**The Effect of Daily Pill Burden on the Probability of Discontinuation of Initial HAART Regimens**

by

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## Abstract

**Background:** Given that lower pill burdens have been shown to be associated with an increased duration of initial therapy, there is a need to understand the effect of daily pill burden on the duration of the initial regimen.

**Objective:** The objective of this study was to analyze the effect of daily pill burden of the initial HAART regimen prescribed to a cohort of mostly minority, underserved female patients on their time to discontinuation of this regimen.

**Methods:** Survival analysis, including Kaplan-Meier curves, log-rank tests, and a Cox proportional hazards model were used to answer research questions, in addition to analyses such as paired samples t-test, Fisher's exact test, and ANOVA procedures.

**Results:** Overall, 1 pill/day regimens were associated with the lowest time to discontinuation of all four categories of pill burden groups. 1 pill/day regimens were shown to have a statistically significant longer time to discontinuation than any other initial regimen prescribed in this cohort.

**Discussion:** Patients started on the only 1 pill/day regimen used at this cohort (Atripla) stayed on this regimen for a statistically significant longer duration than patients started on any other regimen in this cohort. Every pill added to the initial regimen was shown to increase the hazard of discontinuation 23.0% in this cohort.

**Conclusions:** Overall, 1 pill/day regimens were associated with the longest time to discontinuation, and pill burden was shown to be a significant contributor to the hazard of discontinuation.

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## I. Background

*Acquired Immunodeficiency Syndrome*

Acquired Immunodeficiency Syndrome (AIDS) is the clinical end-stage of infection by the Human Immunodeficiency Virus (HIV) [1]. HIV is a retrovirus that mainly targets certain cells in the human immune system called T-helper lymphocytes. These white blood cells are involved in the immune response to secondary antigen exposure. When a pathogen such as a virus or a bacterium is introduced into the body, mature T-helper cells coordinate the cellular immune response responsible for destroying the pathogen [2]. HIV can also infect certain monocytes, macrophages, and dendritic cells [3] [4]. All of these cell types become infected via a surface glycoprotein called cluster of differentiation 4 (CD4) which interacts with a surface glycoprotein on the envelope of HIV called gp120 to facilitate viral docking [2]. T-helper lymphocytes present the CD4 surface glycoprotein upon cellular maturation and use it to interact with other lymphocytes [5] while coordinating the cellular immune response. When T-helper lymphocytes present the CD4 glycoprotein, they are referred to as $CD4^+$ T-cells, as opposed to $CD4^-$ T-cells which do not have this surface glycoprotein. Depletion of $CD4^+$ T-cells has been associated with AIDS as of the first case descriptions in the early 1980s [6].

Because the loss of $CD4^+$ T-cells has been called the "cardinal manifestation" of HIV infection, a count of $CD4^+$ T-cells in the blood can be used to measure the strength of the patient's immune system and the risk for opportunistic infections [2]. Healthy, HIV-negative individuals typically have between 800 to 1,200 $CD4^+$ T-

cells per $mm^3$ of blood. During untreated HIV infection, the number of $CD4^+$ T-cells in the blood gradually declines [2]. Once the number of $CD4^+$ T-cells declines lower than 200 cells per $mm^3$ of blood, the patient loses the cellular immune response because there are not enough healthy T-helper cells [7]. Furthermore, declines in $CD4^+$ T-cells can lead to dangerous opportunistic infections [8], such as Kaposi's sarcoma as seen in the first presentations of AIDS. Declines in $CD4^+$ T-cells lead to these infections because HIV targets the "heart of the immune system" [2], the $CD4^+$ T-helper cells which coordinate the immune response to the pathogen. Once these are depleted, individuals cannot fight off opportunistic infections.

Because $CD4^+$ T-cells can measure the strength of a patient's immune system, the United States (US) Center for Disease Control (CDC) partially bases their clinical criteria for an AIDS diagnosis on the $CD4^+$ T-cell count. According to the CDC, an individual with a laboratory confirmed infection of HIV must have a $CD4^+$ T-lymphocyte count of less than 200 cells/$mm^3$ of blood or have a $CD4^+$ T-lymphocyte percentage of total lymphocytes of less than 14%. Furthermore, the individual must have one of 26 predefined AIDS defining illnesses (Table 1) [9]. Without treatment, the median time between HIV infection and development of AIDS is 9.4 years, and the median time between development of AIDS and patient death is 9.2 months [10].

*Background of HIV and AIDS*

In 1981, Hymes and Colleagues [11] reported the unusual finding of an aggressive form of Kaposi's sarcoma in eight young homosexual men. The main reason this finding was unusual at the time is because of the young age of the

patients. Before the outbreak of the AIDS, Kaposi's sarcoma was seen mainly in elderly Italian and Jewish men [12]. The patients Hymes and colleagues had treated were in their 30s, not in their 60s as was expected with this condition. Furthermore, Hymes and colleagues noted that the sarcoma was more aggressive in these patients. Typically, Kaposi's sarcoma patients have a survival time of 8-13 years, but these patients had a reported survival time of less than 20 months. Also of concern were the large numbers of sexually transmitted diseases present in these eight individuals. Hyme and colleagues noted a "variety of sexually transmitted diseases" in these patients and hypothesized that exposure to these sexually transmitted diseases may increase these individual's risks to Kaposi's sarcoma. While the cause of this illness was unknown to researchers at the time, Hymes's eight cases of Kaposi's sarcoma reported in the Fall of 1981 probably represent the first reported cases of AIDS in the US [13].

Later that year, Masur and colleagues reported eleven cases of pneumocystis carinii pneumonia (PCP), an opportunistic infection targeting immune compromised patients. Masur and colleagues' report highlighted the unusual nature of these cases. Because PCP is an opportunistic infection, it was very rare before the outbreak of AIDS [14], and mostly infected elderly individuals with an immunosuppressive disease. Furthermore, because one of the eleven patients presented with Kaposi's sarcoma, future researchers could link these cases to the etiology of Hymes's eight patients. While researchers were still in the dark about the cause of this mystery illness, this CDC article helped link homosexual behavior and injection drug use to immunosuppression and this mystery syndrome.

1982 marks the first use of the term AIDS, both in the scientific literature [15], as well as in public meetings [13]. The term AIDS denotes the severe immunosuppression seen in these patients while also showing homosexuality to not be a prerequisite for infection. Previously, AIDS had been referred to as gay-related immune deficiency (GRID) or gay compromise syndrome [13], but a 1982 report published by the CDC dispelled the myth that the sole method of AIDS transmission is by homosexual contact.

The CDC report of a 20-month old infant who died of AIDS in August of 1982 [16] provided further clear evidence that homosexual contact was not the only transmission route for AIDS. Because the reported infant was diagnosed with hyperbilirubinemia at birth, the infant was hospitalized for a month following birth while whole blood, packed red blood cells, and platelets from 19 blood donors were given. One of these donors, a 48-year old white male resident of San Francisco, was later shown to have AIDS, and transmitted infection to the infant through infected blood products. While researchers were still unsure of the etiology of AIDS at this point, this case study highlighted individuals receiving blood transfusions as being at greater risk for AIDS like homosexual men and intravenous drug users. Two other studies conducted in 1982, both by the CDC, highlighted Haitian-Americans [17] and hemophiliacs [17] as also being at higher risk for acquiring AIDS. Knowing these risk factors allowed researchers to hypothesize AIDS may be transmitted by an infectious agent which is transmitted sexually or through blood products.

By 1982, researchers knew that the mystery infectious agent targeted $CD4^+$ T-cells, and was transmitted through blood products. Furthermore, researchers

knew the agent could not be a microorganism larger than a virus because of previous CDC reports of AIDS patients with hemophilia who had only received filtered clotting factors [18]. Because the Human T-Lymphocyte Virus (HTLV) targets $CD4^+$ T-cells and is a virus, two independent researchers, Dr. Robert C. Gallo and Dr. Max Essex, began searching for an HTLV-like virus in AIDS patients at this time. In 1983, researchers associated with Dr. Gallo's team isolated an HTLV-like virus from cultured T-lymphocytes derived from a lymph-node-biopsy specimen from a patient with a precursor syndrome to AIDS [19]. This virus, which was different from HTLV in antigenicity and morphology, was the first HIV strand ever isolated.

On April 23rd, 1984, US Secretary for Health and Human Services Margaret Heckler convened a press conference to announce that Dr. Robert Gallo's team had isolated the virus which causes AIDS. She also announced that a blood test to test for this virus would soon be commercially available [13]. Later that afternoon, patents were filed with the US patent office for the first blood tests to test for HIV [20]. This represented a major breakthrough in the fight against AIDS, as providers could now test patients for HIV and donated blood could be tested for infection. These blood tests would later be used to screen the entire US supply of donated blood [13] [21]. Despite these advances, the first treatment options for HIV infected individuals would not be available for another year.

*Prevalence of HIV*

The CDC estimates that in 2012, 1.2 million people are living with HIV in the US [22]. One in five of these people (20%) are unaware of their infection [22]. Since the epidemic began, the CDC estimates that 619,4000 people in the US have died as a result of AIDS [22]. The CDC also estimates that the number of people living with HIV is increasing, possibly due to better testing and treatment conditions which can help to prolong the life of infected individuals. While the number of people living with HIV is increasing, the number of new infections per year appears to remain somewhat stable, albeit high, with approximately 50,000 Americans becoming infected each year [22].

Within these estimates, blacks appear to experience the highest burden of HIV when compared to other races and ethnicities. While blacks only represent approximately 14% of the US population, this race accounted for an estimated 44% of all new HIV infections in the US in 2009. Furthermore, blacks accounted for 46% of people living with HIV infection in 2008. At some point in their life, an estimated 1 in 16 black men will be diagnosed with HIV, as will 1 in 32 black women. The estimated rate of new HIV infections in black women is 15 times that of white women and over three times that of Hispanic/Latina women in 2009 [22].

*Financial Burden*

While antiretroviral therapies have been shown to be clinically effective at increasing $CD4^+$ T-lymphocyte counts [23], decreasing host viral load [24], and increasing disease-specific quality of life [25], cost considerations still limit patient

access to HIV care [26]. In the most recent assessment of direct HIV care costs, Schackman and colleagues analyzed individual lifetime costs associated with HIV care, reported as both discounted and undiscounted values [27]. Discounted values represent a value discounted at an annual rate of 3%based on recommendations made by the U.S. Panel on Cost-Effectiveness in Health and Medicine [28]. Schackman and colleagues reported a discounted lifetime cost of $385,000 and an undiscounted lifetime cost of $618,900 for individuals who initiated antiretroviral therapy with a $CD4^+$ cell count less than 350 cells/$mm^3$ of blood. These individuals had a mean projected life expectancy of 24.2 years, meaning on average they will pay $1325.76 per month in discounted costs or $2131.20 in undiscounted costs over their lifetime. For these individuals, 73% of these direct costs are for antiretroviral medications, 13% are for inpatient care, 9% are for outpatient care, and 5% are for laboratory costs or other HIV-related medications. Schackman and colleagues also reported a discounted lifetime cost of $354,100 and an undiscounted lifetime cost of $567,000 for individuals with a $CD4^+$ cell count greater than 200 cells/$mm^3$ of blood at antiretroviral therapy initiation. These individuals had a mean life expectancy of 22.5 years. While Schackman and colleagues' work helped to shed light on the large individual lifetime financial burden placed on infected individuals, most cost-of-illness estimates are only concerned with direct costs and few have analyzed the indirect costs associated with HIV care [29].

Indirect costs have been defined as the value of lost productivity because of illness, disability, and premature death [30]. These costs are important to understanding the full economic burden placed on individuals diagnosed with HIV,

yet only one published study has analyzed these lifetime costs for individuals with HIV since the advent of antiretroviral therapies. In 2006, Hutchinson and colleagues [30] sought to analyze both direct and indirect lifetime costs of HIV care for patients newly diagnosed with HIV in 2002. Hutchinson and colleagues also sought to describe hypothesized racial disparities in these lifetime costs. Researchers found that the cost of new HIV infections in the United States in 2002 was estimated at $36.4 billion. Of this total, $6.7 billion was attributed to direct medical costs while $29.7 billion (81%) was attributed to productivity losses. Hutchinson and colleagues also estimated a total direct lifetime cost of HIV care for a patient starting antiretroviral therapy with an initial $CD4^+$ cell count of less than or equal to 500 cells/$mm^3$ of blood to be $361,994 ($230,044 discounted) and these patients were estimated to have a life expectancy of 24.4 years. Patients not receiving antiretroviral therapy had an estimated lifetime direct medical cost of $145,218 ($114,938 discounted) and an estimated life expectancy of 12.4 years. The estimated total discounted lifetime cost of new diagnoses in 2002 was almost twice as high for blacks ($20.2 billion) as it was for whites ($10.7 billion). Lifetime direct medical costs of new HIV diagnoses in 2002 were the highest for whites ($180,900) and lowest for blacks ($160,400). Lifetime productivity losses for new HIV diagnoses in 2002 were also highest for whites ($180,900) compared to blacks ($661,100). Researchers attributed these disparities to delays in diagnoses or receiving care, and less access to antiretroviral therapy for minority groups.

*Background of the Problem*

For the 1.2 million US citizens living with HIV in 2012 [22], highly active antiretroviral therapies (HAART) remain the primary treatment option [31] [32] for HIV infection. Despite the decrease in morbidity and mortality rates these therapies can offer patients [33] [34], the nature of HIV infection leaves these patients with a chronic, lifetime need for these medications in spite of limited treatment options. Because of treatment toxicity and drug resistance, these therapies can reach a failure point [35], at which the World Health Organization advises patients to switch to a second-line therapy [32]. Because HAART therapies can fail, researchers would be wise to better understand how to maximize each line of HAART therapy in order to allow for the longest duration of treatment with HAART regimens possible. Furthermore, given that successive HAART regimens have successively shorter durations [36] [37], and that second-line HAART therapies can be six times more expensive than initial HAART therapies [38], researchers would be wise to better understand methods to maximize initial HAART therapies in order to allow for the longest duration of the most effective and accessible therapy for HIV patients.

In order to maximize the duration of initial HAART therapies, drug resistance to the initial HAART therapy must avoided [35]. The World Health Organization defines drug resistance as "the ability of the virus to withstand the effects of a given antiretroviral drug to prevent its replication" [38]. One of the most effective ways of delaying treatment failure caused by drug resistance is through maintenance of a high adherence rate [39]. Given the high standard adherence goal used for

antiretrovirals of 95% [40], researchers seeking to maximize duration of initial HAART therapies would be wise to look into ways to increase HAART adherence.

One method of increasing HAART adherence that has been shown to be effective is reducing HAART pill burden by combining drugs into fixed-dose combinations (FDCs) [41]. In addition to delaying treatment failure, some FDCs have also been shown to have a lower toxicity profile than non-coformulated agents [36] [37]. Given this improved adherence and lower toxicity, researchers attempting to maximize initial HAART regimens would be wise to consider the effect of treating HIV infection with an FDC versus individual, non-coformulated agents on the duration of initial HAART therapy.

*Significance and Implications*

A study analyzing the time to discontinuation of different pill burdens used in initial HAART therapies has the potential to make a significant contribution to the body of literature related to HAART therapies. Since the introduction of the first FDC with a nucleoside reverse transcriptase inhibitor (NRTI) backbone in August 2004 (Epzicom), only one study has evaluated this problem [42]. Furthermore, because the publication of that study predates the introduction of newer FDCs to the US pharmaceutical market, no studies have evaluated the duration of newer FDCs such as Atripla, leaving a significant gap in the literature. A study comparing the time to discontinuation of these and older FDCs to other n HAART agents has the potential to fill this gap in the literature and provide input to practitioners and researchers of the potential benefits of these medications. If this study finds

significant differences in the time to discontinuation between some regimens and others, these findings could influence treatment decisions for HIV patients. If regimens with lower pill burdens offer an increased time to discontinuation of first-line HAART therapies, these regimens could provide potential benefits to patients and providers seeking to maximize duration of initial HAART therapies.

## II. Literature Review

*Antiretroviral Medications*

The development of antiretroviral drugs began in 1970 with the discovery of the RNA-dependent DNA polymerase, which is presently known as reverse transcriptase (RT), by Temin [43] [44]. This was a large breakthrough because it modified the traditional central dogma of genetics, that DNA is converted to RNA, which is then converted into proteins. The discovery of RT showed geneticists and drug developers that this flow could also move backwards from RNA to DNA using the RT enzyme. While the HIV virus would not be discovered for another 13 years, this central discovery lead the way for the development of the first antiretroviral drug: Suramin.

Suramin was first described in 1979 as a potent reverse transcriptase inhibitor in animal models [45]. Later in 1986, Suramin was the first medication to be described as efficacious in reducing HIV viral loads *in vivo* in humans [43] [46]. However, Suramin was found to be too toxic in humans for systemic use [43], and in 1987 the first of a new class of antiretroviral drugs, nucleoside/nucleotide reverse transcriptase inhibitors, gained FDA approval for human use.

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are one of five main classes of antiretroviral drugs that target HIV, along with non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion/entry inhibitors(FIs), and integrase inhibitors (IIs). NRTIs and NNRTIs differentiate themselves from PIs, EIs, and IIs by their target: the viral reverse

transcriptase enzyme that converts viral RNA into double stranded DNA [43]. Furthermore, NRTIs differ from NNRTIs on the basis of their molecular structure: NRTIs are modeled after nucleotide bases found in DNA and RNA whereas NNRTIs are not. Also, NNRTIs target an allosteric site on the reverse transcriptase enzyme near to but not within the catalytic site, whereas NRTIs target the catalytic site of the enzyme[43].

The first FDA approved NRTI was 3'-azido-2',3'-dideoxythymidine, also known as Azidothymidine (AZT). Published in 1987, Fischi and colleagues' study of the efficacy of AZT in HIV infected individuals provided the first evidence of the efficacy of NRTIs at decreasing morbidity and mortality in HIV infected patients as well as decreasing the presence of opportunistic infections in these patients [47]. Also, by using a randomized, double-blind, placebo-controlled trial and rigorous methods, Fischi and colleagues were able to draw early definitive conclusions about the efficacy of antiretrovirals in HIV patients. In this study, Fischi randomized 145 patients to receive AZT and another 137 to receive placebo. At the end of the 24 week follow-up time, nineteen placebo recipients and 1 AZT recipient had died ($p<0.001$). Furthermore, 45 patients receiving placebo developed opportunistic infections compared to 24 receiving AZT. Most importantly, the study showed that individuals taking AZT demonstrated a statistically significant increase in their $CD4^+$ cell counts from baseline to follow-up ($p<0.001$) [47]. Fischi and colleagues' 1987 article opened the door to the subsequent development of more NRTIs in the following years. The second FDA approved NRTI, 2'3'-dideoxyinosine, also known as didanosine (ddI), received approval in 1991 [48]. Presently, there are seven

NRTIs on the market: lamivudine (3TC), abacavir (ABC), zidovudine (AZT), stavudine (d4T), didanosine (ddI), emtricitabine (FTC), and tenofovir (TDF) [48]. There are also presently five NNRTIs approved for use in the US: delavirdine (DLV), efavirenz (EFV), etravirine (ETR), nevirapine (NVP), and rilpivirine [48].

NRTIs and NNRTIs are both potent and durable antiretroviral classes, they can be differentiated by their potential adverse effects [49]. NRTIs can lead to lipodystrophy, peripheral neuropathy, and mitochondrial toxicity, whereas NNRTIs can lead to rash and hepatotoxicity with nevirapine and mood disturbances and central nervous system disorders with efavirenz [49]. Despite these potential adverse effects, NRTIs and NNRTIs are still considered generally less toxic than protease inhibitors [50].

Protease inhibitors differ from NNRTIs and NRTIs in that their target is not the reverse transcriptase enzyme, but rather the viral protease enzyme [51]. This enzyme is necessary to cleave the polypeptide chains into individual, functional viral proteins [51]. Protease inhibitors prevent this cleavage by replacing a peptide linkage [--NH—CO--] in the polypeptide chain with a hydroxyethylene group [--$CH_2$--CH(OH)--] which cannot be cleaved by hydrolysis [43]. The first drug to be designed on this basis, and subsequently the first PI developed was saquinavir [52], which received FDA approval on December 6, 1995 [48]. After this, several PIs were developed containing the same hydroxyethylene scaffold as saquinavir (SQV), such as ritonavir (RTV), indinavir (IDV), nelfinavir (NFV), amprenavir (APV), lopinavir (LPV), atazanavir (ATV), fosamprenavir(FOS-APV), and darunavir (DRV), as well as

tipranavir (TPV) which contains a coumarin scaffold [43]. Presently there are ten FDA approved PIs on the US market.

While PIs are considered to be the most potent antiretroviral class [50], these medications come with high barriers to optimal adherence [49]. PIs are associated with the highest pill burdens of any antiretroviral class and have the most dietary restrictions than any antiretroviral class [50]. Furthermore, PIs can cause lipodystrophy and hyperlipidemia creating more barriers for some patients to attain optimal medication adherence [50].

Fusion inhibitors target host cell membranes to block viral entry [43]. The only FDA approved FI, enfuvirtide (T-20), is the only FDA approved polypeptide antiretroviral. T-20 works by engaging a coil-coil interaction with a part of the viral surface glycoprotein gp41 which is necessary for viral docking with the host cell. After this coil-coil interacting is engaged, fusion of the HIV virus with the host outer cell membrane is blocked. FIs were shown to inhibit viral replication, and thus be effective antiretrovirals, by Kilby and colleagues in 1998 [53]. Because T-20 is not available orally and must be injected twice daily, long-term use can be problematic and the medication is primarily used in salvage therapies [43].

Integrase inhibitors (IIs) target the viral enzyme integrase, which helps the virus integrate its genetic material into the host cell's DNA. Integrase inhibitors were proven to act as antiretroviral agents by Hazuda and colleagues in 2000 [54]. Craigie describes this process in four main steps. First the viral DNA is created by reverse transcriptase, at this point the DNA is linear and blunt ended. Then, two nucleotides are cleaved from each 3' end of the viral DNA (called 3'-processing).

Next, the newly freed hydroxyl groups at the 3' ends of the viral DNA attack a pair of phosphodiester bonds in the host DNA (called strand transfer). Finally, the viral DNA is successfully integrated into the host DNA [55]. The only FDA approved II on the US market presently, Raltegravir (RAL), targets the strand transfer function of the integrase enzyme [48].

While integrase inhibitors are relatively new antiretrovirals, they have been shown to be extremely effective at suppressing viral load quickly [56], and have even been shown to improve viral loads when switched to from a fusion inhibitor [57]. Despite these benefits, integrase inhibitors are associated several adverse events, including possible dizziness, headache, nausea, tiredness, trouble sleeping, and weakness [49]. These adverse events could provide barriers to patients attempting to achieve optimal adherence despite this antiretroviral class's potency and benefits.

Lastly, co-receptor inhibitors (CRIs) have been described as a potential sixth classification of antiretrovirals. In order for the HIV virus to dock with the host cell, the $CD4^+$ host surface glycoprotein must interact with the viral gp120 surface protein, and co-receptors are used to mediate this interaction. In macrophages, this co-receptor is called CCR5 and in T-lymphocytes, this co-receptor is called CXCR4. Both of these co-receptors interact with the viral co-receptor gp41 to mediate viral docking with the host cell. At the present time, there is only one FDA approved CRI: maraviroc (MVC), which targets CCR5 receptors in macrophages [43].

Despite the potency of these medications, one antiretroviral alone is usually not enough to overcome a virus that develops as quickly as HIV [58]. Because of

this, developers of antiretroviral therapies have followed the lead of tuberculosis therapies and combined different classes of antiretrovirals into single, fixed-dose combination (FDC) therapies [43]. Individual HIV therapies are combined with three goals in mind: first, achieving a lower toxicity in the drug regimen; second, preventing drug resistance development in the virus; and, third, to achieve the synergistic effects of certain antiretrovirals working together [43]. While some antiretrovirals are antagonists to each other and others are simply additive when working together, certain antiretroviral therapies achieve greater results than the individual sums of their parts, a response attributed to their synergistic effect [58]. When these drugs work together to create this synergistic effect in patients, they are often referred to as a highly active antiretroviral therapy (HAART) [58].

At the present time, seven FDCs have been approved for use by the FDA. Three of these FDCs combine two NRTIs: Combivir, approved in 1997, combines zidovudine and lamivudine; Epzicom, approved in 2004, combines abacavir and lamivudine; and Truvada approved in 2006, combines emtricitabine and tenofovir. One of these FDCs approved in 2000, Trizivir, combines three NRTIs: abacavir, zidovudine, and lamivudine. Two other FDCs combine two NRTIs with one NNRTIs, representing the first 1 pill/day HAART therapies to be FDA approved. These medications are Atripla (approved in 2006), which combines the NNRTI efavirenz with the NRTIs emtricitabine and tenofovir, and Complera (approved in 2011), which combines the NNRTI rilpivirine with the NRTIs emtricitabine and tenofovir. The last FDC, Kaletra (approved in 2000), represents a special kind of FDC: boosted PIs. When two PIs are used in concert together, their synergistic effects are much

stronger than the single molecules. Designers of HAART therapies combine one PI with a booster PI to enhance the effect of the first PI. This booster PI is usually ritonavir, and in the FDC Kaletra, this booster PI is combined with lopinavir [58].

*Combining Antiretrovirals*

Combining monotherapies to treat a single disease state is not a new concept in the fight against disease. Presently, the WHO recommends combining several malaria treatments into a single regimen to achieve the most effective treatment or malaria. When used correctly, this treatment has been shown to be 95% effective at curing malaria [38]. In addition to malaria, the WHO also recommends combining monotherapies for the treatment of tuberculosis. These tuberculosis treatments have been combined into 2-, 3-, and 4-drug FDCs, which the WHO currently recommends [59]. In a 1999 report, the WHO outlined their reasons for recommending FDC tuberculosis treatments over conventional monotherapies [59]. The WHO highlighted the fact that FDCs decrease the risk for selection of drug resistant strains to develop. Because interruption of treatment due to non-adherent episodes can lead to the development of a drug resistant strain, FDCs with reduced pill burdens are favored over monotherapies with higher pill burdens.

This same argument has been used to advocate for the use of combinations of antiretroviral medications to treat HIV infection [60]. When antiretroviral medications are used in concert with each other, an effect greater than that of the sum of the individual medications is observed [61]. This synergistic combination of antiretrovirals is referred to as a highly active antiretroviral therapy (HAART).

While HAART regimens may provide improved potency by targeting different steps of the viral life cycle, different tissues, or inhibiting antiretroviral resistance, these combinations also have the potential to increase pill burden and toxicity. Fixed-dose combinations (FDCs) overcome these problems by reducing the pill burden to as low as 1 pill/day in some cases, and by having a lower toxicity in some cases than individual non-coformulated agents [42].

Presently, there are only two 1 pill/day HAART therapies available in the US: Atripla and Complera [50]. Atripla was released in July of 2006 and consists of the double NRTI backbone of emtricitabine and tenofovir in combination with a NNRTI, efavirenz. The NRTI backbone of emtricitabine and tenofovir has been previously combined in it's own FDC with the trade name of Truvada. Complera, released in the US in August of 2011, uses this same NRTI backbone of emtricitabine and tenofovir but uses the NNRTI rilpivirine as its 3rd drug instead of efavirenz like Atripla [50].

*Antiretroviral Switching*

Despite the clinical improvements HAART therapies can provide to patients, the majority of patients will require changes to their regimen at some point in their therapy [62]. The reasons for HAART switching are multifactorial, including toxicity, potential drug-drug interactions, and failure of current therapy [62]. In 2010, Davidson and colleagues found that the main reason for switching HAART therapy is toxicity, with 61% of reported switching cases being a result of toxicity. 44% of these cases were from zidovudine, 9% were from tenofovir, 8% were from

stavudine, 8% were from efavirenz, 5% were from lopinavir/ritonavir, 4% were from saquinavir, 4% were from atazanavir, and 4% were from abacavir. The majority of these switchers were reported as having switched after at least 6 months (81%), with 13% of patients switching before 3 months duration due to 'acute toxicity'. Regimen failure was the second leading cause of switching, accounting for 14% of switches, followed by simplification of the regimen (13%), other causes (8%), and drug interactions (4%) [62].

The World Health Organization (WHO) defines treatment failure in three ways: clinical failure based on the presentation of a new or recurrent condition, immunological failure based on $CD4^+$ count, and virologic failure based on the plasma viral load. Of these three methods, virologic failure is considered more sensitive to treatment failure than immunological or clinical failure. Because of this, viral load testing is recommended by the WHO to confirm suspected cases of treatment failure. In these cases, a plasma viral load of less than 5000 copies/mL confirms treatment failure, and indicates the need to switch to second-line HAART (Figure 1) [32].

Because there is no cure for HIV, management of this disease state calls for chronic, lifelong use of a limited number of antiretroviral medications [63]. Since the majority of patients will not stay on their first HAART regimen [62], it is important for practitioners to maximize the duration of HAART therapies so that patients do not over utilize this limited number of antiretroviral options. Furthermore, given previously published evidence that successive HAART therapies have shorter durations than initial therapies [37] [36] [64], maximizing initial

duration of HAART therapies is an important goal for prescribers to HIV patients.[65]

*Prevention of Virologic Failure*

The long-term goal of HIV treatment and antiretroviral therapy is to "improve the length and quality of the patient's life" [66]. The best way to achieve this goal is by long-term viral replication suppression below detectable limits [67]. Viral load testing involves estimating the amount of virus present in a patient's bodily fluids and has been shown to be the most accurate biomarker of HIV load diagnostics [68]. Usually, once the viral load decreases below 20-200 copies/mL it is below the level of quantification and the patient's viral load is said to be undetectable [66]. Guidelines indicate that plasma viral load should decrease to undetectable limits within four to six months of successful antiretroviral treatment. The World Health Organization (WHO) has specified a viral load limit of 5,000 copies/mL to define virologic failure in patients. Once a patient has been confirmed as being in virologic failure, abandonment of the first line HAART in favor of a second-line salvage therapy is recommended [69]. Because the best way to achieve the goal of improving the length and quality of life of HIV patients' lives is by suppressing viral replication to undetectable limits and avoiding virologic failure, determinants of virologic failure must be explored to better understand how to delay this outcome of HAART treatment.

Several determinants of virologic failure have previously been identified in the literature. One such determinant is strength of the patient's immune system, as

measured by $CD4^+$ cell count. Low baseline $CD4^+$ cell count has been associated with virologic failure of treatment regimens in previous studies. In the Adult AIDS Clinical Trials Group, Hammer and colleagues evaluated the ability of a HAART regimen composed of zidovudine, lamivudine, and indinavir to maintain a viral load of less than 500 copies/mL in patients infected with HIV. Researchers reported 51% of patients maintaining viral suppression, but only 39% of patients with a baseline $CD4^+$ cell counts of less than 50 cells / $mm^3$ of blood reported achieving viral suppression compared with 58% of patients with a baseline $CD4^+$ cell count of 51 cells / $mm^3$ to 200 cells / $mm^3$ [70]. This finding highlights the importance of baseline $CD4^+$ cell counts in predicting virologic failure.

$CD4^+$ cell counts help determine virologic response to antiretroviral treatment because of several key factors. First, because HIV targets immune system cells, the ability of the immune system to recognize and suppress viral replication is extremely important in determining virologic response. Initiating antiretroviral therapy early in infection when $CD4^+$ cell counts are high and viral load is low may help maintain the immune response to viral infection [67]. Second, because HIV mutates so quickly, patients early in infection may present a less heterogeneous population of HIV than patients that have been infected for a longer duration [67]. A more heterogeneous population of HIV presents challenges because heterogeneity of viral populations has been associated with an increased risk of drug-resistant virus at baseline [71]. Lastly, some antiretrovirals such as zidovudine are better tolerated early in early stages of HIV progression when $CD4^+$ cell counts are still

relatively high, as compared to later stages. This can affect adherence to the antiretroviral regimen and can help determine treatment outcomes [67].

In addition to baseline $CD4^+$ count, early response to antiretroviral therapy, as measured by viral load decrease, has been shown to predict long-term response to treatment [67]. In the ACTG 320 trial [72], viral load at four weeks after initiation of antiretroviral therapy was the strongest independent predictor of virologic suppression at 24 and 40 week follow-ups. According to recommendations [32], patients should achieve at least a 0.5- to 0.75-log decline in viral load by the fourth to eighth week of antiretroviral therapy, and by weeks twelve to sixteen the patient should have an undetectable viral load. Failure to achieve an undetectable viral load by week 24 could signal early virologic failure and the possible need to switch therapy.

*The Problem of Non-Adherence*

Despite the importance of having a high baseline $CD4^+$ count and showing early viral suppression, adherence to the HAART regimen has been shown to be the strongest predictor of virologic failure [73]. When defined as the percentage of medication doses taken, a 95% adherence rate has been shown to be necessary to achieve an undetectable viral load in greater than 80% of treated patients [74] [75], and has been used as an adherence standard for treated patients [40]. Adherence plays such a large role in predicting virologic suppression because an inconsistent or low adherence rate could result in suboptimal drug concentrations, allowing for viral replication to proceed in the presence of the antiretroviral. This situation

could favor selection of drug resistant strains of HIV over those affected by the antiretroviral therapy, allowing for the theoretical development of a drug resistant strain of HIV in the patient and leading to virologic failure [67]. This idea has been successfully demonstrated in several studies [73] [76] [77]. Because non-adherence to antiretroviral therapy is the strongest predictor of virologic failure, and because prevention of this virologic failure is the best method for achieving the long-term goal of HIV treatment of "improv[ing] the length and quality of the patient's life" [66], understanding determinants of antiretroviral non-adherence is important to realizing the long-term goal of HIV care.

Determinants of adherence to HAART have been previously classified as patient characteristic determinants, medication regimen determinants, and clinic care determinants [40]. In terms of demographic and patient characteristic determinants, few demographic characteristics have been shown to be consistently predictive of increases or decreases in HAART adherence [40]. In terms of race and ethnicity, while blacks have been previously shown to have a lower adherence rate [78], the vast majority of studies have found no relation between adherence and race [40]. Furthermore, there has been no consistent association demonstrated between age and adherence to antiretroviral therapies. While some studies show older patients as having higher adherence rates, others show these patients to have a lower adherence rate, demonstrating the inconclusive evidence in regards to the affect of age on antiretroviral adherence [40]. One demographic factor that has been shown to predict adherence to antiretroviral therapy is health literacy [79]. Patients with a higher education level have been shown to be more adherent with

prescribed HAART regimens than those with lower education or limited literacy levels.

In addition to education level, several patient characteristics have been shown to be strong correlates of HAART adherence. Heavy alcohol use, active injection drug use, and depression have all been found to be consistent predictors of HAART non-adherence [40] [74] [80] [81]. While estimates of predictive strength of each of these predictors varies from study to study, depression has been found to be one of the strongest predictors of adherence to medical treatment for other illnesses, indicating the relative importance of this co-morbid condition on adherence to antiretroviral therapy [40] [82].

Beyond patient and demographic characteristics, several clinical care characteristics and characteristics of the patient-provider relationship have been shown to be strong predictors of HAART adherence [40]. First, provider experience with caring for individuals infected with HIV has been shown to be a strong predictor of antiretroviral adherence [83]. Researchers have hypothesized that this may be due to these practitioners working more actively to enhance their patients' adherence rates [40]. In addition to provider experience, strength of the patient-provider relationship, measured in terms of patient perceived trust, support, and caring, has also been shown to be a strong predictor of patient adherence to the prescribed HAART regimen [40] [84].

While sociodemographic, patient, and patient-provider relationship characteristics all include strong predictors of HAART adherence, characteristics of the medication regimen can also serve as consistently strong predictors of patient

adherence with prescribed HAART therapies [40]. One type of medication regimen characteristic that has been shown to affect HAART adherence is side effect profile [40]. Patients reporting greater than two side effects are less likely to properly adhere to their HAART regimen than other patients [40]. Furthermore, regimen complexity, defined by the number of doses taken per day, the number of pills per dose, the number of different medications taken, the presence of any food-dosing restrictions or requirements, and the presence of any special fluid-intake requirements, can consistently and strongly predict treatment adherence [85]. Researchers have speculated that this could be because complex medication regimens require patients to alter their eating and sleeping patterns and to change their daily routine, which may ultimately result in treatment fatigue and non-adherence [40] [84].

In order to overcome the barriers to adherence presented by regimen complexity, researchers have compared adherence in patients taking complex antiretroviral regimens to those taking simpler regimens and found adherence to be poorer in those taking more complex regimens [65]. Furthermore, additional research has shown that a greater percentage of patients achieved an undetectable viral load when taking fewer HAART regimen pills per day than those patients taking more regimen pills per day [86], demonstrating that a higher adherence rate is associated with a lower pill burden [40]. Given that optimal HAART regimen adherence is necessary to prevent viral resistance and virologic failure of the first and often most effective HAART regimen [37] [36], and that the suppression of virus replication is necessary to achieve the long-term goal for HIV care of "improv[ing]

the length and quality of the patient's life" [66], practitioners, researchers, and stakeholders would be wise to examine the effect of reduced pill burden on duration of first-line HAART therapies.

*Analysis of Time to Discontinuation of Initial HAART Regimens as a Result of Reduced Pill Burden*

Previous research into the effects of reduced pill burden on HAART regimen duration has been conducted. In 2008, Willig and colleagues analyzed a retrospective, unselected cohort of 542 HIV-infected patients beginning antiretroviral (ARV) therapy from January 2000 to July 2007 [42]. Researchers segmented the cohort into two groups: patients who began antiretroviral treatment between January 2000 and July 2004 and patients who began antiretroviral treatment between August 2004 and July 2007. Patients were split on a regimen start date of August 2004 because this is when the first once-daily fixed-dose NRTI (Epzicom) was released. Researchers hypothesized that the decreased pill burden and lower toxicity profiles associated with these two FDCs would lead to prolonged durability of initial HAART therapy in the cohort receiving this treatment.

In order to test this hypothesis, researchers developed several aims. Their first aim of comparing the pre and post time periods on patient and regimen characteristics, was achieved through chi-squared and t-tests. Researchers found that patients starting ARV after August 2004 were less likely to have alcohol and substance abuse disorders as well as higher baseline CD4 counts. Furthermore,

researchers highlighted a decreased rate of discontinuation within 90 days in the later group when compared to the earlier group (14% vs. 6%, $p<0.01$).

Their second objective was to analyze regimen duration based on regimen characteristics. To achieve this objective, researchers used three Kaplan-Meier (KM) survival analyses. Kaplan-Meier survival analysis has been described as "a set of statistical methods used to estimate . . . length of time between two clearly defined events." [87] Furthermore, survival analysis has been differentiated from other types of analyses that utilize dichotomous dependent variables in survival analysis's use of censored observations. This is important, as Ventre and Fine have previously noted, because, "though the event is not actually observed [in the censored patient's observation], the investigator knows that the time to event exceeded a given value (right censoring), such as the last date of contact. A good survival analysis method accounts for both censored and uncensored observations." [87] Based on these descriptions, survival analysis has been found to be appropriate for answering questions analyzing time-to-event with a cohort of patients who may or may not have experienced the event during the study timeframe. [88] The first compared regimen duration between the pre and post August 2004 ARV initiation time groups. This analysis found that regimens started in the pre-August 2004 group had median duration of 263 days fewer than the post group (780 days vs. 1043 days). The second KM analysis compared regimen duration between patients on 1 pill/day therapies to patients on twice or more daily therapies as well as patients on less than or equal to 3 pills per day, 4-5 pills per day, and greater than or equal to 6 pills per day. This analysis found that regimens with

less than or equal to three pills per day had the longest duration while regimens with greater than or equal to six pills per day had the shortest duration. Furthermore, 1 pill/day regimens had a 514 day longer median duration than twice or more daily (1253 days vs. 712 days). The third KM analysis compared regimen characteristics based on NRTI backbone of the HAART and the 3rd drug of the HAART. NRTI backbones were classified as containing didanosine (ddl)/stavudine (D4T), zidovudine (AZT), or abacavir (ABC)/tenofovir(TDF). Regimens with the NRTI backbone of ddl or D4T were found to have the shortest duration while regimens containing ABC or TDF were found to have the longest duration. 3rd HAART drugs were defined as being a NRTI, NNRTI, unboosted PI, or boosted PI, and NNRTIs were found to have the longest median duration (1132 days) whereas unboosted PIs were found to have the shortest (382 days).

Lastly, researchers aimed to evaluate factors that affect regimen longevity while adjusting for covariates. To achieve this objective, researchers developed a three stage multivariate Cox proportional hazard model. The first stage addressed the role of time period of initiation of ARV, and found that the pre-August 2004 group had a significantly higher hazard of discontinuation compared to the post group. The second stage addressed the role of regimen complexity. When these variables were added to the model, time period was no longer found to be significant. Furthermore, patients receiving therapies consisting of twice or more daily dosing had a significantly higher hazard of discontinuation than patients on 1 pill/day dosing regimens. The final stage addressed the role of regimen composition on regimen duration, and found that all 3rd drugs in the HAART other

than NNRTIs had a higher hazard of discontinuation when compared to NNRTIs. Furthermore, ddl and D4T were found to have higher hazards of discontinuation when compared to ABC/TDF. A diagnosis of a mental health disorder significantly increased discontinuation hazards in all three models.

While this study represented a large breakthrough in antiretroviral research as it was the first study to analyze the effects of once-daily FDCs on ARV duration, it was unable to analyze the effect of 1 pill/day HAART regimens because of its time of publication. Willig and colleagues' findings that simpler HAART regimens can provide greater duration of therapy than current FDCs seems to indicate the need for a study to investigate the effects of current 1 pill/day therapies on their time to discontinuation of HAART.

## III. Methods

*Research Design and Methodology*

In order to investigate the effects of 1 pill/day HAART therapies on the time to discontinuation of initial therapies, methods used in this study looked back in time through patient records retrospectively, but moved forward in time from initiation of therapy to discontinuation of therapy. This type of analysis requires a retrospective cohort methodology [89]. Discontinuation in this study was defined as switching any of the medications used in the initial therapy, or a complete discontinuation of treatment for any reason. This definition was established based on previous work analyzing similar research questions [42]. The cohort for this study came from patient data stored by the University of South Alabama's Women and Children Hospital's HIV Clinic and was defined by three inclusion criteria (Figure 2). First, because HAART treatment recommendations differ between adults and adolescents, only adults aged 19 years and older were considered eligible for this study [90] [31]. Furthermore, only patients initiating HAART at some point during the study period (from January 1, 2001 to December 31$^{st}$, 2011) were considered eligible for inclusion in this study. Lastly, because the study clinic sees predominately females and children, only female patients were included in the study sample. Once ineligible patients had been excluded from the dataset, patient and regimen characteristics were collected. Because the primary variable of interest (pill burden of the initial regimen) was an inclusion/exclusion criterion in itself, an analysis of differences between included and excluded patients was not

conducted in this project. Since patients on their initial regimen are inherently different in their disease progression and regimen characteristics from patients on their secondary or subsequent regimens, this analysis was not relevant as part of this study.

*Study Sample*

The sample for the present study were drawn from a cohort of HIV-infected patients at the University of South Alabama's Women and Childrens Hospital's HIV Clinic. This clinic, which treats predominantly HIV-infected single women and HIV-infected mothers with their children, is located in a large urban center in the Southeastern US. Patients at this clinic are predominately black and low-income. Most patients do not have insurance. Clinic providers estimate the clinic currently sees approximately 30 patients every other week and is currently treating an approximate total of 200 patients overall.

*Data Abstraction*

Chart review was conducted based on a preliminary master list of all patients over age 19 who were previously treated at the study clinic from January 1st, 2001 to December 31st, 2011. The study clinic's coordinator provided this list. These dates were chosen because they were the earliest and the latest dates for which the clinic coordinator could provide accurate information on patients being treated at the clinic. Initially, charts from this list were pulled from clinic archives, and each chart was reviewed to determine if that patient met the three study inclusion

criteria. If the patient was determined to meet these inclusion criteria, the patient was included in the study cohort and data were abstracted from the relevant sections of the chart using a previously approved data collection sheet, which can be found in Table 12. Data were abstracted from the study clinic's chart archive over a 5 month period from May to October 2012, in which a single researcher spent approximately 175 hours reviewing charts. Instructional Research Board (IRB) approval was obtained for study protocol from both Auburn University and the University of South Alabama before beginning data collection. A final dataset was created using SPSS 19, and further analyses were conducted using both SPSS 19 and R 2.14.0.

*Research Questions and Statistical Analyses*

In order to fully understand the effects of 1 pill/day HAART therapies on duration of initial therapies, several research questions were developed (Table 2). In order to answer the research question, "what are the demographic and HAART regimen characteristics of this sample, and how do these characteristics compare between groups of patients with pill burdens of 1 pill/day, 2-3 pills/day, and 4-5 pills/day, and 6 or more pills/day" (research question 1), a crosstab analysis was performed stratifying descriptive statistics across the four pill burden groups specified in this question. The results of this crosstab analysis can be found in Table 3. This table shows categorical study variables stratified across the four pill burden groups specified in research question 1. In order to determine how the frequency of patients in each category of the analyzed study variable compares between

subgroups of pill burdens, Fisher's exact test was used for each examined study variable where all cell counts were greater than zero. A significant p-value (where the p-value is less than 0.05) associated with this test implies that patients are unevenly distributed between categories of the study variable and subgroups of pill burdens.

Table 3 also shows continuous study variables stratified across the four subgroups of pill burdens. In order to determine if differences in the means for each study variable are significant across pill burden subgroups, a one-way ANOVA test was used. When significant differences were detected with ANOVA, a Bonferonni post-hoc analysis was conducted to better understand which groups of pill burden were significantly different. Bonferonni post-hoc analysis was chosen based on its use in previous literature [91] [92] [93], and its conservative estimate of significance providing researchers with confidence in the results of this analysis. A significance level of $p<0.05$ was used for both ANOVA tests and Bonferoni post-hoc tests.

In order to answer the question, "are there differences in the time to discontinuation between patients taking a 1 pill/day HAART vs. those who aren't" (research question 2), a Kaplan-Meier survival curve was drawn using the duration of the initial HAART therapy for those patients who were prescribed Atripla for their initial HAART regimen and those who were prescribed another drug regimen. Patients who were lost to follow up, moved, or transferred care were right censored for the purposes of this analysis, meaning their observations were included in the analysis even though these patients did not experience the discontinuation of their

initial therapy during the study timeframe. The survival curves drawn for patients starting HAART therapy on Atripla and for patients starting HAART therapy on a drug regimen other than Atripla were then compared using a log-rank test (Table 4) to test for statistically significant differences in the probability of a patient discontinuing either regimen.

In order to answer the question, "are there any differences in the time to discontinuation between patients utilizing initial HAART regimens with pill burdens of 1 pill/day, 2-3 pills/day, or 4-5 pills/day, and 6 or more pills/day" (research question 3), researchers plotted Kaplan-Meier curves for each of the pill burden subgroups to compare the time to discontinuation of the initial HAART therapy between pill burdens. Patients who were lost to follow up, moved, or transferred care were right censored for the purposes of this analysis. After the Kaplan-Meier survival curves had been drawn for each subgroup, the probability of discontinuing the initial regimen was compared between subgroups to determine if significant differences exist (Table 5).

In order to compare the differences in the time to discontinuation between patients utilizing an initial HAART regimen of Atripla versus patients utilizing an initial HAART regimen with Combivir as the NRTI backbone (research question 4), Kaplan Meier survival analysis is again used. Survival curves for patients initiating HAART using Atripla and for patients initiating HAART with a regimen using Combivir as its NRTI backbone were drawn to compare survival functions. These curves were then compared using the log-rank test to test for statistically significant

differences in the time to discontinuation of the initial regimen between these two subgroups (Table 6).

In order to address potential differences in the time to discontinuation of initial HAART therapy between patients initiating therapy in the pre-Atripla era (January 1, 2001 to June 30, 2006) and patients initiating therapy in the Atripla era (July 1, 2006 to December 31, 2011) (research question 5), Kaplan-Meier analysis was again used to compare the time to discontinuation between these two groups. Once survival curves were drawn for both the pre-Atripla era group and the Atripla era group, the times to discontinuation for each group were compared using the log-rank test (Table 7).

In order to address the research question, "how do patient and regimen characteristics influence hazards of discontinuation of HAART therapies" (research question 6), a Cox proportional hazards model was developed as recommended by Willig and colleagues [42] using the time-dependent covariates CD4 t-cell count and viral load, as well as the independent variables insurance status (yes/no), employment status (employed or in school/not employed or in school), relationship status (single, divorced, or widowed / married, with partner, or dating), smoking status (yes/no), number of children at the initiation of the first HAART, age at the initiation of the first HAART, pill burden used in the first HAART, and the number of co-morbid conditions reported (Table 8). R 2.14.0 was used for the development of this model [94], and the R library of procedures "survival" was used for this analysis [95]. Because a Cox proportional hazards model depends on the assumption of proportional hazards over time in each independent variable, the assumption of

proportional hazards was tested in each included independent variable as well as the two time dependent covariates by using log rank chi-square tests and their associated two-sided p-values (Table 9). Independent variables or time dependent covariates with statistically significant p-values ($p<0.05$) for these log rank tests were considered to be in violation of the proportional hazards assumption, and were dropped from the model. After these significant variables were dropped from the model, the assumption of proportional hazards was re-assessed in all remaining independent variables until all included variables had a non-significant log rank test, indicating the assumption of proportional hazards can be assumed for the developed proportional hazards model. The data format (time1, time2, event) was used for this analysis as recommended by Therneau and Crowson [96], where each patient observation is split based on the number of CD4 counts and viral load measurements. For a patient's first lab measurements, time 1 is 0 and time 2 is the day before the patient's second lab measurement. The patient's next observation uses her second lab measurement as time 1 and the day before the third lab measurement as time 2. This is done until the patient has their final lab measurement, where time 1 is the day of the final measurement, and time 2 is the day of discontinuation of the initial therapy. The structure of this data format can be found in Table 10. The final cox model developed for analysis (Table 11) was:

$h(t) = h0(t) + exp(\beta_1 * CD4\ count + \beta_2 * Log\text{-}10\ viral\ load + \beta_3 * Insurance\ status + \beta_4 * Relationship\ status + \beta_5 * Number\ of\ children + \beta_6 * Age\ at\ initiation\ of\ the\ initial\ HAART + \beta_7 * Pill\ burden\ of\ the\ initial\ HAART\ \beta_8 * Number\ of\ Co\text{-}Morbid\ Conditions + \beta_9 * Pregnancy\ status)$

In order to better understand the effect of the initial HAART therapy on patient characteristics, changes in the number of pills in the initial regimen versus the number of pills in the regimen the patient was switched to were analyzed. In order to analyze changes between baseline and discontinuation measurements for this variable, a paired samples t-test were used and its results are presented in Table 16.

*Research Questions*

Based on the previously stated objectives, the six research questions developed for this project were:

1. What are the demographic and HAART regimen characteristics of this sample, and how do these characteristics compare between groups of patients with pill burdens of 1 pill/day, 2-3 pills/day, 4-5 pills/day and 6 or More pills/day?
2. Are there differences in the probability of discontinuation between patients taking a 1 pill/day HAART vs. those that aren't?
3. Are there any differences in the probability of discontinuation between patients utilizing initial HAART regimens with pill burdens of 1 pill/day, 2-3 pills/day, or 4+ pills/day?

4. Are there differenes in probability of discontinuation between patients utilizing Atripla and Combivir?
5. Are there differenes in probability of discontinuation between patients initiating therapy before 7/1/01 and after this date?
6. How do patient and regimen characteristics influence hazards of discontinuation of HAART therapies?

*Variables Collected*

A copy of the data collection sheet used to gather information from included charts can be found in Table 12. Overall, 21 variables were collected from each included chart, including CD4 cell counts and viral load measurements each time these were collected during the patient's initial HAART therapy. Of these variables, type of insurance, HIV acquisition method, and race were collected from the clinic's computerized database for each included patient. Patient insurance type was dichotomized to reflect if a patient had some type of insurance (public or private), or had no insurance. The Alabama AIDS Drug Assistance Program (ADAP), Alabama's primary drug assistance program for HIV patients [97], covered medications for patients without insurance in this cohort. ADAP is a government-funded program designed in part to provide medications for patients with HIV/AIDS in the state of Alabama who do not have insurance. ADAP lists its purpose as,

"…to provide caring, high quality, and professional services for the improvement and protection of the public's health through disease prevention and

the assurance of public services to resident and transient populations of the state regardless of social circumstances or the ability to pay."[97]

Employment status, marital status, smoking status, and the number of children the patient had at the initiation of the initial HAART were determined from both social worker notes and from metabolic screening questionnaires administered by the clinic and kept in each patient's chart. Patient date of birth (month and year) was collected from the clinic's computerized database and was used to calculate the patient's age at the initiation of the initial HAART regimen. Drugs used in the initial HAART, pill burden, and use of a protease inhibitor (PI)-sparing regimen in the initial HAART were determined based on provider notes in the patient's chart describing the initial regimen. Patient pregnancy status during the initial HAART regimen was determined from provider notes and was included among the study variables.

Information concerning variables describing the patient's status at the time of discontinuation of the initial regimen was collected from provider notes in the patient's chart on the day in which the patient either reported discontinuing the regimen herself, or was switched to a different regimen by the provider. In the cases of patients lost to follow-up, the last measurements before the patients were lost were used. In addition to these variables, the drugs used in the HAART regimen the patient was switched to were recorded if the patient regimen was switched, as were the pill burden of this regimen and the use of a PI-sparing regimen. The reason for discontinuation of the initial HAART regimen, if provided, was also recorded.

Two utilization variables were captured from patient charts: the number of emergency room visits by the patient during the initial HAART regimen, and the number of hospitalizations during the initial HAART regimen. These variables were collected by the providers during patient appointments at the clinic, and were self-reported by the patients. When available, these variables were collected for both the six months before the initial HAART regimen was initiated, and the six months after the regimen was initiated, in addition to during the initial regimen.

The number of medication adherence meetings with clinic pharmacists each patient attended both during the initial HAART therapy, and in the six months before and after were included among study variables as well. While the link between the number of these meetings each patient had with clinic pharmacists and patient adherence is uncertain, these measures were collected as a general measure of the involvement of the clinic's pharmacy with that patient. In addition to these variables, any co-morbid conditions reported by the patient or provider were also collected from the charts, as were any report of substance abuse or domestic violence. Lastly, all CD4 t-cell counts and viral load lab measurements during the patient's initial HAART regimen were collected from patient charts to reflect the relative strength of the patient's immune system, as well as her level of viral suppression throughout the course of initial treatment.

*Adherence Issues as the Reason for Discontinuation of the Initial Regimen*

When the reason for discontinuation of the initial regimen was reported as adherence issues, the determination of non-adherence in the patient was made

using two sources: patient self-reported non-adherence and provider-deduced non-adherence. Patients sometimes self-reported non-adherence with the prescribed regimen to their provider, who subsequently noted this non-adherence in the patient's chart. These notes could be taken by the medical staff (physician, medical assistant, or nurse), by the pharmacy staff in medication adherence meetings held with the patient, or by the social worker. Also, any of these providers could determine non-adherence from patient encounters based on what the patient said concerning her adherence with the prescribed regimen. In addition to this, some prescribers deduced non-adherence from increasing viral loads and decreasing CD4 t-cell counts in addition to the patient not demonstrating any viral resistance to therapy. Furthermore, non-adherence could be determined by the pharmacy staff during medication adherence meetings, in which patients are asked to describe how many doses they have missed in the last week and month. For the purposes of this study, a decision by providers to discontinue the initial therapy due to patient non-adherence through any of these means was considered to be a discontinuation due to adherence issues.

While capturing provider input on patient non-adherence helps to clarify patient non-adherence during the regimen, several problems exist with using only patient self-report and provider-based decisions of non-adherence because both methods introduce a risk of bias into the results of analyses. A patient self-reporting her adherence to a regimen may exhibit social desirability bias, in which she wants to appear favorably adherent to clinic providers thereby overestimating her adherence in retrospect. Furthermore, patients wanting to switch therapies to a

lower pill burden or decreased side-effect profile may want to appear non-adherent to clinic providers and may overestimate their non-adherence in retrospect. Both of these inaccurate estimations can introduce a risk of bias into results of analyses utilizing this data, making interpretation of results problematic. Furthermore, utilizing provider-deduced decisions about non-adherence can introduce a further risk of bias.

Some providers may have different thresholds for what they consider to be non-adherence based on patient recall at medication adherence meetings or based on viral load and CD4 t-cell measurements. This introduced variability acts as an extraneous variable and can mask the true results of an analysis, introducing a risk of bias and making interpretation of results using this data difficult. Overall, collecting non-adherence information subjectively through the use of patient recall and self-report, as well as provider-based decisions, instead of collecting this information with an objective measure, introduces a risk of bias to this data and these results. In spite of this risk of bias, the inclusion of provider-based decisions in the non-adherence classification gives researchers a better understanding of the problem of non-adherence in this sample than simply using patient-self report and recall.

*Sample Size and Power Analysis*

*A priori* power analysis was conducted to determine the minimum sample size required for the 1x4 ANOVA described in research question one. According to Cohen A[31], effect size, or the degree to which the null hypothesis is false, must be

estimated in order to calculate sample size. Effect size in ANOVA is calculated by dividing the standard deviation of the population by the within-group standard deviation of the population. Based on this formula, Cohen states that a Cohen's d effect size of d=0.10 can be considered small, d=0.25 can be considered medium, and d=0.40 can be considered large. Furthermore, researchers must consider the probability of rejecting the null hypothesis, when the null hypothesis is true. This probability is called the alpha level, and it must be pre-determined in order to estimate the necessary sample size. Because previous researchers [42] have used a 0.05 alpha level, the same alpha level was used for this analysis. Furthermore, the likelihood that this study will detect a true effect if it actually exists must be considered. This likelihood is called the power of the study, and Cohen recommends a target of 0.8. With an alpha level of 0.05, a target power of 0.8, and assuming a medium effect size (0.25), a sample size of 45 will be required to achieve the target power. If a smaller effect size is assumed (d=0.10), a sample of 274 will be required, whereas if a larger effect size is assumed (d=0.4), a sample of 18 will be required. Using a conservative approach, a total sample size of 274 was determined to be sufficient to adequately power the ANOVA analyses included in this project.

## IV. Results

*Included Patients and Overall Sample Size*

The clinic coordinator at the University of South Alabama's Women and Childrens' Specialty Clinic provided a listing of all adult female patients who were enrolled in the clinic from January 1st, 2001 to December 31st, 2011, comprising the initial pool of patients to review for inclusion in the study. The determination to include potential patients in the study was made using three inclusion criteria: each patient must have been female, each patient must have been older than 19 years of age at the initiation of her initial HAART regimen, and each patient must have started her initial HAART regimen at the University of South Alabama's Family Specialty Clinic.

The number of charts reviewed for each year included in the study (2001-2011), as well as the number of charts included in the study per year can be found in the inclusion chart provided in Table 13. Overall, 498 charts were reviewed for inclusion in the study and 115 charts were found to match all of the inclusion criteria, warranting inclusion in the study. 383 charts were found to not meet at least one of the inclusion criteria and were excluded, comprising 72.9% of the original 498 reviewed charts. Of these 383 excluded charts, 374 (97.7%) were excluded because the patient did not start her initial HAART at the Women and Children's' Specialty Clinic. 9 of these 383 excluded charts (2.3%) were excluded because the patient was under the age of 19 when she initiated her initial HAART at the Clinic.

*Missing Data*

Overall, missing data for included study variables was not found to be a problem. 51 patients overall were impacted by missing data, 70.0% of collected study variables had no missing values, and only five study variables had more than 5% of missing values. These five variables were the number of medication adherence meetings six months after discontinuation of initial HAART, number of ER visits six months before initiation of initial HAART, number of ER visits six months after discontinuing initial HAART, number of hospitalizations six months before initiating initial HAART, number of hospitalizations six months after discontinuing initial HAART. These five variables were only used in answering research questions 1 and 6, meaning research questions 2 through 5 were not affected by any missing data. The high level of missing data associated with these five variables was determined to not be problematic because of the nature of these variables. It is natural to assume that patients who start their initial HAART therapy at the Clinic will not have many opportunities to record emergency room visits and hospitalizations six months before starting HAART therapy as many of these patients were not being seen at the Clinic in the six months prior to starting their initial HAART therapy. Similarly, the 40 patients who were lost to follow up, transferred care, or moved during their initial therapy will not have any data for the number of hospitalizations or emergency room visits in the six months after discontinuing therapy. Because of this, these variables are expected to have higher amounts of missing data than other study variables. A summary of the number of missing values for each study variable, as well as the percentage of the total study

sample size these missing values comprise can be found in the missing values table found in Table 14.

*Descriptive Statistics*

A means table showing the number of included patients in each study variable as well as the mean value, standard deviation, minimum, and maximum value for each study variable can be found in Table 15. Overall, 87.0% of the study sample patients were black, 100% were female, 54.2% were employed, and 69.0% were described as smokers. 100% of the sample reported acquiring HIV through heterosexual sexual contact, and 42.5% reported being single. 36.5% of patients had no form of health insurance and had their medications covered by ADAP, while 64.5% of patients reported having insurance.

At the initiation of the initial HAART regimen, the average patient in this study was a black female, employed, single, a non-smoker, aged 26.6 years (SD=±5.9) with 1.8 children (SD=±1.5), and had insurance. The average patient acquired HIV through heterosexual sexual transmission, and she initiated her initial HAART regimen with a CD4 t-cell count of 449.33 cells/mL (SD=±235.0), representing a relatively strong immune system. Her initial HAART regimen had a daily pill burden of 4.5 pills per day (SD=±1.8), placing her in the 4-5 pills/day pill burden category. The average patient's regimen was protease inhibitor sparing, and was initiated after the release of Atripla. During her initial HAART, she reported an average of 1.1 co-morbid conditions of any kind (SD=±1.1). She had a mean 0.03 emergency room visits in the six months before initiating her initial HAART

(SD=±0.18), 0.15 visits during her initial HAART (SD=±0.38), and 0.01 visits in the six months after discontinuing her initial HAART (SD=±0.1). She had been hospitalized a mean 0.05 times in the six months before starting her initial HAART regimen (SD=±0.21), 0.56 times during her initial regimen (SD=±0.64), and 0.03 times in the six months after discontinuing her initial regimen (SD=±0.17). The average patient discontinued her initial regimen because of adherence issues, and was switched to a regimen with a daily pill burden of 4.1 pills per day (SD=±1.8).

Reasons for patients discontinuing the initial regimen are compared in the pie graph found in Figure 3. Adherence issues, adverse effects, and loss to follow up appear to be the most common reasons for discontinuation of the initial regimen in this cohort. The combinations of antiretroviral drugs used in the initial HAART regimen are also compared using a pie graph which can be found in Figure 4. Of these combinations, Combivir plus Kaletra (6 pills/day) and Combivir plus Viramune (4 pills/day) make up over half of the regimens prescribed to patients for their initial HAART regimen in this study. Total pill burdens for the initial HAART regimen, and their respective categories (1 pill/day, 2-3 pills/day, 4-5 pills/day, and 6 or more pills/day), were also compared using pie graphs, and can be found in Figure 5 and 6 Of these pill burdens and categories, it appears a pill burden of 6, and an associated category of 6 or more pills/day, comprised the majority of the initial HAART regimens prescribed in this study cohort.

*Analysis of Pill Burden Change Over Initial and Secondary Therapies*

Results of the paired samples t-test comparing the mean pill burden of patients' initial and subsequent regimens are presented in Table 16. While there was a decrease in the mean pill burden from the initial regimen to the secondary regimen of 0.36 pills/day, this difference was found to be statistically non-significant (t=0.848, df=43, p=0.401). This analysis had an n=44 because only 44 patients in this cohort switched their regimens after discontinuing the initial regimen, while the remaining 71 did not switch to a different regimen, generally because of loss to follow up, patient move, transfer of care, or discontinuation after delivery of a child.

*Analysis of Pill Burden in Initial HAART Regimen and the Regimen Patient Switched to After the Initial Regimen*

The number of patients in each category of pill burden (1 pill/day, 2-3 pills/day, 4-5 pills/day, 6+ pills/day) was determined for both the initial HAART regimen, and the regimen the patient switched to after discontinuing the initial regimen. The matrix in Table 17 shows the number and percentage of patients in each pill burden category, stratified by which pill burden category the patient switched to after discontinuing the initial regimen. Because several of the cells in this matrix have n=0, a chi-square analysis could not be performed to describe potential differences in the distribution of patients in this matrix, and results are described descriptively. In spite of this, the matrix in Table 17 appears to demonstrate an apparent prescribing trend. In each row of initial pill burden

category except 6 or more pills/day, patients tended to be switched to the next highest category of pill burden. For example, patients in the 2-3 pills/day category were most commonly switched to the 4-5 pills/day pill burden category (57.1%), whereas patients in the 4-5 pills/day pill burden category were most commonly switched to the 6 or more pills/day pill burden category (63.6%). Patients in the highest pill burden category appear to be somewhat evenly distributed across the pill burden categories they were switched to. Overall, while this matrix shows that some patients on high pill burdens are switched to lower pill burdens for their secondary regimens, patients are most commonly switched to a regimen of a higher pill burden category once they discontinue their initial regimen, if they switch regimens at all.

*Analysis of Types of Drugs Used in the Initial HAART Regimen*

The category of the combination of antiretroviral medications used in the initial HAART was compared on the time to discontinuation of the initial therapy using a Kaplan-Meier survival analysis. Results of this analysis are shown in Table 18. Survival curves were plotted for the four categories of combinations used in the initial HAART regimens of all patients in this study (NRTI only, NRTI/NNRTI, NRTI/PI, and NRTI/PI/PI). The difference in the time to discontinuation between these four categories was then compared using the log rank test, and a statistically significant difference between these four groups was detected (log-rank=19.98, df=3, $p<0.001$). In order to determine in which group this difference exists, the time to discontinuation for the NRTI category was compared to all other categories using

log rank tests. A statistically significant difference was found only between the NRTI category and the NRTI/NNRTI category (log-rank=10.23, df=1, p=0.001), not between the NRTI category and the NRTI/PI or NRTI/PI/PI category.

*Analysis of Patients who Discontinued Therapy Due to Adherence Issues*

A subgroup analysis was conducted examining those patients whose chart notes indicated the patient discontinued the initial regimen because of potential adherence challenges with the initial regimen. Patients who discontinued their initial regimen due to adherence issues were subdivided between the four pill burden subgroups (1 pill/day, 2-3 pills/day, 4-5 pills/day, 6+ pills/day), and the time to discontinuation of this regimen was compared between each of these pill burden subgroups was compared using the log-rank test. Overall, 34 patients discontinued their initial regimen because of provider suspected or patient self-reported adherence issues. Two patients utilizing a 1 pill/day therapy discontinued because of adherence issues, three patients utilizing a 2-3 pills/day regimen discontinued because of this, ten patients utilizing a 4-5 pills/day regimen discontinued because of this, and 19 patients utilizing a 6+ pills/day regimen discontinued because of this. The time to discontinuation was not found to be statistically significantly different between these four pill groups in patients who discontinued because of adherence issues (log-rank=3.635, df=1, p=0.057). Results of this analysis can be found in Table 19.

*Research Question 1*

Overall, an uneven distribution across pill burden subgroups was detected by chi-square analysis in one study variable: relationship status. All other categorical study variables were found to have non-significant chi-squared values, indicating equal distribution among pill burden subgroups can be assumed. Statistically significant differences between the means of two continuous study variables were detected between pill burden subgroups. Mean age at initiation of HAART, and mean hospital stays during the initial HAART were all found to be statistically significantly different across the four subgroups of pill burdens. All other continuous study variables were found to have non-significant F-ratios, indicating that no statistically significant differences existed in the proportion of patients in each pill burden subgroup for these variables.

*Research Question 2*

Results from the survival analysis performed to answer research question 2 indicated a statistically significant difference in the time to discontinuation of the initial HAART regimen between patients initiating therapy with Atripla and patients utilizing any other initial regimen (log-rank=8.948, df=1, p=0.003). The mean duration of therapy for patients initiating HAART with Atripla was 1574.97 days, with a standard error of 214.56 days corresponding to a 95% confidence interval of 114.43 days to 1995.52 days. The mean duration of therapy for patients starting any other HAART besides Atripla was 977.48 days, with a standard error of 149.78

days corresponding to a 95% confidence interval of 683.92 days to 1271.05 days. Overall, 16 patients in the study initiated their initial HAART using Atripla, and 99 patients initiated their therapy with a regimen other than Atripla. 5 patients utilizing Atripla discontinued therapy during the study time points, and 11 patients were right censored. 70 patients utilizing a HAART other than Atripla discontinued therapy during the study time points, and 29 patients were right censored. Overall, 75 patients discontinued therapy during the study time points, and 40 patients were right censored. Results from this analysis can be found in Table 4 and Figure 7.

*Research Question 3*

Overall, 16 patients started therapy with a HAART regimen with a 1 pill/day pill burden, 9 patients started with a 2-3 pills/day pill burden, 36 started with a 4-5 pills/day pill burden, and 54 started with a 6 or more pills/day pill burden. 5 patients in the 1 pill/day category were right censored, 7 in the 2-3 pills/day category,, 23 in the 4-5 pills/day category, and 40 in the 6 or more pills/day category. The mean duration of therapy for patients in the 1 pill/day category was 1574.97 days, with a standard error of 214.56 days corresponding to a 95% confidence interval of 1154.43 days to 1999.52 days. The mean duration of therapy for patients in the 2-3 pills/day category was 635.08 days, with a standard error of 315.94 days corresponding to a 95% confidence interval of 15.84 days to 1254.32 days. Patients in the 4-5 pills/day category had a mean duration of 1370.63 days and a standard error of 289.22 days corresponding to a 95% confidence interval of 803.76 days to 1937.51 days. Patients in the 6 or more pills/day category had a

mean duration of 651.58 days and a standard error of 100.86 days corresponding to a 95% confidence interval of 453.90 days to 849.26 days. A statistically significant difference in the time to discontinuation was detected between these groups (log-rank=16.703, df=3, p=0.001) indicating that differences in the time to discontinuation of the initial HAART regimen between pill burden groups is not due to chance.

In order to determine where this significant difference in the time to discontinuation lies, the 1 pill/day subgroup was analyzed head-to-head against the other three pill burden subgroups using the same Kaplan-Meier survival analysis techniques. A significant difference was detected in the time to discontinuation of therapy between the 1 pill/day group versus the 2-3 pills/day group (log-rank=4.797, df=1, p=0.029), between the 1 pill/day group and the 4-5 pills/day group (log-rank=4.334, df=1, p=0.037), and between the 1 pill/day group and the 6+ pills/day group (log-rank=11.461, df=1, p=0.001). These significant differences indicate that the 1 pill/day group has a significantly higher time to discontinuation than the other three groups. Results of these analyses can be found in Table 15 and in the Kaplan-Meier curves in Table 5 Figures 8a-8d.

*Research Question 4*

Overall, 16 patients initiated HAART using Atripla in this study, 5 of which discontinued during study time points leaving 11 observations as right censored. 88 patients utilized Combivir as the NRTI backbone of their initial HAART therapy, 66 of whom discontinued this therapy during study time points leaving 27 patients to

be right censored in this group. The mean duration of therapy for the Atripla group was 1574.97 days with a standard error of 214.56 days corresponding to a 95% confidence interval of 1154.43 days to 1995.52 days. The mean duration of therapy for the Combivir group was 1020.29 days with a standard error of 170.91 days corresponding to a 95% confidence interval of 685.31 days to 1355.27 days. A statistically significant difference in the time to discontinuation between these two regimens was detected by the log-rank test (log-rank=8.564, df=1, p=0.003), indicating the Atripla group was associated with a higher time to discontinuation than the Combivir group. Results of this analysis can be found in Table 6 and Figure 9.

*Research Question 5*

Overall, 51 patients initiated their initial HAART therapy in the pre-Atripla era, 35 of whom discontinued during study time points, leaving 16 patients in this group right censored for this analysis. 64 patients initiated their initial HAART in the Atripla era; 40 of these discontinued during study time points leaving 24 patients in this group right censored for this analysis. The mean duration of therapy for the pre-Atripla era group was 1247.04 days, with a standard error of 223.11 days corresponding to a 95% confidence interval of 809.75 days to 1684.32 days. The mean duration for the Atripla era group was 864.462 days, with a standard error of 111.27 days corresponding to a 95% confidence interval of 646.37 days to 1082.55 days. No statistically significant difference was detected in the time to discontinuation of the initial HAART regimen between these groups (log-

rank=0.719, df=1, p=0.396), indicating the time to discontinuation of therapy was similar in the pre-Atripla era and the Atripla era. Results from this analysis can be found in Table 7 and Figure 10.

*Research Question 6*

Overall, 11 variables were included in the initial Cox proportional hazards model developed to assess the assumption of proportional hazards in these independent variables. These variables can be found in Table 8. In the first test of the proportional hazards assumption (Table 9), only smoking status was found to be in violation of this assumption (log-rank=5.7891, p=0.0161). This variable was dropped from the model, and the remaining 10 variables were assessed for their adherence to this assumption. Upon reassessment, employment status was found to violate the assumption of proportional hazards (chi-square=4.4149, p=0.0356), and was dropped from the model. The remaining 9 variables were reassessed on their adherence to the assumption of proportional hazards, and all variables were found to follow this assumption upon this analysis, allowing researchers to conclude the developed model meets the assumption of proportional hazards. The final global chi-square test showed the combination of all 9 of these variables to meet this assumption (chi-square=10.299, p=0.3268). Results of these three analyses can be found in Table 19. Because there was no missing data in any of the included variables, missing data were not seen to be a problem in model development.

The significant model:

*h(t) = h0(t) + exp (0.001*CD4 count + 0.362*Log-10 viral load + 0.499*Insurance status + -0.076*Relationship status + 0.078*Number of children + 0.012*Age at initiation of the initial HAART + 0.207*Pill burden of the initial HAART + -0.189*Number of Co-Morbid Conditions Reported + 0.821*Pregnancy status)*

The model was developed using these 9 variables and two time dependent covariates (likelihood ratio=28.1, df=9, p<0.001). Two of the 9 variables were found to be significant in this analysis, including the base-10 logarithm of viral load (hazard ratio (HR)=1.437±0.123), and pill burden in initial regimen (HR=1.230±0.082). The time dependent covariate CD4 count, as well as the remaining six independent variables were all found to have non-significant Z-scores, indicating that while the combination of these variables significantly contributes to the variance associated with the probability of discontinuing the initial regimen, none of these remaining ten independent variables independently contributed to a significant portion of this variance. A table showing the beta values and their standard errors, exp(beta) values and their associated 95% confidence intervals, as well as Z-scores and p-values for all 12 of the included variables can be found in Table 11. A plot of the survival curve showing the time to discontinuation of the initial HAART regimen as a function of duration of therapy for the entire sample can be found in Figure 11.

## V. Discussion

*Missing Data*

While several variables were missing more than five percent of their data, missing data were not seen to be a large issue in this study. Of the 30 variables used in this study and listed in Table 14, nine had any missing data, indicating 70.0% of variables collected had no missing data. Researchers attributed this low level of missing data in the majority of study variables to three factors. First, due to the rigor of the maintenance of the clinic's computerized database, researchers were able to collect study variables stored in this database with no missing data. Second, due to the rigor and thoroughness the clinic providers in the chart notes they took during patient encounters, researchers were able to abstract variables not specifically collected at each clinic visit from these notes. Variables such as marital status are not collected through any forms or surveys given to the clinic patients, but because clinic providers are diligent in their collection and recording of patient social history during patient encounters, these variables were available from provider notes. Lastly, because of the clinic coordinator's rigor in maintaining a complete and easily accessible archive of paper charts, there were no challenges with incomplete or missing charts.

Of the nine variables with missing data, five variables had more than five percent of their data missing, representing 16.7% of the included variables. These variables were the number of medication adherence meetings six months after discontinuing the initial HAART regimen, the number of emergency room visits in

the six months before the start of the initial HAART and in the six months after discontinuing, and the number of emergency room visits in the six months before the start of the initial HAART and six months after discontinuing.

Missing data in these variables was not seen as problematic because missing data in these variables was a reflection of the nature of these variables. Many patients included in the study sample were prescribed their first HAART regimen on one of their first visits to the study clinic. This narrowed the six-month window of data collection for the number of emergency room visits and hospitalizations researchers established. If a patient began her first HAART regimen on her first clinic visit, she would not have any information in her chart for the number of hospitalizations or emergency room visits in the six months before she began her first HAART. Subsequently, if a patient was lost to follow up because she transferred care or moved, she would not have any information in her chart to collect on the number of hospitalizations or emergency room visits in the six months after she discontinued her first HAART regimen. The high level of missing data in these variables was attributed to the high number of patients who either started their initial HAART regimen on their first visit to the clinic, or who were lost to follow up and had no data during the six months after discontinuing the initial HAART regimen. Because of this, researchers determined that replacing missing values for these variables would introduce a risk of bias, and analyzed these data as is. Despite the levels of missing data in these five variables, researchers viewed the results of Table 14 as a reflection of the nature of the study sample, and felt all included variables should be used in study analyses.

*Descriptive Statistics*

Overall, the average patient described in the results section of this project is similar to the majority of patients included in the study sample, which is reflected by the relatively narrow standard deviations seen in Table 15. A large majority of patients included in the study sample were black (87.0%) and non-smokers (69.0%). Employment status and marital status had more variability than these variables, with only 54.2% of patients employed or in school, and only 47.5% of patients being single. Furthermore, high variability associated with patient insurance type means that while 50% of patients utilized public insurance for their insurance, 37% of included patients had no insurance at all. While the average patient had a daily pill regimen of 4.43 pills per day in her initial regimen and 4.07 pills per day in her subsequent regimen, 47.0% of included patients were categorized as being in the six or more pills per day pill burden category, clouding the inferences that can be made from the average patient to the study sample.

Despite these contradictions between the average patient and the distribution of patients across independent variable categories, the means shown in Table 15 demonstrate the underserved nature of this study population. Lack of insurance, employment, and social support can create barriers to patient access to and utilization of healthcare services such as those offered at the study clinic. Because this study aims to analyze the effect of daily pill burden on the time to discontinuation of therapy, reviewers and readers are urged to consider the consequences of these findings. While this study was not designed to explore the causative effects of these findings on the time to discontinuation, the underserved

nature of this population certainly contributes to the findings presented in this study. The time to discontinuation of therapy cannot be considered independently of these findings, and the nature of this sample should be considered when drawing conclusions from the results presented here.

*Analysis of Pill Burden in Initial HAART Regimen and the Regimen Patient Switched to After the Initial Regimen*

When the mean pill burden of the initial prescribed HAART regimen was compared to the mean pill burden of the subsequent HAART regimen, no statistically significant differences were detected. This means that on average, patients were switched to a regimen with a similar number of pills per day compared to their first regimen. This finding speaks not only to prescribing patterns at the study clinic, but also to the difficulties encountered by patients with adherence issues. Because the most frequent reason for discontinuation of the initial therapy was adherence issues, a lower pill burden in the subsequent therapy was expected. Researchers hypothesized that patients struggling with adherence would be switched to a therapy with a lower pill burden, and since many patients discontinue therapy because of adherence issues, this lowering of the pill burden would be detected, but this does not appear to be the case. Researchers speculate that this could be because lowering of pill burdens experienced by patients who started therapy with a high pill burden could be offset by increases in pill burdens utilized by patients who discontinued initial therapies with low pill burdens. If a patient is started on Atripla with 1 pill/day, she has to be switched to a therapy with

a higher pill burden when she discontinues this initial regimen. This increase could potentially offset a pill burden decrease experienced by the 47.0% of patients on a 6 or more pills per day regimen. Because this study did not explore causative effects relating to this change in pill burden, these hypotheses are speculative; the underlying cause of this lack of difference remains unclear.

As previously stated, the small number of patients comprising the study sample lead to the t-test conducted in this analysis being underpowered. The a priori power analysis described in the methods section of this report called for at least 274 patients to be included in these analyses in order for the parametric tests to be adequately powered. Having only including 115 patients can lead to an increased risk of committing an error in judgment, and can mask differences that may exist. Reviewers and readers are urged to interpret these results with caution, understanding that a lack of adequate power can lead to a risk of bias in results.

*Pill Burden Categories Before and After Switching Regimens*

The matrix in Table 17 appears to demonstrate an apparent prescribing trend. In each row of initial pill burden category except 6 or more pills/day, patients tended to be switched to the next highest category of pill burden. For example, patients in the 2-3 pills/day category were most commonly switched to the 4-5 pills/day pill burden category (57.1%), whereas patients in the 4-5 pills/day pill burden category were most commonly switched to the 6 or more pills/day pill burden category (63.6%). Patients in the highest pill burden category appear to be somewhat evenly distributed across the pill burden categories they were switched

to. Overall, while this matrix shows that some patients on high pill burdens are switched to lower pill burdens for their secondary regimens, patients are most commonly switched to a regimen of a higher pill burden category once they discontinue their initial regimen, if they switch regimens at all.

*Types of Drugs Used in the Initial HAART*

Table 18 and Figure 8a shows each of the four types of HAART combinations used in the initial regimens prescribed to patients in the study sample, and the results of the log-rank test used to compare the times to discontinuation between the groups. The statistically significant difference detected in this log-rank test demonstrates that at least one of these categories has a significantly different time to discontinuation than the other categories. Exploration of where this difference lies is difficult because of the increased risk of making a type I or type II error by oversampling. In order to explore this statistically significant difference while attempting to limit the number of tests conducted to minimize the risk of making a judgment error, the NRTI-only category was selected as the reference category since this category had the lowest estimated mean duration of therapy, and this category was directly compared to the other three categories on duration of regimen using log-rank tests. Only the log-rank test comparing the NRTI-only category to the NRTI/NNRTI category was statistically significant, indicating that while NRTI-only regimens appear to have a significantly shorter time to discontinuation associated with them than NRTI/NNRTI regimens, the time to discontinuation of an NRTI-only regimen is similar to that of a non-protease inhibitor-sparing regimen.

Despite the fact that log rank tests used in Kaplan-Meier survival analysis are non-parametric and do not require the large sample size their parametric counterparts require to be adequately powered, the fact that only two patients were included in the NRTI-only category probably introduced some risk of bias into these results. Two patients cannot provide a clear picture of how this category of HAART influences the time to discontinuation of the regimen, and this bias impedes the generalization of these findings. While these analyses are adequately powered, this low sample size certainly affected results, and makes interpretation of these results difficult. In spite of this, findings suggest a difference in the time to discontinuation between these four categories of drugs used in the initial HAART combination.

*Patients Who Discontinued Treatment Because of Adherence Issues*

Overall, 34 patients were discontinued from their initial regimen because of adherence issues, representing 26.1% of the total sample. These patients constitute a unique and important sample because they provide researchers with insight into patients who struggle with their drug regimen. Because a majority of patients were started on initial HAART regimens with a pill burden of six or more pills per day, adherence issues were hypothesized to be prevalent in this sample. Given the extremely high adherence rate required by antiretroviral medications, as well as the underserved nature of this population, 26.1% of patients discontinuing because of adherence issues was perceived as a low figure. Researchers hypothesize this figure could be a low estimate of the true proportion of patients who discontinued their initial therapy due to adherence issues because of the way both the reason for

discontinuation and patient adherence issues are captured and recorded in patient charts at the study clinic. Given the risk of recall bias introduced by including patient self-report as a method of determination of patient non-adherence, as well as a risk of bias introduced by using subjective provider-deduced non-adherence, readers and reviewers are urged to interpret these results with caution.

*Research Question 1*

Overall, few significant differences in patient characteristics and medical history variables were detected across the four categories of daily pill burden. Of the continuous variables analyzed with ANOVA procedures, only two of the nine tested variables showed statistically significant differences in the means across the four categories of pill burden: age at initiation of the initial HAART regimen, and hospital stays during the initial HAART regimen. Because the other nine tested variables showed no statistically significant differences in their means across the four categories of pill burden, it appears that patient characteristics and medical history variables have no differences across the four pill burden categories.

Bonferonni post-hoc analysis (Table 3a) of the variable age at the initiation of the initial HAART showed significant differences when the mean age of patients in the 4-5 pills per day category were compared with all other pill burden categories. This seems to indicate that patients in the 4-5 pills per day category had a significantly different age than the other categories. Examination of the mean ages across the four categories of pill burden show that patients in the 4-5 pills per day category were about three years younger on average than the average patient

included in the study, indicating an apparent pattern of younger patients being prescribed regimens with 4-5 pills per day over other regimens. While the underlying cause of this pattern remains unclear, researchers speculate that this could be due the nature of treating younger patients with antiretrovirals. Clinic prescribers are cautious when prescribing 1 pill/day regimens for younger female patients because of the chance these patients could become pregnant. Since Atripla is contraindicated in pregnancy [98], clinic providers tend to favor prescribing 1 pill/day therapies to older patients who are past child-bearing age. This tendency could be reflected in this finding, but its true cause remains uncertain since this study is not designed to explore causative effects.

When the mean number of hospital stays during the initial regimen were compared across all combinations of the four categories of pill burden using the Bonferonni post-hoc test, statistically significant differences were detected between the 1 pill/day category and the 6+ pills/day category. Examination of the mean number of hospital stays for these two categories reveals a mean difference of 0.58 more hospital stays for the 6 or more pills/day category compared to the 1 pill/day category. Researchers attribute this finding to the low number of reported hospitalizations during the initial regimen. While the cause if this difference remains unclear, this could be due to potential adherence issues in the six or more pills per day category, leading to negative health outcomes requiring increased hospitalizations. Overall, the number of hospitalizations reported by patients in any category of pill burden were low, and all pill burden categories had a mean number of hospital stays of less than one during the initial regimen.

As previously mentioned, because of the low sample size included in this study, parametric tests used here are potentially underpowered, and subsequently present an increased likelihood of making a judgment error. Because of the potential underpowering of these parametric analyses, significant differences that may have existed in the population could have remained hidden. Reviewers and readers are cautioned to keep this in mind when attempting to infer generalizations from these results.

Overall, one of the four analyzed variables was found to significantly deviate from an equal distribution of patients: patient relationship status. Because post-hoc tests are unavailable for Fisher's exact test, post-hoc analysis was not conducted for this variable. While root causes of this difference are unclear, researchers speculate that the unequal distribution of patients in the relationship status variable may be due to prescribing patterns at the study clinic. Because clinic prescribers strongly avoid prescribing the clinic's only 1 pill/day therapy (Atripla) to patients who could possibly get pregnant, patients who are not single have a higher risk of pregnancy because of their relationship status, and would be less likely to receive Atripla as their initial therapy. Furthermore, since the study clinic treats primarily infected women and their children, many patients in the 'not single' category may already have had children when they initiated therapy, putting them at an increased likelihood for having more children in the future and causing clinic providers to tend to prescribe regimens other than 1 pill/day therapies.

*Research Question 2*

The finding that patients using the only 1 pill/day regimen available at the study clinic, Atripla, and patients utilizing any other regimen had a statistically significant difference in the time to discontinuation of the initial regimen between them indicated that patients prescribed Atripla as their initial HAART regimen had a longer time to discontinuation of that regimen when compared to patients who were prescribed any other initial HAART examined in this analysis. While survival analysis and log-rank tests revealed nothing about the cause of this difference in the time to discontinuation between these two groups, researchers speculate it may be due to Atripla's low pill burden. Patients prescribed a 1 pill/day regimen have been shown to have an increased adherence rate when compared with patients prescribed regimens with higher pill burdens [41], and this improved adherence could lead to better health outcomes for this group allowing them to stay on this regimen for a longer duration on average. An increase in medication adherence would lead to a lower likelihood of treatment failure as a result of viral resistance caused by non-adherence. If this hypothesized increase in medication adherence as a result of Atripla's low pill burden happens, it would lead to a lower likelihood of treatment discontinuation due to adherence issues, potentially increasing the mean duration of therapy in this group.

Even though the cause of this difference cannot be determined, this finding of a statistically significantly longer time to discontinuation in the Atripla group is significant in that it demonstrated that patients and providers attempting to maximize the duration of the initial therapy should consider initiating treatment

with Atripla over the other combinations analyzed in this study. In spite of this significance, the low number of patients utilizing Atripla in this study may have introduced a risk of bias. While 16 patients were initiated therapy using Atripla, only 5 of these patients discontinued treatment while at the clinic, leaving 11 patients to be right censored for the purposes of this analysis. Even though the log-rank test is non-parametric, care should be taken when attempting to generalize these results to the general population. It is extremely difficult to make any statement about a population of patients based on the outcomes 16 of these patients experienced, but given the non-parametric nature of the log-rank test, these results are considered valid and significant.

*Research Question 3*

In order to better understand significant differences that were found in the time to discontinuation of the initial HAART regimen across the four categories of pill burden, separate log-rank tests were conducted to test for significant differences in the time to discontinuation of the initial therapy between 1 pill/day and 2-3 pills per day regimens, 1 pill/ day and 4-5 pills per day regimens, and 1 pill/ day and 6 or more pills per day regimens. Each of these subsequent analyses detected significant differences in the time to discontinuation between the 1pill/day group and all other groups, indicating the 1pill/day group had a significantly different time to discontinuation than the other three groups. When the estimated mean duration of therapy was examined between these four pill burden categories, the 1 pill/ day group was associated with an estimated mean duration of therapy almost 400 days

longer than the study average. While the cause of this increase cannot be determined in this project, researchers speculate that the significant difference noted in this analysis between 1 pill/day regimens and all other categories of daily pill burden may be due to the same factors which were hypothesized to contribute to the higher time to discontinuation noted in the Atripla group versus all other medications prescribed for the initial regimen. Researchers again speculate that the low pill burden utilized in this group may increase this group's adherence rate, providing more favorable outcomes compared to other groups. The less favorable outcomes experienced as a result of the hypothesized higher rate of non-adherence associated with these groups could potentially lead to negative outcomes leading to therapy discontinuation, such as adverse events. As with the survival analysis in the previous question, care should be taken when attempting to generalize these results to the general population, as small sub-samples included in each pill burden category could introduce a risk of bias into these results.

*Research Question 4*

Examination of the estimated mean duration of therapy between patients prescribed Atripla for their initial regimen and patients prescribed the most common therapy backbone, Combivir, revealed that patients who were prescribed Atripla for their initial regimen had an estimated mean duration of therapy over 500 days longer than patients prescribed a regimen utilizing Combivir. This finding is

significant, as it demonstrates the apparent increased estimated duration of Atripla regimens over regimens containing the most commonly prescribed HAART backbone utilized at the study clinic. While attempts at generalizing these results to the general population should be made with the same care as noted in the discussion of previous research questions, it appears that patients and providers attempting to maximize the duration of the initial HAART regimen while minimizing the time to discontinuation of this regimen could consider an Atripla regimen over a Combivir-based regimen.

*Research Question 5*

Survival analysis was performed on patients who started therapy both before the introduction of Atripla to the US pharmaceutical market, and after its introduction, in order to better understand how the time to discontinuation of therapy differed between these two time periods. A log-rank test examining the survival curves for patients in these two groups revealed no significant difference in the time to discontinuation of the initial HAART prescribed to patients in both the pre-Atripla era and patients who initiated therapy in the Atripla-era.

This lack of a significant difference in the time to discontinuation between these two groups is hypothesized to be attributable to two main factors. First, because only 16 patients initiated HAART with Atripla in this sample, this sub-sample of patients could not exert enough influence over the variability associated with the duration of the initial regimen in the Atripla-era group despite the indications of previous analyses demonstrating this group's long time to

discontinuation. In addition to this, because a majority of patients in both the pre-Atripla era group and the Atripla era group were not initiated on HAART using Atripla, the estimated means of duration of therapies of the two groups included in this analysis reflected the homogeneous nature of these two time periods, independent of the influence of the patients prescribed Atripla. If this speculation is true, it could imply that the results of this analysis demonstrate that the average patient has an equal time to discontinuation of the initial regimen independent of the time period in which the patient started therapy. This result strengthens the findings of previous analyses in this study examining the effect of Atripla prescription on the time to discontinuation because it rules out the option that the noted improvements in the time to discontinuation between Atripla and other regimens was not due to systemic differences resulting from the time period in which HAART was initiated. If patients prescribed Atripla had a higher time to discontinuation than other regimens, but the average patient prescribed her initial HAART during the Atripla era had no difference in the time to discontinuation of her regimen than any other patient, it is possible to conclude that the higher time to discontinuation noted in the Atripla group was not due to systemic improvements in care implemented during the Atripla era.

*Research Question 6*

In the development of the Cox proportional hazards model, some variables collected at baseline were intentionally excluded from the initial model because of their lack of independence from other included variables. For example, the use of

Atripla in the initial regimen was excluded from the initial analysis because it is essentially a recoded version of the included pill count variable. Patients with a pill count of one utilized Atripla in their initial regimens, and this lack of independence between these two variables leads to an overlapping of variance accounted for in the hazard of discontinuation of the initial therapy by these two variables. Subsequently, each predictor variable has a weaker performance in the model when the other variable is included, and the decision was made to include pill count at the expense of including the use of Atripla because of the increased specificity in the pill count variable. Including the pill count variable allows researchers to compare the hazard of discontinuation ratio between patients on Atripla and patients utilizing therapies with any other pill burden, whereas including the Atripla variable would only allow researchers to compare patients started on Atripla to all other patients. Similar reasoning lead researchers to exclude the use of a protease inhibitor in the initial therapy, pill burden category, and combination type in favor of including the continuous variable pill burden. Lastly, because no non-black patients were prescribed Atripla for their initial regimens, patient race was dropped as an independent variable.

Of the 11 variables included in the initial model developed to assess the assumption of proportional hazards, smoking status and employment status were both found to not adhere to the proportional hazards assumption. It is important to note that the exclusion of these variables does not make an implication as to the relative strength or weakness of these variables' contributions to the proportion of variance in the hazard of discontinuation of the initial therapy compared to the nine

retained study variables. These two variables were excluded based on their violation of the proportionate hazards assumption, meaning their relationship to the underlying hazard function developed in their respective models changed over time. Because this relationship was not constant over time, and these models were not included as time-dependent covariates, a meaningful hazard ratio cannot be calculated for them, and inferences based on these variables' effects on the time to discontinuation of the initial regimen cannot be made.

After these two variables were dropped, the remaining nine variables were developed into a statistically significant proportional hazards model. The $R^2$ of this model was 0.040, indicating that even though the final developed model contributed to a statistically significant proportion of variance associated with the hazard of discontinuation of the initial regimen, this model only accounted for 4.0% of this variance. Despite this small percentage, the model appears to perform relatively well in this sample, with a concordance of 0.681. This means that when individuals in this sample are paired at random with each other, this model accurately predicted the patient who would discontinue therapy first 68.1% of the time based on the included predictors. This is a strong finding, especially when the nature of this measure is considered. Given the fact that 40 observations (34.8%) were right-censored in this analysis, this high concordance value speaks to the predictive ability of the developed model. The unpredictable nature of censored observations tends to make high censor rates problematic for the development of proportional hazards models, but it appears this developed model performs relatively well even under these conditions.

Of the nine variables included in the final model, only viral load and pill burden of the initial regimen were found to contribute to a significant proportion of the variance associated with the hazard of discontinuation of the initial therapy. The time-dependent covariate viral load was found to have a hazard ratio of 1.437, meaning for a one unit increase in the base-10 logarithm of a patient's viral load, that patient's hazard of discontinuation increased 43.7%. This is a significant finding considering the high variability in viral load measurements across patients. The base-10 logarithm of the viral load measurements was used as the time-dependent covariate instead of the raw measurement in an attempt to smooth the distribution of measurements and normalize this variance as much as possible. Apart from its hazard ratio, this finding also speaks to the troubles patients face in their initial regimens at the study clinic. Because this variable was found to be significant, it can be assumed that as patients' viral loads increased, they became more and more likely to switch regimens, creating a dangerous cycle in their long-term course of treatment. While this hazard ratio cannot differentiate between patients who switched therapy because of challenges they faced with the therapy and patients who switched therapy because of a lack of effectiveness in their prescribed treatment, both of which can be reflected in elevated viral loads, it does speak to the cyclical relationship that elevated viral loads and the time to discontinuation share. Patients with elevated viral loads are shown to be more likely to discontinue their initial therapy more quickly, and by switching to subsequent therapies, may be put at a higher risk of negative health outcomes such as further increases in viral load.

The daily pill burden of the first prescribed HAART regimen was also shown to have a statistically significant coefficient, indicating that for each pill added to the initial regimen, the hazard of discontinuation increased 23.0%. This is an important finding, as it shows Atripla's apparent improved time to discontinuation compared to other regimens, as well as showing how this characteristic of the first prescribed regimen affected patients' times to discontinuation of therapy. Because most patients in this study were started on HAART regimens utilizing a daily pill burden of six pills or more per day, and only 16 patients were started on Atripla for their initial regimen utilizing 1pill/day, it appears changes in this prescribing trend could be beneficial to future patients initiating HAART at the study clinic. Furthermore, prescribers aiming to maximize the duration of the initial HAART regimen should consider this 23.0% increase in the hazard of discontinuation when making treatment decisions with their patients.

In addition, patient age at the initiation of the initial HAART regimen was not found to be a statistically significant variable in the developed Cox model. This finding implies that patient age at the initiation of the first regimen did not significantly influence the hazard of discontinuation of that regimen. Because previous literature has shown age to be a poor predictor of adherence to antiretroviral regimens [40], this finding appears to support previous evidence showing patient age to not affect antiretroviral adherence. While this study was not designed to assess causal relations between time to discontinuation and adherence, longer times to discontinuation that are hypothesized to be associated with improved adherence rates were not affected by patient age. This finding implies

that patients of any age had similar times to discontinuation, and adds to the evidence suggesting that patient age does not predict adherence.

The overall survival curve shown in Figure 11 seems to imply somewhat of a trend in the amount of patients discontinuing the initial treatment regimen over time. The initial curve is very steep, and this sharp increase in the number of patients discontinuing the initial regimen within the first 300 days reflects the high rate of patients who discontinue therapy relatively early. After this sharp decrease in the survival curve, the curve appears to flatten out, indicating that after this initial wave of discontinuers, the remaining patients discontinue therapy at a slower rate than those discontinuing early. Because of this, providers would be wise to consider this increased rate of discontinuation within the first 300 days of treatment as it appears to be faster than the rate of discontinuation at later times in treatment. This survival curve shows the importance of the first year of HAART treatment in achieving the goal of avoiding discontinuation of therapy, and provides a good goal for practitioners aiming to maximize the duration of this initial therapy.

Overall, the findings of this analysis are similar to models developed by previous researchers [42]. In the Cox model developed by Willig and colleagues [42], patient insurance status and dosing frequency variables were both found to contribute to a significant portion of the hazard of discontinuation of the initial therapy in their sample. Furthermore, patient age, race, HIV risk factor, and baseline CD4 t-cell counts were all found to be non-significant coefficients in Willig and colleagues' Cox model [42], which is supported by findings of this model.

*Implications for Practice*

Overall, it appears the effect of daily pill burden of the initial HAART regimen on the time to discontinuation of this initial regimen was strong. Kaplan-Meier survival curves demonstrated a statistically significant difference in the times to discontinuation of the initial HAART regimen between patients on Atripla and any other regimen prescribed for the initial HAART. Furthermore, the Cox proportional hazards model demonstrated a 23.0% increase in the hazard of discontinuation for each pill added to the initial daily therapy. When considered together, these results seem to reflect Atripla's ability to prolong discontinuation of the initial HAART regimen. By avoiding therapy switches, providers increase their patients' chances of experiencing more positive outcomes than if the patient had switched regimens [35] [36]. Because Atripla appears to be strongly associated with an increased time to discontinuation of the initial regimen in the study cohort, providers aiming to maximize the duration of this first regimen in order to delay the use of subsequent therapies and maximize their patients' chances of experiencing positive outcomes would be wise to consider this treatment option. Furthermore, as novel 1 pill/day antiretrovirals are released in the future, providers seeking to maximize patients' times to discontinuation of their initial regimens would be wise to consider these regimens, as they have been shown in this analysis to be associated with significantly improved time to discontinuation.

In addition to this implication, results of the Cox proportional hazards model developed seem to identify a possible high-risk time for discontinuation of the initial regimen. Based on the plotted survival curve, it appears the rate of discontinuation

of the initial regimen was highest before approximately 300 days of treatment. Providers seeking to minimize the risk of discontinuation in patients initiating HAART therapy should closely monitor patients during this high-risk time, as the rate of discontinuation is highest here. Furthermore, providers should make it a priority to give medication adherence counseling to patients in the first 300 days of treatment, since these patients were at a higher risk of discontinuing than patients who have been on their regimen for longer durations.

*Implications for Research*

The findings of this study fill some significant gaps in the literature concerning both the duration of initial HAART regimens prescribed to patients, as well as the effect of the pill burdens of these regimens on time to discontinuation. As presented in the literature reviewsection, these questions had not been previously explored in 1 pill/day regimens, and the effect of daily pill burden on the time to discontinuation of the initial regimen had not been previously explored in an all female sample. Overall, these findings appear to build on previous work attempting to address these issues [42], continuing the trend presented by Willig and colleagues showing that decreased pill burdens in the initial HAART regimen can lead to subsequent decreases in the time to discontinuation of these regimens. The findings of this study build on this previous work in that they show 1 pill/day therapies like Atripla follow this trend, and they also show this trend to be apparent in this underserved, all-female sample.

While these findings fill several significant gaps in the literature, several areas for future research remain. Because of the design of this study, researchers were unable to explore causal effects of any of the included variables. This leaves significant questions concerning the cause of the effect of daily pill burden on the time to discontinuation of the initial HAART regimen. Furthermore, because proportional hazards models are not causative in their design, a better understanding of the causes of the effects noted in the variables included in this model on the time to discontinuation is needed. In addition to exploring causative factors, future researchers would be wise to consider the effect of daily pill burden on other facets of the treatment of HIV, specifically in second-line and salvage HAART regimens, and in the development of AIDS-defining illnesses. While this study aimed to fill significant gaps noted in the literature concerning the effect of daily pill burden on the time to discontinuation, there remains much to be understood about this effect and its causes.

*Limitations*

Several limitations in this study warrant the use of caution on the part of readers and reviewers when attempting to generalize the results of these findings to populations. The most notable limitation of this study was the small sample size and subsequent underpowering of the parametric analyses. The conservative power analysis conducted in the methods section of this project suggested a need for at least 274 patients in order to adequately power the parametric analyses used

such as the paired t-tests and ANOVA procedures used to answer research question 1. Because the total included sample of 115 patients was less than half of this requirement, underpowering of some of the analyses included here constitutes a limitation of this study, and could potentially introduce a risk of bias in the results. While a small sample size is less problematic for the semi-parametric Cox proportional hazards model and the non-parametric Kaplan-Meier curves and chi-square tests, small sample sizes can introduce a risk of bias into any analysis conducted, and results of all analyses conducted in this project should be considered with this in mind.

In addition to the underpowering of analyses because of a small sample size, the method of collection of some variables leads to an inherent risk of bias being introduced. As previously discussed, a recall bias is introduced by utilizing patient self-report and provider-based decision making for the determination of adherence to the initial regimen because of the potential for social desirability bias. The lack of an objective adherence measure used at the study clinic hinders the generalizations that can be made based on the analyses that included these variables, such as reasons for discontinuation and discontinuation based on adherence issues. Despite this risk of bias, the incorporation of provider-based decision making in addition to patient self-report in the determination of non-adherence most likely reduces some of the extraneous variability associated with the increased risk of social desirability bias that accompanies the use of patient self-report. Overall, researchers felt the categorization of patients by clinic providers as non-adherent was important to

capture, despite its source, however this risk of bias should be considered when interpreting the results outlined in this report.

In addition to these limitations, the generalizability of these results is limited by the nature of the sample. Because an all-female, majority black and underserved sample is not representative of the overall population of HIV-infected patients, generalizing the results found here to overall populations may lead to an increased risk of bias. Given this fact, readers attempting to extrapolate results from the analyses included here to other patient populations should do so with caution. Also, despite previous research showing patient health literacy to be a significant predictor of antiretroviral adherence [79], patient health literacy was not able to be abstracted from the reviewed patient charts, and this variable was not collected. Because this variable has been previously shown to contribute to a significant proportion of the variance associated with antiretroviral adherence, not collecting this variable constitutes a limitation of this study. Furthermore, because researchers were unable to capture the pill burdens from other co-morbid conditions due to reliability issues with the data, a potentially important contributor to the variance associated with the time to discontinuation in this cohort may have been missed, leading to a risk of bias in these results.

Lastly, the decision to not include the Charleson Co-Morbidity Index (CCI) [99], or any other validated co-morbidity index, introduced a risk of bias into the study by not including a potentially significant contributor to the variance associated with the hazard of discontinuation of the initial therapy. While a co-morbidity index such as the CCI could have provided a summary statistic of co-

morbid conditions experienced by patients, the decision was made to not include this measure in this project because of the distribution of reported co-morbid conditions. While a high number of patients reported co-morbid conditions of diabetes and AIDS, almost no patients reported any of the other co-morbid conditions used in the calculation of the CCI, indicating this measure may not be appropriate for use in this sample. In order to minimize this risk of bias, researchers included a count of the number of co-morbid conditions each patient was reported to experience, and used this measure as a proxy for co-morbidity in the included analyses. While this method cannot quantify severity of co-morbid conditions, researchers attempted to minimize the risk of bias introduced by not including a co-morbidity index by using this count measure to represent co-morbidity in this cohort..

## VI. Conclusions

*Conclusions on the Effect of the Use of Atripla as the Initial HAART Regimen on the Time to Discontinuation*

Because Atripla is the only 1 pill/day therapy used at the study clinic, these research questions two through four indirectly analyzed the subgroup of patients staring therapy using Atripla, and were able to compare this subgroup to the other three subgroups of pill burden used in these analyses. Research question five indirectly addressed the subgroup of patients utilizing Atripla for their initial therapy as well, however the non-significant results of this analysis seem to indicate no statistically significant differences in the likelihood of all patients to discontinue therapy between the pre-Atripla time period and the Atripla time period. This seems to indicate that there are no underlying differences in the treatment provided to all patients between these times, and suggests that extraneous or unaccounted for variables are not causing the statistically significant differences detected in other included analyses. Overall, only 16 patients in this cohort initiated therapy using Atripla (13.9%), introducing a risk of making a judgment error when interpreting the results of these analyses.

In spite of this risk, significant results found in these analyses seem to indicate an association between the use of Atripla in the initial pill burden and an increase in the time to discontinuation of the regimen. This association is evident when Atripla was compared to patients initiating therapy using pill burdens of 2-3 pills/day, 4-5 pills/day, and 6 or more pills/day, as well as patients who utilized Combivir in their initial HAART, and the subgroup of patients who did not utilize

Atripla for their initial HAART. Furthermore, the developed Cox proportional hazards model showed patients utilizing Atripla for their initial regimen had the lowest hazard of discontinuation rate, with this rate increasing 23.0% for every pill added to the regimen. When viewed together, these results seem to indicate that patients who initiate therapy utilizing Atripla are less likely to discontinue that regimen at any given time than patients who initiate therapy using any other HAART regimen. Because subsequent therapies have been shown to be associated with decreased outcomes [34][35], it appears that patients initiating therapy using Atripla minimize their risk of discontinuing therapy and needing to switch therapies in the future, allowing them to delay the use of limited subsequent treatment regimens and maximize the time they stay on their initial therapy, providing them with the best chance of positive treatment outcomes.

*Conclusions on the Effect of Daily Pill Burden on the Time to Discontinuation of the Initial Regimen*

Overall, the two strongest pieces of evidence reflecting the effect of daily pill burden on the time to discontinuation of the initial regimen were from research questions three and six. The log-rank test used to analyze the Kaplan-Meier curves for each category of pill burden showed statistically significant differences between these curves, indicating that significant differences in the times to discontinuation of the initial regimen exist between these pill burden categories. When the pill burden group of 1 pill/day was used as a reference category to compare to all other pill

burden groups, statistically significant differences were detected in each of these analyses. Furthermore, results of the Cox proportional hazards model showed the pill burden variable to be significant in the hazard model, with a 23.0% increase in the hazard of discontinuation associated with each pill added to the pill burden of the initial regimen. When viewed together, these results seem to indicate a potential trend in an association between the hazard of discontinuing the initial regimen and the number of pills in this regimen's daily pill burden. Providers seeking to minimize this hazard of discontinuation could consider these findings in their treatment decision-making, as it appears that pill burden of the initial regimen is directly related to the hazard of discontinuing this regimen.

In spite of these findings, readers and reviewers should take caution when interpreting these results. An unequal distribution of patients across these pill burden categories, as well as a small sample size could introduce a risk of bias in these results. In spite of this, the conclusions based on these results are derived from findings that indicate general trends between pill burden used in the initial regimen and the time to discontinuation. In conclusion, it appears the pill burden of the initial regimen is an important and significant point of consideration for providers initiating HIV+ patients on HAART, especially when the hazard of discontinuation is taken into account. Providers wishing to maximize the duration of the initial therapy in order to delay the use of subsequent therapies, as well as provide patients with the increased positive health outcomes associated with first-line HAART therapies, could consider 1 pill/day therapies, as these are shown to have a significantly lower hazard of discontinuation than other HAART regimens.

**Figure 1: Decision algorithm recommended by the WHO for suspected cases of treatment failure [32]**

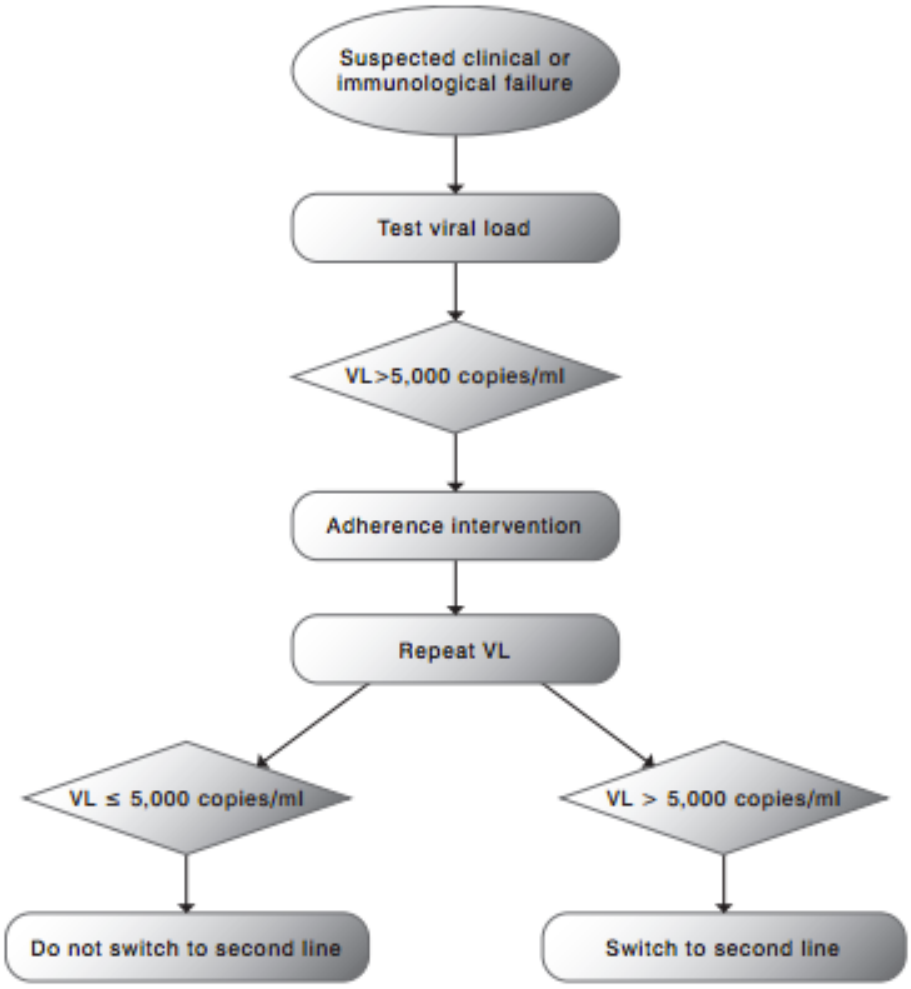

**Figure 2: Exclusion Criteria and Flow Diagram of Included/Excluded Patients**

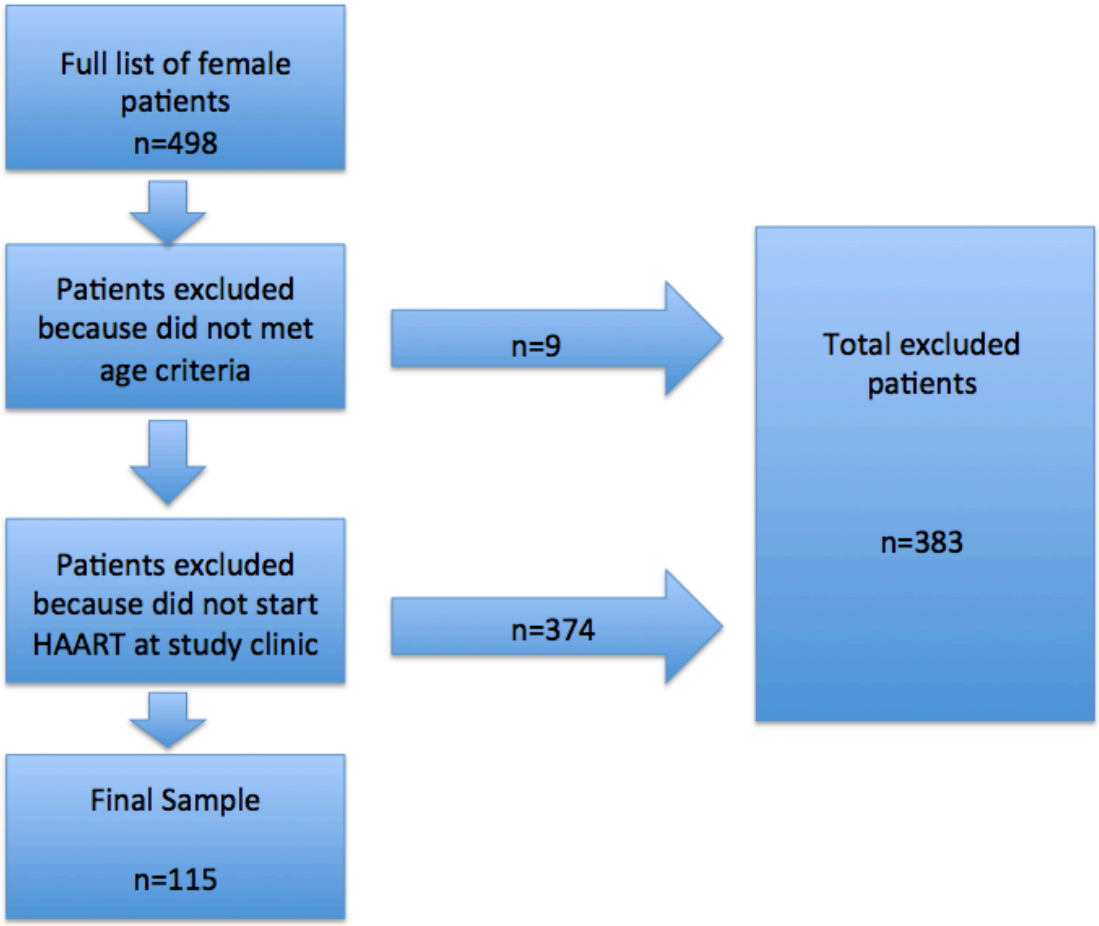

**Figure 3: Reasons for Patients Discontinuing the Initial Regimen**

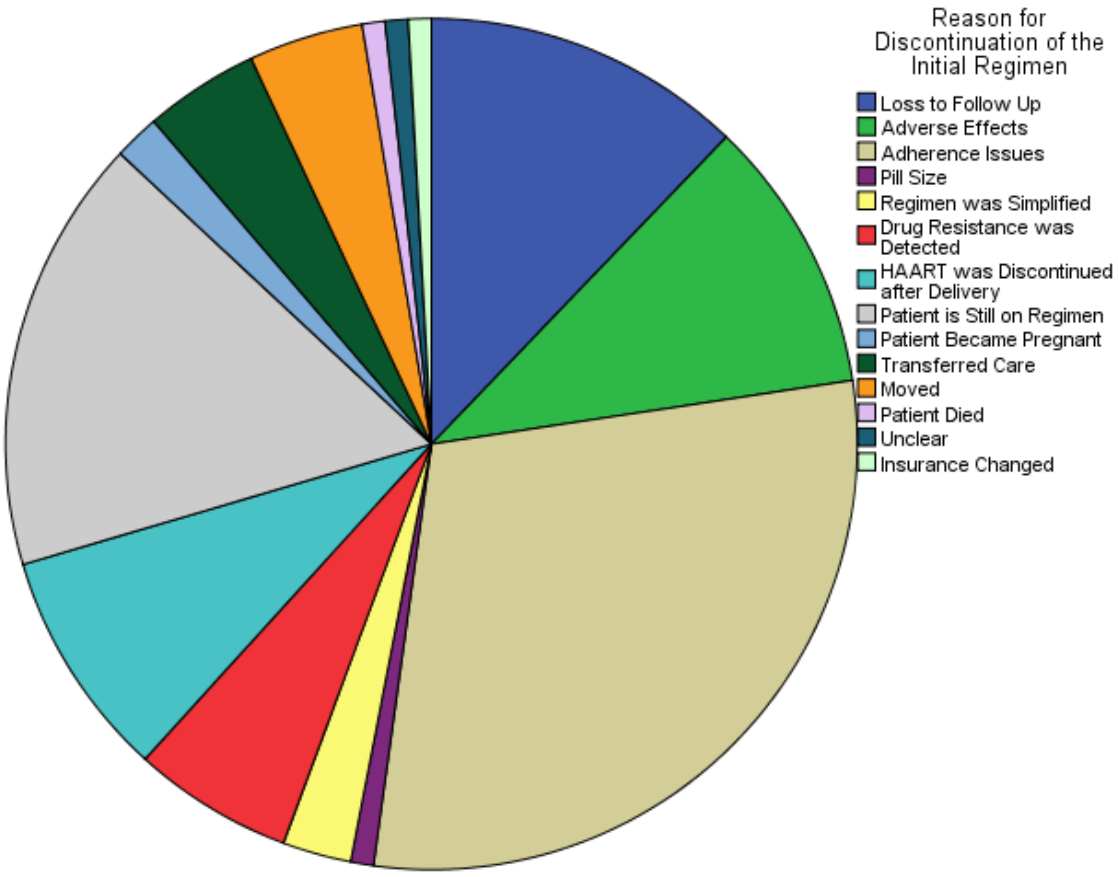

**Figure 4: Combinations of Antiretroviral Drugs Used in the Initial HAART Regimen**

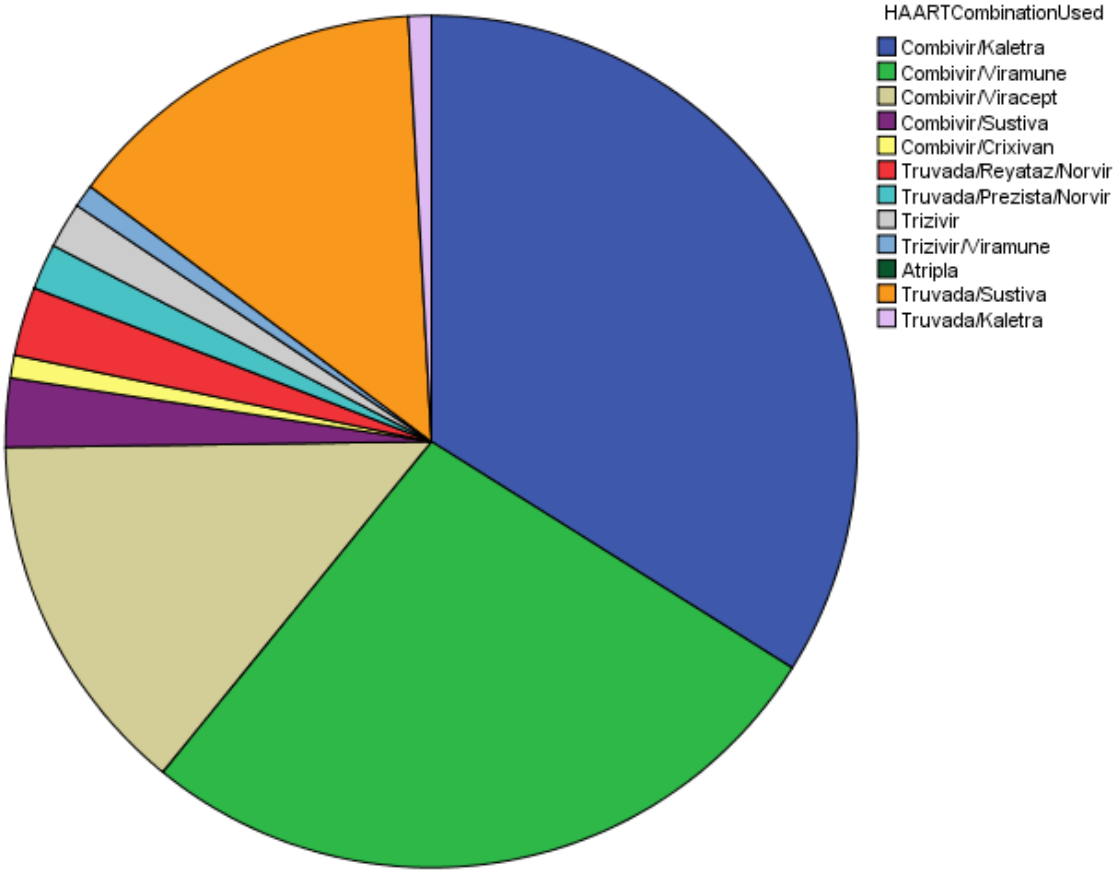

**Figure 5: Total Pill Burdens for the Initial HAART Regimen**

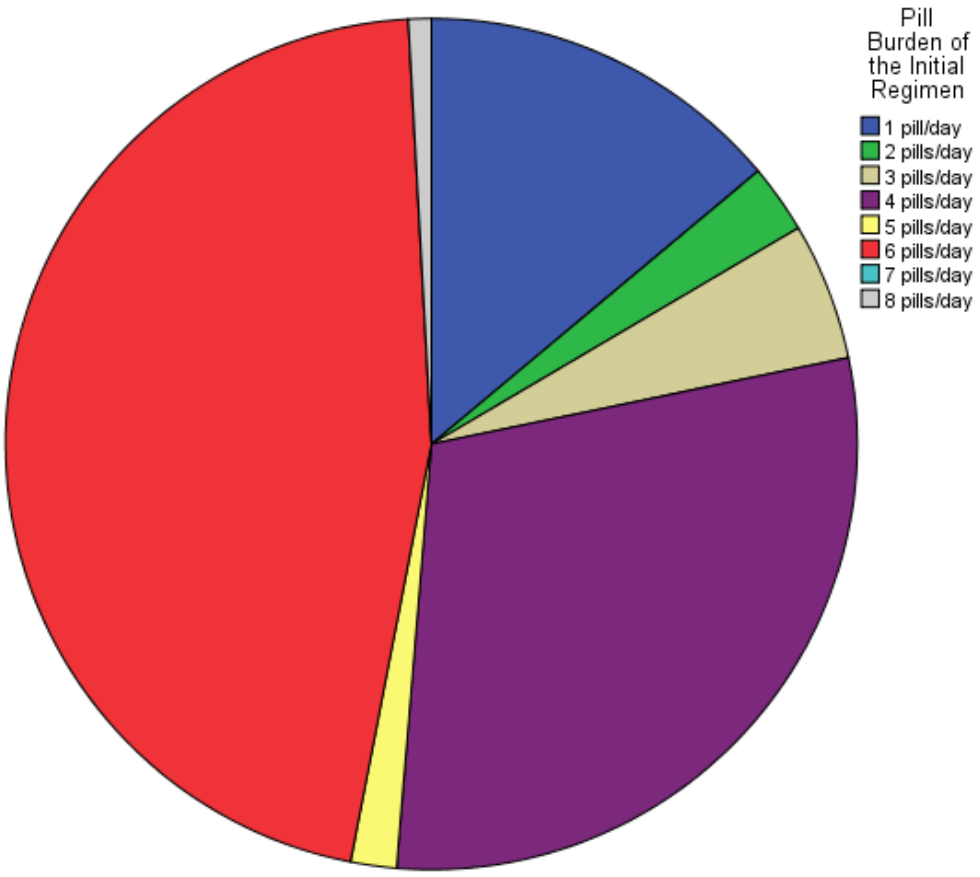

**Figure 6: Pill Burden Categories Used in the Initial Regimen**

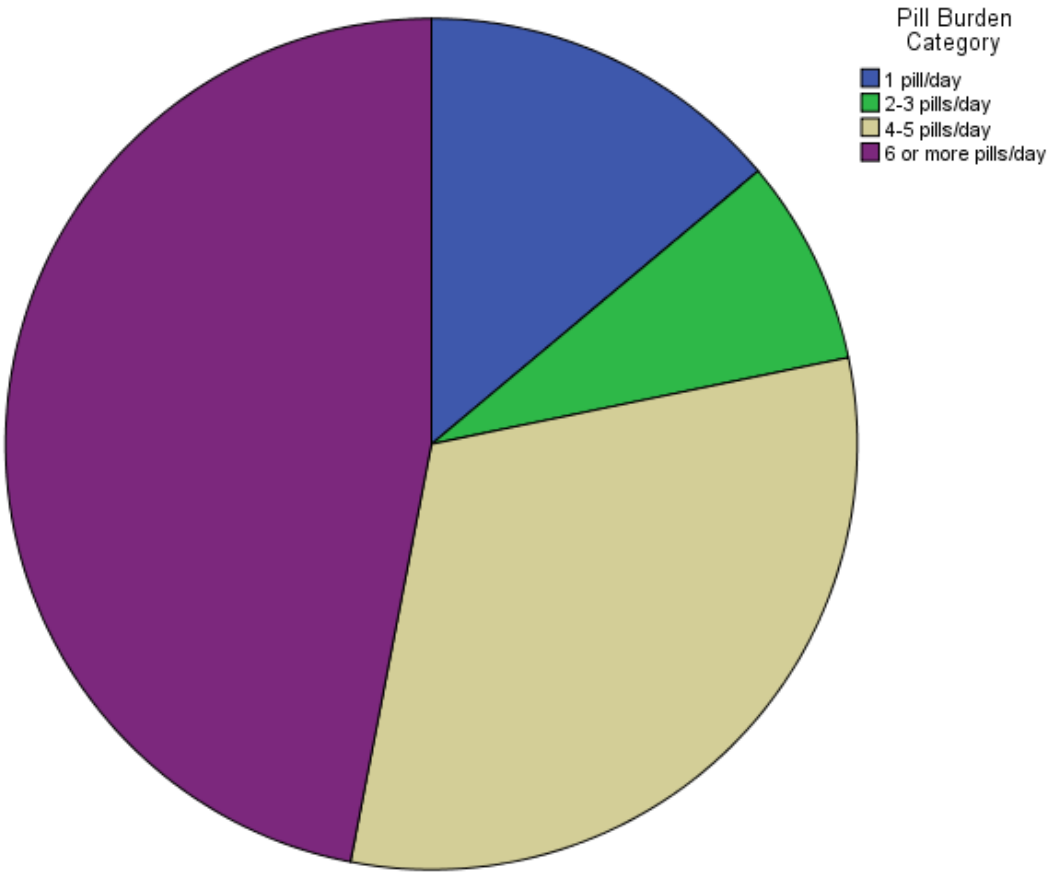

**Figure 7: Kaplan-Meier Analysis of Patients Starting with Atripla vs. Any Other Regimen**

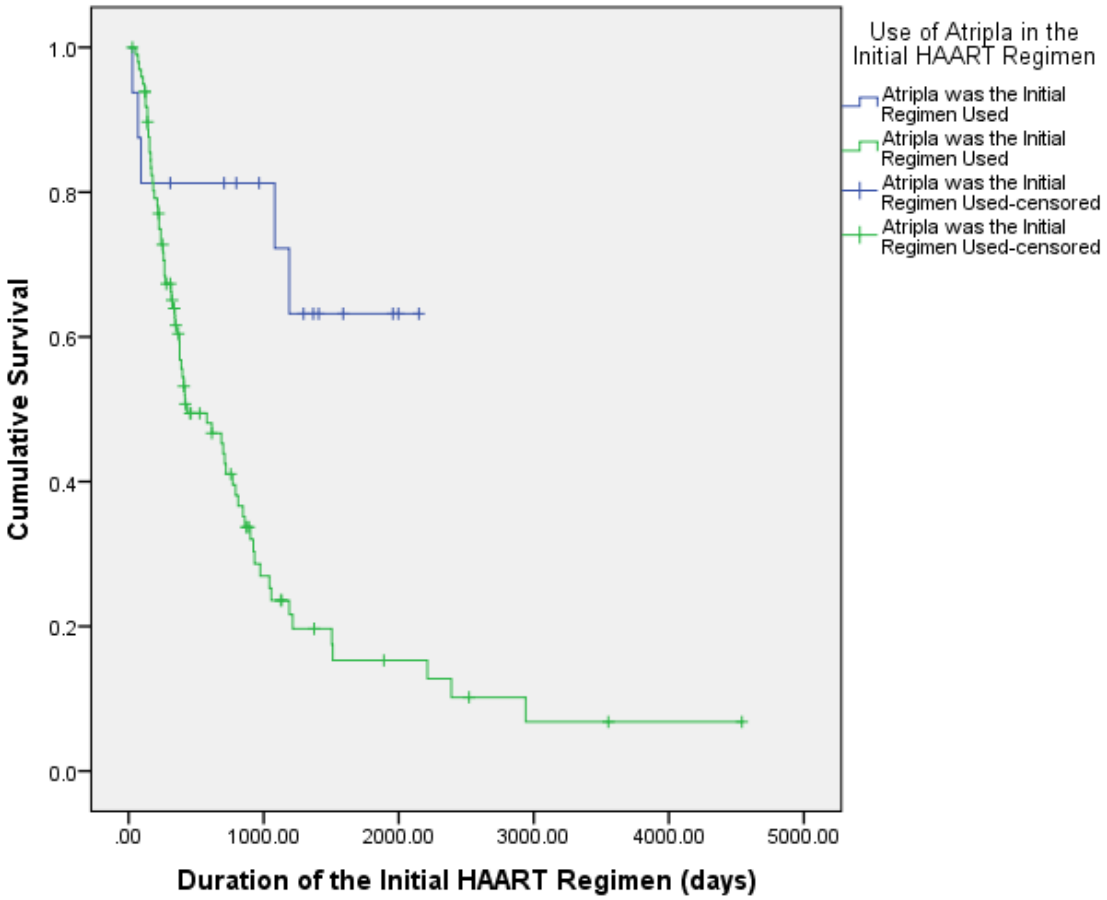

**Figure 8a: Kaplan-Meier Analysis of patients Staring with HAART Using 1 Pill/Day, 2-3 Pills/Day, 4-5 Pills/Day, and 6 or More Pills/Day**

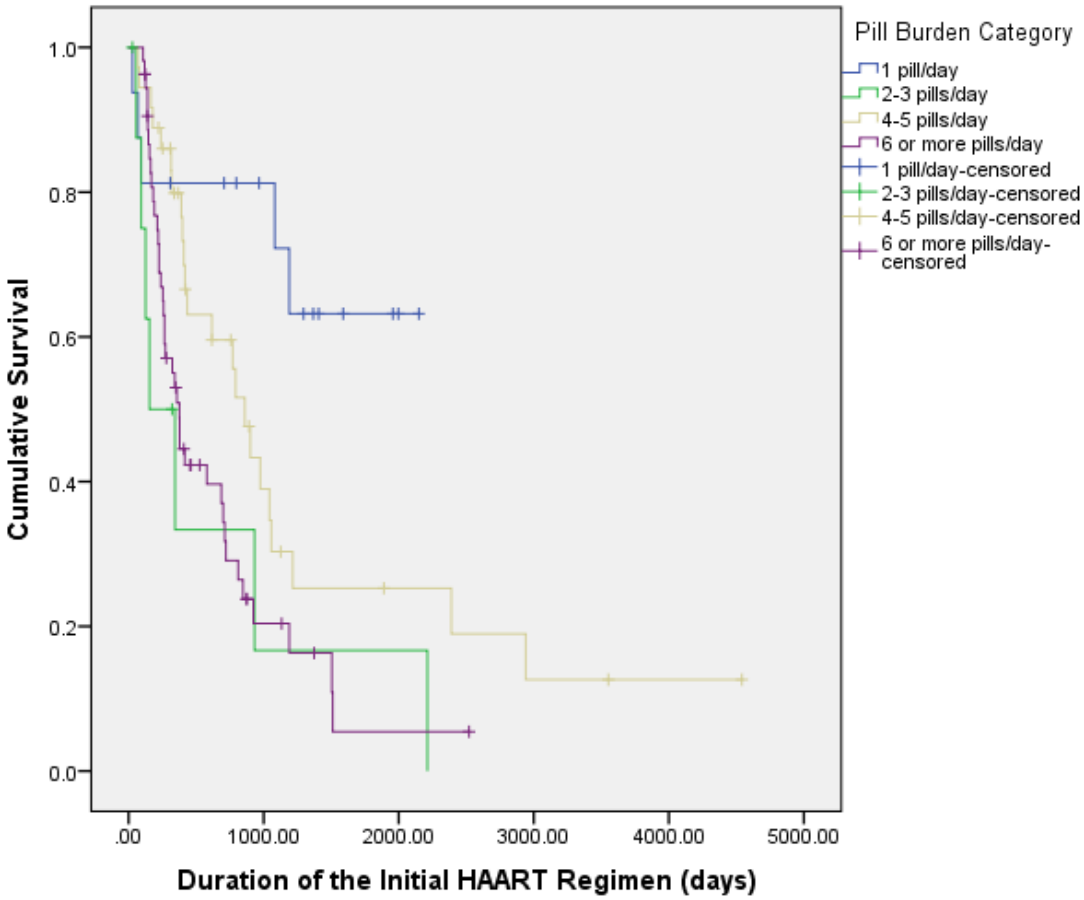

**Figure 8b: Kaplan-Meier Analysis of patients Staring with HAART Using 1 Pill/Day and 2-3 Pills/Day**

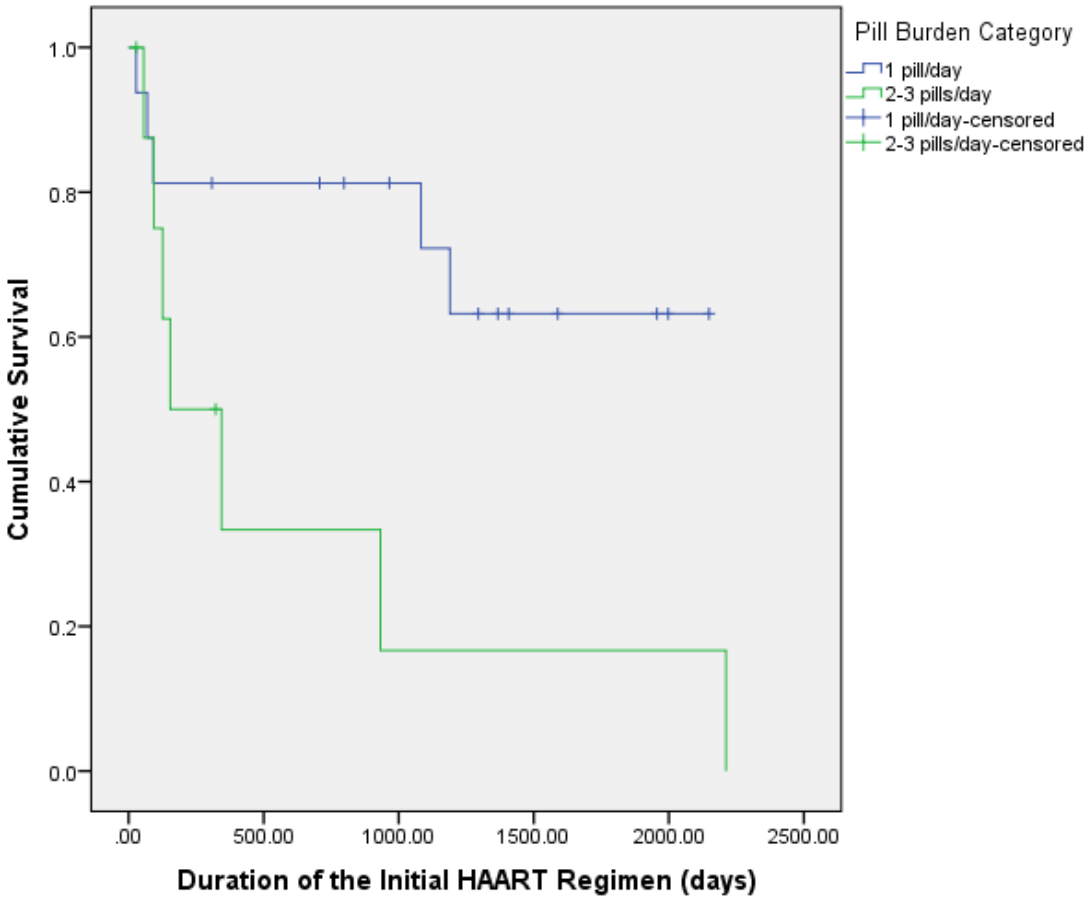

**Figure 8c: Kaplan-Meier Analysis of patients Staring with HAART Using 1 Pill/Day and 4-5 Pills/Day**

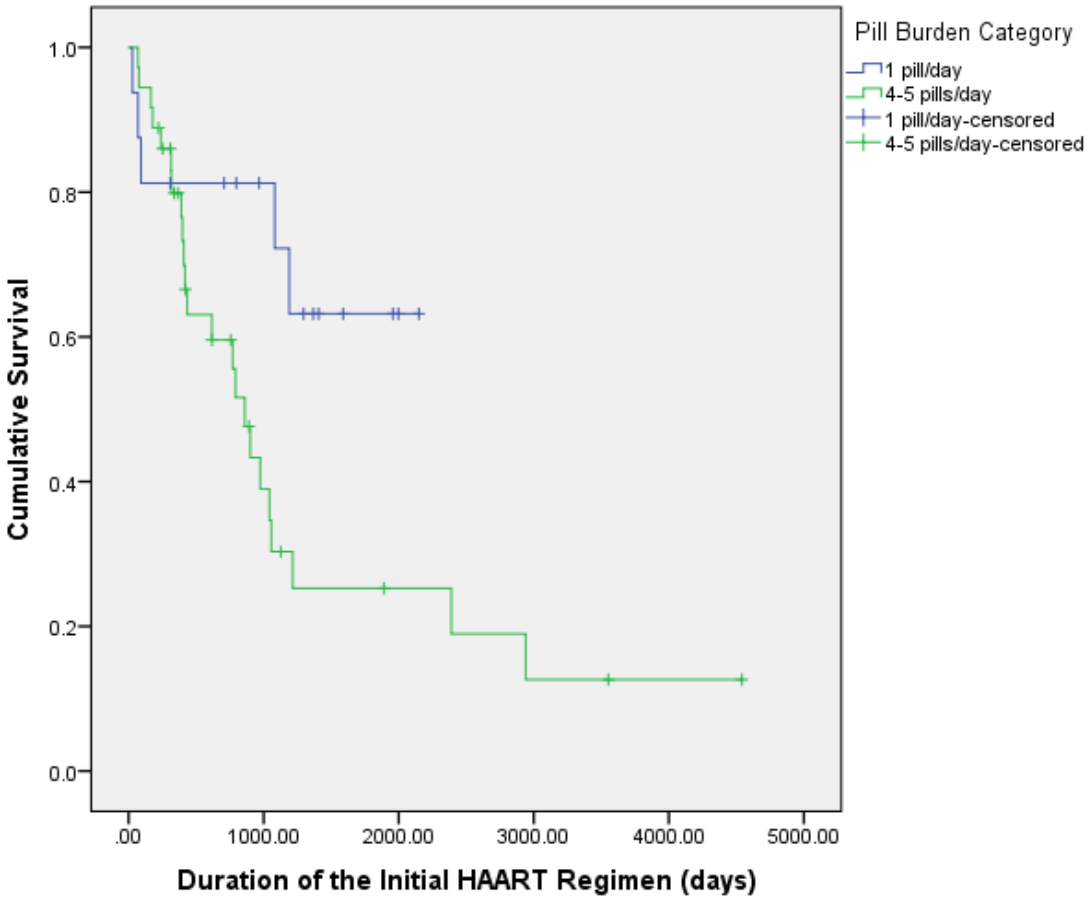

**Figure 8d: Kaplan-Meier Analysis of patients Staring with HAART Using 1 Pill/Day and 6 or More Pills/Day**

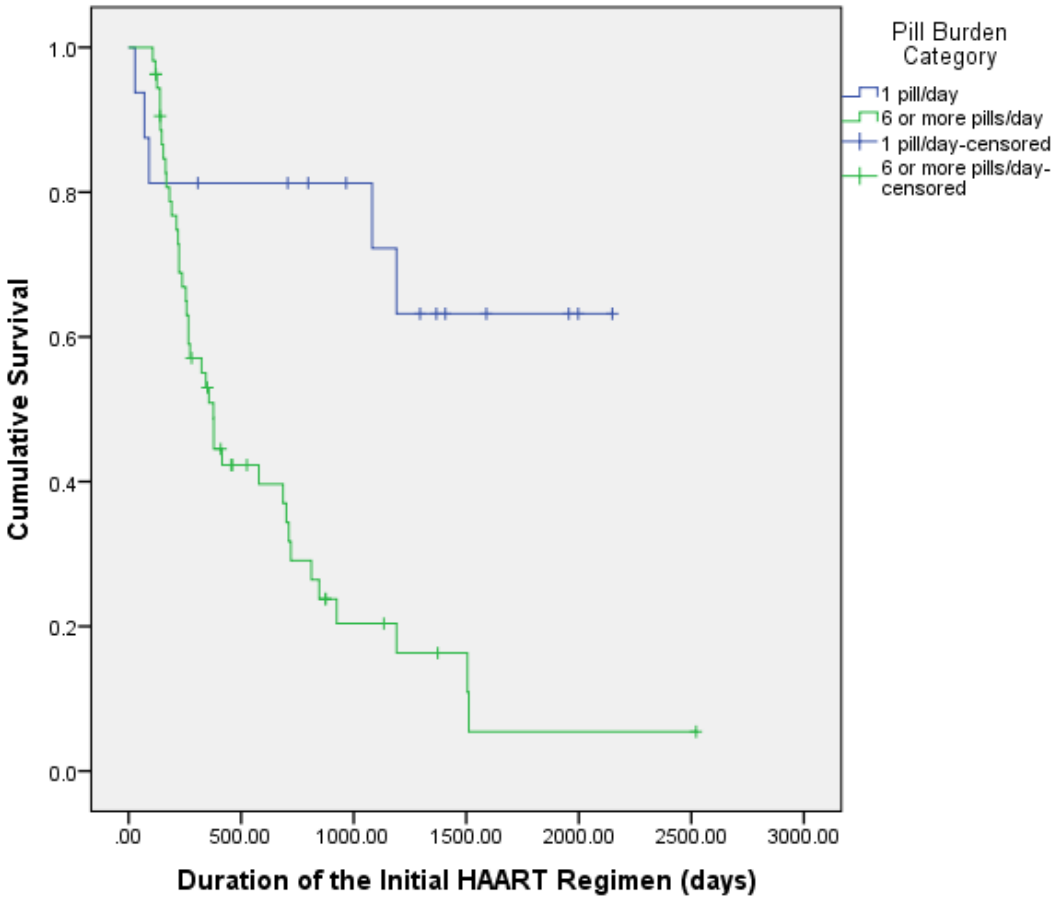

**Figure 9: Kaplan-Meier Analysis of Patients Starting with Atripla vs. Combivir as Treatment Backbone**

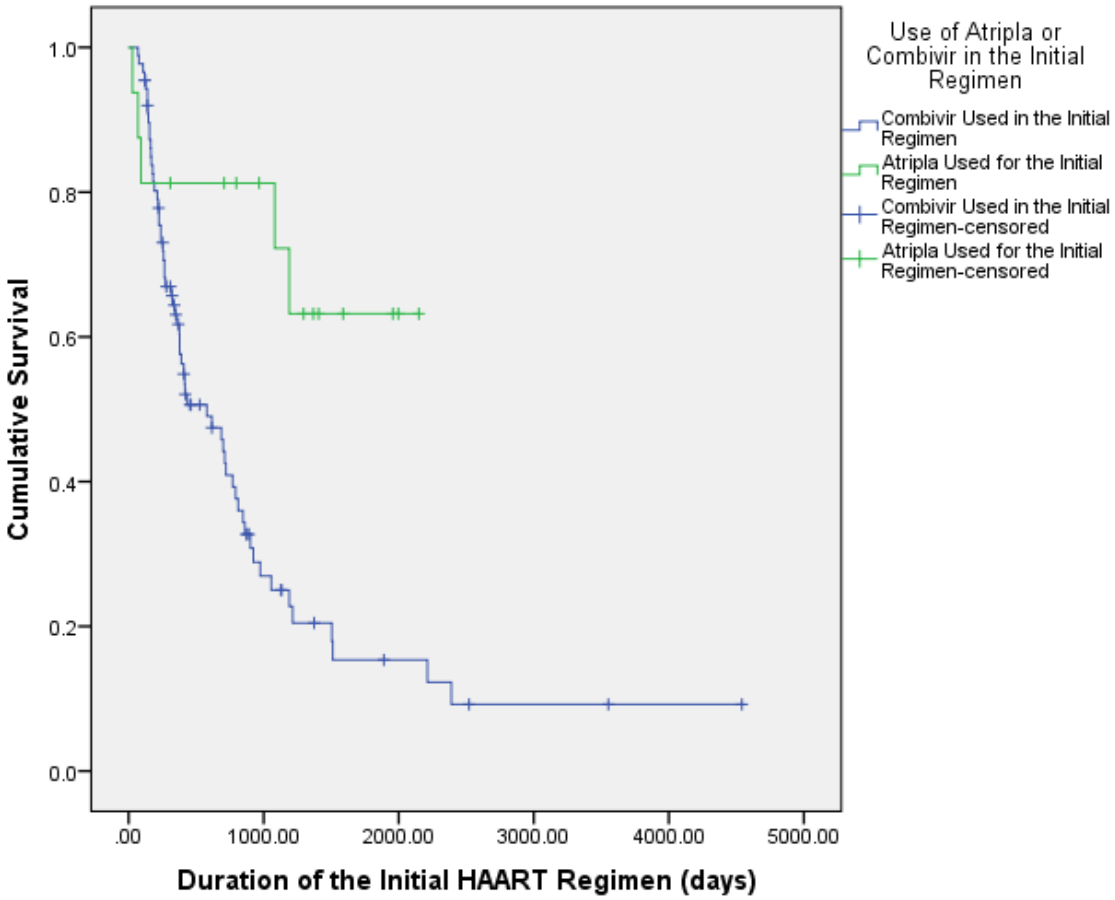

**Figure 10: Kaplan-Meier Analysis of Patients Starting HAART in Pre-Atripla Era vs. Atripla Era**

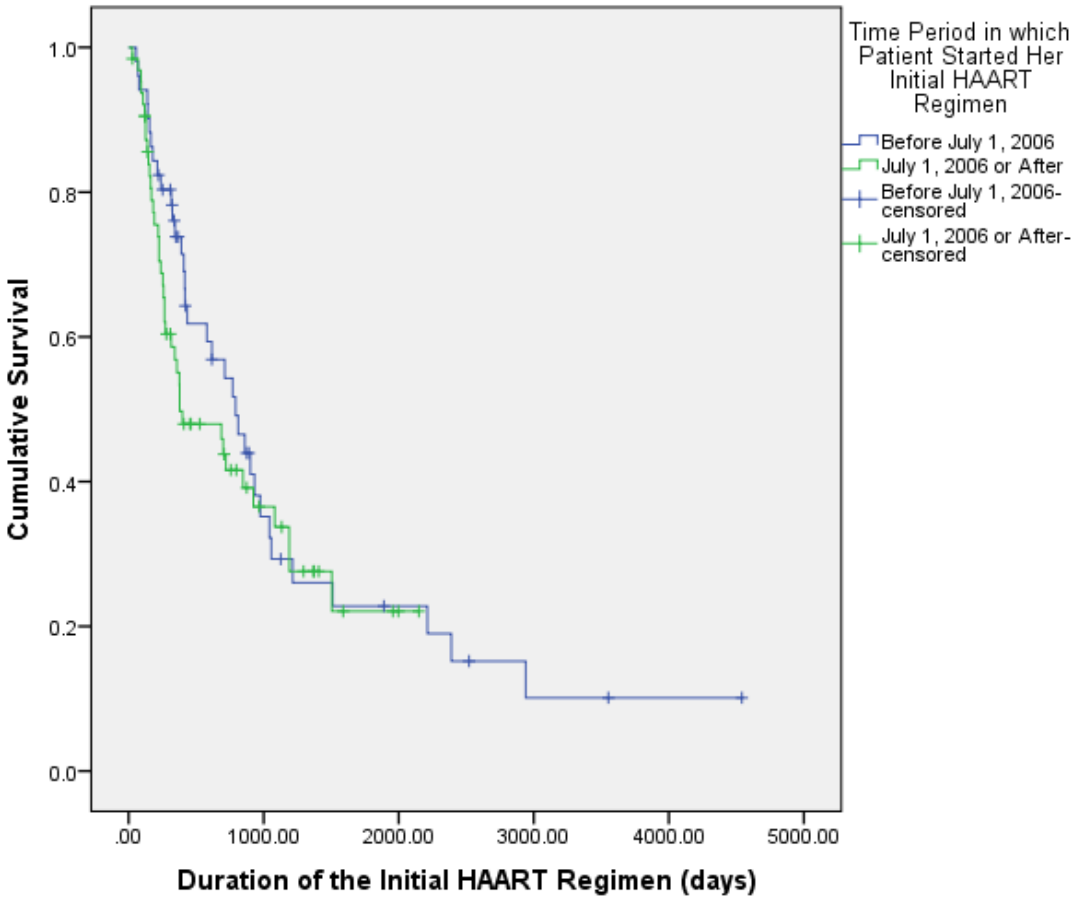

**Figure 11: Survival Curve for Overall Study Sample Developed from Cox Proportional Hazards Model**

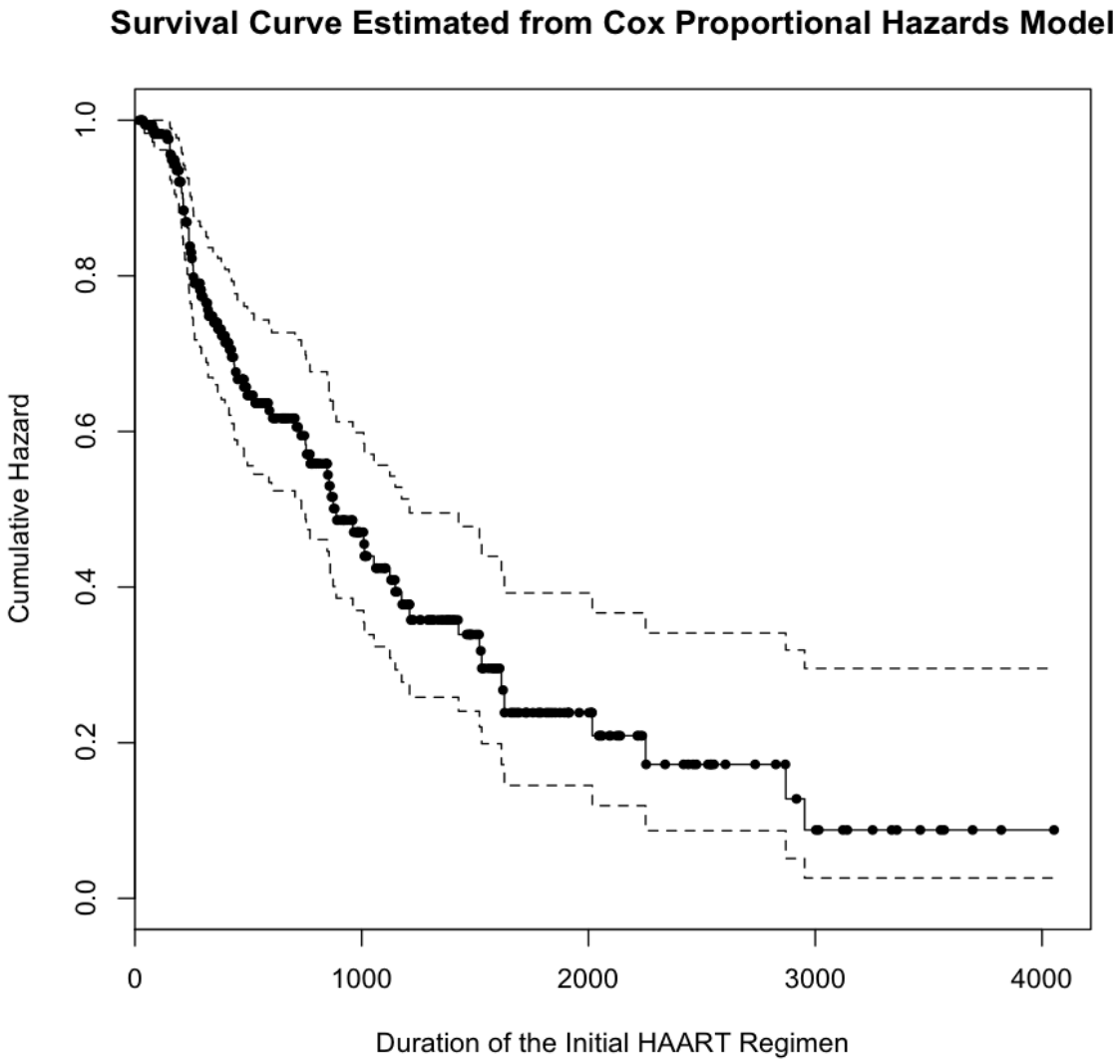

**Table 1**
**List of AIDS defining illnesses [32]**

Bacterial infections, multiple or recurrent*

Candidiasis of bronchi, trachea, or lungs

Candidiasis of esophagus†

Cervical cancer, invasive§

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (>1 month's duration)

Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month

Cytomegalovirus retinitis (with loss of vision)†

Encephalopathy, HIV related

Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (>1 month's duration)

Kaposi sarcoma†

Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex*†

Lymphoma, Burkitt (or equivalent term)

Lymphoma, immunoblastic (or equivalent term)

Lymphoma, primary, of brain

*Mycobacterium avium* complex or *Mycobacterium kansasii,* disseminated or extrapulmonary†

*Mycobacterium tuberculosis* of any site, pulmonary,†§ disseminated,† or extrapulmonary†

*Mycobacterium*, other species or unidentified species, disseminated† or extrapulmonary†

*Pneumocystis jirovecii* pneumonia†

Pneumonia, recurrent†§

Progressive multifocal leukoencephalopathy

*Salmonella* septicemia, recurrent

Toxoplasmosis of brain, onset at age >1 month†

Wasting syndrome attributed to HIV

## Table 2. Research questions, hypotheses, data needed and sources, and analysis required for each research question

| Research Question | Null Hypothesis | Alternative Hypothesis | Data Needed | Data Source | Analysis Required |
|---|---|---|---|---|---|
| What are the demographic and HAART regimen characteristics of this sample, and how do these characteristics compare between groups of patients with pill burdens of 1 pill/day, 2-3 pills/day, 4-5 pills/day and 6 or More pills/day? (Research Question 1) | n/a | n/a | **Demographic Data:**<br>-age<br>-race<br>-HIV risk factors<br>-health insurance status<br>-employment status<br>-smoking status<br>-marital status<br>-number of children<br>-co-morbid conditions reported<br>-ER visits<br>-hospitalizations<br>-weight<br>-blood pressure<br>-BMI<br>-CD4 baseline measurement<br>-Viral Load baseline measurement<br><br>**Mental Health Disorders:**<br>-diagnosis of MH disorder<br>-diagnosis of substance abuse disorder<br>-diagnosis of alcohol abuse disorder<br><br>**Regimen Characteristics:**<br>-date of initiation<br>-pill burden<br>-dosing frequency<br>-NRTI backbone<br>-3rd drug in combination<br>-use of FDC<br>-regimen end date | Clinic database | Descriptive statistics |
| Are there differences in the time to discontinuation between | There is no difference in regimen duration between these | There is a significant difference in duration between these | -1st HAART regimen prescribed<br>-pill burden<br>-dosing | Clinic database | Kaplan-Meier survival analysis |

| | | | | | |
|---|---|---|---|---|---|
| patients taking a 1 pill/day HAART vs. those that aren't? (Research Question 2) | two groups. | two groups. | frequency<br>-HAART initiation date<br>-HAART discontinuation date | | |
| Are there any differences in the time to discontinuation between patients utilizing initial HAART regimens with pill burdens of 1 pill/day, 2-3 pills/day, or 4+ pills/day? (Research Question 3) | There are no differences in regimen duration between these groups. | There are significant differences in regimen duration between these groups. | -1st HAART regimen prescribed<br>-pill burden<br>-HAART initiation date<br>-HAART discontinuation date | Clinic Database | Kaplan-Meier survival analysis |
| Are there differenes in the time to discontinuation between patients utilizing Atripla and Combivir? (Research Question 4) | There is no difference in regimen duration between these two groups. | There is a significant difference in duration between these two groups. | -1st HAART regimen prescribed<br>-HAART initiation date<br>-HAART discontinuation date | Clinic Database | Kaplan-Meier survival analysis |
| Are there differenes in the time to discontinuation between patients initiating therapy before 7/1/01 and after this date? (Research Question 5) | There is no difference in regimen duration between these two groups. | There is a significant difference in duration between these two groups. | -1st HAART regimen prescribed<br>-HAART initiation date<br>-HAART discontinuation date | Clinic Database | Kaplan-Meier survival analysis |
| How do patient and regimen characteristics influence hazards of discontinuation of HAART therapies? (Research Question 6) | These characteristics do not influence hazard of discontinuation. | These characteristics significantly influence hazard of discontinuation. | -demographic, mental health, and regimen data<br>-HAART initiation and discontinuation date | Clinic Database | Cox Proportional Hazard Model |

**Table 3: Crosstab Analysis Using ANOVA and Chi-Square Tests**

| | Daily Pill Burden | | | | | | One-Way ANOVA | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 Pill per Day | 2-3 Pills per Day | 4-5 Pills per Day | 6+ Pills per Day | Missing (n, % total) | Total | F-Ratio | df | p-value | Significant |
| | Mean Lower and Upper 95% Confidence Interval) | | | | | | | | | |
| Number of Children | 2.20 (1.41, 2.99) | 2.25, (0.48, 4.02) | 1.91 (1.35, 2.48) | 1.52 (1.14, 1.90) | 3, 2.6% | 1.79 (1.50, 2.07) | 1.247 | 3, 108 | 0.296 | |
| Age at Initiation of HAART | 28.781 (25.080, 32.482) | 29.98 (26.61, 33.35) | 23.83 (22.41, 25.26) | 27.12 (25.40, 28.83) | 0, 0% | 26.543 (25.442, 27.645) | 4.83 | 3, 111 | 0.003 | * |
| CD4 Cell Count at Initiation of HAART (cells/mL) | 313.06 (239.52, 386.61) | 426.22 (262.62, 589.83) | 484.83 (406.70, 562.97) | 469.89 (400.63, 539.15) | 0, 0% | 449.33 (405.91, 492.75) | 2.31 | 3, 111 | 0.08 | |
| Medication Adherence Meetings During Initial HAART Therapy | 4.47 (6.20, 2.73) | 2.00 (0.32, 3.68) | 2.79 (1.47, 4.10) | 3.40 (2.70, 3.79) | 11, | 3.25 (2.70, 3.79) | 1.852 | 3, 105 | 0.142 | |
| ER Visits During Initial HAART | 0.25 (0.01, 0.49) | 0.22 (0, 0.56) | 0.09 (0, 0.18) | 0.15 (0.04, 0.26) | 2, | 0.15 (0.08, 0.22) | 0.794 | 3, 109 | 0.5 | |
| Hospital Stays During Initial HAART | 0.19 (0, 0.48) | 0.22 (0, 0.56) | 0.50 (0.29, 0.71) | 0.77 (0.60, 0.95) | 3, | 0.56 (0.44, 0.68) | 5.237 | 3, 108 | 0.002 | * |
| ER Visits Six Months Before Initial HAART | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.06 (0, 0.12) | 9, | 0.03 (0, 0.06) | 1.06 | 3, 102 | 0.369 | |
| Hospital Stays Six Months Before Initial HAART | 0 (0,0) | 0.22 (0, 0.56) | 0.03 (0, 0.10) | 0.04 (0, 0.09) | 8, | 0.05 (0.01, 0.09) | 2.48 | 3, 103 | 0.065 | |
| Number of Co-Morbid Conditions During Initial HAART | 1.38 (0.53, 2.22) | 0.89 (0.29, 1.49) | 1.25 (0.88, 1.62) | 0.96 (0.65, 1.27) | 0, 0% | 1.10 (0.89, 1.32) | 0.829 | 3, 111 | 0.481 | |
| | | | | | | | | **Fisher's Exact Test** | | |
| | | | | | | | | df | Significance | Significant |
| **Insurance Status** | | | | | 0, 0% | | | 3 | 0.555 | |
| No Insurance | 7, 43.8% | 5, 55.6% | 12, 33.3% | 18, 33.3% | | 42, 36.5% | | | | |
| Has Insurance | 9, 47.2% | 4, 44.4% | 24, 67.7% | 35, 67.7% | | 57, 64.5% | | | | |
| **Race** | | | | | 0, 0% | | | | | |
| Black | 16, 100% | 8, 88.9% | 31, 886.1% | 45, 83.3% | | 100, 87.0% | | | | |
| White | 0, 0% | 1, 11.1% | 5, 13.9% | 9, 16.4% | | 15, 13.0% | | | | |
| **Employment Status** | | | | | 2, 1.7% | | | | | |
| Employed or in School | 10, 62.5% | 4, 50% | 15, 42.9% | 23, 42.6% | | 64, 54.2% | 3 | 0.696 | | |
| Not Employeed or in School | 6, 37.5% | 4, 50.0% | 20, 57.1% | 31, 57.4% | | 61, 45.8% | | | | |
| **Relationship Status** | | | | | 2, 1.7% | | 3 | 0.018 | * | |
| Not Single | 9, 47.2% | 1, 12.5% | 18, 52.4% | 37, 69.5% | | 65, 52.5% | | | | |
| Single | 7, 43.8% | 7, 87.5% | 17, 48.6% | 17, 31.5% | | 48, 47.5% | | | | |
| **Smoking Status** | | | | | 2, 1.7% | | | | | |
| Non-Smoker | 9, 56.3% | 5, 62.5% | 22, 62.9% | 42, 77.8%% | | 78, 69.0% | 3 | 0.235 | | |
| Smoker | 7, 43.8% | 3, 37.5% | 13, 37.1% | 12, 22.2% | | 35, 31.0% | | | | |
| **Start of Initial HAART Treatment** | | | | | 0, 0% | | | | | |
| Pre-Atripla Era (1/1/2001 to 6/30/2006) | 0, 0% | 6, 66.7% | 33, 91.7% | 12, 22.2% | | 51, 44.3% | | | | |
| Atripla Era (7/1/2006 to 12/31/2011) | 16, 100% | 3, 33.3% | 3, 8.3% | 42, 77.8% | | 64, 55.7% | | | | |
| **Combination Type Used for Initial Therapy** | | | | | 0, 0% | | | | | |
| Only NRTI | 0, 0% | 2, 22.2% | 0, 0% | 0, 0% | | 2, 1.7% | | | | |
| NRTI/NRTI | 16, 100% | 4, 44.4% | 32, 88.9% | 0, 0% | | 52, 45.2%% | | | | |
| NRTI/PI | 0, 0% | 0, 0% | 2, 5.6% | 54, 100% | | 56, 48.7% | | | | |
| NRTI/PI/PI | 0 , 0% | 3, 33.3% | 2, 5.6% | 0, 0% | | 5, 4.3% | | | | |
| **Use of PI Sparing Regimen in Initial Therapy** | | | | | 0, 0% | | | | | |
| PI-Sparing | 0, 0% | 3, 33.3% | 4, 11.1% | 54, 100% | | 61, 53.0% | | | | |
| Not PI-Sparing | 16, 100% | 6, 66.7% | 32, 88.9% | 0, 0% | | 54, 47.0% | | | | |

**Table 3a: Bonferonni Post Hoc Tests for Continuous Independent Variables Found to Have Significant Differences Across Categories of Pill Burden**

| Variable | Category 1 | Category 2 | Mean Difference | Std. Error | 95% Confidence Interval Lower Bound | 95% Confidence Interval Upper Bound | Significance | Significant |
|---|---|---|---|---|---|---|---|---|
| Age at the Time of Initiation of the First HAART Regimen | 1 Pill/Day | 2-3 Pills/Day | -1.17778 | 2.33892 | -7.461 | 5.1054 | 1 | |
| | | 4-5 Pills/Day | 4.91111* | 1.68662 | 0.3802 | 9.442 | 0.026 | * |
| | | 6 or More Pills/Day | 1.62037 | 1.59779 | -2.6719 | 5.9126 | 1 | |
| | 2-3 Pills/Day | 1 Pill/Day | 1.17778 | 2.33892 | -5.1054 | 7.461 | 1 | |
| | | 4-5 Pills/Day | 6.08889* | 2.092 | 0.469 | 11.7088 | 0.026 | * |
| | | 6 or More Pills/Day | 2.79815 | 2.02106 | -2.6312 | 8.2275 | 1 | |
| | 4-5 Pills/Day | 1 Pill/Day | -4.91111* | 1.68662 | -9.442 | -0.3802 | 0.026 | * |
| | | 2-3 Pills/Day | -6.08889* | 2.092 | -11.7088 | -0.469 | 0.026 | * |
| | | 6 or More Pills/Day | -3.29074* | 1.20781 | -6.5354 | -0.0461 | 0.045 | * |
| | 6 or More Pills/Day | 1 Pill/Day | -1.62037 | 1.59779 | -5.9126 | 2.6719 | 1 | |
| | | 2-3 Pills/Day | -2.79815 | 2.02106 | -8.2275 | 2.6312 | 1 | |
| | | 4-5 Pills/Day | 3.29074* | 1.20781 | 0.0461 | 6.5354 | 0.045 | * |
| Hospital Stays During the Initial HAART Regimen | 1 Pill/Day | 2-3 Pills/Day | -0.03472 | 0.25286 | -0.7144 | 0.6449 | 1 | |
| | | 4-5 Pills/Day | -0.3125 | 0.18399 | -0.807 | 0.182 | 0.554 | |
| | | 6 or More Pills/Day | -.58608* | 0.17311 | -1.0514 | -0.1208 | 0.006 | * |
| | 2-3 Pills/Day | 1 Pill/Day | 0.03472 | 0.25286 | -0.6449 | 0.7144 | 1 | |
| | | 4-5 Pills/Day | -0.27778 | 0.2275 | -0.8892 | 0.3337 | 1 | |
| | | 6 or More Pills/Day | -0.55136 | 0.21879 | -1.1394 | 0.0367 | 0.079 | |
| | 4-5 Pills/Day | 1 Pill/Day | 0.3125 | 0.18399 | -0.182 | 0.807 | 0.554 | |
| | | 2-3 Pills/Day | 0.27778 | 0.2275 | -0.3337 | 0.8892 | 1 | |
| | | 6 or More Pills/Day | -0.27358 | 0.13335 | -0.632 | 0.0848 | 0.256 | |
| | 6 or More Pills/Day | 1 Pill/Day | .58608* | 0.17311 | 0.1208 | 1.0514 | 0.006 | * |
| | | 2-3 Pills/Day | 0.55136 | 0.21879 | -0.0367 | 1.1394 | 0.079 | |
| | | 4-5 Pills/Day | 0.27358 | 0.13335 | -0.0848 | 0.632 | 0.256 | |

**Table 4: Kaplan-Meier Analysis of Patients Starting with Atripla vs. Any Other Regimen**

| | n | Discontinued During Study Time Points | Censored | % Censored | Mean Duration of Therapy (Days) | Standard Error | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| Atripla | 16 | 5 | 11 | 68.80% | 1574.97 | 214.56 | 1154.3 | 1995.516 |
| Other Regimen | 99 | 70 | 29 | 29.35 | 977.48 | 149.78 | 683.92 | 1271.05 |
| Total | 115 | 75 | 40 | 34.80% | 1193.58 | 170.75 | 858.9 | 1528.26 |

| Log Rank Test Chi-Square | df | Significance | Significant |
|---|---|---|---|
| 8.948 | 1 | 0.003 | * |

**Table 5: Kaplan-Meier Analysis of Patients Starting with HAART using 1 Pill/Day, 2-3 Pills/Day, 4-5 Pills/Day, and 6 or more Pills/Day**

| | n | Discontinued During Study Time Points | Censored | % Censored | Mean Duration of Therapy (Days) | Standard Error | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| 1 Pill/Day | 16 | 5 | 11 | 68.80% | 1574.97 | 214.56 | 115.429 | 1995.516 |
| 2-3 Pills/Day | 9 | 7 | 2 | 22.20% | 653.08 | 315.94 | 15.844 | 1254.323 |
| 4-5 Pills/Day | 36 | 23 | 13 | 36.10% | 1370.632 | 289.22 | 803.76 | 1937.51 |
| 6 or more Pills/Day | 54 | 40 | 14 | 25.90% | 651.58 | 100.86 | 453.902 | 849.259 |
| Total | 115 | 75 | 40 | 34.80% | 1193.58 | 170.75 | 858.903 | 1528.258 |

**Log Rank Test (All Four Groups)**

| Chi-Square | df | Significance | Significant |
|---|---|---|---|
| 16.703 | 3 | 0.001 | * |

**Log Rank Test (1 Pill/Day vs. 2-3 Pills/Day)**

| Chi-Square | df | Significance | Significant |
|---|---|---|---|
| 4.797 | 1 | 0.029 | * |

**Log Rank Test (1 Pill/Day vs. 4-5 Pills/Day)**

| Chi-Square | df | Significance | Significant |
|---|---|---|---|
| 4.334 | 1 | 0.037 | * |

**Log Rank Test (1 Pill/Day vs. 6+ Pills/Day)**

| Chi-Square | df | Significance | Significant |
|---|---|---|---|
| 11.461 | 1 | 0.001 | * |

**Table 6: Kaplan-Meier Analysis of Patients Starting with Atripla vs. Combivir as NRTI Backbone**

| | n | Discontinued During Study Time Points | Censored | % Censored | Mean Duration of Therapy (Days) | Standard Error | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| Atripla | 16 | 5 | 11 | 68.80% | 1574.97 | 214.56 | 1154.43 | 1995.516 |
| Combivir NRTI Backbone | 88 | 61 | 27 | 30.70% | 1020.29 | 170.91 | 685.31 | 1355.27 |
| Total | 104 | 66 | 38 | 36.50% | 1275.69 | 196.45 | 890.65 | 1660.72 |

**Log Rank Test**

| Chi-Square | df | Significance | Significant |
|---|---|---|---|
| 8.564 | 1 | 0.003 | * |

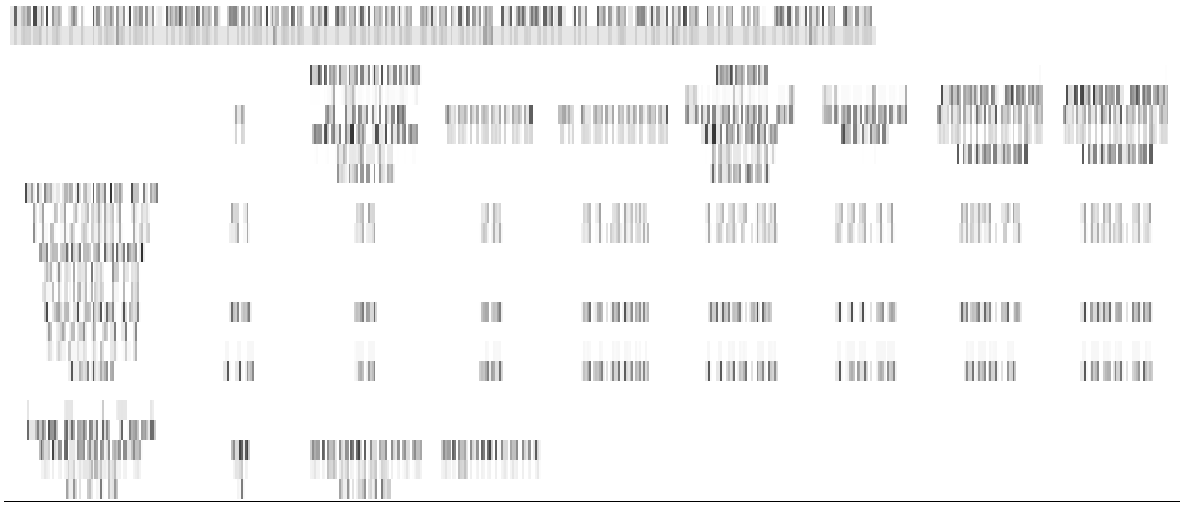

**Table 8: List of Variables Included in the Initial Cox Proportional Hazards Model**

| Variable Name | Variable Description | Values | Reference Category | Type of Variable | Included in Final Model |
|---|---|---|---|---|---|
| **pttime1** | Days elapsed in the patient's initial regimen at the time of the first measurement of CD4 t-cell count and viral load measurement | Ranged from 1 (representing the first day of treamtent), to 3821 (representing the longest duration of treament observed) | n/a | Continuous | Yes |
| **pttime2** | Days elapsed in the patient's initial regimen until the time of the second measurement of CD4 t-cell count and viral load, used in combination with pttime 1 to describe the duration of time which the CD4 t-cell count and viral load measurement represent | Ranged from 19 (representing the first day of treamtent), to 4053 (representing the longest duration of treament observed) | n/a | Continuous | Yes |
| **event** | A binary indicator used to describe if the event (discontinuation of therapy) has occurred in this observation at this timepoint | 0 and 1, where 0 indicated a patient has not yet discontinued at this time, and 1 means the patient discontinued the regimen at this measurement of Viral Load and CD4 t-cell count | n/a | Factor | Yes |
| **CD4Count** | CD4 t-cell count for the time period represented by pttime1 and pttime2 | Ranged from 5 to 2700 cells/mL | n/a | Continuous | Yes |
| **Base10ViralLoad** | The base 10 logarithm of the viral load measurement for the time period represented by pttime1 and ptttime2 | Ranged from 1.903 to 5.994 copies/mL, because viral load measurements of 79 or less are considered to be undetectable, 80 was used as a baseline value and all measurements recorded as <80 were recoded to this baseline value before their base 10 logarithms were taken | n/a | Continuous | Yes |
| **Insurance** | A binary indicator used to describe if the patient had any form of insurance during treatment | 0 and 1, where 0 indicated a patient did not have insurance and 1 indiciated the patient did have insurance | 0 (no insurance) | Factor | Yes |

| | | | | |
|---|---|---|---|---|
| **EmploymentStatus** | A binary variable used to indicate if the patient was employeed or in school at the time of initiation of the initial HAART regimen | 0 and 1, where 0 indicated a patient was not employed or in school and 1 indicated the patient was employeed or in school. | 0 (unemployed and not in school) | Factor |
| **Single** | A binary indicator used to describe if the patient was single or in some sort of relationship | 0 and 1, where 0 indicated a patient was either married, with partner, or in a dating relationship, and 1 indicated the patient was currently single or widdowed. | 0 (married, with partner, or in a dating relationship) | Factor |
| **SmokingStatus** | A binary indicator used to describe if the patient smoked or not | 0 and 1, where 0 indicated a patient did not smoke, and 1 indicated a patient did smoke | 0 (non-smoker) | Factor |
| **NumberChildren** | The number of children the patient had at the initiation of the first HAART regimen | Ranged from 0 to 7 | n/a | Continuous |
| **AgeatHAARTStart** | The patient's age at the initiation of the first HAART regimen | Ranged from 19.1 to 48.7 years | n/a | Continuous |
| **PillBurden** | The number of pills taken per day in the patient's initial HAART regimen | Ranged from 1 (representing Atripla regimens) to 8 | n/a | Continuous |
| **lumber of Comorbid Condition** | A continuous variable used to describe the number of comorbid conditions that were reported by providers in the patient's chart | Ranged from 0 through 5 | n/a | Continuous |
| **PregnantDuringHAART** | A binary indicator used to describe if the patient was pregnant during the time of her initial HAART regimen | 0 and 1, where 0 indicates the patient was not pregnant during the initial regimen, and 1 indicates she was. | 0 (not pregnant during the initial HAART) | Factor |

**Table 9: Tests of the Adherence to the Proportional Hazards Assumption in Variables Included in the Cox Proportional Hazards Models**

| Model Number | Variable Name | Chi-Square V | Significance | Significant | Dropped from the Model |
|---|---|---|---|---|---|
| 1 | CD4Count | 0.1564 | 0.6925 | | No |
| 1 | Base10ViralLoad | 0.8127 | 0.3673 | | No |
| 1 | Insurance | 1.0665 | 0.3017 | | No |
| 1 | EmploymentStatus | 3.335 | 0.0678 | | No |
| 1 | Single | 0.5451 | 0.4603 | | No |
| 1 | SmokingStatus | 5.7891 | 0.0161 | * | Yes |
| 1 | NumberChildren | 2.4529 | 0.1173 | | No |
| 1 | AgeatHAARTStart | 0.6868 | 0.4073 | | No |
| 1 | PillBurden | 3.8225 | 0.0506 | | No |
| 1 | Number of Co-Morbid Conditions | 0.9739 | 0.3237 | | No |
| 1 | PregnantDuringHAART | 0.0739 | 0.7857 | | No |
| 1 | Global Score | 20.2189 | 0.0424 | | |
| 2 | CD4Count | 0.6979 | 0.4035 | | No |
| 2 | Base10ViralLoad | 1.1986 | 0.2736 | | No |
| 2 | Insurance | 0.9089 | 0.3404 | | No |
| 2 | EmploymentStatus | 4.4149 | 0.0356 | * | Yes |
| 2 | Single | 0.5099 | 0.4752 | | No |
| 2 | NumberChildren | 1.6883 | 0.1938 | | No |
| 2 | AgeatHAARTStart | 0.8564 | 0.3547 | | No |
| 2 | PillBurden | 1.0235 | 0.3117 | | No |
| 2 | Number of Co-Morbid Conditons | 0.7745 | 0.3788 | | No |
| 2 | PregnantDuringHAART | 0.0238 | 0.8774 | | No |
| 2 | Global Score | 14.2932 | 0.16 | | |
| 3 | CD4Count | 0.6244 | 0.4294 | | No |
| 3 | Base10ViralLoad | 2.2848 | 0.1306 | | No |
| 3 | Insurance | 1.1972 | 0.2739 | | No |
| 3 | Single | 0.1907 | 0.6623 | | No |
| 3 | NumberChildren | 0.4384 | 0.5079 | | No |
| 3 | AgeatHAARTStart | 1.1136 | 0.2913 | | No |
| 3 | PillBurden | 1.9642 | 0.1611 | | No |
| 3 | Number of Co-Morbid Conditions | 1.3826 | 0.2397 | | No |
| 3 | PregnantDuringHAART | 0.0248 | 0.8749 | | No |
| 3 | Global Score | 10.299 | 0.3268 | | |

**Table 10: Structure of the Datafile Used in the Development of the Cox Proportional Hazards Model**

| ID | pttime1 | pttime2 | event | CD4Count | ViralLoad | Base 10 Log Viral Load | Insurance |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 54 | 0 | 1323 | 80 | 1.90309 | 0 |
| 1 | 55 | 125 | 0 | 828 | 80 | 1.90309 | 0 |
| 1 | 126 | 214 | 0 | 660 | 200 | 2.30103 | 0 |
| 1 | 215 | 284 | 0 | 741 | 3480 | 3.541579 | 0 |
| 1 | 285 | 286 | 0 | 807 | 8380 | 3.923244 | 0 |
| 2 | 1 | 132 | 0 | 1031 | 180 | 2.255273 | 1 |

| Employment Status | Single | SmokingStatus | NumberChildren | AgeatHAARTStart | PillBurden | Number of Comorbid Conditions | Pregnant DuringHAART |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 0 | 1 | 36.1 | 6 | 1 | 1 |
| 1 | 1 | 0 | 1 | 36.1 | 6 | 1 | 1 |
| 1 | 1 | 0 | 1 | 36.1 | 6 | 1 | 1 |
| 1 | 1 | 0 | 1 | 36.1 | 6 | 1 | 1 |
| 1 | 1 | 0 | 1 | 36.1 | 6 | 1 | 1 |
| 0 | 1 | 0 | 1 | 21.8 | 4 | 3 | 0 |

**Table 11: Coefficients of the Final Cox Proportional Hazards Model**

| Variable | Beta | Exp(Beta) | Lower 95% Confidence Interval for Exp(Beta) | Upper 95% Confidence Interval for Exp(Beta) | Standard Error of Beta | Z-score | Significance | Significant |
|---|---|---|---|---|---|---|---|---|
| CD4Count | 0.0004861 | 1.0004862 | 0.9996 | 1.001 | 0.0004494 | 1.082 | 0.27939 | |
| Base10LogViralLoad | 0.3626732 | 1.4371662 | 1.1301 | 1.828 | 0.122661 | 2.957 | 0.00311 | * |
| Insurance | 0.4984648 | 1.6461921 | 0.9741 | 2.782 | 0.2676944 | 1.862 | 0.06259 | |
| Relationship Status | -0.0759122 | 0.9268976 | 0.573 | 1.499 | 0.245077 | -0.309 | 0.75707 | |
| NumberChildren | 0.07856 | 1.0817282 | 0.9223 | 1.269 | 0.0813403 | 0.966 | 0.33413 | |
| AgeatHAARTStart | 0.0124652 | 1.0125432 | 0.9702 | 1.057 | 0.0218146 | 0.571 | 0.56772 | |
| PillBurden | 0.2070535 | 1.2300483 | 1.0478 | 1.444 | 0.0818222 | 2.531 | 0.01139 | * |
| Number of Co-Morbid Conditions | -0.1889695 | 0.8278117 | 0.6534 | 1.049 | 0.1207345 | -1.565 | 0.11754 | |
| PregnantDuringHAART | 0.0821126 | 1.085578 | 0.6381 | 1.847 | 0.2711344 | 0.303 | 0.76201 | |

| | |
|---|---|
| **Concordance** | 0.681 |
| **R Squared** | 0.04 |
| **Likelihood Ratio Test** | 28.1 |
| **Degrees of Freedom for the Likelihood Ratio Test** | 9 |
| **Significance of the Likelihood Ratio Test** | 0.0009172 |

**Table 12: Data Collection Sheet**

| URN | DOB | EnrollDate | DateClosed | InsuranceTyp | HIVRiskFacto | Race | Employment | Marital Statu | Smoking Stat | Number of C | Duration of F | HAART Start | HAART used |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SARY040382 | 11/78 | 10/01 | | 1 | 1 | 1 | 1 | 4 | 0 | 1 | 280 | 3/2/09 | Combivir |
| ARBM06016 | 6/66 | 2/02 | 3/06 | 2 | 1 | 1 | 0 | 3 | 0 | 1 | 317 | 1/5/02 | Combivir |
| TNKO090865 | 9/77 | 12/01 | | 2 | 1 | 1 | 0 | 4 | 1 | 1 | 28 | 5/7/12 | Truvada |
| AGBR092573 | 9/73 | 3/02 | | 1 | 1 | 2 | 2 | 3 | 0 | 1 | 2940 | 4/8/02 | Trizivir |
| FLFA010179 | 7/68 | 9/03 | | 1 | 1 | 2 | 0 | 1 | 0 | 2 | 350 | 6/1/04 | Combivir |

| Additional H | Additional H | CD4BL | CD4BLDate | VLBL | VLDate | CD4-2 | CD4-2Date | VL-2 | VL-2Date | CD4-3 | CD4-33Date | VL-3 | VL-3Date |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kaletra | | 885 | 2/25/09 | <80 | 2/25/09 | 828 | 4/21/09 | <80 | 4/21/09 | 660 | //1/09 | 200 | //1/09 |
| Viramune | | 1031 | 1/8/02 | 180 | 12/26/01 | 851 | 5/21/02 | <80 | 5/21/02 | | | | |
| Reyataz | Norvir | 391 | 3/6/12 | 57100 | 3/6/12 | | | | | | | | |
| Viramune | | 491 | 3/26/02 | 48,000 | 3/26/02 | 498 | 7/9/02 | 340 | 5/13/02 | 674 | 1/8/03 | <80 | 7/9/02 |
| Kaletra | | 347 | 6/25/03 | 59718 | 6/25/03 | 431 | 10/12/04 | 115 | 10/12/04 | 499 | 11/15/04 | <80 | 11/15/04 |

| HAART Disco | Reason for D | Switch To 1 | Switch To 2 | Switch To 3 | MedAdMeet | MedAdMeet | Preg. During | Preg HAART Switch |
|---|---|---|---|---|---|---|---|---|
| 12/7/09 | Loss to follow up | | | | 3 | | 1 | 0 |
| 11/18/02 | Simplify Regi | Viramune | Epivir | Zerit | 0 | 0 | 0 | 0 |
| 6/4/12 | Patient still on regimen | | | | 2 | | 0 | 0 |
| 4/26/10 | Simplify Regi | Atripla | | | 3 | 2 | 0 | 0 |
| 5/17/05 | Patient moved | | | | 1 | | 0 | 0 |

| ER Visits Bef | ER Visits Dur | ER Visits Afte | Hosp. Stay B | Hosp. Stay D | Hosp. Stay A | CMC1 | CMC2 | CMC3 | CMC4 | CMC5 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 1 | 0 | Anemia | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 | Hypertension | | | | |
| 0 | 0 | 0 | 0 | 0 | 0 | Rhinitis | Insomnia | | | |
| 0 | 0 | 0 | 0 | 1 | | Depression | | | | |
| | 0 | | | 0 | | Asthma | Arthritis | T2DM | HTN | Migranes |

**Table 13: Summary of Included/Excluded Patients**

| Included Patients by Year | | | |
|---|---|---|---|
| **Year** | **Total Reviewed (n)** | **Included (n)** | **% Included** |
| 2001 | 16 | 10 | 62.50% |
| 2002 | 38 | 14 | 36.80% |
| 2003 | 40 | 9 | 22.50% |
| 2004 | 28 | 8 | 28.60% |
| 2005 | 46 | 9 | 20.00% |
| 2006 | 46 | 10 | 21.80% |
| 2007 | 56 | 14 | 25% |
| 2008 | 56 | 11 | 20.00% |
| 2009 | 64 | 11 | 17.20% |
| 2010 | 61 | 14 | 23.00% |
| 2011 | 47 | 5 | 10.60% |
| | | | |
| Total Charts Reviewed | 498 | | |
| Patients Included | 115 | | 23.10% |
| Patients Excluded | 383 | | 72.90% |
| Excluded Because Patient Did Not Start at Clinic | 374 | | 97.70% |
| Excluded Because Patient's Age was Less Than 19 | 9 | | 2.30% |

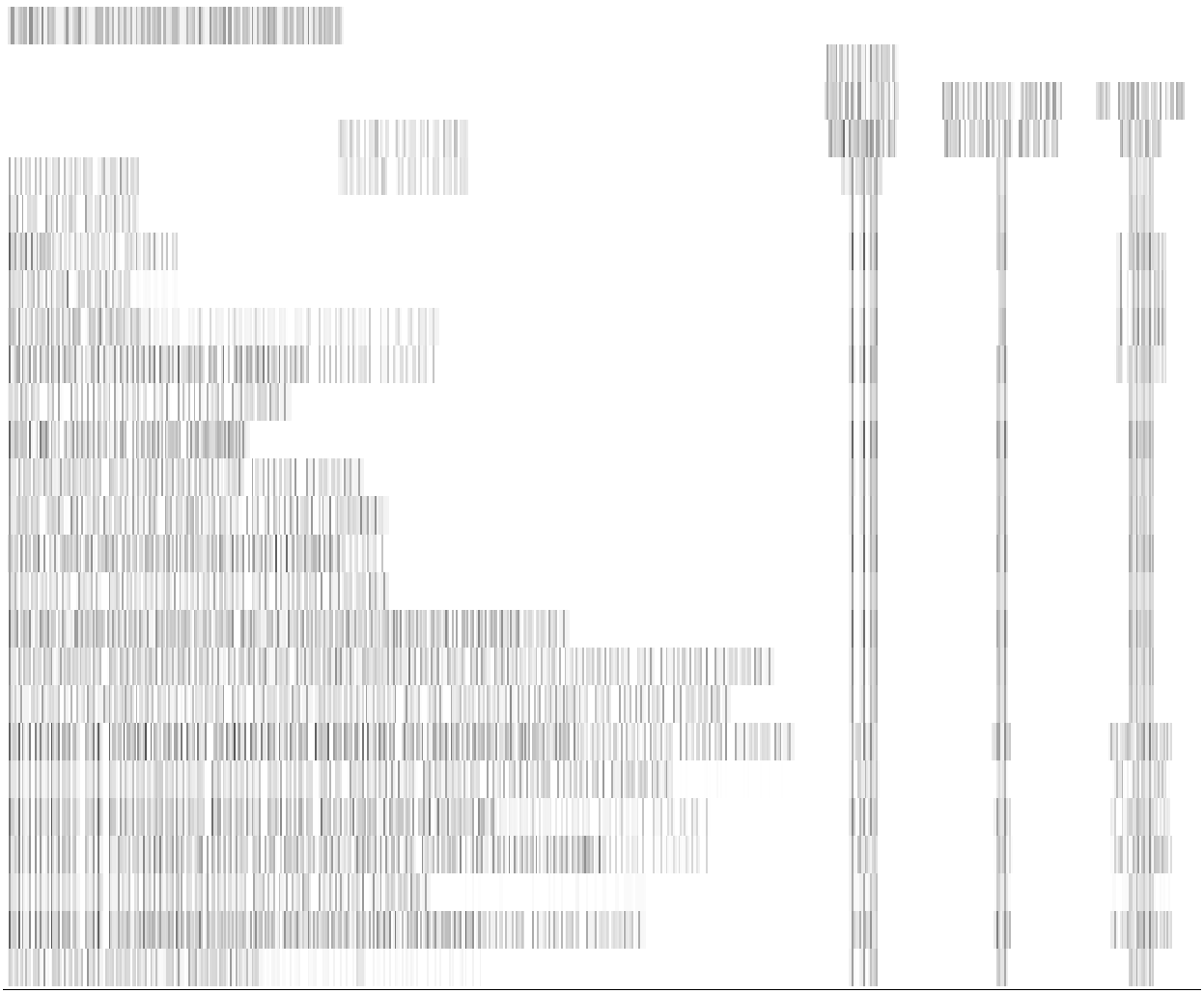

**Table 15: Variable Means and Standard Deviations**

| | n | Mean | Standard Deviation | Minimum | Maximum |
|---|---|---|---|---|---|
| Age at Initiation of HAART (years) | 115 | 26.6 | 5.9 | 19.1 | 48.7 |
| Number of Children | 112 | 1.8 | 1.5 | 0 | 7 |
| Duration of Initial HAART Regimen (days) | 115 | 696.8 | 747.7 | 28 | 4542 |
| Daily Pill Burden | 115 | 4.45 | 1.8 | 1 | 8 |
| CD4 Cell Count at Initiation of HAART (cells/mL) | 115 | 449.33 | 235 | 5 | 1574 |
| Medication Adherence Meetings During Initial HAART | 109 | 3.25 | 2.9 | 0 | 18 |
| Medication Adherence Meetings Six Months After Discontinuing Initial HAART | 70 | 0.71 | 0.725 | 0 | 2 |
| Number of Emergency Room Visits Six Months Before Initiating Initial HAART | 106 | 0.03 | 0.167 | 0 | 1 |
| Number of Emergency Room Visits During Initial HAART | 113 | 0.15 | 0.383 | 0 | 2 |
| Number of Emergency Room Visits Six Months After Discontinuing Initial HAART | 97 | 0.01 | 0.102 | 0 | 1 |
| Number of Hospitalizations Six Months Before Initiating Initial HAART | 107 | 0.05 | 0.212 | 0 | 1 |
| Number of Hospitalizations During Initial HAART | 112 | 0.56 | 0.641 | 0 | 3 |
| Number of Hospitalizations Six Months After Discontinuing Initial HAART | 96 | 0.03 | 0.175 | 0 | 1 |
| Number of Co-Morbid Conditions During Initial HAART | 115 | 1.1 | 1.173 | 0 | 5 |

[illegible]

| [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |
|---|---|---|---|---|---|---|---|
| [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | [illegible] |

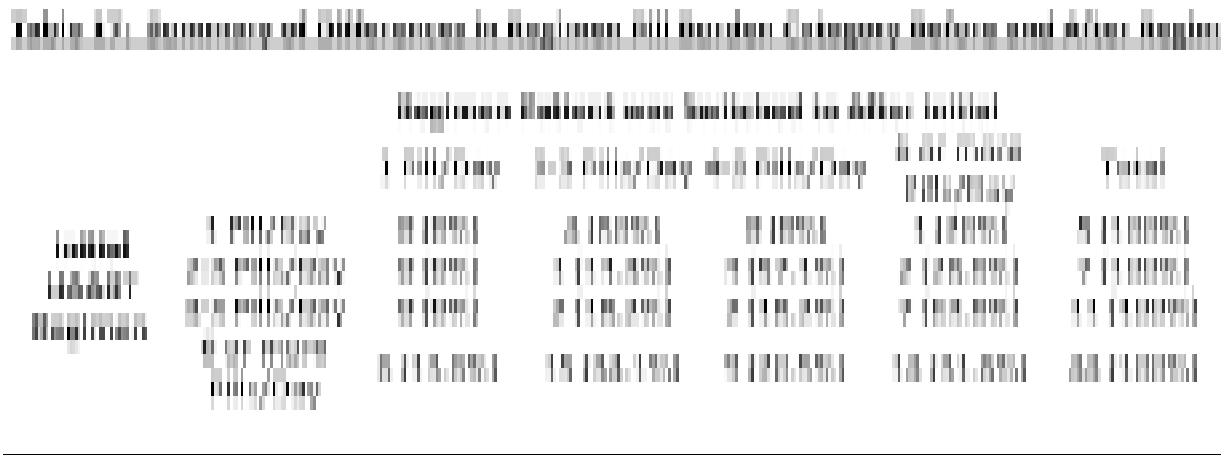

**Table 18: Kaplan-Meier Analysis of Type of Drugs Used in Initial HAART**

| | n | Discontinued During Study Time Points | Censored | % Censored | Mean Duration of Therapy (Days) | Standard Error | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| NRTI Only | 2 | 2 | 0 | 0.00% | 200 | 144 | 0 | 482.24 |
| NRTI/NNRTI | 52 | 28 | 24 | 46.20% | 1708.37 | 284.275 | 1151.19 | 2265.55 |
| NRTI/PI | 56 | 42 | 14 | 25.00% | 649.04 | 95.455 | 461.95 | 836.13 |
| NRTI/PI/PI | 5 | 3 | 2 | 40.00% | 322.75 | 132 | 64.02 | 581.48 |
| Total | 115 | 75 | 40 | 34.80% | 1193.58 | 170.754 | 858.9 | 1528.26 |

**Log Rank Test for all Four Categories**

| Chi-Square | df | Significance |
|---|---|---|
| 19.984 | 3 | <0.001 |

**Log Rank Test for NRTI vs. NRTI/NNRTI**

| Chi-Square | df | Significance |
|---|---|---|
| 10.228 | 1 | 0.001 |

**Log Rank Test for NRTI vs. NRTI/PI**

| Chi-Square | df | Significance |
|---|---|---|
| 2.926 | 1 | 0.087 |

**Log Rank Test for NRTI vs. NRTI/PI/PI**

| Chi-Square | df | Significance |
|---|---|---|
| 0.141 | 1 | 0.707 |

**Table 19: Results of the Analysis of Patients who Discontinued Therapy Due to Adherence Issues**

| | n | Discontinued During Study Time Points | Censored | % Censored | Mean Duration of Therapy (Days) | Standard Error | Lower 95% Confidence Interval | Upper 95% Confidence Interval |
|---|---|---|---|---|---|---|---|---|
| 1 Pill/Day | 2 | 2 | 0 | 0.00% | 59.5 | 31.5 | 0 | 121.24 |
| 2-3 Pills/Day | 3 | 3 | 0 | 0.00% | 164.67 | 90.34 | 0 | 341.72 |
| 4-5 Pills/Day | 10 | 10 | 0 | 0.00% | 656.8 | 213.47 | 238.41 | 1075.19 |
| 6 or More Pills/Day | 19 | 19 | 0 | 0.00% | 489.32 | 91.95 | 309.09 | 669.54 |
| Total | 34 | 34 | 0 | 0.00% | 484.65 | 84.49 | 319.05 | 650.25 |

**Log Rank Test (All Four Groups)**

| Chi-Square | df | Significance |
|---|---|---|
| 3.635 | 1 | 0.057 |

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