MYOCARDIAL INFARCTION AMONG HIV-INFECTED PATIENTS ENROLLED IN THE NORTH CAROLINA MEDICAID PROGRAM

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ABSTRACT

EMILY BROUWER: Myocardial Infarction among HIV-infected patients enrolled in the North Carolina Medicaid program
(Under the direction of Til Stürmer)

The introduction of combination antiretroviral therapy (cART) in the mid-1990s for the treatment of Human Immunodeficiency Virus (HIV)-infection has substantially reduced AIDS related morbidity and mortality. However, non-AIDS related conditions including myocardial infarction (MI) events are an increasing concern to HIV-infected patients, their providers and the HIV care management system. There has been some evidence from observational studies that suggests other antiretroviral agents, including abacavir, may increase the risk of myocardial infarction, independently of their effect on traditional MI risk factors, however, meta-analyses of clinical trial data has not confirmed these findings. Administrative claims data may be a valuable resource for studying long term and rare outcomes related pharmaceutical treatments and little work on HIV clinical outcomes has been attempted using these types of data in the United States. Therefore, we aimed to further investigate the effect of specific antiretrovirals on MI using the North Carolina Medicaid administrative data. In order to evaluate effects of treatments in the absence of a randomized controlled clinical trial (RCT), it is important to design a study that would most closely an RCT, should it be possible to conduct such a study. Therefore, we first validated myocardial infarction outcomes using the UNC HIV CFAR Clinical Cohort (UCHCC) as a gold standard. We showed that the use of ICD-9 codes combined with length of hospitalization criteria has a high specificity and moderate sensitivity for the ascertainment of MI events (Sensitivity: 0.588-0.824, Specificity: 0.982-0.994).

These findings are important as high specificities reduce the potential for bias due to outcome misclassification in comparative safety studies such as this one. We then conducted a new user, active comparator cohort study to investigate the relationship between specific antiretroviral use and myocardial infarction outcomes. We found that the rate of MI among recipients of abacavir with or without zidvoudine as a part of the cART regimen was higher than that of tenofovir (Adjusted Hazard Ratio: 1.43 [95% Confidence Interval: 0.25, 8.31] and Adjusted Hazard Ratio: 2.95 [95% Confidence Interval: 0.89, 9.72] respectively). We did not observe clinically meaningful differences in the effect of other antiretroviral treatments on MI.

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LIST OF ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome

ACTG: AIDS Clinical Trials Group

HIV: Human Immunodeficiency Virus

cART: Combination Antiretroviral Therapy

CHD: Coronary Heart Disease

CVD: Cardiovascular Disease

D:A:D Study: Data Collection on Adverse Events of Anti-HIV Drugs

FDAAA: Food and Drug Administration Amendment Act

ISTI: Integrase Strand Transfer Inhibitor

MI: Myocardial Infarction

NRTI: Nucleoside Reverse Transcriptase Inhibitor

NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor

PI: Protease Inhibitor

SMART Study: Strategies for Management of Anti-Retroviral Therapy

UNC: University of North Carolina at Chapel Hill

UNC-ID: University of North Carolina at Chapel Hill, Infectious Diseases Clinic

UCHCC: UNC-CFAR HIV Clinical Cohort

CHAPTER 1

STATEMENT OF SPECIFIC AIMS

The introduction of combination antiretroviral therapy (cART) in the mid-1990s for the treatment of Human Immunodeficiency Virus (HIV)-infection has substantially reduced AIDS related morbidity and mortality. However, non-AIDS related conditions including coronary heart disease (CHD) in particular, are an increasing concern to HIV-infected patients, their providers and the HIV care management system. Recent evidence suggests that HIV itself may increase CHD risk through a direct effect of HIV infection on inflammation and vascular function. Both antiretroviral therapy and HIV infection have been associated with atherogenic changes in the lipid profile. Longer duration of cART use may also be associated with increased CHD risk and certain antiretrovirals may have a greater effect on CHD risk than other antiretrovirals. Some protease inhibitors may increase the risk of CHD, at least in part, due to their effect on dyslipidemia and insulin resistance. There has been some evidence suggesting that other antiretroviral agents, including abacavir, may increase the risk of myocardial infarction, independently of their effect on traditional CHD risk factors possibly by increasing immune activation and/or thrombogenic potential, as measured by markers such as C-reactive protein and D-dimer.[1, 2] The existing clinical research has not been conclusive, and many of the larger studies evaluating CHD risk have not been conducted in the US, where different patient demographic and clinical characteristics may

result in different CHD risks. Administrative claims data may be a valuable resource for studying long term and rare outcomes related to medical treatments. However, very little work on HIV clinical outcomes has been attempted using these types of data in the United States.

We propose to validate coronary heart disease ascertainment, specifically myocardial infarction, in the Medicaid administrative claims data by linkage to the UNC-CFAR HIV clinical cohort. We will also examine the relationship between use of antiretrovirals and incidence of myocardial infarction, among HIV-infected persons in North Carolina between the years 2002 and 2008. For these analyses, we will rely on the publicly financed North Carolina Medicaid database. We will use advanced pharmacoepidemiologic techniques to adjust for measured confounding and assess unmeasured confounding. These techniques will include propensity scores to control for factors that may lie on the causal pathway. The proposed study will improve our understanding of the antiretroviral use–CHD relationship and the development of CHD in an HIV-infected population receiving care in the United States. Furthermore, validation of outcome measurements obtained from the claims data will enable research opportunities beyond those available in clinical cohort databases.

Drawing on the publicly funded North Carolina Medicaid claims, as well as, the UNC-CFAR HIV Clinical Cohort databases, we will accomplish each of the proposed objectives through the following specific aims:

Aim 1. Validate claims-based myocardial infarction measurements for the association between antiretroviral use and myocardial infarction among HIV patients receiving care in North Carolina.

Hypothesis: Outcome measurements obtained from the Medicaid claims data will be consistent with those measured in the UNC HIV Clinical Cohort (gold standard).

Aim 2. Estimate the association of the use of specific antiretroviral medications on incident myocardial infarction among North Carolina HIV-infected patients in enrolled in Medicaid.

Hypothesis: Recent exposure to abacavir, but not other nucleoside reverse transcriptase inhibitors increases the rate of myocardial infarction. Cumulative exposure to protease inhibitors that are strongly associated with changes in lipid profiles but not other protease inhibitors or non-nucleoside reverse transcriptase inhibitors increase the rate of incident myocardial infarction.

CHAPTER II

BACKGROUND AND SIGNIFICANCE

HIV-infection

HIV infection remains a leading cause of illness and death in the U.S., increasingly affecting women, racial and ethnic minorities, and those with traditionally poorer access to medical care.[3-5] Currently there are approximately 1.1 million people living with HIV/AIDS in the United States and it is estimated that approximately 56,000 new cases occur annually.[4, 6] North Carolina and other states in the Southeastern U.S., are especially affected by the HIV epidemic. From 2000 to 2003 the number of new reported AIDS cases increased over 35% in the South, in comparison to 5% nationally; the overall rate of HIV infection was 11.6 per 100,000 persons nationally, but 14.7 in the Southeastern U.S.[7] The Southeastern U.S., also consistently reports the highest death rates from HIV in the country.[7] However, reasons for these differences are to date poorly understood. Through the end of 2007, 32,583 HIV-infected individuals had been reported to the State of North Carolina, with an estimated 21,593 individuals currently living, and approximately 2,000 new infections diagnosed each year.[8] These figures may underestimate the HIV epidemic in North Carolina because of under-reporting and in-migration of HIV-infected individuals from other states.[8] Moreover many individuals living with HIV do not know that they are infected.[3]

Morbidity and mortality from HIV infection has decreased dramatically since the mid 1990's with the introduction of cART. In the U.S., the number of AIDS deaths has declined from 21,460 in 1996 to 16,316 in 2005, while the number of Americans living with AIDS increased by 28% from 2001 to 2005. A similar phenomenon has been observed in other developed countries where cART is routinely used for treatment of HIV infection.[9-11] A large collaborative project conducted in the U.S., observed striking decreases in mortality rates from 1996 to 2004, however, the proportion of deaths attributed to a non-AIDS defining primary or secondary cause increased over time.[12]

There are currently 28 antiretroviral agents approved by the FDA for the management of HIV-infection, belonging to six classes based on modes of action (please see appendix A for a list of FDA approved antiretrovirals). The most widely used classes include the nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). These agents are given in combination, with standard **initial** treatment including two NRTIs with either one NNRTI or one PI.[13, 14] Most of the widely used PIs are used in combination with a low dose of ritonavir, a PI with inhibitory effect on the cytochrome P450 3A4 isoenzyme. The combination of most PIs with ritonavir increases the plasma half-life of the active PI thereby increasing drug exposure.[15] CD4 cell counts and HIV RNA levels guide the initiation of cART, especially in the presence of one or more AIDS defining clinical conditions. Current guidelines indicate that cART should be initiated once CD4 cell counts drop below 350 cells/mm^3 with a further suggestion that treatment initiation may be beneficial if initiated at higher CD4 cell counts (350-500 cells/mm^3).[15-17]

HIV infection and coronary heart disease

Coronary heart disease (CHD) which includes myocardial infarction, cerebrovascular disease resulting in stroke, peripheral arterial disease and aortic atherosclerosis and thoracic or abdominal aneurysm, are all diagnoses included in the broad definition of cardiovascular disease (CVD). CHD is the most common of the CVD diagnoses. The lifetime risk of CHD is 50% in men and 30% in women.[18] Patients diagnosed with CHD have the presence of one of the following: coronary insufficiency, myocardial infarction, or electrocardiographic or enzyme changes suggesting a myocardial infarction.[18] CHD rates may be higher among HIV-infected individuals than the general population. For example, the estimated myocardial infarction incidence rates among HIV-infected patients range from 1 to 10 myocardial infarction events per 1000 person-years compared to 2 to 4 events per 1000 person-years in the general population.[5, 19-25]

Most PIs and thymidine NRTIs may be associated with dyslipidemia and insulin resistance. HDL cholesterol levels increase by about 15 to 50% with cART.[26, 27] LDL cholesterol levels also increase and PI-based cART is associated with sustained increases in triglyceride levels.[21, 28-30] Additionally, cART has been linked to peripheral fat loss and visceral fat gain, which are associated with insulin resistance, hypertriglyceridemia and low levels of HDL cholesterol.[31, 32] These body shape changes on cART may be associated with reduced levels of insulin sensitizing hormone adiponectin.[33, 34] Low levels of adiponectin lead to reduced fractional clearance rates of VLDL, intermediate-density lipoprotein (IDL) and LDL apolipoprotein B-100 as well as insulin resistance and with greater risk of myocardial infarction.[35] Moreover, some NRTIs, specifically stavudine and zidovudine, are known to alter mitochondrial function which may contribute to the

development of insulin resistance and type 2 diabetes.[36, 37] Finally, relatively high concentrations of certain PIs in vitro, including ritonavir, amprenavir and saquinavir, inhibit endothelium-dependent vasodilatation.[38, 39] However, many of these mechanisms are not well understood and need to be further assessed in larger clinical studies.

Several studies have shown that a greater cumulative cART exposure may be associated with increased CHD event incidence rates, after accounting for important confounding factors, including age.[2, 19, 40-42] The largest study to evaluate CHD events among HIV-infected patients to date is the Data Collection on Adverse Events of Anti-HIV Drugs (D-A-D) study, which is an international collaboration of clinical cohorts in the U.S., Europe, and Australia, with over 30,000 person-years of follow-up.[21] In the D-A-D study the estimated myocardial infarction incidence rate ranged from 1 to 10 myocardial infarction events per 1,000 person-years depending on the patient demographic and clinical characteristics and was greater among patients with longer cART exposure.[19-21] However, another large study, the Strategies for Management of Anti-Retroviral Therapy (SMART) study designed to evaluate intermittent, CD4 cell count-guided antiretroviral therapy, was stopped early when an interim analysis found that intermittent antiretroviral therapy was associated with more deaths and AIDS events, and with greater rates of fatal and nonfatal CHD, as well as other major, non-opportunistic adverse events.[43] Antiretroviral therapy interruption in the SMART study was associated with an increase in the total to HDL cholesterol ratio, which would be expected to confer an increase in CVD risk.[44] Although total and LDL cholesterol levels fell with treatment interruption, HDL cholesterol levels fell proportionately more, presumably because of increased HIV replication with accompanying changes in inflammation and immune activation.

Specific antiretrovirals may increase CHD risk while others have little or no effect.[40, 45] As described above, greater cumulative exposure to PIs is thought to increase the risk of myocardial infarction, in part through their metabolic effects.[20, 40, 46, 47] However, associations may vary depending upon the PI used, for example, patients exposed to the PIs indinavir and lopinavir/ritonavir may be at increased risk of myocardial infarction independent of the effect of ritonavir, while the use of PIs saquinavir and nelfinavir may not have the same effect.[46] Also based on D-A-D study results, recent exposure to the NRTIs, abacavir and didanosine, may increase risk of myocardial infarction in comparison to other NRTIs [Relative Rate: 1.63 (95% CI: 1.30-2.04) and Relative Rate: 1.40 (95% CI: 1.11-1.77) respectively]. An analysis of the SMART study confirmed this effect where current use of abacavir was associated with increased risk of CHD endpoints [Relative Rate 1.80 (95% CI:1.04-3.11)].

However, even for the most well studied relationship of the effect of abacavir on myocardial infarction risk, the available evidence to date is inconclusive**.** In a synthesized analysis of 54 GlaxoSmithKline-sponsored clinical trials there was no effect of abacavir use on 24 to 48 week risk of myocardial infarction or coronary artery disease.[48, 49] Similarly, no evidence of a relationship between recent abacavir use and myocardial infarction or cardiovascular disease was observed in a study of five AIDS Clinical Trials Group (ACTG) studies.[50] A more recent meta-analysis of randomized controlled trials containing abacavir, sponsored by the FDA, revealed no increased risk of myocardial infarction associated with abacavir. In a recent observational study using the Veteran's Administration database, Bedimo et al. also found that after adjusting for age, hyperlipidemia, diagnoses of hypertension, type 2 diabetes, and smoking status there was little relationship between

abacavir use and myocardial infarction. Further, the observed small relationship between abacavir and myocardial infarction in this Veteran's Administration study was attenuated when controlling for chronic kidney disease at onset of the last regimen.[51]

In comparison, the point estimates and associated 95% confidence intervals for the relationship between abacavir use and myocardial infarction incidence rates observed in the D-A-D, SMART, STEAL, French Hospital Database studies as well as a nationwide study of all Danish HIV patients suggest an increased risk of experiencing a CHD event with the use of abacavir. [1, 2, 52, 53] However, additional analyses of the French Hospital Database study found that the relationship between abacavir and myocardial infarction was not seen when assessing cumulative use or upon restriction to non-users of cocaine or intravenous drugs. [52]

Several studies have explored a potential biological mechanism for the observed increased coronary heart disease risk among patients with exposure to abacavir. Two large interval cohort studies of HIV infected patients, the Multicenter AIDS Cohort Study and the Womens' Interagency HIV Study did not show any increase in markers of inflammation among users of abacavir.[54] However, two small studies demonstrated a relationship between endothelial function and platelet hyperreactivity in patients using abacavir. [55, 56]

The majority of the evidence available to date involved a large proportion of HIV-infected patients that living in the European Union and of European descent. Because of possible differences in underlying myocardial infarction risk factors between European and American HIV-infected individuals, results from the European studies may not be generalizable to the U.S., HIV population. Thus further investigation of this relationship in an American HIV-infected population is warranted.

Administrative Claims Data and Clinical Cohort Studies for Drug Safety Research

Randomized controlled trials (RCT) have led to important advances in the management of HIV-infection and the health of HIV-infected patients. The random assignment to treatment interventions allows for a balance in all measured and unmeasured factors resulting in an unbiased assessment of the impact of the treatment on the outcome. However, many HIV antiretroviral therapy RCTs require strict enrollment criteria, maximizing internal validity while compromising the ability to generalize results outside the specified criteria. Moreover, given their expense and experimental nature, RCTs generally include a small number of patients and are of short-duration, especially now that successfully treated HIV-infected individuals are expected to live for decades. Therefore, RCTs are not well suited for studying long-term effectiveness or unintended effects of antiretrovirals that may be rare or have long latency periods.

Clinical cohort studies are currently often used for studies on clinical outcomes of HIV infected patients because they are generally conducted among a heterogeneous patient population leading to results that are more generalizable to the broad HIV population. Most clinical cohort studies also collect information on potential confounding factors of many exposure-outcome relationship including CD4 counts and HIV RNA lab values. However, as the data collected on patients in the clinical cohort study is generally part of clinical care, there is a lack of random intervention assignment that requires special techniques to analyze study results adjusting for possible confounding of the effect of a treatment on a specific outcome. Therefore, while the results presented from a clinical cohort study are often generalizable to a greater population, internal validity is often compromised. Large clinical cohort studies and collaborations among individual clinical cohort studies have contributed

substantially to our understanding the effectiveness of different antiretroviral treatments.[1, 40, 57-59] Notably the largest and most important study conducted to date on CHD risk among HIV-infected patients, and the possible role that certain antiretrovirals may have in increasing CHD risk is a clinical cohort study (e.g. D-A-D).[1, 21, 40, 60]

The Food and Drug Administration (FDA) monitors the safety of medications through the Adverse Event Reporting System (AERS). This system is a "passive system" based on spontaneous adverse events reported to the agency predominantly by drug manufacturers but also by pharmacists, physicians, other care providers, and consumers.[61] The FDA utilizes signal detection methods relying on both frequentist and Bayesian models to identify adverse events that are medication related.[62] This system is effective at identifying severe short-term side effects of medications such as anaphylaxis or torsades de pointes as these events usually occur immediately after the initiation of a medication and are often readily attributable to the use of the medication by the health care provider. However, the current system is not effective at identifying adverse events attributed to the long-term or cumulative use of medications. In addition, events that are common in the general population, like myocardial infarction, may not be reported to the FDA as an adverse drug event. Therefore, it would be challenging to investigate the relationship between CHD and antiretroviral use using the current system.

In order to more comprehensively address the safety of medications, Congress recently passed the Food and Drug Administration Amendment Act (FDAAA) of 2007. The FDAAA aims to strengthen the FDA and its role in the regulation of drug products. Included in the FDAAA is the "Sentinel Initiative" which aims to create a "national, integrated, electronic system monitoring medical product safety". This initiative will transform the

safety surveillance system at the FDA from one based primarily on spontaneous reports to one that uses comprehensive healthcare information including electronic health records, patient registry data, insurance claims data, and other large healthcare information databases.[63] The shift from the passive surveillance system to an active surveillance system will require the use of novel pharmacoepidemiologic methods to analyze comprehensive data sources, including administrative claims databases, registries, and large clinical cohorts.

A variety of questions related to drug safety and health care utilization are answered using administrative claims databases. Research using this type of data include studies on drug utilization, physician prescribing, adverse drug effects and safety, effectiveness, and health policy.[64] Advantages of these types of studies include the ability to investigate rare events due to the size of administrative databases, the capacity to study drug effectiveness and utilization as the data represents routine clinical care, and the relative cost of databases in comparison to the expense of conducting a large randomized controlled study or creating and maintaining large independent clinical cohorts.[64] Administrative databases have been used to investigate a wide range of drug exposures including HMG-CoA reductase inhibitors, beta-blockers, anti-psychotics, proton pump inhibitors, hormone replacement therapy, and non-steroidal anti-inflammatory drugs.[65-69]

Several studies have explored the accuracy of outcome ascertainment in claims data, including coronary heart disease outcomes. [70-78] The predictive probability of ICD-9 and Diagnosis Related Group (DRG) identification of myocardial infarction outcomes was investigated in populations likely to have very low levels of HIV infection, revealing that these types of codes have a high predictive probability (66-97%).[70, 73, 79-82] However,

many of these validation studies do not contain patients that both have and do not have the disease of interest thus limiting the calculation of diagnostic test characteristics to positive and negative predictive values -- results that are dependent on prevalence of disease in the population. Sensitivity and specificity are not dependent on prevalence and an outcome ascertainment algorithm with perfect specificity will insure an unbiased relative effect measures due to outcome misclassification. Finally, much of the validation work thus far has not included validation of these measures in HIV infected individuals.

Administrative claims data have not been widely used to investigate clinical outcomes related to HIV treatment. Important factors related to HIV treatment and outcomes, including CD4 cell counts and HIV RNA levels, are not routinely available in this type of data and are often important confounders in studies evaluating outcomes related to antiretroviral treatment. Adverse events or clinical outcomes that may not be powerfully affected by HIV disease parameters (e.g. CD4 cell counts and HIV RNA level), however, may be amenable to analysis with claims data. For example, administrative claims data were used to identify abacavir associated hypersensitivity reactions among the HIV-infected population. Verification of hypersensitivity through medical chart abstraction revealed a high sensitivity (83.3%-100%) and specificity (93.1%-96.1%) of the outcome identified in the health care claims.[83] While this analysis provided validation of this outcome in the administrative claims data, the association between abacavir use and hypersensitivity was not explored.

In this project, we also propose to use the established UNC CFAR HIV Clinical Cohort study, a large HIV clinical cohort in the Southeastern U.S. to validate the use of documented ICD-9 codes to identify myocardial infarction outcomes in Medicaid

administrative claims data. Further, we propose to use administrative claims data to evaluate the relationship between use of safety antiretrovirals and myocardial infarction morbidity and mortality.

CHAPTER III

PRELMINARY STUDIES

North Carolina Division of Medicaid Assistance Claims Data

These data include health care service reimbursement information including doctor visits, hospital care, outpatient visits, treatments, emergency room use, and prescription medications, as well as, information related to diagnoses, procedures, providers and charges for North Carolina Medicaid beneficiaries.[84] A unique identifier identifies patients in the data. From 2002-2008 there were 12,729 HIV infected patients with at least one claim in the Medicaid data and 341 of these patients have experienced a documented myocardial infarction after diagnosis with HIV (Personal communication, CCQI). Table 2 displays the demographics of the North Carolina Medicaid population by year of enrollment.

The North Carolina Medicaid claims data provides an opportunity to evaluate the association between incident coronary heart disease and antiretroviral exposure. The size of the population will allow for increased power to detect a difference between treatment groups and since enrollment includes all North Carolina residents, analysis with these data will provide additional generalizability of the results. It should be noted, however, that while most individuals enrolled in other insurance programs (private, Medicare) have one chance to enter for eligibility for an entire year, Medicaid eligibility is determined on a monthly basis. Therefore, beneficiaries may have less continuous eligibility time than beneficiaries enrolled in other insurance programs.

Table 1. Characteristics of the North Carolina Medicaid Population by year of enrollment [85]

	Year						
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
	N=1,389,455	N=1,450,218*	N=1,526,268*	N=1,566,047*	N=1,667,247*	N=1,680,209*	N=1,741,471
Age (years), N (%)							
<18	735,862 (53.0)	771,801 (56.5)	813,804 (53.3)	841,731 (53.7)	898,766 (53.9)	914,938 (54.5)	950,452 (54.6)
19-64	474,493 (34.1)	499,602 (26.9)	532,428 (34.9)	543,848 (34.7)	583,898 (35.0)	582,369 (34.7)	607,958 (34.9)
65-84	137,990 (9.9)	137,765 (13.0)	138,752 (9.1)	138,641 (8.9)	142,071 (8.5)	140,406 (8.4)	140,264 (8.1)
>85	41,110 (3.0)	41,049 (3.5)	41,282 (2.7)	41,825 (2.7)	42,496 (2.5)	42,496 (2.5)	42,524 (2.4)
Gender, N (%)							
Male	547,672 (39.4)	575,397 (39.7)	607,894 (39.8)	625,973 (40.0)	669,192 (40.1)	674,156 (40.1)	701,528 (40.3)
Female	841,783 (60.1)	874,821 (60.3)	918,374 (60.2)	940,074 (60.0)	998,055 (59.9)	1,006,056 (59.9)	1,039,943 (59.7)
Race/Ethnicity, N (%)							
White	607,557 (43.7)	634,399 (43.7)	668,841 (43.8)	685,645 (43.8)	726,809 (43.6)	721,309 (42.9)	742,798 (42.7)
Black/African American	569,579 (41.0)	585,665 (40.3)	609,834 (40.1)	625,303 (39.9)	652,843 (39.2)	649,276 (38.6)	661,990 (38.0)
American Indian/Alaska Native	23,854 (1.7)	24,299 (1.7)	25,149 (1.6)	26,010 (1.7)	27,128 (1.6)	27,072 (1.6)	27,682 (1.6)
Asian	12,478 (0.8)	13,428 (0.9)	14,506 (0.9)	15,394 (0.9)	17,082 (1.0)	18,028 (1.1)	19,718 (1.1)
Hispanic or Latino	94,973 (6.8)	107,931 (7.4)	77,777 (5.0)	85,768 (5.5)	109,205 (6.6)	121,196 (7.2)	135,045 (7.8)
Native Hawaiian/Pacific Islander	0 (0.0)	0 (0.0)	64 (0.004)	2 (0.0001)	586 (0.04)	691 (0.04)	864 (0.04)

*Numbers do not sum to total due to beneficiaries in which age group or race is unknown

The UNC CFAR Clinical Cohort Study

The UNC CFAR HIV Clinical Cohort Study (UCHCC) is a large observational clinical cohort initiated in January 2000. To date the UCHCC data has contributed to a number of important areas of HIV clinical inquiry, including validation studies of antiretroviral therapy use,[86] access to care,[87, 88] chronic and acute kidney disease,[89, 90] ARV therapy outcomes,[91, 92] and HIV resistance to antiretroviral therapy.[93, 94]

UCHCC includes all HIV-infected patients receiving HIV primary care at the UNC Infectious Diseases Clinic (UNC-ID). The only exclusion criteria for entry into the cohort are young age (<18 years of age) and the inability to provide written informed consent (English and Spanish language forms are used). This study captures information for all enrolled patients from a variety of sources, including: daily electronic transfers from existing UNC electronic databases, comprehensive medical record abstractions, in-person interviews, and additional data from state and federal agencies, including information on mortality from Federal Death Index. Demographic, laboratory, pathology and insurance data are transferred nightly through a secure ftp from UNC Hospitals and comprehensive medical chart review data is entered through a web-enabled interface into a relational SAS database (SAS/WAREHOUSE ® version 2.2 sofware), developed in collaboration with the SAS Institute (Cary, NC).

Data that is transferred on a nightly basis includes all clinically obtained laboratory values including: HIV RNA levels, CD4 cell counts, lipid levels, fasting blood glucose, as well as safety labs including serum creatinine and liver function tests. All clinical visit information is collected at enrollment and prospectively at 6-month intervals by trained medical chart abstractors. Medical chart abstractors participate in a month-long training

program and often have a background in a clinical field such as nursing. Abstractors obtain data from the electronic medical record including collection of all information on antiretroviral medications including dosage and route of administration.

Other medication history is also abstracted, including all medications for treatment of coronary heart disease and all other comorbidities. In addition to extensive medication information, the chart abstractors also obtain information on diagnoses including both AIDS defining clinical conditions (e.g. Kaposi's Sarcoma, Pneumocystis jiroveci pneumonia) and non-AIDS defining conditions (e.g. myocardial infarction, diabetes, cancer). Chart abstractors identify diagnoses which are subsequently verified by clinical members of the team including a pharmacist, physician and nurse practitioner. The chart abstractors also obtain information on other important health risk factors including smoking history and non-prescription drug use. Data checks for completeness and consistency ensure data integrity. All data is stored on a separate UNC server under extensive security and safety monitoring and maintenance.

Table 2. Demographic characteristics of UCHCC participants, 2000-2010

	N=3,146
Race	**N (%)**
African American	1853 (58.9)
White	954 (30.3)
Hispanic	177 (5.6)
Native American	53 (1.7)
Other	71 (2.3)
Unknown	25 (0.8)
Age, years	
<40	831 (26.4)
40-50	1123 (35.7)
>50	1087 (34.6)
Unknown	105 (3.3)
Gender	
Female	970 (30.8)
Male	2176 (69.2)
Insurance	
Private	728 (23.1)
Medicaid	750 (23.8)
Medicare	226 (7.2)
No Insurance	1220(38.8)
Other	202 (6.4)
Unknown	20 (0.6)

As of August 2010, 3,146 patients have provided informed consent or we have received implicit consent to participate in the UCHCC since January 2000, with less than 2% refusing to participate, enrollment continues on an ongoing basis. Enrolled patients are demographically and clinically similar to all HIV-infected patients seen at UNC and HIV-infected individuals living in North Carolina. Fifty-nine percent of patients are African American, 31% are women and the median age is 46 years (Table 1). The publicly funded Medicaid or Medicare programs enroll approximately 30% of cohort participants and approximately 25% of the Medicaid population is dually eligible for Medicare. The distribution of antiretroviral use in the UCHCC population has changed over time based on available agents, the existing clinical evidence of best practices and established HIV treatment guidelines. In the UCHCC approximately 50% initially received a three drug regimen (50%) containing two NRTIs and a PI (ritonavir boosted (15%) or unboosted (42%) or NNRTI (29%).[94] The most common NRTIs in the UCHCC are lamivudine/emtricitabine (73%) and tenofovir (28%). Nelfinavir is the most common PI (35%) and patients in the UCHCC that are prescribed an NNRTI are likely to receive efavirenz (62%).[94] However, many of our patients have extensive antiretroviral therapy experience, especially those who initiated antiretroviral therapy before 1996 and the availability of cART.[94] Eight percent of patients (N=246) enrolled in the UCHCC have had at least one coronary heart disease event documented in the clinical record. This includes a documentation of myocardial infarction or coronary revascularization. Approximately 1,412 patients have been identified in the UCHCC that also have at least one claim in the Medicaid data between 2002 and 2008. Of these patients, 173 have at least one documented coronary artery disease event as noted in the clinical record and recorded in the UCHCC.

Data Acquisition

Researchers already obtained the data for this study from the Carolina Cost and Quality Initiative (CCQI) at the University of North Carolina at Chapel Hill, Sheps Center for Health Services Research. Dr. Emily Brouwer provided UCHCC researchers at the State Medicaid offices in Raleigh, North Carolina these individuals linked the two data sources in March, 2010. University of North Carolina at Chapel Hill, Institutional Review Board approved the parent studies and this dissertation research (UNC IRB Study Numbers: 99-0956, 09-1783, 10-0036). All UCHCC participants provided written informed consent to participate.

CHAPTER IV

METHODS

Methods Common to Aims 1 and 2

Study design and study population

In order to address our study aims, we used a retrospective cohort study design. We performed a validation study using the Medicaid data obtained from the Carolina Cost and Quality Initiative (described in chapter III) as well as data already collected as part of the UCHCC to address the first aim. To address the second aim we relied solely on the Medicaid administrative data.

Inclusion Criteria

For aims 1 and 2 we included that were enrolled in the UCHCC between the years 2002 and 2008 who met UCHCC inclusion criteria and all HIV-infected adults that had a claim in the North Carolina Medicaid administrative data between the years 2002 and 2008. Our general inclusion criteria for both aims are as follows:

1. Documentation of HIV-infection. In the UCHCC data, HIV-infected patients are enrolled based on positive ELISA or Western Blot and/or a detectable HIV RNA level. In the Medicaid data this will be based on the presence of an HIV diagnosis in the Medicaid data (ICD-9/ICD-9 CM code: 042.xx) or a claim for any of the 26 approved antiretroviral medications.
2. At least 18 years of age

Methods Specific to Aim 1

Myocardial Infarction Ascertainment

We included all patients that had either a definite or probable myocardial infarction as defined in the UCHCC and Medicaid data sources during the study period. In an initial validation analysis, we included the first myocardial infarction event documented in either the UCHCC or Medicaid occurring during the observed period and we did not impose any restriction on dates of events when assessing validation parameters. In a secondary analysis, we accounted for multiple myocardial infarction events per patient, timing of the event, and length of observed time in each source by creating smaller consecutive time increments (3,6,2,24 months) within the previously defined observed period. If the observed period ended in the middle of the final time increment, that observation was not included in the analysis.

UNC CFAR HIV Clinical Cohort (Gold Standard)

Myocardial infarction events were initially identified in the UCHCC through extensive medical chart abstraction using a standardized chart abstraction tool and adjudicated by health care personnel. The myocardial infarction event definition expands upon that defined by the WHO and includes serum markers, ECGs and information pertaining to chest pain. This criteria is also currently used by the CFAR Network of Integrated Clinical Systems (table 3). [95, 96]. For myocardial infarction events, this protocol includes identification of myocardial infarction through laboratory values (cardiac enzymes, ECGs), and written notes. The enzymes that we will use to identify myocardial infarction events will include: creatinine phosphokinase (CPK) and its isoenzyme (CK-MB), serum

lactate and troponin. While troponin was not in use at the time of the MONICA study, this enzyme is currently used for diagnosis of myocardial infarction.[97]

Electrocardiograms (ECG) were coded as outlined by the Minnesota Code Manual of Electrocardio-graphic Findings.[98] We verified the outcomes according to the definitions described in table 3 through an endpoint verification committee comprising three reviewers familiar with endpoint definitions; physicians comprised the endpoint verification committee.

Table 3. Myocardial Infarction Outcome Ascertainment

	Criteria
Definite myocardial infarction	1. Definite ECG findings* 2. Typical or atypical symptom with probable ECG findings† and abnormal cardiac enzymes^ 3. Typical symptoms and abnormal cardiac enzymes^ with ischemic ECG that does not meet criteria for definite/probable ECG findings, or ECG not available. 4. Fatality with naked-eye appearance of fresh myocardial infarction and/or recent coronary occlusion on autopsy
Probable myocardial infarction	1. Patient with typical myocardial infarction symptoms but with ECG or cardiac enzyme findings that do not meet criteria for definite myocardial infarction. 2. Fatal case where there is no good evidence for another cause of death with symptoms that are typical atypical or inadequately described, or with evidence of chronic coronary occlusion/stenosis or old myocardial scarring at autopsy, or with a history of chronic ischemic heart disease.
Definite fatal myocardial infarction	No known nonatherosclerotic probable cause of death and hospitalized definite MI within 4 weeks preceding death

*Serial ECGs showing development of a diagnostic Q wave, evolution of ST Elevation with or without Q-wave or new left bundle branch block (LBBB), evolution of ST-T depression/inversion alone or evolution of minor Q-waves alone, single ECG with major Q-wave or single ECG with LBBB, described as new

†Serial ECGs showing evolution of repolarization changes

^Enzymes: Abnormal if Troponins > upper limit of normal (ULN) or 3 x ULN 48 hours of PTCA or 5 x ULN 72 hours after CABG. Abnormal creatinine phosphokinase (CPK) and its isoenzyme (CK-MB) if > ULN or 2x ULN with muscle trauma other than PTCA/CABG, or 3x ULN 48 hours after PTCA or 5 x ULN 72 hours after CABG.

Medicaid Administrative Claims

Our initial myocardial infarction event definition in the Medicaid claims included a diagnosis code (ICD-9-CM) of 410 in the 1st or 2nd position and a length of stay ≥ 3 days as has been used in previous validation studies. [73, 79, 80] We then used varying algorithms to identify myocardial infarction events in order to determine the algorithm that would best identify myocardial infarction events in this population. The 12 algorithms considered included varying: (i) ICD-9 code 410.xx in 1st or 2nd position, versus any position; (ii) length of stay as any number of day, ≥ 1 day, and ≥ 3 days; and (iii) inclusion of diagnosis related group (DRG) codes 121, 122 and 123.

Validation Study Mechanics

We synchronized periods of continuous Medicaid eligibility with the UCHCC and included all patients in both Medicaid and UCHCC with at least 30 days of observation time in both data sources between 2002 and 2008. Patients contributed observed time from the last of (i) January 1, 2002, (ii) entry into the UCHCC) or (iii) start of Medicaid enrollment. Patients' time was included until the first of (i) December 31, 2008, (ii) 12 months following the last documented CD4 count or HIV RNA measurement in the UCHCC, or (iii) more than 30 days without Medicaid enrollment. If a patient was lost to HIV care in the UCHCC (i.e. more than 12 months without a documented CD4 count or HIV RNA measurement) or stopped being covered by Medicaid for more than 30 days but then reinitiated HIV care or Medicaid enrollment, this time at risk was not considered in these analyses. Among patients who died, observed time was stopped on the date of death.

Statistical Analysis

We examined basic baseline demographic and clinical characteristics of the North Carolina Medicaid population, the UCHCC as well as the entire validation sample for the enrollees identified with a myocardial infarction in the gold standard. We then cross-tabulated myocardial infarction events identified in both cohorts based on the definitions outlined above to estimate sensitivity (proportion of true myocardial infarction events identified in Medicaid among all gold standard defined myocardial infarction events), specificity (proportion of true non-events identified in Medicaid among all gold standard defined non- events), positive predictive value (proportion of true myocardial infarction events identified in Medicaid among all myocardial events identified in Medicaid) and negative predictive value (proportion of true non-events identified in Medicaid among all non-events identified in Medicaid). We used exact binomial 95% confidence intervals (CI) to quantify precision around each validation measure. [99] For our secondary analysis, we used intercept only generalized estimating equation models with a binomial distribution, independent correlation structure and logit link to estimate sensitivity and specificity. These characteristics were calculated for the 3 month, 6 month, 12 month and 24 month time increments.

Finally, we explored the impact of outcome misclassification on relative risk and absolute risk estimates in a hypothetical population of 1,100 individuals, a baseline probability of exposure of 0.09 and a risk of myocardial infarction of 0.1 in the exposed and 0.08 in the unexposed to a hypothetical risk factor(true Risk Ratio [RR]: 1.25, true Risk Difference [RD]: 0.02). We used sensitivities and specificities estimated from our validation study to calculate the expected bias in the estimated RR and RD if under different definitions

of myocardial infarction assuming no misclassification of exposure and non-differential outcome misclassification.

We used the following equations to calculate the observed RR and RD:

$$RR = \frac{a/(a+b)}{c/(c+d)} \quad RD = a/(a+b) - c/(c+d) \text{ where}$$

a=sensitivity x proportion exposed x risk in exposed + (1-specificity) x proportion exposed x (1-risk in exposed)
b=(1-sensitivity) x proportion exposed x risk in exposed + specificity x proportion exposed x (1-risk in exposed)
c=sensitivity x (1-proportion exposed) x incidence in the unexposed + (1-specificity) x (1-proportion exposed) x (1-risk in unexposed)
d=(1-sensitivity) x (1-proportion exposed) x incidence in the unexposed + specificity x (1-proportion exposed) x (1-risk in unexposed)

We quantified the % bias for both the RR and RD using the following equations:

$100*([\ln RR_{true} - \ln RR_{observed}]/\ln RR_{true})$ and $100*(RD_{true} - RD_{observed}/RD_{true})$.

Methods Specific to Aim 2

Study Design

We conducted this intention to treat, new user [100], active comparator cohort study to emulate a population that would be enrolled in a randomized controlled trial evaluating the relationship between the initiation of specific antiretrovirals as part of a standard combination antiretroviral therapy regimen (cART) and myocardial infarction. A cART regimen contains two NRTIs as a backbone and an anchor antiretroviral that is either an NNRTI, a protease inhibitor (PI) boosted or unboosted with ritonavir, an integrase strand transfer inhibitor (ISTI) or an additional NRTI. For this analysis, we considered only cART regimens containing lamivudine or emtricitabine as one of the two nucleoside reverse transcriptase inhibitors in the backbone (see appendix table 1) for a description of antiretroviral classes).

Our study design included four study arms, the first two arms examined the initiation of the nucleoside reverse transcriptase inhibitors (NRTI), abacavir with and without zidovudine (treated), and tenofovir (active comparator). The third and fourth arms examined receipt of lopinavir/ritonavir, atazanavir (treated) and an NNRTI (active comparator). Patients enrolled in this trial would be diagnosed with HIV and unexposed to antiretroviral medications for at least 6 months at baseline.

Patients in our cohort study were required to 1) be $\geq$ 18 years of age 2) be HIV positive based on administrative criteria (ICD-9 code 042.xx or a Medicaid claim for one of the 26 FDA approved antiretroviral medications) 3) have at least 180 days of Medicaid eligibility prior to study entry 4) be new recipients of a combination antiretroviral therapy (cART) regimen including the antiretrovirals from NRTI class, lamividuine or emtricitabine. A regimen was defined as a group of antiretroviral Medicaid claims dispensed within 30 days of each other. A cART regimen was defined as one of guideline recommended standard regimens defined above.

A new cART regimen recipient was defined as a patient receiving a cART regimen without a prescription filled for any antiretroviral in the 180 days prior to study entry. If a patient had a claim for an antiretroviral medication or a group of antiretroviral medications that did not qualify as a cART regimen (e.g. monotherapy or dual therapy) for $\leq$ 30 days and a valid regimen was prescribed thereafter, the second regimen was considered the new cART regimen. We excluded new recipients with a regimen prescribed for < 30 days followed by a non-standard cART regimen as well as patients with any claims for myocardial infarction (acute or chronic), coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the 180 days prior to cART initiation.

Exposure and Outcome Definitions

Our primary outcome was myocardial infarction defined by a diagnosis code of 410.xx in any position and a length of stay $\geq$ 1 day in the Medicaid claims. This algorithm was validated in specific aim 1. We examined exposure to the most common antiretroviral medications contained within the standard cART regimens defined above. We first examined recipients of the most common nucleoside reverse transcriptase inhibitors, abacavir (with or without zidovudine) as part of a new cART regimen as the treatment group to the active comparator, tenofovir. Next we examined recipients of PIs (atazanavir [boosted and unboosted with ritonavir] and lopinavir [boosted with ritonavir]) as the treatment group to NNRTIs as the active comparator group. We compared receipt of atazanavir to the NNRTIs combined and receipt of lopinavir to the NNRTIs combined. For each of the analyses we excluded patients that were on regimens that contained both the exposed (treated) and active comparator antiretroviral (e.g. abacavir and tenofovir).

Confounders/Covariates

We obtained data on potential confounders from the Medicaid claims in the 180 days prior to cART initiation. We included age at study entry, sex, race, regimen type based on anchor antiretroviral (ritonavir boosted PI or ISTI based, NNRTI based, ritonavir unboosted PI based, triple NRTI based), calendar year of antiretroviral initiation (6 indicator variables for calendar year), concomitant cardiovascular medication use (angiotensin converting enzyme receptor (ACE) inhibitors, angiotensin receptor blocking agents, beta receptor blocking agents, calcium channel receptor blocking agents and HMG-CoA receptor inhibitors), comorbidities in the 180 days prior to study entry (based on ICD-9 codes from the Deyo implementation of the Charlson comorbidity score, used separately, i.e., not as a

score), number of hospitalizations (0, 0-2, >2 hospitalizations) and number of medication claims (0, 1-15, 15-20, >20 medications).

Statistical Analysis

To account for baseline differences in treatment and to estimate the effect of treatment in the treated populations, we used propensity score methods and explored the use of matching algorithms as well as Standardized Morbidity/Mortality Ratio (SMR) weights for adjustment. Matching was performed using the Greedy Matching algorithm and we explored 1 to 1 matching as well as 1 to many matching.[101] The SMR weight is calculated as the conditional probability of receiving the patients' actual treatment (treatment or comparator) multiplied by the conditional probability of treatment regardless of the patients' treatment status. Through SMR weighting we created a pseudo-population of patients that had the same probability of receiving the treatment of interest. Patients in the treated group received a weight of 1 and those in the active comparator group receive a weight defined as $\hat{e}(X)/(1-\hat{e}(X))$, where $\hat{e}(X)$ is the propensity score [102, 103]. To calculate the weights, we estimated four propensity score models using logistic regression for each arm of our study 1) abacavir with zidovudine compared with tenofovir 2) abacavir without zidovudine compared with tenofovir 3) atazanavir compared with non-nucleoside reverse transcriptase inhibitors and 4) lopinavir (boosted/unboosted) compared with non-nucleoside reverse transcriptase inhibitors. Logistic models included all the covariates listed above identified as potential confounders of the antiretroviral use-myocardial infarction relation based on expert knowledge on the relationship of these factors with the exposure and the outcome. The following characteristics were included in the abacavir compared to tenofovir propensity score models: race, sex, comorbidities, cardiovascular medication use, hospitalizations, and

overall medication use in the 180 days prior to study entry, year of antiretroviral initiation, regimen type. Propensity score models constructed to predict atazanavir or lopinavir included all of the above with the exception of regimen type as the use of an NNRTI or PI inherently defines regimen type. Prior to creating the weighted pseudo-population, we trimmed the propensity scores to exclude patients always initiated on one of the cART treatments compared (non-positivity).

Follow-up started on the day of the claim for the last antiretroviral medication in the qualifying new cART regimen and continued until the occurrence of 1) myocardial infarction 2) discontinuation of Medicaid eligibility or 3) end of study period (December 31, 2008), whichever came first. We calculated overall unadjusted incidence rates for myocardial infarction using Poisson regression. We then used the SMR weights previously described to create adjusted Kaplan Meier curves for each of the study arms. Finally, we crated Cox proportional hazard regression models to compare unadjusted and SMR adjusted hazard ratios (HR) and corresponding 95% confidence intervals. For the weighted analyses we used robust variance estimation. For all Cox proportional hazard models we tested proportional hazards assumptions by including an interaction term between treatment arm and the log of time.

Finally we conducted two sensitivity analyses to examine the influence of non-adherence and switching as well as unmeasured confounding on our results. To address non-adherence and switching, we attempted an as treated analysis where we censored patients at the first of discontinuation of treatment or switching to another cART regiment. Unfortunately, due to lack of adequate person-time and a small number of events, we were not able to complete this analysis. Our second sensitivity analysis examined the potential for

unmeasured confounding. We excluded patients at the upper and lower 1, 2.5, and 5 percentiles of propensity score distribution and examined the change in HR point estimates. [104]

CHAPTER V

MANUSCRIPT 1: VALIDATION OF MEDICAID CLAIMS-BASED DIAGNOSIS OF MYOCARDIAL INFARCTION USING AN HIV CLINICAL COHORT

Introduction:

Large health care databases can be useful for conducting non-experimental comparative effectiveness research. While certainly not perfect, the population is often closer to ideal than the one of ad hoc studies because it is less selected, Information on drug exposure in these sources is good for prescription drugs in the outpatient setting, the data is generally available, and their large sample size provides an opportunity to examine outcomes that are rare. [105] As these data are collected primarily for administrative purposes and not for research, however, outcome measurements should be validated to quantify or minimize bias due to misclassification.

Measures of accuracy, sensitivity, specificity, positive predictive value and negative predictive value, are used to quantify misclassification. Sensitivity and specificity measures are important for the assessment of outcome and exposure misclassification while positive predictive and negative predictive values are generally more important for population selection. Since there is often a tradeoff between maximizing sensitivity versus specificity in comparative effectiveness and safety studies, the choice of measure should be based on the overarching study question. [106] In these types of studies we usually are interested in estimating relative effects. For relative risk estimates, specificity is the most important test characteristic when validating an outcome because perfect specificity will lead to unbiased

relative risk estimates even if sensitivity is low. [107] A high sensitivity will allow for identification of most events and reduce bias of effect measures on the absolute scale (risk difference or number needed to treat).[108] Many validation studies are conducted starting with a large administrative healthcare database where algorithms to define events are validated against a gold standard (e.g., medical records). These studies are only able to calculate positive predictive values and are unable to evaluate sensitivity and specificity as they do not have access to the gold standard population without the event (true negatives).

Observational clinical cohort studies and collaborations among individual clinical cohort studies have contributed substantially to our understanding of the effectiveness of different antiretroviral treatments for HIV clinical management.[1, 40, 59, 60, 109, 110] Notably, one of the largest studies conducted to date on myocardial infarction risk in HIV patients and the role of antiretroviral treatments was an international collaborative clinical multi-cohort study.[1] The similarities and differences between clinical cohort studies and other more traditional observational studies (e.g. interval cohorts) have been discussed elsewhere. [111] Briefly, participants are enrolled as they seek or receive care and information collected on the participants is usually obtained from the medical record. Observational clinical cohort studies are dynamic cohorts that enroll patients as they seek care. Many HIV clinical cohort studies have been developed over the last two decades to inform the treatment and clinical care of HIV patients in a regular healthcare setting.[112, 113] Despite their use to examine the effect of treatments in a real world setting, these studies may not reach adequate person-time of follow-up required to study rare events.

The accuracy of myocardial infarction ascertainment in varying administrative healthcare data sources has been assessed; however, the majority of these studies only

present positive predictive value due to the lack of true negatives needed to estimate sensitivity and specificity. [71, 73, 79-81, 114] Further, some of the validation studies previously conducted use algorithms to identify myocardial infarction events that may now be outdated due to changes in patient treatment as well as healthcare service and reimbursement.[73, 79, 80] For example, many of the current myocardial infarction ascertainment algorithms contain a length of stay criteria $\geq$ 3 days. Analyses of hospital discharge records from Minnesota and New England suggest that the median length of stay for patients hospitalized with acute myocardial infarction is decreasing over time.[115, 116] These observations justify a periodic reassessment and validation of myocardial infarction algorithms used for outcome ascertainment as changes occur in systems for diagnostic coding, healthcare practices and reimbursement policies. [117, 118]

By linking comprehensive clinical cohort data to administrative healthcare data, it is possible to validate algorithms used to define health outcomes of interest. In this study, we used a specific clinical cohort, the UNC HIV CFAR Clinical Cohort study, and the North Carolina Medicaid database, to validate different claims-based definitions of myocardial infarction within an HIV infected population.

Methods

Study Population

We used the UNC-CFAR HIV Clinical Cohort (UCHCC) and the North Carolina Medicaid administrative data for this validation study. The UCHCC is a dynamic clinical cohort study initiated in 2000 and includes all HIV-infected patients that are 18 years of age or older unless they are unable or unwilling to provide written informed consent in either English or Spanish. The cohort includes data from a variety of sources including existing

hospital electronic databases, comprehensive medical chart abstractions, in-person interviews, and data from state and federal agencies including mortality information from North Carolina and federal agencies. As the UCHCC study relies on existing medical record information, participants are not seen at exact regular intervals, but rather as indicated by clinical care.

The Medicaid program is a joint state and federally funded program that provides healthcare benefits to individuals of low income. Individuals qualify based on age, disability, income and financial resources.[119] The Medicaid data, obtained from the Carolina Cost and Quality Initiative (CCQI) at the University of North Carolina at Chapel Hill, contains health care service reimbursement information including doctor visits, hospital care, outpatient visits, treatments, emergency use, prescription medications, as well as diagnoses, procedures and provider information. We included all HIV infected North Carolina Medicaid beneficiaries and those dually eligible for both Medicaid and Medicare that were greater than 18 years of age with Medicaid enrollment between January 1, 2002 and December 31, 2008. HIV patients were identified in the Medicaid administrative data using the following definition: an ICD-9 code of 042 in any position or a prescription of any of the 27 FDA approved antiretrovirals between 2002 and 2008. Antiretrovirals were identified in the administrative claims data through National Drug Codes (NDC) available on the FDA website. Patients enrolled both in the UCHCC and Medicaid at any point in time between 2002 and 2008 formed the validation sample. For these patients we merged UCHCC data with the Medicaid administrative data based on social security number, first and last name.

Validation study mechanics

For this validation study, we synchronized periods of continuous Medicaid eligibility with the UCHC and included all patients in both Medicaid and UCHCC with at least 30 days of observation time in both data sources between 2002 and 2008. Patients contributed observed time from the last of (i) January 1, 2002, (ii) entry into the UCHCC) or (iii) start of Medicaid enrollment. Patients' time was included until the first of (i) December 31, 2008, (ii) 12 months following the last documented CD4 count or HIV RNA measurement in the UCHCC, or (iii) more than 30 days without Medicaid enrollment. If a patient was lost to HIV care in the UCHCC (i.e. more than 12 months without a documented CD4 count or HIV RNA measurement) or stopped being covered by Medicaid for more than 30 days but then reinitiated HIV care or Medicaid enrollment, this time at risk was not considered in these analyses. Among patients who died, observed time was stopped on the date of death.

Event definitions

We included all patients that had either a definite or probable myocardial infarction as defined in the UCHCC and Medicaid data sources during the study period. In an initial validation analysis, we included the first myocardial infarction event documented in either the UCHCC or Medicaid occurring during the observed period and we did not impose any restriction on dates of events when assessing validation parameters. In a secondary analysis, we accounted for multiple myocardial infarction events per patient, timing of the event, and length of observed time in each source by creating smaller consecutive time increments (3,6,2,24 months) within the previously defined observed period. If the observed period ended in the middle of the final time increment, that observation was not included in the analysis. Figures 1 and 2 display hypothetical patient scenarios that demonstrate how

myocardial infarction events would be classified in each data source with corresponding validation parameters.

Myocardial Infarction definition—UNC CFAR HIV Clinical Cohort (Gold Standard)

Myocardial infarction events were initially identified in the UCHCC through extensive medical chart abstraction and adjudicated by health care personnel. The myocardial infarction event definition expands upon that defined by the WHO and includes serum markers, ECGs and information pertaining to chest pain. [96]

Myocardial Infarction definition—Medicaid Administrative Claims

Our initial myocardial infarction event definition in the Medicaid claims included a diagnosis code (ICD-9-CM) of 410 in the 1st or 2nd position and a length of stay $\geq$ 3 days as has been used in previous validation studies. [73, 79, 80] We then used varying algorithms to identify myocardial infarction events in order to determine the algorithm that would best identify myocardial infarction events in this population. The 12 algorithms considered included varying: (i) ICD-9 code 410.xx in 1st or 2nd position, versus any position; (ii) length of stay as any number of day, $\geq$ 1 day, and $\geq$ 3 days; and (iii) inclusion of diagnosis related group (DRG) codes 121, 122 and 123.

Statistical Analysis:

We examined basic baseline demographic and clinical characteristics of the North Carolina Medicaid population, the UCHCC as well as the entire validation sample for the enrollees identified with a myocardial infarction in the gold standard. We then cross-tabulated myocardial infarction events identified in both cohorts based on the definitions outlined above to estimate sensitivity (proportion of true myocardial infarction events identified in Medicaid among all gold standard defined myocardial infarction events),

specificity (proportion of true non-events identified in Medicaid among all gold standard defined non- events), positive predictive value (proportion of true myocardial infarction events identified in Medicaid among all myocardial events identified in Medicaid) and negative predictive value (proportion of true non-events identified in Medicaid among all non-events identified in Medicaid). We used exact binomial 95% confidence intervals (CI) to quantify precision around each validation measure. [99] For our secondary analysis, we used intercept only generalized estimating equation models with a binomial distribution, independent correlation structure and logit link to estimate sensitivity and specificity. These characteristics were calculated for the 3 month, 6 month, 12 month and 24 month time increments.

Finally, we explored the impact of outcome misclassification on relative risk and absolute risk estimates in a hypothetical population of 1,100 individuals, a baseline probability of exposure of 0.09 and a risk of myocardial infarction of 0.1 in the exposed and 0.08 in the unexposed to a hypothetical risk factor(true Risk Ratio [RR]: 1.25, true Risk Difference [RD]: 0.02). We used sensitivities and specificities estimated from our validation study to calculate the expected bias in the estimated RR and RD if under different definitions of myocardial infarction assuming no misclassification of exposure and non-differential outcome misclassification. We used the following equations to calculate the observed RR and RD:

$$RR = \frac{a/(a+b)}{c/(c+d)} \quad RD = a/a+b-c/(c+d) \text{ where}$$

a=sensitivity x proportion exposed x risk in exposed + (1-specificity) x proportion exposed x (1-risk in exposed)
b=(1-sensitivity) x proportion exposed x risk in exposed + specificity x proportion exposed x (1-risk in exposed)
c=sensitivity x (1-proportion exposed) x incidence in the unexposed + (1-specificity) x (1- proportion exposed) x (1-risk in unexposed)
d=(1-sensitivity) x (1-proportion exposed) x incidence in the unexposed + specificity x (1-proportion exposed) x (1-risk in unexposed)

We quantified the % bias for both the RR and RD using the following equations: $100^* ([\ln RR_{true}-\ln RR_{observed}]/\ln RR_{true})$ and $100^*(RD_{true}-RD_{observed}/RD_{true})$.

All analyses were conducted using either SAS version 9.2 or Intercooled Stata11. The study was approved by the University of North Carolina Committees on the Protection of the Rights of Human Subjects.

Results

Between 2002 and 2008 there were 1,134,986 North Carolina Medicaid beneficiaries $\geq$ 18 years of age of whom 13,006 patients were HIV-infected based on an ICD-9 code of 042 in any position or a prescription for at least one of 27 FDA approved antiretrovirals. Of 2,338 HIV-infected patients in the UCHCC who received care between 2002 and 2008, 1,204 patients were also Medicaid beneficiaries. There were 141 UCHCC and Medicaid beneficiaries that were not included in the sample as they either did not have sufficient follow-up time in either data source or the period of Medicaid eligibility did not overlap with follow-up time in the UCHCC, leaving 1,063 patients included in the validation sample. (Figure 3) The median length of observed time for the validation population was 2.5 years (Interquartile Range: 0.9, 4.7; Full range: 0.2, 7.0). The distribution of most demographic and clinical characteristics of the overall Medicaid population, UCHCC and validation sample were similar. (Table 1) The overall Medicaid population and validation sample had a greater proportion of black, women and younger patients when compared to the UCHCC while the validation sample had a larger proportion of intravenous drug users. Clinically, patients included in the validation sample had similar log HIV RNA and CD4 cell counts at entry into care at UNC. In the validation sample, 17 patients had a myocardial infarction event that

occurred during their observation period and there were 19 total myocardial infarction events.

The validation test characteristics comparing myocardial infarction events in the UCHCC with those identified in the Medicaid data using varying algorithms are displayed in table 2. The current most frequent algorithm used to identify myocardial infarction events in administrative data, ICD-9 code in the 1st or 2nd position and a length of stay $\geq$ 3 days, resulted in a calculated sensitivity of 0.588 (95% CI: 0.329, 0.816) and a specificity of 0.994 (95% CI: 0.988, 0.998). Removing the length of stay criteria increased sensitivity to 0.647 (95% CI: 0.383, 0.857) and decreased specificity to 0.988 (95% CI: 0.980, 0.994). The position of the diagnosis code also influenced validation parameters. Allowing the ICD 9-code 410 to be present in any of the 9 ICD-9 code positions while keeping the $\geq$ 3 day length of stay requirement increased the sensitivity of myocardial infarction identification to 0.765 (95% CI: 0.501, 0.932). Removing the position and length of stay requirement resulted in the highest sensitivity and lowest specificity of event ascertainment (Sensitivity=0.823 [95% CI: 0.566, 0.962]; Specificity=0.982 [95% CI: 0.972, 0.999]). Overall the positive predictive value was low for all of the algorithms explored (Range: 0.438-0.625) while the negative predictive value remained consistently high (0.993-0.997). The addition of DRG codes 121, 122, 123 did not appreciably change the validation parameters (data not shown).

In a secondary analysis we examined the effect of length of observation, timing of events as well as multiple myocardial infarction events per patient. For this analysis we used the most commonly used myocardial infarction ascertainment criteria in the literature (ICD-9 code in 1st or 2nd position and a length of stay $\geq$ 3 days). Since we required the entire length of time for each time increment, the number of unique patients included decreased as the

increments increased from 3 months to 24 months (1,007 patients to 598 patients respectively). When allowing for a 24 month increment of follow-up sensitivity and specificity measurements were similar to those in the first validation analysis (Sensitivity=0.538 [95% CI: 0.268, 0.788]; Specificity=0.998 [95% CI: 0.993, 0.999]). Sensitivity was lowest when allowing for only a 3 month period of eligibility for the event to occur in both data sources (0.444 [95% CI: 0.250, 0.658]), and increased for the 6 and 12 month incremental periods (0.516 [95% CI:0.314, 0.713] and 0.600 [95% CI: 0.338, 0.815]) respectively. (Figure 4)

Table 5 displays the effect of outcome misclassification in a hypothetical population using the sensitivity and specificity measures from the following algorithms: 1) ICD-9 code 410 in the 1st or 2nd position and length of stay $\geq$ 3 days 2) ICD-9 code 410 in 1st or 2nd position and a length of stay $\geq$ 1 day and 3) ICD-9 code 410 in any position and any length of stay. Given a population of 1,100 individuals, a baseline probability of exposure to a hypothetical risk factor of 0.09 and a risk of myocardial infarction of 0.1 in the exposed and 0.08 in the unexposed (true risk ratio: 1.25, true risk difference: 0.02); a sensitivity of 0.588 and a specificity of 0.994 will result in an observed risk ratio of 1.21 and an observed risk difference of 0.015. A sensitivity of 0.824 and a specificity of 0.982 would result in a risk ratio of 1.10 and a risk difference of 0.009. An assessment of bias reveals that the % bias is highest for both relative and absolute measures when specificity is the lowest.

Discussion

We examined sensitivity, specificity, positive predictive value and negative predictive value of various algorithms to identify myocardial infarction events among HIV infected individuals enrolled in the North Carolina Medicaid program relying on events adjudicated in

the UCHCC as the gold standard. We found that using our best algorithm for relative risk effect measures, we achieved a specificity of 0.994 which would translate to a bias of around 11% based on plausible parameter values for a study of antiretrovirals on risk of myocardial infarction using administrative healthcare data. In general specificity measures using all ascertainment algorithms were high (0.982-0.994), however, even small deviations in specificity increased bias of effect measures.

The sensitivity of a commonly used algorithm to identify myocardial infarctions (ICD-9 code 410 in the primary or secondary position and a length of stay $\geq$ 3 days), was low in our study (0.59) compared to other validation studies of myocardial infarction. These studies reported sensitivities ranging from 0.65-0.83 [71, 82]. The low sensitivities observed in our study may be explained by our study population. HIV patients are often admitted to the hospital for varying reasons and a myocardial infarction event that occurs during a hospital stay may not get coded in the 1st or 2nd ICD-9 code position. Therefore, an expansion of the criteria to include all ICD-9 code positions would increase the sensitivity of the ascertainment criteria as was observed in our study. Rosamond et al. noted that sensitivities of ICD-9 code 410 also have been declining over time; this may be due to changes in diagnostic practices as well as the use of differing algorithms for defining myocardial infarction in the gold standard. [120]

In our second analysis we addressed the impact of varying lengths of observed time, timing of events and multiple myocardial infarction events. Sensitivity was lowest for the smallest increment of time indicating that the dates recorded for the events in the Medicaid administrative healthcare data were not the same as the dates recorded in the UCHCC. Sensitivities for the 6 and 12 month were similar to those calculated in the first validation

study. The decrease in sensitivity for the 24 month time frame was likely due to the reduction in number of patients with at least 24 months of observed time for analysis. These results suggest that a requirement for a full 12 months of eligibility in Medicaid may maximize the sensitivity of the administrative healthcare claims-based myocardial infarction identification algorithm. However, sample size and generalizability should also be a consideration.

The positive predictive values calculated using the differing myocardial infarction ascertainment algorithms in our study were substantially lower than values obtained from previous studies (0.93-0.97). [73, 79-81] These results are likely due to the low prevalence of myocardial infarction in this population. However, while positive predictive value is an important measure for some research questions, this measure has less importance in the context of comparative effectiveness research. Nevertheless, the low positive predictive values suggest that the administrative healthcare data used here may not be ideal for the selection of this patient population for a study.

Chubak et al. and Setoguchi et al. explored bias related to outcome misclassification in a hypothetical population (Chubak) and a Medicare population (Setoguchi). [121, 122] Their results quantified the amount of outcome misclassification bias on a relative scale, but did not address bias due to misclassification on an absolute scale. Often absolute measures, like risk difference, are used in comparative safety and effectiveness studies; therefore addressing the impact of less than perfect specificity and sensitivity on both types of effect measures is warranted. In our hypothetical example, we examined the effect of sensitivity and specificity measures from the different administrative healthcare claims-based myocardial infarction algorithms on relative and absolute effect measures. As expected, deviations from perfect specificity led to biased results on the relative scale while increases

in sensitivity decreased bias on the absolute scale. However, both sensitivity and specificity can influence absolute measures as was demonstrated by the increased % bias associated with the lowest specificity and highest sensitivity values. It should be noted that both bias and precision are important considerations when determining an appropriate algorithm for event ascertainment. While a perfect specificity will decrease the bias of the relative effect measure, the reduction of the number of cases identified may decrease precision around estimates substantially. Therefore, the type of ascertainment algorithm used should be prioritized based on the study question and the maximization of the specific validation parameter that will minimize bias while maximizing precision. For this HIV Medicaid population, it may be important to use an algorithm that either reduces the length of stay requirement or expands the ICD-9 code position requirement to maximize sensitivity with minimal decreases in specificity.

Our study has limitations. The number of events obtained for validation was low which influenced the precision around our validation measurements. Further, we intentionally conducted this study in a Medicaid HIV population which may limit the generalizability of these algorithms to other populations or different administrative data sources. Despite these limitations, our study has important implications. Since this population includes patients seeking care in various locations across the state of North Carolina, we will be able to examine the effects of antiretrovirals on myocardial infarction in a population representative of patients seeking care both in and outside of academic health centers like the University of North Carolina. The ascertainment algorithms used in this study have relatively high specificity and can be used to conduct comparative effectiveness studies examining the relationship between antiretroviral use and long term myocardial infarction

outcomes in the NC Medicaid population. Finally, the measures of validity reported here may be used by other researchers to assess the role of outcome misclassification in studies using administrative healthcare databases.

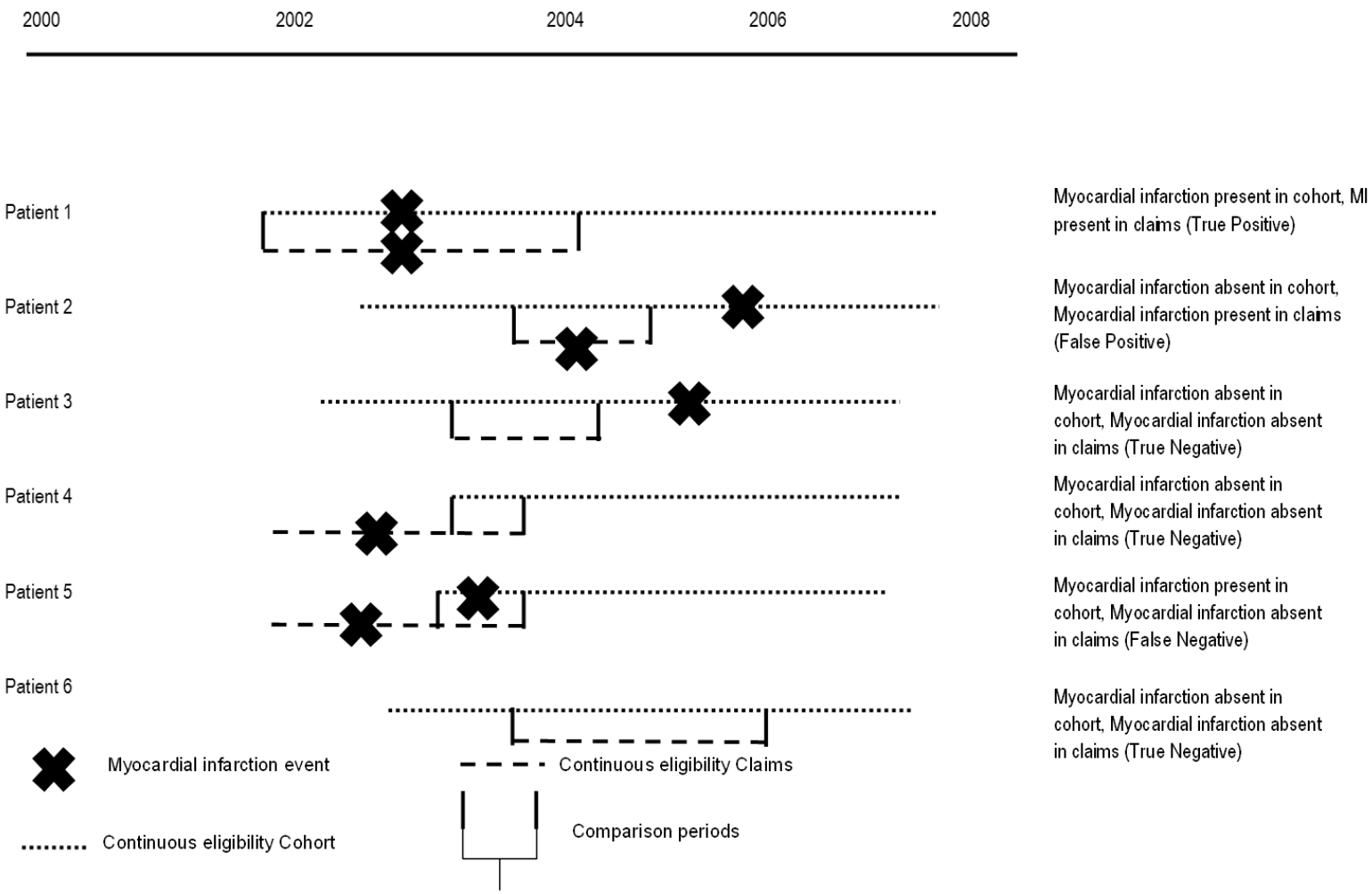


Figure 1. Illustration of the timing of myocardial infarction events in either the Medicaid claims or the UNC-CFAR HIV Clinical Cohort and corresponding validation parameter classification.

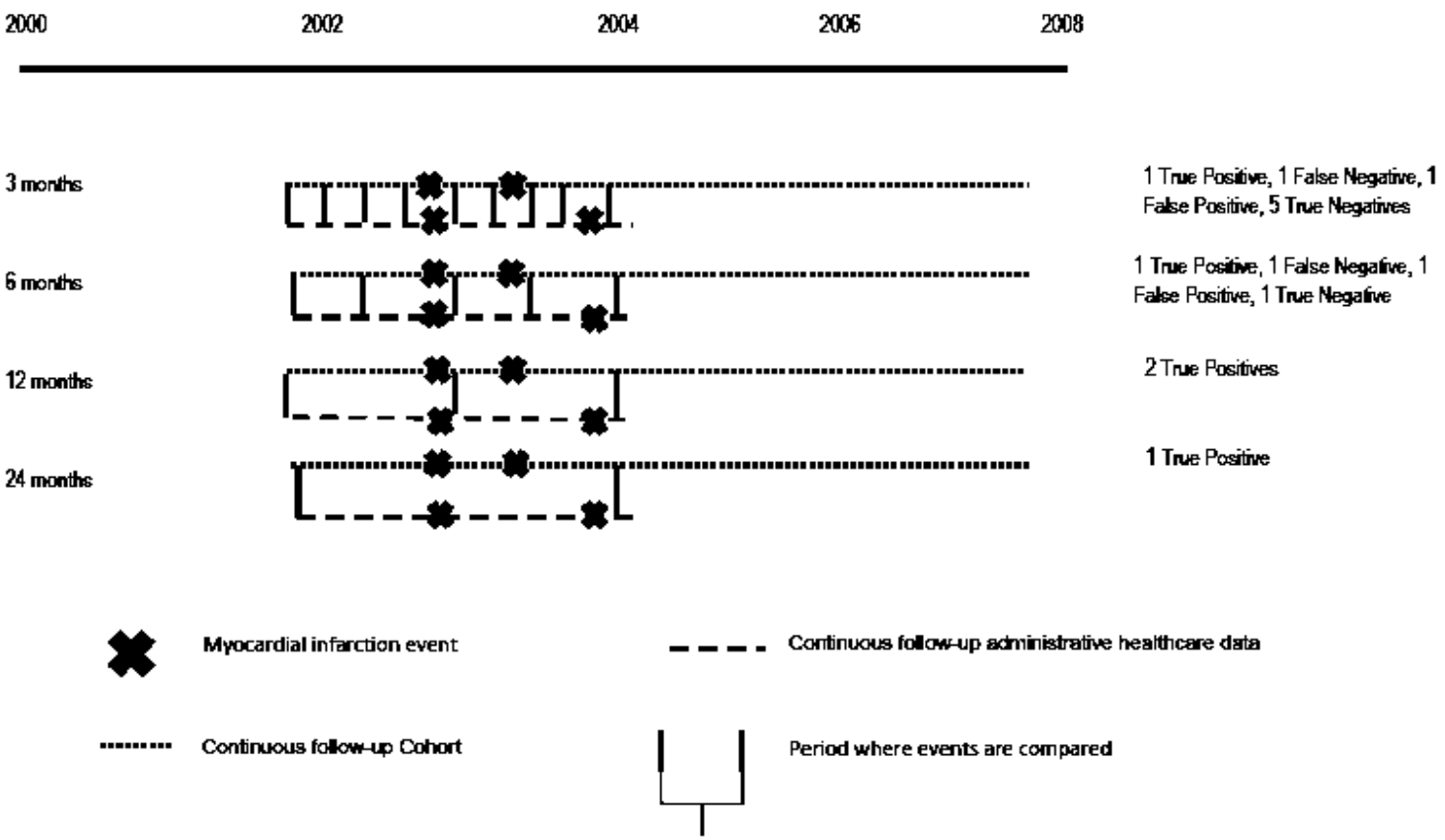


Figure 2. Demonstration of the timing of myocardial infarction events based on parsing out equivalent periods of time (3, 6, 12, 24 months) in either the Medicaid claims or the UNC-CFAR HIV Clinical Cohort and corresponding validation parameter classification.

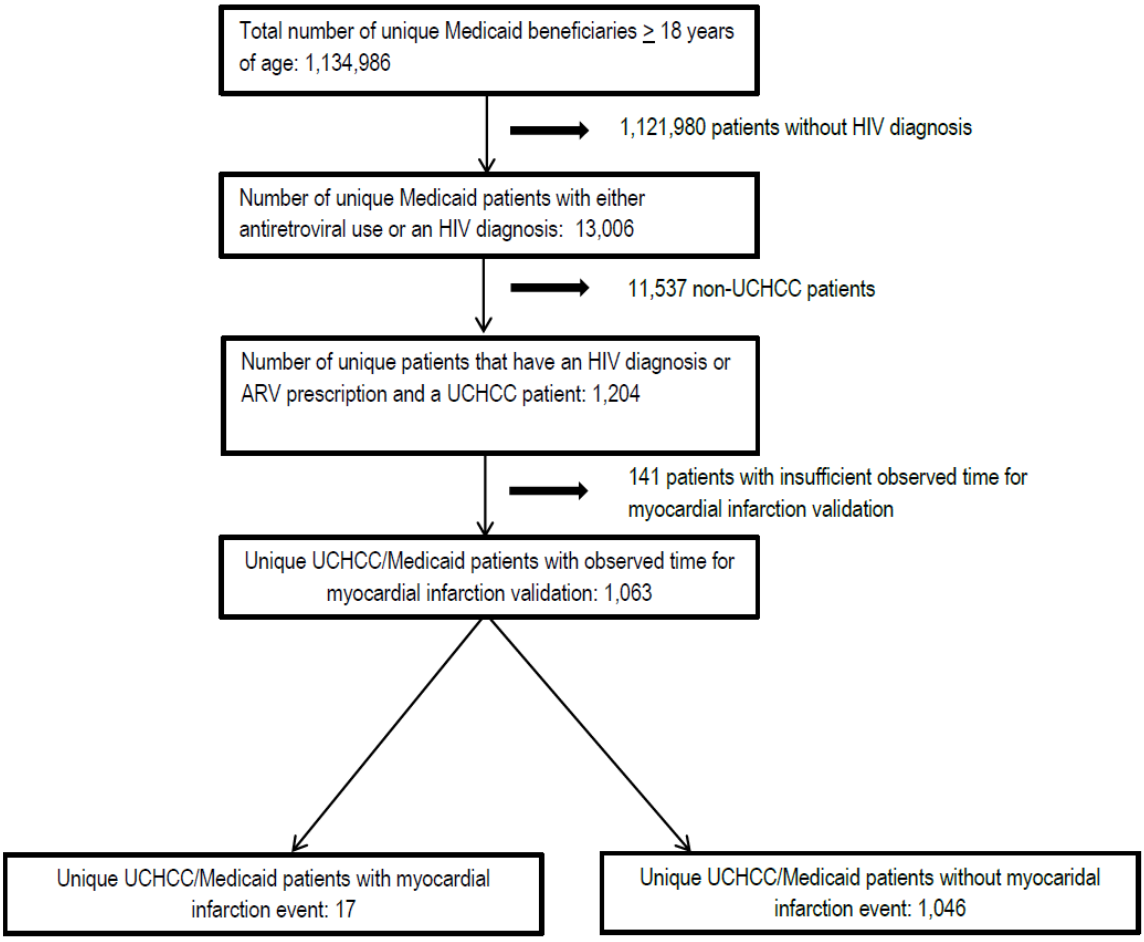


Figure 3. Generation of the sample population used to validate myocardial infarction outcomes ascertained from the North Carolina Medicaid Administrative Data.

Table 4. Clinical and socio-demographic characteristics of Medicaid, UNC HIV Clinical Cohort and Validation Sample populations

	Medicaid N=13,006 n(%)	**UCHCC N=2,338 (%) n (%)**	**Validation Sample N=1,063 n (%)**
Gender			
Female	5,918 (45.5)	949 (29.4)	437 (41.1)
Age at UCHCC/Medicaid entry, years			
<40	5,505 (42.3)	1,382 (59.1)	541 (50.8)
40-50	4,699 (35.1)	681 (29.1)	389 (36.6)
>50	2,802 (21.5)	276 (11.8)	133 (12.5)
Race			
White	2,740 (21.1)	755 (32.3)	232 (21.8)
Black	9,221 (71.0)	1,349 (57.7)	754 (70.9)
Hispanic	0 (0.0)	137 (5.9)	22 (2.1)
Asian	68 (0.5)	*	0 (0.0)
Native American/Pacific Islander	169 (1.3)	41 (1.8)	32 (3.0)
Other	0 (0.0)	52 (2.2)	23 (1.9)
Unknown	808 (6.0)	*	*
Insurance at UCHCC entry			
Medicaid	NA	547 (23.4)	475 (44.6)
Medicare	NA	135 (5.8)	54 (5.1)
Other Public Insurance	NA	148 (6.3)	71 (6.7)
Private	NA	622 (26.6)	118 (11.0)
No Insurance	NA	879 (37.6)	344 (32.4)
Men who have sex with Men (MSM)			
Yes	NA	905 (39.0)	264 (24.8)
Intravenous Drug User (IDU)			
Yes	NA	328 (14.0)	235 (22.1)

CD4 count (cells/μL) most proximal to UCHCC entry (median, IQR)[†]	NA	306 (99, 510)	280 (76, 481)
log HIV RNA (copies/mL) most proximal to UCHCC entry (median, IQR)[††]	NA	4.4 (3.2, 5.1)	4.5 (1,7, 4.2)

[*]Cell counts < 11 not displayed

[**]<0.01 percent missing values for insurance status in the UCHCC and validation cohort respectively

[†]<0.001 percent missing CD4 count values for UCHCC and the validation cohort respectively.

[††]<0.001 percent missing log HIV RNA values for UCHCC and the validation cohort respectively.

Table 5. Sensitivity, specificity, positive predictive value, and negative predictive values resulting from the comparison of different claims based ascertainment criteria of myocardial infarction events with myocardial infarction events observed in the UNC-CFAR

	Se*	95% CI*	Sp*	95% CI*	PPV*	95% CI*	NPV*	95% CI*
Medicaid Claims-based event ascertainment algorithm† n=1,063 (17 UCHCC events)								
- ICD-9 410.xx in 1st or 2nd position -Length of stay ≥ 3 days	0.588	0.329, 0.816	0.994	0.988, 0.998	0.625	0.354, 0.848	0.993	0.986, 0.997
- ICD-9 410.xx in 1st or 2nd position -Length of stay ≥ 1 day	0.588	0.329, 0.816	0.993	0.986, 0.997	0.588	0.329, 0.816	0.993	0.986, 0.997
-ICD-9 410.xx in 1st , or 2nd position -Any length of stay	0.647	0.383, 0.857	0.988	0.980, 0.994	0.478	0.268, 0.694	0.994	0.987, 0.997
-ICD-9 410.xx in any position -Length of stay ≥ 3 days	0.765	0.501, 0.932	0.991	0.984, 0.996	0.591	0.364, 0.793	0.996	0.990, 0.999
-ICD-9 410.xx in any position -Length of stay ≥ 1 days	0.765	0.501, 0.932	0.989	0.980, 0.994	0.520	0.313, 0.64	0.996	0.990, 0.999
-ICD-9 410.xx in any position -Any length of stay	0.824	0.566, 0.962	0.982	0.972, 0.999	0.438	0.264, 0.623	0.997	0.992, 0.999

*__Se__: Sensitivity; __Sp__: Specificity; __PPV__: Positive Predictive Value; __NPV__: Negative Predictive Value; __CI__: Confidence Interval

†Myocardial infarctions were identified in the UNC-CFAR HIV Clinical Cohort through extensive medical chart abstraction and adjudicated by health care personnel using modified WHO Monica criteria.

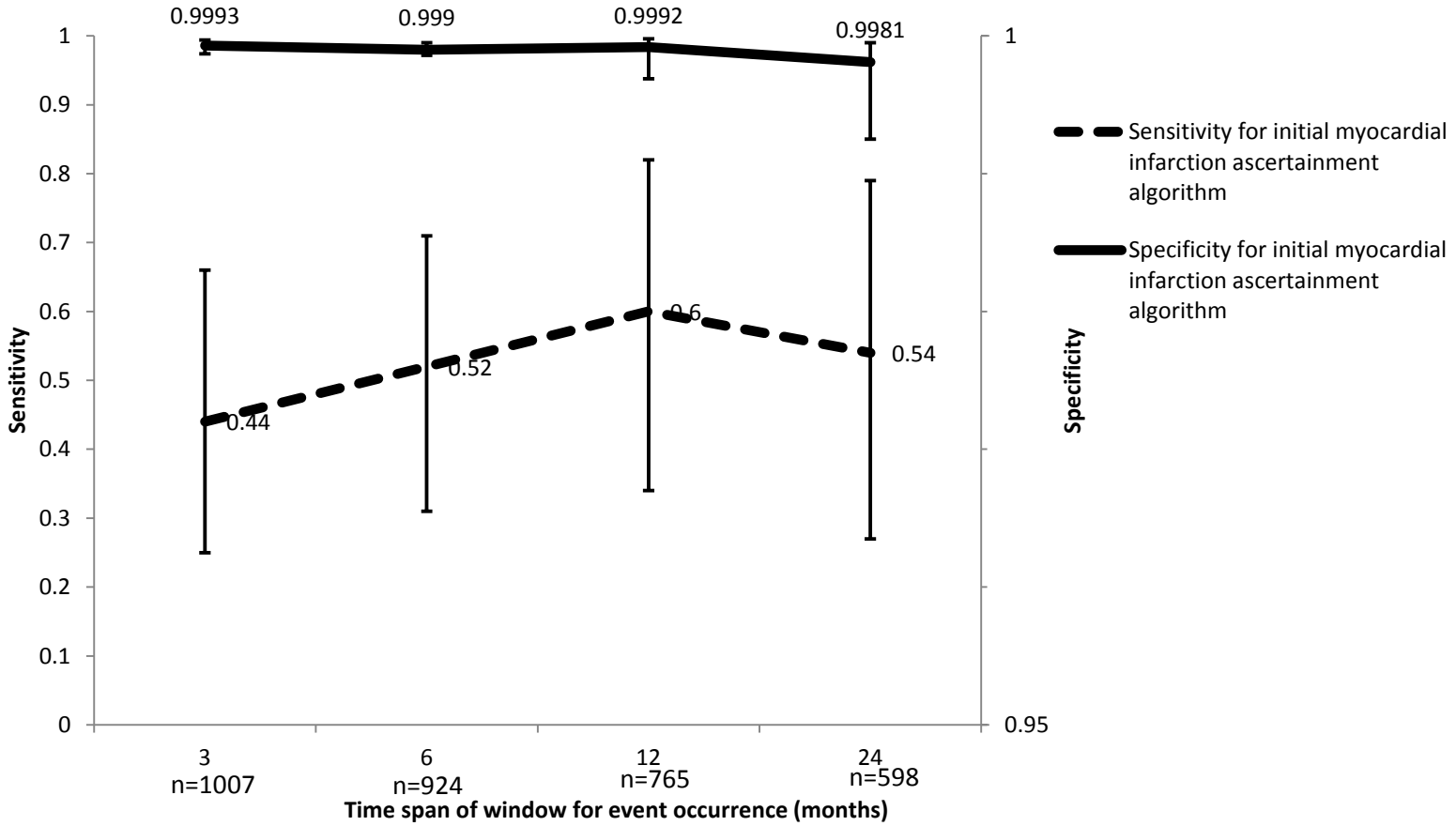


Figure 4. Sensitivity and false positive rate for claims-based identification of myocardial infarctions allowing for varying periods of continuous eligibility (3, 6, 12, 24 months). Myocardial infarction events were identified by ICD-9 code 410 in the 1st or 2nd position and a length of stay $\geq$ 3 days.

Table 6. Bias in relative risk (RR) and relative difference (RD) resulting from misclassification of outcome using three algorithms to ascertain myocardial infarction events in North Carolina Medicaid Administrative data

Outcome Ascertainment Criterion:	True RR*	True RD*	Sensitivity	Specificity	Observed RR†	Observed RD†	% bias ln RR††	% bias RD††
1) -ICD-9 code 410 in 1st or 2nd position -Length of stay ≥ 3 days	1.25	0.012	0.588	0.994	1.22	0.012	11	40
2) -ICD-9 code 410 in any position -Length of stay ≥ 1 day	1.25	0.012	0.765	0.989	1.21	0.015	15	25
3) -ICD-9 code 410 in any position -Any length of stay	1.25	0.012	0.824	0.982	1.10	0.009	58	55

* In this hypothetical population of 1,100 patients, the true risk of a hypothetical adverse event in patients exposed to a hypothetical medication is 0.1, the true risk of the same hypothetical adverse event unexposed to the medication in this population is 0.08. The probability of medication exposure in the population is 0.09.

† $RR = \frac{a/(a+b)}{c/(c+d)}$ RD= $a/a+b-c/(c+d)$ where

a=sensitivity x proportion exposed x risk in exposed + (1-specificity) x proportion exposed x (1-risk in exposed)
b=(1-sensitivity) x proportion exposed x risk in exposed + specificity x proportion exposed x (1-risk in exposed)
c=sensitivity x (1-proportion exposed) x incidence in the unexposed + (1-specificity) x (1- proportion exposed) x (1-risk in unexposed)
d=(1-sensitivity) x (1-proportion exposed) x incidence in the unexposed + specificity x (1-proportion exposed) x (1-risk in unexposed)

†† Bias (Risk Ratio)=100*($\ln(RR)_{true} - \ln(RR)_{observed}$)/$\ln(RR)_{observed}$; Bias (Risk Difference)=100*(RD_{true}-$RD_{observed}$/RD_{true})

CHAPTER VI

MANUSCRIPT 2: COMPARATIVE EFFECTS OF DIFFERENT COMBINATION ANTIRETROVIRAL THERAPIES ON THE RISK FOR MYOCARDIAL INFARCTION AMONG HIV PATIENTS ENROLLED IN MEDICAID: A NEW USER, ACTIVE COMPARATOR COHORT STUDY

Introduction:

The burden of disease among patients with Human Immunodeficiency Virus (HIV) infection has changed since the development of potent combination antiretroviral therapy (cART). With the development of these important new therapies, non-Acquired Immune Deficiency Syndrome (AIDS) related conditions are replacing AIDS related conditions as the major cause of morbidity and mortality in HIV infected patients.[12] Since 2008 there has been much discussion in the literature about the comparative effects of specific antiretroviral entities and coronary artery disease, specifically myocardial infarction. Results from two prospective cohort studies, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study and the Strategies for Management of Antiretroviral Therapy (SMART) suggest an increased risk of myocardial infarction with current or recent but not cumulative use of abacavir [1, 123]. Other more recent observational studies have also shown an increased risk of myocardial infarction associated with abacavir, [51-53, 124] however, meta-analyses of randomized controlled trials have not shown the same increased risk and a Food and Drug Administration sponsored meta-analysis demonstrated a Risk Difference (RD) of

0.01 (95% CI: -0.26-0.27) for the risk of myocardial infarction among abacavir users versus no abacavir use. [49, 125, 126].

Some of the observed increase risk for myocardial infarction in the observational studies may be attributed to channeling bias; patients prescribed abacavir have been shown to be at a higher baseline risk for comorbid conditions that increase the risk of cardiovascular disease. For example, Bedimo et al demonstrated in a cohort of HIV infected Veterans that a larger proportion of patients receiving abacavir were also diagnosed with chronic kidney disease and this condition was associated with an increased risk of myocardial infarction. [51] Many of these studies, including the Veterans study mentioned above, also include patients that are prevalent users of antiretroviral medications. Inclusion of prevalent users of antiretroviral medications makes it difficult to distinguish true confounders from comorbid conditions affected by prior treatment as well as the possibility for under ascertainment of events, particularly if the events occur early in treatment leading to additional bias. [100] Furthermore, these observational studies used different comparison groups making it difficult to compare results. While meta-analyses of randomized controlled trials may not be subject to the same biases as observational studies, the lack of adequate follow-up time to observe an event may lead to a reduction in power to detect a difference between treatment groups.

In order to more fully resolve the discrepancy between observational studies and meta-analyses of randomized controlled trials and further examine the comparative safety of antiretroviral use on myocardial infarction, it is important to design an observational study that would mimic a randomized controlled trial if it were ethical to conduct such a study.[127] The use of an intention to treat, new user design more closely represents the equipoise that is found in a randomized controlled trial thus reducing the potential for

confounding and selection bias. We therefore conducted a new user, active comparator; intention to treat cohort study design to examine the effects of initiating specific antiretroviral therapies on the risk for myocardial infarction among HIV infected patients initially receiving combination antiretroviral therapy (cART).

Materials and Methods:

Data source:

We implemented our cohort study using North Carolina Medicaid administrative data obtained from the Carolina Cost and Quality Initiative at the University of North Carolina at Chapel Hill. The Medicaid program is a joint state and federally funded program that provides healthcare benefits to individuals of low income. Individuals qualify based on age, disability, income and financial resources. Data for the years 2002-2008 was received from the Carolina Cost and Quality Initiative at the Sheps Center for Health Services research at the University of North Carolina at Chapel Hill. The Medicaid administrative data contains health care service reimbursement information including doctor visits, hospital care, outpatient visits, treatments, emergency use, prescription medications, as well as diagnoses, procedures and provider information. This data also includes health service reimbursement information for beneficiaries that are also eligible for Medicare (dual eligibles). [84]

Study Population:

We conducted this intention to treat, new user [100], active comparator cohort study to emulate a population that would be enrolled in a randomized controlled trial evaluating the relationship between the initiation of specific antiretrovirals as part of a standard combination antiretroviral therapy regimen (cART) and myocardial infarction. A cART regimen contains two NRTIs as a backbone and an anchor antiretroviral that is either an NNRTI, a protease inhibitor (PI) boosted or unboosted with ritonavir, an integrase strand transfer inhibitor

(ISTI) or an additional NRTI. For this analysis, we considered only cART regimens containing lamivudine or emtricitabine as one of the two nucleoside reverse transcriptase inhibitors in the backbone (see appendix table 1 for a description of antiretroviral classes). Our study design included three study arms, the first arm examined the initiation of the nucleoside reverse transcriptase inhibitors (NRTI), abacavir (treated) and tenofovir (active comparator). The second and third arms examined receipt of lopinavir/ritonavir, atazanavir (treated) and an NNRTI (active comparator). (figures 1a and 1b).

Patients in our cohort study were required to 1) be $\geq$ 18 years of age 2) be HIV positive based on administrative criteria (ICD-9 code 042.xx or a Medicaid claim for one of the 26 FDA approved antiretroviral medications) 3) have at least 180 days of Medicaid eligibility prior to study entry 4) be new recipients of a combination antiretroviral therapy (cART) regimen including the antiretrovirals from NRTI class, lamividuine or emtricitabine. A regimen was defined as a group of antiretroviral Medicaid claims dispensed within 30 days of each other. A cART regimen was defined as one of guideline recommended standard regimens defined above.

A new cART regimen recipient was defined as a patient receiving a cART regimen without a prescription filled for any antiretroviral in the 180 days prior to study entry. If a patient had a claim for an antiretroviral medication or a group of antiretroviral medications that did not qualify as a cART regimen (e.g. monotherapy or dual therapy) for $\leq$ 30 days and a valid regimen was prescribed thereafter, the second regimen was considered the new cART regimen. We excluded new recipients with a regimen prescribed for < 30 days followed by a non-standard cART regimen as well as patients with any claims for myocardial infarction

(acute or chronic), coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) in the 180 days prior to cART initiation.

Exposure and Outcome Definitions:

Our primary outcome was myocardial infarction defined by a diagnosis code of 410.xx in any position and a length of stay $\geq$ 1 day in the Medicaid claims. This algorithm was previously validated in the North Carolina Medicaid population (sensitivity=0.765 [95% CI: 0.501, 0.932]; specificity=0.989 [95% CI: 980, 994]) [128]. We examined exposure to the most common antiretroviral medications contained within the standard cART regimens defined above. We first examined recipients of the most common nucleoside reverse transcriptase inhibitors, abacavir as part of a new cART regimen as the treatment group to the active comparator, tenofovir. Next we examined recipients of PIs (atazanavir [boosted and unboosted with ritonavir] and lopinavir [boosted with ritonavir]) as the treatment group to NNRTIs as the active comparator group. We compared receipt of atazanavir to the NNRTIs combined and receipt of lopinavir to the NNRTIs combined. For each of the analyses we excluded patients that were on regimens that contained both the exposed (treated) and active comparator antiretroviral (e.g. abacavir and tenofovir).

Confounders/Covariates:

We obtained data on potential confounders from the Medicaid claims in the 180 days prior to cART initiation. We included age at study entry, sex, race, regimen type based on anchor antiretroviral (ritonavir boosted PI or ISTI based, NNRTI based, ritonavir unboosted PI based, triple NRTI based), calendar year of antiretroviral initiation (6 indicator variables for calendar year), concomitant cardiovascular medication use (angiotensin converting enzyme receptor (ACE) inhibitors, angiotensin receptor blocking agents, beta receptor

blocking agents, calcium channel receptor blocking agents and HMG-CoA receptor inhibitors), comorbidities in the 180 days prior to study entry (based on ICD-9 codes from the Deyo implementation of the Charlson comorbidity score, used separately, i.e., not as a score), number of hospitalizations (0, 0-2, >2 hospitalizations) and number of medication claims (0, 1-15, 15-20, >20 medications).

Statistical Analysis:

To account for baseline differences in treatment and to estimate the effect of treatment in the treated populations, we estimated Standardized Morbidity/Mortality Ratio (SMR) weights. The SMR weight is calculated as the conditional probability of receiving the patients' actual treatment (treatment or comparator) multiplied by the conditional probability of treatment regardless of the patients' treatment status. Through SMR weighting we created a pseudo-population of patients that had the same probability of receiving the treatment of interest. Patients either receive a weight of 1 (standard treatment) or a weight defined as $\hat{e}(X)/(1-\hat{e}(X))$ where $\hat{e}(X)$ is the propensity score [102, 103]. As many patients receiving abacavir in our population were on triple NRTI therapy, a regimen that is no longer recommended by the treatment guidelines [129], tenofovir was identified as the standard for the NRTI arm. For the NNRTI/PI arms of this study, atazanavir or lopinavir were the designated standards to avoid extreme weights. To calculate the weights, we estimated three propensity score models using logistic regression for each arm of our study 1) tenofovir compared to abacavir 2) atazanavir compared to NNRTIs and 3) lopinavir (boosted/unboosted) compared to NNRTIs. Logistic models included all the covariates listed above identified as potential confounders of the antiretroviral use-myocardial infarction relation based on expert knowledge on the relationship of these factors with the exposure and

the outcome. The following characteristics were included in the tenofovir compared to abacavir propensity score models: race, sex, comorbidities, cardiovascular medication use, hospitalizations, and overall medication use in the 180 days prior to study entry, year of antiretroviral initiation, regimen type. Propensity score models constructed to predict atazanavir or lopinavir included all of the above with the exception of regimen type as the use of an NNRTI or PI inherently defines regimen type. Prior to creating the weighted pseudo-population, we trimmed the propensity scores to exclude patients always initiated on one of the cART treatments compared (non-positivity).

Follow-up started on the day of the claim for the last antiretroviral medication in the qualifying new cART regimen and continued until the occurrence of 1) myocardial infarction 2) discontinuation of Medicaid eligibility or 3) end of study period (December 31, 2008), whichever came first. We calculated overall unadjusted incidence rates for myocardial infarction using Poisson regression. We then used the SMR weights previously described to create adjusted Kaplan Meier curves for each of the study arms. Finally, we crated Cox proportional hazard regression models to compare unadjusted and SMR adjusted hazard ratios (HR) and corresponding 95% confidence intervals. For the weighted analyses we used robust variance estimation. For all Cox proportional hazard models we tested proportional hazards assumptions by including an interaction term between treatment arm and the log of time. This study was approved by the University of North Carolina Committees on the Protection of the Rights of Human Subjects and all analyses were conducted using SAS version 9.2 or intercooled STATA version 11.

Sensitivity Analyses

We conducted two sensitivity analyses to address non-adherence as well as the potential for unmeasured confounding. We first attempted an as-treated analysis and censored patients either at the first of myocardial infarction, stopping or switching antiretrovirals, or administrative censoring. To address the potential for unmeasured confounding, we conducted a sensitivity analysis where we excluded patients at the upper and lower 1, 2.5, and 5 percentiles of the propensity score distribution.[104]

Results

Study Population and Descriptive Statistics:

There were 13,006 HIV positive beneficiaries enrolled in North Carolina Medicaid between January 1, 2002 and December 31, 2008. Of these, 3,554 beneficiaries were new recipients of a qualifying cART regimen. (Figure 2) The distribution of patient characteristics in the new cART recipient population were generally similar to those of the overall HIV patient population, however, the proportion of patients < 40 years of age was greater in the overall HIV population than among those treated with antiretrovirals (58% vs. 44% respectively). A large proportion of HIV positive beneficiaries that were enrolled in Medicaid between 2002 and 2008 did not receive any antiretroviral treatment (34%). Of patients that were prescribed any antiretroviral (8,586), the majority of patients received cART containing two NRTIs and an NNRTI (27%). This also was the most predominant regimen type among new cART recipients (36%).

The distribution of covariates among new recipients of cART was generally similar among recipients of the specific antiretrovirals. When comparing baseline characteristics of recipients of abacavir and tenofovir, we noted differences in comorbidities, regimen type and

year of antiretroviral initiation (table 1). A greater proportion of abacavir recipients had renal disease (4.1% vs. 1.7%) at baseline. Conversely, a larger proportion of tenofovir recipients had mild liver disease (4.2% vs.2.2%) and cancer (5.6% vs. 4.0%) when compared with patients initiating abacavir. Most abacavir recipients initiated cART before 2006 (58.9%) while the majority of tenofovir recipients initiated cART during or after 2006 (67.7%). A triple NRTI regimen was the most common type of antiretroviral regimen for abacavir recipients (38.4%) while a non-nucleoside reverse transcriptase inhibitor based regimen was the most common for recipients of tenofovir (49.4%). (table 1) Compared to recipients of NNRTIs, a larger proportion of patients receiving atazanvir or lopinavir had heart failure (5.2%, 5.0% vs. 3.6%) and patients receiving atazanavir were less likely to have cancer compared to those receiving NNRTIs (3.7% vs. 5.5%). Patients receiving lopinavir were less likely to have chronic pulmonary disease compared to NNRTI recipients (6.6% vs. 8.0%). Fifty-three percent of patients receiving NNRTIs initiated regimens between prior to 2006 while 63.4% and 75.3% of patients receiving atazanavir and lopinavir respectively initiated regimens in 2006 or later. (Table 2)

Propensity score and SMR weighting results:

Of the 2,299 patients that received abacavir or tenofovir, we excluded 84 patients in the non-overlapping regions of the propensity score distribution for the treated and active comparator group, leaving 2,215 patients. SMR weights created to adjust for receipt of abacavir compared to tenofovir ranged from 0.10 to 11.6. Of patients that received either azatanavir or an NNRTI (2,221), we excluded 55 patients. SMR weights used to adjust for the relationship between receipt of atazanavir compared to an NNRTI ranged from 0.03, 1.80. We excluded 283 patients from the non-overlapping regions of the propensity score

distribution for patients treated with either lopinavir or NNRTI. SMR weights for the comparison between receipt of lopinavir compared to an NNRTI ranged from 0.02, 3.19. After weighting the characteristics of each of treatment groups, including comorbidities that were not balanced at baseline, were comparable (tables 2 and tables 3).

Comparative Safety Results:

The overall unadjusted incidence rate of myocardial infarction for the entire new cART population was 6.7 (95% CI: 4.5, 10.0) per 1000 person-years of follow-up. Patients initiating abacavir or tenofovir had an unadjusted incidence rate of 11.3 (95% CI: 6.7, 19.1) and 4.3 (95% CI: 2.3, 8.0) per 1000 person-years of follow-up. The rates of myocardial infarction for patients receiving atazanvir, lopinavir or an NNRTI were 4.1 (95% CI: 1.5, 11.0), 8.7 (95% CI: 3.3, 23.0) and 5.8 (95% CI: 3.6, 9.5). (Table 3)

Figures 3 and 4 display Kaplan Meier curves for the SMR weighted pseudo-populations for each of the study arms stratified by treatment group. Unadjusted Cox proportional hazard regression models showed an increased hazard rate of myocardial infarction among recipients of abacavir compared to tenofovir (HR: 2.71 [95% CI:1.20, 6.12]). After weighting and balancing the treatment groups, the association remained although the point estimate was reduced and there was loss of precision around the estimate (HR: 2.15, 95% CI: [0.70, 6.58]). Unadjusted and SMR weighted models did not demonstrate clinically meaningful differences in hazard rates of myocardial infarction among the other comparison groups. (Table 3)

Sensitivity Analyses:

To address non-adherence, stopping, and switching antiretroviral treatments, we attempted an as treated analysis, however, we did not have an adequate number of events in

the treatment groups to address this question. We conducted a separate sensitivity analysis to address unmeasured confounding where we excluded patients at the upper and lower 1, 2.5, and 5 percentiles of the propensity score distribution. [104] Trimming the upper and lower 1, 2.5, and 5 percentiles of the propensity score distribution reduced the HR did not change suggesting that unmeasured confounding did not influence our results. Trimming at the upper and lower 1, 2.5, and 5 percentiles of the propensity score distribution for patients receiving atazanavir, lopinavir or an NNRTI did not substantially change the observed results.

Discussion:

We conducted an active comparator, new user cohort study to evaluate the effects of initial treatment with specific antiretroviral medications on the risk for myocardial infarction. In our study we found that patients treated initially with abacavir as part of their new cART regimen had an increased rate of myocardial infarction when compared with patients treated initially with tenofovir. While the 95% confidence interval for this HR overlaps the null and we thus cannot exclude chance as an alternative explanation, the magnitude of the adjusted HR speaks against residual and unmeasured confounding as alternative explanations. We did not find clinically significant increased rates among patients receiving any of the other antiretrovirals compared to their active comparators. The hazard ratio point estimates obtained from our study are consistent, although slightly more pronounced, than results from other observational studies evaluating the relationship between abacavir and myocardial infarction [1, 52, 53, 124]. However, the estimates do not concur with the results from meta-analyses of clinical trials that did not show a relationship between abacavir use and myocardial infarction.[49, 125, 126]

There is some evidence that the increased rates of myocardial infarction associated with abacavir use observed in cohort studies may be due to channeling bias [130] as well as potential effect modification. [52] Using a large cohort of Veterans, Bedimo et al. showed that the observed relationship between abacavir use and myocardial infraction may be due to channeling of patients with baseline comorbidities that increase the risk of myocardial infarction, like chronic kidney disease, away from tenofovir. [51] Lang et al, demonstrated in a French Cohort that the increased risk of myocardial infarction due to abacavir use was limited to patients who used cocaine or intravenous drugs. [52] We also noted baseline differences in kidney disease as well as other comorbidities between antiretroviral exposure groups. We addressed these baseline differences among those treated through SMR weighting using propensity scores and showed that this removed differences in CVD risk factors between the treatment arms, including kidney disease. However, weighting is only able to address measured confounders and not those that are unmeasured.

Researchers have postulated potential biological mechanisms for the observed increased rate of myocardial infarction among patients exposed to abacavir, although the exact mechanism remains unclear. Literature suggests that HIV infection influences factors related to inflammation and endothelial function [25, 131-133], and that initiation of antiretroviral therapy generally improves these factors. [133-135] It has been hypothesized that rather than improve these factors, abacavir may be associated with impaired endothelial function and increased inflammation. However, results are conflicting.[54, 55, 136]

We used an active comparator, new user design in combination with an intention-to-treat analysis and a validated myocardial infarction identification algorithm. To our knowledge, this type of study design has not yet been implemented to examine the

relationship between antiretroviral use and myocardial infarction. The active comparator, new user design is advantageous in that it limits the potential for confounding bias and is a preferred study design for comparative safety and effectiveness research. [105, 127] By restricting our comparison to initiators of cART, we reduce the potential for under ascertainment of events that may have occurred early in therapy (prior to study initiation) as well as the ability to assess confounders at the time of antiretroviral start reducing the influence of time-dependent confounders on the causal pathway. [100] The use of propensity score methods are advantageous in studies such as this one as our outcome is rare and we are also able to limit our population to those with the same probability of treatment [105, 137] Finally, the validated myocardial infarction algorithm with high specificity limits the potential for bias of hazard ratio estimates due to outcome misclassification.

This study also adds to the literature in that we use an active comparison group for both the NRTI and PI/NNRTI analyses. Studies completed to date have defined exposure to specific antiretrovirals as any/recent/cumulative exposure and compared these exposures to no exposure to the antiretroviral in question [1, 51-53, 124]. While important, these types of comparisons make it difficult to compare across studies, particularly studies relating to HIV, as "no-use" is likely to equate to use of some other antiretroviral that likely differs by study. This heterogeneity of the comparison group makes generalization across populations difficult as treatment patterns may differ. Given the active comparator, our study answers a clinically more relevant question, i.e., given the indication for cART, which of the treatment regimens is associated with the lowest risk for myocardial infarction. Finally almost half of our study population was comprised of women patients compared to other observational studies

conducted to date that included between 2% and 25% females.[1, 49, 51, 53, 124-126]. This increased proportion of women allows for improved generalizability of our results.

One main concern regarding the use of administrative data such as that which we used in our study is the inability to obtain information on potentially important confounding variables such as CD4 count, HIV RNA, LDL cholesterol and history of smoking. Therefore, it is possible that our findings could be subject to unmeasured confounding. The active comparator, new user design limits the potential for unmeasured confounding by both indication (likely similar for the treatment regimens compared) and frailty. [104] [1, 105, 123] Given the magnitude of the estimate and our sensitivity results, however, this is not likely the only explanation for our findings. Another limitation of our study is the small sample of new cART recipients resulting in reduced numbers of myocardial infarction events and low precision of estimates. Reduced precision limits our ability to detect a difference between groups, particularly recipients of the protease inhibitors atazanavir and lopinavir. Finally, we only evaluated outcomes related to patients' initiation of specific antiretrovirals as part of cART and did not address non-adherence or duration of exposure to these medications. To address the concern that myocardial infarction events observed may have occurred after a patient stopped or switched to a different antiretroviral and not related to the initial choice of antiretroviral, we attempted an as treated analysis. Unfortunately, we did not have an adequate number of events in the treatment groups to complete this as treated analysis.

In the absence of randomized controlled trials to investigate comparative safety of pharmaceutical treatments, it is necessary to conduct well designed observational studies that most closely emulate a randomized controlled study. This is the first study using an active

comparator, new user design study to investigate the comparative effects of initiating specific antiretrovirals on the risk for myocardial infarction and thus an important contribution to the growing body of literature on this topic. Our study suggests that there may be an increased risk for myocardial infarction among patients initiating abacavir compared to tenofovir as part of cART. However, given sample size limitations, we were unable to conduct an as treated analysis to further validate our results. Therefore, future well-designed studies that include more HIV infected patients initiating cART as well as information on important confounding factors not available in administrative data are warranted to confirm these findings.

Table 7. Baseline characteristics of HIV infected North Carolina Medicaid patients initiating abacavir (ABC) or tenofovir (TDF) as a part of a new combination antiretroviral therapy (cART) regimen before and after SMR weighting

	New cART Recipients		SMR Weighted*	
	ABC Recipients n=628 (%)	TDF Recipients n=1,671 (%)	ABC N (%)	TDF N (%)
Gender				
Female	307 (48.9)	766 (45.8)	734 (44.2)	752 (47.1)
Age, years				
<40	253 (40.3)	737 (44.1)	732 (44.1)	690 (43.2)
40-50	247 (39.3)	632 (37.8)	655 (39.4)	611 (38.3)
>50	128 (20.4)	302 (18.1)	274 (16.5)	295 (18.5)
Race				
Black	468 (74.5)	1,264 (75.6)	1,240 (74.7)	1,204 (75.4)
White	115 (18.3)	311 (18.7)	334 (20.1)	300 (18.8)
Asian	**	**	2 (0.1)	5 (0.3)
Native American/Pacific Islander	**	21 (1.3)	27 (1.6)	18 (1.1)
Unknown	38 (6.1)	69 (4.1)	57 (3.4)	68 (4.3)
Comorbidity at baseline†				
Heart Failure	31 (4.9)	71 (4.3)	75 (4.5)	68 (4.3)
Peripheral Vascular Disease	**	14 (0.8)	7 (0.4)	12 (0.8)
Cerebrovascular Disease	22 (3.5)	48 (2.9)	44 (2.7)	48 (3.0)
Mild Liver Disease	14 (2.2)	70 (4.2)	51 (3.1)	47 (2.9)
Renal Disease	26 (4.1)	29 (1.7)	26 (1.6)	29 (1.8)
Diabetes (uncomplicated)	43 (6.9)	104 (6.2)	104 (6.3)	100 (6.3)
Cancer	25 (4.0)	93 (5.6)	82 (4.9)	84 (5.3)
Chronic Pulmonary Disease	50 (8.0)	135 (8.1)	121 (7.3)	128 (8.0)
Prior Medication Use (180 days before entering study‡				
HMG-CoA Reductase Inhibititors	52 (8.3)	112 (6.7)	108 (6.5)	99 (6.2)
Calcium Channel Blockers	10 (1.6)	29 (1.7)	28 (1.7)	29 (1.8)
Beta Blocking agents	13 (2.1)	50 (3.0)	51 (3.1)	38 (2.4)
Angiotensin Converting Enzyme Inhibitors (ACE-I)	37 (5.9)	97 (5.8)	95 (5.7)	85 (5.3)

Prior Medication Use (180 days before entering study)				
0 Medications	91 (14.5)	120 (7.2)	115 (6.9)	120 (7.5)
1-15 Medications	429 (68.3)	429 (68.3)	1130 (68.1)	1142 (71.6)
15-20 Medications	54 (8.6)	206 (12.3)	236 (14.2)	178 (11.2)
>20 Medications	54 (8.6)	164 (9.8)	179 (10.8)	156 (9.8)
Hospitalizations (180 days before entering study)				
0	396 (63.1)	1,044 (62.5)	990 (59.6)	1,020 (63.9)
0-2	123 (19.6)	332 (19.9)	345 (20.8)	318 (19.9)
>2	109 (17.4)	295 (17.7)	325 (19.6)	258 (16.2)
First Antiretroviral Regimen‡‡				
2NRTI+boosted PI/ISTI	123 (19.6)	618 (37.0)	680 (41.0)	604 (37.8)
2NRTI+NNRTI	144 (22.9)	824 (49.3)	748 (45.1)	764 (47.9)
2NRTI+ unboosted PI	120 (19.1)	156 (9.3)	161 (9.7)	156 (9.8)
Triple NRTI	241 (38.4)	73 (4.4)	72 (4.3)	72 (4.5)
Year of Antiretroviral Initiation				
2002	28 (4.5)	12 (0.7)	8 (0.5)	12 (0.8)
2003	89 (14.2)	63 (3.8)	56 (3.4)	63 (4.0)
2004	84 (13.4)	131 (7.8)	148 (8.9)	130 (8.2)
2005	168 (26.8)	334 (20.0)	380 (22.9)	331 (20.7)
2006	119 (19.0)	426 (25.5)	438 (26.4)	419 (26.3)
2007	37 (5.9)	140 (8.4)	142 (8.5)	136 (8.5)
2008	103 (16.4)	565 (33.8)	488 (29.4)	505 (31.6)

*Propensity score based on the following characteristics: age, race, sex, comorbidities, drug use in the 180 days prior to antiretroviral initiation, cardiovascular drug use in the 180 days prior to antiretroviral initiation, hospitalization in the 180 days prior to antiretroviral initiation, regimen type, year of initiation (6 indicator variables for year).

**Numbers in cell < 11 (cannot be presented based on data use agreement with NC Medicaid).Cells < 11 presented for pseudo-population as persons could be represented more than once.

†Comorbidities include: Heart failure, peripheral vascular disease, cerebrovascular disease, mild liver disease, moderate/severe liver disease, renal disease, diabetes (uncomplicated), diabetes (complicated), cancer, metastatic carcinoma, connective tissue disease, chronic pulmonary disease, dementia. Comorbidities with > 11 subjects in at least one cell of the baseline population presented.

‡Angiotensin receptor blocking agent percentages not presented as there was at least one cell in the baseline population that had < 11 subjects.

‡‡NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor;

Table 8. Baseline characteristics of HIV infected North Carolina Medicaid patients receiving atazanavir (ATV), lopinavir (LPV) or an NNRTI as a part of a new combination antiretroviral therapy (cART) regimen and after before and after SMR weighting

	New cART recipients			SMR Weighted		SMR Weighted	
	ATV n=636 (%)	**LPV n=440 (%)**	**NNRTI n=1,592**	**ATV N (%)**	**NNRTI N (%)**	**LPV N (%)**	**NNRTI N (%)**
Gender							
Female	308 (48.4)	205 (46.6)	719 (45.2)	305 (48.3)	304 (47.9)	205 (46.8)	203 (45.9)
Age, years							
<40	300 (47.2)	202 (45.9)	649 (40.8)	297 (47.0)	308 (48.5)	201 (45.9)	196 (44.3)
40-50	243 (38.2)	156 (35.5)	611 (38.4)	242 (38.3)	230 (36.2)	156 (35.6)	163 (36.9)
>50	93 (14.6)	83 (18.6)	332 (20.9)	93 (14.7)	97 (15.3)	81 (18.5)	83 (18.8)
Race							
Black	464 (73.0)	342 (77.7)	1201 (75.5)	464 (73.4)	466 (73.3)	341 (77.9)	346 (78.3)
White	138 (21.7)	76 (17.3)	295 (18.5)	134 (21.2)	137 (21.6)	75 (17.1)	75 (17.0)
Asian	**	**	**	1 (0.2)	4 (0.6)	1 (0.2)	3 (0.7)
Native American/Pacific Islander	**	**	17 (1.1)	9 (1.4)	7 (1.1)	6 (1.4)	5 (1.1)
Unknown	24 (3.8)	15 (3.4)	71 (4.5)	24 (3.8)	21 (3.3)	15 (3.4)	13 (2.9)
Comorbidity at baseline‡							
Heart Failure	34 (5.4)	22 (5.0)	58 (3.6)	33 (5.2)	32 (5.0)	21 (4.8)	21 (4.8)
Peripheral Vascular Disease	**	**	17 (1.1)	7 (1.1)	7 (1.1)	2 (0.5)	2 (0.5)
Cerebrovascular Disease	19 (3.0)	14 (3.2)	52 (3.3)	19 (3.0)	20 (3.1)	14 (3.2)	15 (3.4)
Mild Liver Disease	21 (3.3)	18 (4.1)	54 (3.4)	21 (3.3)	21 (3.3)	18 (4.1)	17 (3.8)
Renal Disease	18 (2.8)	**	53 (3.3)	18 (2.9)	16 (2.5)	9 (2.1)	7 (1.6)
Diabetes (uncomplicated)	45 (7.1)	21 (4.8)	118 (7.4)	45 (7.1)	44 (6.9)	21 (4.8)	23 (5.2)
Cancer	23 (3.6)	29 (6.6)	88 (5.5)	23 (3.6)	23 (3.6)	29 (6.6)	29 (6.6)
Chronic Pulmonary Disease	57 (9.0)	29 (6.6)	127 (8.0)	57 (9.0)	57 (9.0)	28 (6.4)	27 (6.1)

Prior Medication Use (180 days before entering study‡‡							
Statin	51 (8.0)	35 (8.0)	121 (7.6)	51 (8.1)	51 (8.0)	35 (8.0)	38 (8.6)
Calcium Channel Blockers	**	11 (2.5)	30 (1.9)	9 (1.4)	9 (1.4)	11 (2.5)	13 (2.9)
Beta Blockers	17 (2.7)	17 (3.9)	50 (3.1)	17 (2.7)	18 (2.8)	17 (3.9)	19 (4.3)
Angiotensin Converting Enzyme Inhibitors (ACE-I)	44 (6.9)	29 (6.6)	99 (6.2)	44 (7.0)	43 (6.8)	29 (6.6)	31 (7.0)
Prior Medication Use (180 days before entering study)							
0 Medications	44 (6.9)	25 (5.7)	174 (10.9)	44 (7.0)	44 (6.9)	25 (5.7)	25 (5.7)
1-15 Medications	423 (66.5)	308 (70.0)	1124 (70.6)	423 (66.9)	424 (66.8)	307 (70.1)	305 (69.0)
15-20 Medications	83 (13.1)	56 (12.7)	169 (10.6)	83 (13.1)	83 (13.1)	56 (12.8)	56 (12.7)
>20 Medications	86 (13.5)	51 (11.6)	125 (7.9)	82 (13.0)	84 (13.2)	50 (11.4)	56 (12.7)
Hospitalizations (180 days before entering study)							
0	398 (62.6)	281 (63.9)	1000 (62.8)	397 (62.8)	395 (62.2)	279 (63.7)	275 (62.2)
0-2	129 (20.3)	83 (18.9)	305 (19.2)	127 (20.1)	133 (20.9)	83 (19.0)	88 (20.0)
>2	109 (17.1)	76 (17.3)	287 (18.0)	108 (17.1)	106 (16.7)	76 (17.4)	79 (17.9)
Year of Antiretroviral Initiation							
2002	0 (0.0)	**	40 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2003	**	**	153 (9.6)	8 (1.3)	8 (1.3)	8 (1.8)	8 (1.8)
2004	67 (10.5)	**	209 (13.1)	67 (10.6)	64 (10.1)	1 (0.2)	0 (0.0)
2005	158 (24.8)	13 (3.0)	435 (27.3)	158 (25.0)	158 (24.8)	13 (3.0)	12 (2.7)
2006	172 (27.0)	194 (44.1)	303 (19.0)	170 (26.9)	175 (27.6)	194 (44.3)	193 (43.7)
2007	45 (7.1)	62 (14.1)	91 (5.7)	44 (7.0)	46 (7.2)	61 (13.9)	63 (14.3)
2008	186 (29.3)	162 (36.8)	361 (22.7)	185 (29.3)	185 (29.1)	161 (36.8)	165 (37.3)

[#] Propensity scores based on the following characteristics: age, race, sex, comorbidities, drug use in the 180 days prior to antiretroviral initiation, cardiovascular drug use in the 180 days prior to antiretroviral initiation, hospitalization in the 180 days prior to antiretroviral initiation, year of initiation (indicators for year of initiation)

******Numbers in cell < 11 (cannot be presented based on data use agreement with NC Medicaid). Cells < 11 presented for pseudo-population as persons could be represented more than once.

[†]Comorbidities include: Heart failure, peripheral vascular disease, cerebrovascular disease, mild liver disease, moderate/severe liver disease, renal disease, diabetes (uncomplicated), diabetes (complicated), cancer, metastatic carcinoma, connective tissue disease, chronic pulmonary disease, dementia. Comorbidities with > 11 subjects in at least one cell presented.

[‡]Angiotensin receptor blocking agent percentages not presented as all cells had < 11 subjects.

[‡‡]NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor;

Table 9. Unadjusted and adjusted incidence rates (IR) and hazard ratios (HR) for the rate of myocardial infarction events among HIV infected North Carolina Medicaid patients receiving a new combination antiretroviral therapy (cART) regimen

	N	Myocardial Infarction Events (N)	Person-Time at Risk (years)	Unadjusted IR (95% CI*)	Unadjusted HR (95% CI*)	Adjusted IR** (95% CI*)	Adjusted HR** (95% CI*)
Backbone: Nucleoside Reverse Transcriptase Inhibitors**							
Abacavir	628	14	1,238.9	11.3 (6.7, 19.1)	2.71 (1.20, 6.12)	9.3 (3.7, 23.4)	2.15 (0.70, 6.58)
Tenofovir	1,671	##	2,328.8	4.3 (2.3, 8.0)	1.0	4.4 (2.4, 8.1)	1.0
Anchor Antiretrovirals: Protease Inhibitors/Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) ###							
Atazanvir	636	##	971.12	4.1 (1.5, 11.0)	0.77 (0.25, 2.31)	4.2 (1.6, 11.0)	0.82 (0.26, 2.56)
NNRTI	1,592	16	2,773.46	5.8 (3.6, 9.5)	1.0	5.7 (2.5, 13.0)	1.0
Lopinavir	440	##	459.6	8.7 (3.3, 23.0)	1.68 (0.54, 5.27)	8.7 (3.3, 23.3)	1.52 (0.43, 5.44)
NNRTI	1,592	16	2,760.54	5.8 (3.6, 9.5)	1.0	6.0 (2.6, 13.9)	1.0

*CI: Confidence Interval

**Propensity score used to create SMR weights based on the following characteristics: age, race, sex, comorbidities, drug use in the 180 days prior to antiretroviral initiation, cardiovascular drug use in the 180 days prior to antiretroviral initiation(statin calcium channel blocker, beta-blocker, ace- inhibitor), hospitalization in the 180 days prior to antiretroviral initiation, regimen type (NNRTI, boosted pi/integrase strand transfer inhibitor, unboosted pi, triple NRTI, year of initiation (6 indicator variables for year).

Cells < 11 not presented.

###Propensity score used to create SMR weights based on the following characteristics: age, race, sex, comorbidities, drug use in the 180 days prior to antiretroviral initiation (0, 1-15, 15-20, >20), cardiovascular drug use in the 180 days prior to antiretroviral initiation (statin calcium channel blocker, beta-blocker, ace-inhibitor), hospitalization in the 180 days prior to antiretroviral initiation (0, 0-2, >2), year of initiation (6 indicator variables for year). Robust variance estimator used to calculate variance for SMR weighted data

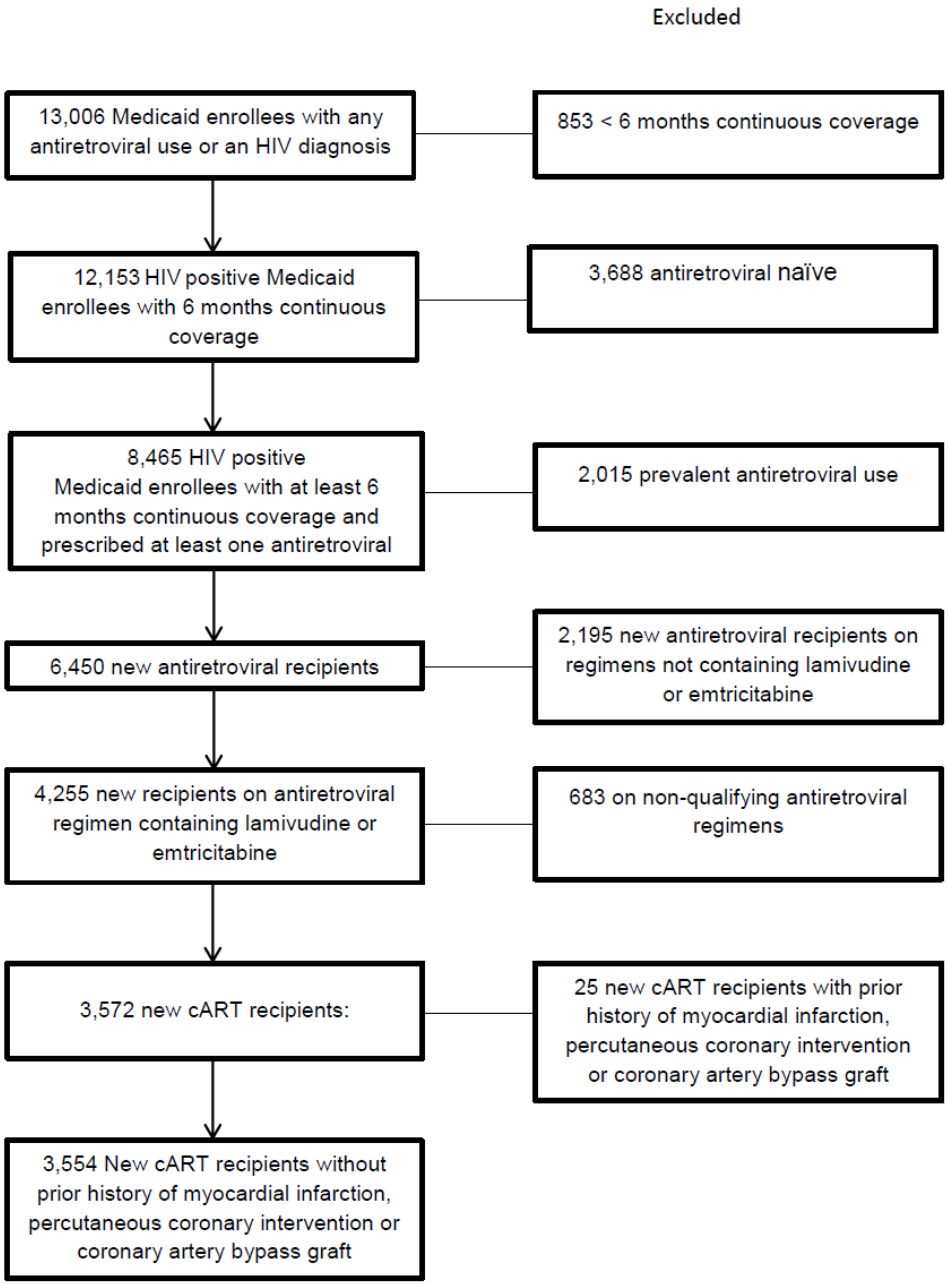


Figure 5. Assembly of the cART (combination antiretroviral therapy) initiator cohort.

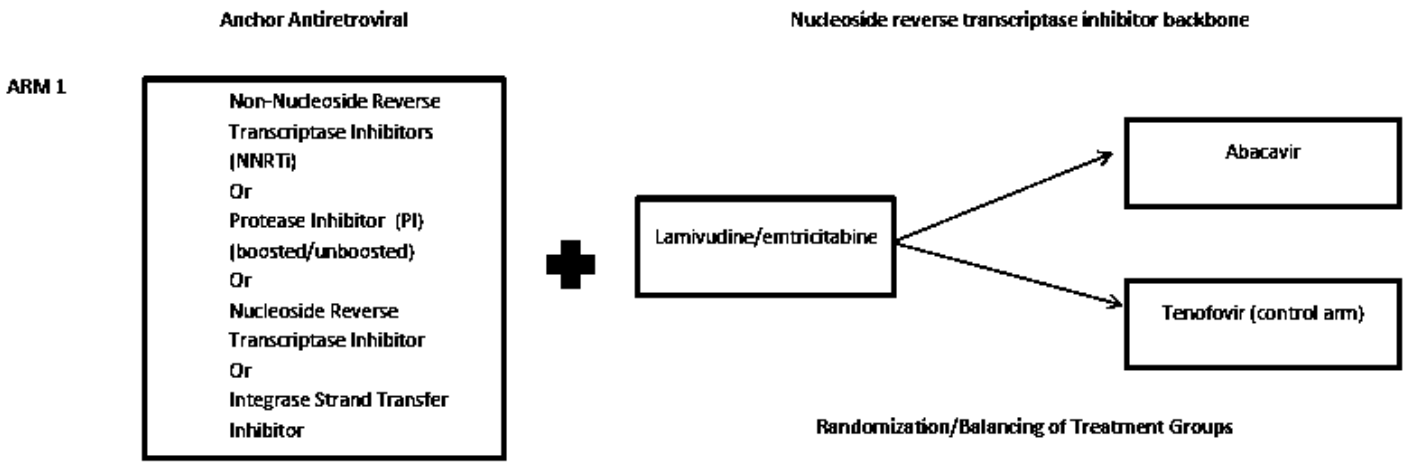


Figure 6. Active comparator, new user study design. Comparisons of the nucleoside reverse transcriptase inhibitors abacavir and tenofovir with any anchor antiretroviral included and lamivudine/emtricitabine as part of the regimen (standard of care). Study population included HIV positive patients that were initiators of combination antiretroviral therapy (cART) in the North Carolina Medicaid program between 2002 and 2008.

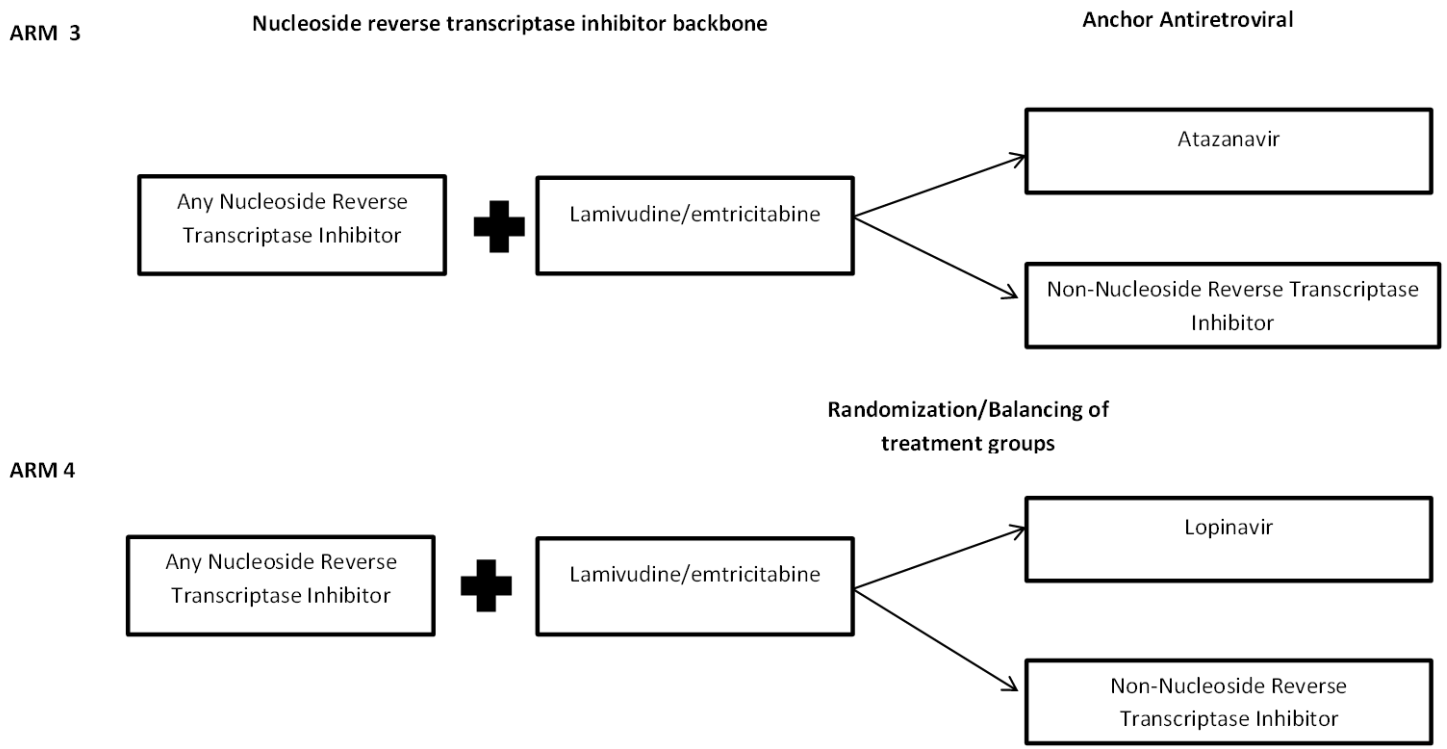


Figure 7. Active comparator, new user study design. Atazanavir, lopinavir vs. non-nucleoside reverse transcriptase inhibitor. Study population included HIV positive patients that were initiators of combination antiretroviral therapy (cART) in the North Carolina Medicaid program between 2002 and 2008.

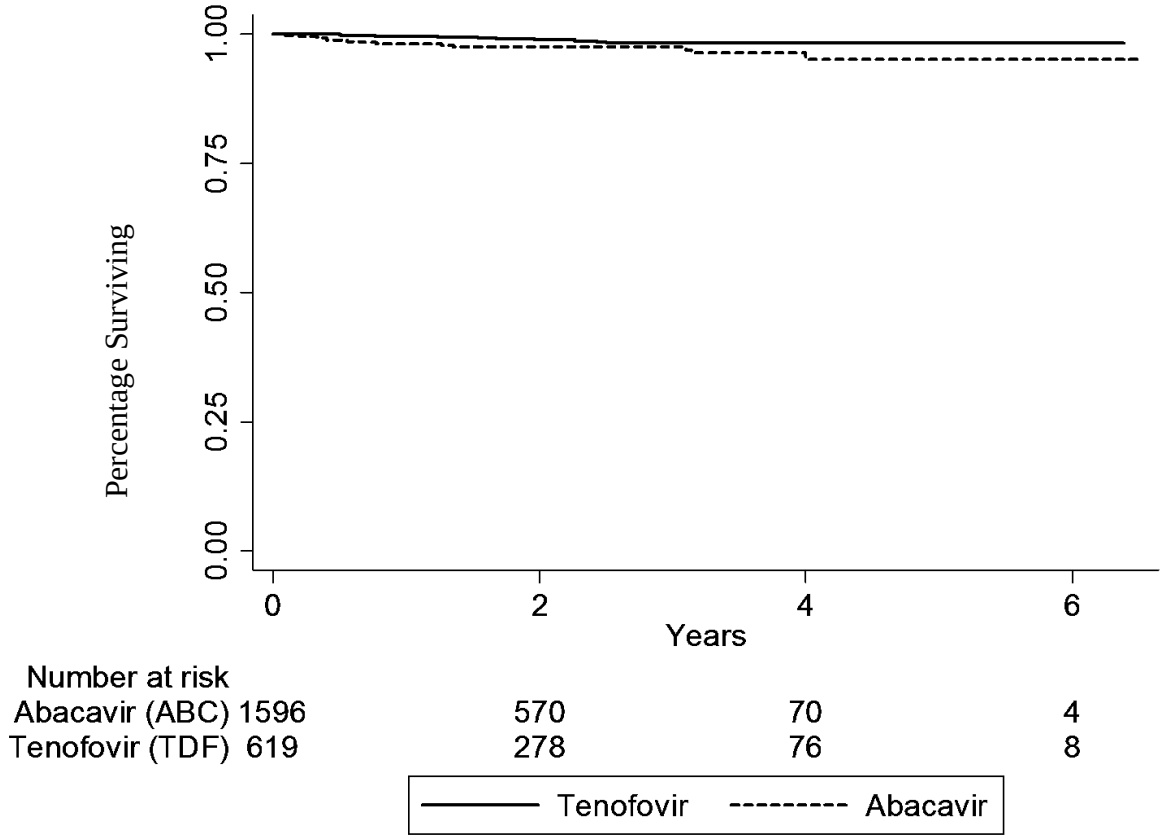
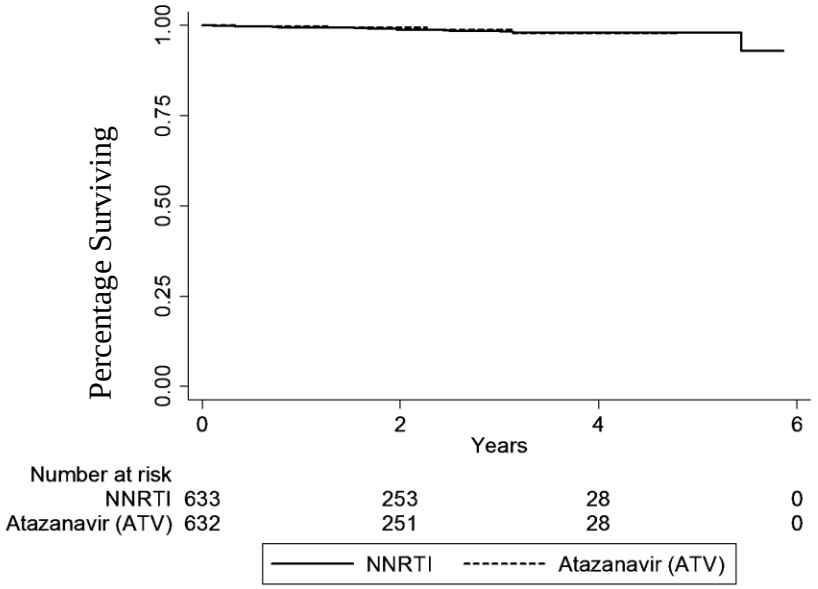


Figure 8. SMR weighted Kaplan-meier survival curves of HIV positive individuals (identified by ICD-9 code and antiretroviral use in administrative claim) for patients receiving nucleoside reverse transcriptase inhibitors as part of a new combination antiretroviral therapy (cART) regimen. Abacavir (hashed line) compared to tenofovir (TDF) (solid line).

a)



b)

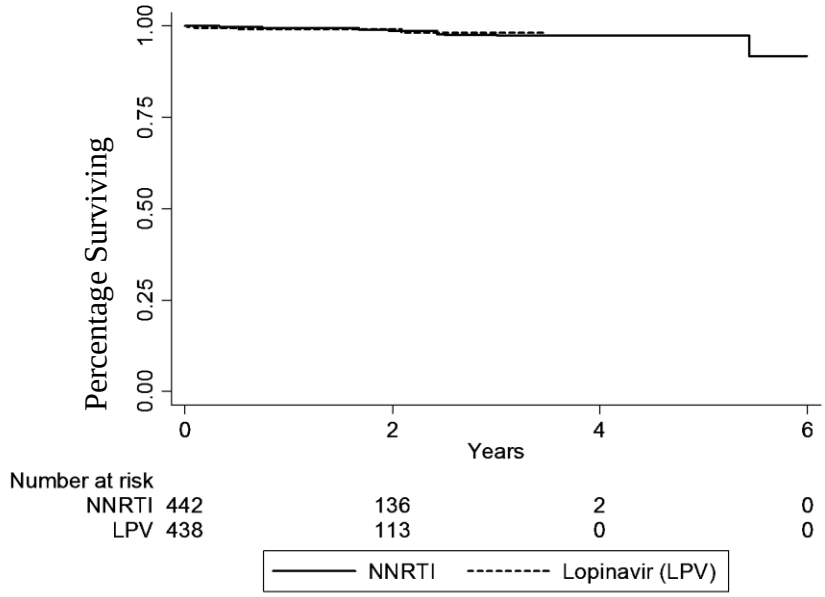


Figure 9. SMR weighted Kaplan-meier survival curves of HIV positive individuals (identified by ICD-9 code and antiretroviral use in administrative claim) for initiators of protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI) a) atazanavir (ATV) alone or in combination with ritonavir (hashed line) compared to non-nucleoside reverse transcriptase inhibitors (efavirenz or nevirapine) (solid line) b) lopinavir (LPV) compared to non-nucleoside reverse transcriptase inhibitors (efavirenz or nevirapine.)

CHAPTER VI

DISCUSSION

Summary of Findings

This dissertation aimed to investigate the comparative safety of antiretroviral use in North Carolina Medicaid beneficiaries by examining the relationship between different cART regimens and coronary heart disease, specifically myocardial infarction. To accomplish this overarching goal, we first validated algorithms to ascertain myocardial infarction in the Medicaid administrative data (manuscript 1) by linking these data to the UNC CFAR Clnical Cohort study as the gold standard. Using the validated algorithm we conducted a new user, active comparator cohort study to examine the comparative effects of combination antiretroviral therapies on the risk for myocardial infarction (manuscript 2).

Validation of myocardial infarction algorithm

In the first part of this dissertation, we found that the specificities of varying claims-based myocardial infarction ascertainment criteria including ICD-9 codes and length of hospitalization requirements are high but small changes impact positive predictive value in a cohort with low incidence. We also found that the sensitivity of current ascertainment algorithms vary based on length of hospitalization, ICD-9 code position and length of follow-up. We determined that the best algorithm maximizes sensitivity while only moderately

reducing specificity. For our study, we used an algorithm that required the ICD-9 code 410.xx in any position and a length of stay greater than one day.

Comparative effects of combination antiretroviral therapy on risk for myocardial infarction

The results of our second aim suggest an increased rate of myocardial infarction among patients initiating abacavir either with or without zidovudine compared to tenofovir as part of cART. The increased rates remained after adjusting for potential confounders using standardized morbidity/mortality ratio weighting. We did not find clinically meaningful differences in the rate of myocardial infarction among patients initiating atazanavir or lopinavir compared to NNRTI. However, our sample size was small and all of the estimates calculated were imprecise.

Interpretation

In the absence of randomized controlled trials to evaluate medication effects it is important to conduct well-designed observational studies that would most closely emulate a randomized trial should it be possible to conduct such a study. Through the use of a validated outcome and a new user, active comparator study design, we were able to more closely mimic a randomized controlled trial that would explore the relationship between use of specific combination antiretroviral therapy regimens and myocardial infarction. Our findings are in agreement with other observational studies and showed that the use of abacavir as part of cART may increase the risk of myocardial infarction when compared to the use of tenofovir as part of cART. We did not find clinically meaningful increases in myocardial infarction rates when comparing the use of atazanavir or lopinavir to NNRTI as a part of cART.

Public Health Significance

As the burden of disease among patients with HIV infection shifts from AIDS-related to non-AIDS related conditions, and as more individuals with HIV are being placed on cART, it is important that both the short and long-term effects of these treatments be evaluated. While very important for the approval of medications, randomized controlled trials usually evaluate relatively short-term effects and therefore it is important that observational studies evaluate long-term effects of treatment. Our study contributes to the growing body of literature suggesting an increased rate of myocardial infarction among patients initiating the antiretroviral abacavir. This is an important contribution because as patients live longer with HIV infection it is paramount that therapies are tailored to the individual patient that will maximize benefits and minimize risks.

Future Work

This dissertation work provided a foundation for future comparative safety and effectiveness studies on antiretroviral therapies using administrative data. Our development of validation algorithms for the identification of myocardial infarction events in the Medicaid healthcare data will allow for the evaluation and adjustment of effect estimates obtained through the use of these data. Future work will include the use of robust clinical cohort data combined with administrative data to more adequately address unmeasured confounding. In addition, next steps will involve the combination of administrative data from other states to allow for more precision of effect estimates as well as increased external reliability of our findings.

APPENDIX

LIST OF APPROVED ANTIRETROVIRALS

	Generic Name	3-Letter Abbreviation	Brand Name
NRTI*	abacavir	ABC	Ziagen®
	didanosine	ddI	Videx®
	emtricitabine	FTC	Emtriva®
	lamivudine	3TC	Epivir®
	stavudine	d4T	Zerit®
	tenofovir	TDF	Viread®
	zidovudine	AZT	Retrovir®
	zidovudine/lamivudine	AZT/3TC	Combivir®
	abacavir/lamivudine	ABC/3TC	Epzicom®
	abacavir/zidovudine/lamivudine	ABC/AZT/3TC	Trizivir®
	tenofovir/emtricitabine	TDF/3TC	Truvada®
NNRTI**	delavirdine	DLV	Rescriptor®
	efavirenz	EFV	Sustiva®
	etravirine	ETR	Intelence®
	nevirapine	NVP	Viramune®
PI^	atazanavir	ATZ	Reyataz®
	darunavir	DRV	Prezista®
	fosamprenavir	FPV	Lexiva®
	indinavir	IDV	Crixivan®
	lopinavir/ritonavir	LPV/r	Kaletra®
	nelfinavir	NFV	Viracept®
	ritonavir	RTV	Norvir®
	saquinavir	SQV	Invirase®
	tipranavir	TPV	Aptivus®
ISTI^^	raltegravir	RAL	Isentress®
FI#	enfuvirtide	t-20	Fuzeon®
CCR5 Antag##	maraviroc	MVC	Salzentry™
Multiple Class Combinations	tenofovir/efavirenz/emtricitabine	TDF/EFV/FTC	Atripla®

*NRTI: Nucleoside Reverse Transcriptase Inhibitor
**NNRTI: Non-nucleoside reverse transcriptase inhibitor
^PI: Protease Inhibitor
CCR5 Antag: CCR5 Antagonist
^^ISTI: Integrase Strand Transfer Inhibitor
#FI: Fusion Inhibitor

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