0.048	-0.030	0.089	-0.033
	(.006)	(.008)	(.022)	(.029)
Decile 8	0.057	-0.047	0.119	-0.066
	(.006)	(.008)	(.022)	(.025)
Decile 9	0.084	-0.056	0.142	-0.008
	(.008)	(.010)	(.021)	(.031)
90th - 95th	0.127	-0.109	0.201	-0.079
	(.012)	(.016)	(.026)	(.052)
95th - 100th	0.164	-0.133	0.250	-0.089
	(.014)	(.018)	(.028)	(.051)
Constant	0.011		0.143	
	(.007)		(.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	

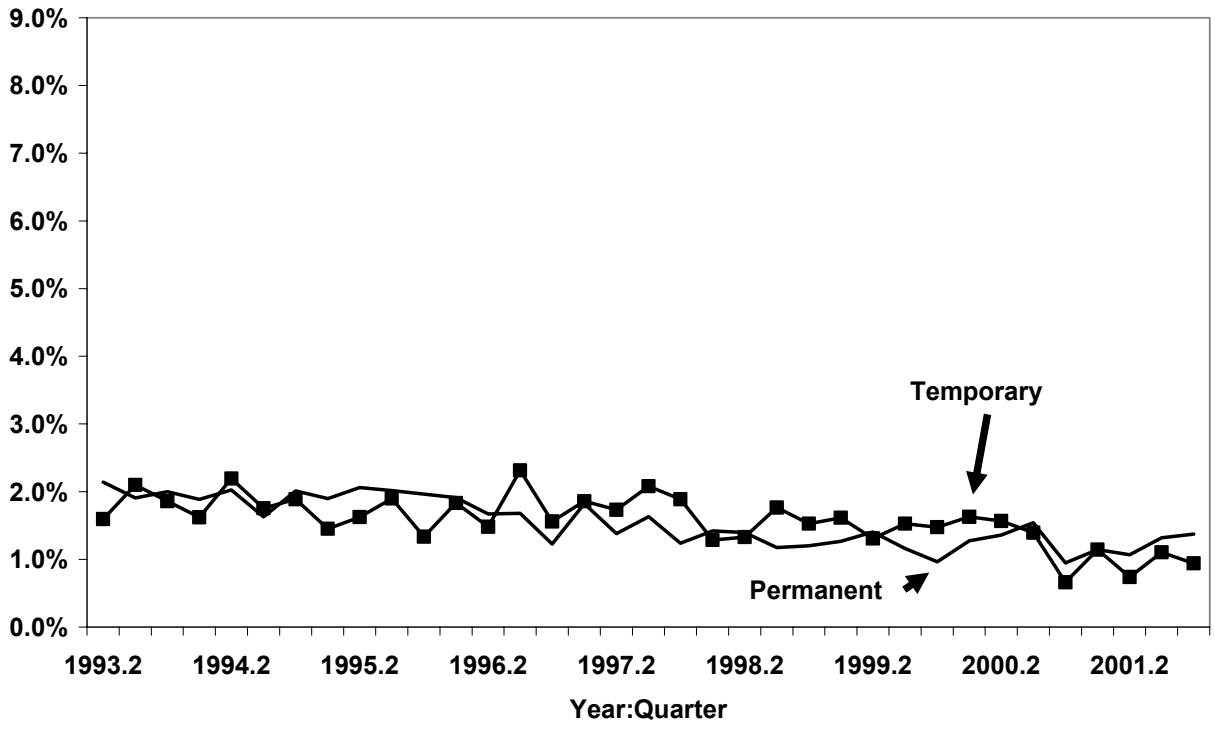
Sample in each quarter includes patients with HIV/AIDS claims by or before that quarter. Patients enter the sample in the quarter of their first HIV/AIDS claim and are placed into deciles based on number of claims in current and previous three quarters. Standard errors allow for arbitrary correlation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

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

	Medicaid Spending			Medicaid Eligible Months		
Percentile	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.

Appendix Figure 1: Other Exit Rates for Medicaid HIV/AIDS Sample



Appendix Table 1: Number of Claims in Each Quarter for NRTI Drugs

Year:Qtr	Retrovir*,**	Videx	Hivid	Zerit	Epivir*,**	Ziagen**	Viread	Emtriva
1993.1	943	446	281	0	0	0	0	0
1993.2	1043	448	327	0	0	0	0	0
1993.3	977	361	322	0	0	0	0	0
1993.4	871	309	307	0	0	0	0	0
1994.1	868	270	314	0	0	0	0	0
1994.2	814	209	307	0	0	0	0	0
1994.3	733	178	286	79	0	0	0	0
1994.4	643	165	286	232	0	0	0	0
1995.1	711	156	282	316	0	0	0	0
1995.2	715	151	262	399	0	0	0	0
1995.3	721	173	267	460	0	0	0	0
1995.4	785	171	285	482	159	0	0	0
1996.1	1022	189	230	517	1103	0	0	0
1996.2	1147	165	170	643	1567	0	0	0
1996.3	1251	203	158	873	1956	0	0	0
1996.4	1297	258	172	1215	2324	0	0	0
1997.1	1338	314	179	1533	2598	0	0	0
1997.2	1413	409	200	1823	2829	0	0	0
1997.3	1426	499	179	1968	2862	0	0	0
1997.4	1375	535	214	2053	2877	0	0	0
1998.1	1422	602	158	2080	2941	0	0	0
1998.2	1362	674	160	2176	2940	0	0	0
1998.3	1367	714	152	2270	3067	0	0	0
1998.4	1411	760	134	2304	3121	2	0	0
1999.1	1401	806	125	2326	3119	325	0	0
1999.2	1516	894	111	2354	3203	608	0	0
1999.3	1571	865	101	2428	3268	750	0	0
1999.4	1605	878	98	2530	3419	845	0	0
2000.1	1607	821	81	2417	3417	891	0	0
2000.2	1660	785	82	2452	3576	999	0	0
2000.3	1701	767	82	2422	3536	1031	0	0
2000.4	1655	782	61	2400	3511	1092	0	0
2001.1	1663	908	63	2439	3542	1194	0	0
2001.2	1604	924	61	2419	3516	1285	0	0
2001.3	1533	956	49	2371	3425	1454	0	0
2001.4	1495	981	46	2336	3460	1545	184	0
2002.1	1428	1002	35	2213	3408	1665	664	0
2002.2	1451	1055	42	2116	3471	1735	1017	0
2002.3	1449	1065	35	2003	3462	1803	1324	0
2002.4	1480	1031	31	1862	3562	1864	1645	0
2003.1	1435	1006	25	1744	3573	1933	1851	0
2003.2	1441	1053	25	1570	3723	1916	2195	0
2003.3	1449	1020	19	1501	3828	1919	2405	55
2003.4	1446	1060	20	1386	3809	1843	2551	165

*Prescriptions for Epivir and Retrovir include prescriptions for Combivir which is a combination of these two drugs.

**Prescriptions for Epivir, Retrovir, and Ziagen include prescriptions for Trizivir which is a combination of these three drugs.

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

Year:Qtr	Invirase	Norvir	Crixivan	Viracept	Fortovase	Agenerase	Kaletra	Lexiva
1993.1	0	0	0	0	0	0	0	0
1993.2	0	0	0	0	0	0	0	0
1993.3	0	0	0	0	0	0	0	0
1993.4	0	0	0	0	0	0	0	0
1994.1	0	0	0	0	0	0	0	0
1994.2	0	0	0	0	0	0	0	0
1994.3	0	0	0	0	0	0	0	0
1994.4	0	0	0	0	0	0	0	0
1995.1	0	0	0	0	0	0	0	0
1995.2	0	0	0	0	0	0	0	0
1995.3	0	0	0	0	0	0	0	0
1995.4	49	0	0	0	0	0	0	0
1996.1	493	77	5	0	0	0	0	0
1996.2	564	268	543	0	0	0	0	0
1996.3	638	284	1027	0	0	0	0	0
1996.4	670	337	1267	0	0	0	0	0
1997.1	709	422	1453	35	0	0	0	0
1997.2	817	465	1344	693	0	0	0	0
1997.3	820	490	1138	1081	0	0	0	0
1997.4	807	541	1146	1224	73	0	0	0
1998.1	564	608	1056	1303	428	0	0	0
1998.2	426	706	1005	1366	654	0	0	0
1998.3	375	749	1064	1382	686	0	0	0
1998.4	290	723	1020	1512	779	0	0	0
1999.1	233	540	1000	1479	720	0	0	0
1999.2	167	517	998	1475	660	188	0	0
1999.3	143	718	1005	1434	658	327	0	0
1999.4	121	756	1017	1357	597	396	0	0
2000.1	94	788	906	1286	549	402	0	0
2000.2	82	888	951	1198	531	446	0	0
2000.3	83	944	902	1139	500	489	21	0
2000.4	62	903	768	1124	462	509	355	0
2001.1	60	852	682	1130	447	493	593	0
2001.2	46	805	646	1052	418	456	813	0
2001.3	58	790	655	1028	403	432	914	0
2001.4	49	759	623	1001	390	407	1041	0
2002.1	59	693	506	972	363	362	1150	0
2002.2	81	652	463	996	333	348	1288	0
2002.3	93	581	451	928	303	313	1390	0
2002.4	114	568	414	916	267	288	1472	0
2003.1	171	580	389	820	234	306	1594	0
2003.2	196	563	346	741	206	288	1730	
2003.3	194	678	312	702	198	270	1764	
2003.4	173	843	282	644	176	222	1786	