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**Relationship between Adherence to Antiretroviral Therapy and the Cost-
Effectiveness of Antiretroviral Therapy and the Patterns of Antiretroviral
Regimen Switches**

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Regimen Switches**

by

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Dedication

**To my loving parents, sister, and brothers for their continuous support,
patience and encouragement**

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Relationship between Adherence to Antiretroviral Therapy and the Cost-
Effectiveness of Antiretroviral Therapy and the Patterns of Antiretroviral
Regimen Switches

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The rapid growth in the number of drugs approved to treat Human Immunodeficiency Virus (HIV) infection has transformed the management of HIV disease. The death rate from HIV-disease has continued to fall since the Food and Drug Administration approval of the newer antiretroviral drugs.

Antiretroviral therapy consists of medication regimens with significant side effects, toxicities, and drug interactions. Adherence to antiretroviral therapies presents special issues that result from the biology of HIV, the magnitude of the required therapeutic effect, and the changing demography of HIV infection. Non-adherent behavior has promoted drug resistance and cross-resistance among drugs in a therapeutic class limiting future treatment options. Recent data suggest that

the level of medication adherence required for optimal treatment effectiveness is extremely high and that adherence levels exceeding 95 percent are required for optimal viral suppression.

The high costs of these drugs, as well as the increased life expectancy of patients with HIV are driving up the overall health care costs associated with HIV infection. Few studies have modeled the pharmacoeconomic impact of non-adherence of therapies in persons with HIV. The objectives of the research study were to assess the relationship between patient adherence to antiretroviral therapy and: (1) cost-effectiveness of antiretroviral regimens; and (2) patterns of antiretroviral regimen switches.

Markov Monte Carlo simulations were conducted to determine the costs and effects of adherence behavior. The results of the study indicate that the mean overall annual HIV-related medical costs were \$22,751. Overall, probabilistic sensitivity analyses indicate that adherent behavior, compared to non-adherent behavior, is associated with an incremental cost-effectiveness ratio below \$15,000/QALY. In addition, the results of this study indicate that there are more treatment switches in non-adherent individuals compared to adherent individuals as the enrollment period increases.

For clinicians and healthcare policy makers, it is important to take into account the impact of adherence behavior on disease progression and the cost-effectiveness of interventions. Future health economic studies to assess the

potential impact of adherence interventions in HIV-infected patients receiving care in the VA setting are needed and the role of pharmacists in managing adherence behavior should be explored.

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

1.1 Overview, Purpose and Objectives of the Study

Through 2004, a cumulative total of 944,305 Acquired Immune Deficiency Syndrome (AIDS) cases had been reported to the United States Centers for Disease Control and Prevention (CDC). Seventy percent of these cases occurred in people between 25 and 44 years of age. The total deaths of persons reported with AIDS were 529,113. In 2004, there were currently an estimated 415,193 persons living with AIDS in the United States (US).¹

AIDS is caused by the Human Immunodeficiency Virus (HIV). The rapid growth in the number of drugs approved to treat persons infected with HIV has transformed the treatment of this disease. Today, there are 20 antiretroviral drugs used to treat HIV disease including eight protease inhibitors (PI), eight nucleoside reverse transcriptase inhibitors (NRTI), three non-nucleoside reverse transcriptase inhibitors (NNRTI) and a recently approved Fusion Inhibitor.² These therapies have been effective in slowing HIV disease progression by decreasing the viral

¹ CDC. HIV/AIDS Surveillance Report: HIV Infection and AIDS in the United States, 2004.

² Bartlett JG, Gallant JE. *Medical management of HIV Infection*. Maryland: The Johns Hopkins University on behalf of its Division of Infectious Diseases and AIDS Service, 2001.

load in the blood.³ Highly Active Antiretroviral Therapy (HAART) is commonly defined as a regimen of three or four antiretroviral medications and has become standard treatment practice.⁴

The death rate from AIDS has continued to fall since the Food and Drug Administration (FDA) approval of the newer antiretroviral drugs. The high costs of these drugs, as well as the increased life expectancy of patients with HIV are driving up the overall health care costs associated with HIV infection. In addition, the new combination drug regimens and the earlier initiation of antiretroviral therapy are driving the overall health care costs even higher.

The economic burden of the early and continuous use of expensive antiretroviral therapies by increasing numbers of persons with HIV disease is not well understood because there are few comprehensive assessments of the cost and financing of care for persons with HIV disease. Nevertheless, the adoption of costly, new drug therapies to treat persons with HIV disease, in addition to the increasing number of persons living with HIV disease, indicate that the cumulative cost of treating HIV disease is rising steeply. Most of the people with HIV disease depend on public sources to pay for needed services and those who are responsible for allocating funds thereby require accurate and timely

³ Martin-Fernandez J, Escobar-Rodriguez I, Campo-Angora M, Rubio-Garcia R. Evaluation of adherence to highly active antiretroviral therapy. *Archives of Internal Medicine* 2001;161(22):2739-40.

⁴ Moore RD. Cost effectiveness of combination HIV therapy: 3 years later. *Pharmacoeconomics* 2000;17(4):325-30.

information about the cost of treating people with HIV disease. Therefore, credible estimates of the costs of treating all people with HIV disease must be made available to aid federal, state, and local policy makers.

HIV combination therapies are complex and may involve six to nineteen pills per day. Regimens which include protease inhibitors generally involve the greatest number of pills and have the greatest dietary restrictions. In addition, patients may be prescribed other non-antiretroviral therapies (e.g., antimicrobials) to manage other HIV-related conditions. As a result, adherence is often difficult. The majority of clinical trials measure efficacy rather than effectiveness. Efficacy trials often achieve higher levels of patient adherence than effectiveness trials. Subsequently, the results from clinical trials may correlate poorly with everyday patient care. Therefore, it is important to account for non-adherence when evaluating effectiveness.

Non-adherence can lead to therapeutic failure, over-dosage, or the emergence of drug resistance. For example, approximately 50 percent of all failures in hypertension treatment can be explained by non-adherence to treatment.^{5,6} Furthermore, unintended pregnancies and up to 80 percent of

⁵ Urquhart J. Some economic consequences of noncompliance. *Current Hypertension Reports*. 2001;3(6):473-80.

⁶ Stephenson J. Noncompliance may cause half of antihypertensive drug failures. *Journal of the American Medical Association* 1999;282(4):313-4.

transplant rejections can be avoided by better adherence with oral contraceptives⁷ and immunosuppressive medications, respectively.⁸ Recent studies have shown that a high level of adherence ($\geq 90\%$) is necessary for long-term suppression of HIV virus load.^{9,10,11,12} Empirical studies of adherence to specific combinations of antiretroviral regimens have been limited.

A “gold-standard” measurement of medication adherence does not exist. Automated pharmacy systems are routinely used for disease management programs and these systems are capable of providing rich data on a population level. As a result, researchers have frequently used automated pharmacy systems to assess prescription filling behavior.

The literature on the causes and consequences of non-adherence with medications is increasing, but relatively little research has been conducted on the economics of HIV medication non-adherence. Few studies have modeled the pharmacoeconomic impact of non-adherence of therapies in persons with

⁷ Rosenberg M, Waugh MS. Causes and consequences of oral contraceptive noncompliance. *American Journal of Obstetrics & Gynecology*. 1999;180(2 Pt 2):276-9.

⁸ Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. *Transplantation Proceedings* 1989;21(1 Pt 1):833-4.

⁹ Turner B. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *Journal of Infectious Diseases* 2002;185(Suppl 2):S143-51.

¹⁰ Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 2000;133(1):21-30.

¹¹ Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care* 2001;13(6):709-20.

¹² Bartlett JA. Addressing the challenges of adherence. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2002;29(Suppl 1):S2-10.

HIV.^{13,14,15} The results of this study will demonstrate the relationship between non-adherence and lifetime treatment costs, and are intended to be useful to both policy decision makers and treatment decision makers.

The objectives of the research study were to assess the relationship between patient adherence to antiretroviral therapy and: (1) cost-effectiveness of antiretroviral regimens; and (2) patterns of antiretroviral regimen switches.

1.2 The Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)

AIDS was first reported in the US in 1981 and has since become a major worldwide pandemic. HIV, type 1, has been identified as the primary cause of AIDS. By destroying or damaging cells of the body's immune system, CD4 T-lymphocytes, HIV progressively destroys the body's ability to fight infections and certain cancers. As a result, the incidence of opportunistic infections increases in people infected with the virus.

¹³ Becker R, Shakur U. The impact of drug compliance on the cost of treating HIV/AIDS in Africa. ISPOR Fourth European Conference; 2001 November 11-13; Cannes, France.

¹⁴ Billups SJ, Malone DC, Carter BL. The relationship between drug therapy noncompliance and patient characteristics, health-related quality-of-life, and health care costs. *Pharmacotherapy* 2000;20(8):941-9.

¹⁵ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

1.2.1 AIDS Case Definition

Case definitions are sets of criteria used by public health agencies in the surveillance, or monitoring of disease syndromes. In the US, case definitions are established by the CDC. One of the most controversial of all case definitions has been that for AIDS which, as a syndrome, is characterized by more than two dozen different illnesses and symptoms as well as by specific indications on blood test findings.

Before HIV was identified as the etiologic agent for AIDS, the CDC defined a case of AIDS as a disease “at least moderately indicative of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to the disease.”¹⁶ Typically, AIDS-defining illnesses or diseases included pneumocystis carinii pneumonia, Kaposi's sarcoma, and many other serious opportunistic infections. In 1985 and 1987, with the identification of HIV as the causative agent for AIDS and the availability of laboratory tests to detect the HIV antibody, the case definition was expanded. These revisions applied to persons with laboratory evidence for HIV infection. Also, among diseases added in 1985 were disseminated histoplasmosis, chronic isosporiasis, and certain non-Hodgkin's lymphomas. In 1987, extrapulmonary tuberculosis, HIV encephalopathy, and HIV wasting syndrome were among the diseases added

¹⁶ CDC. Current trends update: Trends in AIDS diagnosis and reporting under the expanded surveillance definition for adolescents and adults -- United States, 1993. *MMWR* 1994;43(45):826-31.

to the case definition. In addition, the 1987 revision allowed certain indicator diseases to be diagnosed based on clinical presentation rather than "confirmed" by laboratory or diagnostic methods (Appendix A).

To be consistent with standards of medical care for HIV-infected persons and to more accurately capture the number of persons with severe HIV-related immunosuppression who are at highest risk for HIV-related morbidity and who are most in need of close medical follow-up, the surveillance definition was expanded on January 1, 1993. This expansion includes all HIV-infected adults and adolescents who have less than 200 CD4 cells/micro liter (μL) or a CD4 cell percent of total lymphocytes less than 14 regardless of whether a patient shows any symptoms of one or more indicator conditions. Furthermore, the surveillance definition expanded to include patients diagnosed with pulmonary tuberculosis, invasive cervical cancer, or recurrent pneumonia.¹⁷ The addition of pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer in HIV-infected adults and adolescents to the 23 clinical conditions listed in the 1987 surveillance definition reflects their documented or potential importance in the HIV pandemic (Appendix A). Effective January 1, 2000, the surveillance case definition for HIV infection was revised to reflect advances in laboratory HIV virologic tests. The definition incorporates the reporting criteria for HIV infection and AIDS into a single case definition for adults and children.

¹⁷ Ibid.

1.2.2 Clinical Presentation of AIDS

As a complement, rather than a replacement of the AIDS case definition, algorithms have also been developed to classify the stages of HIV infection. The original CDC version used four groups marked I to IV, respectively to indicate: acute infection; asymptomatic infection; persistent generalized lymphadenopathy; and constitutional diseases, neurological diseases, secondary infectious diseases, secondary cancers, and certain other serious conditions.¹⁸ Another system developed in 1985 by the US military, the Walter Reed Staging Classification, used seven stages, ranging from zero, representing a lack of infection and an intact immune system, to six, representing infection and advanced immune damage.¹⁹

The 1993 CDC classification system uses three categories relating to the CD4 cell count: category one includes individuals with CD4 counts of 500 or more cells per microliter; category two includes individuals with counts from 200 to 499; and category three includes individuals with counts below 200 cells.²⁰ The CDC staging system also contains three clinical categories for people who test HIV-positive (Table 1-1). Category A includes people who have been asymptomatic except for persistent generalized lymphadenopathy and/or

¹⁸ CDC. Classification System for Human T-Lymphotropic Virus Type III/Lymphadenopathy-Associated Virus Infections. *MMWR* 1986;35(20):334-9.

¹⁹ Redfield RR, Wright DC, Tramont EC. The Walter Reed staging classification for HTLV-III/LAV infection. *New England Journal of Medicine*. 1986;314(2):131-2.

²⁰ CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992;41(51):961-2.

seroconversion syndrome. At this stage, the infection is latent and people have no symptoms of opportunistic infections. However, the lymph nodes shelter the virus where it can grow and multiply. Immediately following the asymptomatic stage is the symptomatic stage (stage B). Stage B includes people who have never had an AIDS-defining illness but have had some of the less serious complications of HIV infection, including oral or vaginal candidiasis, constitutional symptoms such as fever or persistent diarrhea, oral hairy leukoplakia, herpes zoster, idiopathic thrombocytopenic purpura, listeriosis, peripheral neuropathy, cervical dysplasia, bacillary angiomatosis, or pelvic inflammatory disease. Category C is used to describe those who have had one or more of the AIDS-defining illnesses.

Table 1-1: AIDS Surveillance Case Definition for Adolescents and Adults, 1993²¹

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, or PGL or Acute HIV Infection	B Symptomatic (not A or C)	C* AIDS Indicator Condition (1987)
1) >500/mm ³ (≥29%)	A1	B1	C1
2) 200 to 499/mm ³ (14% to 28%)	A2	B2	C2
3) <200/mm ³ (<14%)	A3	B3	C3

* All patients in categories A3, B3 and C1-3 defined as having AIDS, based on the presence of an AIDS-indicator condition (Appendix A) and/or a CD4 cell count <200/mm³; PGL- Persistent Generalized Lymphadenopathy

²¹ Ibid.

1.2.3 International Classification of Diseases Clinical Modification Official HIV Codes

In recent years, with advances in medical knowledge about the group of illnesses caused by HIV, there has been a demand for continued modifications to the classification of HIV infection as was noted earlier. These modifications have been introduced to simplify the coding of HIV-related illnesses and to improve the accuracy of reporting the diagnoses of HIV infection and AIDS. The International Classification of Diseases (ICD), published by the World Health Organization, is designed to promote international comparability in the collection, processing, classification, and presentation of mortality statistics. A related classification, the International Classification of Diseases Clinical Modification (ICD-CM), is used in assigning codes to diagnoses associated with inpatient, outpatient, and physician office utilization in the US. The ICD-CM is based on the ICD but provides for additional morbidity detail and is annually updated. The latest release of the ICD-CM codes is the 10th version (ICD-10-CM).

In 1991, several HIV-related conditions were added to the lists of inclusions under the 042-044 series of ICD-CM codes. The 042, 043, and 044 categories were originally created to distinguish AIDS (042) from AIDS-related complex (ARC) (043) and other HIV disease (044). The distinctions among the ICD-9-CM categories are no longer clear-cut, and the three-digit categories no longer denote separate clinical entities. As a result of an increased understanding

of the etiology of HIV processes, there was a continued demand to update classification systems, making it a complex and burdensome process. Furthermore, there are few clear guidelines for assigning specific codes to HIV/AIDS subgroups. Also, persons who assign codes were restricted to only using a single code from the 042-044 series which created confusion and inconsistent coding practices in the field.

Effective October 1, 1994, a new addendum replaced the addendum containing the codes for HIV infection (042.0–044.9) that became effective October 1, 1991.²² This was the third revision of codes for the classification of HIV infection. This revised addendum contains the following changes: (1) the 042–044 series of codes has been replaced with a single code, 042, for HIV disease; (2) a new code, V08, has been created for asymptomatic HIV infection; (3) code 795.8 has been deleted; and (4) a new code, 795.71, inconclusive serological findings for HIV, has been created. Infants who test positive on certain serologic tests that may also reflect the serostatus of the mother are coded as 795.71.

1.2.4 Epidemiology of HIV Infection

Epidemiologic studies indicate that semen, cervical and vaginal secretions, breast milk, blood, and blood products are the predominant vehicles for HIV

²² CDC. Official authorized addenda: Human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR* 1994;43(RR-12).

transmission. As a result, HIV is spread most commonly through four principal routes in humans: person to person, through fluid-exchange during unprotected sex with an infected partner; person to person, through fluid-exchange resulting from the sharing of HIV-contaminated injection equipment; through transfusion with infected blood or blood products; and through vertical transmission from mother to child during pregnancy, labor, or breastfeeding. Approximately one-quarter to one-third of all untreated pregnant women infected with HIV will pass the infection to their babies.

According to the most recent United Nations AIDS (UNAIDS) report, the AIDS pandemic “claimed more than three million lives in 2005, and an estimated five million people acquired HIV in 2005.”²³ Globally, the estimated number of people currently living with the virus is 40.3 million (Figure 1-1).²⁴ In 2005, there were 3.1 million deaths as a direct result of HIV/AIDS (Figure 1-2). According to the same report, approximately 65,000 people became infected with HIV in high-income countries in 2005. Also, a total of about 1.9 million people are now living with the virus in high-income countries, where an estimated 30,000 people died of AIDS in 2005. These staggering numbers are most likely underestimations of the true impact of HIV/AIDS due to underreporting, delays in reporting and seeking treatment and inequities in access to medical management. Clearly, HIV infection has reached proportions of a pandemic, having infected millions.

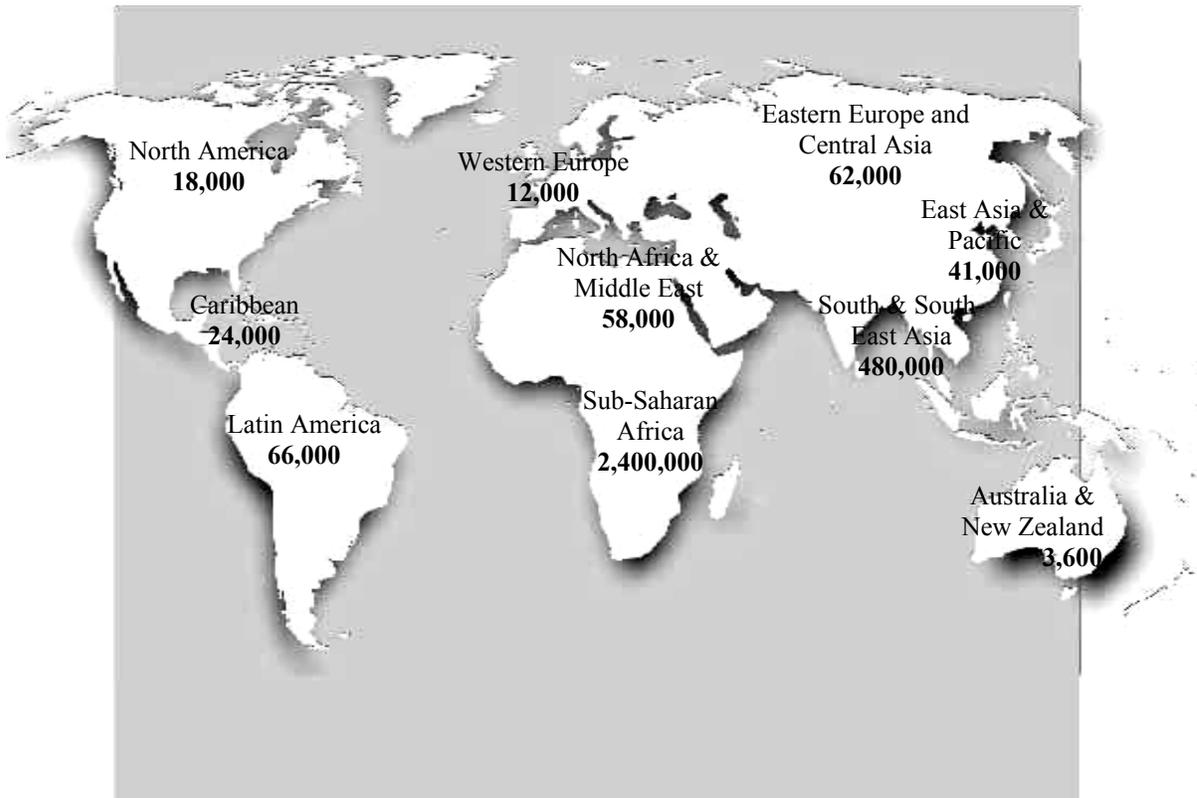
²³ UNAIDS. AIDS epidemic update-December 2005: UNAIDS, 2005.

²⁴ Ibid.

Figure 1-1: Estimated number of persons living with HIV through 2005



Figure 1-2: Estimated number of deaths due to HIV/AIDS during 2005



During the early 1990s, HIV infection became the leading cause of death among American men aged 25 to 44 and the third leading cause of death among women in the same age group, accounting for 19.9 percent and 7.3 percent of deaths, respectively.²⁵ Through 2004, the cumulative number of AIDS cases that had been reported to the CDC was 944,305.²⁶ Adult and adolescent AIDS cases totaled 934,862, with 756,399 cases in males and 178,463 cases in females. Sixty percent of these cases occurred between ages 25 and 44. Approximately 40 percent of the reported AIDS cases were among whites (non-Hispanic) and 40 percent were among blacks (non-Hispanic). Hispanics, Asians, and Pacific Islanders, American Indians and Alaska natives currently account for approximately 20 percent of the total number of reported AIDS cases. Consequently, blacks have the highest rates of AIDS cases per 100,000 (56.4 per 100,000, compared with 18.6 per 100,000 for Hispanics and 6.0 per 100,000 for whites).

The disease is still somewhat concentrated in men, with a large increase in heterosexual infections in women. The incidence of HIV among injection-drug users in several urban areas has fallen dramatically. The CDC has estimated that there are about 40,000-50,000 new cases of HIV infection occurring each year, with most male cases occurring among men who have sex with men, and most

²⁵ CDC. Update: Trends in AIDS incidence - United States, 1996. *HIV/AIDS Surveillance Report* 1997;46(37):861-7.

²⁶ CDC. HIV/AIDS Surveillance Report: HIV Infection and AIDS in the United States, 2004.

female cases acquired through heterosexual transmission. The cumulative reported deaths of people with AIDS in the US were 529,113 by 2004.²⁷ There are currently an estimated 415,193 persons living with AIDS.²⁸

The progression from HIV infection to AIDS may occur over a period of months or it can take up to eight to ten years. This uncertain “latency” period gives rise to variations in the both the duration of prophylactic measures and actual treatment strategies for individual patients.

1.2.5 Diagnostic Methods of HIV Infection

Sensitivity and specificity are the most widely used statistics to describe a diagnostic test in health care. Sensitivity is the proportion of patients with disease who test positive. Specificity is the proportion of patients without disease who test negative. Knowledge of the predictive value of instruments used in health care is important. In particular, the predictive value of instruments used to diagnose HIV infection is crucial since test results may have enormous consequences on employment, health care, and personal relationships. Although there have been technological changes, HIV testing in the US still follows the same basic testing procedure as in 1985. Early HIV infection often causes no symptoms; therefore, diagnosis of infection is conducted by testing a person's blood for the presence of antibodies to HIV. HIV antibodies generally do not

²⁷ Ibid.

²⁸ Ibid.

reach detectable levels in the blood for one to three months following infection, and can take as long as six months to be produced in quantities large enough to show up in standard blood tests.

HIV infection is only considered confirmed after two tests have been performed; therefore, a screening test and a confirmatory test are needed to confirm HIV infection. In an article by the University of California San Francisco's HIV InSite, Niel Constantine explains that "screening tests possess a high degree of sensitivity, whereas confirmatory assays have a high specificity."²⁹ Tests with high sensitivity produce few false-negative results, whereas tests with high specificity produce few false-positive results.³⁰ Since the screening tests can produce false positives, a second screening test is typically run on the same sample. Confirmatory tests are only run on samples that are repeatedly positive.

Health care providers diagnose HIV infection by using two different types of antibody tests. The most common screening test is the enzyme-linked immunosorbent assay (ELISA). The FDA approved the first ELISA test kit to screen for antibodies to HIV in 1985. Two years later, in 1987, the FDA approved the Western blot which is a confirmatory test. Thereafter, more blood-based HIV detection methods have been approved by the FDA, such as the Home Access Express Test, rapid tests-SUDS, Recombigen latex agglutination assay, and Genie HIV-1. Furthermore, non-blood-based tests, such as the saliva test

²⁹ Constantine N. HIV Antibody Assays: HIV InSite Knowledge Base Chapter, 2001.

³⁰ Ibid.

OraSure and the urine test Calypte HIV-1, have been recently approved by the FDA as well. The CDC tested 1400 clinical labs in 1990 and revealed a sensitivity of 99.3 percent and a specificity of 99.7 percent.³¹

1.2.6 Indicators of Disease Progression

Commonly used independent predictors of the risk of developing AIDS are: (1) serum levels of β_2 -microglobulin > 3.0 microgram/ml; (2) CD4 counts < 200 cells/mm³; (3) CD4T-lymphocytes $< 25\%$ of total lymphocytes; (4) the presence of p24 antigen; (5) hematocrit values less than 40; and (6) HIV-ribonucleic acid (HIV-RNA) viral load values. The CD4 cell count has been the most important diagnostic marker of disease progression. Losses of CD4 lymphocytes, accompanied by a reversal of the CD4/CD8 (helper/suppressor) ratio, have been recognized as important diagnostic characteristics of HIV infection.

The Panel on Clinical Practices for the Treatment of HIV Infection recommends that CD4 counts should be measured at the time of diagnosis and every three to six months thereafter.³² A significant decrease in CD4 counts is generally agreed to be a greater than 30 percent decrease from baseline for absolute numbers and a decrease of greater than three percent from baseline in

³¹ CDC. Update: Serologic testing for HIV-1 antibody --United States, 1988 and 1989. *MMWR* 1990;39(22):380-3.

³² Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

percentage cells. After initiation of antiretroviral therapy, the CD4 count typically increases by 50 cells/ μ L at four to eight weeks after antiretroviral therapy has been started or changed. Furthermore, one typically expects an additional increase of 50 to 100 cells/ μ L per year thereafter. Once CD4 cell counts exceed 200 cells/ μ L for three to six months, the risk of acquiring opportunistic infections is greatly decreased and the need for antimicrobial prophylaxis is reduced or in many cases eliminated.

Until now, it had been widely assumed that CD4 counts and viral loads at the beginning of treatment were the best guide to long-term survival and disease progression once treatment was started. This assumption was based on information from individual cohorts such as the British Columbia cohort in Canada, and an analysis of HIV-positive cohorts from Europe and Canada.^{33,34,35,36} However, Chene et al. recently reported that when they controlled for CD4 cell response after six months of treatment, baseline CD4 cell

³³ Binquet C, Chene G, Jacqmin-Gadda H, Journot V, Saves M, Lacoste D, et al. Modeling changes in CD4-positive T-lymphocyte counts after the start of highly active antiretroviral therapy and the relation with risk of opportunistic infections: the Aquitaine Cohort, 1996-1997. *American Journal of Epidemiology*. 2001;153(4):386-93.

³⁴ Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study.[see comment]. *Lancet*. 1999;353(9156):863-8.

³⁵ Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load.[see comment]. *Jama*. 2001;286(20):2560-7.

³⁶ Grabar S, Le Moing V, Goujard C, Leport C, Kazatchkine MD, Costagliola D, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy.[see comment]. *Annals of Internal Medicine*. 2000;133(6):401-10.

count ceased to predict disease progression and the risk of death.³⁷ Chene et al. concluded that prognosis of people with HIV can be more accurately determined after six months of treatment rather than at baseline, and very small increases in CD4 cell count appear to confer big benefits in reducing the risk of disease progression or death. Chene et al. analyzed 9323 adult treatment-naïve patients from 13 cohort studies from Europe and North America. All patients received at least three antiretrovirals. Also, a recent study offers an alternate explanation for disease progression and mortality; specifically, Wood et al. reported that antiretroviral adherence is more critical than initial CD4 count in predicting HIV survival in HIV-infected individuals with CD4 counts greater than 200 cells/ μ L.³⁸

In recent years, the measurement of HIV-RNA viral load in blood has increasingly become a popular and precise indicator of disease progression in infected people.³⁹ Viral load tests measure the amount of HIV in the blood, and this information along with CD4 cell counts and the clinical condition of the patient, are commonly used to evaluate the rate of disease progression.^{40,41,42}

³⁷ Chene G, Sterne JA, May M, Costagliola D, Ledergerber B, Phillips AN, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet* 2003;362(9385):679-86.

³⁸ Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

³⁹ Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *Journal of the American Medical Association* 2001;286(20):2568-77.

⁴⁰ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

Furthermore, viral loads, along with CD4 cell counts, are now also being used to evaluate the efficacy of antiretroviral treatment.⁴³

The most recent guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents note that in approximately 18 trials with viral load monitoring, there was a statistically significant dose-response association between viral load and improved clinical outcome.⁴⁴ These results were stable over a range of baseline characteristics including pre-treatment viral load, CD4 cell counts, and prior drug experience. The Panel on Clinical Practices for the Treatment of HIV Infection recommends that measurement of plasma HIV-RNA levels should be performed at the time of diagnosis and every three to four months thereafter in the antiretroviral-naïve patient. A significant change in HIV-RNA levels is generally agreed to be a 0.2 to 0.3 log₁₀ change (30 percent to 50 percent).^{45,46} Plasma HIV-RNA levels should also be measured before initiation of antiretroviral therapy and again at two to eight weeks after initiation of antiretroviral therapy. This is the approximate time taken to observe a 90 percent

⁴¹ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

⁴² Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: US Public Health Service, 2003.

⁴³ Ibid.

⁴⁴ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

⁴⁵ Ibid.

⁴⁶ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

(1.0 log₁₀) decrease in viral load. The decline of viral load should continue until it is below detectable levels (below 50 copies of HIV-RNA per mL of plasma) by 16 to 20 weeks. Failure to attain a 90 percent reduction by four weeks of therapy suggests poor adherence or viral resistance.

Once the patient is on therapy, HIV-RNA and CD4 testing should be repeated at 4, 8 to 12 and 16 to 24 weeks to evaluate the effectiveness of therapy. Thereafter, viral load testing and CD4 cell counts should be monitored every eight to twelve weeks. As with HIV diagnostic tests, the guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents recommend that CD4 cell counts and HIV-RNA levels should be obtained on at least two occasions to ensure consistency and accuracy of the measurements. However, in cases of advanced disease, clinicians are encouraged to initiate antiretroviral therapy after the first measurement.

1.2.7 Morbidity and Mortality

The death rate from AIDS has continued to fall since FDA approval of antiretroviral drugs. Before 1996, the death rate from AIDS had increased every year since the 1980s. In 1996, the death rate from AIDS dropped by 23 percent from the previous year. During the first six months of 1997, the death rate from

AIDS was 44 percent lower than it was during the first six months of 1996.^{47,48} A report from a cohort study of 1,255 HIV-infected patients receiving combination therapy showed that there was a 70 percent decline in mortality from 1995 to 1997.⁴⁹ By 1997, 94 percent of all patients in this cohort were on antiretroviral therapy and 82 percent received a protease inhibitor as part of this therapy.

Although there has been a decrease in the mortality of patients with AIDS, there has not been a decrease in the number of new infections. The CDC reported that the number of new HIV infections in 26 states with mandatory HIV infection reporting remained unchanged between 1995 and 1997.⁵⁰ The decrease in the death rate resulting from AIDS and the steady incidence of HIV infections have increased the number of people living with HIV/AIDS (Table 1-2).

Table 1-2: Total Number of Persons Living with HIV/AIDS in the US from 1998-2001

	2001	2002	2003	2004
Number of persons living with HIV/AIDS	384,446	410,998	435,364	462,792

⁴⁷ CDC. Guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. *MMWR* 1997;46(Number RR-12).

⁴⁸ CDC. Update: Trends in AIDS incidence - United States, 1996. *HIV/AIDS Surveillance Report* 1997;46(37):861-7.

⁴⁹ Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *New England Journal of Medicine* 1998;338(13):853-60.

⁵⁰ CDC. Guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. *MMWR* 1997;46(Number RR-12).

1.3 Treatment of HIV/AIDS

When AIDS first surfaced in the US, there were no therapies to restore the underlying immune deficiency and few treatments existed for the opportunistic diseases that accompanied HIV infection. However, during the past 10 years, researchers have developed drugs to fight both HIV infection and its associated infections and cancers.

Early in the HIV pandemic, treatment protocols were implemented to control opportunistic infections since no antiretrovirals were available. Nevertheless, even after the introduction of antiretrovirals, the control of opportunistic infections through treatment and/or prophylaxis has remained an important overall management tool for HIV-infected individuals. For example, Osmond et al. concluded that the prophylaxis and treatment of pneumocystis infections outweighed the benefit of zidovudine monotherapy during the mid-1980s.⁵¹

In 1995, the US Public Health Service and the Infectious Disease Society of America developed guidelines to assist practitioners to prevent the occurrence and recurrence of opportunistic infections in individuals infected with HIV.

These guidelines were revised in 1997, 1999, and most recently in 2002.^{52,53} As

⁵¹ Osmond D, Charlebois E, Lang W, Shiboski S, Moss A. Changes in AIDS survival time in two San Francisco cohorts of homosexual men, 1983 to 1993. *Journal of the American Medical Association* 1994;271(14):1083-7.

⁵² Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

stated in the 2002 guidelines, the quality-of-life and survival of HIV patients have improved significantly, partly as a result of the better recognition of opportunistic disease processes and more effective therapies available for the management of opportunistic infections.

Since the isolation of HIV, the FDA has approved a number of drugs for treating HIV infection. This progress has been accelerated by the identification of the virus structure as well as findings from epidemiological and clinical trials. The rapid growth in the number of drugs approved to treat persons with HIV disease, accompanied by improved techniques to monitor the quantity of virus in patients, have transformed the treatment of persons with HIV disease. Today, there are 20 antiretroviral drugs used to treat HIV disease including eight protease inhibitors (PI), eight nucleoside reverse transcriptase inhibitors (NRTI), three non-nucleoside reverse transcriptase inhibitors (NNRTI) and a fusion inhibitor; these drugs are capable of slowing the spread of HIV in the body and delaying the start of opportunistic infections.^{54,55}

The first two groups of drugs used to treat HIV infection were the NRTIs and the NNRTIs. Both NRTIs and NNRTIs interrupt and interfere with early

⁵³ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

⁵⁴ Bartlett JG, Gallant JE. *Medical management of HIV Infection*. Maryland: The Johns Hopkins University on behalf of its Division of Infectious Diseases and AIDS Service, 2001.

⁵⁵ FDA. FDA approves first drug in new class of HIV treatments for HIV Infected adults and children with advanced disease: FDA News, 2003.

viral replication. The FDA has approved a third class of drugs for treating HIV infection. These drugs, called protease inhibitors, interrupt virus replication at a later stage in its life cycle. More recently, the FDA has approved a new class of drugs for treating HIV infection; this class of drugs is called entry inhibitors. The drug enfuvirtide is one of a subset of entry inhibitors known as fusion inhibitors. A fusion inhibitor blocks the activity of HIV where the virus sends out a projectile that anchors the virus to a CD4 T cell.⁵⁶ The virus pulls itself in via this anchor until it makes direct contact with the cell. Once full contact is made, the virus inserts its genetic material into the cell.

The approval of protease inhibitors and fusion inhibitors by the FDA has initiated a new period in the treatment of persons with HIV disease.

1.3.1 Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents

There are an enormous number of possible choices and combinations for the initial treatment of antiretroviral-naïve HIV-infected patients. The current recommendations from the International AIDS Society are that three of four drugs from two or three of the drug classes are to be used in combination to suppress viral replication. Of primary importance is that classes differ in their mechanisms of action and in their target points of activity in the cycle of HIV replication.

⁵⁶ Cervia JS, Smith MA. Enfuvirtide (T-20): a novel human immunodeficiency virus type 1 fusion inhibitor. *Clinical Infectious Diseases* 2003;37(8):1102-6.

Combining classes of medications creates regimens that are able to attack HIV replication at multiple target points. HAART has clearly been shown to decrease HIV-RNA in the plasma (viral load) and viral load suppression has been linked to reduced mortality and morbidity.^{57,58,59,60,61,62} HAART therapy has become the standard of care in the management of HIV-infected individuals in the US. The advantage of using three drugs from two classes is that it preserves another class for subsequent therapy. Using four drugs from the three classes may have more potency, but may also expose the patient to additional toxicity and adherence problems.

1.3.2 Choice of Initial Therapy

With 20 antiretroviral drugs used to treat HIV-infected individuals, there are a plethora of possible choices for initial treatment of HIV-infected individuals. As discussed earlier, the goals of any initial treatment strategy are to promote

⁵⁷ Schapiro JM, Winters MA, Stewart F, Efron B, Norris J, Kozal MJ, et al. The effect of high-dose saquinavir on viral load and CD4+ T-cell counts in HIV-infected patients.[comment]. *Annals of Internal Medicine* 1996;124(12):1039-50.

⁵⁸ Corey L, Holmes KK. Therapy for human immunodeficiency virus infection -- what have we learned? *New England Journal of Medicine* 1996;335(15):1142-4.

⁵⁹ Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. *Behaviour Research & Therapy* 2001;39(10):1151-62.

⁶⁰ Guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus: United States Public Health Service, 2001.

⁶¹ Stone VE. Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. *Clinical Infectious Diseases* 2001;33(6):865-72.

⁶² Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Ibid.*2002;34(8):1115-21.

long-term suppression of viral replication and to increase CD4 counts.

Recommendations for initial treatment include the use of four agents from the three drug classes or the use of three agents from two drug classes; therefore, clinicians are able to preserve another class for subsequent “salvage” therapy. A recent update by the International AIDS Society-USA Panel lists three types of initial combination therapies that are currently considered:⁶³ (1) a PI with two NRTIs (NNRTI-sparing); (2) an NNRTI with two NRTIs (PI-sparing); or (3) three NRTIs (NNRTI- and PI-sparing). Also, other regimen combinations may include a PI with an NNRTI plus one or two NRTIs. Generally, the factors that play a significant role in determining the success of initial therapy include adherence, tolerability, convenience, and baseline virological or immunologic status. For example, regimens with long half-lives as well as those with minimal diet restrictions are preferable; the time taken before these regimens fail is prolonged. Many patients who are initiated on antiretroviral therapy eventually experience initial and subsequent treatment failure; consequently, careful consideration should be given when choosing initial regimens. Since the initial treatment will affect the choice of subsequent treatments, considerations such as intra-class cross-resistance and overlapping adverse events (e.g., lipid abnormalities with PIs and neuropathy with some NRTIs) need to be addressed.

⁶³ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

1.3.3 Protease Inhibitor (PI)-Based Regimens

The first PI, saquinavir (Invirase®), was approved by the FDA in December 1995. Indinavir and ritonavir (Crixivan® and Novir®) were approved in 1996 and nelfinavir (Viracept®) was approved in 1997. Amprenavir (Agenerase®) and the combination of lopinavir and ritonavir (Kaletra®) were more recently approved. Atazanavir (Reyataz®) was approved in June 2003.

The efficacy of PIs in combination with NRTIs has been well documented in randomized clinical trials. Furthermore, recent data also show that there is a boosting effect of PIs when given in combination with low-dose ritonavir.^{64,65} There are currently no studies that have compared and documented the relative effectiveness of the different boosted PI regimens. Low-dose ritonavir has been found to pharmacologically enhance saquinavir, indinavir, amprenavir, or lopinavir by inhibiting cytochrome P450 enzymes. Consequently, ritonavir may act early on absorption and first-pass metabolism, resulting in increased peak plasma concentrations of the second PI. Alternatively, ritonavir may inhibit subsequent metabolism of the second PI and increase trough concentrations of the second PI. The advantage of including ritonavir to the regimen is that it has the potential of reducing the daily medication burden load (e.g., once- or twice-daily dosing).

⁶⁴ Ibid.

⁶⁵ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

The use of PIs in HIV-infected individuals is often associated with non-adherence behaviors. Specifically, many PIs require multiple daily dosing of medications (e.g., three times-a-day regimens) and/or complex and burdening food constraints (e.g., nelfinavir is best absorbed when taken with fatty meals). Also, common side-effects associated with all PIs include lipid abnormalities (e.g., triglyceride level increases), body fat composition abnormalities, glucose intolerance, and to some degree, hepatotoxicity.

1.3.4 Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Based Regimens

The three NNRTIs currently approved by the FDA are nevirapine (Viramune®), delavirdine (Rescriptor®), and efavirenz (Sustiva®). NNRTIs in combination with NRTIs have been used in clinical trials and have shown strong clinical activity in antiretroviral-naïve individuals. Typically, an NNRTI is used in combination with two NRTIs to provide a PI-sparing combination.⁶⁶ No major clinical trials have compared and assessed the relative effectiveness of these three NNRTIs. The side-effect profile for some of these NNRTIs is similar to that of PIs. Conversely, nevirapine has been shown to decrease cholesterol and

⁶⁶ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

triglyceride levels, as well as increase HDL levels in patients who discontinued using PIs.⁶⁷

1.3.5 Triple Nucleoside Reverse Transcriptase Inhibitors (NRTI)-Based Regimens

Substantial evidence exists to support the use of triple NRTI regimens as an alternative to initial therapy although they are not routinely used in patients with high viral loads and low CD4 counts.⁶⁸ The side-effect profiles of these combinations are more favorable than many of the other regimens previously discussed. In addition, the twice-daily regimen and low pill burden of many triple-NRTI regimens are advantages of these regimens. Zidovudine (Retrovir®), lamivudine (Epivir®), abacavir (Ziagen®), didanosine (Videx®), stavudine (Zerit®), zalcitabine (Hivid®), tenofovir disoproxil fumarate (Viread®) are the most commonly prescribed NRTIs. The FDA announced in early July 2003, the approval of emtricitabine (Emtriva®), a new NRTI to be used in combination with other anti-retroviral agents for the treatment of patients with HIV infection.

1.3.6 PI/NNRTI-Based Regimens, With or Without NRTI

For patients who have advanced disease with opportunistic infections, as well as a high risk of mortality, regimens that include a PI, NNRTI and NRTI are

⁶⁷ Ibid.

⁶⁸ Ibid.

considered.^{69,70} These regimens are considered to rapidly restore immunological status. This combination of therapy is also used when other regimens have been unsuccessful (e.g., patients infected with a specific drug-resistant virus strain) in restoring immunological status and is commonly referred to as “salvage” therapy. The use of four-drug combinations from all three classes may have more potency than the three-drug combinations; however, these combinations may also expose the patient to problems of adherence and toxicity. In addition, this approach may exhaust future therapeutic options for patients if they develop cross-resistance to drugs from all three drug classes. However, the main disadvantage of using drug class-sparing options is the greater chance of incomplete viral suppression.

1.3.7 AIDS Clinical Trials Group and Choice of Initial Therapy

The AIDS Control Trials Group 384 (ACTG-384) was designed to address the best initial combination for antiretroviral-naïve patients.^{71,72,73} The study used

⁶⁹ Ibid.

⁷⁰ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

⁷¹ Smeaton LM, DeGruttola V, Robbins GK, Shafer RW. ACTG (AIDS Clinical Trials Group) 384: a strategy trial comparing consecutive treatments for HIV-1. *Controlled Clinical Trials* 2001;22(2):142-59.

⁷² Robbins GK, De Gruttola V, Shafer RW, Smeaton LM, Snyder SW, Pettinelli C, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *New England Journal of Medicine* 2003;349(24):2293-303.

⁷³ Robbins GK, Shafer RW, Smeaton LM, DeGruttola V, Pettinelli C, Snyder S, et al. Antiretroviral strategies in naive HIV+ subjects: comparison of sequential 3-drug regimens (ACTG 384). The XIV International AIDS Conference; 2002 July 7-12; Barcelon, Spain.

a factorial design to compare pairs of sequential three-drug regimens, starting with a regimen including zidovudine and lamivudine or a regimen including didanosine and stavudine in combination with either nelfinavir or efavirenz. The primary end point of the study was the length of time to the failure of the second three-drug regimen. Time to regimen failure was assessed as being the time to virologic failure, toxicity, or premature discontinuation. The results of the data demonstrate that patients who start with a combination of zidovudine, lamivudine and efavirenz (PI-sparing regimen) showed a significant delay to first and sequential regimen failure compared to treatment with a combination of either didanosine, stavudine and efavirenz (PI-sparing regimen) or didanosine, stavudine, and nelfinavir (NNRTI-sparing regimen). The authors could not rule out the possibility that a combination with a different protease inhibitor might have been more effective than zidovudine, lamivudine and efavirenz.

The authors of the study indicate that these findings might have been different had alternative three-drug combinations been investigated; therefore, the results cannot be extrapolated to regimens including other drugs from the same classes.

In a follow-up study, the ACTG group also investigated the time to regimen failure following the administration of three- and four-drug regimens to antiretroviral-naïve patients. Overall there were no significant differences in

endpoints between the two regimens.^{74,75,76} The differences in activity from the varying combinations of three- and four-drug regimens are often too small to document in clinical trials.

1.3.8 When to Initiate Therapy

The results from randomized clinical trials suggest that patients with CD4 counts less than 200 respond well to antiretroviral therapy. The optimal time to initiate therapy for asymptomatic patients with CD4 counts greater than 200 is a topic of much debate.⁷⁷ The decision to begin therapy in the asymptomatic patient with CD4 counts greater than 200 is complex. Clinicians need to assess the risks and potential benefits associated with initiating antiretroviral therapy (e.g., side-effects, adverse events and non-adherence), weigh the readiness of the patient to initiate treatment, and balance immune status and viral load when making decisions on the initiation of antiretroviral therapy.³ The use of viral load and immune status to guide the initiation of therapy for patients with CD4 counts

⁷⁴ Shafer RW, Smeaton LM, Robbins GK, De Gruttola V, Snyder SW, D'Aquila RT, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *New England Journal of Medicine* 2003;349(24):2304-15.

⁷⁵ Smeaton LM, DeGruttola V, Robbins GK, Shafer RW. ACTG (AIDS Clinical Trials Group) 384: a strategy trial comparing consecutive treatments for HIV-1. *Controlled Clinical Trials* 2001;22(2):142-59.

⁷⁶ Shafer RW, Robbins GK, Smeaton LM, DeGruttola V, Pettinelli C, Snyder S, et al. Antiretroviral strategies in naive HIV+ subjects: comparison of 4-drug versus sequential 3-drug regimens (ACTG 384). The XIV International AIDS Conference; 2002 July 7-12; Barcelona, Spain.

⁷⁷ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

greater than 200 is limited since there is an absence of data on clinical endpoints from randomized clinical trials.

Although randomized clinical trials have not been particularly helpful in assessing the impact of antiretroviral therapy in patients with baseline CD4 counts greater than 200, there is evidence from observational studies of untreated patients about the prognostic importance of viral load and CD4 count in the absence of treatment. These studies suggest that therapy should be initiated before the CD4 counts decline to below 200 to slow the progression to AIDS for untreated individuals. In the recent Multicenter AIDS Cohort Study, the three-year risk of progression to AIDS was 39 percent among patients with CD4 counts of 201-350 cells/ μ L compared to 14 percent for patients with CD4 counts greater than 350 cells/ μ L.⁷⁸ However, the risk of progression was also a function of the level of HIV-RNA and the risk is significantly lower in those with <20,000 copies/mL. Therefore, although observational studies of untreated patients do not assess the impact of antiretroviral therapy nor the optimal time to initiate therapy, they do provide information regarding the risk of progression in the absence of therapy.

Similarly, for patients on HAART, observational studies also provide information to guide the use of antiretroviral therapy in asymptomatic

⁷⁸ Ibid.

patients.^{79,80} An analysis of data from 13 cohort studies demonstrates that the three-year probability of progression to AIDS or death was 16 percent among those who initiated therapy with CD4 counts 0-49 cells/ μ L, 13 percent among those with CD4 counts 50-99 cells/ μ L, nine percent among those with CD4 counts of 100-199 cells/ μ L, five percent among those with CD4 counts of 200-349 cells/ μ L, and three percent among those with CD4 counts of 350 cells/ μ L or higher.⁸¹ Therefore, the impact of HAART on the prognosis in patients with CD4 counts greater than 200 is favorable. Also, patients with HIV-RNA levels greater than 100,000 copies per microliter had a considerably higher risk to progression to AIDS. In other cohort studies, HIV disease progression was significantly reduced in patients with CD4 counts greater than 350 cells/ μ L who were on therapy, compared to those who delayed therapy.^{82,83} One limitation of observational studies is the low level of disease progression during the follow-up

⁷⁹ Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *Journal of the American Medical Association* 2001;286(20):2568-77.

⁸⁰ Chen R, Westfall A, Cloud G, Chatham A, Acosta E, Raper J, et al. Long-term survival after initiation of antiretroviral therapy. 8th Conference on Retroviruses and Opportunistic Infections; 2001 February 4-8; Chicago, Ill.

⁸¹ Egger M. Prognosis of HIV-1 Infected Drug-Naive Patients Starting Potent Antiretroviral Therapy: Multi-Cohort Analysis of 12,040 Patients. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC 2001); 2001.

⁸² Kaplan J, Hanson D, Karon J, Cohn D, Thompson M, Buskin S. Early initiation of combination antiretroviral therapy (ART): Does it affect clinical outcome? XIII International Conference on AIDS; 2000; Durban, South Africa.

⁸³ Opravil M, Ledergerber B, Furrer H, Gallant S, Hirschel B, Meienberg F, et al. Clinical benefit of early initiation of HAART in patients with asymptomatic HIV infection and CD4 Counts >350. 8th Conference on Retroviruses and Opportunistic Infections; 2001.

period. Additionally, there may be significant group differences between the cohorts examined.

The potential benefits of early therapy include the early suppression of viral replication, preservation of immune function, longer survival times, and reductions in the risk of viral transmission. However, the risks of early therapy may include the adverse effects of drugs on quality-of-life, long-term non-adherence, development of drug resistance, and drug toxicities.⁸⁴

More recently, Wood et al. analyzed data from an observational study and concluded that baseline CD4 count did not increase mortality in an HIV-infected patient with good medication adherence and with a CD4 count greater than 200 cells/ μ L.⁸⁵ However, mortality rates increased if HAART was initiated in individuals with a CD4 count less than 200 cells/ μ L. Therefore, for individuals with CD4 cell counts greater than 200 cells/ μ L, medication adherence was the critical determinant of survival.

1.3.9 When to Change Therapy

Changing drugs in the absence of virological or immunological failure, as a result of incomplete adherence, adverse effects, or intolerance is common.

⁸⁴ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

⁸⁵ Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

Common adverse events including serum lipid abnormalities and lipodystrophy, often result in changes in therapy. Typically, as long as the antiviral activity of the overall regimen is maintained, clinicians often change individual components of the regimen. For example, substituting stavudine for zidovudine or nevirapine for efavirenz is common practice.

Therapy changes are also recommended for patients who have “failed” therapy. Treatment failure in the first year is common and well documented. Although treatment failures continue in subsequent years, the magnitude of treatment failure is less than in the first year.⁸⁶ According to Yeni et al., “the definition of treatment failure (an umbrella term representing virological, immunologic, or clinical failure) depends on the clinical setting and mirrors the objective of ongoing therapy at a given time in the patient’s treatment course.”⁸⁷ Viral response within the first eight weeks after the initiation of therapy is often used as an indicator of response to therapy. In settings where there are minimal resistant viral mutations, the goal of therapy is to achieve an undetectable viral load of less than 50 copies per milliliter. However, for patients who have experienced multiple treatment failures following adjustments in their antiretroviral regimens, the goal of achieving undetectable viral load is unrealistic.

⁸⁶ Chen R, Westfall A, Cloud G, Chatham A, Acosta E, Raper J, et al. Long-term survival after initiation of antiretroviral therapy. 8th Conference on Retroviruses and Opportunistic Infections; 2001 February 4-8; Chicago, Ill.

⁸⁷ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

In these situations, the goal of therapy is primarily to prevent clinical progression, and failure is defined as a decrease in CD4 cell count or the occurrence of an opportunistic infection.

Treatment failure has also been documented by determining the rates of treatment changes. The rates of combination antiretroviral treatment changes are high. A recent study assessed the extent of antiretroviral changes from an observational database.⁸⁸ Patients were categorized as receiving combination therapy if they received two or more antiretroviral drugs. Changes in combination therapy were identified when patients were started on one or more antiretroviral drugs not included in the immediately preceding combination. Combination regimens were also categorized into the following treatment classes: (1) an NRTI and/or PI but excluding NNRTIs; (2) an NNRTI and a PI; and (3) at least one NNRTI, but excluding PIs. The rate of combination change was calculated as the number of combination changes over the person years of follow-up. The Kaplan-Meier survival technique was used to measure the time to changing the first, second or third combination. Patients remained on their first combination for a median of 646 days. Out of the 596 patients, 322 started a second combination for a median period of 623 days. A total of 140 patients progressed to their third combination for a period of 392 days. The overall rate of antiretroviral change in the study was 0.45 combinations per year.

⁸⁸ Austin D, Baker D, Block M, Brown K, et al. Rates of combination antiretroviral treatment change in Australia, 1997-2000. *HIV Medicine* 2002;3(1):28-36.

In another study, the authors used a similar surrogate marker to document treatment failure; based on the Panel on Clinical Practices for Treatment of HIV Infection, a round of therapy “failed” when a patient was initiated on at least two new antiretroviral agents.⁸⁹ Typically, when an antiretroviral regimen “fails,” clinicians change at least two medications at the same time; in most situations clinicians change the entire regimen. In this study, computer simulation was used to extrapolate short-term survival data and provide estimates of long-term survival. The authors constructed a computer simulation model based on data from the Collaboration in HIV Outcomes Research-US (CHORUS) observational cohort, the published literature, and US Life Tables to estimate expected survival; the authors accounted for baseline CD4 cell count, progressive HAART treatment failure, progressive risk of HAART on treatment mortality, and age-associated mortality. Time to treatment failure for each of three rounds of HAART were modeled and risk of mortality on-treatment were estimated using parametric survival models with censoring of follow-up fit to CHORUS data. Off-treatment survival after HAART failure was estimated from the pre-HAART literature. Age-associated mortality was taken from US Life Tables. Median projected survivals stratified by baseline CD4 cell count subgroups were CD4 > 200 cells/mm³, 15.4 years; CD4 ≤200 cells/mm³, 8.5 years; and CD4 ≤ 50 cells/mm³,

⁸⁹ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

5.5 years. The following section presents the economic burden associated with HIV infection.

1.4 Financing HIV Care

In the early period of the pandemic, before the development of sensitive and reliable instruments to diagnose early infection, only symptomatic patients were seeking treatment; consequently, only patients with advanced disease presented to health care facilities. As a result, the estimates and projections of the costs for HIV/AIDS patients based on observed health care utilization were high. Scitovsky and Rice estimated the annual costs of AIDS care in the United States in 1985, 1986, and 1991 to be \$630 million, \$1.1 billion, and \$8.5 billion, respectively; these costs represented the direct and indirect costs of HIV infection.^{90,91,92} The financial burden HIV imposed on individuals was tremendous.

Since the beginning of the pandemic, economists have been faced with the challenge of evaluating the burden and cost of HIV/AIDS. Hardy et al. used a modeling approach to determine the economic impact following hospitalization

⁹⁰ Scitovsky AA, Rice DP. Estimates of the direct and indirect costs of acquired immunodeficiency syndrome in the United States, 1985, 1986, and 1991. *Public Health Reports* 1987;102(1):5-17.

⁹¹ Scitovsky AA. The economic impact of AIDS in the United States. *Health Affairs* 1988;7(4):32-45.

⁹² Scitovsky AA. Studying the cost of HIV-related illnesses: reflections on the moving target. *Milbank Quarterly* 1989;67(2):318-44.

for the “first” 10,000 patients diagnosed with AIDS in the United States.⁹³ The indirect costs associated with losses in productivity were estimated to be well over \$4.8 billion. The authors estimated that the average lifetime expenditures for hospitalizations for each patient were \$147,000. This estimate included the cumulative costs accrued from diagnosis to death.

The authors determined these costs by using estimates of the initial length-of-stay, the number of days hospitalized from initial hospitalization and death together with the daily charges for inpatient acute care. Since data on HIV/AIDS were scarce, the authors relied on several surveys to arrive at these estimates. For example, Hardy et al. calculated the initial length-of-stay for each patient by using unpublished results from three surveys conducted in New York City, Philadelphia, and San Francisco. The authors noted that the length-of-stay varied by geographic location and explained this variation by the differing patient management practices in the different geographic regions. The costs associated with the management of AIDS patients in New York were significantly higher than those in San Francisco. In particular, the authors cite the availability of non-hospital-based care in the San Francisco area. Also, there was a higher proportion of patients in the San Francisco area with a diagnosis of Kaposi’s sarcoma which can be treated on an outpatient basis. Hardy et al. reported that the CDC

⁹³ Hardy AM, Rauch K, Echenberg D, Morgan WM, Curran JW. The economic impact of the first 10,000 cases of acquired immunodeficiency syndrome in the United States. *Journal of the American Medical Association* 1986;255(2):209-11.

surveillance data indicated that there was a diagnosis of Kaposi's sarcoma in nine percent of New York patients compared to 35 percent in San Francisco patients. To account for the variation in the initial length-of-stay, the authors derived a weighted national average.

Hardy et al. also estimated median survival for the model using data from a sample of 1007 patients followed by the same group of clinicians. AIDS diagnoses were stratified into seven main categories and the median survival times were calculated for each category. The number of patients in each category was used to produce a weighted value for the median survival times for the seven categories. In the methodology section of the report, the authors interchangeably used reported survival time as a mean or median value; therefore, it was not clear whether survival was calculated as a mean or median value. Nevertheless, the estimated survival time for the cohort was 392 days. Subsequent hospital lengths-of-stay after the initial encounter were obtained from a survey administered to clinicians. Clinicians were asked to recall, estimate and indicate the percent of time from initial hospitalization until death that the patients spent in the hospital. Clinicians chose ranges for the estimates of the percentage of time spent in the hospital (i.e., 0%, 0-30%, 30-50%, and over 50%). Subsequently, the midpoint of each range was multiplied by the expected survival (392 days) to obtain the number of hospital days after initial hospitalization. For example, if a clinician recorded a patient as spending greater than 50 percent of the time in the hospital,

the total hospital days were calculated by multiplying the estimated survival time by 75 percent. Clinicians recorded their results on a total of 823 patients who survived their initial hospital stay from 1981 to 1984. The total inpatient days for initial and subsequent hospitalizations were calculated to be 168 days. Charges for inpatient stays were estimated at \$878, and were obtained from a review of 35 admissions at an acute hospital in the Atlanta area. No data were available for outpatient utilization and the results only represent inpatient utilization. Hardy et al. made a valiant attempt to describe the burden of illness of AIDS; nevertheless, there were a number of shortcomings apparent by the methodologies used to estimate the costs and utilization patterns.

Scitovsky et al. also conducted a study to estimate the economic impact of AIDS in a group of patients in San Francisco.⁹⁴ They used primary data to arrive at a more representative description of health care utilization. For example, the number of inpatient-days was obtained from chart review and a mean daily charge was estimated from administrative records. The mean charges per AIDS hospital admission were \$9,024 and the mean charges of patients with AIDS who received all their hospital inpatient and outpatient care at San Francisco General Hospital in 1984 ranged from \$7,026 to \$23,425. The authors also calculated the mean lifetime inpatient charges of patients with AIDS who died and who had received all their inpatient care at the hospital to be \$27,571. These charges were lower

⁹⁴ Scitovsky AA, Cline M, Lee PR. Medical care costs of patients with AIDS in San Francisco. *Ibid.*;256(22):3103-6.

than previously published estimates of lifetime medical care costs of patients with AIDS, and the possible reasons for the differences include lower lifetime use of hospital services and the lower cost per hospital day. The sample size (n=85) for the estimates described in the study was small. In addition, the authors collected limited outpatient data and it was difficult to determine the specific costs that were collected. Also, the authors assumed that no additional care was obtained in other institutions.

Seage et al. also conducted an investigation to document the cost of AIDS.⁹⁵ They assessed inpatient care for 45 AIDS patients at the New England Deaconess Hospital for a period of one year. They also assumed that patients received all their care at the hospital. Again, this may underestimate the true utilization patterns. Since there was variation in the length of time for data collection in the 45 patients, the authors decided to calculate an annualized estimate for hospital inpatient stay of 62 days per person per year. Charge data were converted to cost data using charge/cost ratios from the Massachusetts Rate Setting Commission. As a result, an annual estimated cost of \$42,517 was calculated.

Many of the early reports of the economic impact of HIV infection focused on assessing the cost of patients diagnosed with AIDS. Very little information was available for patients with HIV infection without AIDS.

⁹⁵ Seage GR, 3rd, Landers S, Barry A, Groopman J, Lamb GA, Epstein AM. Medical care costs of AIDS in Massachusetts. *Ibid.*:3107-9.

Therefore, the economic impact of HIV-infection may not be accurately captured in these earlier studies. In the early years of the pandemic, patients presented to hospitals at the later stages of HIV infection; as a result, minimal data for HIV-infected patients without AIDS were available. In fact, Scitovsky acknowledged that “serious gaps in our knowledge remain.” Specifically, he described the inadequacies of the then current data on the number of persons with AIDS and especially on the number of persons infected with HIV. Scitovsky described the “inadequacies and limitations of the data on the medical care costs of persons with AIDS, as well as the almost total lack of data on the number of persons infected with HIV with symptoms and conditions other than AIDS and their medical care costs.”⁹⁶ Calculating the pandemic's costs was difficult.

Also, as noted earlier, many of the studies failed to incorporate estimates of outpatient care in their determination of health care utilization. Furthermore, it was not clear whether or not researchers included both inpatient and outpatient medications in their analyses. It is likely that the estimates of inpatient utilization included medications prescribed as an inpatient; however, it is unlikely that the costs and utilization of outpatient pharmacy encounters were captured. Equally important, many of the earlier studies used “costs” and “charges” interchangeably; data using “charges” may not accurately reflect true costs.

⁹⁶ Scitovsky AA, Rice DP. Estimates of the direct and indirect costs of acquired immunodeficiency syndrome in the United States, 1985, 1986, and 1991. *Public Health Reports* 1987;102(1):5-17.

Drummond and Davies also argued that there may have been incorrect estimates of the survival times and costs in all these early studies since there were no explicit adjustments made for disease severity.⁹⁷ Green et al. also critiqued the methodology of the study conducted by Hardy and his colleagues.⁹⁸ Specifically, Green et al. argue that using a single estimate of lifetime survival (392 days) led to an overestimation of the total inpatient hospital days. The authors postulated that Hardy and his colleagues assumed that all patients spending 75 percent of their time in the hospital lived on average 392 days. This may not describe actual utilization patterns since those spending more time in the hospital may have been sicker and their average survival may have been shorter.

In response to the early reports on the costs of AIDS, researchers, public health officials and other policy makers at the state and federal level, sought more data on the economic impact of AIDS. The CDC was actively collecting and estimating epidemiological data to better understand and characterize the impact of AIDS. Scitovsky and Rice incorporated prevalence data from the CDC in their estimates of the projected cost of AIDS in 1985, 1986 and 1991.^{99,100} These costs included direct and indirect costs of AIDS and the authors conducted sensitivity

⁹⁷ Drummond M, Davies L. Treating AIDS: the economic issues. *Health Policy* 1988;10(1):1-19.

⁹⁸ Green J, Oppenheimer GM, Wintfeld N. The \$147,000 misunderstanding: repercussions of overestimating the cost of AIDS. *Journal of Health Politics, Policy & Law* 1994;19(1):69-90.

⁹⁹ Scitovsky AA, Rice DP. Estimates of the direct and indirect costs of acquired immunodeficiency syndrome in the United States, 1985, 1986, and 1991. *Public Health Reports* 1987;102(1):5-17.

¹⁰⁰ Scitovsky AA, Rice DP. Estimates of the direct and indirect costs of acquired immunodeficiency syndrome in the United States, 1985, 1986, and 1991. *Journal of Medical Practice Management* 1988;3(4):234-41.

analyses on their costs estimates to determine the best- and worst-case scenarios. The authors projected that the personal medical care costs of AIDS would rise from \$630 million in 1985 to \$1.1 billion in 1986 and \$8.5 billion in 1991. In addition, the indirect costs attributable to loss of productivity resulting from morbidity and premature mortality were estimated to rise from \$3.9 billion in 1985 to \$7.0 billion in 1986 to \$55.6 billion in 1991. The authors used the human capital approach to estimate indirect costs. Estimates of personal medical care costs were calculated using data from various sources around the US. Scitovsky and Rice compared their estimates of the burden of AIDS in the US with the 1985 estimates of the medical care costs for end-stage renal disease (\$2.2 billion), traffic accidents (\$5.6 billion), lung cancer (\$2.7 billion) and breast cancer (\$2.2 billion).

Hellinger also conducted studies to project the costs of AIDS; however, Hellinger developed a model that estimated the direct costs of AIDS using incidence-based measures derived from the CDC.^{101,102} Hellinger's findings were similar to those by Scitovsky and Rice; however, Hellinger included the costs of outpatient antiretroviral medications. In this study, Hellinger projected the economic impact of AIDS from 1985 to 1988. In his analyses, Hellinger included persons who were HIV-infected as well as those who were diagnosed with AIDS.

¹⁰¹ Hellinger FJ. Forecasting the personal medical care costs of AIDS from 1988 through 1991. *Public Health Reports* 1988;103(3):309-19.

¹⁰² Hellinger FJ. National forecasts of the medical care costs of AIDS: 1988-1992. *Inquiry* 1988;25(4):469-84.

Hellinger also updated his lifetime estimates and made projections from 1991 to 1994.¹⁰³ These cost estimates were projected to rise from \$5.8 billion in 1991, to \$10.4 billion in 1994. Shortly after publishing these findings, Hellinger re-projected the economic impact of AIDS to account for the high costs of antiretroviral therapy. These revised cost estimates projected a rise in costs from \$10.3 billion in 1992, to \$15.2 billion in 1995.¹⁰⁴

Since FDA approval of zidovudine in 1987, morbidity and mortality have continued to fall. However, the high costs of newer drugs used in patients with HIV, as well as the increased life expectancy of patients with HIV are continuing to drive the overall health care costs associated with HIV infection. In addition, the new combination drug regimens, which are quickly becoming the drug regimen of choice for patients with HIV, are driving the overall health care costs even higher. Furthermore, before the advent of new therapies, antiretroviral therapy was not initiated in many patients until their CD4 counts dropped below 200 cells per milliliter. This is no longer the case and antiretroviral therapy is initiated much earlier. The newly developed antiretroviral drugs are expensive. For example, the average wholesale price of a monthly (30-day) supply of the protease inhibitors ranges from \$546 to \$1347 (Table 1-3).

¹⁰³ Hellinger FJ. Forecasting the medical care costs of the HIV epidemic: 1991-1994. *Inquiry* 1991;28(3):213-25.

¹⁰⁴ Hellinger FJ. Forecasts of the costs of medical care for persons with HIV: 1992-1995. *Inquiry* 1992;29(3):356-65.

Table 1-3: Generic Name, Brand Name, Dosage, and Average Wholesale Price of Antiretroviral Drugs Licensed in the US in December 2002

Generic	Brand	Dosage (mg)	Monthly AWP (\$US) ¹⁰⁵
Nucleoside Reverse Transcriptase Inhibitors			
Zidovudine	Retrovir	300 bid	369
Didanosine	Videx EC	250 od	205
Zalcitabine	Hivid	0.75mg tid	246
Stavudine	Zerit	30 bid	351
Lamivudine	Epivir	150 bid	316
Abacavir Sulfate	Ziagen	300 bid	425
Lamivudine/Zidovudine	Combivir	150/300 bid	685
Abacavir/Lamivudine/Zidovudine	Trizivir	300/150/300 bid	1110
Tenofovir	Viread	300 od	456
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine	Rescriptor	3 X 200 tid	474
Nevirapine	Viramune	200 bid	405
Efavirenz	Sustiva	3 X 200 od	445
Protease Inhibitors			
Saquinavir	Invirase	6 X 200 tid	1347
Indinavir	Crixivan	2 X 400 tid	546
Ritonavir	Norvir	6 X 100 bid	772
Nelfinavir	Viracept	3 250 tid	680
Saquinavir	Fortovase	6 X 200 tid	751
Amprenavir	Agenerase	6 X 150 bid	551
Lopinavir/Ritonavir	Kaletra	3 X 133/33 bid	704

AWP = Average Wholesale Price; **bid** = twice daily; **od** = once daily; **tid** = three times daily

1.4.1 Monthly Costs of HIV/AIDS Treatment

In 1993, Hellinger investigated treatment patterns and costs during the first six months of 1992 using four stages of HIV illness.¹⁰⁶ The four stages of illness categorized by Hellinger were: (1) AIDS [1987 definition]; (2) HIV infection without AIDS with a CD4 cell count less than 200; (3) HIV infection without AIDS with a CD4 count of 200 or higher and less than 500; and (4) HIV

¹⁰⁵ *Red Book*. Montvale, NJ: Medical Economics Company, 2002.

¹⁰⁶ Hellinger FJ. The lifetime cost of treating a person with HIV. *Journal of the American Medical Association* 1993;270(4):474-8.

infection without AIDS with a CD4 count of 500 or higher. The estimated monthly cost of treating a person with AIDS was \$2,764, and more than two thirds of this cost was attributable to inpatient costs (Table 1-4). Drugs accounted for only 10 percent and outpatient costs accounted for about 14 percent of monthly costs.

Table 1-4: Estimates of the Monthly Costs of Treating a Person with AIDS (1987 definition)

Category	Cost (\$)	Percent
Inpatient	1,890	68
Outpatient	380	14
Drugs	265	10
Home Health	174	6
Long-Term Care	55	2
Total	2,764	100

From 1993 to 1996, studies have shown costs similar to those presented by Hellinger. However, a 1997 study showed that the monthly costs due to HIV were significantly greater than previously recorded.¹⁰⁷ This could have coincided with the approval of more antiretroviral drugs by the FDA. In this study, the authors estimated that the monthly costs of treating a person with AIDS was \$3,797. This increase in costs reflects an additional \$1,033 for monthly drug costs with current treatment guidelines. Another study by Holtgrave et al.

¹⁰⁷ Haburchak DR. The economics of AIDS in America. *The AIDS Reader* 1997;7(5):155-60.

demonstrated that the introduction of PIs has also increased the monthly costs of caring for AIDS patients depending on the level of access to care; the monthly costs ranged from \$3,274 to \$4,087.¹⁰⁸

Since the introduction of PIs in 1996, there are two trends that have been reported for the monthly costs of treating persons with AIDS: (1) an increasing proportion of the total costs attributable to drug therapy; and (2) a decreasing proportion of costs attributable to hospitalization. Two studies illustrate these trends. The first, a 1997 study of Maryland Medicaid paid claims, indicated that inpatient hospital costs accounted for 56 percent of the total costs and drug costs accounted for 21 percent.¹⁰⁹ The second, a study by Gable et al., used an expert panel to produce treatment protocols for opportunistic infections and primary antiretroviral therapy.¹¹⁰ Based on these treatment protocols, Gable et al. then estimated the monthly cost of treating a person with HIV disease as \$2,103 and drug costs accounted for 38 percent of the total monthly costs of treating a person with HIV disease. These costs were estimated for individuals who had a CD4 count equal to or below 50 cells/ μ L. They also estimated rates of opportunistic infections based on each of the four stages of HIV illness using CD4 cell counts.

¹⁰⁸ Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;16(1):54-62.

¹⁰⁹ Moore RD, Chaisson RE. Costs to Medicaid of advancing immunosuppression in an urban HIV-infected patient population in Maryland. *Ibid.*;14(3):223-31.

¹¹⁰ Gable CB, Tierce JC, Simison D, Ward D, Motte K. Costs of HIV+/AIDS at CD4+ counts disease stages based on treatment protocols. *Ibid.*1996;12(4):413-20.

Therefore, the costs represented recommended treatment and not the actual experience/treatment of patients.

In 2001, Beck et al. reviewed the costs of HIV treatment and care.¹¹¹ The review documented three studies that assessed the costs of HIV/AIDS therapy since the introduction of PIs. The authors reported that the costs of treating individuals with AIDS have remained constant compared to pre-PI periods; Beck et al. document that the cost of a patient-year of HIV treatment in the period after the introduction of protease inhibitors was \$35,900, which was marginally greater than previous estimates. However, the cost of treating persons with asymptomatic or symptomatic non-AIDS has increased over time. A plausible reason for these differences, as suggested by Beck et al., is that individuals diagnosed with asymptomatic and symptomatic non-AIDS are now receiving earlier and more intensive treatment.

1.4.2 Lifetime Costs of HIV/AIDS Treatment and the Cost-Effectiveness of Antiretrovirals

The lifetime costs of treating a person with HIV have been estimated by Hellinger.^{112,113,114,115} Hellinger determined the average time patients infected

¹¹¹ Beck EJ, Miners AH, Tolley K. The cost of HIV treatment and care. A global review. *Pharmacoeconomics*. 2001;19(1):13-39.

¹¹² Hellinger F. The use of health services by women with HIV infection. *Health Services Research* 1993;28(5):543-61.

¹¹³ Hellinger FJ. The lifetime cost of treating a person with HIV. *Journal of the American Medical Association* 1993;270(4):474-8.

with HIV spent in the four different disease stages and the monthly costs associated with each stage. Using 1992 data from the AIDS Cost and Service Utilization Survey (ACSUS), the lifetime costs were found to be \$119,000 over 12.4 years.¹¹⁶ As noted earlier, Gable et al. estimated the lifetime costs of treating persons with HIV to be \$94,726, using an expert panel to produce treatment protocols for opportunistic infections and primary antiretroviral therapy. They based their lifetime costs on utilization rates from the published literature, surveys, Medicare fee schedules, and insurance databases. Drug costs were based on average wholesale prices and non-HIV-related care was not included in the estimation of costs. Holtgrave and Pinkerton estimated the lifetime costs after the diffusion of new combination therapies.¹¹⁷ Their lifetime estimates, based on an expert international panel, ranged from \$71,143 to \$424,763; the ranges reflected different levels of access to care. Holtgrave and Pinkerton also discounted the costs of care.

Moore and Chaisson used a Markov model to estimate the lifetime costs for 606 Maryland Medicaid patients; their estimated total payment to providers

¹¹⁴ Gable CB, Tierce JC, Simison D, Ward D, Motte K. Costs of HIV+/AIDS at CD4+ counts disease stages based on treatment protocols. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1996;12(4):413-20.

¹¹⁵ DeGraeve D, Lescauwae B, Nonneman W. Patient classification and cost analysis of AIDS and HIV: The case of Belgium. *Health Policy*. 1997;39:93-106.

¹¹⁶ Hellinger FJ. The lifetime cost of treating a person with HIV. *Journal of the American Medical Association* 1993;270(4):474-8.

¹¹⁷ Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;16(1):54-62.

was \$133,000.¹¹⁸ The authors included all HIV-related and non-HIV-related inpatient care, outpatient clinic visits, pharmacy costs, and home health care costs in their analyses. Using a cohort of 128 HIV-infected individuals, Hurley et al. reported the estimates of care from seroconversion to death.¹¹⁹ The goal of the study was to estimate the lifetime costs of health care for HIV infection. Data on the monthly cost of HIV-related health care for homosexual men were linked with published data on disease progression using survival analysis methods. Future costs were discounted at five percent per annum. For a patient diagnosed with a CD4 count below 500, the average present value in 1992 to 1993 of the lifetime cost was approximately \$93,000. These estimates were lower than the lifetime cost of \$119,000 reported in the US by Hellinger et al. The differences in costs in the two studies could be explained by: (1) the inclusion of non-HIV care in the study by Hellinger et al.; and (2) the different discounting rates applied to costs in the studies.

A review of the literature on the cost-effectiveness of antiretrovirals indicates that several of the studies were conducted in the era before the use of HAART in HIV-infected individuals.^{120,121,122} Oddone et al. investigated the

¹¹⁸ Moore RD, Chaisson RE. Costs to Medicaid of advancing immunosuppression in an urban HIV-infected patient population in Maryland. *Ibid.*;14(3):223-31.

¹¹⁹ Hurley SF, Kaldor JM, Gardiner S, Carlin JB, Assuncao RM, Evans DB. Lifetime cost of human immunodeficiency virus-related health care. *Ibid.*1996;12(4):371-8.

¹²⁰ Paltiel AD, Kaplan EH. Modeling zidovudine therapy: a cost-effectiveness analysis. *Journal of Acquired Immune Deficiency Syndromes* 1991;4(8):795-804.

economic impact of early and late use of zidovudine.¹²³ The authors reported that the cost-effectiveness of early treatment with zidovudine was \$5,432 for each extra month without AIDS. Moore et al. reported that the median incremental charge per year of life gained in zidovudine users was \$34,600 compared with nonusers.¹²⁴

More recently, cost-effectiveness analyses have been conducted to reflect the economic impact of HAART. Recent studies have found that HAART decreases mortality and morbidity of HIV disease as well as reduces HIV-related health care utilization.^{125,126,127,128,129,130} Miners et al. assessed the cost-

¹²¹ Oddone EZ, Cowper P, Hamilton JD, Matchar DB, Hartigan P, Samsa G, et al. Cost effectiveness analysis of early zidovudine treatment of HIV infected patients. *British Medical Journal* 1993;307(6915):1322-5.

¹²² Moore RD, Hidalgo J, Bareta JC, Chaisson RE. Zidovudine therapy and health resource utilization in AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1994;7(4):349-54.

¹²³ Oddone EZ, Cowper P, Hamilton JD, Matchar DB, Hartigan P, Samsa G, et al. Cost effectiveness analysis of early zidovudine treatment of HIV infected patients. *British Medical Journal* 1993;307(6915):1322-5.

¹²⁴ Moore RD, Hidalgo J, Bareta JC, Chaisson RE. Zidovudine therapy and health resource utilization in AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1994;7(4):349-54.

¹²⁵ Keiser P, Nassar N, Kvanli MB, Turner D, Smith JW, Skiest D. Long-term impact of highly active antiretroviral therapy on HIV-related health care costs. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2001;27(1):14-9.

¹²⁶ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

¹²⁷ Freedberg KA, Goldie SJ, Paltriel AD. Combination antiretroviral therapy is both effective and cost-effective [abstract no. 2070]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco, CA.

¹²⁸ Mauskopf J, Lacey L, Kempel A, Simpson K. The cost-effectiveness of treatment with lamivudine and zidovudine compared with zidovudine alone: a comparison of Markov model and trial data estimates. *American Journal of Managed Care* 1998;4(7):1004-12.

¹²⁹ Riseborough N, Oh P, Rachlis A. Economic evaluation of triple ART with indinavir or abacavir and ZDV+3TC compared to dual therapy ZDV+3TC (Abstract no. 103). 6th Conference on Retroviruses and Opportunistic Infection; 1999 Jan 31 -Feb 4; Chicago, IL.

¹³⁰ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

effectiveness of HAART and dual NRTI therapy for adults in England using Markov transitions.¹³¹ The authors estimated the lifetime costs following dual NRTI therapy and HAART to be £77,135 and £119,190, respectively. HAART produced an incremental cost-effectiveness ratio of £14,602 per life-year saved and £17,698 per quality adjusted life-year saved. Chancellor et al. also conducted a similar study modelling the cost-effectiveness of dual therapy versus monotherapy.¹³² The researchers estimated the relative risk of progression through the different stages using dual therapy compared to monotherapy. These estimates were derived from a published meta-analysis of clinical trials. The data from the cohort treated at Chelsea and Westminster Hospital were extrapolated using Markov modelling to estimate the costs and lifetime expectancy after a period of 20 years. On the basis of an estimated relative risk of progression of 0.509, treatment with dual therapy was predicted to yield an incremental cost-effectiveness ratio of £6276 per life-year saved. The expected lifetime costs per patient for dual therapy and monotherapy were £50,551 and £44,612, respectively. Treatment with dual therapy yielded an incremental cost-

¹³¹ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

¹³² Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

effectiveness ratio of £6,276 per life-year saved. Also, Gebo et al. found that HAART had enormous clinical benefits at no additional cost.¹³³

In addition, other studies document the cost-effectiveness of specific HAART combination regimens.^{134,135} Velasco et al. concluded that PI-containing regimens were highly cost-effective when they examined a cohort of patients before and after the PI-containing regimens were introduced.¹³⁶ Nevertheless, the newly developed antiretroviral drugs are expensive.

In the past, comparing and interpreting the results of cost-effectiveness studies have been difficult for a number of reasons: (1) studies provide different outcome measures for estimating the effectiveness of interventions; (2) cut-off values for cost-effectiveness ratios vary; and (3) there have been few guidelines and little standardization of the appropriate and necessary costs to be included in economic evaluations. The following section presents the relationship between demographic composition and HIV-related costs.

¹³³ Gebo KA, Chaisson RE, Folkemer JG, Bartlett JG, Moore RD. Costs of HIV medical care in the era of highly active antiretroviral therapy. *Acquired Immune Deficiency Syndromes* 1999;13(8):963-9.

¹³⁴ Keiser P, Kvanli MB, Turner D, Reisch J, Smith JW, Nassar N, et al. Protease inhibitor-based therapy is associated with decreased HIV-related health care costs in men treated at a Veterans Administration hospital. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1999;20(1):28-33.

¹³⁵ Velasco M, Gomez A, Fernandez C, Perez-Cecilia E, Tellez MJ, Roca V, et al. Economic impact of HIV protease inhibitor therapy in the global use of health-care resources. *HIV Medicine* 2000;1(4):246-51.

¹³⁶ Ibid.

1.4.3 Demographics and Their Impact on the Costs of HIV/AIDS

The changing demographics of those infected with the virus are also contributing to the burden and costs of AIDS. Race, gender, and intravenous drug-use have been found to be related to the costs of treating persons with HIV. Socio-demographic differences were found to exist in the access and use of prescription drugs within the 1992 ACSUS cohort.^{137,138,139} The results suggest that women and those aged between 15 and 24 years have poor access to some medications that improve survival in HIV disease. In the 1990 Boston Health Study, females with HIV disease spent an average of 10.8 hospital days compared to men who spent 14.2 hospital days.¹⁴⁰ Consequently, females with HIV disease were found to consume fewer resources and were less costly to treat than males. The authors remarked that these differences may also be related to differential access to HIV-related therapies in the two populations. Also, another study reported that individuals with AIDS who used intravenous drugs had 42 percent longer lengths-of-stay and had 38 percent higher costs per hospitalization,

¹³⁷ Hellinger F. The use of health services by women with HIV infection. *Health Services Research* 1993;28(5):543-61.

¹³⁸ Smith SR, Kirking DM. Access and use of medications in HIV disease. *Ibid.* 1999;34(1Pt1):123-44.

¹³⁹ Smith SR, Kirking DM. The effect of insurance coverage changes on drug utilization in HIV disease. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2001;28(2):140-9.

¹⁴⁰ Epstein AM, Seage G, 3rd., Weissman JS, Cleary PD, Fowler F, Gatsonis C, et al. Costs of medical care and out-of-pocket expenditures for persons with AIDS in the Boston Health Study. *Inquiry* 1995;32(2):211-21.

compared to individuals with AIDS who did not use intravenous drugs. No significant differences in health care utilization were observed in men and women.¹⁴¹ The ACSUS also showed similar findings.^{142,143}

Data from ACSUS and Boston Health Study also showed that there were differences in health care utilization between different ethnic and socio-economic groups. Caucasian patients were found to use fewer resources than non-Caucasian patients.¹⁴⁴ Most of the data indicated that the average number of hospital days in the non-Caucasian groups was greater than that of the Caucasian group. Conversely, two studies by Palella et al. and Denning (Viral Load Surveillance Project) revealed that gender and race were not related to a patient's likelihood of receiving PIs or to the rates of morbidity and mortality.^{145,146} However, data from the Viral Load Surveillance Project found that females, African Americans, and injection drug users had poorer access to viral load tests.

¹⁴¹ Seage GR, Hertz T, Stone VE, Epstein AM. The effects of intravenous drug use and gender on the cost of hospitalization for patients with AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1993;6(7):831-9.

¹⁴² Hellinger F. The use of health services by women with HIV infection. *Health Services Research* 1993;28(5):543-61.

¹⁴³ Smith SR, Kirking DM. Access and use of medications in HIV disease. *Ibid.* 1999;34(1Pt1):123-44.

¹⁴⁴ Moore RD, Stanton D, Gopalan R, Chaisson RE. Racial differences in the use of drug therapy for HIV disease in an urban community. *New England Journal of Medicine* 1994;330(11):763-8.

¹⁴⁵ Denning EH. Beyond Clinical Trials--Population-Based HIV Viral Load Monitoring and Antiretroviral Therapy. Fifth Conference on Retroviruses and Opportunistic Infections; 1998; Chicago, Ill.

¹⁴⁶ Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *New England Journal of Medicine* 1998;338(13):853-60.

Privately insured patients were found to have lower mortality and morbidity and better access to drug therapies and viral load tests.

Race, ethnicity, and risk behavior profiles for persons with HIV have changed in recent years. The proportion of whites with HIV has dropped and the proportion of blacks and Hispanics has increased. In just over a decade, the proportion of all AIDS cases reported among adult and adolescent women more than tripled, from 7 percent in 1985 to 23 percent in 1999. The epidemic has increased most dramatically among women of color; African American and Hispanic women together represent less than one-fourth of all US women, yet in 2002, they accounted for more than three-fourths (77%) of AIDS cases reported to the CDC. In 2002, the CDC estimated that there are between 120,000 and 160,000 adult and adolescent females living with HIV infection in the US. The proportion of HIV among males having sex with males has also dropped. Patients who are black, Hispanic and injection drug users are more likely to have public insurance. As a result, this has placed a tremendous financial burden on federal, state and local agencies.

1.4.4 Public Funding of HIV/AIDS Treatment Programs

The costs of antiretrovirals are high and it has been estimated that only 10 percent of those infected with HIV worldwide can afford combination therapies. Medicaid currently covers almost half of persons living with HIV/AIDS in the

US. The extent of coverage by managed care Medicaid plans is state specific. In 1997, over 20 percent of persons with AIDS were not covered by private, state or federal insurance programs.

In order to alleviate the financial burden of HIV-related costs, soon after the approval of zidovudine in 1987, Congress appropriated funds for states to establish state-administered AIDS Reimbursement Programs to assist low-income individuals in gaining access to zidovudine therapy. In 1990, the Ryan White Comprehensive AIDS Resource Emergency (CARE) Act was passed. The AIDS Drug Assistance Programs are authorized to provide access to HIV medications for low-income, uninsured and underinsured individuals.¹⁴⁷ Since most of the people with HIV disease depend on public sources to pay for needed services, those who are responsible for allocating funds thereby require accurate, comprehensive, and timely information about the cost of treating people with HIV disease.

Not surprisingly, public insurers reimburse less than private insurers for most physician and hospital services. The Physician Payment Review Commission, now the Medicare Payment Advisory Commission, estimated that in 1993, Medicare paid physicians about 60 percent of what private insurers paid and Medicaid paid only 43 percent. These differences were not as great for hospital services. In recent years, Medicaid has been moving patients into

¹⁴⁷ Smith SR, Buchanan RJ. The AIDS drug assistance programs and coverage of HIV-related medications. *The Annals of Pharmacotherapy* 2001;35(2):155-66.

managed care plans and some states have designated a specific monthly rate to be paid to the managed care organizations. Rates in Maryland are set using the Ambulatory Care Group methodology with special capitation rates for persons living with AIDS.¹⁴⁸ Average payment for enrollees with AIDS was about \$2,400 per member per month in 2001.¹⁴⁹

These rates do not include protease inhibitors, other newly approved drugs to treat HIV disease, diagnostic tests such as viral load tests, and mental health services. These services are reimbursed on a fee-for-service basis. These arrangements are also available in the California and Massachusetts Medicaid programs. Many State Medicaid plans are now collaborating with managed care plans to establish special rates for persons with HIV disease and these rates must be based on data reflecting the current costs of care. These rates will need to be updated regularly to reflect the changes in treatment.

The economic burden of the early and continuous use of expensive antiretroviral therapies by increasing numbers of persons with HIV disease, who previously were not receiving antiretroviral drug therapy, is not well understood because there are few comprehensive assessments of the cost and financing of care for persons with HIV disease. Nevertheless, the adoption of costly, new drug therapies among persons with HIV disease in addition to the increasing number of

¹⁴⁸ Fakhraei SH, Kaelin JJ, Conviser R. Comorbidity-based payment methodology for Medicaid enrollees with HIV/AIDS. *Health Care Financing Review* 2001;23(2):53-68.

¹⁴⁹ Ibid.

persons living with HIV disease indicate that the cumulative cost of treating HIV disease is rising steeply. Information on the cost of treatment and care for persons with HIV enables assessment of the economic impact of the disease on health care systems to be made and the affordability of new and existing interventions to be assessed. These assessments also provide a basis for health care resource planning and the identification of resource requirements for HIV service provision. Credible estimates of the cost of treating all people with HIV disease must be made available to aid federal, state, and local policy makers.

1.5 Methodologies of Previous and Recent HIV-Costing Studies

Determining health care utilization and the direct costs of providing medical care to patients with HIV/AIDS is important for long- and short-term decision making. The continuous monitoring of health care resource use is essential if accurate projections of the impact of the pandemic are required. Determining the economic impact of the HIV pandemic is difficult; the changing nature of the pandemic, the management of the disease with HAART, and the frequent adjustments in treatment protocols mandates the continuous monitoring and assessment of resource use to accurately project the economic impact of the disease. Accurate projections are needed to support and inform decision makers on both the optimal care and prevention-related activities that warrant funding. Although many studies have previously examined the direct costs of HIV care,

there is significant variation in the methodology and the extent of costs examined. For example, studies vary in the time-frame of analysis, the extent and categories of health care costs assessed (e.g., inpatient, outpatient, home-based, nursing home, and medications) and the methodologies used for data collection (e.g., self-report, chart reviews, and administrative databases). Also, many studies report costs that are old and may not reflect current treatment needs or practices.

Graves and his colleagues recently published a review of the quality of 45 health economics studies conducted alongside randomized controlled trials.¹⁵⁰ Graves et al. examined the perspectives of the cost analyses, the methods used to determine health care utilization, and how the cost data were reported. Graves et al. concluded that there were few good quality costing studies and that there is greater need for rigor when conducting health economic analyses.¹⁵¹ Graves et al. reported that the majority of researchers adjust for the lack of methodological rigor of costing studies with statistical techniques. However, Graves et al. argue that for the results of clinical studies to be valid, both cost determination methods and the methods used for the statistical analysis of cost data should be of high quality. It is difficult to collect current data; therefore, many studies report costs that do not reflect current needs or trends. Furthermore, the lack of comprehensive costing data systems prohibits the research community and health

¹⁵⁰ Graves N, Walker D, Raine R, Hutchings A, Roberts JA. Cost data for individual patients included in clinical studies: no amount of statistical analysis can compensate for inadequate costing methods. *Health Economics* 2002;11(8):735-9.

¹⁵¹ Ibid.

care policy makers from accurately assessing health care costs.^{152,153,154,155,156,157}

Also, many estimates of the lifetime cost of treating a person with HIV disease exclude the cost of new drug combinations, the cost of monitoring the impact of these drugs (i.e., the cost of viral load assays), and the cost of treating their side effects. Also, many estimates understate the survival period for persons with HIV.

An example of a high quality study is that of Krentz et al. who recently calculated the direct costs of providing care to persons infected with HIV.¹⁵⁸ The authors followed 662 individuals enrolled in the Southern Alberta HIV Clinic from 1995 to 2001. In a concerted effort to accurately estimate health care utilization, Krentz et al. followed the methodologies recommended by Tolley et al. and Graves et al. to identify and evaluate all health-related costs.^{159,160} Direct

¹⁵² Keiser P, Nassar N, Kvanli MB, Turner D, Smith JW, Skiest D. Long-term impact of highly active antiretroviral therapy on HIV-related health care costs. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2001;27(1):14-9.

¹⁵³ Bozzette SA, Joyce G, McCaffrey DF, Leibowitz AA, Morton SC, Berry SH, et al. Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. *New England Journal of Medicine* 2001;344(11):817-23.

¹⁵⁴ Wallace MR, Tasker SA, Shinohara YT, Hill HE, Chapman GD, Miller LK. The changing economics of HIV care. *AIDS Patient Care & Sexually Transmitted Diseases* 2001;15(1):25-9.

¹⁵⁵ Roberts R, Rydman R, Gorosh K, Weinstein R. Actual Costs of HIV/AIDS Care [abstract 498]. 8th Conference on Retrovirus and Opportunistic Infections; 2001 Feb 4-8; Chicago, Ill.

¹⁵⁶ Anis AH, Hogg RS, Yip B, Wang XH, Montaner JS, O'Shaughnessy MV, et al. Average annual drug cost and its determinants in a population based cohort of HIV-positive adult men and women. *Pharmacoeconomics* 1998;13(3):327-36.

¹⁵⁷ Youle M, Trueman P, Simpson K. Health economics in HIV disease. A review of the european literature. *Ibid.* 1999;1:1-12.

¹⁵⁸ Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

¹⁵⁹ Graves N, Walker D, Raine R, Hutchings A, Roberts JA. Cost data for individual patients included in clinical studies: no amount of statistical analysis can compensate for inadequate costing methods. *Health Economics* 2002;11(8):735-9.

costs were divided into four broad categories as per the recommendations of Drummond et al. and the Canadian Coordinating Office for Health Technology Assessment.^{161,162} In summary, Krentz et al. collected the costs of all medications (antiretroviral and non-antiretroviral), inpatient stays (HIV- and non-HIV-related), outpatient visits (including physician and laboratory costs), and home care. Laboratory costs included all HIV-related laboratory tests (CD4 cell count, viral load determination, serologies and chemistries). The costs of community-based care included the costs of acute, long-term and palliative nursing care. The question of including total versus HIV-related costs is a methodological issue that needs to be addressed in order to facilitate comparison in future studies. From the perspective of a payer, the inclusion of all relevant health care costs is appropriate and necessary. Krentz et al. made a concerted effort to collect all health care-related costs and the methodology used in the study was transparent.

Researchers have also employed a number of statistical tools to estimate lifetime costs. Although several investigators have estimated lifetime costs, not all patients were followed for a full follow-up period because of deaths and losses to follow-up. For example, if patients had three months of data on record, it is common to see this value multiplied by four to approximate annual costs. With

¹⁶⁰ Tolley K, Gyldmark M. The treatment and care costs of people with HIV infection or AIDS: development of a standardised cost framework for Europe. *Health Policy*. 1993;24(1):55-70.

¹⁶¹ Drummond M, Stoddart G, Torrance G. *Methods for the economic evaluation of healthcare programs*. New York: Oxford University Press, 1987.

¹⁶² Baladi JF. A guidance document for the costing process. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1996.

this extrapolation, investigators may overestimate costs by assuming patients will live 12 months. Furthermore, some investigators assume that the observed utilization in the first three months remains constant for the remaining nine months. However, as HIV disease progresses, utilization may increase and investigators may underestimate utilization.

Also, there have been inconsistencies in the way decedents have been treated in many studies that have investigated the lifetime treatment costs of patients infected with HIV. For example, only resource use by patients followed to death were investigated in an earlier study.¹⁶³ In another study, patients were followed for two years and 90 percent of the patients died. Lifetime costs were then estimated by calculating total expenditures for all patients. The actual lifetime costs of the remaining 10 percent of patients who survived was not fully incorporated.¹⁶⁴ Failure to include all patients in the analyses as well as not adjusting for survival can lead to erroneous lifetime estimates of resource use. A recent study estimated the impact of HIV PI therapy in the global use of health care resources. The researchers analyzed data from patients who had a full-year follow-up before and after the introduction of protease inhibitors.¹⁶⁵ Patients who

¹⁶³ Andrews RM, Keyes MA, Fanning TR, Kizer KW. Lifetime Medicaid service utilization and expenditures for AIDS in New York and California. *Journal of Acquired Immune Deficiency Syndromes* 1991;4(10):1046-58.

¹⁶⁴ Andrews RM, Keyes MA, Pine P. Longitudinal patterns of California Medicaid recipients with acquired immunodeficiency syndrome. *Health Care Financing Review* 1991;13(2):1-12.

¹⁶⁵ Velasco M, Gomez A, Fernandez C, Perez-Cecilia E, Tellez MJ, Roca V, et al. Economic impact of HIV protease inhibitor therapy in the global use of health-care resources. *HIV Medicine* 2000;1(4):246-51.

were lost to follow-up before the completion of a full year were not included in the analyses. Another group of studies assumed the survival of the study sample was the same as that previously reported by investigators in another patient sample.¹⁶⁶

1.6 Life Expectancy, Lifetime Costs and Survival Analysis

Recent studies have addressed some of the shortcomings of previous investigators in estimating life expectancy and lifetime costs. Researchers have adopted specific statistical tools to estimate life expectancy and lifetime costs accrued by patients. In particular, the adoption of survival analysis as a statistical tool to estimate life expectancy and lifetime costs is evident.^{167,168,169,170,171,172,173,174,175} Life expectancy is defined as the average

¹⁶⁶ Hellinger FJ. The lifetime cost of treating a person with HIV. *Journal of the American Medical Association* 1993;270(4):474-8.

¹⁶⁷ Riseborough N, Oh P, Rachlis A. Economic evaluation of triple ART with indinavir or abacavir and ZDV+3TC compared to dual therapy ZDV+3TC (Abstract no. 103). 6th Conference on Retroviruses and Opportunistic Infection; 1999 Jan 31 -Feb 4; Chicago, IL.

¹⁶⁸ Freedberg KA, Goldie SJ, Paltriel AD. Combination antiretroviral therapy is both effective and cost-effective [abstract no. 2070]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1999 Sep 26-29; San Francisco, CA.

¹⁶⁹ Mauskopf J, Lacey L, Kempel A, Simpson K. The cost-effectiveness of treatment with lamivudine and zidovudine compared with zidovudine alone: a comparison of Markov model and trial data estimates. *American Journal of Managed Care* 1998;4(7):1004-12.

¹⁷⁰ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

¹⁷¹ Lee ET, Go OT. Survival analysis in public health research. *Annual Review of Public Health* 1997;18:105-34.

¹⁷² Lin DY, Feuer EJ, Etzioni R, Wax Y. Estimating medical costs from incomplete follow-up data. *Biometrics* 1997;53(2):419-34.

future lifetime of a cohort of patients with identical clinical features. Life expectancy can be estimated assuming a time invariant, patient-specific mortality risk for a given combination of patient characteristics and co-morbid disease. This is generally referred to as the declining exponential approximation of life expectancy. Other methods for estimating life expectancy include the use of life tables, parametric survival methods (e.g., Weibull, exponential), and non-parametric survival methods (e.g., Kaplan-Meier, Cox-proportional Hazard). Gompertz and Markov models have been used to extrapolate traditional survival curves to infinity.¹⁷⁶

The Kaplan-Meier estimate of survival is a non-parametric survival method of evaluation. The traditional method of using a parametric approach in survival analyses has been abandoned in recent years in preference for non-parametric methods.¹⁷⁷ Non-parametric methods require fewer assumptions than parametric methods. In particular, no distributional assumptions are imposed on survival times. Researchers agree that survival analysis is the preferred approach because all patients are included; therefore, observations for which complete data

¹⁷³ Etzioni R, Urban N, Baker M. Estimating the costs attributable to a disease with application to ovarian cancer. *Journal of Clinical Epidemiology* 1996;49(1):95-103.

¹⁷⁴ Fenn P, McGuire A, Backhouse M, Jones D. Modelling programme costs in economic evaluation. *Journal of Health Economics* 1996;15(1):115-25.

¹⁷⁵ Etzioni RD, Feuer EJ, Sullivan SD, Lin D, Hu C, Ramsey SD. On the use of survival analysis techniques to estimate medical care costs. *Ibid.* 1999;18(3):365-80.

¹⁷⁶ Messori A, Trippoli S. A new method for expressing survival and life expectancy in lifetime cost-effectiveness studies that evaluate cancer patients (review). *Oncology Reports* 1999;6(5):1135-41.

¹⁷⁷ Lee ET, Go OT. Survival analysis in public health research. *Annual Review of Public Health* 1997;18:105-34.

are not available can be included in the analysis. Observations for which complete data are not available are commonly referred to as censored. Specifically, survival analysis allows for the inclusion in the analysis of patients who suffer early death, are lost to follow-up, or enter the system after the start of the study. The central concept in the techniques of survival analysis that have been developed to adjust for censored data are that of the conditional probability of an event taking place.

For any given patient who has undergone treatment for $t (> 0)$ days, there is a given probability that he or she will die (or reach the end point of the analysis) on day $t + 1$.¹⁷⁸ The conditional probability of death (endpoint) is referred to as the hazard rate, where it is estimated by:¹⁷⁹

$$\lambda(t) = \frac{n(t)}{h(t)}$$

where $n(t)$ is the number of deaths observed at time t , and $h(t)$ is the number of people at risk at time t . The estimator for the probability of survival to time t , also known as the Kaplan-Meier or product-limit, is given by:

$$S(t) = \prod_{k=1}^t [1 - \lambda(k)]$$

The Kaplan-Meier estimator “corrects” for censored data by adjusting the value of $h(t)$.

¹⁷⁸ Fenn P, McGuire A, Phillips V, Backhouse M, Jones D. The analysis of censored treatment cost data in economic evaluation. *Medical Care* 1995;33(8):851-63.

¹⁷⁹ Ibid.

A recent review of the literature indicates that investigators typically used either the Kaplan-Meier method or Markov modeling to estimate life expectancy.^{180,181,182,183} In the early years of the HIV pandemic, Quesenberry et al. were one of the few groups of researchers who used and recommended the use of survival analysis methods in the study of utilization among groups of patients with incomplete follow-up.¹⁸⁴ Quesenberry et al. estimated the life expectancy, lifetime number of hospitalizations, and inpatient days associated with HIV infection; Kaplan-Meier estimates were used to model “survival.” Using 1992-1995 data, Moore and Chaisson used the Kaplan-Meier technique and Markov modeling to estimate the life expectancy for Maryland Medicaid patients.¹⁸⁵ Using 1996 data, Holtgrave and Pinkerton also estimated the life expectancy after the diffusion of new combination therapies using the Kaplan-Meier technique and

¹⁸⁰ Moore RD, Chaisson RE. Costs to Medicaid of advancing immunosuppression in an urban HIV-infected patient population in Maryland. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;14(3):223-31.

¹⁸¹ Moore RD, Hidalgo J, Bareta JC, Chaisson RE. Zidovudine therapy and health resource utilization in AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1994;7(4):349-54.

¹⁸² Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

¹⁸³ Seage GR, Hertz T, Stone VE, Epstein AM. The effects of intravenous drug use and gender on the cost of hospitalization for patients with AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1993;6(7):831-9.

¹⁸⁴ Quesenberry CP, Jr., Fireman B, Hiatt RA, Selby JV. A survival analysis of hospitalization among patients with acquired immunodeficiency syndrome. *American Journal of Public Health* 1989;79(12):1643-7.

¹⁸⁵ Moore RD, Chaisson RE. Costs to Medicaid of advancing immunosuppression in an urban HIV-infected patient population in Maryland. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;14(3):223-31.

Markov modeling.¹⁸⁶ Chancellor et al. assessed the life expectancy of dual antiretroviral therapy versus monotherapy. They estimated the life expectancy using a Markov model of progression through three HIV-positive defined states based on CD4 counts. Progression probabilities were derived from a cohort treated at Chelsea and Westminster Hospital in London, using data from 1987 to 1995 and using the Kaplan-Meier survival analysis technique.

King et al. estimated the long term survival following HAART using parametric survival techniques and Monte Carlo Markov simulations.¹⁸⁷ However, instead of employing CD4 counts to determine progression (or treatment failure), they used an alternative operational definition of treatment failure. Specifically, a round of therapy was considered to have “failed” when the patient was switched to a new round of therapy. The authors defined a single round of therapy as the time at which the patient initiated at least two new agents, and the round of therapy ended when the patient started another two new agents. This definition of treatment failure is the standard definition of treatment failure used by the FDA and is currently being considered as an endpoint in clinical drug trials. Determining the expected survival period is not easy because: (1) this

¹⁸⁶ Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Ibid.*;16(1):54-62.

¹⁸⁷ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

period is now long; and (2) there is the constant change in therapies and their impact on life expectancy.

Survival analysis has a long history in economics as well as biomedical applications. Recently, survival analysis approaches have been proposed for analyzing medical costs. In 1995, Fenn et al. suggested that survival analysis techniques that employ non-parametric techniques reduce the potential of biased estimates of costs by accounting for censored data.¹⁸⁸ In cost analyses, a censored patient is one for whom total cost data, for the period analyzed (e.g., one year), is not available. Many studies investigating medical costs focus on estimating the resource consumption over a specified time interval. If individuals are not followed long enough to experience the event during the observation period, or if individuals are otherwise lost to follow-up, they are considered to be censored. In cost analyses, the hazard rate describes the conditional probability of having or accruing the total program costs (\$C). Given that a patient was alive and accrued \$C – X before censoring, the hazard rate is the probability of having accrued \$C of treatment if complete data to follow-up was available.

Many claims databases include individuals who suffer early deaths, patients who leave medical centers or are otherwise lost to follow-up, and patients who enter the system at various times during any particular period of analysis.

Therefore, the costs and health outcomes available in the database may provide

¹⁸⁸ Fenn P, McGuire A, Phillips V, Backhouse M, Jones D. The analysis of censored treatment cost data in economic evaluation. *Medical Care* 1995;33(8):851-63.

some, but not complete, information about utilization, health care costs and life expectancy in the period analyzed. The use of censored data in survival analysis allows data for all patients to be analyzed, and it allows distinction between complete, known data and incomplete, unknown data. For example, a patient may have total annual costs of \$50,000, while another patient may have accrued \$20,000 worth of costs in the six-month period for which the data was collected. The patient may not have been followed for the entire year due to death, loss to follow-up, or the end of the study period occurring prior to one-year follow-up. Therefore, the first patient's costs are known to be \$50,000 and the other patient's costs are known to be at least \$20,000. Furthermore, when examining cost data, early mortality has the potential of skewing the total costs downward. Therefore, interventions resulting in high mortality may be incorrectly designated as being more cost-effective. The use of survival analysis allows inclusion of patients for whom incomplete data are available.

Fenn et al. analyzed the impact of censored treatment cost data in economic evaluations. The researchers observed large variations in the results of the economic evaluations when using different methods to deal with censored cost data.¹⁸⁹ Currently, few researchers have adopted the techniques of survival analyses to adjust for censored cost data. The novel approach suggested by Fenn et al. provides the basis for using more sophisticated techniques for economic

¹⁸⁹ Ibid.

evaluation of clinical trial data; however, the technique of analyzing cost data using survival analysis is still at its infancy and researchers have noted that this technique does not provide unbiased estimation of costs as suggested by Fenn and his colleagues.^{190,191} This a relatively new area of research and some economists conclude that the assumptions needed for valid survival analysis may be violated when the current survival methods are used in cost analyses.¹⁹²

1.7 Overview of Medication Adherence

Patient compliance with medication regimens has been defined as “the extent to which a person’s medication-taking behavior conforms to medical or health care professionals’ advice.”^{193,194,195} This definition reflects a paternalistic view: it assumes that physicians: (1) know what is best for their patients; (2) communicate and inform patients clearly; (3) prescribe effective treatments; and (4) are the only contributors to decisions regarding medication therapy. Many researchers have challenged this definition as they now acknowledge the active role of patients in decisions regarding their treatment.

¹⁹⁰ Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. *Ibid.* 1998;36(3):433-6.

¹⁹¹ Etzioni RD, Feuer EJ, Sullivan SD, Lin D, Hu C, Ramsey SD. On the use of survival analysis techniques to estimate medical care costs. *Journal of Health Economics* 1999;18(3):365-80.

¹⁹² *Ibid.*

¹⁹³ Cramer JA, Spilker B. *Patient compliance in medical practice and clinical trials*. New York: Raven Press, 1991.

¹⁹⁴ Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *Journal of the American Medical Association* 1989;261(22):3273-7.

¹⁹⁵ Haynes RB. *Compliance in Health Care*. Baltimore: Johns Hopkins University Press, 1979.

Concordance is a concept that attempts to model a type of health care professional-patient relationship.^{196,197} It is proposed that, in a truly concordant relationship, all the patient's concerns have been included and the approach to decision-making is explicit, shared and co-operative. Thus, concordance aims to facilitate adherent behavior. The backbone of the concordance model is "the patient as the decision-maker and a cornerstone of the model is professional empathy."¹⁹⁸ Consequently, along with this new interpretation of compliance, alternative terms to compliance have increasingly found their place in the literature. Adherence, patient cooperation, therapeutic alliance and concordance are some of the many terms that incorporate the agreement of the patient and physician.

Clinical trials are research studies often conducted to determine the impact of new drugs or treatments. The majority of clinical trials measure efficacy rather than effectiveness. The question of whether a treatment can work is one of efficacy. Efficacy is established by restricting patients in a study to those who will cooperate fully with medical advice. The results from clinical trials may therefore correlate poorly to those from everyday patient care. One of the

¹⁹⁶ Mullen PD. Compliance becomes concordance. *British Medical Journal* 1997;314(7082):691-2.

¹⁹⁷ Bamforth I. Compliance and concordance with treatment. Coming to an understanding with patients and prepositions. *Ibid.*(7098):1905-6.

¹⁹⁸ Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *Journal of Clinical Pharmacy & Therapeutics* 2001;26(5):331-42.

differences between an efficacy trial and an effectiveness trial can be explained by differences in patient adherence, which is generally better in clinical trials.

Therefore, in order to measure effectiveness, non-adherence should be accounted for. It should be noted, however, that clinical trials do not always guarantee full adherence.

Non-adherence to prescribed medications, including HIV medications, can lead to significant morbidity that could have been otherwise prevented (e.g., treatment of new or more morbid conditions). Non-adherence can lead to therapeutic failure in acute and chronic diseases, over dosage, or the emergence of drug resistance. For example, approximately 50 percent of all failures in hypertension treatment can be explained by non-adherence to treatment.^{199,200} Furthermore, unintended pregnancies and up to 80 percent of transplant rejections can be avoided by better adherence with oral contraceptives and immunosuppressive medications, respectively.^{201,202} Also, Psaty et al. reported that hypertensive patients taking beta blockers who were less than 80 percent adherent had a four-fold risk of cardiovascular disease, while those who were greater than 80 percent adherent had a two-fold increased risk; therefore, partial

¹⁹⁹ Urquhart J. Some economic consequences of noncompliance. *Current Hypertension Reports*. 2001;3(6):473-80.

²⁰⁰ Stephenson J. AIDS researchers target poor adherence. *Journal of the American Medical Association* 1999;281(12):1069.

²⁰¹ Rosenberg M, Waugh MS. Causes and consequences of oral contraceptive noncompliance. *American Journal of Obstetrics & Gynecology*. 1999;180(2 Pt 2):276-9.

²⁰² Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. *Transplantation Proceedings* 1989;21(1 Pt 1):833-4.

adherence with beta blockers might do more transient harm than the overall beneficial effect of treatment.²⁰³ Another review of records to evaluate the under-use of anti-hypertensive medications and associated hospitalizations revealed that patients who were re-admitted to the hospital because of uncontrolled blood pressure had used significantly less medication than patients who were not re-admitted.²⁰⁴ These types of studies demonstrate the importance of using adherence data linked to medical events before making general interpretations of outcomes.

Therapeutic non-adherence may increase the quality-of-life of patients because they may deliberately adapt their medication schedules to their own lifestyle, but it may also decrease the quality-of-life because of increased morbidity and side effects. In addition, non-adherence may impair quality-of-life and in turn further decrease adherence.

1.7.1 Prevalence of Medication Non-Adherence

In a recent article, the five most common forms of non-adherence to medications identified were: (1) not having a prescription filled; (2) taking an incorrect dose; (3) taking the medication at the wrong time; (4) forgetting to take

²⁰³ Psaty BM, Koepsell TD, Wagner EH, LoGerfo JP, Inui TS. The relative risk of incident coronary heart disease associated with recently stopping the use of beta-blockers. *Journal of the American Medical Association* 1990;263(12):1653-7.

²⁰⁴ Maronde RF, Chan LS, Larsen FJ, Strandberg LR, Laventurier MF, Sullivan SR. Underutilization of antihypertensive drugs and associated hospitalization. *Medical Care* 1989;27(12):1159-66.

one or more medications; and (5) stopping the medication too soon.²⁰⁵ Two large surveys documented that up to 20 percent of all patients who had received a prescription did not have it filled.^{206,207} The most commonly cited reason for not having the prescription filled was the patients' beliefs that they did not need the medication. Moreover, this behavior is even more prevalent among patients with asymptomatic conditions. With regard to patients not taking the medication or taking it at the wrong time, reports indicate that as little as 50 to 60 percent of patients achieve near-optimal or excellent adherence, and as much as five to ten percent of patients display low levels of adherence.²⁰⁸

Although there has been a resurgence in interest in patient adherence by health care professionals and behavioral scientists, the quality of health care research in this area warrants further attention. Specifically, there has been a lack of methodologic standards among published work related to patient adherence. The lack of standards has led to significant variations in the conclusions drawn about medication adherence. These differences could be attributed to the limitations of the data collected as well as the differences in study designs. In order to describe the extent of these differences, Nichol et al. reviewed and

²⁰⁵ Miller NH. Compliance with treatment regimens in chronic asymptomatic diseases. *American Journal of Medicine* 1997;102(2A):43-9.

²⁰⁶ Survey by Applied Research Techniques conducted for the American Association of Retired Persons. Washington DC: American Association of Retired Persons, 1984.

²⁰⁷ National Prescription Buyers Survey. Kalamazoo, Michigan: The Upjohn Company, 1985.

²⁰⁸ Rudd P. Clinicians and patients with hypertension: unsettled issues about compliance. *American Heart Journal*. 1995;130(3 Pt 1):572-9.

evaluated the methodology of the literature on medication adherence for the years 1980 to 1996.²⁰⁹ This review was preceded by a review by Haynes et al. who showed that the methodologic rigor of the studies published prior to 1979 varied widely.²¹⁰ Over twenty years later, Haynes et al. documented that the large increase in adherence literature had not been accompanied by an improvement in methodologic rigor. For example, many of the articles failed to describe the adherence measurements used in the studies. In addition, because of a lack of a gold standard for adherence definition and measurement, there were a variety of measures and definitions used. Some of these studies used their own non-validated adherence measurement instruments. As a result, it is difficult to assess, compare, replicate, and validate these study findings in other settings. Furthermore, two-thirds of the studies were descriptive in nature which further enforces concern about study design.

1.7.2 Reasons for and Factors Associated with Medication Non-Adherence

There are many factors that predict non-adherence to medication. Fogarty et al. conducted a literature search to collect published articles reporting correlates

²⁰⁹ Nichol MB, Venturini F, Sung JC. A critical evaluation of the methodology of the literature on medication compliance. *Annals of Pharmacotherapy*. 1999;33(5):531-40.

²¹⁰ Haynes RB. *Compliance in Health Care*. Baltimore: Johns Hopkins University Press, 1979.

of HIV medication adherence.²¹¹ In summary, four broad categories of adherence-related factors were identified: characteristics of treatment regimens, social and psychological factors, institutional resources, and personal attributes. The following section will describe the four categories of adherence-related factors.

The first group of factors that could potentially impact adherence are the treatment regimen factors. The characteristics of treatment regimens that were negatively associated with adherence include complex and demanding regimens in terms of scheduling and lifestyle accommodation and those that were often accompanied with side effects. The complexity of administration and the number of pills taken was strongly related to adherence. Across therapeutic areas, difficulties in taking a large number of pills are common and have consistently been associated with non-adherence in the literature.²¹² Sometimes, as much as six to nineteen HAART drugs are used at different times of the day with specific dietary instructions. For instance, patients may need to take medications with or without food. These drugs are often taken with other drugs such as those used for prophylaxis of opportunistic infections. Research on hypertension has shown that

²¹¹ Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Education and Counseling* 2002;46(2):93-108.

²¹² Wang W, Husan F, Chow SC. The impact of patient compliance on drug concentration profile in multiple doses. *Statistics in Medicine* 1996;15(6):659-69.

medication adherence decreases as the number of pills per day increases.^{213,214}

Strategies aimed at helping patients cope with the complex regimens and scheduling demands (e.g., pill boxes, timers, beepers, and fitting drug schedules into a daily routine) have been found to be effective in improving adherence.

Also, regimens that involve drugs taken twice a day are likely to be associated with better adherence than those involving drugs taken three or more times a day; once daily regimens may further facilitate adherence.²¹⁵

Many of the HAART medications have unpleasant side effects, (diarrhea, nausea, vomiting, and peripheral neuropathy) and the treatment of asymptomatic disease is of long duration. It is often not easy to determine whether adverse events are related to medications, the underlying disease progression, or a combination of both. Side effects and adverse events have been reported as common reasons for non-adherence to medications in many therapeutic areas and may likely have similar influences for HIV/AIDS therapies.²¹⁶ Earlier HIV/AIDS

²¹³ Detry JM. Patient compliance and therapeutic coverage: amlodipine versus nifedipine SR in the treatment of hypertension and angina: interim results. Steering committee and cardiologists and general practitioners involved in the Belgium multicentre study on patient compliance. *Clinical Cardiology* 1994;17(9 Suppl 3).

²¹⁴ Detry JM, Block P, De Backer G, Degaute JP. Patient compliance and therapeutic coverage: comparison of amlodipine and slow release nifedipine in the treatment of hypertension. The Belgian Collaborative Study Group.[erratum appears in *European Journal of Clinical Pharmacology* 1995;48(3-4):314]. *European Journal of Clinical Pharmacology* 1995;47(6):477-81.

²¹⁵ Stone VE, Hogan JW, Schuman P, Rompalo AM, Howard AA, Korkontzelou C, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HER study. *Journal of Acquired Immune Deficiency Syndromes* 2001;28(2):124-31.

²¹⁶ Bartlett JA. Addressing the challenges of adherence. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2002;29(Suppl 1):S2-10.

therapies required demanding dietary restrictions, were expensive, caused unpleasant side-effects and required a large number of pills. Table 1-5 illustrates an early triple therapy regimen used in the treatment of HIV/AIDS disease.²¹⁷

Table 1-5: The Generic Name, Dose, Frequency, Daily Number of Pills, Monthly Costs, Side-Effects and Dietary Restrictions of a Triple Therapy Regimen

Generic	Dose (mg) & Frequency	Daily Number of Pills	Costs/Month (US\$)	Common Side-Effects	Dietary Restrictions
Zidovudine	300 bid	2	288	Anemia, headache, malaise	None
Lamivudine	150 bid	2	225	Headache, malaise, nasal symptoms, fever, nausea, diarrhea, vomiting, anorexia, neuropathy, dizziness, insomnia	None
Indinavir	800 q8h	6	450	Kidney stones, nausea, diarrhea, headache	Take pills one hour before or two hours after eating ; drink at least 48 oz. water/day
Total		10	963		

Walsh et al. recently investigated the common reasons for non-adherence to HAART.²¹⁸ The most frequent reasons for at least 'sometimes' missing a dose

²¹⁷ Sanford J. *The Sanford guide to HIV/AIDS therapies*. Vienna, Virginia: Roche Laboratories, Antimicrobial Therapy Inc, 1997.

²¹⁸ Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care* 2001;13(6):709-20.

were eating a meal at the wrong time (38.2%), oversleeping (36.3%), forgetting (35.0%) and being in a social situation (30.5%). The categories listed below are in order of decreasing complexity; therefore, regimens that include medications from all three classes are potentially more complex and may impact patient adherence more negatively.

- NRTI plus NNRTI plus PI
- NRTI plus PI
- NRTI plus NNRTI
- NRTI only

Non-adherence to these complex regimens is not uncommon. Combined regimens of antiretrovirals have alleviated some of the difficulty in combination therapies through once-daily formulations. Few empirical studies of adherence to specific antiretroviral regimens have been published.²¹⁹

The second group of factors that could also impact adherence are the social and psychological factors. Social and psychological factors, emotional health and adjustment to having HIV/AIDS, are all related to adherence to medications. The third group of factors that Fogarty et al. reviewed were the institutional resources; access to institutional resources was associated with better adherence. The fourth group of factors that could impact adherence are the personal attributes factors; however, the impact of personal attributes to

²¹⁹ Ibid.

adherence is mixed. Gender is not consistently related to adherence.²²⁰

Conversely, age, race, and history of substance abuse are generally associated with adherence. In a recent study, Laine et al. concluded that teenagers and women of minority groups had greater risks of poor antiretroviral adherence than women in other groups.²²¹ Van Servellen et al. also examined the effects of system enabling factors in addition to individual predisposing and enabling factors.²²² Individual enabling factors (hopefulness and access to health care), as well as good treatment by clinic staff, a system-enabling factor, were positively associated with adherence. Molassiotis et al. also concluded that high self-efficacy (defined as being certain that the medication schedule will be followed all or most of the time), low tension-anxiety scores, and low intensity of nausea and vomiting were positively associated with adherence.²²³

²²⁰ Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Education and Counseling* 2002;46(2):93-108.

²²¹ Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstetrics & Gynecology* 2000;95(2):167-73.

²²² van Servellen G, Chang B, Garcia L, Lombardi E. Individual and system level factors associated with treatment nonadherence in human immunodeficiency virus-infected men and women. *AIDS Patient Care & Sexually Transmitted Diseases* 2002;16(6):269-81.

²²³ Molassiotis A, Nahas-Lopez V, Chung WY, Lam SW, Li CK, Lau TF. Factors associated with adherence to antiretroviral medication in HIV-infected patients. *International Journal of STD & AIDS* 2002;13(5):301-10.

1.7.3 Measurement of Medication Non-Adherence

Adherence to medications can be measured by use of a variety of methods including patients' self-reports, pharmacy-based approaches, pill counts, biochemical assays, and electronic monitoring.

Sensitivity and specificity are frequently used to describe diagnostic tests in health care. In the context of instruments assessing medication adherence, sensitivity can be defined as the fraction of "true" non-adherent patients who are correctly identified as being non-adherent by the instrument. A sensitive test should be chosen when there is an important penalty for missing a 'disease.' Likewise, specificity can be defined as the fraction of "true" adherent patients who are correctly identified as being adherent by the instrument. Specific tests are commonly used to confirm a diagnosis that has been confirmed by other data; highly specific tests are rarely positive in the absence of 'disease.' Although self-reports are easier to collect, they have relatively low sensitivity but generally high specificity.²²⁴ Generally, estimates of treatment adherence from patients' self-reports are less complex to obtain. Electronic measures, on the other hand, have high sensitivity but low specificity because patients may be decanting extra doses. There has also been some concern that electronic monitoring may not only

²²⁴ Turner B. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *Journal of Infectious Diseases* 2002;185(Suppl 2):S143-51.

measure adherence, but may also improve adherence.²²⁵ Burnier et al. have demonstrated this potential “Hawthorne” effect.²²⁶ However, Wagner and Ghosh-Dastidar conducted a study to determine whether electronic monitoring alters adherence and their results suggest that electronic monitoring does not significantly alter pill taking behavior.²²⁷ Patients are also less likely to participate in studies using electronic monitoring and if they do, they are likely to use the monitor inappropriately; patients often refuse to participate when the study uses a large bottle with an electronic cap instead of a pillbox that can help them organize and remember their medication.²²⁸

Pharmacy-based measures that use health insurance claims data offer a much less intrusive way than pill counts to monitor adherence.^{229,230} Adherence assessed by pharmacy-based measures are only possible under the assumption that all medications used by the patient are billed to the same payer such as with Medicaid enrollees and patients enrolled in the Department of Veterans Affairs (VA). Stephenson et al. and Wannemacher et al. recently assessed medication

²²⁵ Wagner GJ, Ghosh-Dastidar B. Electronic monitoring: adherence assessment or intervention? *HIV Clinical Trials*. 2002;3(1):45-51.

²²⁶ Burnier M, Schneider MP, Chioloro A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. *Journal of Hypertension* 2001;19(2):335-41.

²²⁷ Wagner GJ, Ghosh-Dastidar B. Electronic monitoring: adherence assessment or intervention? *HIV Clinical Trials*. 2002;3(1):45-51.

²²⁸ Wendel CS, Mohler MJ, Kroesen K, Ampel NM, Gifford AL, Coons SJ. Barriers to use of electronic adherence monitoring in an HIV clinic. *Annals of Pharmacotherapy* 2001;35(9):1010-5.

²²⁹ Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *Journal of Clinical Epidemiology*. 1997;50(5):619-25.

²³⁰ Saunders K, Simon G, Bush T, Grothaus L. Assessing the feasibility of using computerized pharmacy refill data to monitor antidepressant treatment on a population basis: a comparison of automated and self-report data. *Ibid.* 1998;51(10):883-90.

adherence by pharmacy-based approaches using prescription data of patients enrolled in the VA system.^{231,232}

Steiner and Prochazka identified four studies that correlated prescription refill measures of adherence with self-reported adherence.²³³ Two of the studies showed strong correlations between these two measures and the remaining two found no significant association. Recently, Grossberg et al. also conducted an observational study at the Philadelphia Veterans Medical Center to compare pharmacy refill adherence with self-reported adherence and their associations with viral load change.²³⁴ Patients who were on a stable HAART regimen for the previous three months were included in the study protocol. Self-reported adherence was assessed using the AIDS Clinical Trials Group adherence self-report questionnaire.²³⁵ Self-reported adherence for the four days preceding selected study visits was very high and may represent an overestimate of actual adherence. Pharmacy-based adherence was calculated using refill percent adherence obtained from the prescription records (medication possession ratios).

²³¹ Wannemacher AJ, Schepers GP, Townsend KA. Antihypertensive medication compliance in a veterans affairs healthcare system. *The Annals of Pharmacotherapy* 2002;36(6):986-91.

²³² Stephenson J. Noncompliance may cause half of antihypertensive drug failures. *Journal of the American Medical Association* 1999;282(4):313-4.

²³³ Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of Clinical Epidemiology* 1997;50(1):105-16.

²³⁴ Grossberg RM, Gross R. Pharmacy refill adherence is a better predictor of HIV outcome than self-report [abstract 487]. 40th Annual Meeting of the Infectious Diseases Society of America; 2002 October 24-27; Chicago, Ill.

²³⁵ Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000;12(3):255-66.

The correlation between refill percent adherence and change in viral load was 0.228 (95% CI: 0.033 to 0.406, $p < 0.05$) while the correlation between self-reported adherence and change in viral load was 0.118 (95% CI: -0.080 to 0.307, $p = 0.24$). As a result, Grossberg et al. suggest that pharmacy refill percent adherence is a valid measure, as demonstrated by the significant correlation with viral load change. Furthermore, the authors also suggest that pharmacy-based adherence measurements are better measures than self-reported adherence measures which were not correlated with virologic outcome.

Although pharmacy-based measures are not prone to report bias as are the self-report measures, pharmacy-based measures cannot prove that patients picked up and took their medications. Also, pharmacy-based measures are better at estimating under-adherence and less effective at estimating over-adherence since the measured over-adherence may be a result of true over-adherence or early refills due to other reasons.

Adherence is not only a complex variable with multiple determinants, but it is a continuous variable. Therefore, once a method of measurement is chosen, a level of acceptable adherence must be defined. The convention has been to define good adherence as carrying out 80 percent of the recommended behaviors. Early studies of antiretroviral adherence also used a cut-off point for adherence of 80 percent or greater. Recent data suggests that adherence needs to be particularly high for patients on antiretroviral therapy for optimal effectiveness. Studies have

shown that an even higher level of adherence ($\geq 95\%$) is necessary for long-term suppression of HIV virus load.^{236,237,238,239,240}

1.7.4 Antiretroviral Therapy Non-Adherence

Before treatment with HAART, studies reported low adherence in patients receiving zidovudine.^{241,242,243,244} In 1998, Frick et al. also assessed the prevalence of non-adherence to zidovudine over a two-month period.²⁴⁵ In this study, medication adherence from a convenience sample of 23 ambulatory patients was assessed by three methods: patient self-report, pharmacy refill records, and electronic monitoring. The mean rates of adherence determined by

²³⁶ Turner B. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *Journal of Infectious Diseases* 2002;185(Suppl 2):S143-51.

²³⁷ Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 2000;133(1):21-30.

²³⁸ Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care* 2001;13(6):709-20.

²³⁹ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

²⁴⁰ Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Education and Counseling* 2002;46(2):93-108.

²⁴¹ Samet JH, Libman H, Steger KA, Dhawan RK, Chen J, Shevitz AH, et al. Compliance with zidovudine therapy in patients infected with human immunodeficiency virus, type 1: a cross-sectional study in a municipal hospital clinic. *American Journal of Medicine*. 1992;92(5):495-502.

²⁴² Samuels JE, Hendrix J, Hilton M, Marantz PR, Sloan V, Small CB. Zidovudine therapy in an inner city population. *Journal of Acquired Immune Deficiency Syndromes*. 1990;3(9):877-83.

²⁴³ Singh N, Squier C, Sivek C, Wagener M, Nguyen MH, Yu VL. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care*. 1996;8(3):261-9.

²⁴⁴ Muma RD, Ross MW, Parcel GS, Pollard RB. Zidovudine adherence among individuals with HIV infection. *Ibid*. 1995;7(4):439-47.

²⁴⁵ Frick PA, Gal P, Lane TW, Sewell PC. Antiretroviral medication compliance in patients with AIDS. *AIDS Patient Care & Sexually Transmitted Diseases* 1998;12(6):463-70.

pharmacy refill records (78%) and electronic monitoring systems (66%) were below 80 percent; however, among patients whose adherence was electronically measured, 88 percent reported taking their ZDV according to the directions all of the time. Frick et al. suggest that these results demonstrate that reliance upon patient self-report of medication adherence is less accurate than electronic monitoring or pharmacy refill records and that reliance on self-reporting could lead to erroneous assumptions of the patient's true drug adherence. In addition, the authors suggest that pharmacy refill records may provide a method of assessing compliance that is equivalent to electronic monitoring. More recently, similar findings have been reported with patients on HAART.²⁴⁶

Since the introduction of HAART in 1996, the hope of extending life in HIV-infected individuals has been realized. The new combination regimens have proved highly effective in clinical trials by decreasing HIV viral loads and increasing CD4 levels. As a result, HIV-related morbidity and mortality have been reduced. Despite the continued optimism since the introduction of HAART, two groups of patients are currently experiencing virologic failure. The two groups of patients are those who have developed resistant virus strains and those who adhere poorly to their antiretroviral regimens. These two groups are not mutually exclusive; there is empirical evidence to suggest that the successful

²⁴⁶ Eldred LJ, Wu AW, Chaisson RE, Moore RD. Adherence to antiretroviral and pneumocystis prophylaxis in HIV disease. *Journal of Acquired Immune Deficiency Syndromes* 1998;18(2):117-25.

suppression of the HIV virus needs near perfect adherence to HAART to achieve clinical success.²⁴⁷ Incomplete adherence to one or more prescribed medications is a key cause of virological failure of antiretroviral medications.²⁴⁸ According to Sethi et al., suboptimal adherence to HAART is thought to lead to HIV drug resistance.²⁴⁹ Sethi et al. assessed adherence to HAART for individuals enrolled in the study from February through December 2000. Data on genotypic resistance testing and viral suppression were also collected. Using multivariate Cox proportional hazard regression, the authors concluded that a cumulative adherence of 70 percent to 89 percent, a CD4 count of less than 200 cells/ μ L, and the missing of a scheduled clinic visit in the previous month were independently associated with an increased hazard of viral rebound with clinically significant resistance.

Turner et al. also report that failure to adhere to antiretroviral medication therapy has serious consequences for HIV-infected individuals, including failure to prevent viral replication and an increased risk of developing viral resistance.²⁵⁰ Viral drug resistance and cross-resistance have the potential of rendering many of the HAART combination therapies ineffective. When the virus mutates in the

²⁴⁷ Friedland GH, Williams A. Attaining higher goals in HIV treatment: the central importance of adherence. *Acquired Immune Deficiency Syndromes* 1999;13(Suppl 1):S61-72.

²⁴⁸ Deeks SG. Determinants of virological response to antiretroviral therapy: implications for long-term strategies. *Clinical Infectious Diseases*. 2000;30(Suppl 2):S177-84.

²⁴⁹ Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clinical Infectious Diseases* 2003;37(8):1112-8.

²⁵⁰ Turner B. Adherence to antiretroviral therapy by human immunodeficiency virus-infected patients. *Journal of Infectious Diseases* 2002;185(Suppl 2):S143-51.

presence of sub-optimal drug levels, the virus potentially becomes resistant to the activity of the medication. Non-adherence to drug therapy, particularly PIs, has led to the development of HIV resistance.²⁵¹ From a societal perspective, this could cause a major public health problem if other patients are infected.^{252,253}

Although the seriousness of adherence to HAART therapies has been well documented, there has been relatively little adherence research published. Fogarty et al. documented several meta-analysis studies of medication adherence interventions between 1977 and 1996 but they did not identify any meta-analysis studies that were related to HIV/AIDS. Although published material suggests that there is not much activity in this research area, this conclusion is misleading; proceedings of HIV/AIDS conferences since 1996 suggests that there is much interest and activity in this area. Fogarty et al. reviewed the literature on patient adherence to HIV medication regimens and found 80 percent of the descriptive studies in conference proceedings.²⁵⁴ In one of the studies reviewed by Fogarty et al., only 50 percent of patients who were 80 to 90 percent adherent had successful viral suppression compared to 81 percent of patients who had more than 95

²⁵¹ Bayer R, Stryker J. Ethical challenges posed by clinical progress in AIDS. *American Journal of Public Health* 1997;87(10):1599-602.

²⁵² Ibid.

²⁵³ Martin-Fernandez J, Escobar-Rodriguez I, Campo-Angora M, Rubio-Garcia R. Evaluation of adherence to highly active antiretroviral therapy. *Archives of Internal Medicine* 2001;161(22):2739-40.

²⁵⁴ Fogarty L, Roter D, Larson S, Burke J, Gillespie J, Levy R. Patient adherence to HIV medication regimens: a review of published and abstract reports. *Patient Education and Counseling* 2002;46(2):93-108.

percent adherence.²⁵⁵ In another study, Chessney documented that patients who reported less than 80 percent adherence to HIV medication were twice as likely as those who reported complete adherence, to have detectable viral loads.²⁵⁶ On the other hand, Lazzarini et al. assessed adherence to triple antiretroviral therapy and found that there were no significant differences in plasma viraemia or CD4 counts one year after the treatment between adherent and non-adherent patients. However, the study was a retrospective analysis with a small sample size (only nine [10%] of the patients were non-adherent).²⁵⁷ In response to Lazzarini et al., Murri et al. suggested that the definition of adherence used in the study could have led to misclassification of patients and, subsequently, to the underestimation of the effects of non-adherence.²⁵⁸

Paterson et al. also assessed the effects of different levels of adherence to therapy on virologic, immunologic, and clinical outcomes using a prospective observational database.²⁵⁹ Patients were followed for a median of six months and Paterson et al. concluded that 95 percent or greater adherence to PI therapy optimized virologic outcomes for patients with HIV infection. A recent study

²⁵⁵ Stephenson J. AIDS researchers target poor adherence. *Journal of the American Medical Association* 1999;281(12):1069.

²⁵⁶ Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clinical Infectious Diseases*. 2000;30(Suppl 2):S171-6.

²⁵⁷ Lazzarini L, Lanzafame M, Trevenzoli M, Vento S, Concia E. Adherence to HAART in HIV. *Lancet*. 1999;353(9155):841.

²⁵⁸ Murri R, Ammassari A, De Luca A, Cingolani A, Antinori A. Definition and measurement of adherence to antiretroviral drugs in HIV-1-infected patients. *Lancet* 1999;353(9168):1974.

²⁵⁹ Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 2000;133(1):21-30.

showed that for every 10 percent decrease in adherence there was an associated doubling of the viral load.²⁶⁰ Another study demonstrated that mortality rates associated with non-adherence were increased 2.5 fold even among patients whose baseline CD4 counts were 350 cells/ μ L or greater.²⁶¹

Another study in Vancouver used pharmacy-based measures, over a twelve-month period, to demonstrate that there was a 1.17 fold increased risk of death and/or progression to AIDS for each ten percent decline in treatment adherence with HAART.²⁶² Laine et al. also assessed adherence to antiretroviral therapy using Medicaid pharmacy claims data for HIV-infected pregnant women.²⁶³ The authors retrospectively studied a cohort of 2,714 HIV-infected women in New York State who delivered live infants from 1993 to 1996. Refill fraction adherence was calculated by dividing the number of days of medications prescribed over the prescribed period by the number of days between the first and last recorded refill dates. Laine et al. found that 34 percent of the HIV-infected

²⁶⁰ Bangsberg DR, Hecht FM, Charlebois ED, Zolopa AR, Holodniy M, Sheiner L, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *Acquired Immune Deficiency Syndromes* 2000;14(4):357-66.

²⁶¹ Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

²⁶² Hogg R, Yip B, Chan K, O'Shaughnessy MV, Montaner JSG. Nonadherence to triple combination therapy is predictive of AIDS progression and death in HIV-positive men and women. 7th Conference on Retroviruses and Opportunistic Infections; 2000; San Francisco.

²⁶³ Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstetrics & Gynecology* 2000;95(2):167-73.

women had at least 80 percent adherence based on pharmacy data, a rate that remained stable over time.²⁶⁴

Grossberg et al. used an observational database to calculate refill percent adherence from prescription records.²⁶⁵ Refill percent adherence was calculated by dividing the number of days of medications prescribed over the prior three refills (e.g., 90 days) by the number of days between the first and last recorded refill dates. The correlations between refill percent adherence and change in viral load was 0.228 (95% CI: 0.333 to 0.406, $p < 0.05$).

Wood and his colleagues also measured adherence of individuals infected with HIV using an observational database.²⁶⁶ Wood et al. evaluated the effect of baseline CD4 cell count and adherence on survival rates after the initiation of HAART in 1,422 HIV-infected patients. Patients were stratified by baseline CD4 cell count and adherence level. Their definition of adherence was based on the time that medication dispensed would last as a proportion of the follow-up time. To estimate the effect of moderate adherence, Wood et al. categorized patients as non-adherent only if they received antiretroviral medications less than 75 percent of the time during the first year of therapy. Wood et al. concluded that baseline

²⁶⁴ Ibid.

²⁶⁵ Grossberg RM, Gross R. Pharmacy refill adherence is a better predictor of HIV outcome than self-report [abstract 487]. 40th Annual Meeting of the Infectious Diseases Society of America; 2002 October 24-27; Chicago, Ill.

²⁶⁶ Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

CD4 count did not increase the mortality rate in an HIV-infected patient with good medication adherence and with a CD4 count greater than 200 cells/ μ L. However, mortality rates increased if HAART was initiated in individuals with a CD4 count less than 200 cells/ μ L. Therefore, for individuals with CD4 cell counts greater than 200 cells/ μ L, medication adherence is the critical determinant of survival.

Vincent and his colleagues also used medication possession ratio as a measure of adherence of individuals on HAART.²⁶⁷ Specifically, the number of days of antiretroviral medication filled by the patient was divided by the total count of days from the date of first antiretroviral prescription fill through the date of the last prescription plus 34 days (average days filled in one prescription). The period between the first and last prescription was considered as the potential exposure time for refill adherence. The study sample included 6,016 HIV-infected individuals followed for an average of 1.3 years for refill adherence. An average refill adherence of 82 percent was achieved by the study sample with nearly 1,200 (19.9%) reaching perfect refill adherence.

²⁶⁷ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

1.7.5 Pharmacoeconomics and Medication Non-Adherence

Non-adherence can often lead to increased health care costs and resource utilization because of the reduction in effectiveness. Changes in resource utilization may include increased physician consultation or hospitalization rates, unwarranted increases in doses or changes in prescribed agents and requirements for more frequent testing. Two studies concluded that approximately five percent to 11 percent of hospital admissions are due to medication related non-adherence.^{268,269} The incidence of adverse drug events may be precipitated by non-adherence followed by resumption of drug regimen after drug “holidays” leading to increased costs.²⁷⁰ Conversely, non-adherence could also lead to averted costs from the avoidance of episodes of adverse drug reactions.

In recent years, there has been an increasing concern over the rising costs of health care. This has drawn attention to the unnecessary costs of illness resulting from non-adherence. In 1993, the American Task Forces for Compliance estimated the unnecessary health care costs of non-adherence to exceed US\$100 billion each year in the United States.²⁷¹

²⁶⁸ Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Archives of Internal Medicine* 1990;150(4):841-5.

²⁶⁹ Sullivan SD, Kreling DH, Hazlet TK. Noncompliance with medication regimens and subsequent hospitalizations: a literature analysis and cost of hospitalization estimate. *Journal of Research in Pharmaceutical Economics* 1990;2(2):19-33.

²⁷⁰ Urquhart J. Erratic patient compliance with prescribed drug regimens: target for drug delivery systems. *Clinical Pharmacology & Therapeutics* 2000;67(4):331-4.

²⁷¹ Smith MC, Levy R. Noncompliance with medications: An economic tragedy. Baltimore: The task force for compliance, 1994:32.

Similarly, Coombs and his colleagues developed a cost model of non-adherence based on cost estimates of the major chronic diseases in Canada.²⁷² Their conservative estimates suggest that the economic burden of non-adherence is significant. The authors estimated the direct costs of treating non-adherent patients to be between CAN\$3.53 and CAN\$4.49 billion. Their direct costs included: (1) additional hospital expenditures; (2) additional nursing home expenditures; (3) additional treatment costs in ambulatory settings, such as additional physician visits, pharmacy visits, and various lab tests; and (4) potential expenditures associated with the detection and promotion of adherence in outpatient and inpatient settings. The authors estimated the additional hospital expenditures due to non-adherence by multiplying the estimated rate of non-adherence-related hospital admissions by figures for the total hospital expenditures obtained from the National Health Expenditures Survey (NHES). NHES was conducted from 1975 to 1993. A meta-analysis, conducted by Einarson and his colleagues between 1966 and 1989, showed that 6.5 to 10 percent of all hospital admissions were related to non-adherence.²⁷³ Using this rate of non-adherence and applying it to the total hospital expenditures, Coombs

²⁷² Coombs RB, Jensen P, Her MH, Ferguson BS, JL J, W WJS, et al. Review on the scientific literature on the prevalence, consequences, and health costs of noncompliance and inappropriate use of prescription medication in Canada: Pharmaceutical Manufacturers Association of Canada, 1995:103-20.

²⁷³ Einarson TR. Drug-related hospital admissions. *Annals of Pharmacotherapy* 1993;27(7-8):832-40.

and his colleagues estimated the cost of treating non-adherent hospital patients to range from CAN\$1.78 to CAN\$2.74 billion.

An estimate of the additional nursing expenditures due to non-adherence was made by multiplying the estimated rate of non-adherent-related nursing home admissions by the total nursing home expenditures in Canada in 1993. At the time Coombs and his colleagues conducted their study, data on the proportion of nursing home admissions due to non-adherence was not available. Instead, the authors used the results from an American study, conducted by Strandberg, which investigated the effects of medication non-adherence on nursing home admissions in Oregon.²⁷⁴ Strandberg found that “the single most important reason for residence of elderly patients in nursing homes was their inability to manage complex drug therapies.”^{275,276} Strandberg reported that 23 percent of the patients enrolled in the study showed no serious medical impairment other than their inability to manage their medication regimens; therefore, his findings suggests that up to 23 percent of nursing home patients in Oregon were likely to be non-adherent to their medications. Using this rate of non-adherence and multiplying it

²⁷⁴ Strandberg LR. Drugs as a reason for nursing home admissions. *American Health Care Association Journal* 1984;10(4):20-3.

²⁷⁵ Ibid.

²⁷⁶ Coombs RB, Jensen P, Her MH, Ferguson BS, JL J, W WJS, et al. Review on the scientific literature on the prevalence, consequences, and health costs of noncompliance and inappropriate use of prescription medication in Canada: Pharmaceutical Manufacturers Association of Canada, 1995:103-20.

by the total nursing home expenditures, Coombs and his colleagues estimated the cost of treating non-adherent nursing home patients to be CAN\$0.66 billion.

An estimate of the additional ambulatory care expenditures due to non-adherence was made by multiplying the estimated rate of non-adherent-related ambulatory care visits by the total ambulatory care expenditures in 1993.

Measurement of non-adherent related visits is difficult. As noted earlier, an estimated 6.5 percent to 10 percent of non-adherent behavior results in severe illness leading to hospitalization. In their study, Coombs et al. assumed that the proportion of non-adherent-related ambulatory care visits was greater or at least equal to the proportion of hospitalizations due to non-adherent behavior. Using these estimates, Coombs et al. estimated the costs of treating non-adherent patients in the ambulatory setting to be CAN\$1.09 billion.

Studies rarely calculate the indirect costs of disease. There are a number of methods that have been developed to aid researchers assess the indirect costs of diseases. Koopmanschap recently proposed the friction method of estimating indirect costs of disease.^{277,278,279,280,281} Many studies that have employed this

²⁷⁷ Koopmanschap MA, van Ineveld BM. Towards a new approach for estimating indirect costs of disease. *Social Science & Medicine* 1992;34(9):1005-10.

²⁷⁸ Koopmanschap MA, Rutten FF. Indirect costs in economic studies: confronting the confusion. *Pharmacoeconomics* 1993;4(6):446-54.

²⁷⁹ Koopmanschap MA, Rutten FF. The impact of indirect costs on outcomes of health care programs. *Health Economics* 1994;3(6):385-93.

²⁸⁰ Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *Journal of Health Economics* 1995;14(2):171-89.

²⁸¹ van Roijen L, Koopmanschap MA, Rutten FF, van der Maas PJ. Indirect costs of disease; an international comparison. *Health Policy* 1995;33(1):15-29.

technique have estimated that the indirect costs of disease are similar to the direct costs. Given that the direct costs of non-adherence were estimated at CAN\$3.53 to CAN\$4.49 billion, Coombs et al. suggest that the indirect costs of an equal value would bring the range of total costs associated with non-adherent behavior to CAN\$7.06 to CAN\$9.0 billion.

The lack of methodological rigor in studies assessing adherence has been described. The following section will describe the lack of methodological rigor in studies assessing the economics of therapeutic non-adherence. Cleemput et al. reviewed the literature on the economics of therapeutic non-adherence in patients and explored the methodological problems of studying the economic consequences of non-adherence.²⁸²

Cleemput et al. reported only 18 studies that assessed the economic impact of non-adherence from 1982 to 2000. Five of the studies assessed the overall cost of medication non-adherence in non-specific disease states, seven looked at the costs of medication non-adherence in specific disease states, and six assessed the cost-effectiveness of adherence enhancing interventions. The authors identified a number of methodological problems with many of the published studies on the economic impact of non-adherence. Specifically, there were problems relating to: (1) the definition and measurement of medication non-adherence; (2) study design; and (3) cost calculation and outcome measurement.

²⁸² Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. *Health Policy*. 2002;59(1):65-94.

One of the factors that have slowed the progress in adherence research (e.g., adherence improving interventions) is the difficulty in obtaining accurate and specific measures of adherence. Multiple measures of adherence have been used as discussed earlier. Within the same study, rates of adherence may vary widely based on the method used to measure adherence. Four of the studies reviewed by Cleemput et al. obtained adherence measurements directly from the literature. Three of the studies used prescription refill measures while six studies used self-report measures.^{283,284,285} Furthermore, a variety of operational definitions were used to describe non-adherence. These differences have implications for the techniques used to measure non-adherence which may lead to varying non-adherence rates. The absence of a “gold standard” for the definition and assessment of medication non-adherence makes interpretation and evaluation of results challenging.

Cleemput et al. also reviewed the study conducted by Brickman et al.; Cleemput and his colleagues noted that Brickman et al. did not directly estimate the costs of non-adherence.²⁸⁶ Instead, the authors developed a model that explained the relationship between non-adherence and certain psychosocial

²⁸³ McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive drug therapy in a Medicaid population. *Medical Care* 1994;32(3):214-26.

²⁸⁴ Rizzo JA, Simons WR. Variations in compliance among hypertensive patients by drug class: implications for health care costs. *Clinical Therapeutics* 1997;19(6):1446-57; discussion 1424-5.

²⁸⁵ Billups SJ, Malone DC, Carter BL. The relationship between drug therapy noncompliance and patient characteristics, health-related quality-of-life, and health care costs. *Pharmacotherapy* 2000;20(8):941-9.

²⁸⁶ Brickman AL, Yount SE. Noncompliance in end-stage renal disease: a threat to quality of care and cost containment. *Journal of Clinical Psychology in Medical Settings* 1996;3(4):399-412.

factors. These psychosocial factors were, in turn, related to health care utilization. From these relationships, the authors inferred a third relationship between non-adherence and health care utilization.

Billups et al. calculated costs by measuring the inputs in the care of compliant and non-compliant patients and by multiplying them by the respective unit costs of the inputs.²⁸⁷ Billups et al. examined computer pharmacy records from nine Veterans Affairs Medical Centers for 1,054 patients at risk for medication non-adherence to evaluate economic outcomes of non-adherence. Patients were defined as adherent if the average adherence measurement reached 0.8 and non-adherent if it was less than 0.8. The adherent and non-adherent groups did not differ significantly in health care utilization during the study period. Other studies used national annual hospitalization cost estimates,^{288,289} annual mean hospital charges per patient,²⁹⁰ Medicaid paid claims data,^{291,292}

²⁸⁷ Billups SJ, Malone DC, Carter BL. The relationship between drug therapy noncompliance and patient characteristics, health-related quality-of-life, and health care costs. *Pharmacotherapy* 2000;20(8):941-9.

²⁸⁸ Sullivan SD, Kreling DH, Hazlet TK. Noncompliance with medication regimens and subsequent hospitalizations: a literature analysis and cost of hospitalization estimate. *Journal of Research in Pharmaceutical Economics* 1990;2(2):19-33.

²⁸⁹ Iskedjian M, Addis A, Einarson TR. Estimating the cost of hospital admissions due to patient nonadherence in Ontario, Canada. *Pharmacoepidemiology and Drug Safety*;7:S92-3.

²⁹⁰ Levenson T, Grammer LC, Yarnold PR, Patterson R. Cost-effective management of malignant potentially fatal asthma. *Allergy & Asthma Proceedings* 1997;18(2):73-8.

²⁹¹ McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive drug therapy in a Medicaid population. *Medical Care* 1994;32(3):214-26.

²⁹² Rizzo JA, Simons WR. Variations in compliance among hypertensive patients by drug class: implications for health care costs. *Clinical Therapeutics* 1997;19(6):1446-57; discussion 1424-5.

annual hospital and nursing home expenditures,²⁹³ and average ambulatory care expenditures to determine cost estimates.²⁹⁴

Recently, researchers at the University of Minnesota used logistic regression to explore the relationships between refill adherence and specified HIV medications and combinations in a managed care organization.²⁹⁵ The researchers also examined the economic impact of medication adherence using ordinary least squares regression. Separate regressions were conducted using two separate adherence thresholds (75 percent and 95 percent). Health care costs were found to be significantly lower when the adherence rate was at least 95 percent.

Many of these economic studies did not provide comprehensive descriptions of the costs and methods for valuing the costs in the final analyses. Most studies considered only hospitalization costs. However, the studies by Rizzo et al. and Billups et al. did provide comprehensive descriptions of the valuation and assessment of costs related to non-adherence.^{296,297} These two studies included costs of clinic visits, physician office visits, nursing home

²⁹³ Coombs RB, Jensen P, Her MH, Ferguson BS, JL J, W WJS, et al. Review on the scientific literature on the prevalence, consequences, and health costs of noncompliance and inappropriate use of prescription medication in Canada: Pharmaceutical Manufacturers Association of Canada, 1995:103-20.

²⁹⁴ Ibid.

²⁹⁵ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

²⁹⁶ Billups SJ, Malone DC, Carter BL. The relationship between drug therapy noncompliance and patient characteristics, health-related quality-of-life, and health care costs. *Pharmacotherapy* 2000;20(8):941-9.

²⁹⁷ Rizzo JA, Simons WR. Variations in compliance among hypertensive patients by drug class: implications for health care costs. *Clinical Therapeutics* 1997;19(6):1446-57; discussion 1424-5.

admissions, laboratory tests, and drugs. Billups et al. reported no significant relationship between non-adherence and risk of hospitalization, mortality, and health care resource use after controlling for age, gender, and health status. Conversely, non-adherence was found to significantly increase health care utilization in many of the studies that analyzed data in specific disease states.^{298,299} In addition to reporting the impact of non-adherence on direct medical costs, the studies conducted by Sullivan et al. and Coombs et al. also calculated the impact of non-adherence on productivity costs.^{300,301} The study by Keeler et al. looked at the impact of improved adherence on health status, physical functioning and quality-adjusted-life-years (QALY).³⁰²

Hughes et al. also recently reviewed pharmacoeconomic studies which applied sensitivity analyses to non-adherence rates and found very few studies employing this methodology.^{303,304} The economic impact of non-adherence to

²⁹⁸ Ibid.

²⁹⁹ McCombs JS, Nichol MB, Newman CM, Sclar DA. The costs of interrupting antihypertensive drug therapy in a Medicaid population. *Medical Care* 1994;32(3):214-26.

³⁰⁰ Sullivan SD, Kreling DH, Hazlet TK. Noncompliance with medication regimens and subsequent hospitalizations: a literature analysis and cost of hospitalization estimate. *Journal of Research in Pharmaceutical Economics* 1990;2(2):19-33.

³⁰¹ Coombs RB, Jensen P, Her MH, Ferguson BS, JL J, W WJS, et al. Review on the scientific literature on the prevalence, consequences, and health costs of noncompliance and inappropriate use of prescription medication in Canada: Pharmaceutical Manufacturers Association of Canada, 1995:103-20.

³⁰² Keeler EB, Robalino DA, Frank JC, Hirsch SH, Maly RC, Reuben DB. Cost-effectiveness of outpatient geriatric assessment with an intervention to increase adherence. *Medical Care* 1999;37(12):1199-206.

³⁰³ Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health Economics*. 2001;10(7):601-15.

³⁰⁴ Hughes DA, Bagust A, Haycox A, Walley T. Accounting for noncompliance in pharmacoeconomic evaluations. *Pharmacoeconomics*. 2001;19(12):1185-97.

antiretroviral therapy can be significant. A recent study presented at the Fourth Annual European International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Conference investigated the impact of drug adherence on the cost of treating HIV/AIDS in Africa. They documented that HIV/AIDS costs for patients in Africa may be understated by more than 23 percent if adherence is taken into account.³⁰⁵ Similarly, Munakata et al. conducted a study to quantify the clinical and economic effects of non-adherence with triple therapy in treatment-naïve HIV patients.¹⁶⁵ A Markov model was developed to project quality-adjusted life expectancy and direct medical costs for HIV patients (mean age = 37 years) on an initial regimen of highly active antiretroviral therapy (HAART) with efavirenz, lamivudine and extended release stavudine given once daily. Each month, patients faced a risk of transition to AIDS that was a function of viral load, CD4 count, and adherence to drug therapy. Patients were assumed to change to another triple-therapy regimen if their viral load was ≥ 400 copies/mL or if they transitioned to AIDS. After four regimens, patients followed the natural history of the disease. The authors compared clinical and economic outcomes for two adherence scenarios: “clinical trial” (representing ideal utilization observed in clinical trials) and “typical” (based on observational studies in actual practice). Costs were derived from the HIV/AIDS Costs and Services Utilization Survey and average wholesale drug prices. Future costs and

³⁰⁵ Becker R, Shakur U. The impact of drug compliance on the cost of treating HIV/AIDS in Africa. ISPOR Fourth European Conference; 2001 November 11-13; Cannes, France.

QALYs were discounted 3%. Mean discounted quality-adjusted life expectancy was 8.6 and 10.0 QALYs under the typical and clinical trial adherence scenarios, respectively. Lifetime direct medical costs in the typical and trial scenarios were US\$295,000 and US\$336,000, respectively. Compared with typical adherence, clinical trial adherence conferred an average gain of 1.4 QALYs at an incremental cost of US\$29,000 per QALY gained.

Pharmacoeconomic evaluations using data from clinical trials are not appropriately designed to address issues of effectiveness. Consequently, researchers use observational studies to study real-life settings. In the absence of effectiveness data, researchers should allow for the differences in adherence which exist by applying appropriate modeling techniques to simulate the anticipated benefits offered by a drug given that in reality, non-adherence is greater than in the clinical setting. In practice, few economic analyses (e.g., cost-effectiveness) correct for the factor of non-adherence. For economic analyses that correct for the factors of non-adherence, the correction usually occurs in a sensitivity analysis in which the impact of varying adherence rates on the cost-effectiveness ratio is tested.

1.8 HIV and Health Related Quality-of-Life

The accurate measurement of health status is essential to assess the burden of illness and the impact of therapies. Survival measurements, alone, are no longer sufficient to describe patients' health; consequently, the impact of disease on health must be considered as well. The quality-adjusted-life-year (QALY) and disability-adjusted-life year are now considered necessary and useful measures to capture changes in life expectancy as well as the quality of those years.

Typically, QALYs are calculated by assigning weights to the amount of time spent in various health states. Each health state is ascribed a number between zero and one reflecting the preference for the health state. The values assigned to the health states are then summed across the years of survival yielding utilities or quality-of-life weights. Take for example a patient who is infected with HIV with a CD4 count less than 200 cells/ μ L. Let us assume that the assigned utility for this state is 0.5 and he lives in this state for five years. His total quality-adjusted life years will be 2.5 (5 years X 0.5).

There is variation in the way researchers define the upper and lower bounds of the utility scales; some researchers define 0 as "death," whereas others define 0 as "the worst possible health." Thus, scale boundary labels may influence the estimates of utility. Furthermore, there are a variety of methods used to assess these utilities which may further lead to variation in the utility

estimates. For example, the three main methods used to directly elicit utilities are the standard gamble, time trade off (TTO) and the rating scale.

The standard gamble involves asking respondents to make trade-offs between a particular health state (e.g., CD4 count less than 200) and a gamble involving some chance of a better or worse outcome (e.g., 0.6 chance of perfect health or 0.4 chance of death because of side-effects of medication). The probability of achieving perfect health is then varied until the respondent is indifferent between this chance and being in a health state with CD4 count less than 200. Then, if a respondent is indifferent when the probability of attaining perfect health is 0.6, then the assigned utility when the CD4 count is less than 200 is 0.6.

Conversely, the time-trade off method involves asking the respondent to make a trade-off between a shorter life span in perfect health or a longer life span in a particular health state (e.g., CD count less than 200). If the respondent is indifferent between spending 60 percent of her projected life expectancy in perfect health over living the remainder of her life (100% life expectancy) with CD4 counts less than 200, then the assigned utility will be 0.6.

The rating scale is a conceptually easier method to assess utilities. The rating scale is a method of assessing preferences using a tool, typically a line, with one end representing the best health state and one end representing the worst. The respondent is asked to evaluate a given health state by placing it on the scale

between these anchors. These scales are considered continuous and may be divided into discrete intervals or appear as visual analog scales with no markers.

There are a number of indirect methods for soliciting health state utilities including the use of quality-of-life instruments such as the Short Form-36, Health Utilities Index, Quality of Well-Being scale and the Medical Outcomes Study HIV Survey (MOS-HIV). Coupled with the fact that there are different assessments methods used to solicit QOL measures, another possible source of variation of these estimates is that authors collecting these estimates do so from different types of respondents (e.g., patients, clinicians, personal judgments and the general population); therefore, published estimates of QOL may vary over a wide range.

In recent years, many studies have reported the health related quality-of-life of patients infected with HIV (Table 1-6).^{88,112,113,231,236} Most recently, Honiden et al. sought to understand how diagnosis with HIV affects health-related quality of life.¹¹³ The authors assessed health related quality of life using utility-based measures in a VA clinic and a University-based clinic. A computer-based tool was used to assess patients' health related quality of life, using the TTO method. Respondents rated their current health as well as three hypothetical states for asymptomatic HIV, symptomatic HIV and AIDS. For the hypothetical states, a detailed description of the health states was provided to respondents. Briefly, 'asymptomatic HIV infection' described HIV-positive individuals who

are otherwise healthy. ‘Symptomatic HIV infection’ described HIV positive-individuals with minor symptoms (e.g., weight loss, chronic diarrhea, fever and swollen glands). ‘AIDS’ described HIV-positive individuals with AIDS defining illnesses. Overall, respondents from the VA had a lower utility for current health (0.79) compared with respondents from the University (0.95); however, respondents from the VA had a mean CD4 count that was substantially lower than that of respondents from the University. The mean current-health utilities for VA patients who had asymptomatic HIV infection (n=2), symptomatic infection (n=14) and AIDS (n=24) were 0.99, 0.75 and 0.80, respectively. The mean VA-specific utilities for the hypothetical states for the HIV asymptomatic (n=40), HIV symptomatic (n=40), and AIDS (n=40) states were 0.9, 0.75, and 0.56, respectively (Table 1-6).

Tengs and Wallace reported the utilities of one thousand health related quality-of-life estimates.³⁰⁶ As suspected, the variability of the reported utility estimates for any particular disease state was large depending on the instruments used and/or the target audience (respondents). For example, many of the reported QOL estimates for AIDS range from 0.24 to 0.79. Also, the QOL estimates for symptomatic infection range from 0.48 to 0.82. Furthermore, the QOL estimates of asymptomatic HIV infection range from 0.69 to 0.88. In response to the heterogeneity of study design characteristics and variation of the resulting

³⁰⁶ Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Medical Care*. 2000;38(6):583-637.

utilities, Tengs and Lin performed a meta-analysis to derive pooled utilities for HIV/AIDS (Table 1-6).³⁰⁷ The estimated pooled utility for AIDS using the time trade-off method with patients was 0.702. The estimated pooled utility for symptomatic HIV infection using the same method was 0.82. The estimated pooled utility for asymptomatic HIV infection using the same method was 0.94. If non-patients were used instead, the utility weights for AIDS, symptomatic HIV and asymptomatic HIV were 0.44, 0.56, and 0.68, respectively. Therefore, patients offered a utility 0.26 higher than non-patients. These results were consistent with the current body of literature which document higher utility weights offered by patients than non-patients. Finally, although utility scores obtained from using different assessment methods were different, these differences were not significant. Nevertheless, utilities elicited from TTO were 0.10 points higher than utilities assessed from the standard gamble method and 0.12 points higher than those elicited from the rating scale. However, the literature suggests that higher utility estimates are obtained with the standard gamble than with the TTO (and, in turn, with the rating scale).

Although this is currently the only meta-analysis of HIV/AIDS utilities, the methodology employed in the analysis was not transparent. In 1988, Einarson et al. presented a stepwise approach for conducting meta-analysis studies which listed six major areas that should be addressed in meta-analysis: study design,

³⁰⁷ Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. *Medical Decision Making* 2002;22(6):475-81.

combinability, control bias, statistical analysis, sensitivity analysis and application of results.³⁰⁸ The meta-analysis conducted by Tengs and Lin did not explicitly address the six major areas that Einarson et al. recommended.

Table 1-6: Quality-of-Life Utility Values

Quality-of-Life Utility Values							
CD4 counts (cells/ μ L)	Scale 1 ^{113,†}	Scale 2 ^{113,*}	Scale 3 ²³¹	Scale 4 ³⁰⁹	Scale 5 ³¹⁰	Scale 6 ³¹¹	Scale 7 ³¹²
> 500	0.90	0.99	0.94	1	0.69	0.72	0.94
350-500	0.90	0.99	0.94	1	0.68	0.66	0.94
200-350	0.90	0.99	0.94	0.76	0.68	0.66	0.94
<200	0.75	0.75	0.82	0.65	0.64	0.63	0.87
AIDS	0.56	0.80	0.70	0.62	0.64	0.63	0.80

† Hypothetical states derived utilities; original data stratified into three categories (asymptomatic HIV infection, symptomatic HIV infection and AIDS).

* Current health states derived utilities; original data stratified into three categories (asymptomatic HIV infection, symptomatic HIV infection and AIDS).

³⁰⁸ Einarson TR, Leeder JS, Koren G. A method for meta-analysis of epidemiological studies. *Drug Intelligence & Clinical Pharmacy* 1988;22(10):813-24.

³⁰⁹ Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;16(1):54-62.

³¹⁰ Tsevat J, Solzan JG, Kuntz KM, Ragland J, Currier JS, Sell RL, et al. Health values of patients infected with human immunodeficiency virus. Relationship to mental health and physical functioning. *Medical Care* 1996;34(1):44-57.

³¹¹ Ibid.

³¹² Freedberg KA, Losina E, Weinstein MC, Paltiel AD, Cohen CJ, Seage GR, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *New England Journal of Medicine* 2001;344(11):824-31.

1.9 Study Rationale and Objectives

1.9.1 Study Rationale

Few empirical studies of adherence to specific combination regimens in HIV/AIDS have been conducted.³¹³ Pre-HAART studies examining the determinants of adherence were typically cross-sectional, involved monotherapy, and primarily focused on intravenous drug users.³¹⁴ Since the adoption of HAART as standard care, studies examining adherence, are few and limited in size. Reported adherence rates for combination antiretroviral therapy in the literature are scarce and there is much variance in the results. The literature indicates an adherence level of at least 90 percent and perhaps more than 95 percent may be required to sustain low levels of HIV.³¹⁵

Patients and clinicians need to know to what extent multi-drug antiretroviral therapy improves long-term survival and whether this improvement depends on adherence to medication regimens. The purpose of this study was to investigate the impact of non-adherence, and determine if non-adherence represents a real and costly problem affecting the VA health care system.

Unfortunately, HAART has only been available since 1996, and no long-term

³¹³ Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care* 2001;13(6):709-20.

³¹⁴ Ickovics JR, Meisler AW. Adherence in AIDS clinical trials: a framework for clinical research and clinical care. *Journal of Clinical Epidemiology* 1997;50(4):385-91.

³¹⁵ Walsh JC, Horne R, Dalton M, Burgess AP, Gazzard BG. Reasons for non-adherence to antiretroviral therapy: patients' perspectives provide evidence of multiple causes. *AIDS Care* 2001;13(6):709-20.

survival data are available. One approach to this problem is computer simulation modeling using short-term data on the timing of treatment failure, on-treatment mortality, and the competing risk of mortality due to aging. By fitting parametric and non-parametric statistical models, it is possible to extrapolate long-term estimates of each of these effects from short-term data. Markov modeling is a powerful method of integrating information from each of these components into a single long-term estimate of survival.

Given the wide range of issues at stake, promoting a more appropriate use of prescription medicines will necessarily involve a variety of health care stakeholders, including the pharmaceutical industry, if the potential cost savings available to health care institutions are to be achieved. The results of this study may lend further support to the implementation of strategies that improve patient adherence (e.g., pharmacy-based adherence clinics, education programs and the use of drug adherence devices). Increasing patient knowledge of prescription medications through educational materials and communications with physicians and pharmacists is fundamental to improving adherence. This is may reduce the mortality and morbidity attributable to non-adherence.

1.9.2 Objectives

The objectives of the research study were to assess the relationship between patient adherence to antiretroviral therapy and: (1) cost-effectiveness of antiretroviral regimens; and (2) patterns of antiretroviral regimen switches.

CHAPTER 2

DECISION ANALYSIS AND MARKOV MODELING

2.1 Overview of Decision Analysis and Markov Modeling

Decision analysis and Markov modeling will be conducted to investigate the impact of non-adherence on life expectancy and health care utilization; therefore, an in-depth discussion of the applicability of decision-analytical modeling is warranted. A review of the literature indicates that, in recent years, decision analysis modeling has been widely accepted by researchers in health care. In addition, it is frequently used in economic evaluations. These models have a number of uses including the synthesis of data from various sources and extrapolation from primary data sources. Unfortunately, there are several shortcomings with using simple decision trees in economic evaluation. For example, a patient may experience an event more than once in the future. In addition, simple decision trees are not able to specify when events occur. This problem may be addressed by making the assumption that an event occurs at the average time consistent with the known rate of each complication. For example, if the rate of acquiring an opportunistic infection in a patient with AIDS is a constant 0.8 per person year, then the average time before the occurrence of an

infection is 1/0.8 or 1.25 years. Therefore, the event of having an opportunistic infection will be associated with a utility of 1.25 years of normal-quality survival. However, if a patient lives only six months after an opportunistic infection, assigning a utility of 1.25 years will have the effect of “improving” the patient’s life expectancy.³¹⁶ Therefore, simple decision trees are not able to adequately address the uncertain timing of events, nor are they able to adequately represent events that are repetitive. When describing a decision analysis model, it is common to classify it as either deterministic or probabilistic. The following section will describe the two types of processes commonly used in decision making: (1) deterministic models, and; (2) probability models.

A deterministic mathematical model is one in which the parameters and variables are not subject to random fluctuations, so that at any time the system is completely defined by its initial conditions and the dynamics of the system over time. A deterministic process is one which can be completely predicted beforehand given the initial conditions. Antiretroviral therapy and the suppression of viral load is one example. Assuming there are no resistant strains of the virus, and that the antiretroviral is effective, the system tends towards “non-randomness.” A non-health related example of a system which leans towards being deterministic is the overall motion of the billiard ball when it is hit by another one. Since the initial conditions of the system can be controlled (e.g.,

³¹⁶ Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Medical Decision Making* 1993;13(4):322-38.

angle of contact, speed, friction of table), the unique parameters can be used to predict what will happen to the second ball. Of important note is that no system is completely deterministic; rather, a system can be described by the extent to which it is deterministic. Deterministic models that change continuously over time are typically described by differential equations. A differential equation model is one in which the system changes continuously over time. Derivatives are used for describing the rate of change of key variables (such as the prevalence of HIV infection in the population).

Likewise, no system is completely probabilistic; nevertheless, probability models are more representative of real-life situations than deterministic models. Probability models are needed in medical-decision making to evaluate resource use and health outcomes following interventions. Stochastic processes are frequently used in health care modeling and they are processes that approach the probability model. Stochastic processes are sequences of random variables generated by probabilistic laws which evolve over time. The stochastic model is unique in that it is a mathematical model which takes into consideration the presence of some randomness in one or more of its parameters or variables. The predictions of the model are not unique, and so such models have to be run a number of times to produce a probability distribution of possible outcomes. A stochastic process is one for which there is a relatively high amount of uncertainty in the physical law/reasons for observations. Using our previous example, since

viruses mutate and resistant strains emerge and patients are non-adherent to antiretroviral therapy, the health outcomes are now subject to random variation; this model approaches a probabilistic model. In terms of the billiard ball, its motion in the first 1×10^{-6} seconds after impact may not be deterministic because there are many factors that we may not have identified or taken into consideration that may also affect it.

'Random' is a misunderstood word when used without qualification. Typically it refers to the outcome of unpredictable physical processes or 'experiments.' Random numbers quantify and translate observations from the event/occurrence space to the number space. They represent randomness and allow further analysis and interpretation using mathematical principles. It is a way of looking at events and trying to predict them. If everything is known about the nature of a system, it is not random; alternatively, if no patterns are seen, it may appear random to the observer. A more appropriate phrase to use may be 'apparently' random. Randomness is observed due to non-linear, recursive processes with extreme sensitivity to initial conditions. No process is truly random or truly deterministic. It is a way of looking and modeling processes depending on assumptions made and questions to be answered.

A stochastic process in a probability space is characterized by a set of states and an index parameter t , which is an element of an index set T .¹²⁵ In mathematical terms, this family of random variables is described as $[X(t), t \in T]$,

where $X(t)$ denotes the observation at time t . The parameter, t , is usually a time variable that ranges between 0 and ∞ . States designated by $x(t)$ are the values assumed by the random variable $X(t)$. The set of all possible states is called the state space in stochastic processes. The space can be regarded as continuous or discrete. If a CD4 count is used as primary state indicator for HIV/AIDS patients, then $CD4 > 200$ could be classified as a discrete state which does not overlap another state of $100 < CD4 \leq 200$. A state space for any HIV patient can be defined as $[(CD4 \leq 100), (100 < CD4 \leq 200), CD4 > 200]$. An example of a continuous state is temperature in a furnace. Therefore, a stochastic process could be classified based on whether the index set T is continuous, e.g., $T = [t: 0 \leq t \leq +\infty]$, or discrete, e.g., $T = [t: 0, 1, 2, \dots]$. The system is defined by one parameter, t , because all states are functions of time.

In 1983, Markov models were first used to describe and determine prognosis in the medical field. Markov processes are a class of stochastic processes that are characterized by the Markov property which is described below. The Markov model provides a convenient way of modeling the natural history and prognosis of clinical problems with ongoing risk. Markov decision models are often used to model the prognosis or natural history of patients following a particular management strategy. Importantly, Markov decision trees need to reflect current clinical practice and the natural history of the disease. For example, a strategy that may involve surgery would need to model the events of

death from surgery, complications from surgery, and various other outcomes that may follow surgery.³¹⁷ The modeler also needs to assign a finite time-frame for analysis, which may or may not include death, depending on the questions being addressed.

Markov processes could be discrete or continuous with respect to time and/or states. Depending on the nature of the state space and state time, Markov processes can be divided into four different classes:³¹⁸

- a) discrete state space and discrete time, t ;
- b) discrete state space and continuous time, t ;
- c) continuous state space and discrete time, t ; and
- d) continuous state space and continuous time, t .

If a finite time index is assumed [$T = (0, 1, \dots, n)$], the successive observations (X_0, X_1, \dots, X_n) define the set of random variables at time steps.³¹⁹ When a system moves from one state to another, the set of random variables $X(t_1), \dots, X(t_n)$, where $T = [t: 1 \leq t \leq n]$, is a discrete and finite index set exhibiting some sort of dependence (Markov property). For example, the quality-of-life of an individual with a CD4 count between 100 and 200/mm³ is a function of the individual's quality-of-life when in a state of CD4 cell counts $\geq 200/\text{mm}^3$. Time dependence in probability models can be hard to deal with and the simplest

³¹⁷ Ibid.

³¹⁸ Kijima M. *Markov Processes for Stochastic Modeling*. 1st ed. Tokyo: Chapman & Hall, 1997.

³¹⁹ Ibid.

type of dependence is called the Markovian dependence, where the state in which a system finds itself at time t , depends only where it was at time $t - 1$. This phenomenon is called the “memoryless” property (Markov property). Therefore, the process has no memory for earlier cycles. In other words, to make the best prediction of what happens at time $t + 1$, one only needs to consider what happens at time t . The probability of the occurrence of the state X_n depends only on the immediately preceding state X_{n-1} .^{320,321,322} Therefore, past times give no additional information. In the earlier example, the probability that the patient will end in the dead state can be predicted if he/she started in the AIDS state. This is the only information that can be used and whatever occurs in previous states (e.g., how long a patient spends in the AIDS or pre-AIDS state) is irrelevant in a true Markov process. The Markov property or a similar property entailing limited, finite memory is necessary to model prognosis in a model with a finite number of states.

The Markov model is also distinguished from other stochastic processes by the characterization of six basic attributes: structure, initial probabilities, transition probabilities, rewards, and termination condition. Microcomputer software has been developed to aid medical decision makers construct and

³²⁰ Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Medical Decision Making* 1993;13(4):322-38.

³²¹ Beck JR, Pauker SG. The Markov process in medical prognosis. *Ibid.* 1983;3:419-58.

³²² Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17(5):479-500.

evaluate Markov models more easily. Some of the more popular applications that are currently used to handle the complex decision analysis calculations to produce parameter estimates for Markov models include BMDP™, DATA™, SMLTREE™, and Decision Maker™. The following section will describe the main attributes of a Markov model.

2.1.1 Structure

In Markov modeling, the disease is generally divided into distinct states and it assumes that the patient is always in one of a finite number of states. These states are commonly referred to as Markov states. The states should also be clearly defined and mutually exclusive; therefore, a patient cannot be in more than one state at any one time. The set of possible states should represent clinically and economically important events in the course of the disease. These states are commonly derived from the literature, databases, or expert panels. Table 2-1 shows a hypothetical state space which consists of a number of mutually exclusive disease states for patients diagnosed with HIV disease. The state space for this example consists of (HIV₁, HIV₂, HIV₃, AIDS, and DEAD). The model consists of five states to characterize HIV disease.

Table 2-1: Hypothetical State Space in Stochastic Models

States	Name	Description
Non-absorbing	HIV_j	HIV+ but not AIDS
	1) HIV ₁ : CD4 ≥ 400	
	2) HIV ₂ : 300 ≤ CD4 < 400	
Absorbing	3) HIV ₃ : 200 ≤ CD4 < 300	
	AIDS	CD4 < 200
	D	DEAD

The next step in building a Markov model is to specify different state transitions possible in the system. Disease progression can be considered as being described by patients moving from one discrete state to another as a function of time. DEAD in such an instance is a state of being where there is no transition out from it. For the sake of simplicity, researchers could assume that no reversals of CD4 counts from more progressive disease states to better clinical states will be considered in a Markov model describing disease progression in HIV-infected individuals. However, with aggressive antiretroviral therapy, CD4 counts have been found to improve in patients. Therefore, these reversible transitions need to be considered in models that represent the course of HIV disease after the introduction of HAART. To ensure that a Markov process terminates, it is essential that there is an ‘absorbing’ state. States of Markov models from which it is impossible to leave are known as ‘absorbing states’.^{323,324} In medical decision

³²³ Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Medical Decision Making* 1993;13(4):322-38.

³²⁴ Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17(5):479-500.

making, this absorption state is generally represented by DEAD since patients cannot leave this state. Also, it is possible for patients to remain in states they were in during the previous cycle.

2.1.2 Cycle Length, Transition Probabilities, Time-Independent Markov Chains and Time-Dependent Markov Processes

The cycle length of a Markov model is the length of time represented by a single cycle of a Markov process. This number is not explicitly stated in the model; however, it is implicit in the assignment of probabilities, rewards, and the termination condition. The time cycles may be discrete or continuous and the length of the cycle is generally chosen to represent a clinically meaningful time interval. Long time frames (e.g., one year) may be used for models that span the entire life history of a patient, while short time frames (e.g., one month) may be used for events that may occur more frequently.³²⁵ Usually, the choice of cycle time may depend on the availability of probability data. During each cycle, patients may transition from one state to another, and transition probabilities are then assigned to describe transition between these states. It is assumed that patients in a given state can only make a single transition or remain in that same state during a cycle.

³²⁵ Beck JR, Pauker SG. The Markov process in medical prognosis. *Medical Decision Making* 1983;3(4):419-58.

The net probability of moving from one state to another is called a transition probability. During each cycle, transitions are assumed to take place. The Markov process can be completely defined by the probability distribution among the starting states and the transition probabilities. If a model has k states, of which j are absorbing, then all possible transitions between states can be seen in a $k \times k$ matrix and there will be k^2 transition probabilities although $j \cdot (k-1)$ will be constrained to have the value 0 and j will be constrained to have the value 1.³⁴ Disease progression can be considered as being described by patients moving from one discrete state to the other as a function of time. Each state is commonly represented by a circle or rectangle, and arrows that connect two different states indicate allowed transitions. As discussed previously, depending on the clinical prognosis of the disease state, only certain transitions are allowed. For example, a patient in the DEAD state cannot make any transitions to other states. Furthermore, arrows leading from a state back to itself represent patients that remain in the same state after a cycle (e.g., DEAD).

In the literature, state transitions are commonly expressed as rates and not probabilities. The rate describes the occurrence of an event for a given number of patients per unit time. However, probabilities range from zero to one, and have time built into them implicitly; probabilities describe the likelihood that an event will occur in a given length of time. In order to determine life expectancy, Markov processes require rates to be converted to probabilities. The relationship

between rates and probabilities is illustrated below. Sonnenberg and Beck noted that the “probability of transition in time t is always less than the corresponding rate per time t because as the cohort members die, fewer are at risk for the transition later in the time period.”³²⁶ The probability (P) of an event that occurs at a constant rate (r) in a specified time (t) is given by the equation:³²⁷

$$P = 1 - e^{-rt}$$

In the following illustrative model there are five states resulting in a total of 25 transition probabilities (Table 2.2). However, if it is assumed that individuals do not recover from progressive disease, a number of transitions can be eliminated. Also determining the probability of remaining in the initial state at the beginning of the cycle is not necessary since it is simply one minus the probability of leaving that state. Therefore, there are only ten transition probabilities to estimate. Constraints may also be introduced into the Markov process to incorporate computational or medical/scientific logic within the system. For example, because of the timing of the observations, a patient may appear to have skipped a state during a cycle. In these instances, it is assumed that the patient moved through the “skipped” state during the cycle. The correlation matrix for the illustrative model is seen in Table 2-2.

³²⁶ Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Ibid.*1993;13:322-38.

³²⁷ *Ibid.*

Table 2-2: Transition Matrix for the Illustrative Model

Transition From	To					Total
	HIV ₁	HIV ₂	HIV ₃	AIDS	DEAD	
HIV ₁	1-(tpA+tpB+tpC+tpD)	tpA	tpB	tpC	tpD	1
HIV ₂	0	1-(tpE+tpF+tpG)	tpE	tpF	tpG	1
HIV ₃	0	0	1-(tpH+tpI)	tpH	tpI	1
AIDS	0	0	0	1-tpJ	tpJ	1
DEAD	0	0	0	0	1	1

tp = transition probability

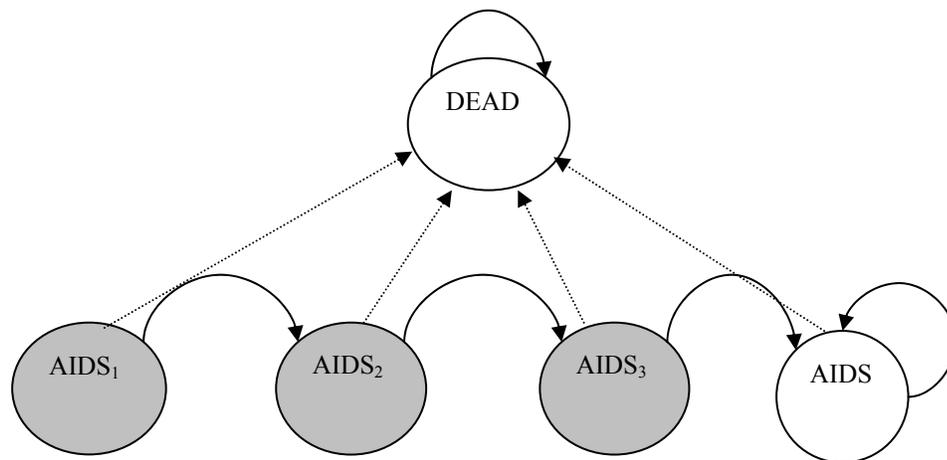
Next, there are two different types of Markov processes that can be characterized by the form of the transition probabilities: time-independent Markov chains and time-dependent Markov processes. In time-independent Markov chains, all the transition probabilities are assumed to be constant over time. The behavior of a time-independent Markov chain over time can be determined as an exact solution by simple matrix algebra if the model has an absorbing state. However, this time-independent transition assumption may not be realistic in many health care models where, for example, the risk of death increases exponentially with time. For example, the transition probability for the transition from AIDS to DEAD consists of the probability of dying from “natural causes” (e.g., exponential) and the probability of dying from AIDS; the probability of dying from AIDS may or may not be constant over time.

Therefore, to more accurately model transition probabilities that vary over time, time-dependent Markov processes need to be considered. For example, let us assume that the transitional probability of moving from HIV₁ to HIV₂ is an increasing function of the time or cycle of the model. In other words, the more cycles an individual traverses, the more likely it is that the individual will progress from HIV₁ to HIV₂. Also, the risk of death from all causes is assumed to be time-dependent. In other words, the risk of death from AIDS varies with the time a patient has been in the AIDS state. The “memoryless” feature of Markov models does not allow for adjustment of different probabilities for patients who have spent varying times in a particular state. Therefore, the Markovian assumption restricts transitions from AIDS state to the DEAD state to be dependent on the time patients have spent in the AIDS state since the Markov model treats all patients in the AIDS state as equal.

Fortunately, a number of techniques can be employed to get around this problem. The following discussion will introduce the concept of temporary states as one of the tools that a Markov model can use to adjust for these varying transitional probabilities. Temporary states have two uses: (1) temporary states can be used to assign specific temporary transitional probabilities for the different states; and (2) temporary states can be used to assign a utility or cost adjustment specific to that particular state. Temporary states are normally required whenever there is an event that has only short-term effects.

For example, a temporary state can describe an opportunistic infection resulting from HIV infection. Also, temporary states make transitions to other states only. Therefore, temporary states cannot make transition back to themselves. This guarantees that a patient only spends one cycle in any particular temporary state. A special arrangement of temporary states, tunnel states, consists of a sequence of temporary states that must be visited in fixed sequence. Based on our previous example of patients progressing from AIDS to DEAD, one could create a series temporary states based on how long a patient has been in an AIDS state (Figure 2-1).

Figure 2-1: Temporary States



The probability of death may be higher in the AIDS₃ state than in any of the previous AIDS states. These states can be visited only in a fixed sequence.

2.1.3 Rewards

Analysis of a Markov process yields the average number of cycles spent by a patient in each of the states. If survival is the primary endpoint of interest, one need only add together the times spent in all states.³²⁸

$$\text{Expected Utility} = \sum_{s=1}^{n-1} T_s$$

T_s is the time spent in state, s . However, if the quality of survival is sought, the incremental utility can be calculated. The incremental utility is the utility that is described when spending one cycle in a particular state. Utility calculated for the entire Markov process is the sum of the total number of cycles spent in each state, multiplied by the incremental utility for each state.

$$\text{Expected Utility} = \sum_{s=1}^{n-1} T_s \times U_s$$

For example, consider a patient who spends four cycles in the state HIV₁, two cycles in HIV₂, three cycles in HIV₃ and two cycles in the AIDS state. Also, assume that the incremental utilities, U_s , for states HIV₁, HIV₂, HIV₃, and AIDS are 0.5, 0.4, 0.3, and 0.2, respectively. Therefore, the utility assigned to the patient would be $(4 \times 0.5) + (2 \times 0.4) + (3 \times 0.3) + (2 \times 0.2)$ or 4.1 quality adjusted cycles (quality-adjusted life expectancy).

³²⁸ Ibid.

2.2 Calculation of Life Expectancy with the Markov Model

The assignment of transitional probabilities to pre-determined states is sufficient to calculate life expectancy with the model. For any Markov process with an absorbing state (e.g., DEAD) that can be reached from every other state, the probability of eventual absorption (or death) is one. In addition, the time before absorption is finite; therefore, the expected time before absorption is the life expectancy of the cohort of patients modeled by the process. The expected time before absorption can be calculated in three ways: (1) matrix algebraic solutions; (2) Markov cohort simulation; and (3) first-order Monte Carlo simulations.

For a time-independent Markov chain, in which all transition probabilities are assumed to be constant over time, a matrix algebraic solution can be used to calculate life expectancy. Time-independent Markov chains are simple to calculate since the probability of being in a particular state at a particular point in time can be calculated using simple matrix algebra. This yields the “fundamental matrix” which provides an exact solution to estimate the length of time spent by a patient from their starting states. The fundamental matrix solution is very fast because it involves only matrix algebra and provides an exact solution that is not sensitive to cycle time. However, the matrix formulation is restricted to problems with constant transition probabilities. Sonnenberg and Beck note that the main disadvantage for using the fundamental matrix to estimate “survival” is the

assumption of constant transition probabilities may be too restrictive for many potential health care applications.³²⁹ For example, for most time periods, it would be incorrect to assume that the risk of death was constant. In summary, such models rarely characterize disease processes and an assumption of constant transition probabilities may be too restrictive for many potential applications in the health field.

For Markov processes, in which transition probabilities can vary over time (time-dependent), a deterministic simulation of a cohort of patients (Markov cohort simulation) or a probabilistic first-order Monte Carlo simulation of a large series of individual patients can be used to calculate life expectancy. The two approaches used to calculate time-dependent Markov processes should give similar results and, in fact, identical results for an “ergodic” system of an infinite cohort. The “ergodic” property specifies that average value over time equals average value over space. For example, the proportion of heads and tails will be statistically equal if a million coins are flipped at the same time, or if a coin is flipped a million times. The analysis and presentation of Markov models using time-dependent Markov processes will be described in the following section.

2.2.1 Markov Cohort Simulation

In this approach, a large number of hypothetical patients are followed as a cohort. The patients are deterministically distributed among the model’s states at each

³²⁹ Ibid.

cycle of the process. For a specified set of inputs, the Markov model always returns the same result. The entire cohort is reallocated to states according to the transition matrix probabilities. The Markov cohort is a simulation although patients are not followed individually. Figure 2-2 shows the initial distribution of all patients in the HIV3 state, as well as the distribution partway through the simulation, and the final distribution, with the entire cohort in the DEAD state. Initially, in our cohort, all patients are in the HIV3 state but this is not a necessary condition; patients may be dispersed in different states at the beginning of the simulation. For each cycle, patients distribute into different states according to transitional probabilities, resulting in a new distribution of states. The cohort simulation can also be represented by Table 2-3. The “start” cycle represents the starting states and the distribution of patients in the different states. There are 10,000 patients in the HIV3 state. Suppose the transition probabilities between all states are represented in Table 2-4. Therefore, the new distribution of patients after the first cycle is represented in Table 2-3; 6,000 patients remain in the HIV₃ state, 2,000 will “migrate” to the AIDS and DEAD states. This process is repeated for subsequent cycles. If the incremental utilities of the HIV₃, AIDS, and DEAD states are 1.0, 0.7, and 0, respectively, then the cycle sum during the first cycle is equal to $(6,000 \times 1) + (2,000 \times 0.7) + (2,000 \times 0.0) = 7,400$. The cycle sum is defined as the sum of the number of cohort members in each state multiplied by the incremental utility for that state.

Since the probabilities of leaving the HIV₃ and AIDS states are finite, and the probability of leaving the DEAD state is zero, the cohort gradually migrates to the DEAD state. However, although the fraction of people migrating to the DEAD state approaches one, there is still a finite probability of a patient remaining alive. Therefore, the simulation ends when the fraction of the cohort remaining alive falls below a certain arbitrary amount.

Figure 2-2: Cohort Simulation

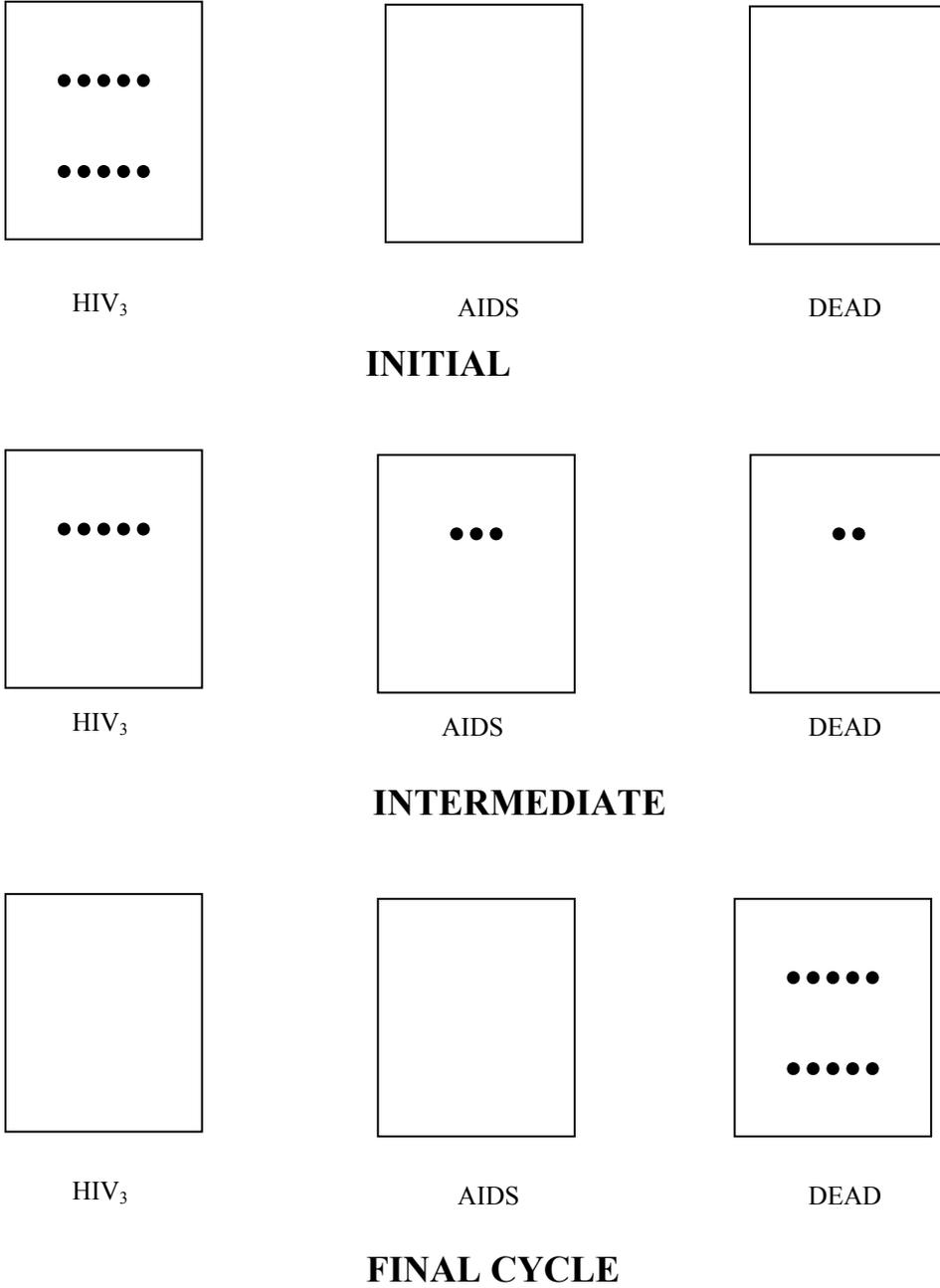


Table 2-3: Markov Cohort Simulation

Cycle	HIV ₃	AIDS	DEAD	Cycle Sum*	Cumulative Utility
Start	10,000	0	0	-	-
1	6,000	2,000	2,000	7,400	7,400
2	3,600	2,400	4,000	5,280	12,680
.
.
23	0	1	9,999	7	23,752
24	0	0	10,000	<1	23,752
Total	15,000	12,500		23,752	23,752

*The cycle sum is defined as the sum of the number of cohort members in each state multiplied by the incremental utility for that state. Incremental utilities for HIV₃, AIDS, DEAD are 1.0, 0.7, and 0, respectively.

Table 2-4: Fundamental Matrix

From	To		
	HIV ₃	AIDS	DEAD
HIV ₃	0.6	0.2	0.2
AIDS	0	0.6	0.4
DEAD	0	0	1

2.2.2 First-Order Markov Monte Carlo Simulation

In this approach, a large number of patients are followed through the model individually (Figure 2-3). In other words, patients traverse a Markov process one by one in a probabilistic manner according to the transition matrix probabilities. This approach, involving probabilistic transitions, is where the first-

order Monte Carlo simulation appears.^{330,331,332} First-order simulations (trials) are a kind of stochastic analysis; two trials using the same inputs can return very different results due to randomization at chance nodes.

Each patient begins in a particular state, and at each cycle, the patient changes states according to the laws of chance, as dictated by the transition probabilities. The difference between the cohort simulation and the first-order Monte Carlo simulation is that although individual patients are subjected to the same probabilities of transitions, they may or may not migrate between states in any given cycle. Therefore, the paths followed by different patients may be different due to random variation.

Typically, a random number between zero and one is generated, and this is used together with the transitional probabilities to determine what happens to the individual at each cycle of the process. The range from zero to one is then subdivided into ranges proportional for each of the possible transitions. Then, the transition is made according to which sub-range in the zero to one interval contains the randomly drawn number. For example, if an individual is in HIV₁ state with a transition probability to HIV₂ of 0.4, a transitional probability to HIV₃ of 0.5, and a probability of remaining in HIV₁ equal to 0.1, then the range could

³³⁰ Beck JR, Pauker SG. The Markov process in medical prognosis. *Ibid.* 1983;3:419-58.

³³¹ Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Ibid.* 1993;13:322-38.

³³² Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17(5):479-500.

be divided so that 0-0.4 corresponds to a transition to HIV₂, the range 0.4-0.9, corresponds to a transition to HIV₃, and 0.9-1.0 corresponds to remaining in HIV₁.³³³

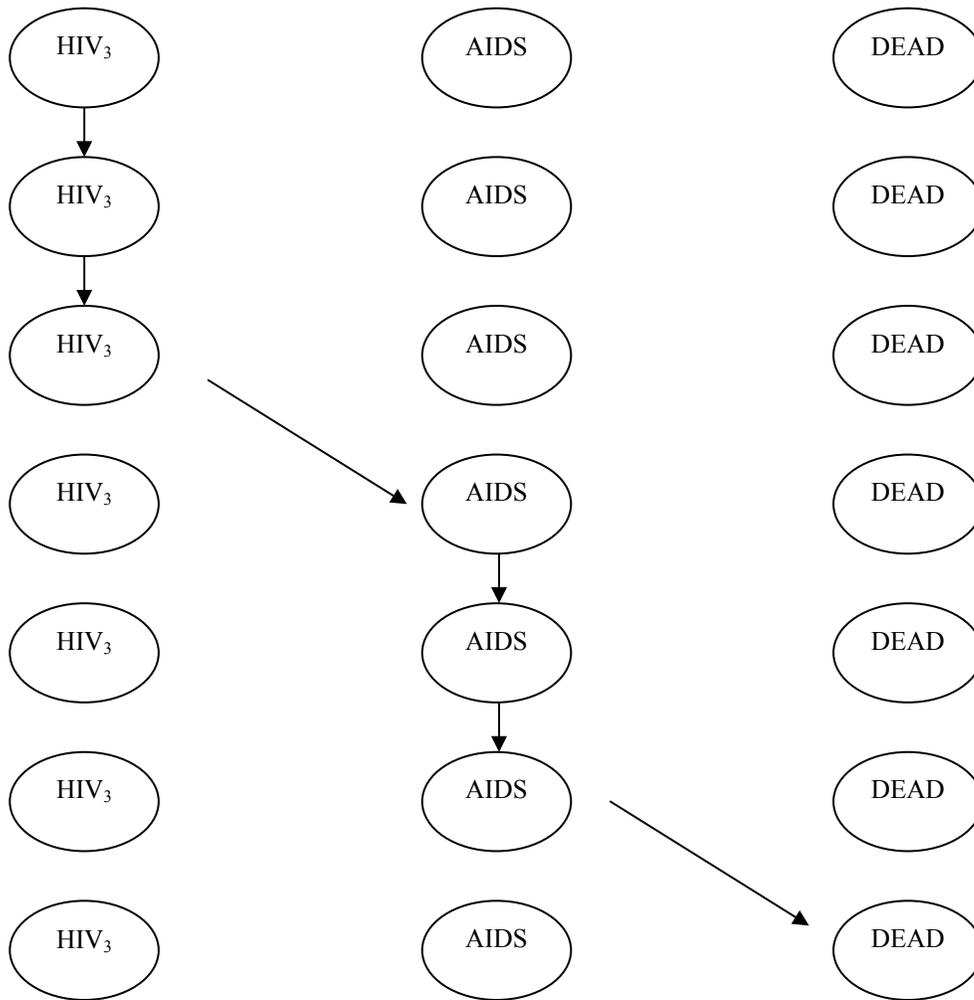
Each patient may or may not begin the simulation in the same state. If the clinical picture of the disease indicates that patients may be in one of many different states, it is common to see the initial states of the simulated patients distributed so as to correspond to the distribution of the patients' initial states of health. As discussed previously, the patient is then given credit for each cycle spent in the different states and each state may be adjusted for quality-of-life. Typically, the simulation terminates for each individual when the patient enters the absorption state (e.g., DEAD). After the first person has completed the simulation (DEAD), another patient begins in one of the initial stages and a new simulation is performed.

As a result of the random simulation, this method is not likely to give the same results on any two occasions. However, if the number of simulations over which the results are averaged is large (e.g., 10,000), the results will approach the values obtained from the Markov cohort simulation; however, the cohort method gives an exact solution. The accuracy of the results of the simulation is as good as the number of patients simulated, the quality of the random number generator

³³³ Eakin T. Information Technology Services Research Consulting at the University of Texas. Austin, 2003.

used, and the knowledge about the initial state and transition probability distributions.

Figure 2-3: First-Order Markov Monte Carlo Simulation



2.3 Advanced Properties and Advantages of Using First-Order Markov Monte Carlo Simulation in Health Care Settings

The probabilistic Monte Carlo simulation (first order) takes a lot more computational time than the deterministic redistribution Markov cohort simulation; however, in addition to mean survival calculations, statistical measures such as variance and standard deviation of the parameters estimated by the model (e.g., expected utility) may be determined from this distribution.

In addition, the Monte Carlo simulation method is often employed in health care decision analyses to more accurately model clinical progression of disease. Specifically, this method is commonly used if detailed patient “memory” is required (for modeling or reporting purposes), beyond that which can be managed by adding some states (section 2.1.2). As stated earlier, one of the most important assumptions in a Markov cohort analysis is that the model maintains no memory of patients’ previous events. Since probabilistic calculations are used with an infinitely large cohort, there are no “individuals” to carry memories with them through the process. Without memory of earlier stages of Markov processes, a given state’s transition probabilities, rewards, and other values cannot depend on knowledge of prior events. Similarly, prior events cannot be directly inferred from current membership. In the health care setting, many Markov modeling problems will require memory of some kind. For example, the overall rate of combination antiretroviral treatment changes in a recent article of HIV

patients was found to be 0.45 combinations per year.³³⁴ If one treatment has failed, that knowledge should be carried with the patient so that the same treatment will not be modeled later. The importance of patient memory in health care decision analysis can be further illustrated by the following example. The risk of death to a patient who experiences a myocardial infarction is different in a patient who has experienced previous myocardial infarctions than it is in a patient who has not experienced a prior myocardial infarction. In a Markov cohort analysis, the only way to remember where a particular portion of the cohort has been is to keep separate those cohort members who experience different events. Even when some form of memory can be accomplished in this manner, it usually requires a complex model.

The most common and efficient way to introduce detailed memory into a Markov process is to analyze it using Monte Carlo simulation trials, rather than cohort analysis. Special “tracker” variables can be used to track each individual’s particular steps through the process, creating a flexible form of memory that can be used in assigning rewards and determining transitions. Tracker variables can be used to recall each individual’s path through the process, creating a flexible form of memory that can be used in assigning rewards and determining transitions.³³⁵ Therefore, to enable tracking of individual patient history in

³³⁴ Austin D, Baker D, Block M, Brown K, et al. Rates of combination antiretroviral treatment change in Australia, 1997-2000. *HIV Medicine* 2002;3(1):28-36.

³³⁵ TreeAge. *TreeAge Health Care Users Manual*. Williamstown: TreeAge, 2001.

Markov processes, analysis must be done via Monte Carlo simulation trials (first-order trials). Although first-order Monte Carlo simulations can be computationally burdensome, they can be conducted with relative ease with a number of decision analysis software packages.

In summary, Table 2-5 lists and illustrates the characteristics of matrix algebra solutions, Markov cohort simulations and the Monte Carlo Markov simulations.

Table 2-5: Characteristics of Matrix Algebra Solutions, Markov Cohort Simulations, and Monte Carlo Simulations

Feature	Matrix Algebra Solution	Markov Cohort Simulations	Monte Carlo Markov Simulations
Transition Probabilities	Constant	Time dependent	Time dependent
Incremental Utilities	Constant	Time dependent	Time dependent
Accuracy	Invariant	Cycle dependent	Cycle dependent
Computation Required	Least	Moderate	Most
Expected Utility Measures	Yes	Yes	Yes
Variability Measures	Yes	No	Yes
Sensitivity Analysis	Yes	Yes	Yes

2.4 Second-Order Markov Monte Carlo Simulations

First-order uncertainty characterizes the random variation in outcomes of individuals, based on the underlying parameter values such as disease prevalence, mortality rates, treatment efficacy and mean resource utilization. With first-order

simulations, the variation observed is purely a result of the different pathways followed by the individuals. Therefore, each individual is different and uncertainty is at the individual's level. This section will describe another group of Monte Carlo simulations, the second-order Monte Carlo simulations, and their applications in Markov modeling.

In health economic analyses, the incremental cost-effectiveness ratio (ICER) is an important statistic that is used to assist in policy making. The ICER statistic represents the difference in the mean treatment costs and the mean treatment effects across patient populations. Although there may be uncertainty in individual treatment effects and costs following an intervention, health economists are also interested in the average outcomes across a group of patients following an intervention. In order to do this, second order uncertainty needs to be accounted for. Second-order uncertainty characterizes the imprecision of knowledge regarding the parameters themselves. Second-order simulations are also commonly referred to as probabilistic sensitivity analyses. In essence, second-order simulations are sensitivity analyses used to assess the impact on outcomes of varying the baseline parameter values. They are similar in principle to normal, deterministic (e.g., one-way) sensitivity analysis, where the impact on the model following changes in a single input parameter are assessed. Second-order simulations can answer questions like: What confidence does one have of the results of the model, given the uncertainty in the input parameters? When

parameters are few, deterministic sensitivity analyses are commonly employed; however, when there are many parameters in a model, even a two-way expected value sensitivity analysis can be difficult.³³⁶ Second-order simulations can show the effects of simultaneous variation in any number of uncertain parameters in both Markov cohort simulations and first-order simulations.³³⁷ Second-order simulations are stochastic at the summary level (the mean and confidence levels vary from one simulation to the next), but deterministic at the detail level; a cohort analysis of the model will always return the same result if the same set of randomly sampled values is used.

Probabilistic sensitivity analysis also has the advantage of incorporating probability distributions for the different parameters. The probability distributions of the variables are chosen depending on the nature of variables. For example, if there are concerns that cost data are positively skewed, a log-normal or gamma distribution could be used to represent the distribution of costs. Sensitivity analyses are then conducted based on these specific probability distributions. Uncertainty intervals are generally chosen to represent the minimum and maximum likely values for each parameter. In addition, triangular and beta distributions are often used to describe the distribution of probability and utility values since these distributions are bounded on a 0-1 interval. If

³³⁶ Ibid.

³³⁷ Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics* 2000;17(5):479-500.

probability values are calculated from original data, then Bayesian methods can be applied directly.³³⁸

2.5 Combining First-Order and Second-Order Uncertainties in Monte Carlo Simulations

Probabilistic sensitivity analysis can be implemented with first-order Monte Carlo simulation. To investigate the impact of parameter uncertainty on a Markov model, the model is repeatedly evaluated using many sets of second-order samples. As mentioned earlier, if the model uses tracker variables (or other trial-based features, such as first-order distributions), first-order trials would have to be used, instead. However, combining first- and second-order simulations should be done with caution. Typically, the first-order uncertainty introduced by first-order individual simulations are not of primary interest to medical decision analysis researchers, and can complicate the results following second-order probabilistic sensitivity analyses. Previously, many simulation software applications ran a single individual through the model for each set of parameter samples. Craig et al. and Halpern et al. have demonstrated that such simulations are likely to overestimate the variance in outcomes associated with parameter

³³⁸ Ibid.

uncertainty.^{339,340} Halpern et al. argue that this occurs because a single individual outcome is used to represent the effect of each parameter sample on the entire model. However, if a large group of trials is performed for each sample, the effects of parameter uncertainty can be appropriately isolated from the effects of individual variability. Groups of trials are used, in effect, to repeatedly approximate expected values based on each set of parameter samples.

³³⁹ Craig BA, Black MA, Sendi PP. Uncertainty in decision models analyzing cost-effectiveness. *Medical Decision Making* 2000;20(1):135-7.

³⁴⁰ Halpern EF, Weinstein MC, Hunink MG, Gazelle GS. Representing both first- and second-order uncertainties by Monte Carlo simulation for groups of patients. *Ibid.*(3):314-22.

CHAPTER 3

VETERANS HEALTH ADMINISTRATION UTILIZATION AND COST DATA

3.1 Overview

The following section presents an in-depth description and discussion of the sources of the Department of Veterans Affairs (VA) data that were used to assess the relationship between patient non-adherence to antiretroviral therapy and: (1) survival of HIV-infected individuals; (2) health care costs; (3) cost-effectiveness of antiretroviral regimens; (4) quality-of-life of HIV-infected individuals; and (5) patterns of antiretroviral regimen switches.

The Veterans Health Administration (VHA) has had a long history of operating computerized clinical information systems and it currently operates the largest centrally directed health care system in the United States. Currently, all episodes of care, commonly referred to as encounters, are reported by staff at the different VA centers using nationally distributed software. The data are extracted to a central location, the Austin Automation Center (AAC), where specific clinical and administrative data are compiled into datasets.³⁴¹ The computerized databases maintained by the VHA are ideal for economic evaluation of drug

³⁴¹ Murphy PA, Cowper DC, Seppala G, Stroupe KT, Hynes DM. Veterans health administration inpatient and outpatient care data: an overview. *Effective Clinical Practice* 2002;5(3 Suppl):E4.

therapy. This chapter is divided into three main sections: (1) VA inpatient and outpatient data; (2) VA pharmacy data; and (3) methods used to derive inpatient, outpatient and pharmacy cost estimates.

3.2 Inpatient and Outpatient Data

The VA maintains databases on inpatient and outpatient care. The following section describes the most commonly accessible sources of VA inpatient and outpatient data.

3.2.1 Inpatient and Outpatient Utilization Data

The Veterans Integrated Health Systems Technology & Architecture (VISTA) is the primary database of detailed clinical and utilization data for every individual treated at each VA medical center.^{342,343} It consists of computer systems at each VA medical center and the national network that links them. Under the “umbrella” of VISTA are a large number of separate 'modules' or 'packages' designed to collect and store data from specific departments (e.g., laboratory). Data are extracted from local VISTAs to create the National Patient

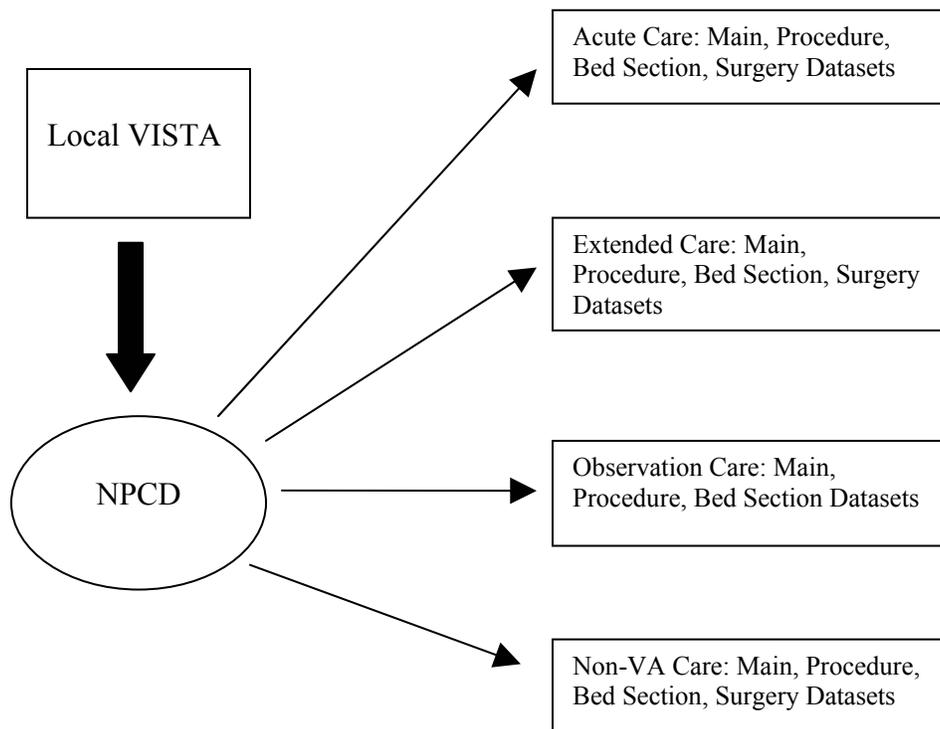
³⁴² Ibid.

³⁴³ Murphy PA. Request to VIREC for information. Hines, Ill, 2003.

Care Database (NPCD).³⁴⁴ The NPCD is the source of data for the Patient

Treatment File (PTF) and Outpatient Clinic File (OPC).³⁴⁵

Figure 3-1: Schematic Representation of the Relationship between the Veterans Information Systems Technology Architecture (VISTA) and the National Patient Care Database (NPCD) and the Inpatient Datasets



Source: VIREC Research user guide: FY 2002 medical inpatient datasets ³⁴⁶

³⁴⁴ Murphy PA, Cowper DC, Seppala G, Stroupe KT, Hynes DM. Veterans health administration inpatient and outpatient care data: an overview. *Effective Clinical Practice* 2002;5(3 Suppl):E4.

³⁴⁵ Ibid.

³⁴⁶ Colin P, Hynes DM, Joseph GJ, Kok L, Murphy PA, Perrin R, et al. VIREC Research user guide: FY 2002 medical SAS inpatient datasets: Veterans Affairs Information Resource Center, 2003.

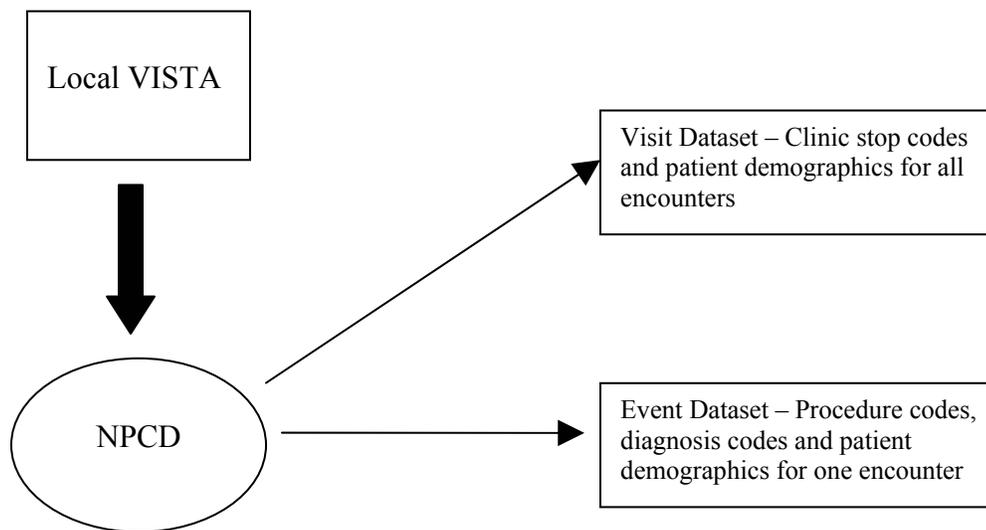
PTF is a hospital discharge data set that characterizes hospitalized patients (inpatient) and the category of care that they received. There are four main categories of care in the inpatient dataset: (1) acute (non-extended); (2) observation; (3) extended; and (4) non-VA (Figure 3-1).³⁴⁷ For all categories of inpatient care, except observation, there are four datasets: (1) inpatient main; (2) bed-section; (3) procedure; and (4) surgery. PTF admission inpatient variables include date of admission, time, facility, and diagnosis. Discharge data include date, time, destination (e.g., home, hospice, community nursing home), and the type of discharge (e.g., regular, transfer, death). ICD-9 codes, procedures, and surgeries performed (dates/times, specialty of care providers, CPT codes) are also documented.

The OPC characterizes ambulatory patients (outpatient) and the diagnoses assigned and procedures performed in outpatient visits. The four datasets for VHA providing outpatient care include: (1) visits; (2) events; (3) diagnoses; and (4) procedures; however, diagnosis and procedure datasets were phased out in fiscal year (FY) 2001 (Figure 3-2). The Event dataset provides information about each encounter (clinic stop) during a day's outpatient care, identifying the specific location of encounters. The visit dataset provides information about a day's outpatient care encounters. The outpatient data includes date/time of the

³⁴⁷ Murphy PA, Cowper DC, Seppala G, Stroupe KT, Hynes DM. Veterans health administration inpatient and outpatient care data: an overview. *Effective Clinical Practice* 2002;5(3 Suppl):E4.

encounter, facility identifier, and the type of clinic where the care was provided. Typically, ICD-9 codes and current procedure terminology (CPT) codes are used to report diagnoses.

Figure 3-2: Schematic Representation of the Relationship between the Veterans Information Systems Technology Architecture (VISTA) and the National Patient Care Database (NPCD) and Outpatient Datasets



Source: VIREC Research user guide: FY 2002 medical SAS outpatient datasets³⁴⁸

³⁴⁸ Colin P, Hynes DM, Joseph GJ, Kok L, Murphy PA, Perrin R, et al. VIREC Research user guide: FY 2002 medical SAS outpatient datasets: Veterans Affairs Information Resource Center, 2003.

3.2.2 Inpatient and Outpatient Cost Data

The VA is a challenging environment for pharmacoeconomic research because it does not routinely bill for the services it provides.³⁴⁹ For many years, the VA's automated cost systems were designed to provide reports to Congress on the use of resources for veterans. Specifically, the Financial Management System (FMS), together with the Cost Distribution System (CDR), were developed to account for and control overall resource expenditures.³⁵⁰ In order to better understand the methods used by researchers to estimate the costs of VA care, a description of the FMS and the CDR is necessary.

3.2.2.1 Financial Management Systems

The FMS is the major accounting ledger system in the VA. Each VA medical center is organized into service disciplines (e.g., psychiatry, nursing) and a cost ceiling is assigned to each of the services allowed in the budget (e.g., personnel, supplies, travel).³⁵¹ The FMS reports the cost of supplies and the quantity and cost of each type of staff. Therefore, the FMS provides accounting records about expenditures for each service but does not provide detailed

³⁴⁹ Barnett PG. Research without billing data. Econometric estimation of patient-specific costs. *Medical Care* 1997;35(6):553-63.

³⁵⁰ Swindle R, Lukas CV, Meyer DA, Barnett PG, Hendricks AM. Cost analysis in the Department of Veterans Affairs: consensus and future directions. *Ibid.* 1999;37(4 Suppl Va):AS3-8.

³⁵¹ Barnett PG. Research without billing data. Econometric estimation of patient-specific costs. *Ibid.* 1997;35(6):553-63.

expenditures for specific clinical programs (e.g., clinics, wards, operating rooms, psychiatry inpatient bed section) or individual patients.

3.2.2.2 Cost Distribution Report

The cost distribution reports (CDR) are used to estimate expenditures for specific clinical programs. Representatives from each service discipline estimate the time spent by staff in each clinical program. From this report, a budget is then distributed to each clinical program. The CDR reports costs of departments at each VA medical center. It is created by allocating the costs reported in the FMS, using cost allocation estimates solicited from representatives from each service discipline. This costing system accurately reflects the costs of each medical facility; however, at the patient level or the clinical program level, the CDR may not be accurate and sensitive to actual resources used in the treatment of individual patients. The Veterans Equitable Resource Allocation (VERA) system allocates funds to VA regional networks based on information in a database created by the VA Allocation Resource Center. The VERA database includes patient-level costs estimated using the CDR, OPC, PTF, and other sources; however, it does not include the cost of specific encounters.

To address the difficulty of obtaining representative costing data for VA clinical programs and patient-level costs, there are a number of methods that have been developed by researchers to assign costs to health care encounters in the VA.

VA costs (e.g., FMS and CDR) and utilization (OPC and PTF) databases are generally used with non-VA measures of relative value to estimate VA health care cost. Non-VA data are used to serve as proxies for VA costs, to estimate comparable costs where none exist in the VA, and to identify the costs of non-VA health care utilization of VA patients. For example, Medicare databases have been used by researchers to estimate VA medical care costs. Specifically, cost estimates have been created by researchers at the Health Economics Resource Center (HERC), a national center that has been set up to assist VA researchers in assessing the cost-effectiveness of medical technologies and evaluating the efficiency of VA programs and providers.³⁵²

3.2.2.3 HERC Cost Estimates

HERC has created a comprehensive set of estimates for the cost of each VA health care encounter that has occurred since October 1, 1998. These estimates are based on the costs reported in the CDR, FMS, and utilization from the PTF and OPC, as well as non-VA data on the relative costs of health care encounters. These data rely on the assumption that the VA uses the same relative quantity of resources as non-VA providers, and that encounters with the same characteristics have the same cost. HERC data are designed to provide cost estimates for care recorded in the PTF (inpatient care) and the OPC (outpatient

³⁵² Ibid.

care). Essentially, HERC data are cost estimates for the PTF and OPC care. HERC data are not designed to vary at medical centers as the prices represent national inputs (e.g., a single wage input price, etc). Although inpatient prescription costs are included in the HERC inpatient cost estimates, outpatient prescription costs are not.

3.3 Pharmacy Data

The VA also maintains databases on pharmacy care. Prescriptions dispensed by VA pharmacies are available from a number of sources. The following section describes the most commonly accessible sources of VA pharmacy data: VISTA, and the pharmacy benefits management (PBM) database.³⁵³

3.3.1 Pharmacy Utilization Data

As noted earlier, VISTA is the VA's main database for medical services data.¹⁶⁶ The VISTA pharmacy package comprises 13 applications related to prescriptions and orders written and filled within the VA system. Completed pharmacy transactions are stored in two locations in VISTA: the Prescription File for outpatient prescriptions, and the inpatient Pharmacy Patient File.

³⁵³ Smith MW, Joseph GJ. Pharmacy data in VA health care system. *Medical Care Research Review* 2003;60(3):S92-123.

Although VISTA is a rich source of data, it generally must be exported from VISTA to another “user-friendly” format for research use. Prescription-level data from a single facility can be obtained by creating an extract from the "pharmacy package" and other modules of the local system. This process can be labor-intensive and separate programs may need to be created for each VA site.

Instead of directly developing individual extraction programs, most VA researchers make use of data sources that draw data directly from VISTA. Specifically, for pharmacy data, the PBM database extracts data directly from VISTA. The pharmacy benefits management strategic health care group (PBM/SHG) is responsible for managing the national VA drug formulary process. It carries out a broad set of activities related to pharmacy purchasing, clinical guidelines, and outcomes research. PBM/SHG has developed software systems and databases to organize and analyze drug data. The prescription database contains extensive detail on the medications prescribed and characteristics of the prescriptions (e.g., days supplied, quantity supplied, fill/refill status). Each month, 128 VISTA systems run the PBM software which extracts all data elements and are eventually transmitted to the PBM. Outpatient data covering every VA pharmacy are available starting from October 1998. A prescription-level inpatient PBM extract is currently not available but under development.

3.3.2 Sources of Pharmacy Costs

A centralized database on outpatient prescriptions filled by the VA is not available. For this reason, the HERC cost estimates only include the cost of prescriptions provided during inpatient encounters. Conversely, the VA Pharmacy Benefits Management database includes information on pharmaceuticals dispensed for each VA outpatient encounter, and their associated costs.³⁵⁴

For each National Drug Code (NDC), the VA has up to five purchase prices associated with it. There are three federal-wide purchase prices and two VA-specific purchase prices. Only about three percent of medication expenditures occur outside of the VA-specific and federal-wide agreements. The federal-wide costs come from the Federal Schedule Supply (FSS), the FSS Tier schedule, and the federal ceiling price schedule (FCP). The Federal Supply Schedule is the collection of multiple award contracts used by federal agencies (including the VA), US territories, Indian tribes and other specified entities to purchase supplies and services from outside vendors. FSS prices for the pharmaceutical schedule are negotiated by the VA and are based on the prices that manufacturers charge their "most-favored" non-federal customers under comparable terms and conditions. FSS prices are publicly available.³⁵⁵ The two prices specific to the VA come from the agency's National Contracts and Blanket

³⁵⁴ Drug & Pharmaceutical Prices: Department of Veterans Affairs, 2003.

³⁵⁵ Ibid.

Purchase Agreements (BPAs). The VA, the Department of Defense, Public Health Service and the Coast Guard (Big 4) also negotiate contracts with manufacturers.

The costs associated with an NDC vary across the different schedules and the costs also vary year-round as a result of contract changes. Using NDCs, the PBM data can be linked to other commercial costs (e.g., average wholesale price (AWP), maximum allowable cost, or average wholesale acquisition cost). Table 3-1 illustrates the deep discounts available to the VA system (e.g., Federal Supply Schedule) when compared to AWP of antiretrovirals. Smith and Joseph strongly advise against the use of AWP to estimate drug expenditures since the VA cost for a supply of medications may be as much as one-twentieth that of the AWP.³⁵⁶

³⁵⁶Smith MW, Joseph GJ. Pharmacy data in VA health care system. *Medical Care Research Review* 2003;60(3):S92-123.

Table 3-1: Generic Name, Brand Name, Average Wholesale Price, Federal Supply Schedule Price, and Big 4 Price of Antiretroviral Drugs Licensed in the US in December 2002

Generic	Brand	Monthly AWP (\$US)	FSS / Big 4 Price (\$US)
Nucleoside Reverse Transcriptase Inhibitors			
Zidovudine	Retrovir	369	262 / 203
Didanosine	Videx EC	205	152 / 111
Zalcitabine	Hivid	246	192 / 144
Stavudine	Zerit	351	264 / 178
Lamivudine	Epivir	316	224 / 177
Abacavir Sulfate	Ziagen	425	315 / 235
Lamivudine/Zidovudine	Combivir	685	486 / 377
Abacavir/Lamivudine/Zidovudine	Trizivir	1110	835 / 612
Tenofovir	Viread	456	255 / NA
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine	Rescriptor	474	266 / NA
Nevirapine	Viramune	405	119 / NA
Efavirenz	Sustiva	445	250 / NA
Protease Inhibitors			
Saquinavir	Invirase	1347	1048 / 801
Indinavir	Crixivan	546	288 / NA
Ritonavir	Norvir	772	409 / NA
Nelfinavir	Viracept	680	382 / NA
Saquinavir	Fortovase	751	534 / 386
Amprenavir	Agenerase	551	410 / 305
Lopinavir/Ritonavir	Kaletra	704	397 / NA

Sources: Red Book and Drug & Pharmaceutical Prices.^{357,358}

Note: AWP = Average Wholesale Price; FSS = Federal Supply Schedule; Big 4 = VA, Department of Defense, Public Health Service and Coast Guard; NA = not available.

3.4 Techniques Used by HERC to Estimate VA Health Care Costs

This section provides an in-depth discussion on the methods HERC employs to estimate the costs of inpatient and outpatient care. There are a number of methods that VA researchers have used to estimate the costs of health care

³⁵⁷ Drug & Pharmaceutical Prices: Department of Veterans Affairs, 2003.

³⁵⁸ Red Book. Montvale, NJ: Medical Economics Company, 2002.

encounters and they vary depending upon the level of precision required.^{359,360,361}

Typically, VA researchers have used average cost methods and micro-costing methods (e.g., direct measurement, preparation of pseudo-bills, estimation of cost functions) to assess the cost of health care encounters (Table 3-2).³⁶² HERC researchers have used both the average cost method and micro-costing methods to put a dollar value to each health care encounter.

³⁵⁹ Barnett PG. Research without billing data. Econometric estimation of patient-specific costs. *Medical Care* 1997;35(6):553-63.

³⁶⁰ Barnett PG. Review of methods to determine VA health care costs. *Medical Care* 1999;37(4 Suppl VA):AS9-17.

³⁶¹ Barnett PG, Rodgers JH. Use of the decision support system for VA cost-effectiveness research. *Ibid.*

³⁶² Barnett PG. Review of methods to determine VA health care costs. *Ibid.*:AS9-17.

Table 3-2: HERC Average Cost Methods Used to Estimate the Cost of VA Provided Health Care

Method	Source of Data	Assumptions	Advantages/Disadvantages
HERC average cost of acute medical and surgical stays method	CDR matched to Patient Treatment File Relative Values from Analysis of Cost of Veterans' Medicare Stays	VA use of resources for different diagnoses and lengths of stay are the same as for non-VA hospitals	Pro: Avoids bias of assuming all days of equal cost. Can estimate cost from administrative data. Con: Only appropriate for acute medical and surgical stays. Not sensitive to all sources of variation in resource use cost.
HERC average cost of long-term care method	CDR matched to Patient Treatment File and Patient Assessment file	Cost of long-term care days is proportionate to Weighted Work Units assigned in long-term care patient assessment.	Pro: Captures variation associated with resource case-mix intensity of long-term care patients. Con: Method has greater complexity. Relies on patient assessment data and assumptions about resources used to care for patients in each assessment category.
HERC outpatient average cost method: Charges based on CPT codes adjusted for costs in CDR	CDR matched to Outpatient Care File	All visits with the same CPT codes have the same cost	Pro: Can estimate cost from administrative data Con: Assumes that VA characterizes care with appropriate CPT codes, and that non-VA charge schedules represent VA relative cost of production.

Source: Smith MW, Joseph GJ. Pharmacy data in VA health care system. *Medical Care Research Review*. 2003.³⁶³

3.4.1 Average Cost Method

The average cost method assumes that every health encounter has a cost that represents the average cost of all encounters which are in a similar category. Cost data consist of department-level costs normally reported in the CDR. The utilization data are obtained from the PTF and the OPC. Second, information

³⁶³ Smith MW, Joseph GJ. Pharmacy data in VA health care system. *Medical Care Research Review* 2003;60(3):S92-123.

from non-VA sources is used to estimate the relative cost of each VA health care encounter. The CDR is used in conjunction with data from non-VA sources to give a more representative cost of each encounter. Since non-VA “weights” are used to calculate relative costs, HERC researchers assume that these external weights accurately represent the VA health care system.

To find the cost of outpatient visits, HERC uses the relative values (RVU) of all CPT codes assigned to a visit.³⁶⁴ HERC uses the relative values from the resource based relative value system, which is used to reimburse providers for services provided to Medicare patients. HERC assigns every VA visit to one of 14 different categories of outpatient care. HERC created a “HERC” value which is the hypothetical reimbursement calculated based on Medicare and other reimbursement methods such as the Health Care Cost and Utilization Project. Cost estimates were created to represent the average cost of a visit given the CPT codes, clinic types and expenditures reported in the CDR. For each category, HERC researchers find a specific factor to convert the relative value to a VA cost estimate. HERC assumes that the resources used to provide VA outpatient care are proportionate to the relative values assigned in the Medicare reimbursement. These data has been made available via the Austin Automation Center. Table 3-3 lists the 14 categories of care listed in the HERC manual.

³⁶⁴ Phibbs CS, Yu W, Barnett PG. HERC’S outpatient average cost dataset for VA care: Fiscal Years 1999-2002: Health Economic Resource Center, 2003.

Table 3-3: HERC-Defined Outpatient Categories of Care

Account	Category of Care
21	Outpatient Medicine
22	Outpatient Dialysis
23	Outpatient Ancillary Services
24	Outpatient Rehabilitation
25	Outpatient Diagnostic Services
26	Outpatient Pharmacy *
27	Outpatient Prosthetics
28	Outpatient Surgery
29	Outpatient Psychiatry
30	Outpatient Substance Abuse Treatment
31	Outpatient Dental
32	Outpatient Adult Day
33	Home Care
99	Unidentified Stops

* Outpatient pharmacy is not used in the HERC outpatient dataset since pharmacy utilization does not appear in VA outpatient databases.

HERC has also created 11 categories to characterize inpatient care (Table 3-4).³⁶⁵ To find the cost of non-medical/non-surgical inpatient stays (e.g., rehabilitation, blind rehabilitation, spinal cord injury, domiciliary, psychiatric, substance abuse, psychosocial residential rehabilitation stays, and intermediate medicine treatment units), HERC initially estimates the total costs allocated by the CDR to each bedsection in the PTF. Next, HERC documents the total non-medical/non-surgical inpatient stays derived from the PTF. With this information, a daily rate is calculated. This rate is referred to as the daily cost estimate.³⁶⁶ This makes the assumption that every day of stay has the same cost; therefore, costs are proportionate to the length of stay. Each encounter has a cost.

³⁶⁵ Wagner TH, Chen S, Yu W, Barnett PG. HERC's inpatient average cost datasets for VA Care - Version 4: Fiscal Years 1998-2002: Health Economic Research Center, 2003.

³⁶⁶ Ibid.

Table 3-4: HERC-Defined Inpatient Categories of Care

Account	Category of Care
0	Inpatient Medicine
1	Inpatient Rehabilitation
2	Inpatient Blind Rehabilitation
3	Inpatient Spinal Cord
4	Inpatient Surgery
5	Inpatient Psychiatry
6	Inpatient Substance Abuse
7	Inpatient Intermediate
8	Inpatient Domiciliary
9	Inpatient Long Term
10	Psychosocial Residential Rehabilitation Treatment Programs (PRRT)

The following variables are a sample representation of the elements included in the HERC inpatient data set:

1. Local estimates for categories of care 0-10;
2. National estimates for categories of care 0-10;
3. Length of stay estimates for categories of care 0-10;
4. Diagnostic Related Groupings (DRG);
5. Number of days in intensive care unit;
6. Unique patient identifier, admit day, and discharge day.

A similar technique is employed to estimate the daily cost for acute medical/surgical encounters. However, the cost of acute medical/surgical hospital care in VA is estimated by incorporating diagnostic information from the administrative record; all persons who have the same clinical and patient characteristics have the same cost. Such methods avoid the assumption that every

day of stay is of equal cost. To find the cost of acute medical and surgical hospital inpatient care, HERC uses RVUs and discharge data from the non-VA sector. The RVUs (e.g., DRGs) are based on the relationship between cost-adjusted charges, diagnosis, and length of stay. The use of RVUs is preferred because, unlike charges, they are explicitly chosen to represent the relative cost of producing different patient care products. RVUs reflect the effect of diagnosis on the relative quantity of resources used in a hospital stay. HERC uses the Healthcare Cost and Utilization Project and Medicare discharge data to determine the RVUs. RVUs were used so that the cost estimates would reflect the effect of diagnosis on resource use. The method employed makes the following assumptions: (1) the relative value units (e.g., DRG weights and length of stay), based on non-VA costs, reflect the relative costs of VA hospital stays; and (2) all stays with the same characteristics have the same cost. Once the RVUs were assigned to health care encounters, a cost function was built to determine the average costs of resources used by individual patients.

3.4.2 Micro-Cost Methods

HERC regularly employs the micro-costing methods to determine resource utilization costs. The micro-costing methods are another set of methods for determining the cost of health care. Micro-costing can be used when average costing is not precise. Specifically, this method allows distinctions between the

costs of two patients in the same bed section on the same day, or two patients who have visits characterized by the same procedure code. In other words, micro-costing is used when patterns of resource use cannot be determined solely by examining procedure codes, bed sections, or DRGs.

Micro-costing can also be used to capture out-of-pocket expenses and opportunity costs. Micro-cost methods include three main approaches: direct measurement, preparation of pseudo-bills, and the estimation of a cost function. The level of accuracy required in a cost analysis and the level of resources available dictate which of the three methods to use.

CHAPTER 4

METHODOLOGY

4.1 Study Overview

Patient adherence profiles have the potential of having a significant impact on determining the selection of initial antiretroviral regimens. Also, the effectiveness of antiretroviral medications is largely dictated by the adherence profiles of patients. The objectives of the research study are to determine the relationship between adherence to antiretroviral therapy and: (1) cost-effectiveness of antiretroviral regimens; and (2) patterns of antiretroviral regimen switches. Survival analysis and Monte Carlo Markov (time-dependent) simulations were employed to estimate and project the relationship between adherence and survival, health care utilization, health care costs, and quality-of-life.

4.1.1 Study Design

A retrospective analysis of non-adherence, survival, quality-of-life, resource utilization, antiretroviral regimen switches and costs associated with the

use of antiretroviral drug therapy for treatment of HIV-infected patients was conducted. The patient cohort includes HIV-infected patients cared for by the Central and South Texas Veterans Health Care Systems. Approval from Institutional Review Boards at The University of Texas at Austin and the South, Central and North Veterans Health Care Systems was obtained.

4.1.2 Inclusion Criteria, Population and Study Time Frame

The study subjects are HIV/AIDS patients in the North, Central and South Texas Veteran Health Care Systems enrolled from the index date to time of death, loss to follow-up or the end of Fiscal Year (FY) 2003 (September 30, 2003). The index date was defined as the date when the first prescription of antiretroviral drug was filled for a patient between FY 1998 (October 1, 1997) and the end of FY 2003 (September 30, 2003). To determine if the index date accurately represents a patient's first antiretroviral prescription, a three-month, pre-index washout-period with no antiretroviral prescription was ascertained. Patients who were less than 18 years of age at the index date were excluded. Patient utilization records commenced from the date of entry into the cohort until death, the date the patient was determined to have left the cohort due to loss to follow-up, or the end of data collection period, whichever was earliest.

4.1.3 Identification of Persons with HIV and AIDS

One of the major challenges in using administrative databases is to correctly identify persons with HIV and AIDS. Although insurers or health care organizations usually require practitioners to provide information on diagnoses, this information is often missing. For example, a patient who has been diagnosed with HIV for several years may not have diagnostic codes indicating his/her condition. Also, a patient with pneumonia may only have a diagnosis for pneumonia and not HIV/AIDS. A number of coding mechanisms that can be used to identify people living with HIV and AIDS include the ICD-9 codes and diagnosis related groups (DRG). Researchers may also identify drug claims for antiretrovirals suggesting HIV/AIDS diagnosis. For example, National Drug Codes (NDC) are routinely used to identify the drugs patients are prescribed. This process of using concurrent case finding methodologies for the identification of diagnoses is frequently employed; however, good database management and analysis are also essential.

Based on an algorithm developed by Dennis Tsui of the New York State Department of Health AIDS Institute, AIDS patients can be identified as follows:³⁶⁷

³⁶⁷ Tsui D. Description of the coding nets for New York State: New York State Department of Health AIDS Institute, 2001.

1. Based on the ICD-9 codes, when a recipient is coded with any diagnosis listed in Appendix B, Part 1, that person will be classified as having AIDS;
2. Based on the ICD-9 codes, if the recipient is coded with any diagnosis from Appendix B, Part 2 and one or more codes with one of the diagnoses listed in Appendix B, Part 3, the recipient will also be classified as having AIDS; and
3. Based on pharmacy claims as indicated by the NDCs of antiretroviral medications.

This algorithm is more accurate in identifying persons with AIDS than those with only HIV infection since persons diagnosed with AIDS have a diagnosis which indicates a specific disease. Conversely, persons with HIV infection (without AIDS) may have an ICD-9 diagnosis for HIV (e.g., 042) in addition to an ICD-9 HIV-defining condition (e.g., 279.19). The HIV-defining condition (279.19) only indicates that the person has a disease involving the immune system. While this may be used as evidence for HIV infection, it could also be an indication of other disease processes or treatments (e.g., immunosuppressant drugs following organ transplants). The ICD-9 codes for HIV and AIDS are the same (042) since individuals with AIDS are infected with HIV. Consequently, the ICD-9 codes for the HIV-defining conditions need to be

used in conjunction with at least one of the ICD-9 HIV diagnoses (e.g., 042 – 044, 044.9).

The 042, 043, and 044 categories were originally created to distinguish AIDS (042) from AIDS-related complex (ARC) (043) and other HIV disease (044). These distinctions among the ICD-9 categories are no longer clear-cut, and the categories no longer denote separate clinical entities. An increased understanding of the etiology of HIV processes has led to a continued demand to update classification systems, making it a complex and burdensome process. Also, there are few clear guidelines for the sequencing of the HIV codes. In addition, persons who assign codes are restricted to only using a single code from the 042-044 series which has created confusion and inconsistent coding practices in the field.

Effective October 1, 1994, a new addendum replaced the addendum containing the codes for HIV infection (042.0–044.9).³⁶⁸ This revised addendum contains the following changes: (1) the current 042–044 series of codes has been replaced with a single code, 042, for HIV disease (symptomatic or previously symptomatic HIV infection and all cases of physician-diagnosed AIDS); (2) a new code, V08, has been created for asymptomatic HIV infection; (3) code 795.8, inconclusive HIV test results, has been deleted; and (4) a new code, 795.71, inconclusive serological findings for HIV, has been created. Infants who test

³⁶⁸ CDC. Official authorized addenda: Human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. *MMWR* 1994;43(RR-12).

positive on certain serologic tests that may also reflect the serostatus of the mother are coded as 795.71.

Therefore, the current 042-044 series of codes has been replaced with a single code, 042, HIV disease, to be used for all symptomatic (or previously symptomatic) HIV infections. This code includes all cases of physician-diagnosed AIDS, whether asymptomatic (e.g., a diagnosis based on CD4 criteria alone) or symptomatic. In addition, a new code, V08, has been created for asymptomatic HIV infection. The new code, 795.71, is applicable only to those patients who test positive on a preliminary screening test, but whose HIV infection status is not yet confirmed.

According to the 1994 CDC Official Authorized Addenda, the 042 code should be listed as the principal diagnosis when a patient is admitted to a health-care facility for an HIV-related condition.³⁶⁹ Additional codes for all HIV-related conditions should be assigned as other diagnoses. Also, a patient with HIV disease may be admitted to a health care facility for an unrelated condition. In these cases, the unrelated condition should be the principal diagnosis, with the 042 code listed as an additional diagnosis, followed by the codes for the manifestations of the HIV disease.

For the purposes of this study, HIV/AIDS identification will be conducted using a combination of the recommendations of Tsui et al. and the official

³⁶⁹ Ibid.

guidelines for coding and reporting by the CDC.^{370,371} Individuals with HIV/AIDS will be identified based on the following criteria:

1. ICD-9 codes, when a recipient is coded with 042, 042.0, 042.1, 042.2, 042.9, 043.0, 043.1, 043.2, 043.3, 043.9, 044.0, 044.9, 0795.3, 279.10, 279.19, V08, 795.8 or 795.71; and/or
2. pharmacy claims as indicated by NDCs of antiretroviral medications.

The list of ICD-9 codes selected includes the codes for HIV and AIDS derived before the 1994 addendum to capture patients that may since be incorrectly coded by the VA.

4.1.4 Data Collection

The nation's largest single provider of health care to those infected with HIV is the VA. More than 45,000 people with HIV infection and AIDS have been treated in the VA since the disease was first recognized in the United States in 1981. Today, more than 20,000 patients with HIV infection are treated at VA facilities across the nation. The VA supplies outpatient drug therapies; thus, eligible veterans who have private health insurance with limited coverage for outpatient drugs or are on Medicare, which did not cover outpatient drugs at the

³⁷⁰ Ibid.

³⁷¹ Tsui D. Description of the coding nets for New York State: New York State Department of Health AIDS Institute, 2001.

time of the study, are increasingly likely to seek care from the VA to obtain expensive outpatient drug therapies.³⁷²

The VA data includes a demographic file and utilization data files (e.g., inpatient, outpatient, laboratory, and prescription). The data files were used to extract information on patient demographic characteristics, clinical conditions, and use of health care resources for the treatment of the conditions (HIV/AIDS-related medical, institutional and prescription costs incurred by the VA). The data collected are longitudinal clinical and administrative records of all patients.

Kaplan-Meier estimates and time-dependent Markov processes were used to model survival and cost profiles of HIV-infected persons in the VA population. CD4 counts and viral loads were employed as diagnostic markers of disease progression. Utilization and cost data derived from HERC were identified to estimate inpatient and outpatient costs. The costs of drug therapy were also estimated. All patient utilization profiles, from the index date were included in the analyses.

Utilization data were obtained for three main categories: inpatient, outpatient, and pharmacy. Data fields sought in each category are listed below:

³⁷² Keiser P, Kvanli MB, Turner D, Reisch J, Smith JW, Nassar N, et al. Protease inhibitor-based therapy is associated with decreased HIV-related health care costs in men treated at a Veterans Administration hospital. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1999;20(1):28-33.

1. Inpatient (HERC datasets) – Unique identifier, date, inpatient category, length-of-stay, primary diagnosis, other additional ICD-9-CM codes;
2. Outpatient (HERC datasets) – Unique identifier, date, outpatient clinic category; and
3. Pharmacy (PBM and VISTA extracts) – Unique identifier, prescription number, drug name, VA Drug Class, quantity, days supply, dates of original fill and refill. The PBM database provided outpatient prescription utilization; similarly, the PTF inpatient files provided inpatient prescription utilization.

4.1.5 Medical Costs

The negative economic effects of non-adherence behaviors can include: (1) morbidity costs associated with non-adherence; (2) additional medical treatment; (3) use of additional medications; and (4) hospital admissions/readmissions. Modeling the relationship of non-adherence and health care costs was done using estimated costs of all “claims” (e.g., inpatient, outpatient, and prescription).

Primary HIV-related costs included: (1) all medications approved by the FDA for the treatment of HIV-infection, AIDS, and AIDS-related conditions; (2) all medications recommended for use in treating and/or preventing opportunistic

infections as listed in guidelines prepared by an expert panel;^{373,374} (3) hospital admissions determined to be HIV-related based on discharge summaries; and (4) all clinic visits.

Supplemental costs included all non-antiretroviral drugs (e.g., nutritional supplements, antibiotics), blood products (e.g., erythropoietin) and visits to eye dermatology, and hematology/oncology clinics. Anemia is recognized to be a significant clinical problem in patients with HIV infection.^{375,376} Anemia can occur at any stage of infection; however, there is a strong correlation between the severity of anemia and disease progression (immune status). Various risk factors for HIV-related anemia have been identified, including clinical AIDS, CD4 cell counts less than 200 cells/ μ L, high plasma viral load, female sex, African-American ethnicity, and zidovudine use.^{377,378,379,380} Data suggest that treatment

³⁷³ Tolley K, Gyldmark M. The treatment and care costs of people with HIV infection or AIDS: development of a standardised cost framework for Europe. *Health Policy*. 1993;24(1):55-70.

³⁷⁴ Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

³⁷⁵ Mildvan D. Implications of anemia in human immunodeficiency virus, cancer, and hepatitis C virus. *Clinical Infectious Diseases* 2003;37(Suppl 4):S293-6.

³⁷⁶ Lundgren JD, Mocroft A. Anemia and survival in human immunodeficiency virus. *Ibid.*:S297-302.

³⁷⁷ Sullivan PS, Hanson DL, Chu SY, Jones JL, Ward JW. Epidemiology of anemia in human immunodeficiency virus (HIV)-infected persons: results from the multistate adult and adolescent spectrum of HIV disease surveillance project. *Blood* 1998;91(1):301-8.

³⁷⁸ Levine AM, Berhane K, Masri-Lavine L, Sanchez M, Young M, Augenbraun M, et al.

Prevalence and correlates of anemia in a large cohort of HIV-infected women: Women's Interagency HIV Study. *Journal of Acquired Immune Deficiency Syndromes* 2001;26(1):28-35.

³⁷⁹ Levine AM, Scadden DT, Zaia JA, Krishnan A. Hematologic aspects of HIV/AIDS. *Hematology* 2001.

³⁸⁰ Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. *Acquired Immune Deficiency Syndromes* 1999;13(8):943-50.

with HAART may have a positive impact on reducing the prevalence of anemia of chronic disease in patients infected with HIV.³⁸¹ As a first-line therapy, clinicians typically manage HIV-infected individuals who present with anemia with Epoetin alpha. Epoetin alpha is a synthetic form of erythropoietin. The costs of Epoetin are considerable and studies examining the direct medical costs of HIV-infected individuals need to include the costs of managing anemia (Table 4-1). Typically, the weekly dose of erythropoietin administered to individuals to correct their underlying anemic disorder is 40,000 units.³⁸²

Table 4-1: Generic Name, Brand Name, Strength, and Average Wholesale Price of Recombinant Human Erythropoietin in the US in December 2002

Generic	Brand	Strength (Units/ml)	AWP (\$US) ³⁸³
Epoetin alpha	Procrit	4,000	\$53.42
		10,000	\$133.56
		20,000	\$267.12
	Epogen	4,000	\$53.42
		10,000	\$134.90
		20,000	\$267.12

Note: AWP = Average Wholesale Price

Costs were adjusted for inflation and were discounted to reflect costs in 2003 US dollars. Discount rates were based on government recommended rates (0-7%). Discount rates were applied to both costs and treatment effects.³⁸⁴

³⁸¹ Brokering KL, Qaqish RB. Management of anemia of chronic disease in patients with the human immunodeficiency virus. *Pharmacotherapy* 2003;23(11):1475-85.

³⁸² Grossman H, Bowers P, Leitz G. Once-weekly dosing of 40,000 U Epoetin alfa is as effective as thrice-weekly dosing among HIV-positive patients. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001; Chicago, Ill.

³⁸³ *Red Book*. Montvale, NJ: Medical Economics Company, 2002.

³⁸⁴ Bootman JL, Townsend RJ, McGhan WF. *Principles of Pharmacoeconomics*. Second ed. Cincinnati: Harvey Whitney Books Company, 1996.

4.1.6 Inpatient Costs

HIV-related inpatient costs were obtained from HERC using data from FY 1998 to FY 2003. Inpatient costs reported by HERC are average inpatient costs calculated for patients with similar characteristics. Therefore, the average inpatient costs calculated by HERC include laboratory costs, prescription costs, and other related inpatient costs. However, the costs are presented as aggregate costs. A comprehensive assessment of the costs of HIV care was conducted using the methodologies reported by the HIV Economic Study Group and Tolley et al.^{385,386} In addition, an HIV expert panel was consulted to identify and confirm HIV-related conditions. Appendix D presents a list of HIV-related ICD9 disease categories that were included in the cost analyses. All costs that occurred from the index date to the end-date of the last prescription, or the end of data collection (September 30, 2003), whichever came first, were included. Specifically, antiretroviral adherence episodes were identified for each patient and the costs that were incurred during these episodes were identified. A description of adherence episodes is found in section 4.2. Next, inpatient costs were assigned to clinical disease states and annualized (one-year Markov cycle) inpatient costs were calculated for each clinical state. The disease states corresponding to the Markov model structure are described in section 4.4. Briefly, the disease states

³⁸⁵ Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

³⁸⁶ Tolley K, Gyldmark M. The treatment and care costs of people with HIV infection or AIDS: development of a standardised cost framework for Europe. *Health Policy*. 1993;24(1):55-70.

were based on the clinical categories reported in the most recent guidelines for the use of antiretroviral agents in HIV-infected individuals.³⁸⁷

- 1) State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/ μ L;
- 2) State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/ μ L but \leq 350 cells/ μ L;
- 3) State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/ μ L;
- 4) State D: HIV positive, symptomatic AIDS or severe symptoms;

ICD-9 codes and laboratory data (e.g., CD4 counts) were used to categorize patients into the different clinical states.

4.1.7 Outpatient Costs

Outpatient costs were calculated in a similar manner to inpatient costs. However, unlike the inpatient data, the HERC outpatient data does not have an ICD-9 field to identify HIV-related disease. Alternatively, the HERC outpatient file has a CPT code field to identify procedures. It is difficult to identify specific HIV-related conditions using CPT codes; therefore, all outpatient costs were included for calculations of annualized, clinical state-specific costs.

³⁸⁷ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: US Public Health Service, 2003.

4.1.8 Pharmacy Costs

Prescription costs were calculated in a similar manner to inpatient and outpatient costs. PBM prices were used to estimate the average costs of pharmaceuticals.³⁸⁸ An HIV expert panel was consulted to identify and confirm HIV-related prescriptions. Appendix E lists all medications included in the cost analysis.

4.2 Patient Non-Adherence to Antiretroviral Drugs

Clinical trial data may not be an appropriate source for studying patient non-adherence since many trials and protocols may exclude non-adherent patients. As a result, collecting data from normal care settings is essential in order to assess the economic and clinical impact of non-adherence to antiretroviral therapy.

Patient non-adherence, assessed by prescription refill records, has been used and validated in other retrospective population-based studies that assessed drug exposure.^{389,390,391,392,393,394,395,396} Adherence was primarily assessed using VA

³⁸⁸ Drug & Pharmaceutical Prices: Department of Veterans Affairs, 2003.

³⁸⁹ Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstetrics & Gynecology* 2000;95(2):167-73.

³⁹⁰ Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *Journal of Clinical Epidemiology*. 1997;50(5):619-25.

³⁹¹ Saunders K, Simon G, Bush T, Grothaus L. Assessing the feasibility of using computerized pharmacy refill data to monitor antidepressant treatment on a population basis: a comparison of automated and self-report data. *Ibid.* 1998;51(10):883-90.

PBM refill records. Prescription records, obtained from VISTA, were included to capture inpatient prescription activity; however, the costs of inpatient prescriptions were not included as the aggregate inpatient costs provided by HERC include prescription costs. In a recent review by Hughes et al., the various forms of non-adherence may be categorized according to the following phases: (1) the acceptance of the drug treatment and regimen during the initial patient-doctor consultation leading to prescription redemption; (2) adherence with the dosing regimen; and (3) persistence with therapy once initiated.³⁹⁷ Typically, the definition of adherence using refill records encompasses the first and third phase in the process of adherence described by Hughes et al.³⁹⁸ The middle phase, adherence with dosing regimens (according to time, food, or activity restrictions), is not captured by pharmacy refill records. However, as described earlier, there is significant evidence for the relationship between adherence to HAART and decreasing viral loads. Subsequently, a decrease in viral load has also been

³⁹² Wannemacher AJ, Schepers GP, Townsend KA. Antihypertensive medication compliance in a veterans affairs healthcare system. *The Annals of Pharmacotherapy* 2002;36(6):986-91.

³⁹³ Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of Clinical Epidemiology* 1997;50(1):105-16.

³⁹⁴ Grossberg RM, Gross R. Pharmacy refill adherence is a better predictor of HIV outcome than self-report [abstract 487]. 40th Annual Meeting of the Infectious Diseases Society of America; 2002 October 24-27; Chicago, Ill.

³⁹⁵ Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

³⁹⁶ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

³⁹⁷ Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health Economics*. 2001;10(7):601-15.

³⁹⁸ Ibid.

associated with a reduction in disease progression. Hence, a significant inverse relationship between viral load and medication refill-adherence strongly suggests a relationship between refill-adherence and the second phase in Hughes et al.'s definition of adherence.

The following section describes the method used to calculate refill adherence. The methodology used to assess adherence was adapted from a recent report by Huang.³⁹⁹ This technique employs a modified form of the medication-possession-ratio (MPR) to assess non-adherent behavior using prescription refill records. First, a drug-specific treatment episode was defined as a period in which a patient had at least two consecutive prescription claims for a given antiretroviral drug; a patient may have more than one drug-specific treatment episode if a drug is discontinued by a clinician and then re-introduced into treatment therapy in subsequent periods. For example, this is often observed when a patient is a candidate for salvage therapy and a previously discontinued drug is added to a triple therapy regimen. Each drug-specific treatment episode was defined as the period elapsed from the date of the first prescription to the end-date of the last prescription. Within a drug-specific treatment-episode, a drug-specific adherent day was defined as a day with a specific drug according to days-supply of prescriptions in the episode. It is difficult to determine solely from refill records whether gaps in drug episodes are a result of true non-adherent behavior (initiated

³⁹⁹ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

by patient - i.e., a patient stops taking medication for a period of time and then fills a prescription) or a treatment change (initiated by a clinician because of failed therapy which is not related to non-adherent behavior) because of treatment failure. Since the MPR was used to calculate non-adherent behavior in a population that may experience frequent changes in therapy, it was necessary to assign an arbitrary cut-off period for gaps in therapy in order to minimize underestimating non-adherent behavior. The current algorithm used to calculate adherence, developed in consultation with clinicians at the Infectious Diseases Clinic in San Antonio, does not include gaps greater than 180 days as non-adherent days in the MPR calculations. Gaps in drug-specific treatment episodes, 180 days or less, were assumed to be a result of patient non-adherence rather than a decision to stop therapy with a particular drug for a period, with the intention of resuming therapy subsequently. Clinicians at the Infectious Disease Clinic at the VA in San Antonio typically schedule appointments with their patients every 4-6 months and if a clinician has noticed that there has been minimal refill activity since the last visit, the clinic will order a refill. Therefore, if a patient has been non-adherent, according to prescription refill activity, a refill will be initiated by the clinician within six months following the earlier visit. Consequently only gaps six-months or less were included as non-adherent periods.

Drug-specific adherence ratios were calculated using the ratio of total days supply (in all treatment episodes for a drug) to the number of days of all treatment episodes (for a drug) reported by Huang:⁴⁰⁰

$$\text{Drug - specific adherence - ratio} = \frac{\sum (\text{total days supply in all treatment episodes})}{\sum (\text{drug - specific treatment episode days})}$$

Since many patients may receive three to four different antiretrovirals for the different treatment regimens, a patient overall adherence ratio (POA) is needed. The overall adherence rate was calculated as the weighted (by the corresponding length of drug-specific treatment episode days) average of drug-specific adherence ratio:

$$\text{POA ratio} = \frac{\sum_{i=1}^n (\text{total days supply for all treatment episodes})}{\sum_{i=1}^n \text{treatment episode days for a drug in the study period}}$$

, where n= the number of antiretroviral medications. The end point for the analysis of adherence behavior was the date the last prescription was filled plus the last days supply.

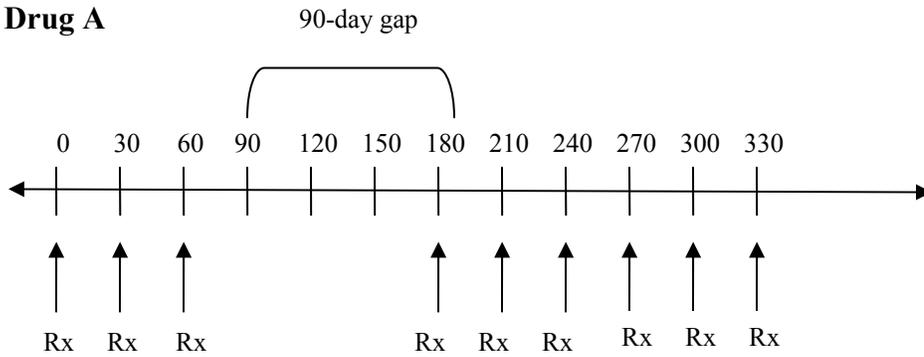
⁴⁰⁰ Ibid.

Figure 4-1 illustrates the calculation of the POA ratios for a hypothetical patient on salvage therapy who receives 30-day supply prescription refills on all antiretroviral medications. As indicated in Figure 4-1, HIV patients within the VA health care system are able to refill their medications considerably earlier than expected (Drug B). The possible reasons veterans may refill their prescriptions include: (1) sharing medications with families and friends; (2) filling prescriptions during social visits or other unrelated clinic visits to VA facilities; and (3) access to internet mail order and telephone ordering systems. As a result, drug-specific adherence ratios and POA ratios could potentially be over-estimated using the methodology described above, if early refills occur after a gap less than 180 days. Therefore, to minimize over-estimating adherence, an algorithm was developed to avoid the potential impact of early refills (following gaps less than 180 days) on POA and drug-specific adherence ratios.

Figure 4-1 also illustrates the calculation of ‘adjusted’ drug-specific adherence ratios and POA ratios. The syntax used to derive adherence ratios was created in SPSS, SAS and MATLAB.

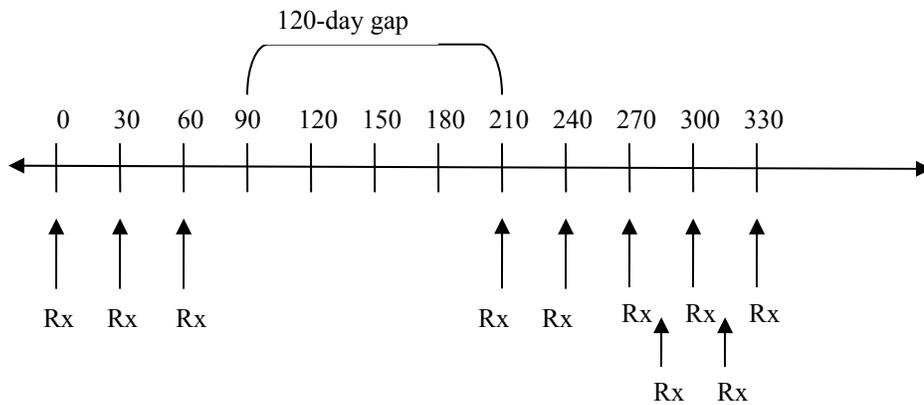
Figure 4-1: Hypothetical Patient

i) Drug A



$$\text{Drug - specific - adherence - ratio} = \frac{270}{(330 - 0) + 30} = 0.75$$

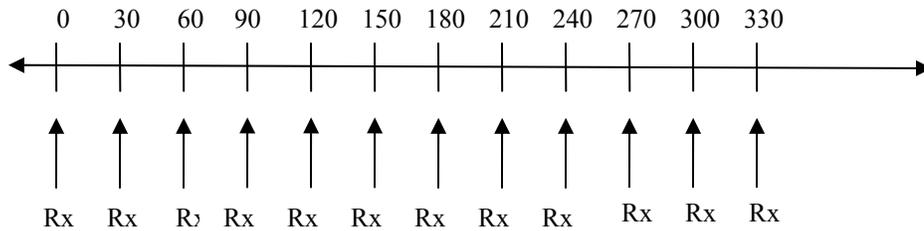
ii) Drug B



$$\text{Drug - specific - adherence - ratio} = \frac{300}{(330 - 0) + 30} = 0.83$$

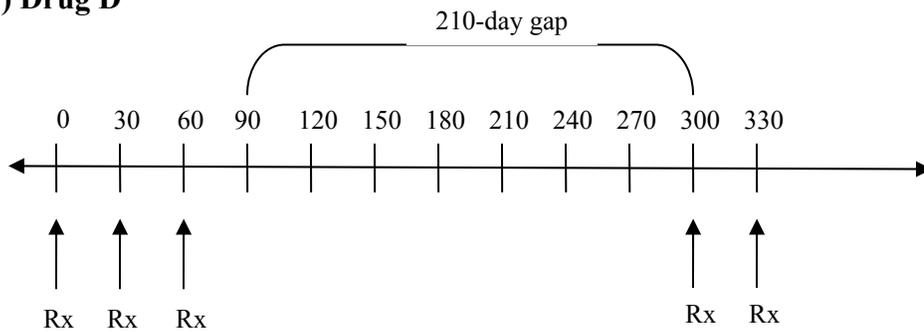
$$\text{Adjusted - drug - specific - adherence - ratio} = \frac{90 + 210}{(210 - 0) + ((330 - 210) + 30) + (30 + 30)} = 0.71$$

iii) Drug C



$$\text{Drug-specific-adherence-ratio} = \frac{360}{330 + 30} = 1.0$$

iv) Drug D



$$\text{Episode...1-specific-adherence-ratio} = \frac{90}{(60 - 0) + 30} = 1.0$$

$$\text{Episode...2-specific-adherence-ratio} = \frac{60}{(330 - 300) + 30} = 1.0$$

$$\text{Drug-specific-adherence-ratio} = \left[\frac{90 + 60}{90 + 60} \right] = 1.0$$

Patient Overall Adherence

$$\text{POA ratio} = \frac{270 + 300 + 360 + 90 + 60}{360 + 360 + 360 + 90 + 60} = 0.88$$

$$\text{Adjusted-POA ratio} = \frac{270 + 300 + 360 + 90 + 60}{360 + 420 + 360 + 90 + 60} = 0.84$$

Studies have shown that a high level of adherence (≥ 95 percent) is necessary for long-term suppression of HIV virus load. Patient overall adherence (POA) ratios were dichotomized. Patients with POA ratios of ninety-five percent and greater were categorized as adherent. Patients with POA ratios less than ninety-five percent were categorized as non-adherent.

4.3 Markov Model Structures

Markov models were used to simulate the progression of HIV infection (Appendix F). The structure of the model is based on models previously used to estimate the effectiveness of antiretroviral therapies.^{401,402,403,404,405,406} When assessing the relationship between non-adherence and HIV-disease progression, health states were based on CD4 counts, which provide the basis upon which to

⁴⁰¹ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

⁴⁰² Trueman P, Youle M, Sabin CA, Miners AH, Beck EJ. The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. *HIV Clinical Trials* 2000;1(1):27-35.

⁴⁰³ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

⁴⁰⁴ Sendi PP, Bucher HC, Harr T, Craig BA, Schwietert M, Pfluger D, et al. Cost effectiveness of highly active antiretroviral therapy in HIV-infected patients. Swiss HIV Cohort Study. *Acquired Immune Deficiency Syndromes* 1999;13(9):1115-22.

⁴⁰⁵ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

⁴⁰⁶ Cook J, Dasbach E, Coplan P, Markson L, Yin D, Meibohm A, et al. Modeling the long-term outcomes and costs of HIV antiretroviral therapy using HIV RNA levels: application to a clinical trial. *AIDS Research & Human Retroviruses* 1999;15(6):499-508.

model the lifetime cost-effectiveness of HIV therapies. The effectiveness of the interventions was assessed using life-years and quality-adjusted-life-years.

4.4 Analyses - HIV-Disease Progression and Health Care Costs Model

The relationship between non-adherence to HAART and HIV-disease progression was assessed using observational data from the North, Central and South Texas Veterans Health Care Systems. Statistical issues in cost-effectiveness studies are different from those that arise in experiments or other data analyses. Rather than testing hypotheses using traditional statistical significance as a criterion, model-based evaluation studies aim to portray the scope and nature of uncertainties that surround the estimates of costs, benefits, and cost-effectiveness ratios that they produce through the use of sensitivity analyses. A probabilistic simulation (Monte Carlo) analysis was constructed for a hypothetical cohort of HIV-infected individuals. This enabled the effects of uncertainty surrounding the different variables to be examined.

The Panel on Clinical Practices for the Treatment of HIV Infection recommends that a minimum of three antiretrovirals should be used to manage HIV infection; however, there are patients who respond well to dual therapy and

those who do not tolerate the side-effects and adverse events of triple regimens.⁴⁰⁷

Although an analysis of refill records indicates that some patients are on dual therapy, these patients may be enrolled in clinical trials with a third antiretroviral that is not recorded in the pharmacy records. Since patients may have received dual-therapy in any of the rounds of therapy, the analyses will include all VA patients that have received two or more antiretroviral drugs at baseline. The following section describes the methodology used to estimate the relationship between adherence, total medical costs, and disease progression.

Step 1 (Estimating Adherence). Patient overall adherence rates (POA) were calculated for all individuals. Individuals were stratified into two groups based on their POA scores. Individuals with POA scores greater than or equal to ninety-five percent were considered adherent to antiretroviral therapy. Likewise, individuals with POA scores less than ninety-five percent were considered non-adherent to antiretroviral therapy.

Step 2 (Developing Model Structure). The model included five health states listed below to represent the progression through disease states to eventual death. A schematic diagram representing the Markov states is shown in Appendix F. The disease states were based on the clinical categories reported in the most

⁴⁰⁷ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

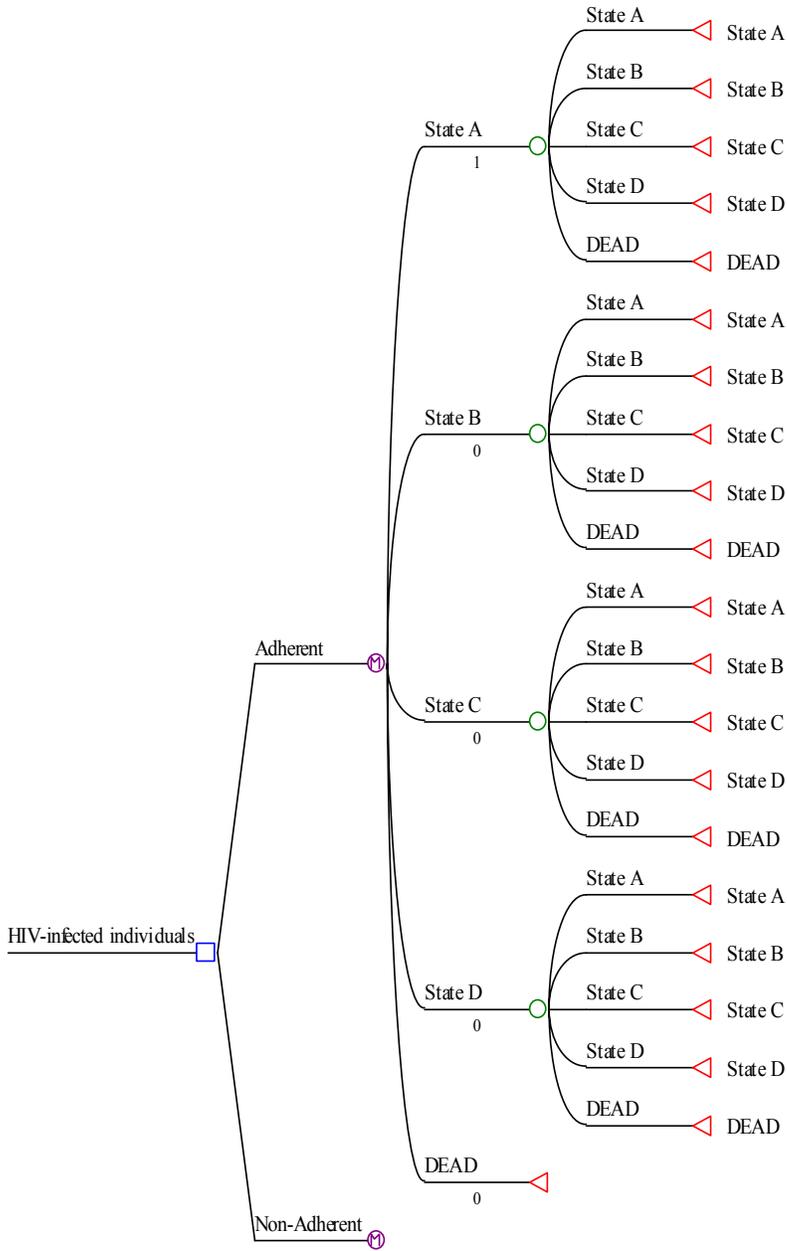
recent guidelines for the use of antiretroviral agents in HIV-infected individuals.⁴⁰⁸

- 1) State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/ μ L,
- 2) State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/ μ L but \leq 350 cells/ μ L;
- 3) State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/ μ L;
- 4) State D: HIV positive, symptomatic AIDS or severe symptoms;
and
- 5) State E: DEAD (age- and disease-related).

Figure 4-2 shows the prototype for the model used to extrapolate the long-term cost-effectiveness of adherence to antiretroviral regimens.

⁴⁰⁸ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: US Public Health Service, 2003.

Figure 4-2: Cost-Effectiveness Prototype Model



The two arms from the first choice node are those corresponding to the adherent and non-adherent arms of the study. All individuals start in State A,

remain in State A or move to any of the other four states. Each individual's subsequent disease status will either remain the same, progress or reverse.

The Markov model cycle is one year. All individuals in the model started at a baseline age of 48 years. The model was developed to simulate two periods: (1) 20 years and (2) 40 years. Also, four different scenarios were modeled dependent on the duration of antiretroviral treatment effect: (1) a six-year effect; (2) an eight-year effect; (3) a ten-year effect; and (4) a continuous effect. An individual's life expectancy is dependent on age- and disease-adjusted mortality. Age-adjusted mortality was modeled using US Life Tables (2003). Individuals who died during a Markov cycle were included in the DEAD state, whereas individuals who had an AIDS-related (Appendix B and Appendix C) event within the last six months were included in health state D. Conversely, individuals who are alive at the end of a cycle or who had no AIDS-related event within the last six months were categorized based on their immune status.

In a recent study, disease progression, measured by the CD4 count at the end of each cycle, was estimated using a linear interpolation technique using the values immediately preceding and following the end of a one-year period.⁴⁰⁹ Another study used a different methodology to stratify disease progression using CD4 values; specifically, Chancellor et al. elected to assume that patients progressed into the next immunological stage only if they had two consecutive

⁴⁰⁹ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

CD4 counts measured below that level.⁴¹⁰ To minimize the effect of random variation in measurements, patients were not considered to have progressed to a lower CD4 count stratum (state) until the date of the first of two consecutive measurements in the lower stratum. Clinicians at the San Antonio VA HIV clinic recommend using the methodology proposed by Chancellor et al.

Step 3 (Estimating Transition Probabilities). The majority of the transitions included in the model reflect the clinical progression experienced with the HIV-infected cohort. All transition probabilities were calculated by grouping individuals according to their health state at baseline. Patients can die while in any health state, and their transition to the DEAD state also depends on their age and their baseline CD4 cell counts when they enter the model. The baseline CD4 cell count is a measure of the state of the immune system soon after HIV/AIDS diagnosis. Although baseline CD4 count has traditionally been regarded as a good predictor of HIV/AIDS disease-progression, Chene et al. concluded that prognosis of people with HIV can be more accurately determined after six months of treatment rather than at baseline.⁴¹¹ Recent data suggests that medication

⁴¹⁰ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

⁴¹¹ Chene G, Sterne JA, May M, Costagliola D, Ledergerber B, Phillips AN, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet* 2003;362(9385):679-86.

adherence is the critical determinant of survival, not the CD4 cell count at which HAART is begun in patients with CD4 counts greater than 200 cells/ μ L.⁴¹²

Disease progression and mortality were modeled using the methodologies developed by previous researchers.^{413,414,415,416,417,418} As described in section 4.4, treatment mortality rates were obtained by adding all-cause age-stratified mortality rates derived from US life tables to on-treatment mortality estimates derived from the VA data. VA data (e.g., CD4 counts and ICD-9 codes) were used to determine disease progression using non-parametric modeling techniques; specifically, the Kaplan-Meier survival analysis technique and exponential distribution was used to estimate the yearly transition probabilities from the data obtained from the VA database. Non-parametric survival methods require fewer assumptions than parametric methods. In particular, no distributional

⁴¹² Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

⁴¹³ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

⁴¹⁴ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

⁴¹⁵ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

⁴¹⁶ Trueman P, Youle M, Sabin CA, Miners AH, Beck EJ. The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. *HIV Clinical Trials* 2000;1(1):27-35.

⁴¹⁷ Cook J, Dasbach E, Coplan P, Markson L, Yin D, Meibohm A, et al. Modeling the long-term outcomes and costs of HIV antiretroviral therapy using HIV RNA levels: application to a clinical trial. *AIDS Research & Human Retroviruses* 1999;15(6):499-508.

⁴¹⁸ Sendi PP, Bucher HC, Harr T, Craig BA, Schwietert M, Pfluger D, et al. Cost effectiveness of highly active antiretroviral therapy in HIV-infected patients. Swiss HIV Cohort Study. *Acquired Immune Deficiency Syndromes* 1999;13(9):1115-22.

assumptions are imposed on survival times. A recent review of the literature indicates that investigators typically use the Kaplan-Meier method to estimate life expectancy and lifetime costs.^{419,420,421,422,423} Separate transition probabilities were calculated for adherent and non-adherent individuals.

At the end of every cycle, each individual's disease status will either remain the same, progress or regress. According to current standard practice, patient status is assessed every three months.^{424,425} However, transition between health states will occur during each year-long cycle of the model. The literature indicates that antiretroviral-naïve individuals infected with HIV are considered to have a better initial response to medication therapy than individuals who have received previous antiretroviral treatment; therefore, patients on their first year of therapy typically may have a better response to HAART than patients who have received treatment in previous years. Due to the development of viral resistance

⁴¹⁹ Seage GR, Hertz T, Stone VE, Epstein AM. The effects of intravenous drug use and gender on the cost of hospitalization for patients with AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1993;6(7):831-9.

⁴²⁰ Moore RD, Chaisson RE. Costs to Medicaid of advancing immunosuppression in an urban HIV-infected patient population in Maryland. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 1997;14(3):223-31.

⁴²¹ Moore RD, Hidalgo J, Baretta JC, Chaisson RE. Zidovudine therapy and health resource utilization in AIDS. *Journal of Acquired Immune Deficiency Syndromes* 1994;7(4):349-54.

⁴²² Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

⁴²³ Fenn P, McGuire A, Phillips V, Backhouse M, Jones D. The analysis of censored treatment cost data in economic evaluation. *Medical Care* 1995;33(8):851-63.

⁴²⁴ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

⁴²⁵ Carpenter CC, Cooper DA, Fischl MA, Gatell JM, Gazzard BG, Hammer SM, et al. Antiretroviral therapy in adults: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2000;283(3):381-90.

with increasing patient treatment experience, each second-line and subsequent regimen may have a decreasing probability of suppressing viral load and of stopping CD4 cell count decline. However, since disease progression did not vary significantly with time, Kaplan Meier survival estimates were assumed to be constant over time. Log survival curves describing transitions between states were plotted and the resulting slope of the line was used to estimate the probability of progressing or regressing to different states.

Estimating the duration of treatment effect of any particular antiretroviral therapy is difficult. The ‘duration of effect’ is defined as the period that antiretroviral therapy is documented to offer adequate suppression of viral load and restoration of immune function; viral resistance has the potential of reducing the ‘duration of effect.’ The ‘duration of effect’ of HAART still remains largely unknown and will only be truly assessed through the use of long-term cohort studies or the extended follow-up of clinical trials. Surrogate marker data from trials following patients on dual therapy indicate that a duration effect may persist for at least one year. Eron followed patients for 76 weeks and the results suggest that the effects of dual therapy may persist for at least two years.⁴²⁶ Using data from these clinical trials, Chancellor et al. incorporated three different scenarios in their Markov model: (1) a one-year effect; (2) a two-year effect; and (3) a

⁴²⁶ Eron JJ, Jr. The treatment of antiretroviral-naive subjects with the 3TC/zidovudine combination: a review of North American (NUCA 3001) and European (NUCB 3001) trials. *Acquired Immune Deficiency Syndrome* 1996;10(5).

continuous effect.⁴²⁷ For example, if an individual has a one-year response following dual therapy, the transition probabilities for subsequent years will revert to baseline transition probabilities before dual therapy was available. In a more recent study, Miners et al. assumed that the effect of HAART was closer to five years with a minimum and maximum duration of two and eight years after which transition probabilities revert to baseline values.⁴²⁸ Similarly, King et al. also estimated the duration of treatment effect; however, they used parametric survival estimates.⁴²⁹

For the purposes of this study, four different scenarios were modeled: (1) a six-year effect; (2) an eight-year effect; (3) a ten-year effect; and (4) a continuous effect. After modeling the duration of treatment effect of HAART, subsequent disease progression and mortality rates were adjusted using a relative-risk statistic obtained from an observational study to adjust transition probabilities.⁴³⁰ To characterize survival and to compare disease progression for HIV-infected patients, Lee et al. conducted a population-based analysis of HIV-infected individuals in British Columbia, Canada. Lee et al. investigated the differences in

⁴²⁷ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

⁴²⁸ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

⁴²⁹ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

⁴³⁰ Lee N, Hogg RS, Yip B, Harrigan PR, Harris M, O'Shaughnessy MV, et al. Rates of disease progression among human immunodeficiency virus-infected persons initiating multiple-drug rescue therapy. *Journal of Infectious Diseases* 2003;188(1):137-41.

disease progression between individuals initiating multiple-drug rescue therapy ('treatment-experienced') and individuals who were recently initiated on triple-drug antiretroviral therapy ('treatment-inexperienced'); multiple-drug rescue therapy is used to treat patients who have failed previous antiretroviral therapy regimens and who are considered to be not likely to achieve a durable virologic response with most standard HAART regimens.⁴³¹ Lee et al. estimated the cumulative mortality rates using Kaplan-Meier methods and Cox-proportional hazard regressions to model the simultaneous effect of prognostic variables on survival. Lee et al. estimated the relative risk of progression for the 'treatment-experienced' group compared to the 'treatment-inexperienced' group. The relative risk statistic of 1.17, reported by Lee et al., will be selected as a conservative estimate to adjust for disease progression and mortality after the 'grace-period.' Finally, simulations will be conducted for two periods: 20 years and 40 years.

Step 4 (Assigning Utilities to Clinical States). As discussed earlier, Honiden et al. assessed the health related utilities of asymptomatic HIV-infected individuals, symptomatic HIV-infected individuals and individuals with AIDS in a Department of Veterans Affairs clinic. Also, Tengs and Lin conducted a meta-analysis to derive composite incremental utility scores to measure the quality-of-

⁴³¹ Ibid.

life of individuals infected with HIV.⁴³² The utility scales reported by Tengs and Honiden et al. were stratified into three HIV-related groups, independent of CD4 counts. The scales reported by Richter et al. classify CD4 counts into categories similar to those described in the proposed Markov model. The three categories reported by Tengs and Honiden et al. were re-categorized into similar CD4 dependent states reported by Richter et al. The utility values presented by Honiden et al. were used as baseline utility values in the model and the utility scores reported by Tengs and Richter et al. were used to provide data for sensitivity analyses (Table 4-2).

Table 4-2: Quality-of-Life Utility Values Stratified by CD4 counts

CD4 counts (cells/ μ L)	HIV-Related Utility Scores		
	Minimum (Sensitivity Analyses)	Baseline	Maximum (Sensitivity Analyses)
> 350	0.66	0.90	1.0
200-350	0.66	0.90	0.99
<200	0.63	0.75	0.87
AIDS	0.55	0.56	0.80

Step 5 (Assigning Costs to Clinical States). Each Markov state was assigned a cost. Indirect costs were not included in the analyses; therefore, the analyses were conducted from the VA public finance perspective.

⁴³² Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. *Medical Decision Making* 2002;22(6):475-81.

Step 6 (Monte Carlo Time-Dependent Markov Simulations). The cost-effectiveness of antiretroviral medications for adherent and non-adherent individuals was modeled.

Step 7 (Sensitivity Analyses). Extensive sensitivity analyses were conducted to evaluate the stability of the ICERs over a wide range of parameter estimates and structural assumptions. One-way sensitivity and probabilistic sensitivity analyses were conducted. Second-order Monte Carlo simulations (probabilistic sensitivity analyses) allow health economists to characterize the uncertainty of the parameters themselves. Therefore, second-order simulations were used to assess the impact on outcomes of varying the baseline parameter values. Second-order Monte Carlo simulations also have the advantage of incorporating probability distributions for the different parameters. For the purpose of the study, probabilistic sensitivity analyses were conducted on four categories of parameters: (1) costs; (2) discount rates (health and cost outcomes), (3) utility values, and (4) the relative risk adjustment statistic. Appropriate probability distributions were employed for each parameter:

- (1) Cost parameters were described by the log-normal distribution^{433,434}, and

⁴³³ Pasta DJ, Taylor JL, Henning JM. Probabilistic sensitivity analysis incorporating the bootstrap: an example comparing treatments for the eradication of *Helicobacter pylori*. *Ibid.* 1999;19(3):353-63.

⁴³⁴ Fairclough DL. Summary measures and statistics for comparison of quality of life in a clinical trial of cancer therapy. *Statistics in Medicine* 1997;16(11):1197-209.

(2) The triangular distribution was used for discounting values, utilities and the relative risk adjustment statistic.

4.5 Analyses - Antiretroviral Regimen Switches Model

The following section describes the methodology used and the essential steps that were followed to determine the relationship between adherence and antiretroviral regimen changes.

Step 1 (Estimating Adherence). Patient overall adherence rates (POA) was calculated for all individuals. Individuals were stratified into two groups based on their POA scores. Individuals with POA scores greater than or equal to ninety-five percent were considered adherent to antiretroviral therapy. Likewise, individuals with POA scores less than ninety-five percent were considered non-adherent to antiretroviral therapy.

Step 2 (Identifying Antiretroviral Regimen Changes). An operational definition of “treatment failure” was considered when a patient’s antiretroviral regimen was switched to a new round of therapy. The end of a round of therapy (failed treatment round) was defined as the point at which a patient’s antiretroviral regimen was changed to at least two new agents; a new round of therapy begins at this point. This definition is based on the guidelines of the Panel on Clinical

Practices for the Treatment of HIV Infection.^{435,436,437} This is the standard definition of treatment failure used by the FDA and is being considered as a major endpoint in drug trials. Typically, a change of two drugs indicates viral resistance and subsequent treatment failure. Since current treatment guidelines recommend changing at least two antiretroviral drugs whenever a treatment failure occurs, a change of one drug was assumed to be due to side effects or patient preference and was not be considered a treatment failure. The syntax used to derive adherence ratios was created in SPSS, SAS and MATLAB.

To determine whether there was a significant difference in the number of treatment rounds observed between adherent and non-adherent individuals, analysis of covariance (ANCOVA) using the enrollment period as a covariate was conducted.

⁴³⁵ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: United States Public Health Service, 2002.

⁴³⁶ Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Journal of the American Medical Association* 2002;288(2):222-35.

⁴³⁷ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: US Public Health Service, 2003.

CHAPTER 5

RESULTS

This chapter presents the major findings of the analyses conducted to assess the relationship between patient non-adherence to antiretroviral therapy and: (1) disease progression of HIV-infected individuals; (2) quality-of-life of HIV-infected individuals; (3) health care costs estimated for HIV-infected individuals; (4) cost-effectiveness of antiretroviral regimens; and (5) patterns of antiretroviral regimen switches. Survival analyses and Markov Monte Carlo simulations were conducted to analyze these relationships.

The results are presented in seven main sections. The first section describes the characteristics of the VA HIV-infected cohort. Specifically, HIV-infected individuals' demographics and antiretroviral prescribing patterns are presented. The second section of the chapter characterizes adherence behavior of the cohort; the results from two techniques used to quantify and categorize adherence to antiretroviral therapy are presented. A more in-depth discussion of the techniques employed to assess adherence is presented in the methodology chapter. The third section of the chapter presents the estimated transition probabilities between clinical states. Special emphasis has been given to the transition probability differences between adherent and non-adherent individuals.

Life expectancy and quality-adjusted life-years associated with the period spent in the different clinical states were obtained from Markov Monte Carlo simulations. Fourth, prescription, inpatient and outpatient costs were estimated for the HIV-infected cohort; the costs were annualized and assigned to the different clinical states. Lifetime costs and the total costs accrued in the different clinical states were obtained from the Markov Monte Carlo simulations. Fifth, the cost-effectiveness (costs per life year and costs per quality adjusted life year) of antiretroviral therapy for adherent and non-adherent HIV-infected individuals was estimated. Sixth, deterministic and probabilistic sensitivity analyses were conducted. Seventh, the results describing antiretroviral regimen changes for adherent and non-adherent HIV-infected individuals are presented.

5.1 Descriptive Analyses

The following section presents the demographic characteristics of the study cohort and the antiretroviral prescribing patterns. Male and female patients, 18 years of age or older, were identified if they had at least one medical encounter from the North, Central or South Veterans Healthcare Systems. Next, patients were included in the study if they had a medical encounter with an associated HIV/AIDS infection or disease diagnosis, with at least two prescription claims for an antiretroviral medication from the index date to date of death, loss to follow-up or the end of Fiscal Year (FY) 2003 (September 30, 2003). The index date was

defined as the date when the first prescription of antiretroviral drug was filled for a patient between FY 1998 (October 1, 1997) and the end of FY 2003 (September 30, 2003). A six month pre-index date period was constructed to identify antiretroviral-naïve patients. The literature indicates that antiretroviral-naïve individuals are considered to have a better initial response to medication therapy than individuals who have received previous antiretroviral treatment; therefore, patients on their first year of therapy typically have better response to HAART than patients who receive treatment in subsequent years.

Data for a total 1,029 HIV-infected individuals were identified. Approximately two-thirds of the cohort (N = 686) had baseline CD4 counts greater than or equal to 200 cells/ μ L; baseline CD4 counts were defined as the first CD4 count measurements from the index date. As noted previously, Woods et al. reported that medication adherence is the critical determinant of survival, not the CD4 cell count at which HAART is begun in individuals with CD4 counts greater than 200 cells/ μ L.⁴³⁸ For the purpose of this study, only data for individuals with baseline CD4 counts greater than 200 cells/ μ L were analyzed; the average baseline CD4 cell count for the HIV-infected cohort was 359 cells/ μ L (Table 5-1). There was no significant difference in overall baseline CD4 cell counts between adherent and non-adherent individuals ($p = 0.16$).

⁴³⁸ Wood E, Hogg RS, Yip B, Harrigan PR, O'Shaughnessy MV, Montaner JSG. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4 cell count is 200 to 350 cells/microliter. *Annals of Internal Medicine* 2003;139(10):810-6.

Table 5-1: Baseline HIV Surrogate Marker Levels for All, Non-Adherent and Adherent Individuals

Group	Surrogate Marker Levels	Mean	Standard Deviation	Minimum	Maximum
All N=686	Viral Load (copies/mL)	58,396	125,419	50	750,000
	CD4 (cells/ μ L)	359	282	202	1,874
Adherent N=204	Viral Load (copies/mL)	33,660	90,645	50	506,113
	CD4 (cells/ μ L)	377	264	203	1,296
Non-Adherent N=482	Viral Load (copies/mL)	66,367	131,557	50	750,000
	CD4 (cells/ μ L)	356	292	202	1,874

The mean follow-up period of individuals in our study sample, from the index date to date of death, loss to follow-up or the end of FY 2003 (September 30, 2003) was 770 days (SD = 632); however, 50 percent of the study cohort were followed for less than 571 days. Baseline patient characteristics are summarized in Table 5-2. The cohort of HIV-infected individuals from North, Central and South Texas Veterans Healthcare Systems included 648 (94.5%) males and 38 (5.5%) females. The mean age of the HIV-infected cohort, calculated at index date, was 48 years (SD = 10.2). HIV-infected individuals from the North Texas Veterans Healthcare System included 340 individuals, 330 (97.1%) males and 10 (2.9%) females. HIV-infected individuals from the Central Texas Veterans Healthcare System included 143 patients, 123 (86.0%) males and 20 (14.0%) females. Similarly, HIV-infected individuals from the South Texas Veterans

Healthcare System included 203 individuals, 195 (96.1%) males and 8 (3.9%) females. Overall, race information for approximately 55 percent of the study cohort was missing; white patients accounted for approximately 24 percent of the sample whereas blacks and other races (including Hispanics, Native Americans, and Asian Americans) accounted for approximately 16 and five percent, respectively (Table 5-2).

Table 5-2: Baseline Patient Characteristics by Texas Veterans Healthcare Region

Texas Veterans Healthcare Region	Mean Age (SD)	Gender N (%)		Race N (%)			
		Male	Female	Black	White	Other	Missing
North	47 (9.7)	330 (97.1)	10 (2.9)	52 (15.3)	73 (21.5)	10 (2.9)	205 (60.3)
Central	53 (10.5)	123 (86.0)	20 (14.0)	42 (29.4)	55 (38.5)	7 (4.9)	39 (27.2)
South	46 (10.0)	195 (96.1)	8 (3.9)	18 (8.9)	34 (16.7)	20 (9.9)	131 (64.5)
All	48 (10.2)	648 (95.0)	38 (5.0)	112 (16.3)	162 (23.6)	37 (5.4)	375 (54.7)

Overall, 336 (49.0%) individuals were initiated on a PI-based antiretroviral, 223 (32.5%) on an NNRTI-based regimen and 85 (12.4%) on an NRTI-based regimen. Forty-two (6.1%) individuals were initiated on regimens that were neither classified as PI-based, NNRTI-based nor NRTI-based regimens. The proportion of patients initiated on a PI-based regimen decreased from FY 1998 through to FY 2003; conversely, the proportion of patients initiated on an

NNRTI-based regimen increased from FY 1998 through to FY 2003. Table 5-3 presents the number and the percent of individuals initiated on specific antiretroviral regimens, by fiscal year.

Table 5-3: Frequency and Percent of Patients Initiated on Specific Antiretroviral Regimens, by Fiscal Year

Fiscal Year	Initial Treatment Regimen			
	PI-based N (%)	NNRTI-based N (%)	NRTI-based N (%)	Other N (%)
1998	90 (72.6)	8 (6.4)	12 (9.7)	14 (11.3)
1999	71 (65.1)	28 (25.7)	6 (5.5)	4 (3.7)
2000	52 (51.5)	38 (37.6)	6 (5.9)	5 (5.0)
2001	45 (41.7)	46 (42.6)	14 (13.0)	3 (2.7)
2002	34 (28.6)	49 (41.2)	25 (21.0)	11 (9.2)
2003	44 (35.2)	54 (43.2)	22 (17.6)	5 (4.0)

PI- Protease inhibitor; NNRTI-non-nucleoside reverse transcriptase inhibitors; NRTI – nucleosidereverse transcriptase inhibitors

5.2 Patient Overall Adherence

The following section describes the adherence profiles of the HIV-infected cohort. Treatment episodes were constructed for 686 HIV-infected individuals. A drug-specific treatment episode was defined as a period in which an HIV-infected individual had at least two consecutive prescription claims for a given antiretroviral drug. Adherence was estimated by two techniques: (1) patient

overall adherence (POA) ratios; and (2) adjusted POA ratios. The adherence ratios are presented below.

First, POA ratios were calculated for all HIV-infected individuals; an in-depth discussion of the calculation of POA ratios is presented in the methodology chapter. Overall, 306 (44.6%) individuals had POA ratios ninety-five percent and greater and were categorized as adherent. One-hundred and eighty six (27.1%) had POA ratios greater than 1.0. The mean POA ratio for the HIV-infected cohort was 0.90; when POA ratios greater than 1.0 were constrained to equal 1.0, the mean POA ratio for the cohort was 0.87 (Table 5-4).

Table 5-4: Mean, Median and Distribution of Patient Overall Adherence Ratios

Adherence Measure	N	Mean	Median	SD	Skewness	Kurtosis	Min - Max
POA*	686	0.90	0.92	0.20	0.39	4.75	0.07 – 2.35
POA†	686	0.87	0.92	0.15	-1.26	1.43	0.07 – 1.0

* POA ratios

† POA ratios greater than 1.0, constrained to equal 1.0

The range of POA ratios was large. When POA ratios greater than 1.0 were constrained to equal 1.0, the skewness coefficient of the POA ratios was -1.26 and the kurtosis coefficient was 1.43. The kurtosis coefficient describes the thickness of the distribution tail; typically, a kurtosis coefficient of 3.00 describes a normal distribution. A kurtosis coefficient of 1.43 indicates that the left tail produced

from the POA ratios' distribution is approximately half the thickness expected in a symmetric distribution. The distributions of POA ratios are presented below (Figure 5-1 and Figure 5-2).

Figure 5-1: Distribution of Patient Overall Adherence Ratios

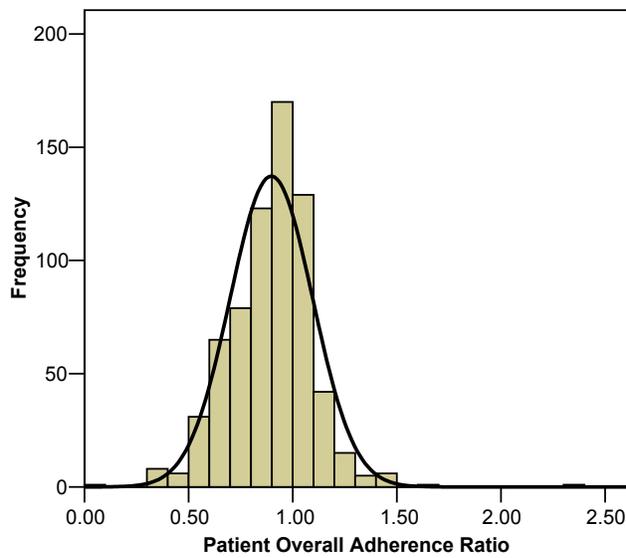
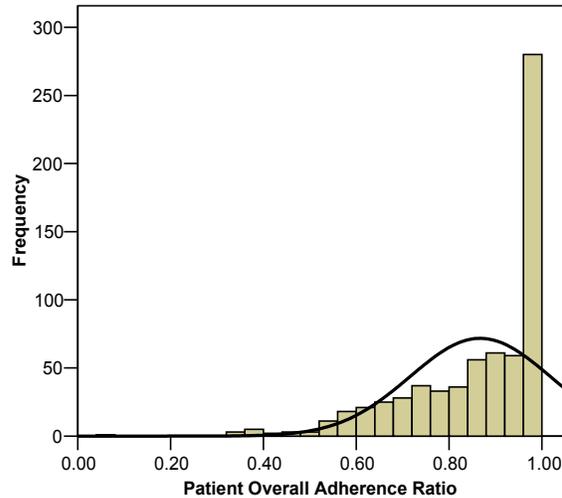


Figure 5-2: Distribution of Constrained Patient Overall Adherence Ratios†



†POA ratios greater than 1.0, constrained to equal 1.0

The following section presents the distribution of POA ratios for individuals initiated on the different antiretroviral regimens. One-hundred and eight (48.4%) of the 223 individuals initiated on NNRTI-based regimens had POA ratios ninety-five percent and greater. One-hundred and fifty (44.6%) of the 336 individuals initiated on PI-based regimens had POA ratios ninety-five percent and greater. Thirty-three (38.8%) of the 85 individuals initiated on NRTI-based regimens had POA ratios ninety-five percent and greater. The distributions of POA ratios for individuals initiated on PI-based, NNRTI-based, NRTI-based and other regimens are presented below (Table 5-5).

Table 5-5: Mean, Median and Distribution of Patient Overall Adherence Ratios, by Starting Regimen

Starting Regimen	Adherence Measure	N	Mean	Median	SD	Skewness	Kurtosi	Min - Max
PI-based	POA*	336	0.89	0.91	0.21	0.36	6.74	0.34 – 2.4
	POA†	336	0.86	0.91	0.15	0.36	0.43	0.34 – 1.0
NNRTI-based	POA*	223	0.91	0.93	0.17	-0.55	0.60	0.36 – 1.5
	POA†	223	0.88	0.93	0.13	-1.46	0.94	0.36 – 1.0
NRTI-based	POA*	85	0.86	0.89	0.21	-0.55	1.83	0.07 – 1.5
	POA†	85	0.83	0.89	0.18	-1.46	3.06	0.07 – 1.0
Other	POA*	42	0.88	0.91	0.16	0.93	1.48	0.41 – 1.2
	POA†	42	0.87	0.91	0.14	-1.09	2.31	0.41 – 1.0

* POA ratios

† POA ratios greater than 1.0, constrained to equal 1.0

For all starting regimens, the range of individuals' POA ratios was large and the distributions were asymmetric and skewed to the left. Also, the mean POA ratios for all starting regimens were similar (Figure 5-3 and Figure 5-4).

Figure 5-3: Mean Patient Overall Adherence Ratios, by Starting Regimen

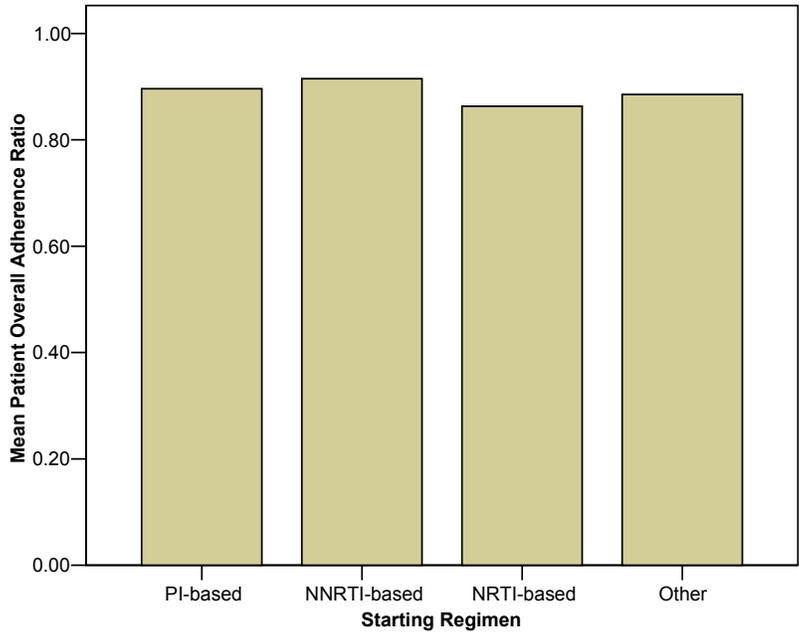
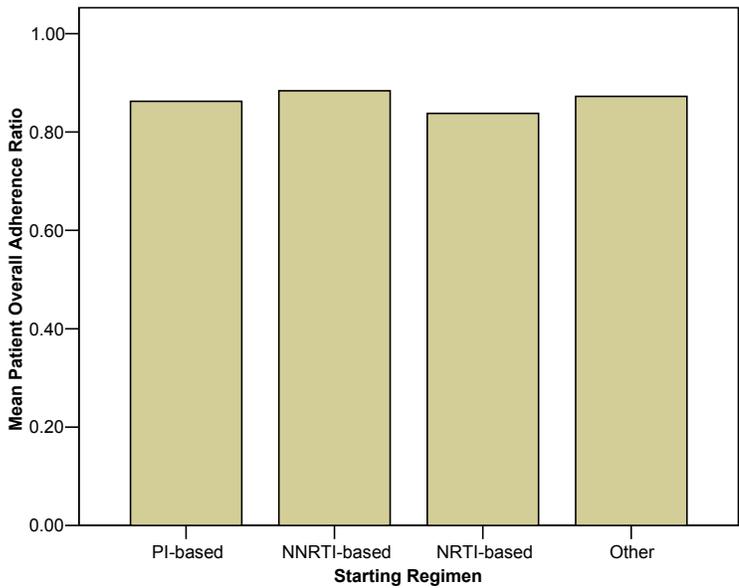


Figure 5-4: Mean Constrained Patient Overall Adherence Ratios, by Starting Regimen†



† POA ratios greater than 1.0, constrained to equal 1.0

As discussed in the methodology section, to avoid potentially over-estimating adherence ratios, an algorithm was developed to minimize the potential impact of early refills (following gaps less than or equal to 180 days) on POA ratios. The second technique used to assess adherence behavior, the ‘adjusted-POA’ ratios technique, was constructed to correct for POA ratios when early refills, following gaps less than or equal to 180 days, occurred. As a result, 204 (29.7%) of the 686 individuals had adjusted-POA ratios ninety-five percent and greater; the proportion of individuals categorized as adherent decreased after the POA ratios were adjusted. The mean adjusted POA ratio for the cohort was 0.80 (Table 5-6).

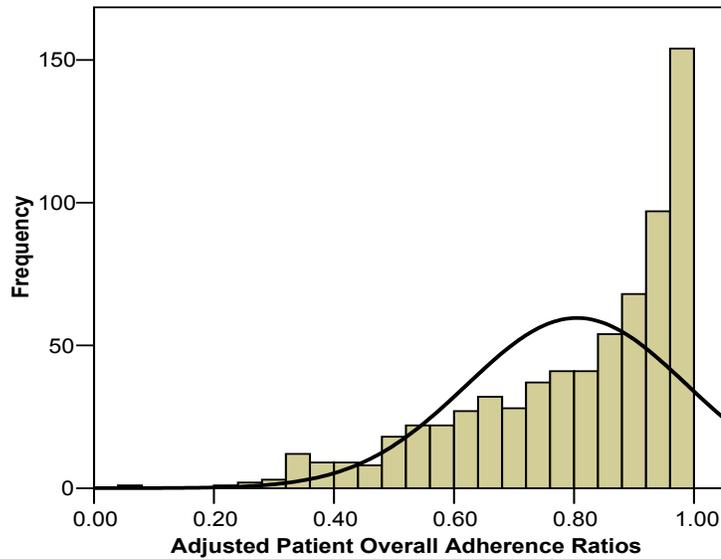
Table 5-6: Mean, Median, and Distribution of Adjusted Patient Overall Adherence Ratios

Adherence Measure	N	Mean	Median	SD	Skewness	Kurtosis	Min - Max
Adjusted POA [†]	686	0.80	0.86	0.18	-1.00	0.28	0.07 – 1.0

[†] POA Ratios greater than 1.0, constrained to equal 1.0

The range of adjusted POA ratios was large and the distribution was asymmetric and skewed to the left. The skewness coefficient of the adjusted POA ratios was -1.00 and the kurtosis coefficient was 0.28. The distributions of adjusted POA ratios are presented below (Figure 5-5).

Figure 5-5: Distribution of Constrained Adjusted Patient Overall Adherence Ratios†



† POA ratios greater than 1.0, constrained to equal 1.0

The following section presents the distribution of adjusted POA ratios for individuals initiated on the different antiretroviral regimens. Seventy-seven (34.5%) of the 223 individuals initiated on NNRTI-based regimens had adjusted POA ratios ninety-five percent and greater. Ninety-seven (28.9%) of the 336 individuals initiated on PI-based regimens had adjusted POA ratios of ninety-five percent and greater. Seventeen (20.0%) of the 85 individuals initiated on NRTI-based regimens had adjusted POA ratios of ninety-five percent and greater.

The mean adjusted POA ratios for individuals initiated on PI-based, NNRTI-based, NRTI-based and other regimens are presented below (Table 5-7).

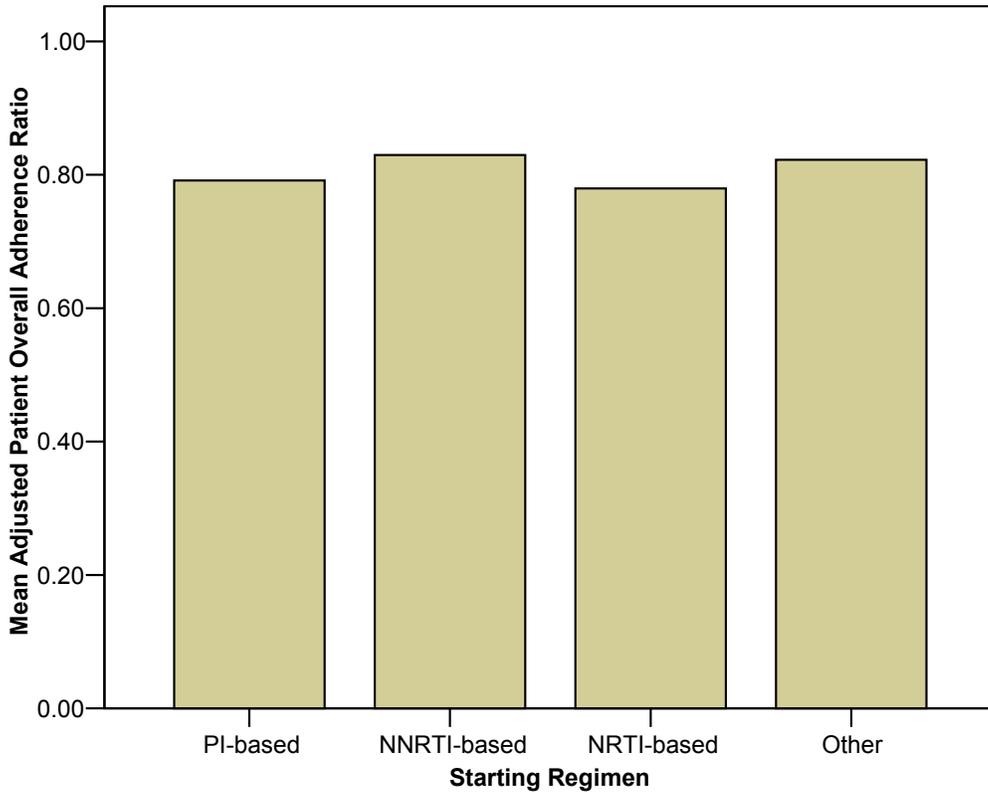
Table 5-7: Mean, Median and Distribution of Adjusted Patient Overall Adherence Ratios, by Starting Regimen†

Starting Regimen	N	Mean Adjusted POA†	Median Adjusted POA	SD	Skewness	Kurtosis	Min - Max
PI-based	336	0.79	0.84	0.18	-0.80	-0.34	0.24 – 1.00
NNRTI-based	223	0.83	0.89	0.16	-1.11	0.44	0.32 – 1.00
NRTI-based	85	0.78	0.82	0.19	-1.13	1.59	0.07 – 1.00
Other	42	0.82	0.87	0.17	-1.49	1.67	0.33 – 1.00

† Adjusted POA ratios greater than 1.0, constrained to equal 1.0

The range of adjusted POA ratios, by starting regimen, was large and the distributions were asymmetric and skewed to the left. Also, the mean adjusted constrained POA ratios were similar for all starting regimens (Figure 5-6).

Figure 5-6: Mean Adjusted Constrained Patient Overall Adherence Ratios, by Starting Regimen†



† Adjusted POA ratios greater than 1.0, constrained to equal 1.0

For the purposes of this study, the adjusted POA ratio technique was selected as the appropriate measure to categorize adherence behavior; the categorization of adherent behavior obtained through this technique was used to populate the model investigating the relationship between adherence and HIV-disease progression, health care costs, and treatment switches.

5.3 Clinical Outcomes

The following section summarizes the estimated transition probabilities of disease progression obtained from Kaplan-Meier survival analyses. Special emphasis is given to the probability differences between the adherent and non-adherent groups. The transitions included in the model reflect the clinical progression experienced by the HIV-infected cohort. The number of transitions between clinical states based on the proposed clinical categories is presented in Table 5-8.

Table 5-8: Transitions between Clinical States (N=648)

From State	Number of Transitions				
	To State†				
	A	B	C	D	E
A	364	74	5	15	7
B	123	128	68	19	11
C	2	104	92	59	21
D	17	20	51	34	13

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms; and State E: DEAD.

As noted earlier, only data for individuals with baseline CD4 counts greater than 200 cells/μL were included in analyses. Data for 648 individuals were used to assess clinical disease progression and the average baseline CD4 cell count for the cohort was 359 cells/μL; therefore, for the purposes of this study, all

individuals were assumed to enter the model with baseline CD4 counts greater than or equal to 350 cells/ μ L.

To determine whether response to antiretroviral therapy remains constant (e.g., inverse exponential survival distribution) or whether it varies with treatment experience (time), log survival-time curves were plotted; a straight line relationship indicates that the hazard function (or transition between clinical states) is constant with time. Appendix G displays the log survival-time scatter plots, and their corresponding R-squared values, for transitions between clinical states; the large R-squared values suggest that it is appropriate to assume constant transition probabilities between clinical states over time; therefore, for the purposes of this study, transition probabilities between clinical states were assumed to be constant over time and transitions to the DEAD state were adjusted to reflect mortality based on United States Life Tables for Males, 2002.

Overall, annual transition probabilities between clinical states were calculated using the value of the slope (β) derived from the natural logarithm survival – time regression equations. Mathematically, plots of survival as a function of time begin with a survival of 1 at a relative time of zero; therefore, plots of natural logarithm of survival as a function of time should begin with a logarithm value of zero. As a result, the constant coefficients (y-intercept) of the natural logarithm survival – time plots, were constrained to equal zero for the

slope (β) calculations. The annual transition probabilities, between clinical states, for adherent and non-adherent individuals were calculated using the following formula and are presented in Table 5-9 and Table 5-10:

$$\text{Annual transition probability between clinical states} = 1 - \exp(\beta)$$

The probabilities of remaining in state B (and D) were calculated as one minus the sum of the probabilities of progressing and regressing to other states. For example, the probability of remaining in state B = $1 - [(\text{probability of regressing to state A}) + (\text{probability of progressing to state C}) + (\text{probability of progressing to state D}) + (\text{probability of progressing to the DEAD state})]$. Since the sample sizes for transitions from state A to state C and from state C to state A were small, these progression probabilities were calculated as: 1 minus the sum of the probabilities of progressing and regressing to other states and of remaining in the starting state. For example, the probability of progressing from state A to state C = $1 - [(\text{probability of progressing to state B}) + (\text{probability of progressing to state D}) + (\text{probability of progressing to the DEAD state}) + (\text{probability of remaining in state A})]$.

All simulations assumed that individuals were male and entered the Markov model at age 48 years; the mean age of the cohort was 48 years. Appendix G displays the Kaplan –Meier survival curves for the different transitions; survival, in the context of this study, refers to individuals remaining in the clinical state they started in.

Table 5-9: Transition Probability Matrix for Adherent Individuals

From State	Annual Transition Probability To State†				
	A	B	C	D	E
A	0.8571	0.1167	0.0004	0.0258	0.0000
B	0.3717	0.4521	0.1101	0.0556	0.0105
C	0.0001	0.4621	0.3122	0.1576	0.0680
D	0.1509	0.2550	0.4080	0.1170	0.0691

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms; and State E: DEAD (HIV-related).

Table 5-10: Transition Probability Matrix for Non-Adherent Individuals

From State	Annual Transition Probability To State†				
	A	B	C	D	E
A	0.8115	0.1478	0.0040	0.0238	0.0129
B	0.2049	0.5511	0.1838	0.0315	0.0287
C	0.0090	0.2460	0.4782	0.1976	0.0692
D	0.1192	0.1304	0.3915	0.2011	0.1578

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms; and State E: DEAD (HIV-related).

The assigned transition probabilities indicate that an individual in state D is much more likely to transition back to State A than is an individual in State C. This does not seem intuitive but there are two possible explanations to these observed probabilities: (1) small sample size used to calculate the transition probabilities; and (2) individuals in advanced disease are treated more

aggressively resulting in greater disease regression. The transition probability from state C to state A in non-adherent individuals is 90 times the value of the same transition in adherent individuals. In other words, non-adherent individuals may be 90 times more likely to revert to a healthy state than adherent individuals. Again, these estimations that do not appear intuitively or clinically appropriate, may be a result of the small sample size used to calculate transition probabilities.

5.4 Economic Outcomes

Each Markov state was assigned a cost. The model estimating life-time treatment costs of adherent and non-adherent individuals included five states which represent the progression through HIV disease to eventual death: (1) State A: HIV positive, asymptomatic, non-AIDS, $CD4 > 350$ cells/ μ L; (2) State B: HIV positive, asymptomatic, non-AIDS, $CD4 > 200$ cells/ μ L but ≤ 350 cells/ μ L; (3) State C: HIV positive, asymptomatic, AIDS, $CD4 < 200$ cells/ μ L; (4) State D: HIV positive, symptomatic AIDS or severe symptoms; and (5) State E: DEAD. Costs were assigned to all health states. HIV-related costs for the DEAD state were assumed to be zero.

Patients may remain for a specified time period in a particular clinical state, transition to another clinical state, or transition back to a prior clinical state depending on their immune status, viral load or diagnoses; therefore, patients may transition in and out of multiple clinical states multiple times. To assign costs to

clinical states, the first step was to identify the time periods that individuals remained in a clinical state. Next, costs were assigned to each time period. Direct annual costs estimated for the cohort included prescription, inpatient and outpatient costs. A comprehensive assessment of the costs of HIV care was conducted using the methodologies reported by the HIV Economic Study group and Tolley et al.^{439,440} The inpatient and outpatient costs were estimated using the VA's Health Economics Resource Center average cost datasets while the prescription costs were estimated using the VA's Pharmacy Benefit Management unit costs. All costs for the different time periods and clinical states were annualized.

Primary HIV-related costs include: (1) all medications approved by the FDA for the treatment of HIV-infection, AIDS, and AIDS-related conditions; (2) all medications recommended for use in treating and/or preventing opportunistic infections as listed in guidelines prepared by an expert panel;^{441,442} (3) hospital admissions determined to be HIV-related based on PTF discharge summaries; and (4) clinic visits. Supplemental costs included all non-antiretroviral drugs (e.g., nutritional supplements, antibiotics), blood products (e.g., erythropoietin) and

⁴³⁹ Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

⁴⁴⁰ Tolley K, Gyldmark M. The treatment and care costs of people with HIV infection or AIDS: development of a standardised cost framework for Europe. *Health Policy*. 1993;24(1):55-70.

⁴⁴¹ Ibid.

⁴⁴² Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

visits to eye, dermatology, and hematology/oncology clinics. Indirect costs were not included in the analyses; therefore, the analyses were conducted from the VA public finance perspective.

Medical costs, along with most other costs, increase over time; these increases have been significant in recent years. The Consumer Price Index (CPI), which is determined by the US Department of Commerce's Bureau of Labor Statistics, provides a US Medical Care Services inflation value for each year, based on a review of the costs of medical services. Costs were adjusted for inflation to reflect costs in 2003 US dollars.

Typically, health care utilization and cost variables are not normally distributed, and they tend to have a long, heavy right tail. As a result, the assumptions required to conduct parametric statistical analyses on utilization and cost data may be violated and the data may need to be transformed or non-parametric techniques used for inferential statistical analyses.

The next section presents the annual prescription, inpatient, and outpatient costs derived from the VA databases.

5.4.1 Prescription Costs

As discussed earlier, individuals can transition in and out of a clinical state more than once; therefore, from a total of 648 individuals, there were a total of 1,106 time periods from which the annual prescription costs for the four clinical states were estimated. The annual HIV-related prescription costs for all health states are presented in Table 5-11; the mean and median annual HIV-related prescription costs generally increased with HIV-disease progression.

Table 5-11: Median and Mean Annual HIV-Related Prescription Costs by Clinical State

Clinical State† (N*)	Median Cost (\$)	Mean Cost (\$)	SD (\$)	SE (\$)	95% CI (\$)	Min – Max (\$)
A (416)	7,882	7,552	5,292	259	7,042 – 8,062	0 – 37,031
B (314)	8,729	9,054	6,285	355	8,357 – 9,752	0 – 42,455
C (254)	8,520	9,987	7,876	494	9,014 – 10,961	0 – 73,717
D (122)	11,315	12,682	10,021	907	10,886 – 14,478	0 – 57,393
All (1106)	8,491	9,104	7,029	211	8,689 – 9,518	0 – 73,717

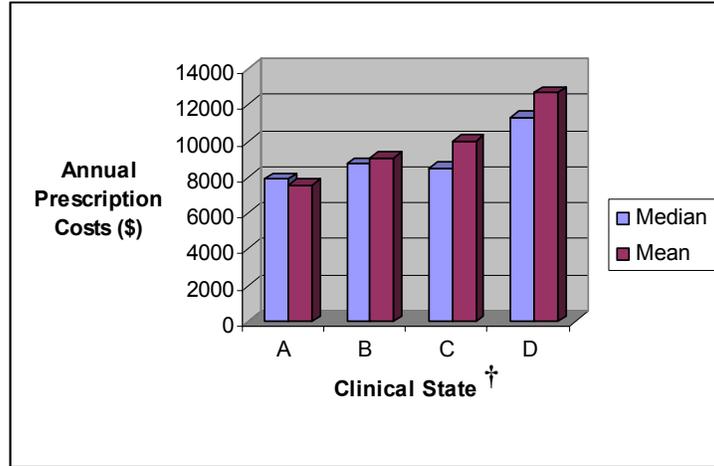
* Each patient may transition in and out of a clinical state more than once; therefore, from a total of 648 patients, there were a total of 1106 annualized prescription costs calculated for the different clinical states.

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-7 presents the annual HIV-related prescription costs in each health state.

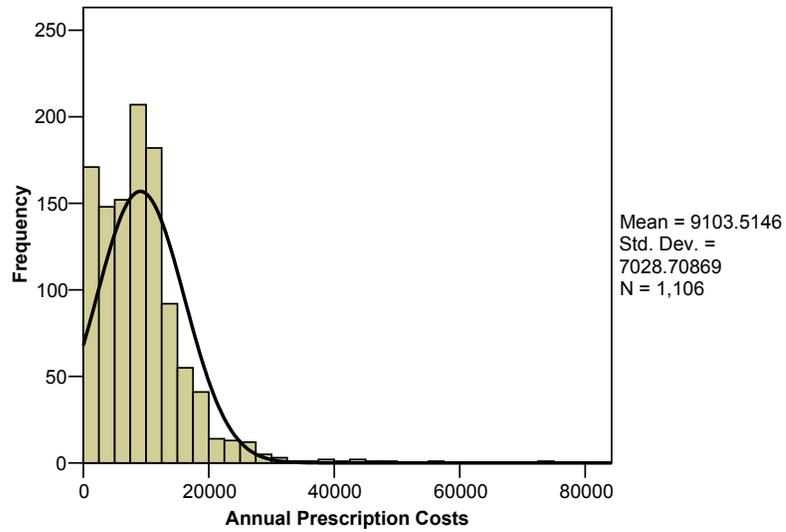
Also, as expected, the distribution of prescription costs is skewed to the right and is presented in Figure 5-8.

Figure 5-7: Mean and Median Annual HIV-Related Prescription Costs by Clinical State



† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-8: Histogram of Annual HIV-Related Prescription Costs



There were 34 annualized time periods (3.1%) where the annual HIV-related prescription costs for the different clinical states were zero; during these time periods, no prescriptions were dispensed by the VA.

Shapiro-Wilk's and K-S Lilliefors tests of normality also suggest that the data are not normally distributed (Table 5-12).

Table 5-12: Tests of Normality for Annual HIV-Related Prescription Costs

Test	Statistic	df	Sig.
Kolmogorov-Smirnov	0.10	1106	p < 0.001
Shapiro-Wilk	0.86	1106	p < 0.001

5.4.2 Outpatient Costs

There were a total of 1,106 time periods from which the annual outpatient costs for the four clinical states were estimated. From a total of 648 individuals, 580 were recorded to have visited an outpatient clinic. The annual outpatient costs for all health states are presented in Table 5-13; the mean (median) annual outpatient costs increased with HIV-disease progression.

Table 5-13: Median and Mean Annual Outpatient Costs by Clinical State

Clinical State† (N*)	Median Cost (\$)	Mean Cost (\$)	SD (\$)	SE (\$)	95% CI (\$)	Min– Max (\$)
A (416)	2,743	3,961	4,283	210	3,548 – 4,374	0 – 39,992
B (314)	3,207	5,881	8,209	463	4,969 – 6,793	0 – 66,888
C (254)	4,368	8,927	18,593	1,167	6,630 – 11,225	0 – 230,933
D (122)	5,822	11,413	26,534	2,402	6,657 – 16,169	0 – 264,828
All (1106)	3,546	6,469	13,739	413	5,658 – 7,279	0 – 264,828

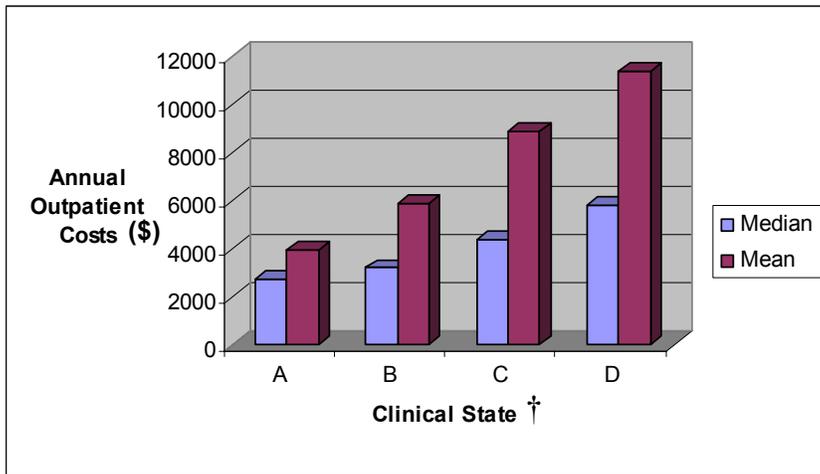
* Each patient may move in and out of a clinical state more than once; therefore, from a total of 648 patients, there were a total of 1106 annualized outpatient costs calculated for the different clinical states.

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-9 presents the annual HIV-related outpatient costs in each health state.

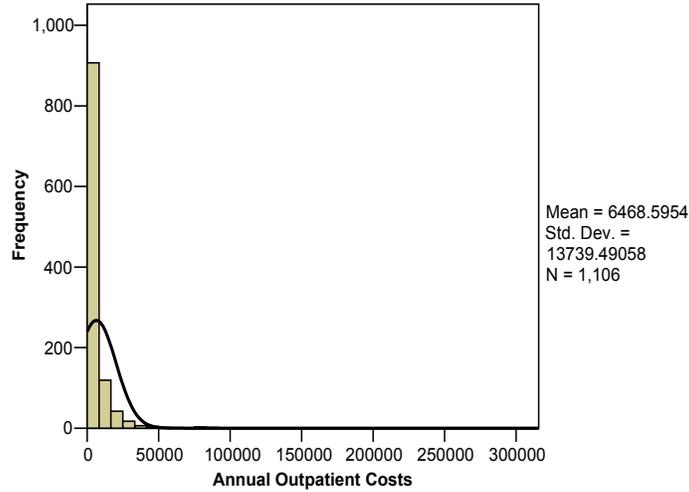
Also, as expected, the distribution of outpatient costs is skewed to the right and is presented in Figure 5-10.

Figure 5-9: Mean and Median Annual Outpatient Costs by Clinical State



† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-10: Histogram of Annual Outpatient Costs



There were 54 annualized time periods (4.9%) where the annual outpatient costs for the different clinical states were zero; during these time periods, no outpatient visits were recorded by the VA HERC databases. Shapiro-Wilk’s and K-S Lilliefors tests of normality also suggest that the data are not normally distributed (Table 5-14).

Table 5-14: Tests of Normality for Annual Outpatient Costs

Test	Statistic	df	Sig.
Kolmogorov-Smirnov	0.32	1056	p < 0.001
Shapiro-Wilk	0.33	1056	p < 0.001

5.4.3 Inpatient Costs

From a total of 648 individuals, there were a total of 1,106 time periods from which the annual inpatient costs for the four clinical states were estimated. Annual HIV-related inpatient costs for all health states are presented in Table 5-15; the mean annual HIV-related inpatient costs increased with HIV-disease progression.

Table 5-15: Mean Annual Inpatient Costs by Clinical State

Clinical State† (N*)	Mean Cost (\$)	SD (\$)	SE (\$)	95% CI (\$)	Min - Max (\$)
1 (416)	3,056	12,667	621	1,835 – 4,276	0 – 175,011
2 (314)	5,350	16,189	913	3,552 – 7,148	0 – 172,823
3 (254)	12,793	33,261	2,087	8,683 – 16,903	0 – 209,729
4 (122)	14,257	28,950	2,621	9,068 – 19,446	0 – 155,342
All (1106)	7,179	22,354	672	5,860 – 8,498	0 – 209,729

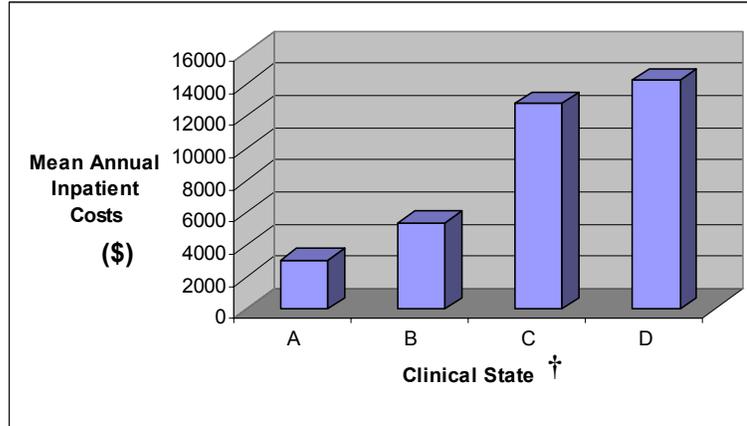
* Each patient may move in and out of a clinical state more than once; therefore, from a total of 648 patients, there were a total of 1106 annualized inpatient costs calculated for the different clinical states.

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-11 presents the annual HIV-related inpatient costs in each health state.

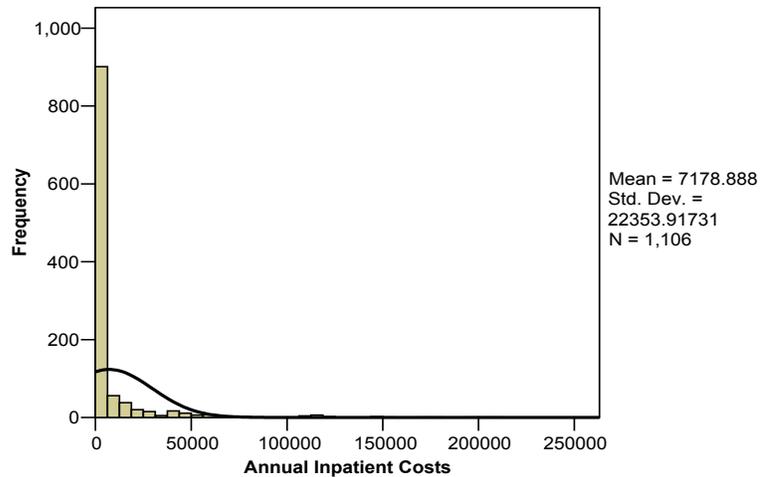
The median annual cost for all states was zero. Also, as expected, the distribution of inpatient costs is skewed to the right and is presented in Figure 5-12.

Figure 5-11: Mean Annual Inpatient Costs by Clinical State



† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-12: Histogram of Annual Inpatient Costs



There were 808 observations (73.1%) where the annual costs calculated for the different clinical states were zero; during these periods, no inpatient stays were recorded. Shapiro-Wilk's and K-S Lilliefors tests of normality also suggest that the data are not normally distributed (Table 5-16).

Table 5-16: Tests of Normality for Annual Inpatient Costs

Test	Statistic	df	Sig.
Kolmogorov-Smirnov	0.37	1106	p < 0.001
Shapiro-Wilk	0.36	1106	p < 0.001

5.4.4 Total Medical Costs

From a total of 648 individuals, there were a total of 1,106 time periods from which the annual medical costs for the four clinical states were estimated. Medical costs represent the total prescription, inpatient, and outpatient costs. The annual medical costs for all health states are presented in Table 5-17; the mean (median) annual medical costs increased with HIV-disease progression.

Table 5-17: Median and Mean Annual Total Medical Costs by Clinical State

Clinical State† (N*)	Median Cost (\$)	Mean Cost (\$)	SD (\$)	SE (\$)	95% CI (\$)	Min – Max (\$)
1 (416)	11,570	14,568	15,531	761	13,071 – 16,065	0 – 193,852
2 (314)	14,066	20,285	21,749	1,227	17,871 – 22,700	0 – 193,289
3 (254)	18,039	31,708	43,403	2,723	26,345 – 37,072	0 – 261,954
4 (122)	22,091	38,352	45,908	4,156	30,123 – 46,580	0 – 356,014
All (1106)	14,240	22,751	30,966	931	20,924 – 24,578	0 – 356,014

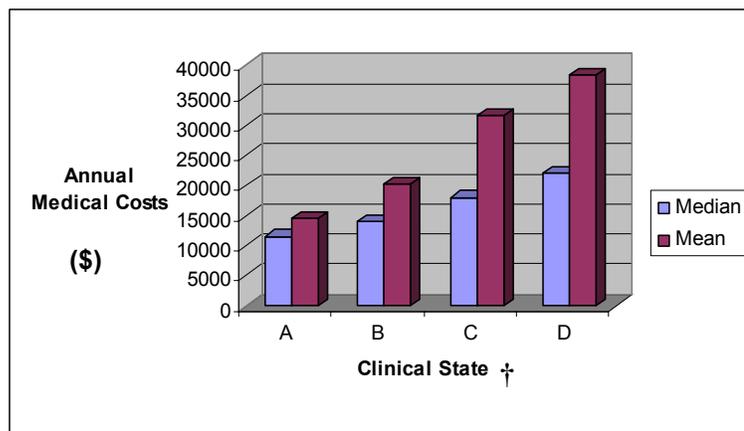
* Each patient may move in and out of a clinical state more than once; therefore, from a total of 648 patients, there were a total of 1106 annualized medical costs calculated for the different clinical states.

† State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/μL; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/μL, but ≤ 350 cells/μL; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/μL; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-13 presents the annual HIV-related medical costs in each health state.

Also, as expected, the distribution of medical costs is skewed to the right and is presented in Figure 5-14.

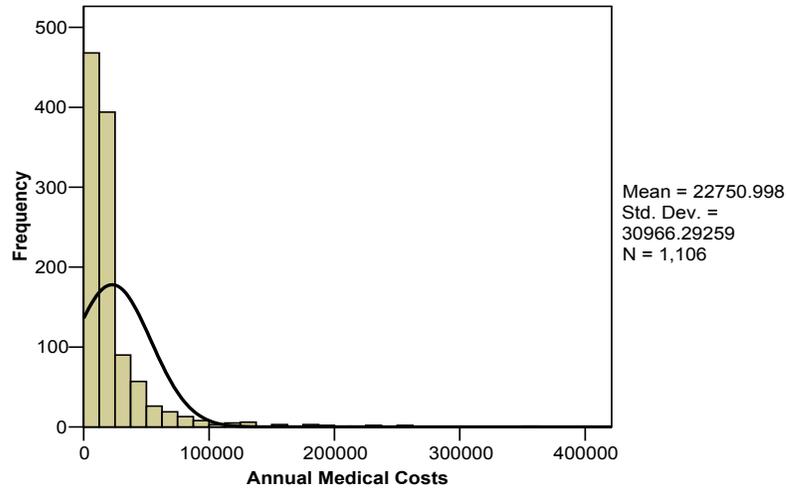
Figure 5-13: Mean and Median Annual Total Medical Costs by Clinical State



†

State A: HIV positive, asymptomatic, non-AIDS, CD4 > 350 cells/ μ L; State B: HIV positive, asymptomatic, non-AIDS, CD4 > 200 cells/ μ L but \leq 350 cells/ μ L; State C: HIV positive, asymptomatic, AIDS, CD4 < 200 cells/ μ L; State D: HIV positive, symptomatic AIDS or severe symptoms.

Figure 5-14: Histogram of Annual Total Medical Costs



There were 16 observations (1.4%) where the annual medical costs for the different clinical states were zero; during these periods, no prescription, inpatient or outpatient encounters were recorded.

Shapiro-Wilk's and K-S Lilliefors tests of normality also suggest that the data are not normally distributed (Table 5-18).

Table 5-18: Tests of Normality for Annual Total Medical Costs

Test	Statistic	df	Sig.
Kolmogorov-Smirnov	.255	1106	p < 0.001
Shapiro-Wilk	.546	1106	p < 0.001

5.5 Markov Cohort Cost-Effectiveness Simulations

For illustrative purposes, Figure 5-15 presents the 20-year Markov model structure developed for cost-effectiveness simulations. The model specifications presented in Figure 5-15 assume an antiretroviral treatment duration effect of six years, after which disease progression rates increase. Details of the parameter inputs, distributions and structural specifications are presented in Table 5-19.

Figure 5-15: 20-Year Markov Model (Six-Year Antiretroviral Duration Effect)

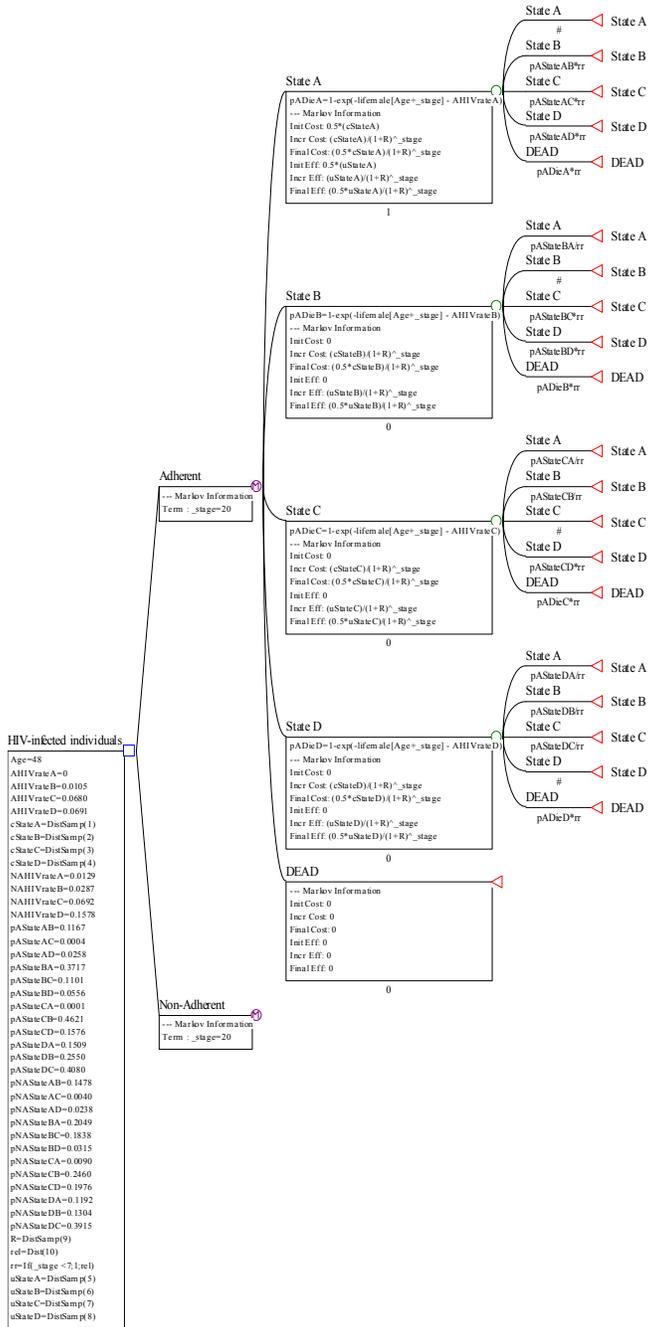


Table 5-19: Markov Model Variable Information

Variable	Definition	Formula/ Distribution
Age	Age in years: Mean age (baseline) of the HIV-infected cohort (calculated at index date)	48 years
AHIVrate A	Hazard ratio of mortality for adherent individuals in state A (all-cause mortality at baseline): Annual probability of progressing from state A to the DEAD state for adherent individuals (calculated from survival analysis curves)	0
AHIVrate B	Hazard ratio of mortality for adherent individuals in clinical state B (all-cause mortality at baseline): Annual probability of progressing from state B to the DEAD state for adherent individuals (calculated from survival analysis curves)	0.0105
AHIVrate C	Hazard ratio of mortality for adherent individuals in clinical state C (all-cause mortality at baseline): Annual probability of progressing from state C to the DEAD state for adherent individuals (calculated from survival analysis curves)	0.0680
AHIVrate D	Hazard ratio of mortality for adherent individuals in clinical state D (all-cause mortality at baseline): Annual probability of progressing from state D to the DEAD state for adherent individuals (calculated from survival analysis curves)	0.0691
NAHIVrate A	Hazard ratio of mortality for non-adherent individuals in clinical state A (all-cause mortality at baseline): Annual probability of progressing from state A to the DEAD state for non-adherent individuals (calculated from survival analysis curves)	0.0129
NAHIVrate B	Hazard ratio of mortality for non-adherent individuals in clinical state B (all-cause mortality at baseline): Annual probability of progressing from state B to the DEAD state for non-adherent individuals (calculated from survival analysis curves)	0.0287
NAHIVrate C	Hazard ratio of mortality for non-adherent individuals in clinical state C (all-cause mortality at baseline): Annual probability of progressing from state C to the DEAD state for non-adherent individuals (calculated from survival analysis curves)	0.0692
NAHIVrate D	Hazard ratio of mortality for non-adherent individuals in clinical state D (all-cause mortality at baseline): Annual probability of progressing from state D to the DEAD state for non-adherent individuals (calculated from survival analysis curves)	0.1578

Table 5-19 (continued):

Variable	Definition	Formula/Distribution
cState A	Medical costs (inpatient and outpatient) associated with clinical state A: Annualized costs for individuals in clinical state A derived from HERC (inpatient medical care, inpatient prescription care, and outpatient medical care) and PBM (outpatient prescription care) databases	DistSamp(1) - Log Normal distribution: <u>Parameters</u> $\mu = 9.36$ (ln (median costs); $\sigma = 0.68$ (ln (mean costs/median costs)*2) ^{1/2}
cState B	Medical costs (inpatient and outpatient) associated with clinical state B: Annualized costs for individuals in clinical state B derived from HERC (inpatient medical care, inpatient prescription care, and outpatient medical care) and PBM (outpatient prescription care) databases	DistSamp(2) - Log Normal distribution: <u>Parameters</u> $\mu = 9.55$ (ln (median costs); $\sigma = 0.86$ (ln (mean costs/median costs)*2) ^{1/2}
cState C	Medical costs (inpatient and outpatient) associated with clinical state C: Annualized costs for individuals in clinical state C derived from HERC (inpatient medical care, inpatient prescription care, and outpatient medical care) and PBM (outpatient prescription care) databases	DistSamp(3) - Log Normal distribution: <u>Parameters</u> $\mu = 9.80$ (ln (median costs); $\sigma = 1.06$ (ln (mean costs/median costs)*2) ^{1/2}
cState D	Medical costs (inpatient and outpatient) associated with clinical state D: Annualized costs for individuals in clinical state D derived from HERC (inpatient medical care, inpatient prescription care, and outpatient medical care) and PBM (outpatient prescription care) databases	DistSamp(4) - Log Normal distribution: <u>Parameters</u> $\mu = 10.00$ (ln (median costs); $\sigma = 1.05$ (ln (mean costs/median costs)*2) ^{1/2}
pA State AB	Transition probability from state A to B for adherent individuals: Annual probability of progressing from clinical state A to B for adherent individuals (calculated from survival analysis curves)	0.1167
pA State AC	Transition probability from clinical state A to C for adherent individuals: Annual probability of progressing from clinical state A to C for adherent individuals (calculated from survival analysis curves)	0.0004
pA State AD	Transition probability from clinical state A to D for adherent individuals: Annual probability of progressing from clinical state A to D for adherent individuals (calculated from survival analysis curves)	0.0258
pA State BA	Transition probability from clinical state B to A for adherent individuals: Annual probability of progressing from clinical state B to A for adherent individuals (calculated from survival analysis curves)	0.3717
pA State BC	Transition probability from clinical state B to C for adherent individuals: Annual probability of progressing from clinical state B to C for adherent individuals (calculated from survival analysis curves)	0.1101

Table 5-19 (continued):

Variable	Definition	Formula/ Distribution
pA State BD	Transition probability from clinical state B to D for adherent individuals: Annual probability of progressing from clinical state B to D for adherent individuals (calculated from survival analysis curves)	0.0556
pA State CA	Transition probability from clinical state C to A for adherent individuals: Annual probability of progressing from clinical state C to A for adherent individuals (calculated from survival analysis curves)	0.0001
pA State CB	Transition probability from clinical state C to B for adherent individuals: Annual probability of progressing from clinical state C to B for adherent individuals (calculated from survival analysis curves)	0.4621
pA State CD	Transition probability from clinical state C to D for adherent individuals: Annual probability of progressing from clinical state C to D for adherent individuals (calculated from survival analysis curves)	0.1576
pA State DA	Transition probability from clinical state D to A for adherent individuals: Annual probability of progressing from clinical state D to A for adherent individuals (calculated from survival analysis curves)	0.1509
pA State DB	Transition probability from clinical state D to B for adherent individuals: Annual probability of progressing from clinical state D to B for adherent individuals (calculated from survival analysis curves)	0.2550
pA State DC	Transition probability from clinical state D to C for adherent individuals: Annual probability of progressing from clinical state D to C for adherent individuals (calculated from survival analysis curves)	0.4080
pNA State AB	Transition probability from clinical state A to B for non-adherent individuals: Annual probability of progressing from clinical state A to B for non-adherent individuals (calculated from survival analysis curves)	0.1478
pNA State AC	Transition probability from clinical state A to C for non-adherent individuals: Annual probability of progressing from clinical state A to C for non-adherent individuals (calculated from survival analysis curves)	0.0040
pNA State AD	Transition probability from clinical state A to D for non-adherent individuals: Annual probability of progressing from clinical state A to D for non-adherent individuals (calculated from survival analysis curves)	0.0238
pNA State BA	Transition probability from clinical state B to A for non-adherent individuals: Annual probability of progressing from clinical state B to A for non-adherent individuals (calculated from survival analysis curves)	0.2049
pNA State BC	Transition probability from clinical state B to C for non-adherent individuals: Annual probability of progressing from clinical state B to C for non-adherent individuals (calculated from survival analysis curves)	0.1838
pNA State BD	Transition probability from clinical state B to D for non-adherent individuals: Annual probability of progressing from clinical state B to D for non-adherent individuals (calculated from survival analysis curves)	0.0315

Table 5-19 (continued):

Variable	Definition	Formula/ Distribution
pNA State CA	Transition probability from clinical state C to A for non-adherent individuals: Annual probability of progressing from clinical state C to A for non-adherent individuals (calculated from survival analysis curves)	0.0090
pNA State CB	Transition probability from clinical state C to B for non-adherent individuals: Annual probability of progressing from clinical state C to B for non-adherent individuals (calculated from survival analysis curves)	0.2460
pNA State CD	Transition probability from clinical state C to D for non-adherent individuals: Annual probability of progressing from clinical state C to D for non-adherent individuals (calculated from survival analysis curves)	0.1976
pNA State DA	Annual probability of progressing from clinical state D to A for non-adherent individuals (calculated from survival analysis curves)	0.1192
pNA State DB	Transition probability from clinical state D to B for non-adherent individuals: Annual probability of progressing from clinical state D to B for non-adherent individuals (calculated from survival analysis curves)	0.1304
pNA State DC	Transition probability from clinical state D to C for non-adherent individuals: Annual probability of progressing from clinical state D to C for non-adherent individuals (calculated from survival analysis curves)	0.3915
R	Discount rate: Discount rate applied to calculate the present values of costs and consequences which accrue in the future	DistSamp(9) - Triangular distribution: <u>Parameters</u> Minimum = 0; Likeliest = 0.03; Maximum = 0.07.
rel	Relative risk adjustment applied to transition probabilities depending on the duration of antiretroviral treatment effect assumptions.	Dist(10) - Triangular distribution: <u>Parameters</u> Minimum =1.085; Likeliest = 1.17; Maximum = 1.255.

Table 5-19 (continued):

Variable	Definition	Formula/Distribution
rr	Relative risk adjustment formula for duration of treatment effect: The following TreeAge Pro function was used to assign relative risk adjustments for disease progression: If(condition; truvalue; falseval) This function evaluates a condition and returns 'trueval' if the condition is true or 'falseval' if the condition is false.	'If(_stage <11;1;rel)' would return 1 if _stage was less than 11 and a value derived from 'rel' if _stage were greater than 10
u State A	Utility values assigned to individuals in clinical state A	DistSamp(5) - Triangular distribution: <u>Parameters</u> Minimum =0.66; Likeliest = 0.90; Maximum = 1.00.
u State B	Utility values assigned to individuals in clinical state B	Dist(6) - Triangular distribution: <u>Parameters</u> Minimum = 0.66; Likeliest = 0.90; Maximum = 0.99.
u State C	Utility values assigned to individuals in clinical state C	Dist(7) - Triangular distribution: <u>Parameters</u> Minimum = 0.63; Likeliest = 0.75; Maximum = 0.87.
u State D	Utility values assigned to individuals in clinical state D	Dist(8) - Triangular distribution: <u>Parameters</u> Minimum =0.55; Likeliest = 0.56; Maximum = 0.80.
lifemale	US Life tables for males (2002)	
pADieA	Annual , markov cycle-specific transition probability from clinical state A to the DEAD state (all-cause mortality) for adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age} + \text{_stage}] - \text{AHIVrateA})$
pADieB	Annual markov cycle-specific transition probability from clinical state B to the DEAD state (all-cause mortality) for adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age} + \text{_stage}] - \text{AHIVrateB})$

Table 5-19 (continued):

Variable	Definition	Formula/Distribution
pADieC	Annual markov cycle-specific transition probability from clinical state C to the DEAD state (all-cause mortality) for adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age+_stage}] - \text{AHIVrateC})$
pADieD	Annual markov cycle-specific transition probability from clinical state D to the DEAD state (all-cause mortality) for adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age+_stage}] - \text{AHIVrateD})$
pNADieA	Annual markov cycle-specific transition probability from clinical state A to the DEAD state (all-cause mortality) for non-adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age+_stage}] - \text{NAHIVrateA})$
pNADieB	Annual markov cycle-specific transition probability from clinical state B to the DEAD state (all-cause mortality) for non-adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age+_stage}] - \text{NAHIVrateB})$
pNADieC	Annual markov cycle-specific transition probability from clinical state C to the DEAD state (all-cause mortality) for non-adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age+_stage}] - \text{NAHIVrateC})$
pNADieD	Annual markov cycle-specific transition probability from clinical state D to the DEAD state (all-cause mortality) for non-adherent individuals	$1 - \exp(-\text{lifemale}[\text{Age+_stage}] - \text{NAHIVrateD})$

The cost-effectiveness of adherence behavior is presented in Table 5-20 and Table 5-21. Simulations were conducted for two time periods: 1) 20-year simulations; and 2) 40-year simulations. Also, analyses were conducted for four different antiretroviral treatment effect duration scenarios: 1) a continuous effect, 2) a six-year effect, 3) an eight-year effect, and 4) a ten-year effect.

For the 20-year simulations, the ICERs for adherent behavior, compared to non-adherent behavior, increased from \$8,722/QALY to \$10,240/QALY when antiretroviral treatment effect duration decreased. Similar patterns were also noted for the 40-year simulations; overall, the ICERs for adherent behavior, compared to non-adherent behavior, obtained from the 40-year simulations were greater than those obtained for the 20-year simulations. Specifically, the ICERs for adherent behavior, compared to non-adherent behavior, for the 40-year simulations increased from \$12,676/QALY to \$14,198/QALY when antiretroviral treatment effect duration decreased.

Table 5-20: Total Medical Costs, Life Years, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (20-Year Simulations)

Adherence Behavior	Total Medical Costs (\$)	LYs	QALYs	Incremental Cost-Effectiveness Ratio (\$/LY)	Incremental Cost-Effectiveness Ratio (\$/QALY)
Six-Year Antiretroviral Treatment Duration Effect					
Adherent	228,984	12.74	10.65	9,101	10,240
Non-Adherent	209,766	10.63	8.77	-	-
Eight-Year Antiretroviral Treatment Duration Effect					
Adherent	228,939	12.81	10.71	8,778	9,862
Non-Adherent	210,744	10.73	8.87	-	-
Ten-Year Antiretroviral Treatment Duration Effect					
Adherent	228,764	12.86	10.77	8,493	9,528
Non-Adherent	211,408	10.82	8.95	-	-
Continuous Antiretroviral Treatment Duration Effect					
Adherent	227,329	12.96	10.87	7,799	8,722
Non-Adherent	211,709	10.96	9.08	-	-

LY: Life Years; QALY: Quality Adjusted Life Years

Table 5-21: Total Medical Costs, Life Years, Quality Adjusted Life Years and Incremental Cost-effectiveness Ratios (40 Year Simulations)

Adherence Behavior	Total Medical Cost (\$)	LYs	QALYs	Incremental Cost-Effectiveness Ratio (\$/LY)	Incremental Cost-Effectiveness Ratio (\$/QALY)
Six Year Antiretroviral Treatment Duration Effect					
Adherent	285,991	15.71	13.11	12,354	14,198
Non-Adherent	239,527	11.95	9.84	-	-
Eight Year Antiretroviral Treatment Duration Effect					
Adherent	286,731	15.82	13.21	12,173	13,977
Non-Adherent	241,422	12.82	9.97	-	-
Ten Year Antiretroviral Treatment Duration Effect					
Adherent	287,375	15.92	13.30	12,003	13,771
Non-Adherent	243,051	12.23	10.08	-	-
Continuous Antiretroviral Treatment Duration Effect					
Adherent	291,205	16.50	13.83	11,104	12,676
Non-Adherent	249,924	12.78	10.57	-	-

LY: Life Years ; QALY: Quality Adjusted Life Years

5.6 Sensitivity Analyses

Extensive sensitivity analyses were conducted to evaluate the stability of the ICERs over a wide range of parameter estimates and structural assumptions (Table 5-22). Certain variables in the simulations were varied over plausible ranges, and the ICERs recalculated. The resulting differences in the ratios provide some indication of how sensitive the results were to variation in parameter values. The following sections present the results of sensitivity analyses.

Table 5-22: Markov Model Baseline and Sensitivity Analyses Ranges

Variable	Minimum	Baseline	Maximum	Distribution Type
Medical Costs (State A)	\$13,071	\$14,568	\$16,065	Log Normal
Medical Costs (State B)	\$17,871	\$20,285	\$22,700	Log Normal
Medical Costs (State C)	\$26,345	\$31,708	\$37,072	Log Normal
Medical Costs (State D)	\$30,123	\$38,352	\$46,580	Log Normal
Utility (State A)	0.66	0.90	1.0	Triangular
Utility (State B)	0.66	0.90	0.99	Triangular
Utility (State C)	0.63	0.75	0.87	Triangular
Utility (State D)	0.55	0.56	0.80	Triangular
Discount Rate	0	0.03	0.07	Triangular
Relative Risk Adjustment	1.085	1.17	1.255	Triangular

5.6.1 One-way sensitivity analyses

One-way sensitivity analyses were conducted on medical costs, utilities, discount rates and the relative risk disease progression statistic. To estimate the effect of varying parameter values, one-way sensitivity analyses were conducted for both the 20- and 40-year simulations; however, one-way sensitivity analyses

were only conducted for two antiretroviral treatment effect duration scenarios: 1) a six-year effect, and 2) a continuous effect.

5.6.1.1 Twenty-Year Simulations

One-way sensitivity analyses were conducted for both the continuous and six-year antiretroviral treatment effect duration scenarios. The results of one-way sensitivity analyses for the 20-year simulations, assuming continuous antiretroviral treatment effect duration, are presented below. When varied, the utility and medical costs in state A resulted in the greatest variation in outcomes; expected values (costs) are presented in the tornado diagram (Figure 5-16).

The following section summarizes the effect of varying the parameters on the ICERs. Although one-way sensitivity analyses have been conducted on all parameters, the impact of sensitivity analyses on ICERs will only be presented for the two parameters that showed the greatest variation.

Decreasing the utility values in State A from 0.90 to 0.66 increased the ICER of adherent behavior, compared to non-adherent behavior, from \$8,722/QALY to \$12,738/QALY (Table 5-23). Conversely, increasing the utility values in State A from 0.90 to 1.0 decreased the ICER of adherent behavior, compared to non-adherent behavior, from \$8,722/QALY to \$7,038/QALY.

Figure 5-16: Parameters and Expected Values (20-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

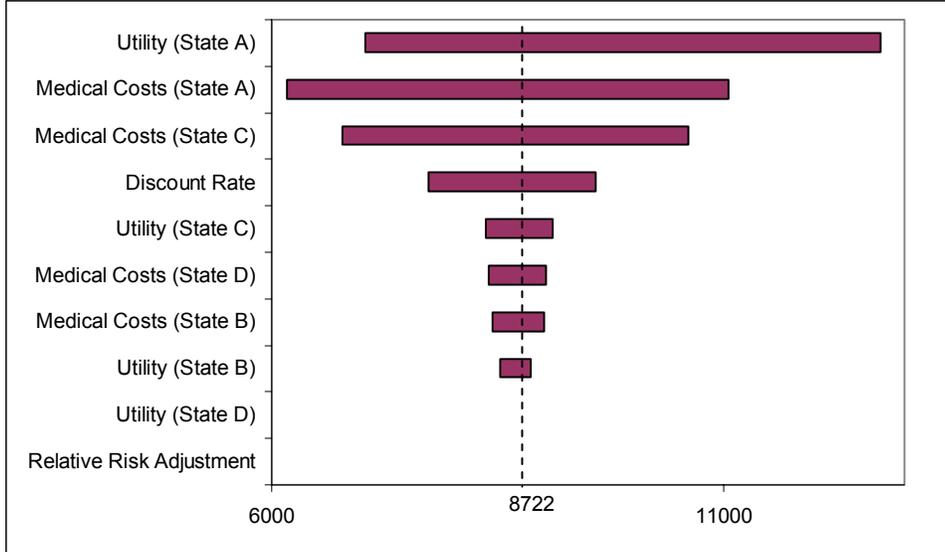
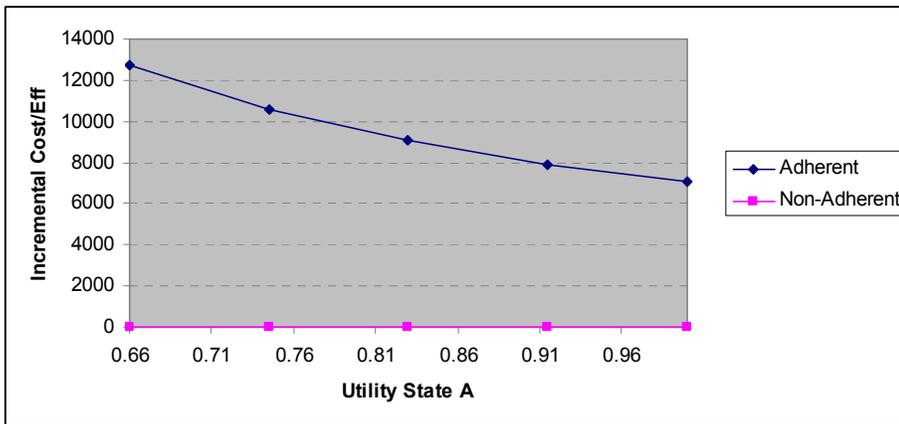


Table 5-23: Utility Values in State A, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (20-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

Utility (State A)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
0.66	Non-Adherent	211,709		7.86		
	Adherent	227,329	15,620	9.08	1.23	12,738
1.0	Non-Adherent	211,709		10.02		
	Adherent	227,329	15,620	12.24	2.22	7,038

Figure 5-17 displays the relationship between ICERs and varying the utility values in State A.

Figure 5-17: Relationship between Utility in State A and Incremental Costs Per Quality Adjusted Life Year (20-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)



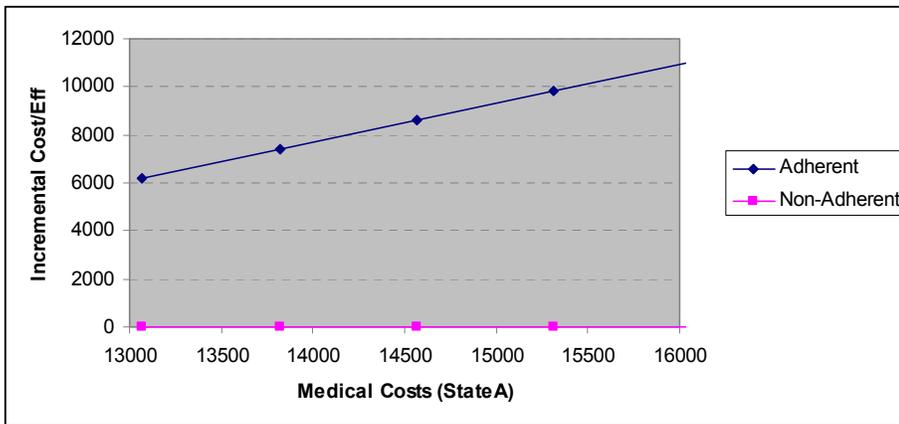
Decreasing the annual medical costs in State A from \$14,568 to \$13,071 decreased the ICER of adherent behavior, compared to non-adherent behavior, from \$8,722/QALY to \$6,171/QALY (Table 5-24). Conversely, increasing the annual medical costs in State A from \$14,568 to \$16,065 increased the ICER of adherent behavior, compared to non-adherent behavior, from \$8,722/QALY to \$11,053/QALY.

Table 5-24: Annual Medical Costs in State A, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios of HIV-infected Individuals (20-Year Simulations, Continuous Antiretroviral Treatment Duration Effect)

Annual Medical Cost (\$) (State A)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
\$13,071	Non-Adherent	201,760		9.09		
	Adherent	212,811	11,051	10.88	1.79	6,171
\$16,065	Non-Adherent	220,900		9.09		
	Adherent	240,595	19,796	10.88	1.79	11,053

Figure 5-18 displays the relationship between ICERs and the annual medical costs in State A.

Figure 5-18: Relationship between Medical Costs in State A and Incremental Costs per Quality Adjusted Life Year (20-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)



The results of one-way sensitivity analyses for 20-year simulations, assuming a six-year antiretroviral treatment effect, are presented below. When varied, the utility and medical costs in state A resulted in the greatest variation in outcomes; expected values (costs) are presented in the tornado diagram (Figure 5-19).

Decreasing the utility values in State A from 0.90 to 0.66 increased the ICER of adherent behavior, compared to non-adherent behavior, from \$10,240/QALY to \$14,366/QALY (Table 5-25). Conversely, increasing the utility values in State A from 0.90 to 1.0 decreased the ICER of adherent behavior, compared to non-adherent behavior, from \$10,240/QALY to \$8,408/QALY.

Figure 5-19: Parameters and Expected Values (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

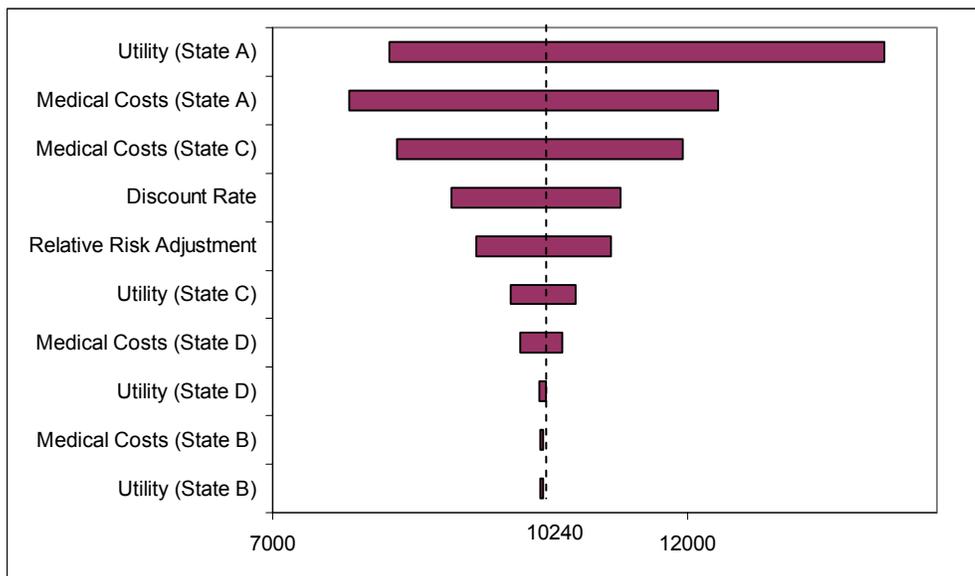
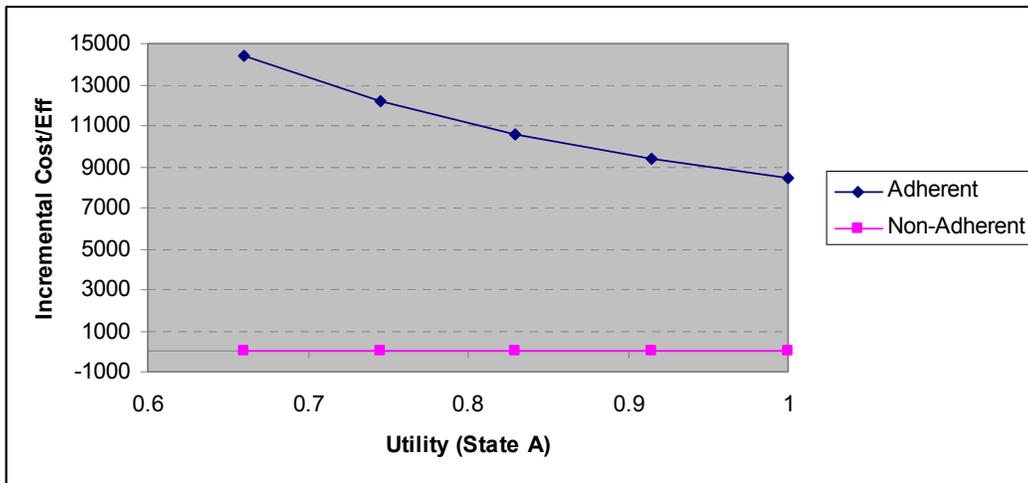


Table 5-25: Utility Values in State A, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

Utility (State A)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
0.66	Non-Adherent	209,766		7.63		
	Adherent	228,984	19,219	8.97	1.34	14,366
1	Non-Adherent	209,766		9.65		
	Adherent	228,984	19,219	11.93	2.29	8,408

Figure 5-20 displays the relationship between ICERs and the utility values of individuals in State A.

Figure 5-20: Relationship between Utility Values in State A and Incremental Costs Per Quality Adjusted Life Year (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)



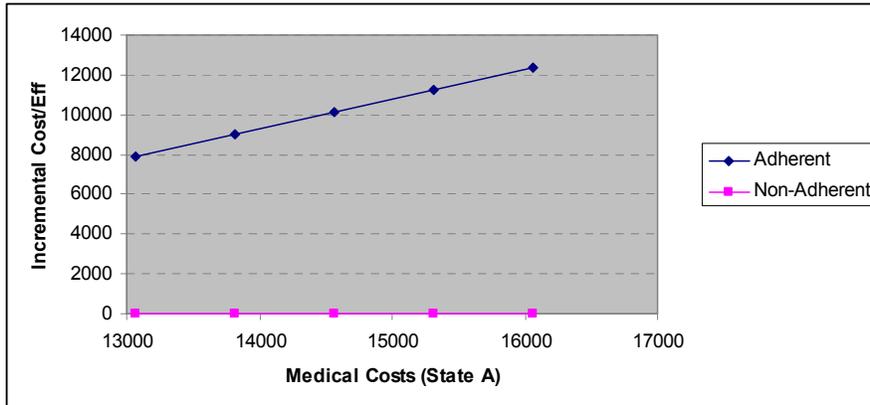
Decreasing the annual medical costs in State A from \$14,568 to \$13,071 decreased the ICER of adherent behavior, compared to non-adherent behavior, from \$10,240/QALY to \$7,917/QALY (Table 5-26). Conversely, increasing the medical costs in State A from \$14,568 to \$16,065 increased the ICER for adherent behavior, compared to non-adherent behavior, from \$10,240/QALY to \$12,364/QALY.

Table 5-26: Annual Medical Costs in State A, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

Annual Medical Cost (\$) (State A)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
\$13,071	Non-Adherent	200,483		8.78		
	Adherent	215,340	14,857	10.65	1.88	7,917
\$16,065	Non-Adherent	218,248		8.78		
	Adherent	241,452	23,204	10.65	1.88	12,364

Figure 5-21 displays the relationship between the ICERs and the annual medical costs of individuals in State A.

Figure 5-21: Relationship between Annual Medical Costs in State A and Incremental Costs Per Quality Adjusted Life Year (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)



5.6.1.2 Forty-Year Simulations

The results of the one-way sensitivity analyses for 40-year simulations, assuming continuous antiretroviral treatment effect, are presented below. When varied, the utility values in state A and discount rates resulted in the greatest variation in outcomes (Figure 5-22). Decreasing the utility values in State A from 0.90 to 0.66 increased the ICER for adherent behavior, compared to non-adherent behavior, from \$12,676/QALY to \$17,221/QALY (Table 5-27). Conversely, increasing the utility values in State A from 0.90 to 1.0 decreased the ICER of adherent behavior, compared to non-adherent behavior, from \$12,676/QALY to \$10,561/QALY.

Figure 5-22: Parameters and Expected Values (40-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

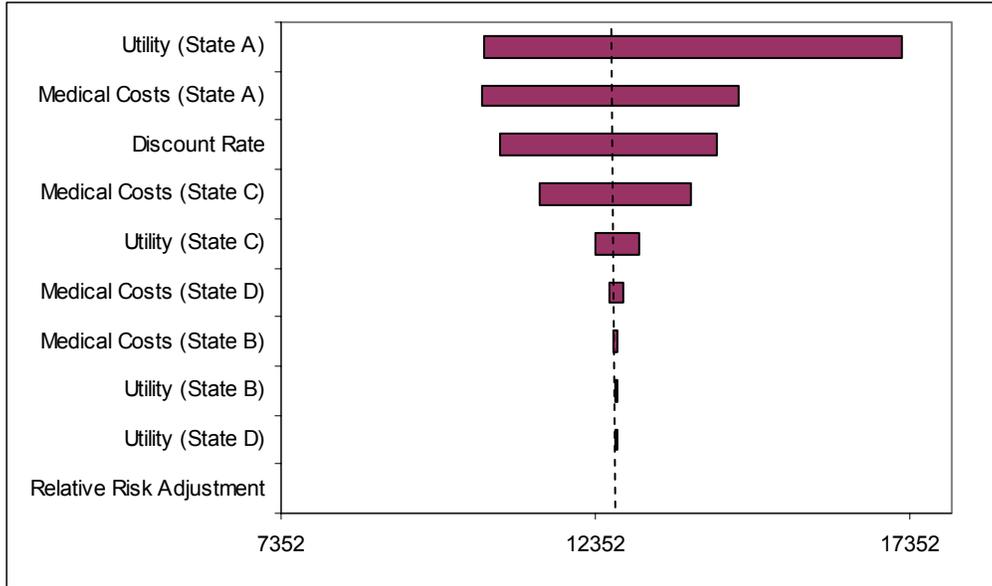
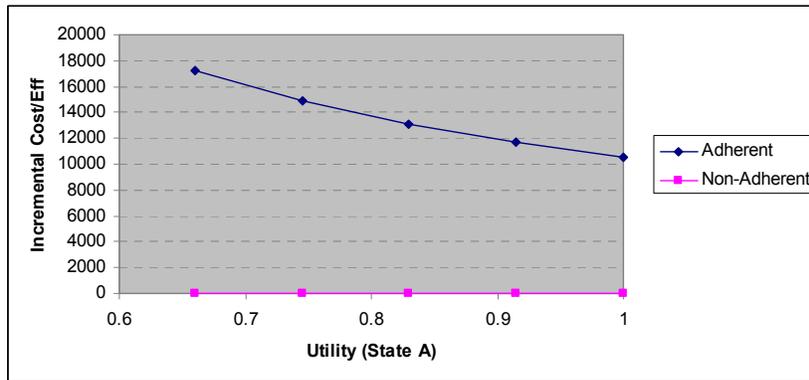


Table 5-27: Utility Values in State A, Total Medical Costs, Life Years, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (40-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

Utility (State A)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
0.66	Non-Adherent	249,924		9.19		
	Adherent	291,205	41,281	11.58	2.40	17,221
1	Non-Adherent	249,924		11.63		
	Adherent	291,205	41,281	15.54	3.91	10,561

Figure 5-23 displays the relationship between ICERs and the utility values of individuals in State A.

Figure 5-23: Relationship between Utility in State A and Incremental Costs Per Quality Adjusted Life Year (40-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)



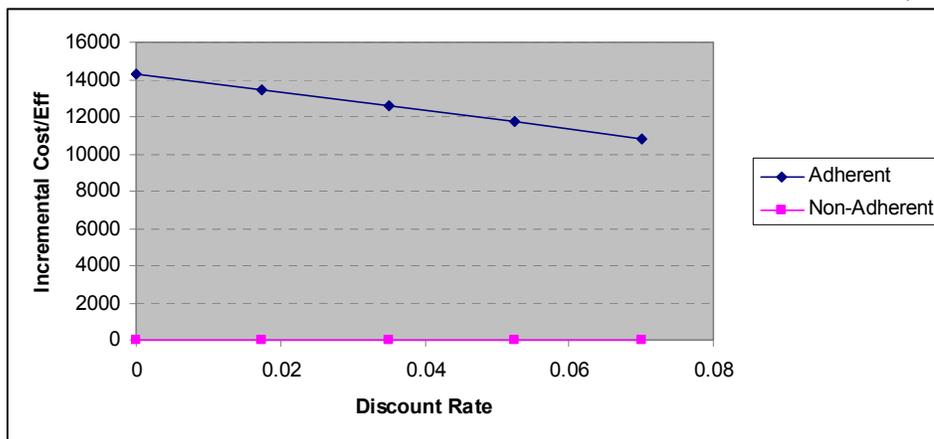
Decreasing the discount rate from three percent to zero percent increased the ICER of adherent behavior, compared to non-adherent behavior, from \$12,676/QALY to \$14,259/QALY (Table 5-28). Conversely, increasing the discount rate from zero to seven percent decreased the ICER from \$12,676/QALY to \$10,834/QALY.

Table 5-28: Discount Rate, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (40-Year Simulations, Continuous Antiretroviral Treatment Duration Effect)

Discount Rate (%)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
0	Non-Adherent	371,490		15.40		
	Adherent	462,715	91,224	21.79	6.40	14,259
7	Non-Adherent	178,361		7.72		
	Adherent	197,344	18,984	9.47	1.75	10,834

Figure 5-24 displays the relationship between the ICERs and varying discount rates.

Figure 5-24: Relationship between the Discount Rate and Incremental Costs per Quality Adjusted Life Year (40-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)



The results of the one-way sensitivity analyses for 40-year simulations, assuming six-year antiretroviral treatment effect duration, are presented below.

When varied, the utility values in state A and B resulted in the greatest variation

in outcomes; expected values (costs) are presented in the tornado diagram (Figure 5-25). Decreasing the utility values in State A from 0.90 to 0.66 increased the ICER of adherent behavior, compared to non-adherent behavior, from \$12,676/QALY to \$18,642/QALY (Table 5-29). Conversely, increasing the utility values in State A from 0.90 to 1.0 decreased the ICER of adherent behavior, compared to non-adherent behavior, from \$12,676/QALY to \$12,023/QALY.

Figure 5-25: Parameters and Expected Values (40-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

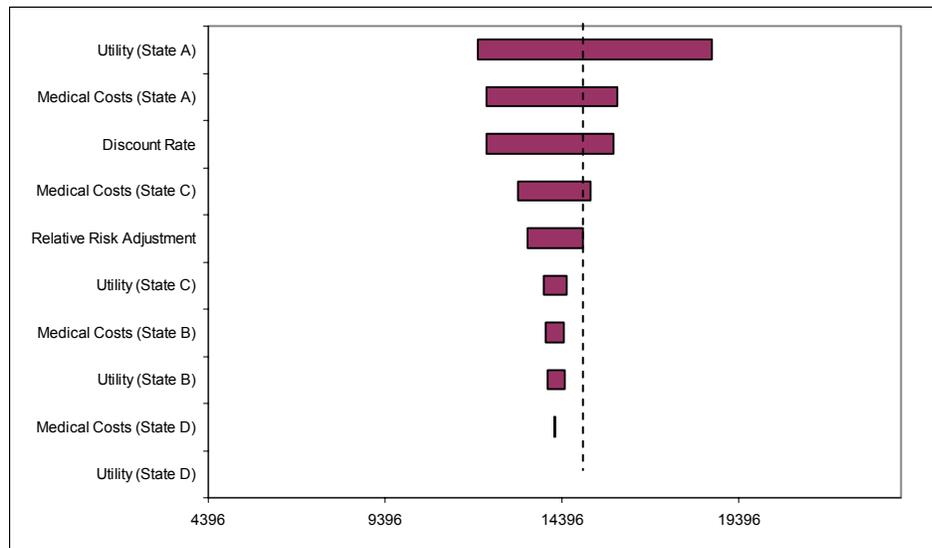
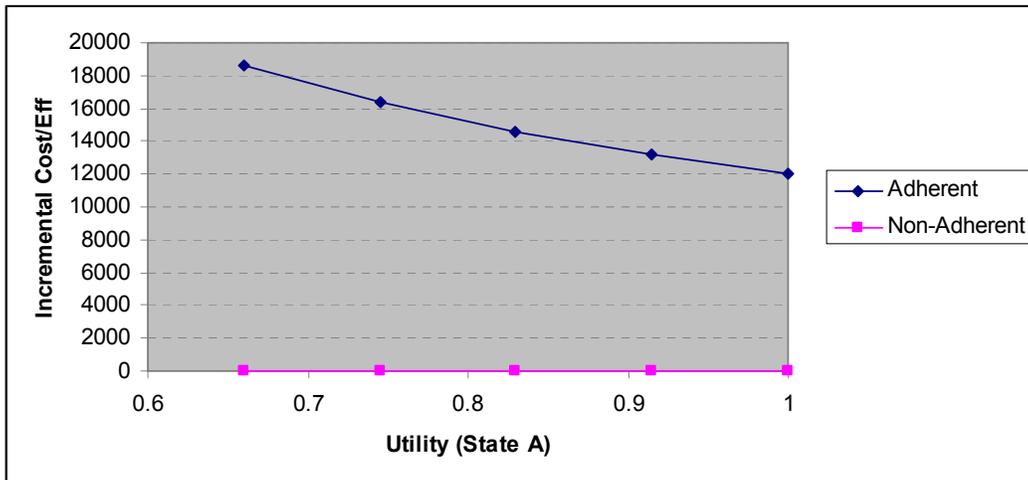


Table 5-29: Utility Values in State A, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (40-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

Utility (State A)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
0.66	Non-Adherent	239,527		8.60		
	Adherent	285,991	46,464	11.09	2.49	18,642
1	Non-Adherent	239,527		10.79		
	Adherent	285,991	46,464	14.65	3.86	12,023

Figure 5-26 displays the relationship between ICERs and the utility values of individuals in State A.

Figure 5-26: Relationship between Utility in State A and Incremental Costs Per Quality Adjusted Life Year (40-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)



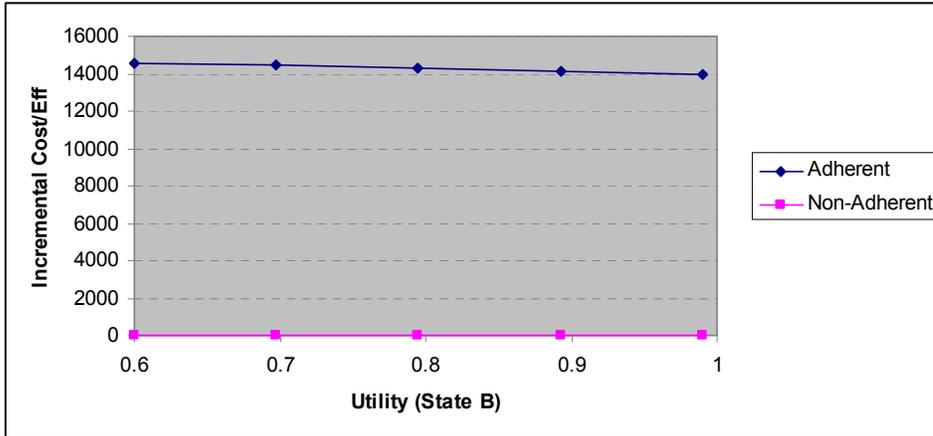
Decreasing utility values in State B from 0.90 to 0.66 increased the ICER from \$14,198/QALY to \$14,585/QALY (Table 5-30). Conversely, increasing the utility values in State B from 0.90 to 0.99 decreased the ICER from \$14,198/QALY to \$13,990/QALY.

Table 5-30: Utility Values in State B, Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratios (40-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

Utility (State B)	Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
0.66	Non-Adherent	239,527		9.08		
	Adherent	285,991	46,464	12.26	3.19	14,585
0.99	Non-Adherent	239,527		10.27		
	Adherent	285,991	46,464	13.59	3.32	13,990

Figure 5-27 displays the relationship between the incremental cost-effectiveness ratio of adherent behavior and the costs of varying utility values in state B.

Figure 5-27: Relationship between Utility Values in State B and Incremental Costs per Quality Adjusted Life Year (40-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)



5.6.2 Probabilistic Sensitivity Analyses

Traditionally, conducting one-way sensitivity analyses has been sufficient for the purposes of characterizing decision uncertainty. More recently, a probabilistic approach (second-order Monte Carlo simulations) to assess the robustness of the ICERs to variations in individual parameters, has been proposed as the most appropriate framework to conduct sensitivity analyses. In the United Kingdom, the National Institute for Clinical Excellence (NICE), has recently updated its methods guidance for technology assessment; one aspect of the new guidance is to require the use of probabilistic sensitivity analysis with all cost-effectiveness models submitted to the institute.⁵³

5.6.2.1 Twenty-Year Simulation, Continuous Antiretroviral

Treatment Effect Duration

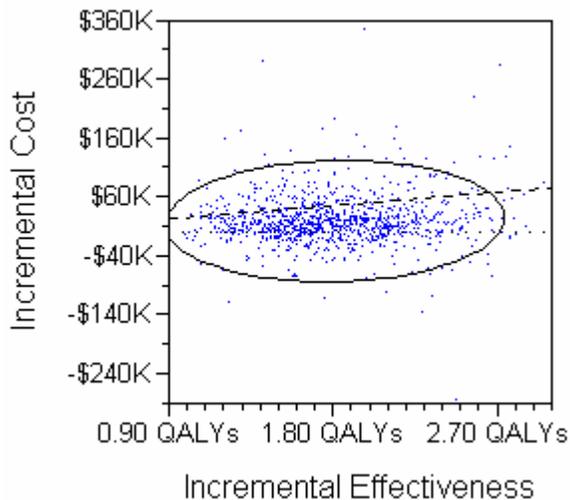
Probabilistic sensitivity analyses were conducted by simultaneously varying all parameters with distributions (costs, utilities, discount rate, and relative risk disease adjustment) in the cost-effectiveness analysis. One thousand simulations, sampling all distributions, were conducted. Table 5-31 presents the ICER generated after the second-order Monte Carlo simulations.

Table 5-31: Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratio (20-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

Adherence Behavior	Total Medical Cost (\$)	Incremental Cost (\$)	QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
Non-Adherent	213,004		9.1745		
Adherent	229,619	16,615	10.9979	1.8234	9,112

The cost-effectiveness scatterplot, showing the points of the 1,000 iterations in the simulation, is presented in Figure 5-28. The willingness to pay (WTP) for an incremental quality adjusted life year was assumed to be \$25,000.

Figure 5-28: Incremental Cost-Effectiveness Scatterplot of Adherent Behavior Compared to Non-Adherent Behavior (20-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)



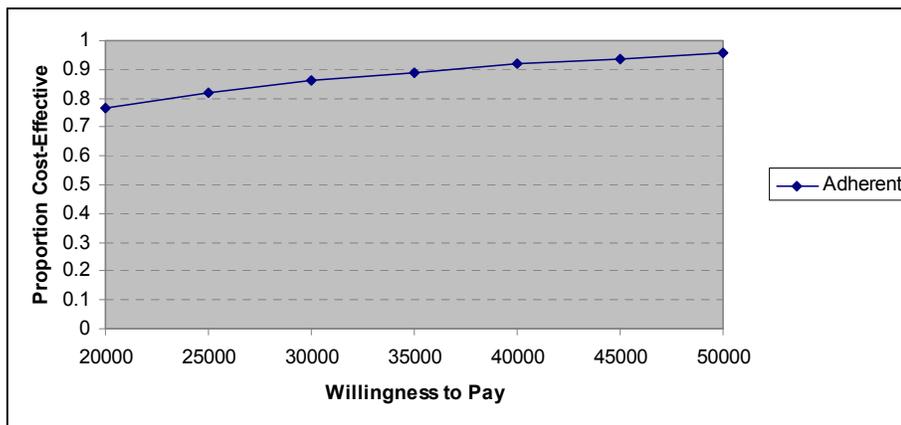
The area below the WTP line defines the region of cost-effective points; the majority of points lie below the threshold value. Additionally, a 95% confidence ellipse of all points was plotted. Confidence ellipses have been developed to estimate confidence interval limits for ICERs.⁴⁴³ For approximately 29% of the simulations, adherent behavior was less costly and more effective. Additionally, for 54% of the simulations, adherent behavior was more costly but the ICER of adherent behavior, compared to non-adherent behavior, was less than

⁴⁴³ Briggs A, Fenn P. Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. *Health Economics* 1998;7(8 (Print)):723-740.

\$25,000/QALY. Conversely, 17% of the simulations indicate that adherent behavior is more costly, and lie above the WTP threshold.

Finally, an acceptability curve was generated to present the results of the probabilistic sensitivity analyses (Figure 5-29). The graph indicates that at a \$25,000/QALY threshold, the probability of adherent behavior being cost-effective is approximately 0.8.

Figure 5-29: Cost-Effectiveness Acceptability Curve for Adherent Behavior



5.6.2.2 Twenty-Year Simulation, Six-Year Antiretroviral

Treatment Effect Duration

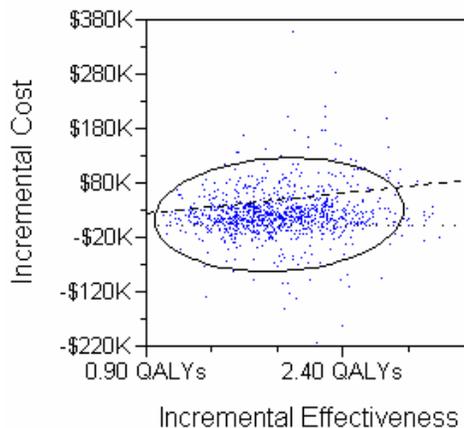
Table 5-32 presents the ICER generated after the second-order Monte Carlo simulations.

Table 5-32: Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratio (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

Adherence Behavior	Total Medical Costs (\$)	Incremental Costs (\$)	Total QALYs	Incremental QALYs	Incremental Costs (\$) Per QALY
Non-Adherent	216,000		8.87		
Adherent	236,000	20,000	10.79	1.92	10,564

The cost-effectiveness scatterplot, showing the points of the 1,000 iterations in the simulation, is presented in Figure 5-30.

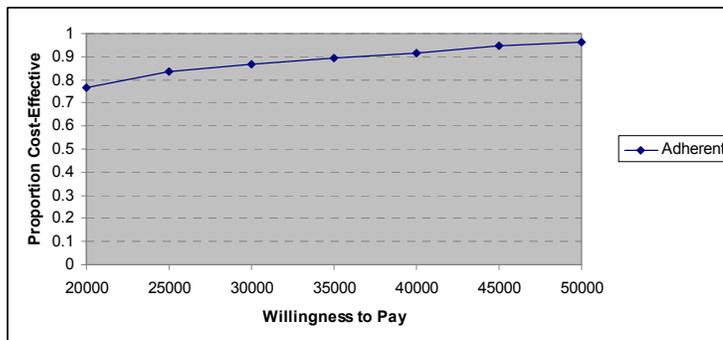
Figure 5-30: Incremental Cost-Effectiveness Scatterplot of Adherent versus Non-Adherent Behavior (20-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)



For approximately 22% of the simulations, adherent behavior was less costly and more effective. Additionally, for 61% of the simulations, adherent behavior was more costly but the ICER of adherent behavior, compared to non-adherent behavior, was less than \$25,000/QALY. Conversely, 17% of simulations indicate that adherent behavior is more costly, and lie above the WTP threshold.

Finally, an acceptability curve was generated to present the results of the probabilistic sensitivity analyses (Figure 5-31). The graph indicates that at a \$25,000/QALY threshold, the probability of adherent behavior being cost effective is approximately 0.8.

Figure 5-31: Cost-Effectiveness Acceptability Curve for Adherent Behavior



5.6.2.3 Forty-Year Simulation, Continuous Antiretroviral

Treatment Effect Duration

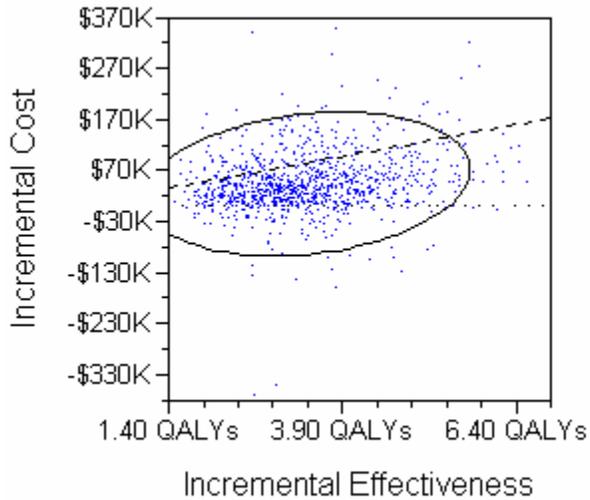
Table 5-33 presents the ICER generated after the second-order Monte Carlo simulations.

Table 5-33: Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratio (40-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

Adherence Behavior	Total Costs (\$)	Incremental Costs (\$)	Total QALYs	Incremental QALYs	Incremental Cost (\$ Per QALY)
Non-Adherent	258,000		10.76		
Adherent	301,000	43,000	14.15	3.39	12,769

The cost-effectiveness scatterplot, showing the points of the 1000 iterations in the simulation, is presented in Figure 5-32.

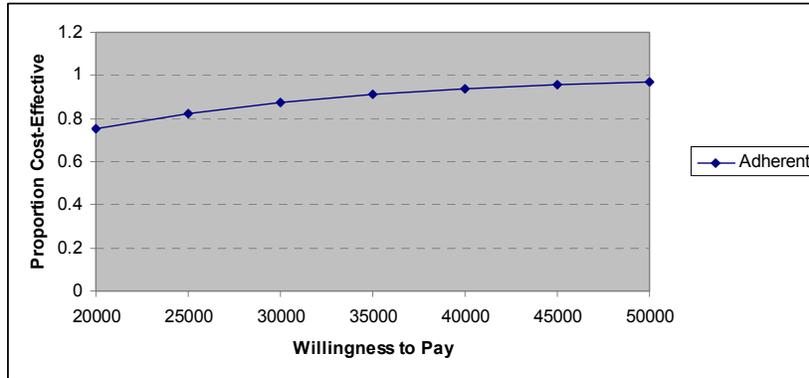
Figure 5-32: Incremental Cost-Effectiveness Scatterplot of Adherent versus Non-Adherent Behavior (Forty-Year Simulation, Continuous Antiretroviral Treatment Effect Duration)



For approximately 13% of the simulations, adherent behavior was less costly and more effective. Additionally, for 69% of the simulations, adherent behavior was more costly but the ICER of adherent behavior, compared to non-adherent behavior, was less than \$25,000/QALY. Conversely, 18% of simulations indicate that adherent behavior is more costly, and lie above the WTP threshold.

Finally, an acceptability curve was generated to communicate the results of the probabilistic sensitivity analyses (Figure 5-33). The results of the graph indicate that at a WTP of \$25,000, the probability of adherent behavior being cost-effective is approximately 0.8, and it increases as the WTP increases.

Figure 5-33: Cost-Effectiveness Acceptability Curve for Adherent Behavior



5.6.2.4 Forty-Year Simulation, Six-Year Antiretroviral Treatment Effect Duration

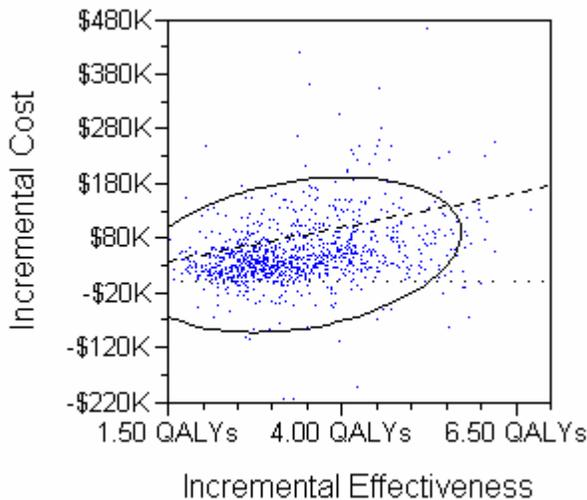
Table 5-34 presents the ICER generated after the second-order Monte Carlo simulations.

Table 5-34: Total Medical Costs, Quality Adjusted Life Years and Incremental Cost-Effectiveness Ratio (40-Year Simulations, Six-Year Antiretroviral Treatment Effect Duration)

Adherence Behavior	Total Costs (\$)	Incremental Costs (\$)	QALYs	Incremental QALYs	Incremental Cost (\$) Per QALY
Non-Adherent	242,000		9.94		
Adherent	291,000	50,000	13.32	3.38	14,712

Figure 5-34 presents the incremental cost-effectiveness scatterplot produced from the probabilistic sensitivity analysis.

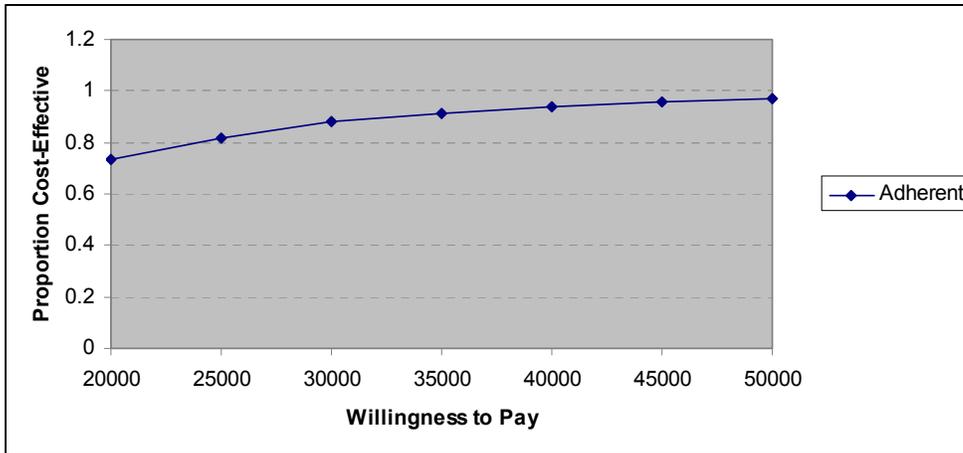
Figure 5-34: Incremental Cost-Effectiveness Scatterplot of Adherent Compared to Non-Adherent Behavior (40Year Simulations, Six Year Antiretroviral Treatment Effect Duration)



For approximately 9% of the simulations, adherent behavior was less costly and more effective. Additionally, for 72% of the simulations, adherent behavior was more costly but the ICER of adherent behavior, compared to non-adherent behavior, was less than \$25,000/QALY. Conversely, 19% of simulations indicate that adherent behavior is more costly, and lie above the WTP threshold.

Finally, an acceptability curve was generated to communicate the results of the probabilistic sensitivity analyses (Figure 5-35). The results of the graph indicate that at a WTP of \$25,000, the probability of adherent behavior being cost-effective is approximately 0.8, and it increases as the WTP increases.

Figure 5-35: Cost-Effectiveness Acceptability Curve for Adherent Behavior



5.6.3 Net Monetary Benefit

The calculation of net monetary benefits (NMB) and net health benefits (NHB) in health economic evaluations, while not as common yet as the usage of ICERs, is coming into increasing favor. Several supporting rationales have been advanced for the use of net benefit calculations as a supplement or alternative to incremental cost-effectiveness ratio calculations, particularly when trying to describe the uncertainty in incremental costs and/or effectiveness values. The net monetary benefit (NMB) of an alternative is calculated using the following formula:

$$\text{NMB} = \Delta E * \text{WTP} - \Delta C,$$

where E represents effectiveness, C represents cost, and WTP is the willingness to pay (i.e., the decision maker's threshold ICER).

One advantage of using net benefits is that the most cost-effective comparator is simply the one with the highest net benefit, given the same threshold ICER. This is the case for comparisons of any number of strategies. Another advantage of the net benefits framework is the straightforward manner in which the probability distribution of net benefits can be presented and analyzed (compared to the joint distribution of incremental cost and effectiveness values or a distribution of ratios). For the purposes of this study, the WTP is assumed to be \$25,000.

5.6.3.1 Twenty-Year Simulation, Continuous Antiretroviral

Treatment Effect Duration

The results of the probabilistic sensitivity analyses for the 20-year simulations, assuming continuous antiretroviral treatment effect, are presented below (Table 5-35). The NMB of adherent behavior is greater than that of non-adherent behavior, given the \$25,000 threshold, indicating that adherent behavior is more cost-effective than non-adherent behavior.

Table 5-35: Mean, Median, Minimum, Maximum Costs and QALYs for Adherent and Non-Adherent HIV-infected Individuals (Twenty-Year Simulation, Continuous Antiretroviral Treatment Effect Duration)

Statistic	Adherent			Non-Adherent		
	Cost (\$)	QALYs	Net Monetary Benefit	Cost (\$)	QALYs	Net Monetary Benefit
Mean	229,619	11.00	45,329	213,004	9.17	16,359
Std Dev	129,719	1.43	127,804	117,926	1.07	115,952
Minimum	30,480	7.10	-1,516,016	27,537	6.19	-1,651,455
Median	200,581	10.92	71,503	188,318	9.13	40,507
Maximum	1,804,862	15.94	303,475	1,913,530	12.89	228,941

5.6.3.2 Twenty-Year Simulation, Six-Year Antiretroviral

Treatment Effect Duration

The results of the probabilistic sensitivity analyses for the 20-year simulations, assuming a six-year antiretroviral treatment effect, are presented below (Table 5-36). The NMB of adherent behavior is greater than that of non-adherent behavior, given the \$25,000 threshold, indicating that adherent behavior is more cost-effective than non-adherent behavior.

Table 5-36: Mean, Median, Minimum, Maximum Costs and QALYs for Adherent and Non-Adherent HIV-infected Individuals (Twenty-Year Simulation, Six-Year Antiretroviral Treatment Effect Duration)

Statistic	Adherent			Non-Adherent		
	Cost (\$)	QALYs	Net Monetary Benefit	Cost (\$)	QALYs	Net Monetary Benefit
Mean	236,243	10.79	33,423	216,005	8.87	5,767
Std Dev	130,720	1.39	127,765	116,106	1.02	113,566
Minimum	50,846	7.11	-960,437	47,242	6.13	-686,478
Median	200,874	10.68	60,375	188,732	8.79	29,969
Maximum	1,256,322	15.20	276,858	947,897	12.11	215,683

5.6.3.3 Forty-Year Simulation, Continuous Antiretroviral Treatment Effect Duration

The results of the probabilistic sensitivity analyses for the 40-year simulations, assuming continuous antiretroviral treatment effect, are presented below (Table 5-37). The NMB of adherent behavior is greater than that of non-adherent behavior, given the \$25,000 threshold, indicating that adherent behavior is more cost-effective than non-adherent behavior.

Table 5-37: Mean, Median, Minimum, Maximum Costs, QALYs and Net Monetary Benefit for Adherent and Non-Adherent HIV-infected Individuals (40-Year Simulations, Continuous Antiretroviral Treatment Effect Duration)

Statistic	Adherent			Non-Adherent		
	Cost (\$)	QALYs	Net Monetary Benefit	Cost (\$)	QALYs	Net Monetary Benefit
Mean	300,859	14.15	52,850	257,529	10.76	11,348
Std Dev	161,780	2.56	155,488	140,664	1.61	135,994
Minimum	53,446	8.65	-936,463	49,591	6.98	-818,030
Median	259,721	13.94	88,786	220,992	10.65	43,010
Maximum	1,240,538	22.39	327,570	1,067,003	15.83	242,569

5.6.3.4 Forty-Year Simulation, Six-Year Antiretroviral

Treatment Effect Duration

The results of the probabilistic sensitivity analyses for the 40-year simulations, assuming six-year antiretroviral treatment effect, are presented below (Table 5-38). The NMB of adherent behavior is greater than that of non-adherent behavior, given the \$25,000 threshold, indicating that adherent behavior is the more cost-effective than non-adherent behavior.

Table 5-38: Mean, Median, Minimum, Maximum Costs, QALYs and Net Monetary Benefit for Adherent and Non-Adherent HIV-infected Individuals (40-Year Simulations, Six-year Antiretroviral Treatment Effect Duration)

Statistic	Adherent			Non-adherent		
	Costs (\$)	QALYs	Net Monetary Benefit	Costs (\$)	QALYs	Net Monetary Benefit
Mean	291,367	13.32	41,677	241,591	9.94	6,866
Std Dev	166,568	2.36	157,070	135,770	1.42	130,105
Minimum	43,069	8.29	-1,042,799	36,396	6.69	-1,042,460
Median	254,919	13.07	76,846	213,305	9.80	31,506
Maximum	1,441,183	21.61	337,012	1,328,895	14.89	227,955

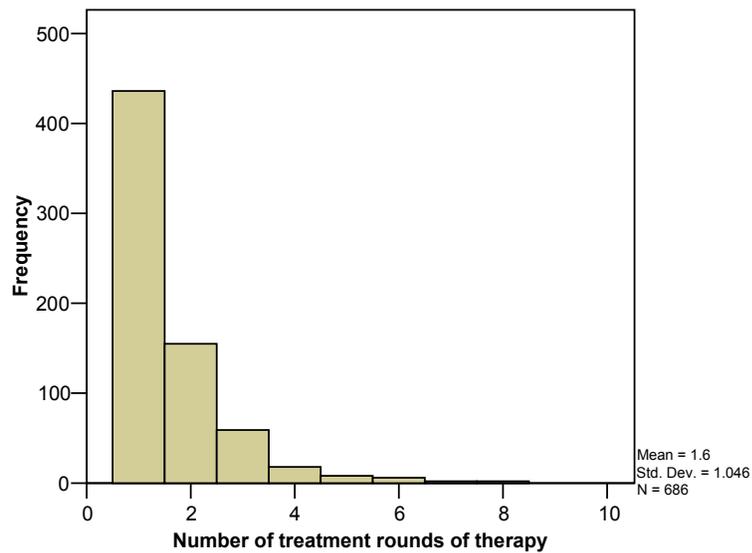
5.7 Antiretroviral Regimen Changes

An operational definition of antiretroviral “treatment failure” was considered when a patient was changed to a new antiretroviral regimen (treatment round). The end of a round of antiretroviral regimen (failed treatment round) was defined as the point at which a patient was changed to at least two new agents; a new round of antiretroviral regimen begins at this point.

Overall, there were 436 individuals (63.6%) who did not change regimens, 155 (22.6%) who changed regimens only once, 59 (8.6%) who changed regimens only twice and 36 (5.25) who experienced more than two antiretroviral regimen changes (Figure 5-36). Also, there were 34 (7%) non-adherent individuals and

two (1%) adherent individuals who experienced three or more antiretroviral regimen changes.

Figure 5-36: Histogram of the Number of Treatment Rounds of Therapy



The mean number of treatment rounds calculated for adherent and non-adherent individuals, not accounting for enrollment period (follow-up period), was 1.32 (SD = 0.64) and 1.73 (SD = 1.16), respectively. To determine whether there was a significant difference in the number of treatment rounds observed between adherent and non-adherent individuals, analysis of covariance (ANCOVA) using the enrollment period as a covariate was conducted. The following equation represents the ANCOVA model used to test whether there was

a significant difference in the number of treatment rounds experienced between adherent and non-adherent individuals:

$$\text{Number of treatment rounds} = \beta_1 \text{Adherence (Adherent/Non-Adherent)} + \beta_2 \text{Enrollment Period} + \beta_3 \text{Adherence (Adherent/Non-Adherent)} * \text{Enrollment Period} + \text{Constant}$$

An assumption of ANCOVA is that there is no significant interaction between the covariate (Enrollment Period) and factor (Adherence), so it is usual to begin by fitting a model with an interaction term as shown above. If the assumption of homogeneity of regression slopes is violated, the model may be inaccurate. Table 5-39 displays the parameter estimates of the model and the interaction between adherence and enrollment period was significant ($p < 0.001$).

Table 5-39: Analysis of Covariance Parameter Estimates

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Intercept	1.010	.091	11.118	.000	.831	1.188
Non-Adherent Behavior	-.123	.117	-1.054	.292	-.352	.106
Adherent Behavior	0 ^a
Enrollment Period	.000	.000	4.682	.000	.000	.001
Non-Adherent Behavior* Enrollment Period	.000	.000	3.461	.001	.000	.001
Adherent Behavior* Enrollment Period	0 ^a

^a This parameter is set to zero because it is redundant

By specifying an interaction between the covariate and factor, the homogeneity of the covariate parameter estimates across levels of the factor was tested. Since the interaction term was significant, indicating the covariate parameter estimates are not homogenous, an analysis of covariance was not conducted; assessing the number of treatment rounds is complicated by the presence of the interaction. Therefore, because the interaction term was significant, the relationship between the enrollment period and the number of treatment switches is different for the adherent and non-adherent groups. As depicted in Figure 5-37 and Figure 5-38 , all that can be deduced is that there are more treatment switches in non-adherent individuals compared to adherent individuals as the enrollment period increases.

Figure 5-37: Scatterplot of the Number of Treatment Rounds versus Enrollment Period for Non-adherent Individuals

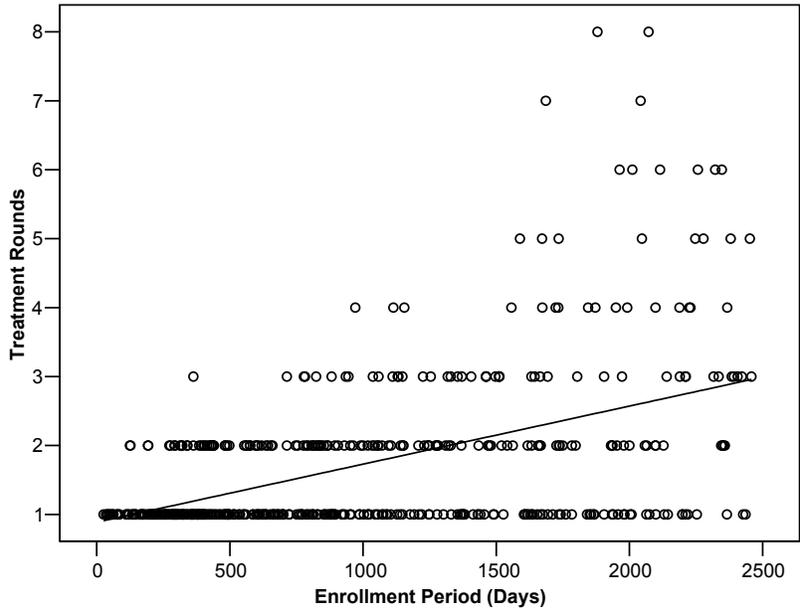
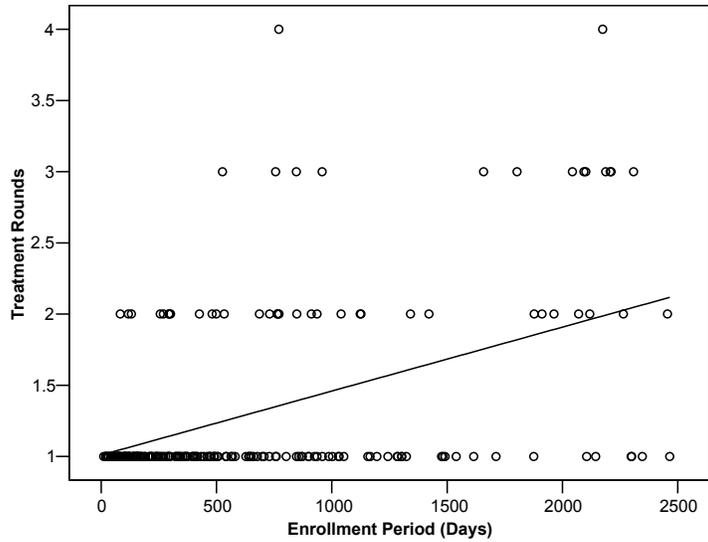


Figure 5-38: Scatterplot of the Number of Treatment Rounds versus Enrollment Period for Adherent Individuals



5.8 Summary

5.8.1 Markov Monte Carlo Simulations

Statistical issues in cost-effectiveness studies are different from those that arise in experiments or other data analyses. Rather than testing hypotheses using traditional statistical significance as a criterion, model-based evaluation studies aim to portray the scope and nature of uncertainties that surround the estimates of costs, benefits, and cost-effectiveness ratios that they produce through the use of sensitivity analyses. A probabilistic simulation (Monte Carlo) analysis was constructed for a hypothetical cohort of HIV-infected individuals. The results of probabilistic Monte Carlo simulations indicate that the incremental cost-effectiveness of adherent behavior, compared to non-adherent behavior is below a willingness-to-pay of \$25,000/QALY.

5.8.2 Antiretroviral Regimen Changes

To determine whether there was a significant difference in the number of treatment rounds observed between adherent and non-adherent individuals, ANCOVA was proposed to account for the period (enrollment) individuals were followed for. Since the interaction term (adherence-enrollment period) was significant, indicating the covariate parameter estimates are not homogenous, an analysis of covariance was not conducted; assessing the number of treatment rounds is complicated by the presence of the interaction. Therefore, because the

interaction term was significant, the relationship between the enrollment period and the number of treatment switches is different for the adherent and non-adherent groups. All that can be deduced is that there are more treatment switches in non-adherent individuals compared to adherent individuals as the enrollment period increases.

CHAPTER 6

DISCUSSION

This chapter reviews and discusses the major findings of the study. The chapter is presented in eight main sections. The first section describes the characteristics of the VA HIV-infected cohort. Specifically, HIV-infected individuals' demographics and antiretroviral prescribing patterns are summarized. The second section summarizes the adherence behavior of the HIV-infected cohort. The results are compared to the findings of other studies. The third section summarizes the clinical outcomes projected by the present study and a brief synopsis of the clinical outcomes reported by others is presented. Fourth, the costs associated with HIV disease are summarized; again, a brief synopsis of the economic outcomes reported by others is presented. Fifth, changes in antiretroviral regimens are summarized and a brief review of the findings reported by others is presented. Sixth, the potential implications of the results of this study are presented. Special emphasis is given to highlight the potential implications of study findings from patients' and the VA's perspectives. Additionally, the potential impact of the findings of this study on future HIV adherence-related research is presented. Seventh, the limitations of the study are addressed, and finally, the conclusions drawn from the study findings are presented.

Presently, there are four broad classes of HIV medications which collectively comprise HAART: 1) protease inhibitors, 2) nucleoside analogue reverse transcriptase inhibitors (NRTIs), 3) non-nucleoside reverse transcriptase inhibitors (NNRTIs), and 4) cell membrane fusion inhibitors. The protease inhibitors are selective, competitive inhibitors of protease, an enzyme crucial to viral maturation, infection, and replication. The NRTIs inhibit viral replication by interfering with viral RNA-directed DNA polymerase (reverse transcriptase). Similarly, NNRTIs inhibit viral replication by acting as a specific, non-competitive reverse transcriptase inhibitor, disrupting that enzyme's catalytic site. The recently introduced cell membrane fusion inhibitor enfuvirtide blocks uptake of the virus by the lymphocyte.

Although HAART has greatly reduced morbidity and mortality of persons with HIV, problems remain with these therapies. Replication of HIV is rapid and frequently results in the emergence of drug resistant species. HAART consists of a complicated group of medications with significant side effects, toxicities, and drug interactions. Adherence to antiretroviral therapies presents special issues that result from the biology of HIV, the magnitude of the required therapeutic effect, and the changing demography of HIV infection. Non-adherent behavior has promoted drug resistance and cross-resistance among drugs in a therapeutic class limiting future treatment options. Recent data suggest that the level of medication adherence required for optimal treatment effectiveness is extremely

high. Many studies have shown that adherence levels exceeding 95 percent are required for optimal viral suppression. Therefore, the importance of maximal suppression and strict adherence in HIV treatment is a necessary goal in the management of HIV-related disease.

6.1 Descriptive

Nearly 43 percent of the HIV-positive veterans who receive their care in the VA are in their 40s, and an additional 30 percent of them are in their 50s. Overall, more than three-quarters of the HIV-infected population served by the VA are 40 or older; the VA HIV-positive population is older than the national HIV-positive population. The VA HIV-positive population is also disproportionately black; nearly 49 percent of the HIV-positive veterans are African-Americans. The cohort of HIV-infected individuals from the North, Central, and South Texas Veterans Healthcare Systems included 648 males (95%) and 38 females (5%). At the index date, the mean age of the cohort was 48 years (SD=10.2).

Overall, race information for approximately 55 percent of the study cohort was missing. A recent report by VA Information Resource Center (VIREC) suggests that researchers utilizing data on race before FY 2004 face two major limitations. First, over 30% of the race values in the VA database are missing. Second, race values for veterans enrolled since the beginning of FY 2003 are

unavailable.⁴⁴⁴ For VA researchers that require quality race data before FY 2004, VIREC suggests using alternative data sources that can be linked to the VA database (e.g., Medicare).⁴⁴⁵ VIREC is taking the necessary steps to improve the quality of race data in future datasets.

The VA population is distinctly different from the US population. At the end of 2004, the '40-44 years' age group had the most cases (22%) of persons living with HIV/AIDS in the US. With respect to race/ethnicity, 48 percent were African-American, 34 percent Caucasian, 17 percent Hispanic, and remaining were American Indian/Alaska Native and Asian/Pacific Islander. Additionally, 73 percent of adults and adolescents living with HIV/AIDS were male.

In the current study, the proportion of patients initiated on PI-based regimens decreased from 1998 to 2003 and the proportion of patients initiated on NNRTI-based regimens increased. These changes are consistent with the changes in antiretroviral guidelines during the study period.⁴⁴⁶ Overall, from 1998 to 2003, approximately 49 percent of patients were initiated on a PI-based regimen, 33 percent on an NNRTI-based regimen and 12 percent on an NRTI-based regimen. In a retrospective study conducted between 2000 and 2001, 41 percent of patients were initiated on PI-based regimens, 40 percent on NNRTI-based

⁴⁴⁴ VIREC researchers guide to VA data: Data issues brief: VIREC, 2004.

⁴⁴⁵ Yu W. VA research use of Medicare data: Using Medicare data in the end-of-life care project: VIREC, 2004.

⁴⁴⁶ Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents: US Public Health Service, 2003.

regimens, 10 percent on PI- and NNRTI-based regimens, five percent on NRTI-only regimens, and four percent on regimens containing NNRTIs and PIs only.⁴⁴⁷ Similarly, between 2000 and 2001, the results of the current study indicate that 42 percent of patients received PI-based regimens, 43 percent received NNRTI-based regimens and 13 percent received NRTI-only regimens.

6.2 Adherence

The overall adherence for HIV-infected patients in the North, Central and South Texas Veterans Healthcare Systems was approximately 80 percent. Approximately 30 percent of the cohort had adherence greater than or equal to 95 percent. The results of this study are similar to other published reports. The following section presents a summary of adherence reported by other studies.

In a recent prospective study of HIV-infected individuals, the overall adherence assessed by microelectronic monitoring systems devices (MEMS) was 75 percent (N=99).⁴⁴⁸ Raboud et al. assessed adherence using self-reported measurement from the INCAS, AVANTI 2 and AVANTI 3 trials.⁴⁴⁹ The proportion of patients who were adherent was 70 percent for INCAS, 64 percent

⁴⁴⁷ Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. *Clinical Infectious Diseases* 2003;37(8):1112-8.

⁴⁴⁸ Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 2000;133(1):21-30.

⁴⁴⁹ Raboud JM, Harris M, Rae S, Montaner JS. Impact of adherence on duration of virological suppression among patients receiving combination antiretroviral therapy. *HIV Medicine* 2002;3(2):118-24.

for AVANTI 2, and 72 percent for AVANTI 3. In another study conducted over a two-month period, the mean adherence of zidovudine, measured by MEMS and pharmacy records, was 66 percent and 78 percent, respectively.⁴⁵⁰ Vincent et al. reported that in their retrospective database analysis covering 1997 to 2001, the mean adherence level, measured by prescription refill methods, was 82 percent and approximately 35 percent of the patients achieved adherence levels greater than 95 percent.⁴⁵¹ In a study of Maryland Medicaid recipients (N=1,418) who received antiretroviral therapy, the mean antiretroviral adherence was 80 percent; approximately 12 percent had an adherence measure greater than or equal to 95 percent.¹¹⁴ Using New York State Medicaid prescription claims data (N=292), Turner et al. found that 28 percent of patients reported adherence estimates greater than or equal to 80 percent.⁴⁵²

The adherence estimates obtained for the cohort in the current study are less than those reported by Wagner et al. who explored the impact of MEMS on adherence behavior.⁴⁵³ Overall, the mean adherence reported for the patient cohort was 92.6 percent in the Wagner et al. study. Also, approximately 68 percent of the cohort achieved 95 percent adherence during the follow-up period.

⁴⁵⁰ Frick PA, Gal P, Lane TW, Sewell PC. Antiretroviral medication compliance in patients with AIDS. *AIDS Patient Care & Sexually Transmitted Diseases* 1998;12(6):463-70.

⁴⁵¹ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

⁴⁵² Turner BJ, Newschaffer CJ, Zhang D, Cosler L, Hauck WW. Antiretroviral use and pharmacy-based measurement of adherence in postpartum HIV-infected women. *Medical Care* 2000;38(9 (Print)):911-25.

⁴⁵³ Wagner GJ, Ghosh-Dastidar B. Electronic monitoring: adherence assessment or intervention? *HIV Clinical Trials*. 2002;3(1):45-51.

In another prospective study, 75 percent of the cohort (N=26) reached 95 percent adherence as measured by MEMS.⁴⁵⁴ Overall, the mean adherence reported by the cohort of patients was 98.9 percent (10.1% to 102.0%). Montessori et al. also conducted a population-based study using prescription claims data.⁴⁵⁵ They reported that 57 percent of patients had adherence measures greater than or equal to 95 percent. The patient cohort in the current study is older than the one reported by Montessori which could partly explain the lower adherence estimates. Other studies have reported negative associations between adherence and age.^{456, 457,458}

There is conflicting data on whether adherence changes markedly for patients over time. In 2005, Rathburn et al. conducted a randomized, controlled pilot study to examine the impact of a pharmacy-operated clinic on adherence to HAART.⁴⁵⁹ In addition, Rathburn et al. assessed changes in adherence over time.

⁴⁵⁴ Hugen PW, Langebeek N, Burger DM, Zomer B, van Leusen R, Schuurman R, et al. Assessment of adherence to HIV protease inhibitors: comparison and combination of various methods, including MEMS (electronic monitoring), patient and nurse report, and therapeutic drug monitoring. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2002;30(3):324-34.

⁴⁵⁵ Montessori V, Heath KV, Yip B. Predictors of adherence with triple combination antiretroviral therapy. 7th Conference on Retrovirus and Opportunistic Infections; 2000 January 30 - February 2; San Francisco, LA.

⁴⁵⁶ Ibid.

⁴⁵⁷ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

⁴⁵⁸ Wenger N, Gifford AL, Liu H. Patient characteristics and attitudes associated with antiretroviral. 6th Conference on Retrovirus and Opportunistic Infections; 1999 January 31 - February 4; Chicago, Ill.

⁴⁵⁹ Rathburn RC, Farmer KC, Stephens JR, Lockhart SM. Impact of an adherence clinic on behavioral outcomes and virologic response in treatment of HIV infection: a prospective, randomized, controlled pilot study. *Clinical Therapeutics* 2005;27(2 (Print)):199-209.

A total of 33 patients were randomized into the study and adherence was assessed by MEMS. Mean adherence at weeks 4, 16, and 28 was 86 percent, 77 percent, and 74 percent in the adherence clinic group versus the 73 percent, 56 percent and 51 percent in the standard care. Martini et al. also assessed the adherence behavior of a cohort of 63 HIV-infected individuals every four months over a one-year period.⁴⁶⁰ Their results indicate that adherence changes markedly for patients over time. In another study, assessing adherent behavior was conducted using an electronic monitoring system; the mean adherence declined from 92 percent in week 1 to 85 percent in week 4.⁴⁶¹ Conversely, Manheimer et al. examined the correlation between self-reported adherence and successful HAART responses among 1,095 patients followed over a specific time frame; the level of self-reported adherence remained constant over time.⁴⁶² In the present study, adherence was assessed over the complete period from the index date to time of death, loss to follow-up or September 30, 2003.

Although many studies have estimated adherence with antiretroviral regimens in persons with HIV, very few have reported between-medication differences in adherence. The issue of between-medication differences in

⁴⁶⁰ Martini M, D'Elia S, Paoletti F, Cargnel A, Adriani B, Carosi G, et al. Adherence to HIV treatment: results from a 1-year follow-up study. *HIV Medicine* 2002;3(1):62-4.

⁴⁶¹ Mathews WC, Mar-Tang M, Ballard C, Colwell B, Abulhosn K, Noonan C, et al. Prevalence, predictors, and outcomes of early adherence after starting or changing antiretroviral therapy. *AIDS Patient Care and STDs* 2002;16(4 (Print)):157-172.

⁴⁶² Mannheimer S, Friedland G, Matts J, Child C, Chesney M. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clinical Infectious Diseases* 2002;34(8):1115-21.

adherence is of considerable importance to clinicians and researchers. In this study, the differences in adherence estimates between patients initiated on different regimens was small; specifically, adherence estimates, stratified by the starting regimen, varied between 78 percent and 83 percent. In a recent study, Wilson et al. also concluded that there was no significant relationship between adherence and the antiretroviral regimens patients were prescribed; however, if patients were non-adherent to one medication in a regimen, they were likely to be non-adherent to all the medications in the regimen.⁴⁶³ Most of the variability in antiretroviral adherence in their study was accounted for by between-patient differences in overall adherence rather than by within-patient differences in adherence patterns across medications. In this study, the effect of between-medication adherence was not explored; however, adherence behavior was similar for patients initiated on different regimens.

6.3 Clinical Outcomes

The projected life expectancy of HIV-infected patients in the North, Central and South Texas Veterans Healthcare Systems is presented next. For the 40-year simulations, the mean survival time for adherent individuals was between 15.7 and 16.5 years, depending on the assumptions of antiretroviral treatment

⁴⁶³ Wilson IB, Tchetgen E, Spiegelman D. Patterns of adherence with antiretroviral medications: an examination of between-medication differences. *Journal of Acquired Immune Deficiency Syndromes & Human Retrovirology* 2001;28(3):259-63.

effect duration. Similarly, for individuals categorized as non-adherent, the mean survival time was between 11.9 and 12.8 years. The following section presents a summary of life expectancy reported by other studies.

In a meta-analysis study estimating the impact of pre-HAART antiretroviral therapies from 1983 to 1996 in Europe and Australia, the median projected long-term survival for individuals with baseline CD4 counts greater than or equal to 200 cells/ μ L was 9.1 years; the median age at baseline of individuals enrolled in the study was 38 years.⁴⁶⁴ Chancellor et al. modeled the cost-effectiveness of dual antiretroviral therapy based on data collected between 1987 and 1995.⁴⁶⁵ Life expectancy was between 9 and 14.5 years, depending on the whether patients received single or dual antiretroviral therapy. Between 1992 and 1999, the outcomes associated with HAART and dual NRTI therapy were also assessed by a Markov model.⁴⁶⁶ The life expectancy for individuals treated for 20 years with dual therapy was 11.6 years. For individuals receiving HAART, the life expectancy associated with treatment was 14.5 years. Trueman et al. also modeled the life expectancy of individuals on antiretroviral therapy; estimates of life expectancy were between 9.6 and 17.2 years, depending on the initial regimen

⁴⁶⁴ Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Collaborative Group on AIDS Incubation and HIV Survival including the CASCADE EU Concerted Action. Concerted Action on SeroConversion to AIDS and Death in Europe. *Lancet* 2000;355(9210):1131-7.

⁴⁶⁵ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Pharmacoeconomics* 1997;12(1):54-66.

⁴⁶⁶ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *HIV Medicine* 2001;2(1):52-8.

prescribed.⁴⁶⁷ The results of their study were based on a clinical trial conducted between 1995 and 1999. Richter et al. estimated the median survival of patients initiated on different antiretroviral regimens with data obtained between 1995 and 1998.⁴⁶⁸ The median survival for patients initiated on PI- and NNRTI-based therapies was approximately 14 years. Based on data obtained from a prospective study in 1997, Schackman et al. modeled the life expectancy of individuals with baseline CD4 counts less than 200 cells/ μ L as well as for individuals with CD4 counts greater than or equal to 200 cells/ μ L who were on HAART; the mean projected life expectancy was between 13.7 and 16.5 years depending on baseline CD4 counts.⁴⁶⁹ King et al. also modeled the long-term survival of patients initiated on HAART therapy between 1997 and 2000 and the median projected long-term survival for individuals with baseline CD4 counts greater than 200 cells/ μ L was 15.4 years; the median age of individuals enrolled in the study was 39 years.⁴⁷⁰ Overall, the impact of antiretroviral therapy on life expectancy in this study is similar to that shown in the modeling studies conducted by other researchers.

⁴⁶⁷ Trueman P, Youle M, Sabin CA, Miners AH, Beck EJ. The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. *HIV Clinical Trials* 2000;1(1):27-35.

⁴⁶⁸ Richter A, Hauber B, Simpson K, Mauskopf JA, Yin D. A Monte Carlo simulation for modelling outcomes of AIDS treatment regimens. *Pharmacoeconomics* 2002;20(4):215-24.

⁴⁶⁹ Schackman BR, Freedberg KA, Weinstein MC, Sax PE, Losina E, Zhang H, et al. Cost-effectiveness implications of the timing of antiretroviral therapy in HIV-infected adults. *Archives Of Internal Medicine* 2002;162(21 (Print)):2478-86.

⁴⁷⁰ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

6.4 Economic Outcomes

Although most HIV-infected veterans receive most their healthcare from the VA, some are also eligible to receive Medicare support and other forms of state or federal support. To model the impact of adherence behavior for individuals receiving VA healthcare over their lifetime, 40-year simulations were conducted. Twenty-year simulations were conducted to model individuals who receive no more than 20 years of VA healthcare following which they receive other forms of public support (e.g., Medicare). Overall, to model the impact of adherence on the cost-effectiveness of antiretroviral therapies, 20-year simulations are likely the most appropriate to model since most HIV-infected veterans typically have short life expectancies. Also, many HIV-infected veterans are African-American and have relatively shorter life expectancies compared to other races.

The medical cost estimates for 20- and 40-year simulations are presented below. The mean overall annual HIV-related costs were \$22,751. For the 40-year simulations, the mean cost for adherent individuals was between \$241,422 and \$287,375 depending on the assumption of antiretroviral treatment effect duration. Similarly, the estimated lifetime cost for non-adherent individuals was between \$239,527 and \$291,205. For the 20-year simulations, the mean cost for adherent individuals was between \$227,329 and \$228,984 depending on the assumption of antiretroviral treatment effect duration. Similarly, the estimated

lifetime cost for non-adherent individuals was between \$209,766 and \$211,709. For the 20- and 40-year simulations, the costs of adherent behavior are higher than the costs of non-adherent behavior predominantly because of the increase in life expectancy associated with adherent behavior; however, the costs are also greater because of the costs of therapy. Overall, probabilistic sensitivity analyses indicate that adherent behavior, compared to non-adherent behavior, is associated with an incremental cost-effectiveness ratio below \$15,000/QALY.

Short simulation periods are typically conducted to support decision making in a managed care setting because individuals are enrolled in plans for shorter periods. Nevertheless, for exploratory purposes, five-year simulations were conducted to estimate the impact of adherence behavior on the cost-effectiveness of antiretroviral therapies. When five-year simulations were conducted, the overall costs of adherent behavior were lower than the costs of non-adherent behavior. Unlike the longer period simulations, the cost-effectiveness of non-adherent behavior was dominated by adherent behavior; therefore, adherent behavior was less costly and more effective in managing HIV disease.

The following section presents a summary of the costs reported by other researchers. In an observational cohort study conducted by Huang between 1995 and 1997, the mean monthly cost of HIV-related care was between US\$503 and US\$808 depending on age; young patients (18 to 25 years) and older patients (56

years and over) had lower monthly costs. Overall, the mean monthly HIV-related cost was US\$733 (SD=1,030, median =US\$420). Recently, Richter et al. estimated the costs of patients initiated on different antiretroviral regimens.⁴⁷¹ For patients initiated on PI- and NNRTI-based regimens, the total direct costs over the five-year period were US\$60,753 (SD=6,734) and US\$63,216 (SD=8,024), respectively. Chancellor et al. modeled the cost-effectiveness of dual antiretroviral therapy between 1994 and 1995.⁴⁷² The mean annual costs estimated for patients with baseline CD4 cell counts greater than 200 cells/ μ L, with baseline CD4 cell counts less than 200 cells/ μ L, and with AIDS were £7,119, £7,415, and £13,370, respectively. Similarly, the projected lifetime costs were between £44,612 and £79,782, depending on whether they received single or dual therapy. Using data for patients between 1995 and 1999, Trueman et al. modeled the cost-effectiveness of antiretroviral therapy.⁴⁷³ The mean annual costs estimated for patients with baseline CD4 cell counts greater than 200 cells/ μ L, CD4 cell counts less than 200 cells/ μ L, and AIDS were £8,743, £9,597, and £19,139, respectively. In addition, the lifetime costs of individuals ranged between £78,161 and £138,806, depending on the starting antiretroviral regimen.

⁴⁷¹ Richter A, Hauber B, Simpson K, Mauskopf JA, Yin D. A Monte Carlo simulation for modelling outcomes of AIDS treatment regimens. *Pharmacoeconomics* 2002;20(4):215-24.

⁴⁷² Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Ibid.* 1997;12(1):54-66.

⁴⁷³ Trueman P, Youle M, Sabin CA, Miners AH, Beck EJ. The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. *HIV Clinical Trials* 2000;1(1):27-35.

Velasco et al. also evaluated the economic impact of PI therapy in a cohort of 155 HIV-infected individuals in a teaching hospital in Madrid between 1997 and 1999.⁴⁷⁴ The mean annual medical costs for AIDS patients were €9,670 (SD=983) and €8,536 (SD=455) before and after the introduction of PI therapy. The mean annual costs for non-AIDS, HIV-infected patients were €4,364 (SD=337) and €7,057 (SD=199) before and after the introduction of PI therapy. The mean annual costs for all HIV-infected patients were €6,139 (SD=440) and €7,589 (SD=206) before and after the introduction of PI therapy. In another study, Miner et al. obtained cost data from a teaching hospital between 1992 and 1999 and projected the 20-year HIV-related costs associated with HAART and dual NRTIs.⁴⁷⁵ The total cost for individuals treated with dual therapy was £77,135. For individuals receiving HAART, the total cost associated with treatment was £119,190. Le Pen et al. estimated the effect of HAART on total costs of HIV-infected patients with baseline CD4 counts less than 250 cells/ μ L between 1995 and 1997. The mean monthly pre- and post-HAART costs were Fr 7,279 and Fr 6,229, respectively.⁴⁷⁶

⁴⁷⁴ Velasco M, Gomez A, Fernandez C, Perez-Cecilia E, Tellez MJ, Roca V, et al. Economic impact of HIV protease inhibitor therapy in the global use of health-care resources. *HIV Medicine* 2000;1(4):246-51.

⁴⁷⁵ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *Ibid.*2001;2(1):52-8.

⁴⁷⁶ Le Pen C, Rozenbaum W, Downs A, Maurel F, Lilliu H, Brun C. Effect of HAART on health status and hospital costs of severe HIV-infected patients: a modeling approach. *HIV Clinical Trials* 2001;2(2):136-45.

In a retrospective analysis conducted on data collected between 1997 and 2001, Vincent et al. reported that the mean annual HIV-related cost was US\$20,681.⁴⁷⁷ From 1996 to 1998, the mean annual HIV-related costs calculated for patients visiting a VA facility increased from US\$12,716 to US\$14,402.⁴⁷⁸ In 2004, Munakata et al. also developed a Markov model to quantify the clinical and economic effects of non-adherence with triple therapy in treatment-naïve HIV patients.⁴⁷⁹ Annual costs of HIV infection (non-AIDS) and AIDS were US\$19,367 and US\$24,238, respectively. Lifetime direct medical costs in the typical and trial scenarios were US\$295,000 and US\$336,000, respectively. Compared with ‘typical’ adherence, the incremental cost-effectiveness ratio of clinical trial adherence was \$29,000/QALY. A summary table is also provided (Table 6-1)

Overall, the costs of HIV disease in the current study are greater than those reported by others. There are two possible explanations for the higher costs in this study: (1) the costs of providing medical care to HIV-positive patients have increased over time; and (2) the costs included in this analysis are more comprehensive than the cost estimates included by other researchers. Krentz et al.

⁴⁷⁷ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

⁴⁷⁸ McCollum M, MaWhinney S, Brown ER. Predictors of resource utilization in HIV/AIDS patients at a Veterans Affairs Medical Center. Int Conf AIDS; 1998.

⁴⁷⁹ Munakata J, Benner JS, Becker SL, Dezil CM, Hazard EH, Tierce JC. Clinical and economic outcomes of non-adherence to antiretroviral therapy in patients with HIV. International Society For Pharmacoeconomics and Outcomes Research; 2004 May 2005; Washington DC.

conducted a comprehensive assessment of HIV-related costs for patients who received care in southern Alberta between 1995 and 2001.⁴⁸⁰ They observed an increase in total costs between 1995 and 1999, primarily because of an increase in the number of drugs in a regimen. In addition, the costs of newer therapies have increased. Although the overall costs in their study increased over time, the costs of inpatient care, home care and other non-antiretroviral drugs for managing HIV-related illness decreased. Costs estimated in this VA study may also be higher because the costing methodology developed for this study was comprehensive. Earlier studies may have under-estimated total HIV-related costs because not all relevant HIV-related conditions and medications were included. In a concerted effort to accurately estimate health care utilization, this study adopted the methodologies recommended by Tolley et al. and Graves et al. to identify and evaluate HIV-related utilization.^{481,482} VA clinicians were recruited to determine which diagnoses and medications were related to HIV disease (Appendix A through Appendix E).

⁴⁸⁰ Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

⁴⁸¹ Tolley K, Gyldmark M. The treatment and care costs of people with HIV infection or AIDS: development of a standardised cost framework for Europe. *Health Policy*. 1993;24(1):55-70.

⁴⁸² Graves N, Walker D, Raine R, Hutchings A, Roberts JA. Cost data for individual patients included in clinical studies: no amount of statistical analysis can compensate for inadequate costing methods. *Health Economics* 2002;11(8):735-9.

Table 6-1: Monthly, Annual and Lifetime Costs Associated with HIV Infection

Reference (Period)	Monthly Costs	Annual Costs	Lifetime Costs
Huang et al. ⁴⁸³ (1995-1997)	US\$733	NA	NA
Richter et al. ⁴⁸⁴ (1995-1998)	US\$259 (CD4>500cells/μL); US\$443 (200 cells/μL ≤ CD4 <500 cells/μL); US\$661 (CD4 <200 cells/μL); US\$1,334 (AIDS)	<u>PI</u> US\$12,150 <u>NNRTI</u> US\$12,463	NA
Chancellor et al. ⁴⁸⁵ (1994-1995)	NA	£7,119 (CD4>200 cells/μL); £7,415 (CD4<200 cells/μL); £13,370 (AIDS)	<u>Monotherapy</u> £44,612 <u>Dual therapy</u> £79,782
Trueman et al. ⁴⁸⁶ (1995-1999)	NA	£8,743 (CD4>200); £9,597 (CD4<200); £19,139 (AIDS)	£78,161-£138,806
Velasco et al. ⁴⁸⁷ (1997-1999)	NA	<u>Before PI</u> *€9,670 (AIDS); €4,364 (Non-AIDS, HIV); €6,139 (all HIV-positive)	NA

⁴⁸³ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

⁴⁸⁴ Richter A, Hauber B, Simpson K, Mausekopf JA, Yin D. A Monte Carlo simulation for modelling outcomes of AIDS treatment regimens. *Pharmacoeconomics* 2002;20(4):215-24.

⁴⁸⁵ Chancellor JV, Hill AM, Sabin CA, Simpson KN, Youle M. Modelling the cost effectiveness of lamivudine/zidovudine combination therapy in HIV infection. *Ibid.* 1997;12(1):54-66.

⁴⁸⁶ Trueman P, Youle M, Sabin CA, Miners AH, Beck EJ. The cost-effectiveness of triple nucleoside analogue therapy antiretroviral regimens in the treatment of HIV in the United Kingdom. *HIV Clinical Trials* 2000;1(1):27-35.

⁴⁸⁷ Velasco M, Gomez A, Fernandez C, Perez-Cecilia E, Tellez MJ, Roca V, et al. Economic impact of HIV protease inhibitor therapy in the global use of health-care resources. *HIV Medicine* 2000;1(4):246-51.

Reference (Period)	Monthly Costs	Annual Costs	Lifetime Costs
Miners et al. ⁴⁸⁸ (1992-1999)	NA	<u>After PI</u> €8,536 (AIDS); €7,057 (Non-AIDS, HIV); €7,589 (all HIV-positive) <u>Dual therapy</u> £8,743 (CD4 ≥200 cells/μL); £9,597 (CD4 <200 cells/μL); £1,9138 (AIDS)	<u>Dual therapy</u> £77,135 <u>HAART</u> £119,190
Krentz et al. ⁴⁸⁹ (2001)	CAN\$1,119	NA	NA
Le Pen et al. ⁴⁹⁰ (1995-1997)	<u>Pre-HAART</u> Fr 7,279 <u>Post-HAART</u> Fr 6,229	NA	NA
Vincent et al. ⁴⁹¹ (1997-2001)	NA	US\$20,681	NA
McCollum et al. ⁴⁹² (1996-1998)	NA	US\$12,716 -US \$14,402	NA
Munakata et al. ⁴⁹³ (2004)	NA	US\$19,367 (non-AIDS); US\$24,238 (AIDS)	<u>Typical scenario</u> US\$295,000;

⁴⁸⁸ Miners AH, Sabin CA, Trueman P, Youle M, Mocroft A, Johnson M, et al. Assessing the cost-effectiveness of HAART for adults with HIV in England. *Ibid.* 2001;2(1):52-8.

⁴⁸⁹ Krentz HB, Auld MC, Gill MJ. The changing direct costs of medical care for patients with HIV/AIDS, 1995-2001. *Canadian Medical Association Journal* 2003;169(2):106-10.

⁴⁹⁰ Le Pen C, Rozenbaum W, Downs A, Maurel F, Lilliu H, Brun C. Effect of HAART on health status and hospital costs of severe HIV-infected patients: a modeling approach. *HIV Clinical Trials* 2001;2(2):136-45.

⁴⁹¹ Vincent LG. A study of adherence to HIV antiretroviral therapies and the economic impact in a managed care organization. Minnesota, 2003.

⁴⁹² McCollum M, MaWhinney S, Brown ER. Predictors of resource utilization in HIV/AIDS patients at a Veterans Affairs Medical Center. *Int Conf AIDS*; 1998.

Reference (Period)	Monthly Costs	Annual Costs	Lifetime Costs
Present study (1998-2003)	NA	\$14,568 (CD4 > 350 cells/μL); \$20,285(350 cells/μL ≥ CD4 > 200 cells/μL); \$31,708(CD4 < 200 cells/μL); \$38,352(symptomatic AIDS)	<u>Trial scenario</u> \$336,000
			<u>Adherent</u> \$241,422 - \$285,991* <u>Non-adherent</u> \$239,527-\$291,205*

* Depending on treatment duration effects; NA- data not available; PI – Protease Inhibitor; NNRTI – Non-nucleoside reverse transcriptase inhibitor; NRTI – Nucleoside reverse transcriptase inhibitor

⁴⁹³ Munakata J, Benner JS, Becker SL, Dezil CM, Hazard EH, Tierce JC. Clinical and economic outcomes of non-adherence to antiretroviral therapy in patients with HIV. International Society For Pharmacoeconomics and Outcomes Research; 2004 May 2005; Washington DC.

6.5 Antiretroviral Regimen Changes

Between 1998 and 2003, 63.6 percent of the VA patients from the North, Central and South Healthcare Systems did not change regimens, 22.6 percent changed regimens only once, 8.6 percent changed regimens only twice and 5.2 percent experienced more than two antiretroviral regimen changes. The number of antiretroviral regimen changes observed in the CHORUS study was higher.⁴⁹⁴ Between 1997 and 2001, 45 percent of patients in the CHORUS study did not change regimens, 34 percent changed regimens only once, 15 percent changed regimens only twice and 6 percent experienced more than two antiretroviral regimen changes. Patients enrolled in the CHORUS study were largely treatment-experienced prior to enrollment which may explain the high number of treatment changes.

In the current study, the mean number of treatment rounds calculated for adherent and non-adherent individuals, not accounting for enrollment period, was 1.32 (SD=0.64) and 1.73 (SD=1.16), respectively. The results of this study indicate that there are more treatment switches in non-adherent individuals compared to adherent individuals as the enrollment period increases. Austin et al. estimated the rate of change of combination antiretroviral treatment among

⁴⁹⁴ King JT, Jr., Justice AC, Roberts MS, Chang CC, Fusco JS, Collaboration in HIVOR-USPT. Long-term HIV/AIDS survival estimation in the highly active antiretroviral therapy era. *Medical Decision Making* 2003;23(1):9-20.

patients in the Australian HIV Observational Database.⁴⁹⁵ A combination change was defined as starting one or more antiretroviral drugs not included in the immediately preceding combination. A total of 596 patients were included in the analysis, with a median follow-up of 2.3 years. The overall change of antiretroviral treatment change in that group was 0.45 combinations per year. Patients remained on their first combination for a median of 646 days. Three hundred and twenty two patients started a second combination for a median duration of 632 days and 149 patients progressed to a third combination for a median duration of 392 days. Overall, the definition of treatment switches in the current VA study is more conservative than the definition modeled by Austin et al.

6.6 Study Implications

The US President's FY 2007 federal budget request includes an estimated \$22.8 billion for domestic and global HIV/AIDS activities.⁴⁹⁶ This represents an 8.3% increase (\$1.7 billion) over FY 2006 funding for HIV/AIDS of \$21.1 billion. Federal funding for HIV/AIDS has increased significantly over the course of the epidemic (although it represents less than 1% of the overall federal budget). Approximately \$18.9 billion (83%) of the FY 2007 HIV/AIDS request is for

⁴⁹⁵ Austin D, Baker D, Block M, Brown K, et al. Rates of combination antiretroviral treatment change in Australia, 1997-2000. *HIV Medicine* 2002;3(1):28-36.

⁴⁹⁶ US federal funding for HIV/AIDS: The FY 2007 budget request: The Henry J. Kaiser Family Foundation, 2006.

domestic programs. Congress will now consider the budget request and is expected to finalize spending levels in late 2006.

The largest component of federal funding for HIV/AIDS is healthcare for people living with HIV/AIDS in the US, which totals \$13.2 billion in the FY 2007 budget request. This represents an increase of 7% over FY 2006. Most federal HIV/AIDS healthcare funding is for Medicaid and Medicare, which are slated to receive \$6.8 billion and \$3.5 billion, respectively. The HIV/AIDS Initiative, the Ryan White CARE Act, the largest discretionary HIV/AIDS grant program, is slated to receive \$2.9 billion. Also, the VA has requested \$478 million for FY 2007.

The nation's largest, single provider of health care to those infected with HIV is the VA. Approximately 55,000 veterans with HIV infection and AIDS have been treated in VA since the disease was first recognized in the United States in 1981. In 2003, approximately 20,000 patients with HIV infection were treated at VA facilities across the nation. Of the total, more than 8,500 received inpatient treatment, a number that has declined steadily in recent years. Reduction of inpatient care reflects dramatic advances in treatment of HIV/AIDS. In the outpatient setting, most VA care is provided in infectious disease clinics.

The VA's clinical guidance on management of HIV/AIDS is based upon the Department of Health and Human Services-Kaiser Family Foundation's "Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and

Adolescents." These guidelines were developed by a panel of leading international clinical and research experts, including the VA's HIV/AIDS experts. The guidelines are updated periodically and include the results of most recent research related to anti-HIV drugs and drug combinations, prevention of HIV/AIDS complications, patient adherence to therapy, management of drug side effects and interactions, and the use of diagnostic tests including drug resistance assays. VA guidelines require that all antiretroviral drugs on the national VA formulary be made available at each facility.

Use of currently available HAART has resulted in improved survival and fewer complications for people living with HIV/AIDS. The VA system encourages HIV care providers and patients to develop effective regimens from among the many drugs available after consideration of side-effect profiles, patient preferences and information about resistance to individual drugs. The VA's HIV/AIDS care programs take a comprehensive approach with increased emphasis on outpatient services, active case management and tracking of data on HIV-positive veterans through a registry that provides clinical, administrative and management reports. As a result, this comprehensive multidisciplinary effort to manage HIV infection has significantly increased the economic burden of HIV-related disease to the VA. The following section provides a review of the types of health economic studies initiated by federally sponsored institutions. In

particular, it is evident that the research efforts to improve clinical and economic outcomes for those infected with HIV are being supported.

A recent study by Siegel et al. demonstrated the interest in federally sponsored health economics research.²¹³ Siegel et al. conducted a review of federally sponsored cost-effectiveness and other health economics research to provide insight into the functioning of the research support systems that are currently in place. They identified cost-effectiveness and related economic publications citing support from a US government entity and published during the period of 1997 through 2001, and audited them for information on funding sources, study type, and content focus. Overall, five Department of Health and Human Services agencies and the VA were cited as funding health economic research in 74 percent of 520 federally supported health economics publications identified. Three-quarters of federally supported publications addressed five areas of high disease burden: infections, cancer, HIV/AIDS, cardiovascular disease, and substance abuse. The five areas emphasized in federal health economics studies rank among important disease areas as measured by indicators of years of potential life lost, actual causes of death, and/or economic burden. All are focus areas used to define the leading health indicators in Healthy People 2010. Sixty-four health economics studies address HIV infection which, although not a leading cause of death in the United States, is responsible for a disproportionate number of lost life-years. Seventeen of the studies address pharmacologic

treatment or prophylaxis for HIV-infected populations, including both treatment of opportunistic infections and antiretroviral therapy, and several additional studies address screening for opportunistic infections.

Overall, federally supported health economic studies are concentrated in several intervention areas. Economic analyses of pharmaceuticals account for 28 percent of the articles that consider specific interventions. Health education was the next most frequent intervention type, examined in 18 percent of the articles. Forty-eight of the 77 health education studies deal with education and behavioral interventions in substance abuse, mental health, and HIV/AIDS prevention. The study by Siegel et al. indicates that there is great interest by federally sponsored programs, including the VA, to adopt more efficient healthcare practices to improve the quality of care and at the same time contain or decrease costs. The results of this present study confirm earlier research observations indicating that adherence behavior is closely related to clinical and economic outcomes. The VA's HIV/AIDS care programs take a comprehensive approach with increased emphasis on outpatient services, active case management and tracking of data on HIV-positive veterans. As a result, this comprehensive multidisciplinary effort to manage HIV infection has significantly increased the economic burden of HIV-related disease to the VA, and the VA should continue with its efforts to constrain the costs of HIV-related care and to improve the quality-of-life HIV-infected individuals.

Interventions to improve medication adherence often encompass self-management programs that include educational and behavioral strategies provided in a multidisciplinary healthcare setting. The VA system has an existing infrastructure in place to implement a multidisciplinary approach to improve adherence to HIV regimens. Interventions focusing on patient education by providing instructions about treatment, reducing the number of medications and the frequency of doses, providing education about expected side effects, and encouraging patients to adhere to the lifestyle changes caused by therapy are examples of the multidisciplinary approach that can be adopted to manage HIV-disease. The goals of adherence-improving interventions include improving quality-of-life, decreasing overall costs, and improving the cost-effectiveness of antiretroviral therapies. This study shows that the incremental cost-effectiveness ratio of adherent behavior, compared to non-adherent behavior, is well below the acceptable WTP threshold. Additionally, this study shows that the incremental cost-effectiveness ratio of adherent behavior, compared to non-adherent behavior, decreases with time. This is an important consideration for the VA because the decision to implement interventions to improve adherence is related to the enrollment period of patients within a VA facility or within the VA healthcare system. From a managed care perspective, the justification to support adherence-based programs may not be as attractive because of the generally shorter enrollment periods.

Although evidence that non-adherence with effective medication regimens is associated with worse clinical outcomes, the perceived outcome by the patient may be different. Looking at possible reasons for non-adherent behavior from an economic point of view is challenging. Even in optimal conditions, in which the patient holds correct health beliefs and there is good communication between the patient and physician, patients might 'choose' to be non-adherent. The reason might be that patients make a personal trade-off between the efficacy of treatment and the side effects it generates. The non-adherent patient may not take the negative externalities of his behavior fully into account in his decision. The negative externality of his non-adherence might be the development of new resistant strains of HIV. From a societal perspective, these externalities are important and should be included in economic evaluations.⁴⁹⁷ Given that non-adherent patients may experience clinical consequences that are very different from those experienced by adherent patients (e.g., adherent patients may suffer more from a drug's side effects, whereas non-adherent patients may suffer more from recurrence or worsening of their underlying disease), and given that different outcomes may be important for adherent and non-adherent patients, quality-of-life measures that include the utility decrements of the side-effects and adverse events of medications will improve our understanding of the cost-effectiveness of antiretroviral medications. Also, from a patient's perspective, some of the costs

⁴⁹⁷ Cleemput I, Kesteloot K, DeGeest S. A review of the literature on the economics of noncompliance. Room for methodological improvement. *Health Policy*. 2002;59(1):65-94.

associated with the treatment of non-adherent-related complications are also non-healthcare related: production losses, travel expenses and time costs of friends and relatives. In HIV, these costs can be substantial.

Similar to the focus of the current study, the economic implications of non-adherence to drug therapies has predominantly been assessed from a cost perspective and understood as the impact of non-adherence behaviors on the cost-effectiveness ratios of particular therapies. There is a growing need to measure the costs and effects of adherence interventions. In 1999, the Department of Health and Human Services, Health Resources and Services Administration, HIV/AIDS Bureau, Special Projects of National Significance program funded 12 sites to evaluate interventions designed to improve medication adherence among people living with HIV/AIDS. In this study, Schackman et al. reported that the median direct monthly cost associated with adherence interventions was US\$35 (\$5-\$58) per patient, which included the costs to healthcare providers (66%); the costs of providing incentives to patients (17%); the costs of reminding patients (8%); and administrative time costs, transportation costs, and training costs (9%).⁴⁹⁸ The median direct monthly cost from a societal perspective, including patient time and travel, was \$47 (\$24-\$114) per patient. Adherence interventions with moderate efficacy, costing less than \$100 a month, were estimated to achieve

⁴⁹⁸ Schackman BR, Finkelstein R, Neukermans CP, Lewis L, Eldred L. The cost of HIV medication adherence support interventions: results of a cross-site evaluation. *AIDS Care* 2005;17(8):927-37.

favorable cost-effectiveness ratios. Similarly, Goldie et al. developed a model with data derived from clinical studies to explore the cost-effectiveness of interventions to improve adherence to combination antiretroviral therapy in HIV-infected patients.⁴⁹⁹ The results of their study indicate that even expensive, moderately effective adherence interventions are likely to confer cost-effectiveness benefits that compare favorably with other interventions. Future health economic studies to assess the potential impact of adherence interventions in HIV-infected patients receiving care in the VA setting are needed and the role of pharmacists in managing adherence behavior should be explored.

6.7 Limitations

The study limitations should be considered while interpreting the results of the study. In FY 2001, approximately 17,595 HIV-positive individuals were documented to have received care within the VA system. The VA population is distinctly different from the US population. HIV-infected veterans are predominantly male. Nearly 43 percent of the HIV-positive veterans who receive their care in the VA are in their 40s, and an additional 30 percent of them are in their 50s. Overall, more than three-quarters of the HIV-infected population served by the VA are 40 or older; the VA HIV-positive population is older than the national HIV-positive population. The VA HIV-positive population is also

⁴⁹⁹ Goldie SJ. Projecting the cost-effectiveness of adherence interventions in persons with human immunodeficiency virus infection. *The American Journal of Medicine* 2003;115(8):632-42.

disproportionately black; nearly 49 percent of the HIV-positive veterans are African-Americans. In the study conducted by Huang, 83 percent of the Maryland Medicaid recipients who received at least one prescription claim for an antiretroviral drug in 1995 were African-American.⁵⁰⁰ The average age was 39 years old (SD=8) and 61 percent of the population was male. Huang et al. also reported that Caucasian patients had higher overall adherence rates than non-Caucasian patients.⁵⁰¹ These findings also concur with conclusions from other published studies; for example, both Singh et al. and Laine et al. reported that being non-white was significantly associated with non-adherence.^{502,503} With regard to gender effect, studies suggest that male patients have a higher adherence rate than female patients.^{504,505,506} Differences in gender and age may have an impact on the results of the present study; therefore, the results cannot be generalized to other HIV-infected populations. Some studies have reported

⁵⁰⁰ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

⁵⁰¹ Ibid.

⁵⁰² Singh N, Squier C, Sivek C, Wagener M, Nguyen MH, Yu VL. Determinants of compliance with antiretroviral therapy in patients with human immunodeficiency virus: prospective assessment with implications for enhancing compliance. *AIDS Care*. 1996;8(3):261-9.

⁵⁰³ Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. *Obstetrics & Gynecology* 2000;95(2):167-73.

⁵⁰⁴ Montessori V, Heath KV, Yip B. Predictors of adherence with triple combination antiretroviral therapy. 7th Conference on Retrovirus and Opportunistic Infections; 2000 January 30 - February 2; San Francisco, LA.

⁵⁰⁵ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

⁵⁰⁶ Wenger N, Gifford AL, Liu H. Patient characteristics and attitudes associated with antiretroviral. 6th Conference on Retrovirus and Opportunistic Infections; 1999 January 31 - February 4; Chicago, Ill.

negative associations between adherence and age.^{507, 508,509} Additionally, there is conflicting data on whether adherence changes markedly for patients over time. If adherence changes significantly with time, the model developed in the present study will over estimate adherence. Additionally, disease progression adjusted for potentially lower adherence values over time cannot be modeled in the present study. Also, there are differences in the care, access to care, and services provided to HIV-infected veterans compared to individuals enrolled in other health care systems.

There are a number of ways (quantitatively and qualitatively) to describe adherence to antiretroviral therapy, each with its own strengths and weaknesses. Prescription refill according to pharmacy records was selected as the measurement of adherence for the proposed study primarily due to data availability. Investigators have used pharmacy records to measure adherence in HIV-infected individuals as well as individuals in other disease states. Using pharmacy records to measure adherence is most useful when patients receive all their care from an institution that uses a centralized pharmacy or when prescriptions can be linked to a common data source. The VA centralized data

⁵⁰⁷ Montessori V, Heath KV, Yip B. Predictors of adherence with triple combination antiretroviral therapy. 7th Conference on Retrovirus and Opportunistic Infections; 2000 January 30 - February 2; San Francisco, LA.

⁵⁰⁸ Huang X. Modeling costs and opportunistic infections for Maryland Medicaid HIV/AIDS patients: Effects of patient non-adherence to antiretroviral drugs. University of Maryland, 2001.

⁵⁰⁹ Wenger N, Gifford AL, Liu H. Patient characteristics and attitudes associated with antiretroviral. 6th Conference on Retrovirus and Opportunistic Infections; 1999 January 31 - February 4; Chicago, Ill.

system allows us to capture the majority of prescription activity of individuals. As with any measurement process, limitations should be acknowledged and caution is warranted in the interpretation of the results. Hughes et al. categorized adherence as a process involving three phases:⁵¹⁰ (1) acceptance of a medication regimen, following which a prescription is filled; (2) adherence with dosing according to the instructions of a health care provider; and (3) persistence with a medication regimen after initiation. This study examined the first phase; however, medication regimens for patients on HAART typically requires strict adherence with dosing instructions and this is not captured in pharmacy refill records. Also, prescription refill methods of assessing adherence rely on the assumption that filling a prescription correlates strongly with adherence. Although there is supporting data that demonstrates the validity of this assumption, there is ample data to suggest that filled prescriptions may never be taken by individuals. While limitations are evident in using pharmacy data systems, they do provide some insight into the prescribing and filling behavior in a health care system. As a result, pharmacy refill records are used in the HIV research to describe adherence behavior.

The natural history of HIV/AIDS has extreme longitudinal variation. Age, race, gender, and socio-economic status of patients may have significant impact on how the disease progresses. For example, women were more likely to have

⁵¹⁰ Hughes DA, Bagust A, Haycox A, Walley T. The impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. *Health Economics*. 2001;10(7):601-15.

Kaposi's sarcoma if their partners were bisexual men rather than intravenous drug users.⁵¹¹ Other factors that may have a significant impact on how the disease progresses and on the costs of HIV-related care include provider characteristics. For example, clinical location, practice patterns, adequacy and experience of staff, and the charge structure are factors that may influence health outcomes and costs in HIV-related disease. The VA offers comprehensive HIV-related care to its patients. For example, all eligible patients have free access to all antiretrovirals approved by the FDA. In addition, the clinical services provided to VA patients involve a multidisciplinary team approach. Although designating a single probability to represent transitions from one state to another is attractive, different populations of patients may show a range of values of these transition dynamics depending on the demographics and socio-economic conditions underlying the system. This problem, commonly referred to as cohort dependent heterogeneity of probabilities, can be significant when applying estimates of adherence rates to the dynamics of the model. For example, Huang et al. found that results of univariate analyses indicated that average monthly HIV/AIDS-related total cost was the same for adherent and non-adherent patients; however, after adjusting for covariates, patients categorized as adherent had significantly lower monthly costs than non-adherent patients.

⁵¹¹ Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 1990;335(8682):123-8.

The simulation model used in this study incorporated non-adherence, treatment failure and the independent effect of aging on mortality. However, the model did not account for long-term toxicity from treatment. Also, the model did not account for the potential interaction of treatment, HIV infection and co-morbid diseases. In addition it was assumed that the efficacy of drug therapy was only related to a patient's CD4 cell count, and adherence, although a patient's history of opportunistic infections, physical condition, as well the rates of change in these predictors are potentially important determinants of successful therapy.

Non-parametric techniques to estimate survival were employed using a limited number of events; extrapolation of short-term survival data to obtain long-term survival estimates could be improved with longer follow-up of individuals. Longer follow-up will provide more accurate transition probabilities. In addition, the sample size used to determine transitions between certain states was small; therefore, the confidence in these probabilities should be tested rigorously. In recent years, formal techniques to determine the 'statistical' power of cost-effectiveness models have and continue to be developed.⁵¹² Future modeling efforts should account for uncertainties in transition probabilities. In addition, probabilistic sensitivity analyses conducted on transition probabilities has also been proposed. This is an area that has received significant attention in recent

⁵¹² Briggs AH, Gray AM. Power and sample size calculations for stochastic cost-effectiveness analysis. *Medical Decision Making: An International Journal Of The Society For Medical Decision Making* 1998;18(2 Suppl (Print)):S81-92.

years and the methods to conduct sensitivity analyses on transition probabilities are maturing.

The VA does not routinely bill patients and as a result, estimates of expenditure by the VA were derived from a number of sources. The costs used in this study consisted of: (1) HERC derived estimates (inpatient and outpatient); and (2) PBM (pharmacy) estimates. HERC estimates are average costs created for researchers to quantify resource utilization; however, they may not be true characterizations of the actual costs of HIV care. Only micro-costing methods will approach true costs of care of individuals and these data are not available. Also, the cost estimates may not reflect the deep discounts the VA may receive. In particular, it was not possible to ascertain exact prescription costs since deep discounts vary between medical centers and geographical regions. Although average costs derived by HERC were used to estimate inpatient costs, these costs may have under-estimated the costs associated with HIV therapy; HAART and HIV-related laboratory tests are significantly more costly than other non-HIV therapies and tests and these disparities in costs may not have been captured by the HERC estimates. Also, future costs of antiretroviral therapy were not modeled. Cost projections in this study were based on current HAART regimens and did not account for newer and more effective therapies that may receive FDA approval in the future. For example, the introduction of fusion inhibitors may transform the treatment algorithms and management of HIV-infected individuals.

6.8 Conclusion

The clinical effectiveness of antiretroviral therapy for HIV infection depends considerably on the patient's ability to adhere closely to complicated drug regimens. Medication non-adherence in chronic conditions is a recognized public health problem. The association between medication adherence and improved health outcomes is well documented and the results of this study provide further evidence of this relationship. Generally, healthcare costs have shown to differ vastly among patients with high and low adherence, with a clear relationship seen between increased medication adherence and lower healthcare costs. In the present study, the costs of adherent behavior are marginally higher than the costs of non-adherent behavior predominantly because of the increase in life expectancy associated with adherent behavior. Non-adherent behavior can lead to increased costs and decreased cost-effectiveness of interventions. For clinicians, healthcare policy makers, and patients, it is important to take into account the impact of non-adherent behavior on the cost-effectiveness of interventions.

The ideal study design to demonstrate the possible health outcomes and costs associated with a new drug, and similarly, adherence behavior, would be a naturalistic prospective study. However, a prospective naturalistic study cannot always be performed for ethical, logistical, and budgetary reasons. In addition, trials have limited external validity, because they have strict inclusion and exclusion criteria and treatments are protocol-driven, leading to overestimation of

units of healthcare utilization; on the other hand, the units of utilization collected may not be complete. In these cases, decision analytic models may provide some of the missing information. However, a main concern with modeling studies continues to be the use of protocol-driven clinical data and the use of a panel of experts for data which can not be derived from the literature. In this study, an observational database was used as an alternative data source for modeling disease progression. The overall design may be considered a hybrid between a naturalistic prospective study and a modeling study by maximizing the pros and minimizing the cons of both types of designs.⁵¹³ Although this modeling study involved many necessary assumptions, it provided an indication of the potential benefits of adherent behavior. The results of this study indicate that the marginal costs and effects associated with adherent behavior, compared to non-adherent behavior, are well below acceptable willingness-to-pay thresholds.

⁵¹³ Nuijten MJ. Bridging decision analytic modelling with a cross-sectional study. Application to Parkinson's disease. *Pharmacoeconomics* 2000;17(3):227-236.

APPENDICES

Appendix A: Indicator conditions included in the 1993 AIDS Surveillance Case Definition

Candidiasis of bronchi, trachea, or lungs (Fungal Infection)

Candidiasis, esophageal (Fungal Infection)

Cervical cancer, invasive‡

Coccidioidomycosis, disseminated (Fungal Infections)

Cryptococcosis, extrapulmonary (Fungal Infections)

Cryptosporidiosis, chronic intestinal (>1 month duration) (Enteric Diseases)

Cytomegalovirus disease (other than liver, spleen, or lymph nodes)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV-related † (Dementia)

Herpes simplex: chronic ulcer(s) (>1 month duration) or bronchitis, pneumonitis, or esophagitis

Histoplasmosis, disseminated (Fungal Infections)

Isosporiasis, chronic intestinal (>1 month duration) (Enteric Diseases)

Kaposi's sarcoma

Lymphoma, Burkitt's

Lymphoma, immunoblastic

Lymphoma, primary, of brain (primary central nervous system lymphoma)

Mycobacterium avium complex or disease caused by *M. Kansasii*, disseminated

Disease caused by *Mycobacterium tuberculosis*, any site (pulmonary ‡ or extrapulmonary †)

Disease caused by *Mycobacterium*, other species or unidentified species, disseminated

Pneumocystis carinii pneumonia

Pneumonia, recurrent‡ (Bacterial Infections)

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent (Bacterial Infections)

Toxoplasmosis of brain (Encephalitis)

Wasting syndrome caused by HIV infection†

† Added in the 1987 expansion; ‡ Added in the 1993 expansion

Appendix B: AIDS Diagnoses (ICD-9 Codes)

Part 1 – Diagnoses

042	AIDS with specified conditions
042.0	AIDS with specified infections
042.1	AIDS causing other specified infections
042.2	AIDS with specified malignant neoplasms
042.9	AIDS, unspecified
043.	HIV infection causing other specified conditions
043.0	HIV infection causing lymphadenopathy
043.1	HIV infection causing specified diseases of the CNS
043.2	HIV infection causing other disorders involving the immune mechanism
043.3	HIV infection causing other specified conditions
043.9	AIDS related complex, unspecified

Part 2 – Diagnosis Requiring AIDS Defining Condition

044.	Other HIV infection
044.9	HIV infection, unspecified

Part 3 – AIDS Defining Conditions

112.4	Candidiasis of bronchi, trachea, or lungs
112.84	Candidiasis of esophagus
180. – 180.9	Cervical cancer, invasive
114.1, 114.3	Coccidioidomycosis
117.5	Cryptococcosis, extrapulmonary
78.5	Cytomegalovirus disease (other than liver, spleen, or nodes)
348.3	Encephalopathy, HIV-related
115.01 – 115.09	Histoplasmosis, disseminated or extrapulmonary (except 115.05)
176.0 – 176.9	Kaposi's sarcoma
200.2	Lymphoma, Burkitt's (or equivalent term)
200.8	Lymphoma, immunoblastic (or equivalent term)
202.8	Lymphoma, primary, of brain
31.8, 31.9	Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
10.0 – 18.9	Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
136.3	Pneumocystis carinii pneumonia
46.3	Progressive multifocal leukoencephalopathy
130.0	Toxoplasmosis of the brain
799.4	Wasting due to HIV
033.22, 481.x, 482.x, 484.6x, 485.x, 486.x, 494.x, 511.1x, 513.x	Pneumonia
0.31	Salmonella septicemia, recurrent (> 1 episode)
54.71	Herpes simplex, chronic ulcer(s), or esophagitis, bronchitis, pneumonitis

Appendix C: HIV Diagnoses (ICD-9 Codes)

HIV Diagnoses

042	HIV disease
043	HIV infection causing other specified conditions
044.	Other HIV infection
044.9	HIV infection, unspecified
V08.x	Asymptomatic HIV infection status
795.8	Positive serological or viral culture findings for HIV
795.71	Nonspecified serological evidence of HIV

HIV-Defining Conditions

279.10	Immunodeficiency with predominant T-cell defect, unspecified
279.19	Deficiency of cell-mediated immunity (other)
279.3	Unspecified immunity deficiency
647.6	Infectious and parasitic conditions in the mother complicating pregnancy, childbirth, or puerperium (conditions classifiable to ICD-9 042 and other infectious diseases)

Appendix D: HIV-Related ICD9 Categories†

ICD 9- Codes	Description
001-009	Intestinal Infectious Diseases
010-018	Tuberculosis
030-041	Other Bacterial Diseases
042	Human Immunodeficiency Virus Infection
070-079	Other Diseases due to Viruses and Chlamydiae
090-099	Syphilis and other Venereal Diseases
110-118	Mycoses
130-136	Other Infectious and Parasitic Diseases
137-139	Late Effects of Infectious and Parasitic Diseases
170-176	Malignant Neoplasm of Bone, Connective Tissue, Skin, and Breast
200-208	Malignant Neoplasm of lymphatic and hematopoietic tissue
240-246	Disorders of the Thyroid Gland
250-259	Diseases of other Endocrine Glands
260-269	Nutritional Deficiencies
270-279	Other Metabolic Disorders and Immunity Disorders
280-289	Diseases of Blood and Blood-Forming Organs
290-294	Organic Psychotic Conditions
295-299	Other Psychoses
320-326	Inflammatory Diseases of the Central Nervous System
330-337	Hereditary and Degenerative Diseases of the CNS
340-349	Other Disorders of the Central Nervous System
350-359	Disorders of the Peripheral Nervous System
360-379	Disorders of the Eye and Adnexa
415-417	Diseases of Pulmonary Circulation e.g., pulmonary hypertension
480-487	Pneumonia and Influenza
510-519	Other Diseases of Respiratory System
520-529	Diseases of Oral Cavity, Salivary Glands and Jaws (e.g., Aphthous ulcers)
580-589	Nephritis, Nephrotic Syndrome, and Nephrosis (e.g., HIV nephropathy)
610-611	Disorders of Breast (e.g., gynomastia)
617-629	Other Disorders of Female Genital Tract (e.g., cervical dysplasia)
680-686	Infections of Skin and Subcutaneous Tissue (e.g., psoriasis, atopic dermatitis, seborrhea, folliculitis)
690-698	Other Inflammatory Conditions of Skin and Subcutaneous Tissue
700-709	Other Diseases of Skin and Subcutaneous Tissue
730-739	Osteopathies, Chondropathies, and Acquired Musculoskeletal Deformities (e.g., AVN)
797-799	Ill-Defined and Unknown Causes of Morbidity and Mortality (e.g., wasting disease)
E930-E949	Effects in Drugs, Medicinal and Biological Substances Causing Adverse Therapeutic Use (e.g., Abacavir HSR)
V01-V09	Persons with Potential Health Hazards Related to Communicable Disease

† Only specific HIV-related ICD-9 codes within the broad categories, identified by an expert panel, were included in the study.

Appendix E: HIV-Related Conditions and Medications

Disease	Drugs
Mycobacterium Avium Complex	Clarithromycin Azithromycin Ethambutol Rifabutin Ciprofloxacin
Mycobacterium Kansasii	Rifampin Rifabutin Ethambutol Clarithromycin Azithromycin Isoniazid Pyridoxine
Salmonellosis	Ciprofloxacin Ampicillin Chloramphenicol Trimethoprim- Sulfamethoxazole
Syphilis & Neurosyphilis	Penicillin Injection Non-Steroidal Anti-Inflammatory Drugs Benadryl Narcotic Drugs Muscle relaxants
Tuberculosis	Isoniazid Rifampin Rifabutin Pyrazinamide Ethambutol Streptomycin Rifamate® Rifater® Capreomycin Kanamycin Amikacin Ethionamide Ciprofloxacin Ofloxacin Lomefloxacin Clofazimine Cycloserine Aminosalicic acid
Anal Dysplasia/Cancer & Cervical Dysplasia/Cancer	Podofilox Podophyllum Trichloroacetic acid Imiquimod Cryotherapy

Disease	Drugs
	Laser treatment LEEP (loop electrical excision procedure) Surgery/cold-knife cone biopsy Radical surgery/radiation/chemotherapy
Kaposi's Sarcoma	Alitretinoin Cryotherapy Radiation therapy Intralesional therapy Vinblastine Interferon-alfa Liposomal chemotherapy Standard chemotherapy (doxorubicin, vincristine, bleomycin, etoposide, paclitaxel)
Lymphomas	Surgery Radiation (radiotherapy) Methotrexate Bleomycin Cyclophosphamide Vincristine Dexamethasone hydroxydaunomycin (doxorubicin) Prednisone Doxorubicin Etoposide Rituximab Bleomycin Vinblastine Dacarbazine Cytarabine (Ara-C) Neupogen® Leukine® Leucovorin calcium Epoetin-alfa
Cytomegalovirus	Foscarnet Ganciclovir Cidofovir Valganciclovir Fomivirsen Valcyte®
Hepatitis C	Interferon-alfa Pegylated interferon Ribavirin

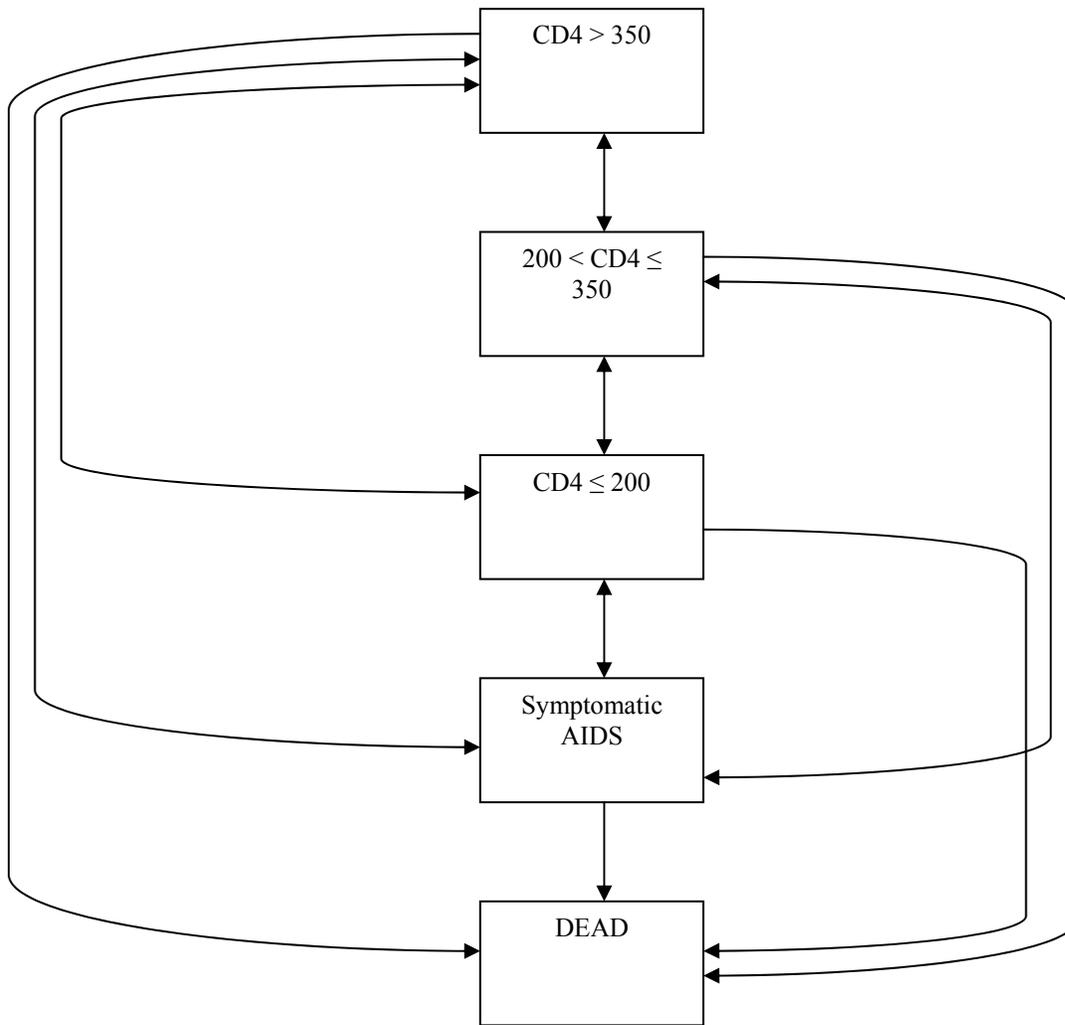
Disease	Drugs
Herpes Simplex Virus (oral & genital herpes)	Acyclovir Valacyclovir Famciclovir Foscarnet Cidofovir Trifluridine
Herpes Zoster Virus (shingles)	Acyclovir Valacyclovir Famciclovir Foscarnet
Human Papiloma Virus (HPV, genital warts, anal/cervical dysplasia/cancer) Molluscum Contagiosum	Podophyllum Trichloroacetic acid Cantharidin Tretinoin Tincture of iodine, Silver nitrate Phenol Cryotherapy Laser treatment Curettage Electrocautery Griseofulvin Cimetidine
Oral Hairy Leukoplakia	Acyclovir Valacyclovir Famciclovir Tretinoin Podophyllin resin Liquid nitrogen
Progressive Multifocal Leukoencephalopathy	Cytarabine Topotecan Cidofovir Probenecid Probalan®
Aspergillosis	Amphotericin B Abelcet® Amphotec® AmBisome® Itraconazole Caspofungin
Candidiasis (thrush, yeast infection)	Clotrimazole Nystatin Amphotericin B Ketoconazole Itraconazole Fluconazole Gentian violet Miconazole

Disease	Drugs
	Terconazole Tioconazole Butoconazole Gentian violet Standard amphotericin B and liposomal amphotericin B
Coccidioidomycosis	Amphotericin B Abelcet® Amphotec®, AmBisome® Fluconazole Itraconazole
Cryptococcal Meningitis	Fluconazole Flucytosine Liposomal amphotericin B Amphotericin B Fungizone AmBisome® Abelcet® or Amphotec® Acetazolamide Corticosteroids
Histoplasmosis	Amphotericin B Itraconazole Fluconazole
Cryptosporidiosis	Nitazoxanide Azithromycin Paromomycin Dapsone Octreotide Lomotil® Loperamide Paregoric, and Pepto-Bismol® Non-Steroidal Anti-Inflammatory Drugs Nutritional supplementation Human growth hormone and anabolic steroids
Isosporiasis	Trimethoprim and Sulfamethoxazole Pyrimethamine Folinic acid Octreotide Diphenoxylate Loperamide Paregoric, and Pepto-Bismol® Ibuprofen Thalidomide

Disease	Drugs
Microsporidiosis	Metronidazole Albendazole Dapsone Octreotide Diphenoxylate Loperamide Laregoric Pepto-Bismol® Ibuprofen Thalidomide Ensure, Sustacal, Citrisource, Jevity, and Replete Marinol® Megestrol acetate <u>Serostim</u> Testosterone Oxandrolone Nandrolone Oxymethalone
Pneumocystis Carinii Pneumonia	Pentamidine Clindamycin-primaquine Trimethoprim -dapsone Trimetrexate-leucovorin Aerosolized pentamidine Prednisone Trimethoprim and Sulfamethoxazole Dapsone
Toxoplasmosis	Pyrimethamine Folic Acid, Vitamin B ₉ Sulfadiazine Clindamycin Azithromycin Corticosteroids
AIDS Dementia Complex	Haloperidol Methylphenidate Chlorpromazine and thioridazine Lorazepam and diazepam Antidepressants: These include fluoxetine (Prozac®) and bupropion (Wellbutrin®)
Peripheral Neuropathy	Non-narcotic pain relievers. These include aspirin, acetaminophen, ibuprofen, and naproxen Topical medications. 5% Lidocaine gel Tricyclic antidepressants - Amitriptyline Anticonvulsants - Carbamazepine and phenytoin are two of the most common anticonvulsants used for pain associated

Disease	Drugs
	<p>with peripheral neuropathy. Two new anticonvulsants, gabapentin and lamotrigine</p> <p>Narcotic pain relievers - morphine, oxycodone, codeine, and meperidine.</p> <p>For severe pain requiring heavy-duty relief, the options are usually sustained-release morphine, methadone, and fentanyl patches.</p> <p>Complimentary therapies. Some of the complimentary or "alternative" therapies that have been used to help manage peripheral neuropathy symptoms include peptide T, α-lipoic acid, L-carnitine, & acupuncture.</p>
Aphthous Ulcers (Canker Sores)	<p>Betamethasone</p> <p>Diprolene®</p> <p>Maxivate®)</p> <p>Fluocinonide</p> <p>Fluocinolone</p> <p>Clobetasol</p> <p>Hydrocortisone</p> <p>Triamcinolone</p> <p>Prednisone</p> <p>Thalidomide</p>
Thrombocytopenia (low platelets)	<p>Prednisone</p> <p>Gamma Globulin</p> <p>Rh₀ [D] Immune Globulin</p>
Wasting Syndrome	<p>Oral supplements - including Ensure, Sustacal, Citrisource, Jevity, and Replete</p> <p>Drugs to control nausea and vomiting (antiemetics), diarrhea (antidiarrheals), and decreased appetite (appetite stimulants). Treatments such as Marinol and megestrol acetate (Megace) have been shown to help boost appetite</p> <p><u>Serostim</u></p> <p>Thalidomide (Synovir)</p>

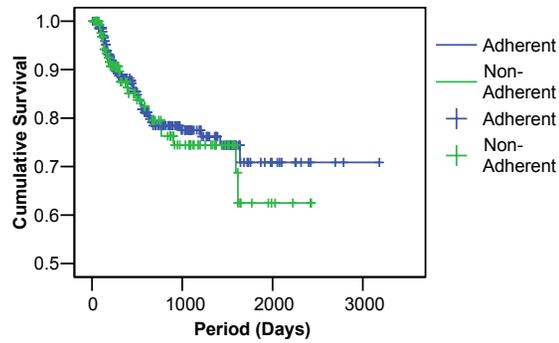
Appendix F: Structure of the Decision Model Describing the Progression of Patients through Disease States to Eventual Death



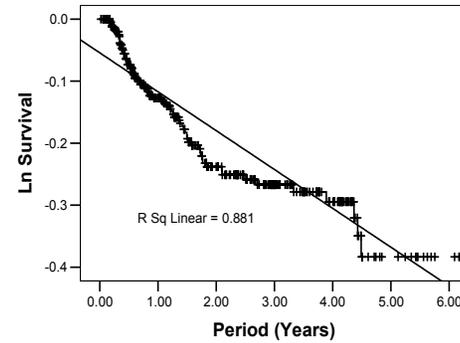
Appendix G

Survival Curve and Scatter Plots: Transitions from Clinical State A to Clinical State B*

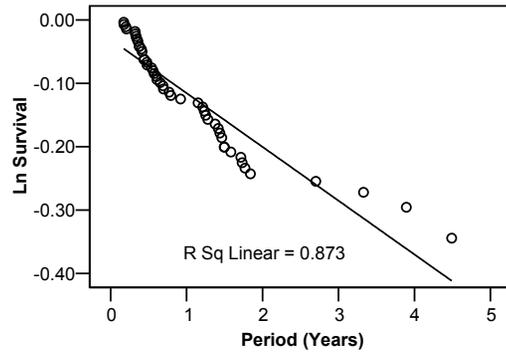
Survival Curve Displaying the Transition between Clinical State A and Clinical State B for Adherent and Non-Adherent Individuals



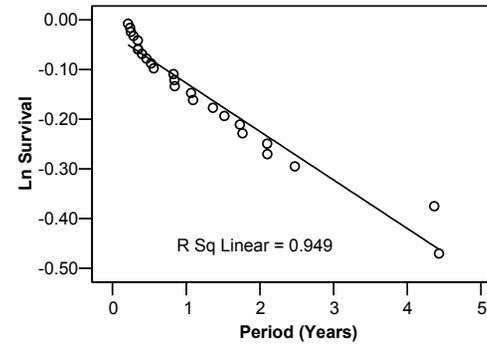
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



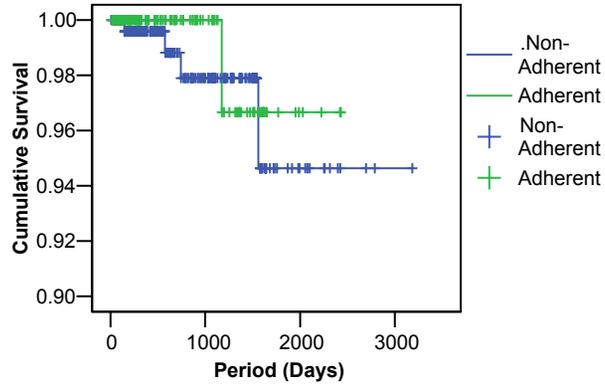
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



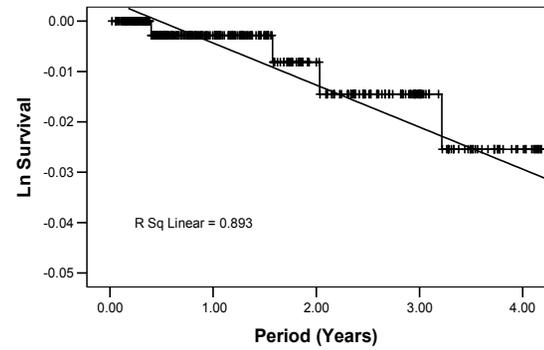
*Survival refers to individuals who began and remained in Clinical State A during the follow-up period

Survival Curve and Scatter Plots: Transitions from Clinical State A to Clinical State C*

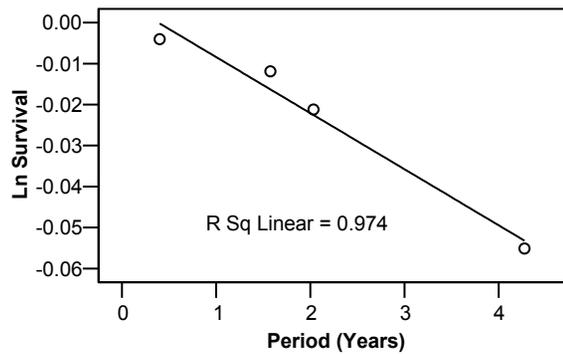
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Relationship Between Log Survival and Follow-up Period for All Individuals



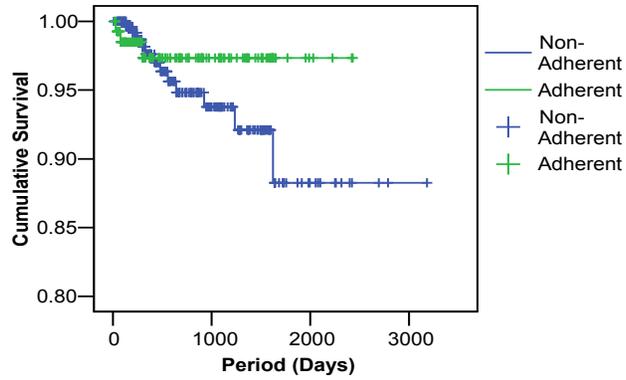
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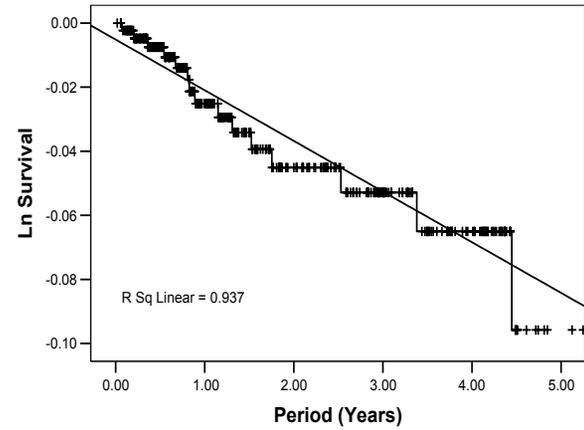
*Survival refers to individuals who began and remained in Clinical State A during the follow-up period

Survival Curve and Scatter Plots: Transition from Clinical State A to Clinical State D*

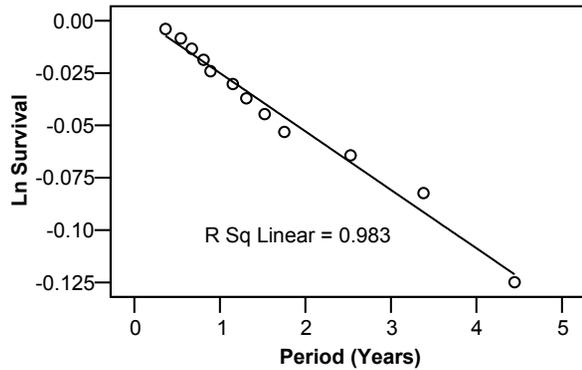
Survival Curve Displaying the Transition between Clinical State A and Clinical State D for Adherent and Non-Adherent Individuals



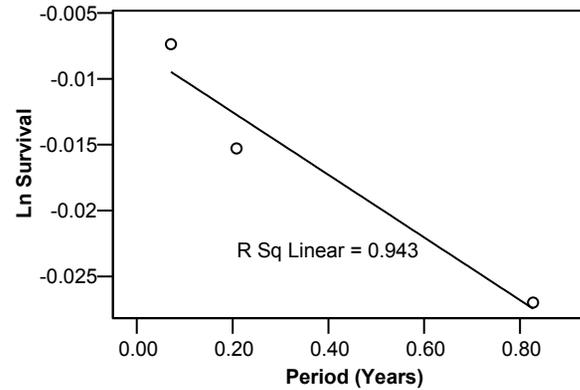
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



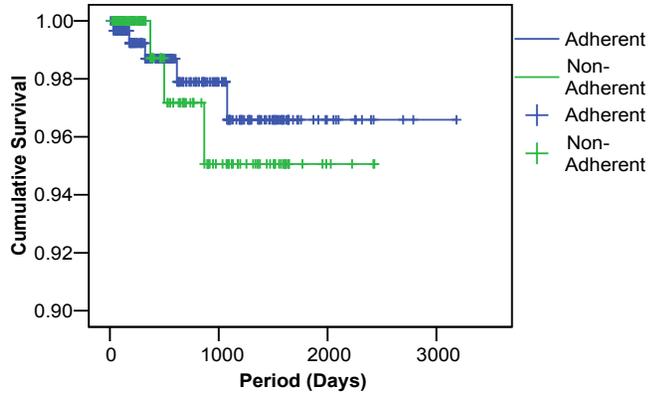
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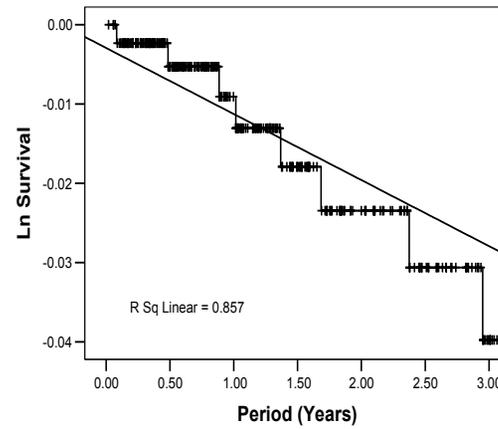
*Survival refers to individuals who began and remained in Clinical State A during the follow-up period

Survival Curve and Scatter Plots: Transitions from Clinical State A to the DEAD State*

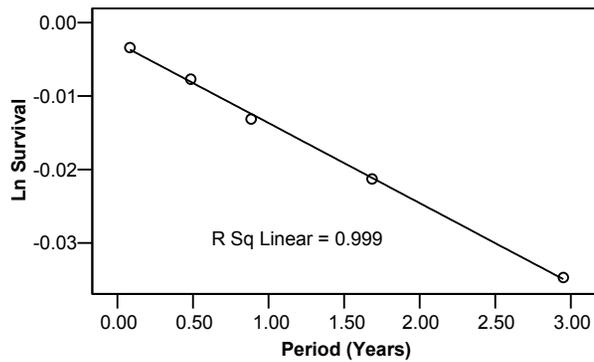
Survival Curve Displaying the Transition between Clinical State A and Clinical State E for Adherent and Non-Adherent Individuals



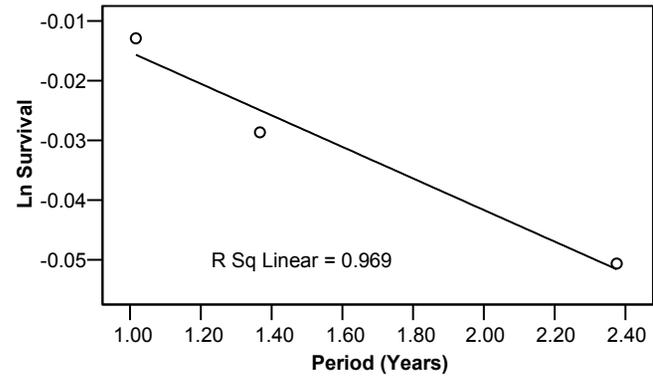
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



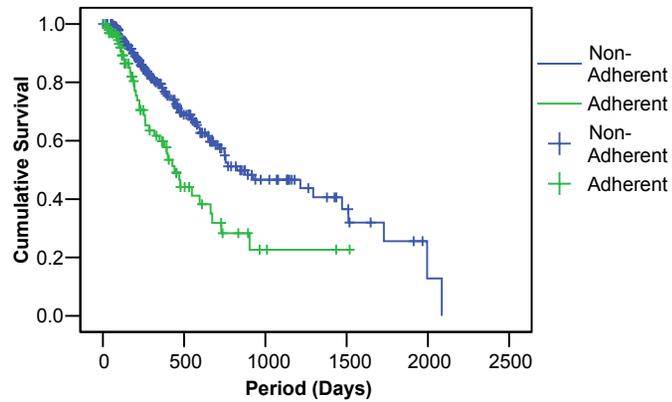
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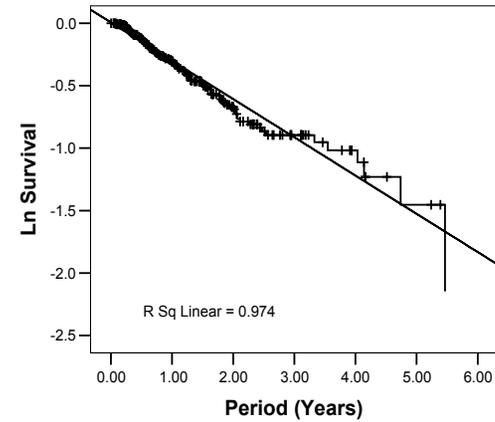
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Survival Curve and Scatter Plots: Transitions from Clinical State B to Clinical State A*

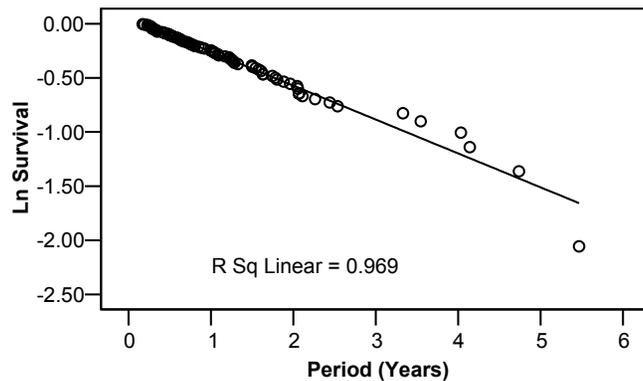
Survival Curve Displaying the Transition between Clinical State B and Clinical State A for Adherent and Non-Adherent Individuals



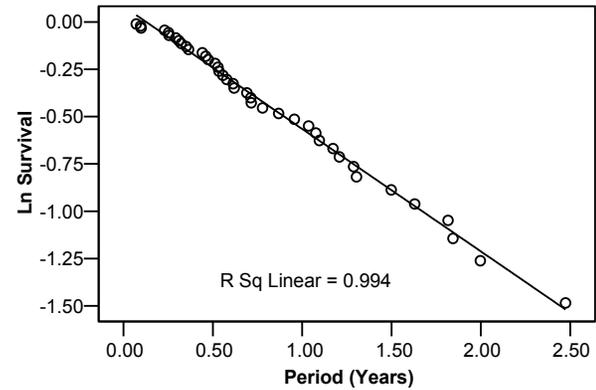
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



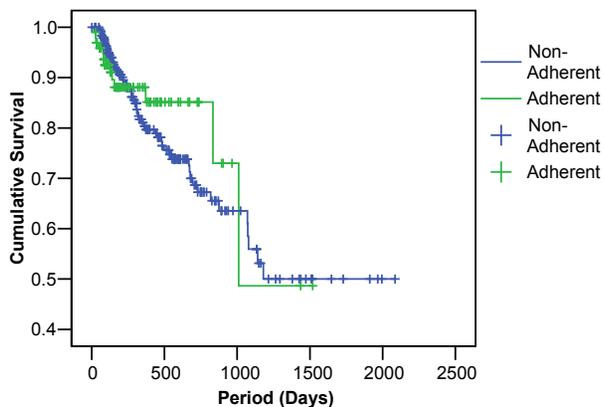
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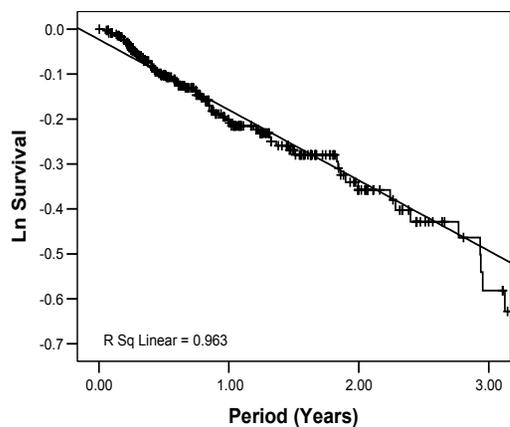
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Survival Curve and Scatter Plots: Transitions from Clinical State B to Clinical State C*

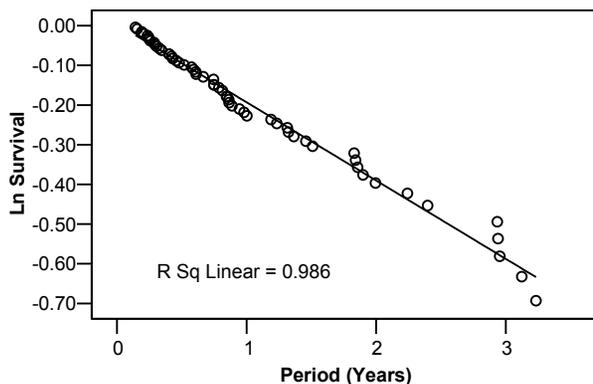
Survival Curve Displaying the Transition between Clinical State B and Clinical State C for Adherent and Non-Adherent Individuals



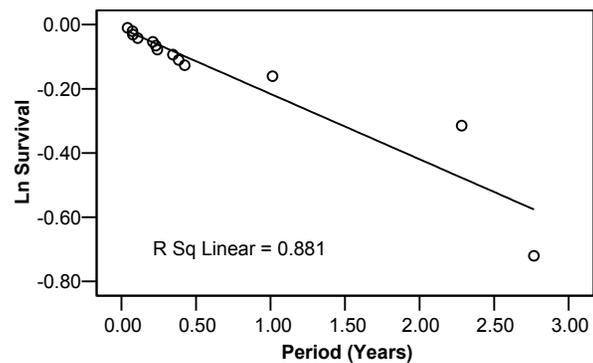
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



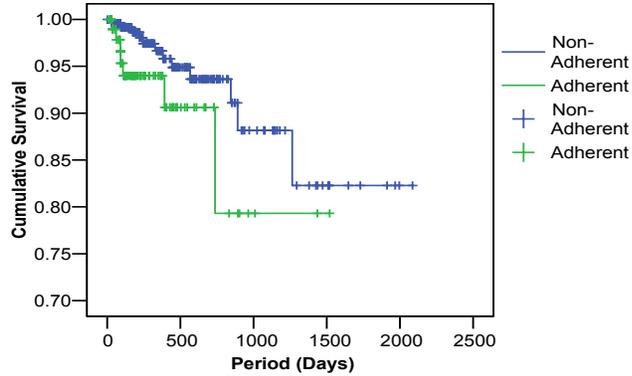
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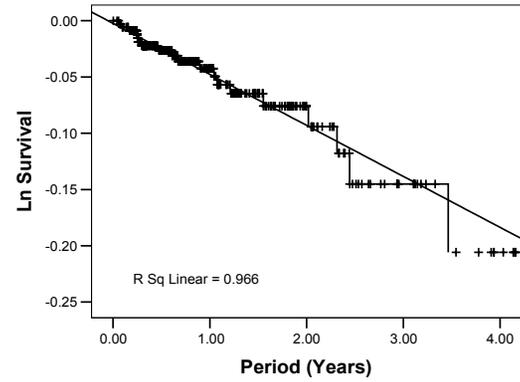
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Survival Curve and Scatter Plots: Transitions from Clinical State B to Clinical State D*

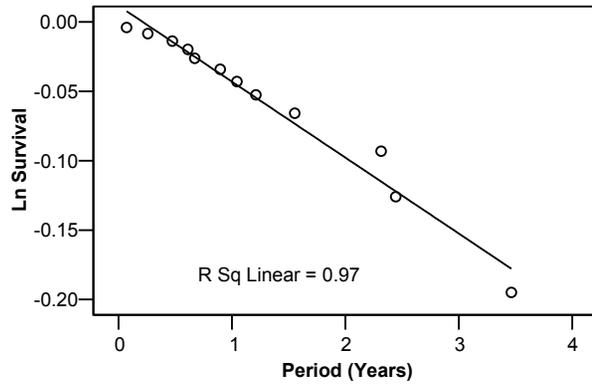
Survival Curve Displaying the Transition between Clinical State B and Clinical State D for Adherent and Non-Adherent Individuals



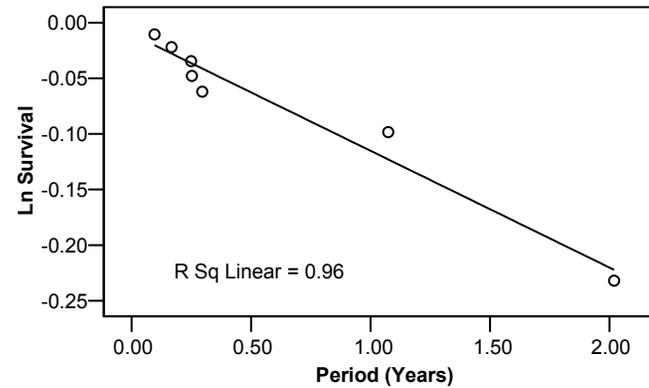
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



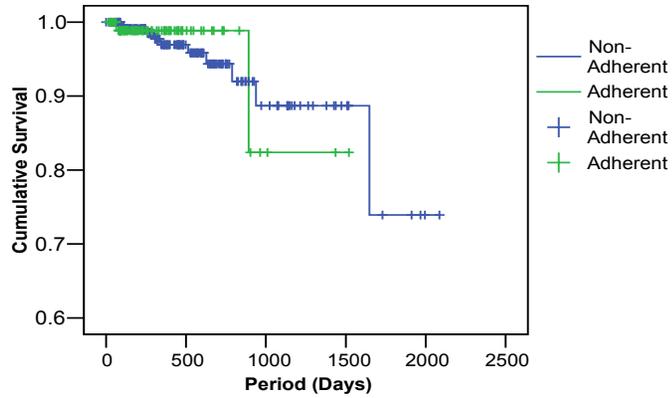
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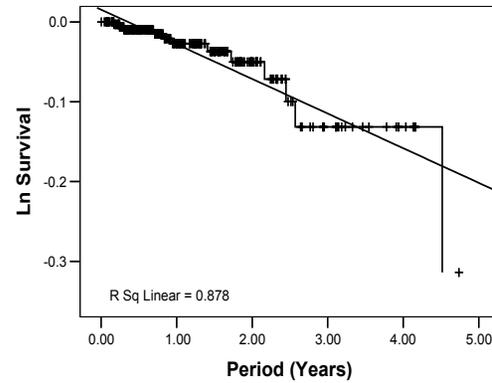
*Survival refers to individuals who began and remained in Clinical State B during the follow-up period

Survival Curve and Scatter Plots: Transitions from Clinical State B to the DEAD State*

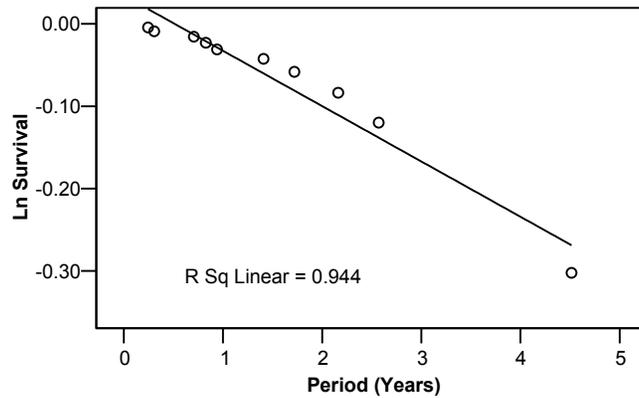
Survival Curve Displaying the Transition between Clinical State B and the DEAD State for Adherent and Non-Adherent Individuals



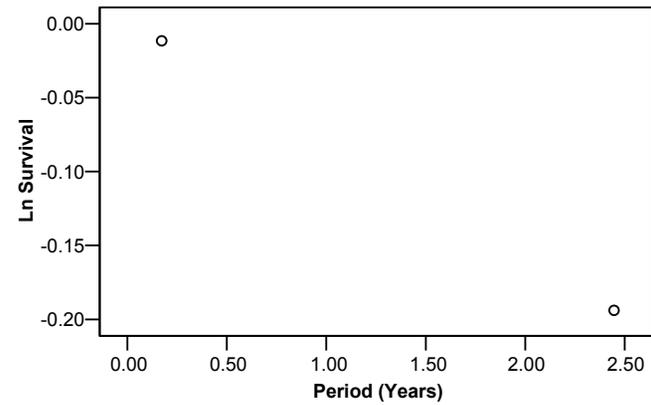
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



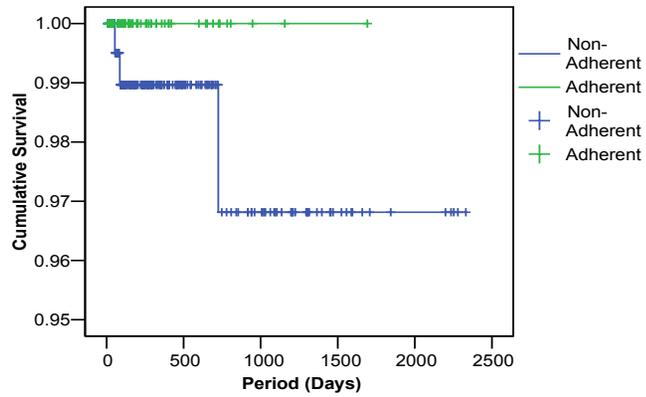
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



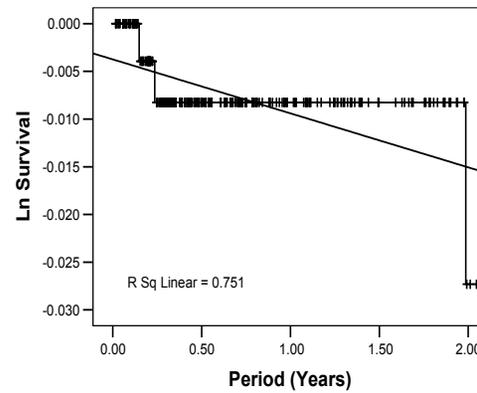
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Survival Curve and Scatter Plots: Transitions from Clinical State C to Clinical State A*

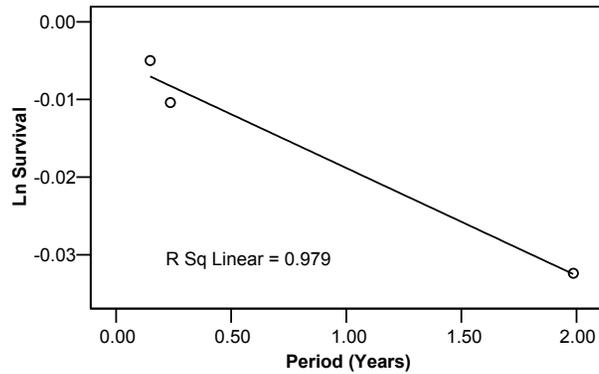
Survival Curve Displaying the Transition between Clinical State C and Clinical State A for Adherent and Non-Adherent Individuals



Relationship Between Log Survival and Follow-up Period for All Individual



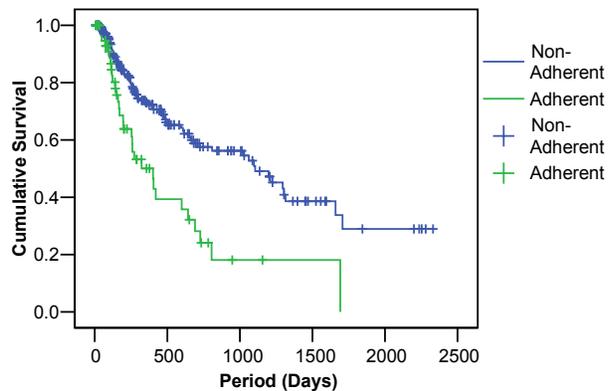
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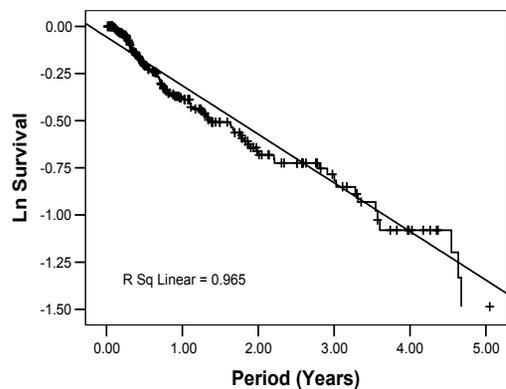
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Survival Curve and Scatter Plots: Transition from Clinical State C to Clinical State B*

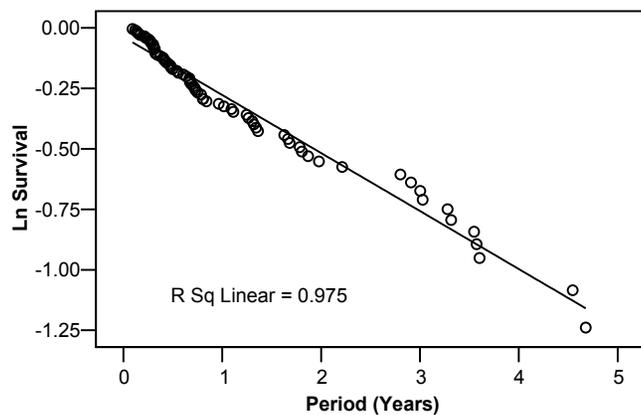
Survival Curve Displaying the Transition between Clinical State C and Clinical State B for Adherent and Non-Adherent Individuals



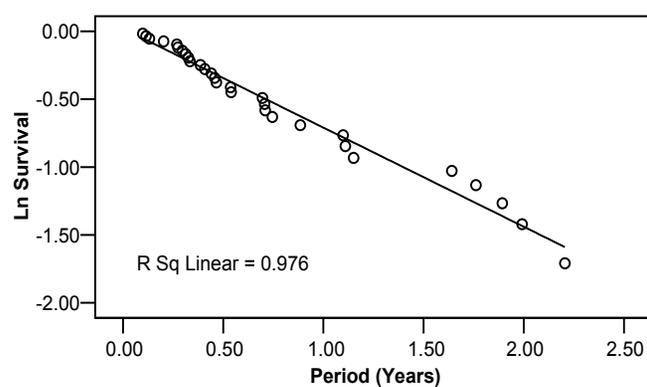
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



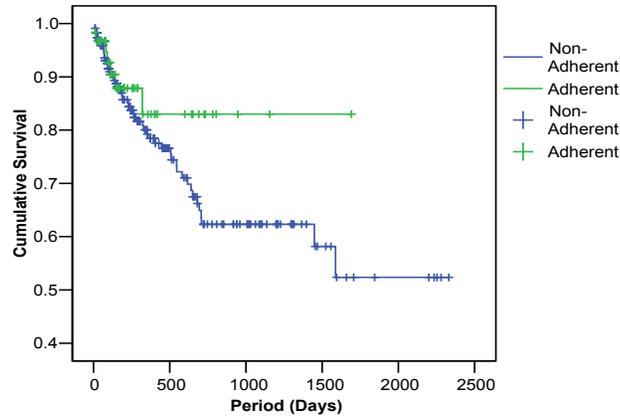
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



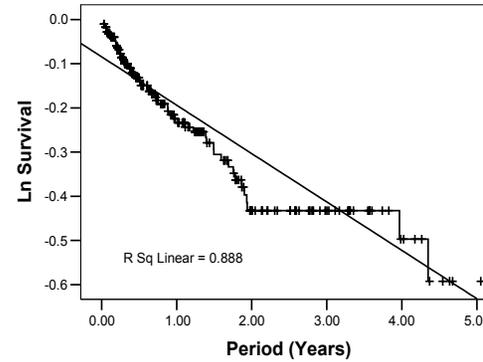
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Survival Curve and Scatter Plots: Transition from Clinical State C to Clinical State D*

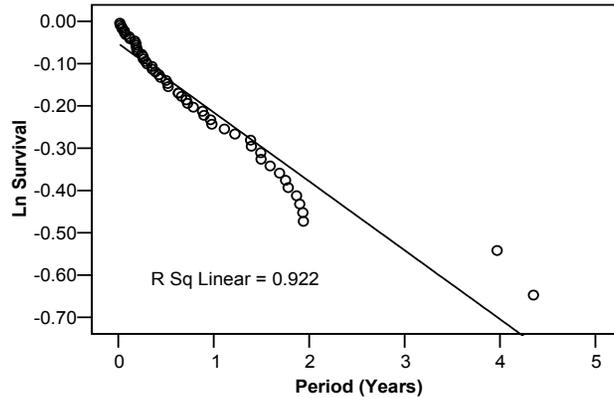
Survival Curve Displaying the Transition between Clinical State C and Clinical State D for Adherent and Non-Adherent Individuals



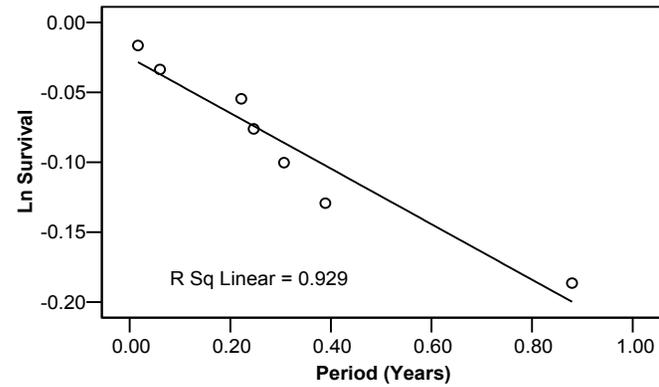
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



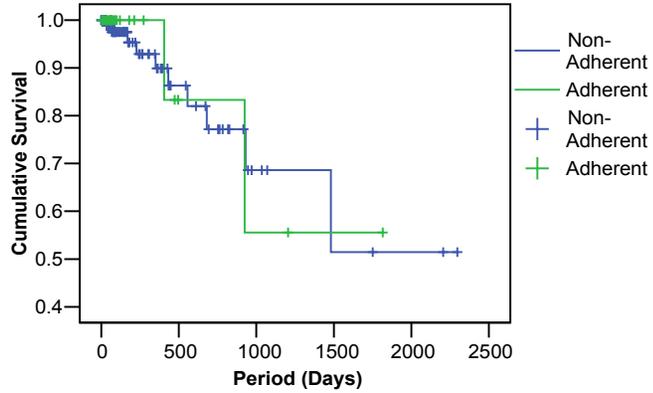
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



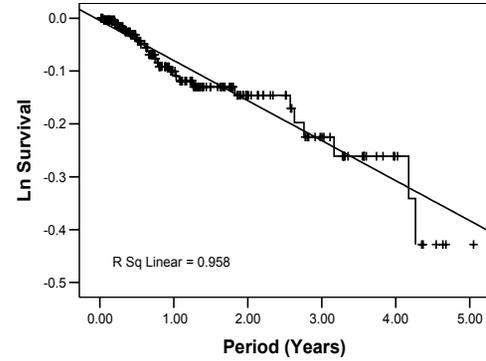
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Survival Curve and Scatter Plots: Transitions from Clinical State C to the DEAD State*

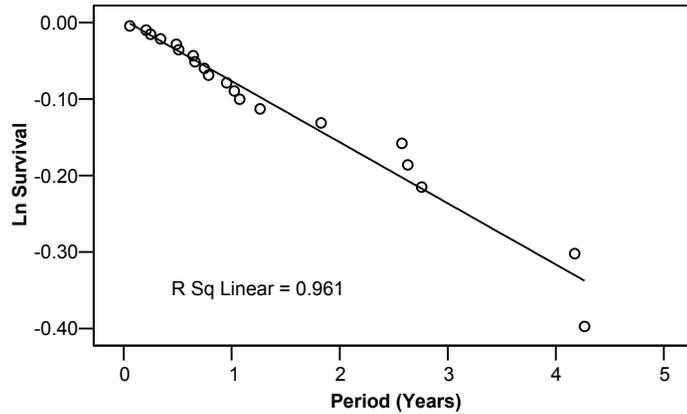
Survival Curve Displaying the Transition between Clinical State C and the DEAD State for Adherent and Non-Adherent Individuals



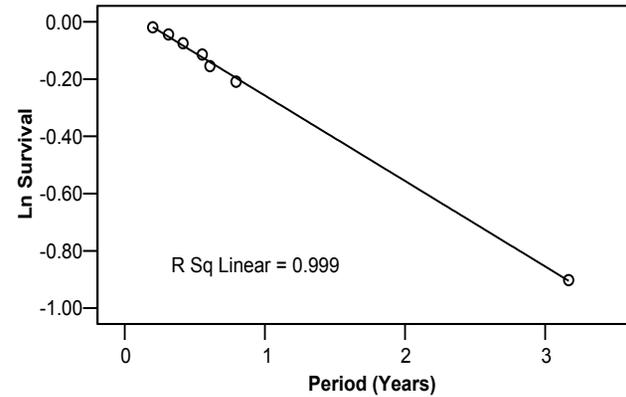
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



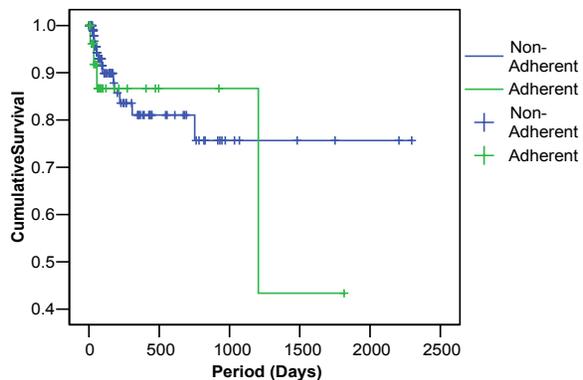
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



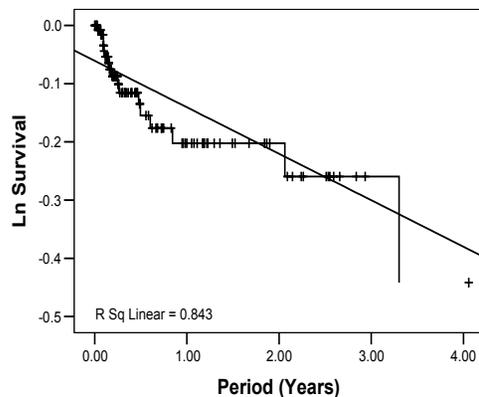
*Survival refers to individuals who began and remained in Clinical State C during the follow-up period

Survival Curve and Scatter Plots: Transition from Clinical State D to Clinical State A*

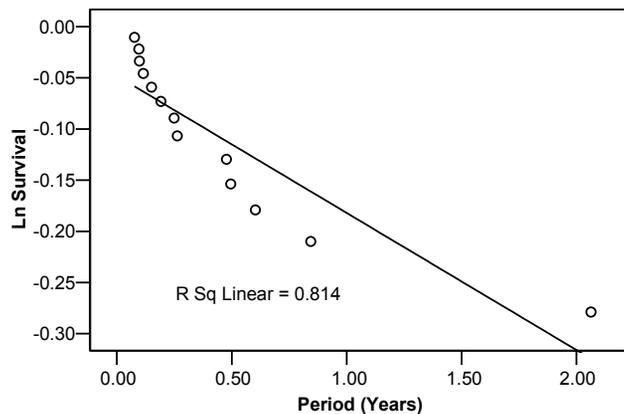
Survival Curve Displaying the Transition between Clinical State D and Clinical State A for Adherent and Non-Adherent Individuals



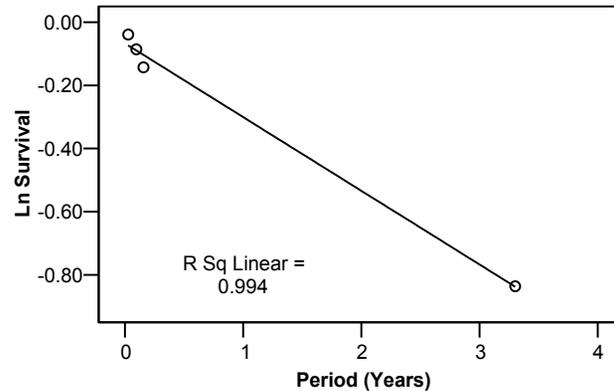
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



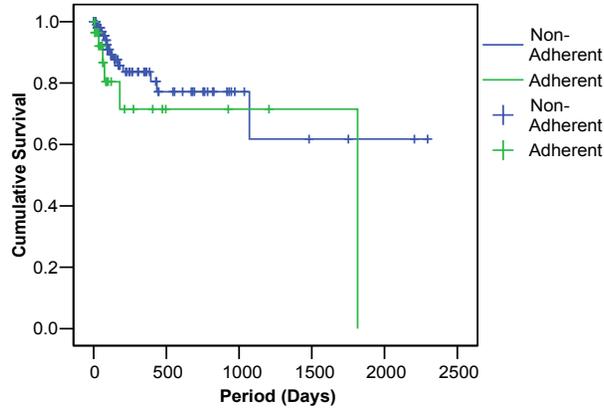
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



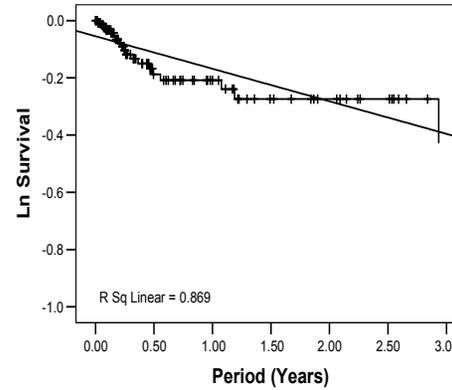
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Survival Curve and Scatter Plots: Transitions from Clinical State D to Clinical State B*

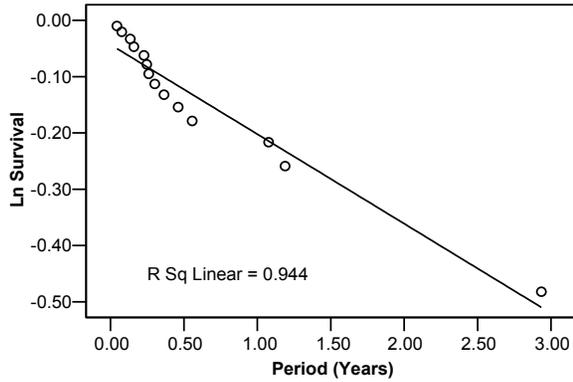
Survival Curve Displaying the Transition between Clinical State D and Clinical State B for Adherent and Non-Adherent Individuals



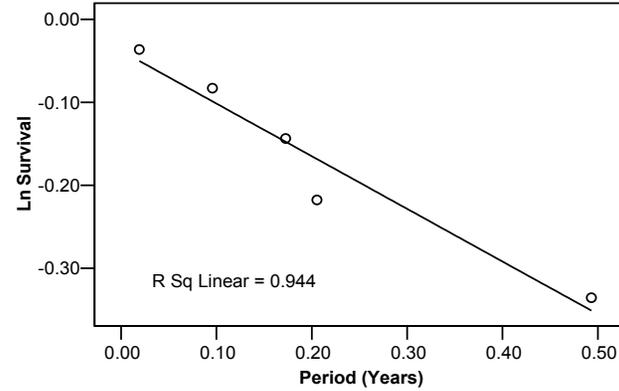
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



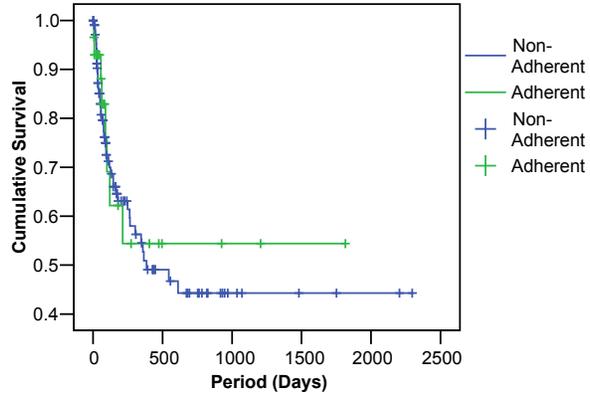
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



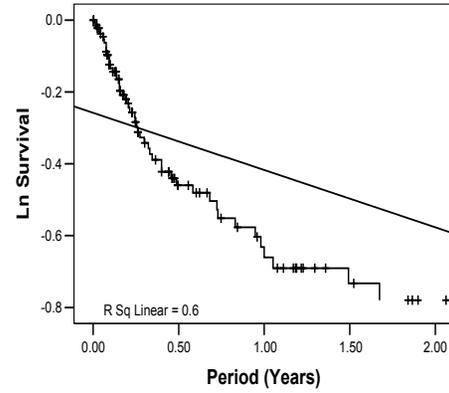
*Survival refers to individuals who began and remained in Clinical State D during the follow-up period

Survival Curve and Scatter Plots: Transition from Clinical State D to Clinical State C*

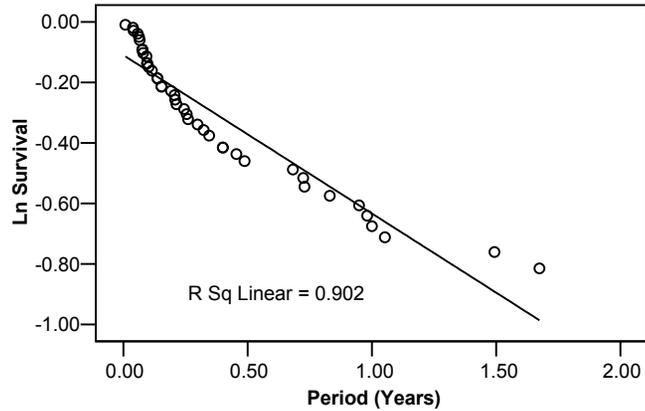
Survival Curve Displaying the Transition between Clinical State D and Clinical State C for Adherent and Non-Adherent Individuals



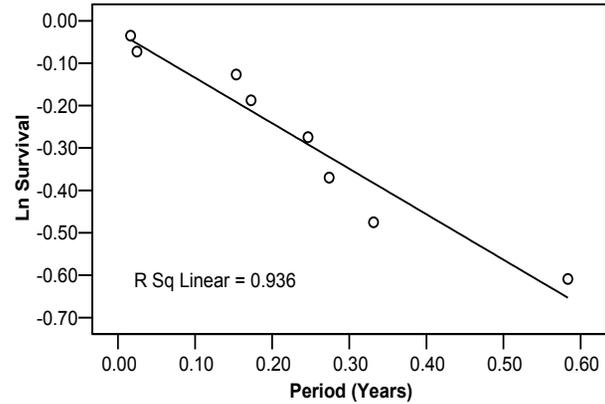
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



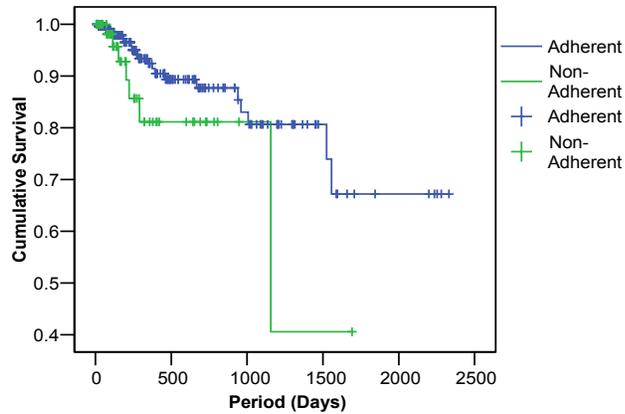
Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Adherent Individuals



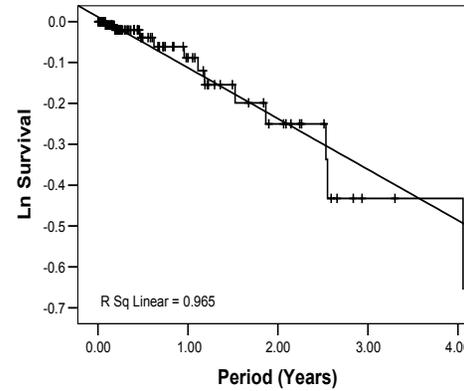
*Survival refers to individuals who began and remained in Clinical State D during the follow-up period

Survival Curve and Scatter Plots: Transitions from Clinical State D to the DEAD State*

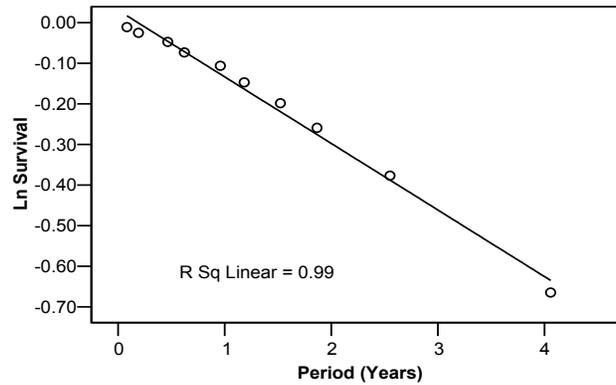
Survival Curve Displaying the Transition between Clinical State D and the DEAD State for Adherent and Non-Adherent Individuals



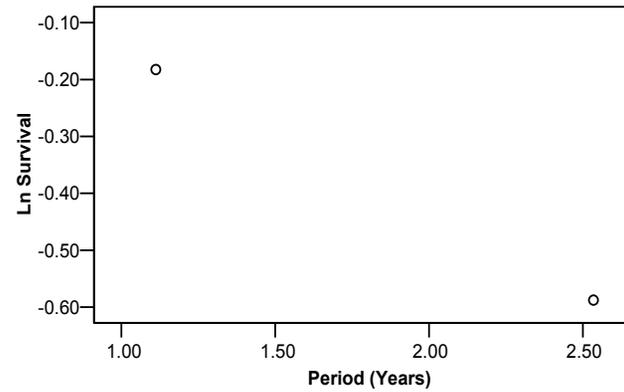
Relationship Between Log Survival and Follow-up Period for All Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



Scatter Plot Displaying the Relationship Between Log Survival and Follow-Up Period for Non-Adherent Individuals



*Survival refers to individuals who began and remained in Clinical State D during the follow-up period

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