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HIV and Hepatitis infection among End Stage Renal Disease Patients in Brazil

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Abstract

HIV and Hepatitis infection among End Stage Renal Disease Patients in Brazil

By Isabel Pereira de Almeida

Background: This study aims to examine the survival differences of HIV, HCV, and HBV-positive positive patients among the ESRD population in Brazil. This study will compare survival amongst groups of mono-infected people in the population as well as the survival associated with patients who seroconverted to become co- or multiply-infected with a second infection of HIV, HCV, or HBV during renal replacement therapy.

Methods: The dataset used in this study is part of a larger database of all ESRD patients in hemodialysis treatment through SUS in Brazil. The inclusion criteria for the final dataset include having one of the following infections: HIV, HCV, or HBV at the initiation of ESRD treatment or start of study period (January 2000-December 2012). The covariates are age, sex, race, region of residence, and year of entry into study. The outcome variable of interest is death, and the time-dependent covariate is seroconversion with another infection. The time-dependent covariate defines the two study groups being compared; mono-infected and multiply-infected. Statistical analyses used in this study include univariate and multivariate analysis, Kaplan-Meier curves, and an extended Cox model to calculate hazard ratios and determine if there is any significant difference in survival time between the two groups of interest.

Results: Multiple-infection (HR 1.68, 95% CI (1.36, 2.08)) is significantly associated with increased risk of mortality when compared to mono-infected patients in ESRD treatment in SUS in Brazil. Male sex (OR 1.43, 95% CI (1.19, 1.71)) and residence in the South region (OR 1.38, 95% CI (1.13, 1.67)) are associated with increased odds of seroconversion in this population.

Discussion: There is a significant risk of mortality in multiply-infected patients in ESRD treatment in Brazil when compared to mono-infected patients. Although there were several limitations to this study, like grouping of similar yet different diseases into the same category, the strengths include having a large sample size, long study period and comparable demographic distributions matched to other studies in similar populations. The results of this study are important and relevant to the treatment of ESRD patients in Brazil, especially for the continued study of multiply-infected individuals.

HIV and Hepatitis infection among End Stage Renal Disease Patients in Brazil

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Contents

Abbreviations

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
HCV	Hepatitis C
HBV	Hepatitis B
SUS	Brazilian Unified Healthcare System (Sistema Única de Saúde)
ESRD	End-Stage Renal Disease
HAART	Highly Active Antiretroviral Therapy
CD4+	Cluster of differentiation (less than 200 defined as AIDS)
VCT	Voluntary Counseling and Testing
NACP	National AIDS Control Program
STI	Sexually Transmitted Infection
RRT	Renal Replacement Therapy

Chapter 1: Introduction

This chapter is an introduction to Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) in the End-Stage Renal Disease (ESRD) population of Brazil. The aim of the study is to examine the survival differences among HIV, HCV, and HBV-positive individuals in ESRD treatment. In order to better understand the study, this chapter also details the context of the problem of increasing morbidity in co-infected patients, which will further be explored in the literature review chapter. The purpose statement, research questions and statement of significance are also described in this chapter.

Study Aims

This study aims to examine the survival differences of HIV, HCV, and HBV-positive positive patients among the ESRD population in Brazil. This study will compare survival amongst groups of mono-infected people in the population as well as the survival associated with patients who seroconverted to become co- or multiply-infected with a second infection of HIV, HCV, or HBV during renal replacement therapy (RRT). All patients in this population underwent RRT in the form of hemodialysis in a Brazilian Unified Healthcare System (SUS) facility between January 2000 and December 2012. Geospatial analysis will also be used to compare rates of baseline and end-of-treatment infection across the different geographic regions in Brazil.

Background

A significant proportion of HIV infected people are also living with HBV and/or HCV. While both Hepatitis diseases affect functions of the liver and both can be transmitted from infected blood, like needle-sharing, HBV is mostly associated with sexual transmission (1). HBV or HCV can significantly reduce the morbidity and disability-adjusted life-years of the individual. A portion of the Brazilian population is living with HIV and Hepatitis co-infection. This dual diagnosis not only increases an individual's susceptibility to other infections, it also makes treatment of one or both diseases more difficult. Brazil has a co-infection prevalence of HBV and/or HCV in HIV infected individuals ranging between 3.3% and 82.4%; the higher of which is the prevalence among drug users. The average co-infection rate in Brazil among the HIV infected population in 2013 was 20.3% (2). Co-infection puts patients at higher risk of mortality and increases the burden of treatment. In Brazil, treatment for HIV and Hepatitis is fully covered under the Brazilian Unified Health System (SUS) for people who choose to seek care through this universal healthcare program (3). The most advanced stages of co-infection require dialysis treatment and in some cases transplantation of the liver.

There were an estimated 97,586 patients in dialysis treatment in Brazil, in July 2012, 85% of which utilize SUS for treatment (4). Most of these patients are on dialysis treatment because they are in the most severe stages of kidney disease, also known as End-stage renal disease (ESRD). Due to the increased exposure to blood products which ESRD patients receive during maintenance hemodialysis therapy, they are at an increased risk of infection with Hepatitis viruses, and other blood transmitted infections.

This study seeks to examine the survival rates of mono-infected patients undergoing hemodialysis treatment (dialysis related to kidney malfunction) compared to the survival rates of patients who were mono-infected at baseline (Jan 2000, or start of treatment) but became multiply-infected throughout the course of treatment, which in some cases can be several years. The database being used in this study is of ESRD patients on hemodialysis treatment through SUS. The database from which the subset of data being used in this study is a part of is housed at the Federal University of Rio Grande do Sul. Looking at HIV and Hepatitis infection among this population is essential because it allows an examination of the associations the diseases have with dialysis treatment and ESRD treatment outcome, especially since this population is at increased risk of developing other blood transmitted infection due to their increased exposure to blood products. Studies conducted on the prevalence of HBV and HCV infection in hemodialysis patients are not common in Brazil, and therefore there is a need to conduct research on the rates of infection among this vulnerable population as well as other infections associated with increased morbidity and mortality. As demonstrated in the next chapter, this combination of diseases is rarely studied, which presents a unique opportunity to investigate the disease progression among the population. ESRD treatment is usually end-of-life or lifelong treatment for very sick patients. Some patients leave treatment due to receiving a successful kidney transplant, which no longer necessitates hemodialysis, but many are in treatment for several years before this occurs or they die waiting for a transplant.

The aim of this study is to compare survival rates among HIV and viral Hepatitis infected patients also being treated for ESRD in Brazil. This study will investigate

whether being mono-infected (defined as being infected with one of the following: HIV, HCV or HBV) at baseline and becoming multiply-infected (defined as being infected with two or all of the following: HIV, HCV, or HBV) has an effect on survival rates. Differences in survival rates could indicate a need for improved treatment regimens of multiply-infected individuals. The analysis will also examine the geographic distribution of infection (mono- and multiple-infections) throughout Brazil.

Purpose Statement

The purpose of this study is to study the population characteristics of mono- and multiple-infections of HIV and Hepatitis among patients with ESRD in the Brazilian population, using a national database of ESRD patients from 2000 to 2012. The treatment timeline and associated diagnoses of patients with HIV, HCV, and HBV and the overall survival among different groups will be examined. Survival rates will be compared between mono-infected patients and those who started out as mono-infected at baseline but acquired a second or in some cases third infection to become multiply-infected, as well as geographic and demographic associations with survival time and mortality.

Research Questions

The research questions for this study are:

1) Is there a difference in survival between mono-infected patients and multiply-infected patients?
2) What covariates can be associated with survival rates among the HIV, and Hepatitis-infected individuals seeking RRT for ESRD?

Significance Statement

There are very few studies investigating the rates of co-infection (and multiple-infection) of HIV and Hepatitis in Brazil, specifically among the ESRD population. Since SUS is the universal healthcare provider in Brazil and millions of Brazilians choose to seek care through their system (about 85% of all dialysis patients use SUS), investigating infection rates and survival in this population is very important for the future success of the treatment program. This paper seeks to calculate the rate of co-infection among all End-Stage Renal Disease patients in Brazil and the variability in these rates among different geographic regions of the country, as well as compare survival time among the different groups of patients.

Chapter 2: Literature Review

This chapter serves to give a comprehensive review of the current literature on the context of this study. It has four sections; the first section is an outline of the HIV context in Brazil and the response to the epidemic. The second section gives an overview of Hepatitis disease and gives background to the disease in the Brazilian setting. Following is a section on co-infection of HIV and Hepatitis virus in both the global and Brazilian context. Lastly, ESRD is discussed in detail and in the context of both HIV and Hepatitis.

HIV

There are over 30 million people living with the human immunodeficiency virus (HIV) worldwide (5). Survival among the HIV-infected population has improved drastically within the past several decades. There are more and more effective drugs being introduced to the market to treat HIV and they have increased the overall survival among HIV-infected individuals worldwide.

HIV in Brazil

HIV has been present in Brazil since the beginning of the epidemic in the 1980's. The first case of HIV was reported in 1982. Throughout the beginning of the epidemic, AIDS cases were predominantly attributed to transmission between men who have sex with men (MSM) in big cities like Rio de Janeiro and São Paulo. Since 1993, there has been a shift in the highest transmission population and the majority of AIDS cases have been attributed to heterosexual transmission (3). Brazil does not mandate Sexually Transmitted Infections (STI) reporting, but AIDS cases are registered in a national database, making prevalence and incidence calculations on HIV infection rather difficult.

Currently, Brazil has the highest rate of infection among Latin American countries with an estimated 530,000 to 660,000 infected individuals. The population of Brazil was nearly 193 million in 2010. Although that number is the highest in Latin America, the HIV prevalence in 2012 was estimated between 0.4% and 0.5% in people aged 15-49, and 11,000-19,000 deaths are estimated to be due to AIDS (6). The response efforts of the Brazilian government have long been regarded as one of the best and most effective methods of controlling the spread of this disease. Their efforts are considered among the global community as innovative, aggressive, and effective (3). A national response began in 1985, a time when Brazil had returned to democracy from military rule. At the time only 4 AIDS cases had been reported. The National AIDS Control Program (NACP) was established the next year in 1986 by the Brazilian Ministry of Health (7). That same year, mandatory blood screenings were implemented for blood banks in São Paulo, and by 1988 this testing was mandatory nationwide (6). Highly Active Anti-Retroviral Therapy (HAART) was introduced in the 1990s and Brazil decided early on that the use of these effective drugs would be the basis of their response efforts and be provided to every HIV patient through SUS. New treatment guidelines from a 2013 report outline the recommendation for the use of early treatment. With this newly developed policy, Brazil was at the time, the first and only developing country to implement such aggressive treatment-as-prevention guidelines (6). Brazil also leads the efforts to secure drug patents to produce several HAART drugs domestically and import from other countries. Access to safe, effective, yet affordable treatment is the main goal in the battle against HIV in Brazil. In 2010 there were 517 official VCT (voluntary counseling and testing) sites in Brazil, with many other HIV testing facilities (3).

HIV Population shift

Since the introduction of HAART medications, HIV has shifted from a death-sentence into a chronic and manageable condition. At the end of 2011, 60-79% of eligible people in Brazil were receiving antiretroviral therapy (6). Brazil has offered free HAART treatment through the SUS healthcare system since December of 1996, which was mandated by federal law 9313 (8) (6). Increased HAART availability, especially in Brazil, is contributing to longer survival of HIV patients, which leads to an older population of individuals being treated for HIV/AIDS. With this shift in the HIV population to an older group, more co-morbidities in these patients have been seen. These include renal disease and other chronic conditions that also afflict the HIV-negative aging population (9). In a review on the aging HIV population written by Cardoso et al. this aging population is also shown to present a higher incidence of clinical AIDS, "in Brazil, the incidence of AIDS among the population aged over 50 years doubled between 1996 and 2006". This trend shows that not only are there more older patients surviving with HIV, and according to this study, there are more patients in an AIDS-stage of disease, which can complicate treatment as well as increase the severity of co-morbidities (9).

The future of HIV treatment is increasingly focused on this older population. It is estimated that half of all HIV patients in Brazil will be over 50 years of age by the year 2014 (9). The presence of other chronic conditions associated with aging, but non-AIDS related have also been reported to have increased among this elderly HIV/AIDS population, including end-organ diseases like kidney disease (10).

Hepatitis

Hepatitis B Virus

Hepatitis B Virus (HBV) is one of the most frequently diagnosed infectious diseases worldwide. There are approximately 2 billion individuals infected with HBV in the world (1). This high rate of infection could be due to the efficient modes of transmission this virus uses. The active virus can be transmitted not only via blood, semen, and vaginal secretions, but saliva as well, making it a difficult infection to contain spread. HBV it is a sexually transmitted disease that affects the liver and chronic infection can lead to cirrhosis. Risk factors include multiple sexual partners, hemodialysis and injection drug use (9). Unlike the other infectious diseases being investigated in this study (HIV and HCV), there is a vaccine to prevent HBV infection. The HBV vaccine, which is given to infants under six months of age in three doses, was introduced in Brazil in 1989 for use in hyper-endemic regions like Acre, Rondônia and the western part of the Amazon. The immunization program was extended to the whole country beginning in 1996 (11). Currently, the HBV vaccine is also given to as part of the drug treatment therapy for all RRT patients in SUS, which includes the ESRD population in this study (12). HBV is classified into 8 different genotypes, of which 3 are predominant in Brazil. Genotypes A, D and F are all found in Brazil and each has different geographic distributions (13). The Western Amazon basin has one of the highest prevalence rates of HBV in the world (14). The universal childhood HBV vaccine was introduced in Brazil in 1989 and has significantly reduced the rate of HBV throughout the country, although a study done on the prevalence of Hepatitis viruses in the Amazon basin shows that there is still a large adult population at risk for HBV that includes HIV infected individuals (14).

Despite the universal coverage of HBV vaccine in the RRT population, the latest report showed the prevalence of HBV among chronic dialysis patients to be at 4.6% (4).

Hepatitis C Virus

Hepatitis C Virus (HCV) is also a viral infection that affects liver function. HCV is more is efficiently transmitted through blood and less efficiently through sexual transmission (15). HCV is currently the leading cause of liver cirrhosis and liver transplantation worldwide (1). The incidence of new cases of HCV has decreased in the last several years, mainly attributed to the improvement of blood product testing for markers of infection in most countries (16). The most common means of transmission in the developed world is through the use of injecting drugs, with needle sharing being the main exposure (17). Other risk factors for HCV transmission include hemodialysis, previous infection with HBV and exposure to healthcare settings (18). In a cross-sectional study conducted in Brazil from 2005 to 2009, the prevalence of HCV was estimated to be 1.89% (19). This rate has been seen as high as 27.7% in a population of high-risk, female crack users in Porto Alegre (20). Despite the lack of symptoms in the majority of HCV infections, the disease may become chronic in up to 80% of cases. Chronic infection could evolve into hepatitis cirrhosis (5-20% of cases), hepatocellular carcinoma (1-5%) or hepatic failure (4%) (18).

Co-infection

HIV/HCV co-infection globally

Hepatitis C (HCV) is a very common infection among HIV patients worldwide. It has been reported that as many as 30% of all HIV-infected patients are co-infected with

HCV (21). HCV and HIV are transmitted through common pathways, but HCV is more efficiently transmitted through blood-to-blood products and less effectively through sexual intercourse (15). This difference in effective transmission routes demonstrates itself in the distribution of co-infection among different populations. The rate of co-infection is much higher among vulnerable populations like Intravenous Drug Users, where infection rates are reported as high as 85% (21).

Since the implementation of HAART in HIV treatment worldwide, we have seen liver disease become the leading cause of death among HIV-infected patients (21). The mechanisms involved in HIV/HCV co-infection are still unknown, but one study suggests that the immunosuppression brought on by HIV infection allows HCV replication to occur more rapidly leading to more severe liver disease which could include fibrosis and cirrhosis in these co-infected patients (21).

Studies suggest that not only does HIV infection have a negative effect on the course of HCV-related liver disease, but HCV may also negatively impact the course of HIV disease (21). A Swiss cohort showed the association between HIV/HCV co-infection and an increased likelihood of AIDS-defining events when compared to patients with HIV infection alone (21). It is clear that there is evidence to show that both HIV and HCV impact the other infection in a negative manner.

HIV/HCV co-infection in Brazil

Both HIV and HCV share the same transmission routes of sexual and blood-to-blood transmission, thus the rates of co-infection with both viruses are fairly high compared to other viruses with differing transmission routes. In Brazil, co-infection is higher in HIV patients who acquired their infection via blood-to-blood transmission like

injecting drug use or blood transfusions when compared to those HIV patients who acquired their virus through sexual intercourse (22). The Epidemiological Bulletin on Viral Hepatitis (2011) reported the HIV/HCV co-infection rate in Brazil to be 11.4% among HIV seropositive patients, although these rates are highly variable among the different high-risk groups in Brazil like drug-users and sex workers (2). A study of HIV/HCV co-infection conducted in Brazil estimated the number of people living in Brazil with co-infection to be around 200,000 (23). This is a significant portion of the population that is infected with two severe diseases, and warrants further studies to understand why the rate is so high. Carvalho et al. reported this variation of co-infection prevalence among the different regions of Brazil to be between 8.9% and 54% (22). It has also been reported that HIV/HCV co-infection is a significant risk-factor for liver fibrosis. This is most likely due to the accelerated process of liver damage caused by HIV seropositivity and low CD4+ count (2). The rate in which liver fibrosis occurs in HIV/HCV co-infected patients is on average three years (2). HCV also has a deleterious effect on the progression of HIV disease. HCV has been associated with the faster progression to AIDS (2), but has also been published to have no increased risk of AIDS-related mortality in a study conducted on a Brazilian HIV cohort on HAART (8). These contradicting findings show the lack of consensus in the research community about the relationship HIV/HCV co-infection has on mortality, and demonstrates the need for further research on their relationship in a larger population context. This paper seeks to calculate the rate of co-infection among all End-Stage Renal Disease patients in Brazil and the variability in these rates among different geographic regions of the country, as well as compare survival rates among the different groups of patients.

The importance of studying the disease interaction between HIV and Hepatitis C in co-infected individuals has been stressed in the literature. Their interaction has been described as "one of the most important public health problems faced by health professionals and authorities worldwide" (24).

HIV/HBV co-infection in Brazil

HIV/HBV co-infection has also been associated with more severe infection and more aggressive cases of cirrhosis and liver cancer. Among the 370,672 (86.3%) reported AIDS cases between 1999 to 2010 in Brazil, there were 3,724 (prevalence 1.0%) HIV/HBV co-infections (25). A study conducted on 848 HIV patients showed a prevalence of 2.5% (95% CI: 1.4-3.5%) (26). Although the prevalence of co-infection with HIV and HBV are low, the severity of disease when individuals present with both infections is severe. With the introduction of the HBV vaccine into Brazil in 1989, presence of HBV infection in an HIV-positive and immunocompromised individual is distressing.

End Stage Renal Disease

ESRD is categorized as the fifth and most progressive stage of chronic kidney disease. Patients with ESRD who receive hemodialysis, a necessary life-saving treatment, have a 20-fold higher mortality compared to individuals with normal kidney function (27). ESRD treatment consists of renal replacement therapy (RRT) in the form of chronic hemodialysis or kidney transplantation.

ESRD in Brazil

In Brazil, RRT is mainly funded by the Brazilian Ministry of Health, with less than 5% of the procedures being covered by private insurance providers (12). The medical specialty, nephrology, has been well-established since the 1960s. Currently Brazil has 1 nephrologist per 55,000 inhabitants who provide care for thee approximately 18,000 new patients with ESRD beginning chronic dialysis every year in Brazil (12).

ESRD patients have complicated treatment regimens that usually include routine hemodialysis treatment that must be performed several times a week at an outpatient clinic. In Brazil, SUS provides dialysis treatment to renal disease patients in several clinics throughout the country. Approximately 85% of all dialysis patients (estimated 97,586 in July 2012) in Brazil utilize SUS to provide them with treatment (4). More than half of all dialysis patients in Brazil live in the Southeast region which includes both of Brazil's largest cities; São Paulo and Rio de Janeiro.

Infection control among the ESRD population is an important challenge facing Brazil. Due to the nature of RRT, these patients are at an increased risk of bloodstream infections; the leading cause of hospitalization and the second most common cause of death among hemodialysis patients (28). 90.6% of all ESRD patients undergo hemodialysis treatment which is an invasive procedure that possesses an inherent risk for infection, compounded by the fact that these patients are immunodeficient (28). The national regulatory agency of Brazil (ANVISA) regulates all RRT guidelines. The guidelines include procedures to decrease the susceptibility of transmitting blood-borne pathogens including HIV, HCV and HBV. Currently the specific guidelines for HIV patients include discarding dialyzers after a single use. For the general ESRD population, dialyzers are allowed to be reprocessed up to a maximum of 12 times. For HCV patients,

dialyzers must be reprocessed in a separate room and HBV patients must be treated in a separate room and their dialyzers must also be reprocessed in a separate room. Compliance with these guidelines is regulated by annual visits by ANVISA or its affiliates (29). These prevention and isolation techniques are in place to decrease the transmission of these infections among dialysis patients. In recent years these techniques have shown to lower both the incidence of HCV and HBV (12).

ESRD and Hepatitis in Brazil

Due to the increased exposure to blood products which ESRD patients receive during maintenance hemodialysis therapy, they are at an increased risk of infection with Hepatitis viruses. Studies conducted on the prevalence of HBV and HCV infection in hemodialysis patients are not common in Brazil, and therefore there is a need to conduct research on the rates of infection among this vulnerable population as well as other infections associated with increased morbidity and mortality in this population. The Brazilian Society of Nephrology (SBN) conducts an annual survey on dialysis treatment facilities and in 2012 they sampled 255 clinics from 696 total SBN registered dialysis clinics in Brazil. The published survey reported in 2012 the prevalence of HBV, HCV, and HIV in hemodialysis patients to be 4.6%, 1.0% and 0.8%, respectively (4). HBV infection in this population is noticeably higher than the other infections, as well as the national prevalence of 1.0%. Another study estimated the prevalence of HBV and HCV to be much higher; 3% and 15%, respectively (12). In one study conducted in seven hemodialysis centers in Belém, Pará in the northern region of Brazil, among 798 chronic renal disease patients, 8.4% (n=67) of patients tested positive for anti-HCV antibodies (30). This indicates that the rate of infection with HCV among ESRD patients varies

between the different regions in Brazil. In another study looking at the genotypic distribution of HBV in hemodialysis patients, the national prevalence of HBV was also considered to be high in the hemodialysis treatment population (31). In a study conducted in Ontario, Canada, chronic infection with HBV in ESRD patients was seen to be associated with a negative prognosis which affects hepatic function as well as high morbidity and mortality (32). It is clear that both HCV and HBV have negative impacts on the outcome of ESRD patients, but studies on co-infection are very scarce in this population of ESRD patients. A study that was conducted on a cohort of ESRD patients between March 1999 and May 2003 that compared HBV-infected patients and HCV/HBV co-infected patients. The results of the study showed that co-infection was related to a longer time on dialysis, longer duration of infection, and a history of blood transfusion (33).

ESRD and HIV

Due to the increased survival of HIV patients because of the improved treatment of the disease, patients are living longer and the prevalence of comorbidities is increasing. One of the most significant comorbidities that are associated with HIV today is kidney disease, which includes HIV-associated nephropathy, acute renal failure and chronic kidney disease (CKD). These comorbidities are very highly associated with other risk factors like hypertension, diabetes, older age, and HCV infection (34). In one study conducted in Germany on the Frankfurt HIV cohort, ESRD in HIV-patients was associated with black race, injecting drug use, and HCV infection. This study compared 3 different groups of HIV patients based on time periods. The 3 distinct time periods were based on the timeline of availability and use of HAART, they included pre-HAART from

1989-1996, early HAART from 1997-2003, and late HAART from 2004-2010. There was an increase in the prevalence of ESRD over time, and a decrease in mortality of ESRD patients along the 3 time periods, although mortality is still highly associated with ESRD among HIV patients (35). HAART is still the main form of treatment for HIV-infected renal disease patients, along with other RRT. Unfortunately, drug induced hepatoxicity or progression to ESRD is a significant risk in co-infected patients being treated with HAART, due to the toxicity some HAART drugs have on the kidneys (22). The risk of ESRD is also increased in renal disease patients with HIV, not just co-infected individuals (34). This phenomenon makes treatment for co-infected individuals much more complicated. In a study conducted in a Brazilian cohort, several risk factors were associated with CKD in HIV patients, including hypertension, time on HAART, and exposure to Tenofovir, one of the most commonly prescribed HIV drugs worldwide (36)

ESRD, HIV and Hepatitis

Studies on the associations between ESRD, HIV and Hepatitis are very limited, although some studies suggest HIV/HCV co-infection to be a risk factor for CKD (37). One study conducted using the Evaluation of Subcutaneous Proleukin in a Randomized Trial (ESPRIT) data looked at HBV and HCV co-infection with HIV to see if there was any correlation to developing CKD. In this population, it was found that HCV/HIV co-infection had an OR (odds ratio) of 1.72 (95% CI 1.07-2.76) of progression to CKD, and HBV/HIV co-infection had an OR of 2.26 (95% CI 1.15-4.44), which means that patients with HBV/HIV co-infection had an odds of progressing to CKD 2.26 times greater than patients mono-infected with HIV (38). This same study noted the lack of research on the relationship between HBV mono-infection and chronic kidney disease (39) (40).

There have been several studies mentioned previously that have studied the relationships between two of these diseases or conditions, but looking at survival differences of them in combination has not been done. There is evidence to suggest there is a difference in survival between mono-infected individuals and multiply-infected individuals since in the general population, the HIV virus is known to accelerate the evolution of liver diseases caused by HCV and HBV, especially for immunocompromised patients, which could occur with dialysis treatment. The consequences of co-infection on morbidity and mortality have been documented to be more severe than for mono-infected patients in the general population (25).

Conclusion

This study seeks to determine whether there is a difference in survival among ESRD patients that have one (mono-infected) of these three infections (HIV, HCV, or HBV) compared to patients that acquire a second or in some cases, third infection (multiply-infected). This chapter served as a comprehensive review of the current literature surrounding the topic of HIV, HCV and HBV infection in the ESRD population in Brazil. HIV has been present in Brazil since the very beginning of the global epidemic in the early 1980s. This infection alone can cause severe disease and shortened life expectancy. When combined with ESRD, the treatment of one or both conditions becomes much more complicated. The same complications that are associated with HIV in ESRD patients are also true about HCV and HBV in ESRD patients. Co-infection with any two of these Hepatitis infections in an otherwise healthy individual has been reported to increase risk of morbidity and mortality, and when presented with the added treatment

of ESRD, this co-morbidity could potentially compound the negative outcomes. These several, multiple-disease diagnoses have not been studied in depth. This study will compare the survival of patients in ESRD treatment with one of the infections of interest (HIV, HCV or HBV) to patients who become multiply-infected during their ESRD treatment.

Chapter 3: Methods

This chapter outlines the methodologies and procedures used in data collection, variable creation and analysis of this study. The dataset used in this study is part of a larger database of all ESRD patients in hemodialysis treatment through SUS in Brazil. The inclusion criteria for the final dataset include having one of the following infections: HIV, HCV, or HBV at the initiation of ESRD treatment or start of study period during the time period of January 2000 through December 2012. The covariates used in statistical analysis are age, sex, race, region of residence, and year of entry into study. The outcome variable of interest is death, and the time-dependent covariate is seroconversion of another infection. The time-dependent covariate defines the two study groups being compared; mono-infected individuals and those who began mono-infected but seroconverted to become multiply-infected during ESRD treatment. The statistical analyses used in this study include univariate and multivariate analysis to determine significant differences in demographic characteristics of the study population, Kaplan-Meier curves to determine overall survival differences with respect to the different covariates of interest, and an extended Cox model that determines if there is any significant difference in survival time between the two groups of interest while treating seroconversion as a time-dependent covariate.

Research Question

The primary research question being assessed is if there exists a significant difference in survival time between mono-infected patients and multiply-infected patients in ESRD treatment in SUS in Brazil. The literature has shown increased morbidity in co-

infected individuals when compared to mono-infected individuals. The survival of multiply-infected patients in this ESRD population is expected to be shorter when compared to the mono-infected patients.

Study Population

The data for this analysis are a subset of patients from the ESRD database on all SUS patients in dialysis treatment from January 2000 to December 2012. SUS treats around 85% of all the dialysis patients in Brazil. The SUS database is an ongoing data collection project sponsored by the Brazilian Ministry of Health and is housed at the Federal University of Rio Grande do Sul. The data are collected via patient providers in the SUS system. Information regarding a patient's renal replacement therapy and many other treatments are collected in this database. This study was submitted and approved by the Emory University Institutional Review Board (IRB) as an exempt review (Study ID: IRB00071685).

Inclusion criteria

The subset of data used in this analysis began with 44,329 ESRD patients in this system from January 2000 to December 2012 that have had one or more of the following: a positive HIV test, a positive HBV test as indicated by the presence of the Hsbag antibody, or a positive HCV test as indicated by the presence of the HCV antibody. All test results were reported to the SUS database by a healthcare provider that performed the test. Only patients with one positive test at baseline were included in the analysis (N=15,958). The term "mono-infected" is used to describe these patients. Baseline was

defined as either the start of the study period (Jan 2000) or the earliest date of treatment per individual. All HIV and Hepatitis testing was performed at a clinic outpatient facility, a hospital, or another treatment facility associated with SUS.

Covariates

The covariates included in the analysis are demographic characteristics (age, sex, race, and region). The year of entry into the study was also included as a covariate in the analysis. Age was defined as the age at entry into treatment, or for those patients already in treatment in January 2000, age was defined as the age at that date (Jan 2000). Sex is defined as the most frequent value for sex across all treatment visits. Race is also defined as the most frequent value for race across all treatment visits. Data for race was missing a substantial amount of the time, so this covariate was not included in the final Cox model, but was included in the demographic analysis. Region is defined as the most frequent value for region throughout treatment time. If a patient moved to another region during their time in treatment, the region in which they lived most of the time was considered their region of residence in the context of this study. The outcomes of interest were death and survival time in months. The time-dependent covariate was seroconversion status. This variable was created by comparing infection status (dichotomous) at initiation of treatment to infection status at the end of treatment (or study period). If these values changed from 0 (not infected) to 1 (infected), an individual was considered to have seroconverted during treatment.

Survival Time

Survival time was calculated as the time in months from the first date of treatment or beginning of study period until one of the following: date of death, last date of treatment, or end of study period (December 2012). Any outcome other than death was censored. Among 15,958 mono-infected patients included in the analysis, 2,307 deaths occurred. For those individuals who met the seroconversion criteria, their survival time up until event (seroconversion) was also considered in the final Extended Cox model.

Statistical Analysis

All analysis and database management procedures were performed using SAS 9.3 (SAS Institute, Cary, NC) and ArcMap (version 10.1). Descriptive analysis was performed on the baseline data to obtain demographic characteristics of the study population. Pearson's chi-square test was performed on categorical variables to compare the two comparison groups; patients who continued to stay mono-infected throughout treatment and patients who seroconverted to become multiply-infected during treatment. ANOVA was performed on continuous variables to determine any significant differences among the two groups at baseline. Logistic regression was performed on all the covariates of interest to obtain the odds ratios and 95% confidence intervals in respect to odds of seroconversion during treatment. Kaplan-Meier curves were used to compare crude survival among the different groups along with the covariates (AGE, SEX, RACE, STATE, REGION, and YEAR of diagnosis). The Log-rank test was performed to assess the significance between the two curves. Multivariate analysis was performed using Cox proportional hazards model to assess the association between survival and the covariates

of interest. Dummy variables were used to assess the survival differences according to the different categories within each variable. The proportional hazards assumption was evaluated using the log-log rank survival functions and the goodness of fit methods. The extended Cox model was then used to assess the primary research question, treating time to seroconversion as an internal time-dependent covariate. The results of the multivariate analyses were expressed with adjusted hazard ratios (HR) along with their corresponding 95% confidence intervals (CI) and p-values. Statistically significant values were determined using a p-value cut-off of less than 0.05.

Conclusion

The dataset used in the analysis is a subset of 15,958 patients in a national ESRD database of SUS patients in Brazil. The patients were categorized into two groups (mono-infected and multiply-infected) to compare their overall survival in ESRD treatment. Univariate and multivariate analysis was performed to assess the significance of the covariates used in analysis. Kaplan-Meier curves and Cox regression modeling was used to compare crude survival between the two groups. An extended Cox Model was used in order to compare the two groups' survival, taking time to seroconversion in to consideration as a time-dependent covariate.

Chapter 4: Results

This chapter is divided into two main sections, demographics and survival analysis. The section on demographics first describes the descriptive statistics of the demographic characteristics in the baseline population. This section also compares the demographic characteristics between the two exposure groups (mono-infected and multiply-infected) and describes the results of the Chi-square tests to assess any significant variability between the distributions of covariates in the two groups of interest. The second section describes the results from the different survival analysis methods used to compare survival of the two exposure groups. Survival time is compared among the two groups by using log rank statistics. Kaplan-Meier curves are utilized to describe differences in overall survival time. The Cox proportional hazard model is used to assess which covariates are associated with crude risk of mortality. Finally, the extended Cox model is used to assess whether there is any difference in survival time between the two groups while treating seroconversion as a time-dependent covariate.

Demographics

Of the 44,329 patients in the initial dataset, 15,958 were included in the final analysis because they met the inclusion criteria of having one infection at baseline. Overall the incidence density was 7.7 cases of seroconversion per 10,000 person-years.

Demographics at baseline

Table 1 shows the demographic characteristics of these patients that were seeking ESRD treatment in SUS from January 2000 to December 2012. The population is

comprised of 58.9% males. For each infection, HIV, HCV, and HBV, males are the predominant infected group with HIV infection having 62.3% males, the HCV group was comprised of 57.3% males, and the HBV group was comprised of 64.9% males.

The race variable was missing for 83.5% of the patients, so race was not used as a covariate in the survival analysis portion of the statistical analysis. Despite this, race was still included in the demographic analysis. Racial distribution among the population shows a predominantly white population n=1,466 (9.2%). There were 419 (2.6%) blacks, 733 (4.6%) multiracial patients, and 17 (0.1%) Asian patients in the overall population.

The mean age at entry into the study is 53 years (SD 13.7).

The patients' geographical distribution among regions is displayed in table 1 and in detail including state-level distribution in table 3. The majority of individuals reside in the Southeast region of Brazil (n=8,397, 52.6%), which comprises the states of Minas Gerais, Espirito Santo, Rio de Janeiro, and São Paulo. A map of the 26 states of Brazil and the regions they make up are shown in Figure 1. The second largest population of patients is in the South (n=3,975, 24.9%) followed by the Northeast (n=2,349, 14.7%), the Central-West (n=687, 4.3%) and lastly the North had the smallest population of patients (n=550, 3.5%).

Most patients started treatment in the year 2000 (n=8,498, 53.3%), at the beginning of the study period. In the HIV mono-infected group, most patients entered into treatment in 2012, with 211 (14.7%) patients entering into ESRD treatment in that year. The HIV mono-infected group was the only group that the year 2000 was not the largest category of entry year into treatment.

Demographics of exposure groups

The demographic distribution of characteristics of the two exposure groups (mono-infected throughout the whole study period, and patients who became multiply-infected during the study period) are shown in table 2. The two groups of interest are patient that stayed mono-infected (unexposed) throughout treatment (n=15,375), and patients that seroconverted (exposed) with another infection of HIV, HCV, and/or HBV during the study period (n=537).

Figure 2 details the groups of infection and how many patients in each category became co- or multiply-infected with each specific infections. The largest ovals represent the 15, 958 mono-infected patients at baseline, and the smaller ovals represent the 537 seroconverted individuals and the co-infection or multiple-infection category they fell into at the end of the study period or end of treatment. For example, there were 1,436 individuals that started treatment mono-infected with HIV. Sixty-three of these patients seroconverted with HCV to become HIV/HCV co-infected, as indicated by the arrow. Another thirteen HIV patients seroconverted with HBV to become HIV/HBV co-infected. The arrow indicating the five HIV patients that became multiply-infected with HIV/HCV/HBV does not detail in which order the second and third seroconversions took place.

The distribution of sex is significantly different (p-value 0.0001) between the two groups. Both groups have a majority population of males; 58.6% (n=9,006) males in the mono-infected group and 67.2% (n=359) males in the multiply-infected group. Male sex

was significantly associated with seroconversion during treatment (OR 1.43, 95% CI (1.19, 1.71)).

Race is also significantly different between the two groups (p-value 0.0309), although, there is a large proportion of missing values; 83.3% missing for the mono-infected group and 87.9% missing for the multiply-infected group. The largest race category for both groups is white race with 9.3% (n=1,431) of the mono-infected patients reported as white race and 6.5% (n=35) multiply-infected patients reported as white race. Logistic regression to obtain odds ratios for the race categories was not performed due to the significant proportion of missing values.

Mean age is not significantly different between the two exposure groups, 52.6 years (SD 13.7) versus 49.5 years (SD 13.6) for mono-infected and multiply-infected, respectively. The age group categories are also not significantly different between the two groups. Using the age category 60-69 as the referent group, the age group 30-39 had an increased odds of seroconversion during treatment (OR 1.35, 95% CI (0.97, 1.88)).

Region is significantly different between the two groups (p-value 0.0008) with the largest populations in the Southeast region; 52.7% (n=8,108) of all mono-infected patients and 50.1% (n=269) of all multiply-infected patients received treatment in the Southeast region. The odds of seroconversion was increased in the South region when compared to the referent group, Southeast (OR 1.38, 95% CI (1.13, 1.67)). This was the only region category with increased odds of seroconversion.

Year of entry was also significantly different between the two groups (p-value <0.0001). Year of entry as 2000 was the largest category in both groups; 52.8% (n=8,120) of mono-infected patients and 63.7% (n=342) of multiply-infected patients had

a start of entry as 2000. The odds of seroconversion for each year category were all decreased when compared to the referent category, year of entry as 2000.

Survival Analysis

Overall survival

Throughout the study period, there were 2,307 deaths. The mono-infected group accounted for 2,219 of the deaths and the multiply-infected group accounted for 88 of the deaths. The overall risk of death for multiply-infected individuals was increased when compared to mono-infected individuals (HR 1.67, 95% CI (1.34, 2.07)) with respect to seroconversion as a time-dependent covariate.

Survival time

The median survival of all patients in the study is 28 months as shown in table 4. The median survival among mono-infected patients (n=15,375) is also 28 months and the median survival for multiply-infected patients (n= 537) is 36 months. The log-rank test shows that there is a statistically significant difference in survival time among the age groups in both groups of patients.

There is also a statistically significant difference in survival among the different regions for mono-infected patients (p-value <0.0001). The shortest survival time for this group is in the North (19 months), followed by the South (24 months), the Northeast (26 months), the Central-West and the Southeast have the same median survival time (31 months). There is not a significant difference in survival time for multiply-infected patients by region (p-value 0.41).

Survival time between the different years of entry into the study is significantly different in both groups. For mono-infected individuals the year of entry with the longest median survival time is the year 2000 (44 months). The shortest survival time is seen in year 2012 (4 months). For multiply-infected individuals, the longest survival time is in year 2004 (66 months) and the shortest survival time is also in year 2012 (6 months).

Race was not significant to the outcome or exposure of interest, therefore was dropped from the model.

Kaplan-Meier curves

The crude survival of the two groups is compared using the Kaplan-Meier method. The survival probability of both groups is relatively similar until around month 100. After 100 months in ESRD treatment, the multiply-infected group has a lower survival probability when compared to the mono-infected group. This change can be seen in figure 3, where the red line represents the multiply-infected (exposed) group and the blue line represents the mono-infected group. The curve suggests the Proportional Hazard (PH) assumptions are not met (log-rank p-value 0.86). The log-log curve shows a relatively parallel relationship between the two curves.

Extended Cox Model with time-dependent covariate

The extended Cox model demonstrates that there is a significant difference in survival among multiply-infected and mono-infected patients in ESRD treatment. Multiply-infected patients have a hazard ratio of 1.68 (95% CI (1.36, 2.08)). The final model, detailed in table 5, also includes all the covariates of interest that fulfill the PH assumptions (sex, age group, region, and year of entry). Thee covariate sex is not significant to survival time between the two groups.

The covariate for age group follows an increasing risk pattern from youngest to oldest age group. The age category 60-69 is again used as the referent group. The lowest risk age group is 20-29 years (HR 0.49, 95% CI (0.37, 0.65)). The highest risk age group is 90-99 years (HR 2.32, 95% CI (1.82, 2.96)).

Two of the regions, Northeast (HR 1.22, 95% CI (0.98, 1.51) and South (HR 1.12, 95% CI (1.01, 1.23)) are significantly associated with increased mortality when seroconversion is considered as the time-dependent covariate.

The increasing risk trend is also evident in the covariate for year of entry. The lowest risk category is the year 2001 (HR 1.81, 95% CI (1.33, 2.47)) and the highest risk category is year 2011 (HR 290.30, 95% CI (216.47, 389.29)).

Conclusion

The main finding of this analysis is the survival difference between multiply-infected individuals and mono-infected individuals in ESRD treatment. Seroconversion is associated with increased mortality (HR 1.68, 95% CI (1.36, 2.08)) when compared to the mono-infected group in this population.

Chapter 5: Discussion

This chapter discusses the overall findings of this study. The analysis demonstrates that there exists a significant risk of mortality in multiply-infected patients in ESRD treatment in Brazil when compared to mono-infected patients. The results from this study can be supported by the current and previous literature. The public health implications form the results of this analysis are also described in this chapter, followed by the strengths and limitation.

Summary of Findings

The overall goal of this study is to determine if there is a difference in survival between mono-infected and multiply-infected patients in ESRD treatment in Brazil. The extended Cox model allows for such a comparison. In this model, multiple-infection is associated with increased risk of mortality. An interpretation of this association can be described as the following; at any given time a patient that is multiply-infected has an increased risk of mortality when compared to mono-infected individuals (HR 1.68, 95% CI (1.36, 2.08)). By the end of follow-up, 16.4% of multiply-infected patients died and 14.4% of mono-infected patients died. The crude survival of both groups was also compared using Kaplan-Meier curves. Looking at the curves, difference in survival between the two groups seems to begin only after 100 months of treatment. After 100 months, the survival of multiply-infected individuals is worse than mono-infected individuals. This cross-over suggests the role of a time-dependent covariate, which was taken into consideration in the final extended Cox model described previously.

Other noteworthy results from the analysis include the associations of certain covariates with the odds of seroconverting during ESRD treatment. Among the 537 individuals who seroconverted during treatment, the covariates that were significantly associated with increased odds of seroconversion were male sex (OR 1.43, 95% CI (1.19, 1.71)) and region of residence in the South region (OR 1.38, 95% CI (1.13, 1.67)) of Brazil.

Although this study population will not give us a snapshot of the current state of HIV, HCV and/or HBV infection among the entire Brazilian population, it will be helpful in understanding the burden of infection among the sickest patients. This population will be more likely to be in an Acquired Immunodeficiency Syndrome (AIDS) stage of HIV infection and an advanced stage of Hepatitis. This will allow us to look at the survival of patients with severe disease.

This study population has similar demographic distributions compared to the literature involving co-infection populations in Brazil. The demographics of a study conducted on 14,1111 ESRD patients found the majority of the patients to be male with age ranging from 45 to 64, with an average age of 52 years (41). In a study conducted on survival analysis of HIV/HCV co-infected individuals in São Paulo, Brazil, sex and race were not significantly associated with risk of mortality (42). Sex and race were not significantly associated with risk of mortality in this study as well.

The literature suggests there is a relationship between increased mortality and multiple infections. There is also general consensus that concurrent infection by two or more agents is more harmful to human health, regardless of the type of infection (43). There have been several studies that demonstrate the negative impacts that HCV or HBV

have on HIV infection (14, 44-46). In the context of ESRD treatment, there have been fewer studies conducted on survival of multiple-infected patients. In a meta-analysis of the impact of HCV on HIV-infected patients with kidney disease, concluded that the literature suggest that HIV/HCV co-infection is associated with an increased risk of kidney disease compared to HIV infection alone (5). These studies support the results seen in this study that mortality is increased in the multiply-infected group compared to the mono-infected group, although this type of analysis looking at these specific groups in ESRD treatment has never been conducted.

Public Health implications

In the context of ESRD treatment in Brazil, this study could implicate re-evaluating treatment practices for multiply-infected patients. The increased mortality of this population provides a basis to try to understand the reason the mortality rates are so different. It is important to emphasize that this study did not look at specific facility or facility-type mortality; therefore future studies should include a more micro approach to the geographic analysis of increased mortality among the different ESRD treatment facilities.

Limitations

There are several limitations to this study. This is an analysis of an existing dataset from a database of provider-reported patient information. Data collection was not performed with respect to this type of analysis; therefore there are some limitations to using the data in this type of analysis. Data were collected at various health clinics,

therefore uniformity in the method in which data were collected cannot be assumed. The test to determine HCV and HBV positivity was based on the presence of antibodies to HCV and Hsbag, respectively, therefore this does not indicate whether or not the patient has active hepatitis disease. There is no covariate to measure the severity of disease for any of the patients, like CD4 count or viral load, in the context of HIV infection.

The baseline population inclusion criteria include infection with one of the following: HIV, HCV or HBV at the beginning of the study period. For those patients who are reported with year of entry as 2000 (n=8,498, 53.3%), the start of the study period, it is not possible to decipher if these are incident or prevalent cases of infection. The rest of the patients with later start times, we can assume they began ESRD treatment with that mono-infection, and are therefore prevalent cases. In the final analysis, all types of mono-infection and multiple-infection were grouped together. Therefore, comparing which diagnoses are associated with increased mortality was not possible in this type of analysis.

Strengths

Despite the limitations, this study does possess many strengths. The study population comes from the database of all SUS ESRD patients in treatment in Brazil. About 85% of all ESRD patients utilize SUS for this type of treatment (4). This comprehensive database allows for the analysis of survival of this population in the entire country of Brazil. Although this study population will not give us a snapshot of the current state of HIV/HCV and/or HBV infection among the entire Brazilian population, it will be helpful in understanding the burden of infection among the sickest patients. This

population will be more likely to be in an Acquired Immunodeficiency Syndrome (AIDS) stage of HIV infection and an advanced stage of Hepatitis. This will allow us to look at the survival of patients with severe disease. The study period spanned over 12 years, which allowed for patients to be followed throughout the course of their long ESRD treatments.

Future studies

For future studies, it would be important to look at disease-specific survival within the multiple- and mono-infected groups. Discovering which specific infections or combination of infections is associated with increased mortality is pertinent to understanding the problem. This study used data from a time period of 12 years, which is one of its strength, but looking at an even longer study period could help understanding the disease progression of some of the longer surviving patients. A possible direction to take with future studies is to look at status of transplant and if any covariates are associated with odds of receiving a renal transplant.

Conclusion

This study showed a significant association with risk of mortality and multiple-infection among ESRD patients in Brazil (HR 1.67, 95% CI (1.34, 2.07)). Male sex (OR 1.43, 95% CI (1.19, 1.71)) and residence in the South region (OR 1.38, 95% CI (1.13, 1.67)) are associated with increased odds of seroconversion in this population. The study findings were comparable to the current literature on mono- and co-infection with these infections in the general population as well as the ESRD population, and specifically in

Brazil. Although there were several limitations to this study, like grouping of similar yet different diseases into the same category, the strengths include having a large sample size, long study period and comparable demographic distributions matched to other studies in similar populations.

The results of this study are important and relevant to the treatment of ESRD patients in Brazil, especially for the continued study of multiply-infected individuals.

Tables and Figures

Table 1. Demographic characteristics of patients in ESRD treatment in Brazil's SUS healthcare from 2000-2012 at Baseline (start of study period Jan 2000)

	All monoinfected patients		HIV monoinfection		HCV monoinfection		HBV monoinfection	
	N = 15,958		N = 1,436		N = 12,126		N = 2,396	
	N	%	N	%	N	%	N	%
Sex								
Male	9,391	58.85	894	62.26	6,942	57.25	1,555	64.90
Female	6,567	41.15	542	37.74	5,184	42.75	841	35.10
Race								
White	1,466	9.19	358	24.93	853	7.03	255	10.64
Black	419	2.63	122	8.50	229	1.89	68	2.84
Multiracial	733	4.59	192	13.37	400	3.30	141	5.88
Asian	17	0.11	--	--	11	0.09	6	0.25
Indigenous	--	--	--	--	--	--	--	--
Missing	13,323	83.49	764	53.20	10,633	87.69	1,926	80.38
Age[1]								
Mean age	53	13.73	46.19	12.78	56.06	12.76	53.51	15.05
Age Group								
10-19	17	0.11	6	0.42	4	0.03	7	0.29
20-29	146	0.91	63	4.39	45	0.37	38	1.59
30-39	333	2.09	163	11.35	129	1.06	41	1.71
40-49	645	4.04	229	15.95	313	2.58	103	4.30
50-59	813	5.09	170	11.84	496	4.09	147	6.14
60-69	578	3.62	74	5.15	400	3.30	104	4.34
70-79	246	1.54	30	2.09	155	1.28	61	2.55
80-89	61	0.38	4	0.28	43	0.35	14	0.58
90-98	3	0.02	--	--	2	0.02	1	0.04
Missing	13,116	82.19	697	48.54	10,539	86.91	1,880	78.46
Region								
North	550	3.45	37	2.58	406	3.35	107	4.47
Northeast	2,349	14.72	230	16.02	1,670	13.77	449	18.74
Central-West	687	4.31	49	3.41	501	4.13	137	5.72
Southeast	8,397	52.62	782	54.46	6,440	53.11	1,175	49.04
South	3,975	24.91	338	23.54	3,109	25.64	528	22.04
Year of Entry								
2000	8,498	53.25	108	7.52	7,244	59.74	1,146	47.83
2001	449	2.81	84	5.85	264	2.18	101	4.22
2002	422	2.64	78	5.43	267	2.20	77	3.21
2003	604	3.78	102	7.10	399	3.29	103	4.30
2004	357	2.24	57	3.97	211	1.74	89	3.71
2005	1,230	7.71	81	5.64	985	8.12	164	6.84
2006	1,199	7.51	83	5.78	980	8.08	136	5.68
2007	345	2.16	100	6.96	185	1.53	60	2.50
2008	515	3.23	104	7.24	300	2.47	111	4.63
2009	575	3.60	125	8.70	354	2.92	96	4.01
2010	562	3.52	136	9.47	310	2.56	116	4.84
2011	580	3.63	167	11.63	309	2.55	104	4.34
2012	622	3.90	211	14.69	318	2.62	93	3.88

[1]Age at start of treatment

Table 2. Demographic characteristics of mono-infected patients (from baseline to end of study) and multiply-infected patients (that started out mono-infected) in ESRD treatment in Brazil's SUS healthcare from 2000-2012 at End of treatment

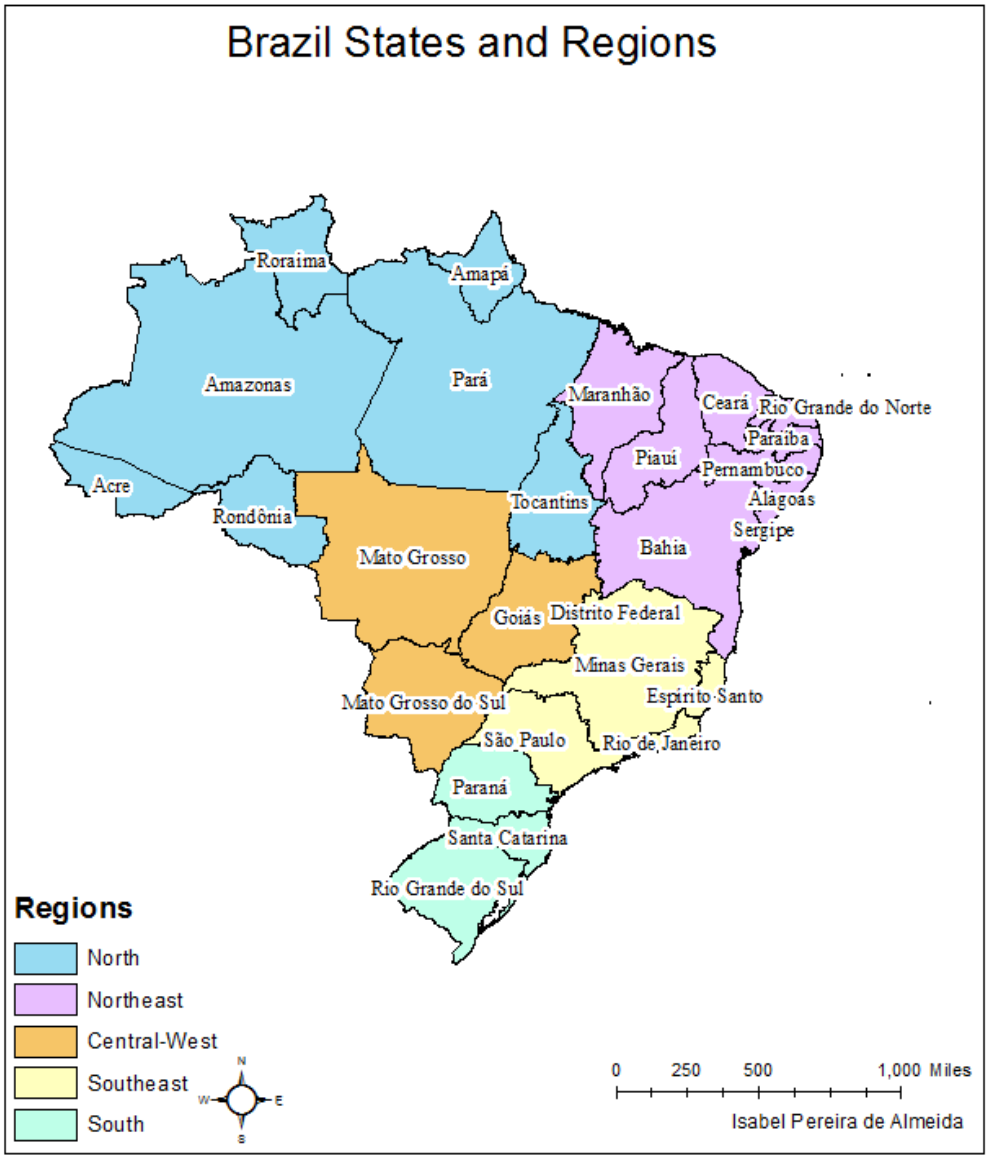
	Mono-infected		Multiply-infected		P-value[1]	OR	95% CI
	N= 15,375		N = 537				
	N	%	N	%			
Sex					0.0001		
Male	9,006	58.58	359	67.23		1.43	(1.19, 1.71)
Female	6,369	41.42	178	32.77		Ref.	--
Race[2]					0.0309		
White	1,431	9.31	35	6.52		--	--
Black	413	2.69	6	1.12		--	--
Multiracial	711	4.62	22	4.10		--	--
Asian	15	0.10	2	0.37		--	--
Indigenous	--	--	--	--		--	--
Missing	12,805	83.28	472	87.90		--	--
Age[3]					0.0570*		
Mean age	52.55	13.73	49.49	13.58		--	--
Age Group					0.1403		
10-19	37	0.24	--	--		--	--
20-29	259	1.68	7	1.30		0.81	(0.38, 1.74)
30-39	916	5.96	41	7.64		1.35	(0.97, 1.88)
40-49	1,642	10.68	67	12.48		1.23	(0.94, 1.61)
50-59	1,835	11.93	65	12.10		1.07	(0.81, 1.40)
60-69	1,268	8.25	28	5.21		Ref.	--
70-79	550	3.58	17	3.17		0.93	(0.57, 1.53)
80-89	131	0.85	5	0.93		1.15	(0.47, 2.83)
90-98	8	0.05	--	--		--	--
Missing	8,729	56.77	307	57.17		--	--
Region					0.0008		
North	536	3.49	14	2.61		0.79	(0.46, 1.36)
Northeast	2,270	14.76	66	12.29		0.87	(0.67, 1.15)
Central-West	671	4.36	15	2.79		0.67	(0.40, 1.14)
Southeast	8,108	52.73	269	50.09		Ref.	--
South	3,790	24.65	173	32.22		1.38	(1.13, 1.67)
Year of Entry					<0.0001		
2000	8,120	52.81	342	63.69		Ref.	--
2001	422	2.74	26	4.84		0.97	(0.97, 2.21)
2002	407	2.65	14	2.61		0.82	(0.48, 1.41)
2003	584	3.80	16	2.98		0.65	(0.39, 1.08)
2004	344	2.24	10	1.86		0.69	(0.36, 1.30)
2005	1,208	7.86	21	3.91		0.41	(0.27, 0.65)
2006	1,175	7.64	24	4.47		0.49	(0.32, 0.74)
2007	336	2.19	9	1.68		0.64	(0.33, 1.25)
2008	505	3.28	10	1.86		0.47	(0.25, 0.89)
2009	561	3.65	14	2.61		0.60	(0.35, 1.02)
2010	541	3.52	21	3.91		0.93	(0.59, 1.45)
2011	564	3.67	16	2.98		0.68	(0.41, 1.13)
2012	608	3.95	14	2.61		0.55	(0.32, 0.94)

[1]P-value was obtained with Chi-square test. Statistical significance was fixed at p≤0.05
[2]ORs not calculated for race categories due to % of missing values
[3]Age at start of treatment
*ANOVA

Table 3. Geographic Distribution of baseline population by State, Region and Infection

	Total Population (N = 15,958)		HIV monoinfected (N= 1,436)		HCV monoinfected (N= 12,126)		HBV monoinfected (N= 2,396)	
UF	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Rondônia	64	0.40	12	0.84	46	0.38	6	0.25
Acre	21	0.13	--	--	19	0.16	2	0.08
Amazonas	140	0.88	6	0.42	116	0.96	18	0.75
Roraima	37	0.23	2	0.14	13	0.11	22	0.92
Pará	249	1.56	16	1.11	184	1.52	49	2.05
Amapá	10	0.06	--	--	9	0.07	1	0.04
Tocantins	29	0.18	1	0.07	19	0.16	9	0.38
Maranhão	255	1.60	10	0.70	192	1.58	53	2.21
Piauí	108	0.68	7	0.49	73	0.60	28	1.17
Ceará	566	3.55	30	2.09	476	3.93	60	2.50
Rio Grande do Norte	150	0.94	16	1.11	118	0.97	16	0.67
Paraíba	48	0.30	5	0.35	26	0.21	17	0.71
Pernambuco	588	3.68	69	4.81	393	3.24	126	5.26
Alagoas	150	0.94	29	2.02	87	0.72	34	1.42
Sergipe	8	0.05	1	0.07	5	0.04	2	0.08
Bahia	476	2.98	63	4.39	300	2.47	113	4.72
Minas Gerais	1,578	9.89	139	9.68	1,172	9.67	267	11.14
Espírito Santo	240	1.50	24	1.67	167	1.38	49	2.05
Rio de Janeiro	3,236	20.28	286	19.92	2,661	21.94	289	12.06
São Paulo	3,343	20.95	333	23.19	2,440	20.12	570	23.79
Paraná	670	4.20	39	2.72	509	4.20	122	5.09
Santa Catarina	600	3.76	76	5.29	410	3.38	114	4.76
Rio Grande do Sul	2,705	16.95	223	15.53	2,190	18.06	292	12.19
Mato Grosso do Sul	150	0.94	15	1.04	101	0.83	34	1.42
Mato Grosso	186	1.17	18	1.25	136	1.12	32	1.34
Goiás	244	1.53	11	0.77	189	1.56	44	1.84
Distrito Federal RUN	107	0.67	5	0.35	75	0.62	27	1.13
REGION								
NORTH	550	3.45	37	2.58	406	3.36	107	4.47
NORTHEAST	2,349	14.72	230	16.03	1,670	13.76	449	18.74
CENTRAL-WEST	687	4.31	49	3.41	501	4.13	137	5.73
SOUTHEAST	8,397	52.62	782	54.46	6,440	53.11	1,175	49.04
SOUTH	3,975	24.91	338	23.54	3,109	25.64	528	22.04

Figure 1. Map of Brazil States



Source: DIVA-GIS.org

Figure 2. Diagram of patients from baseline (mono-infected) to the end of study (multiply-infected).

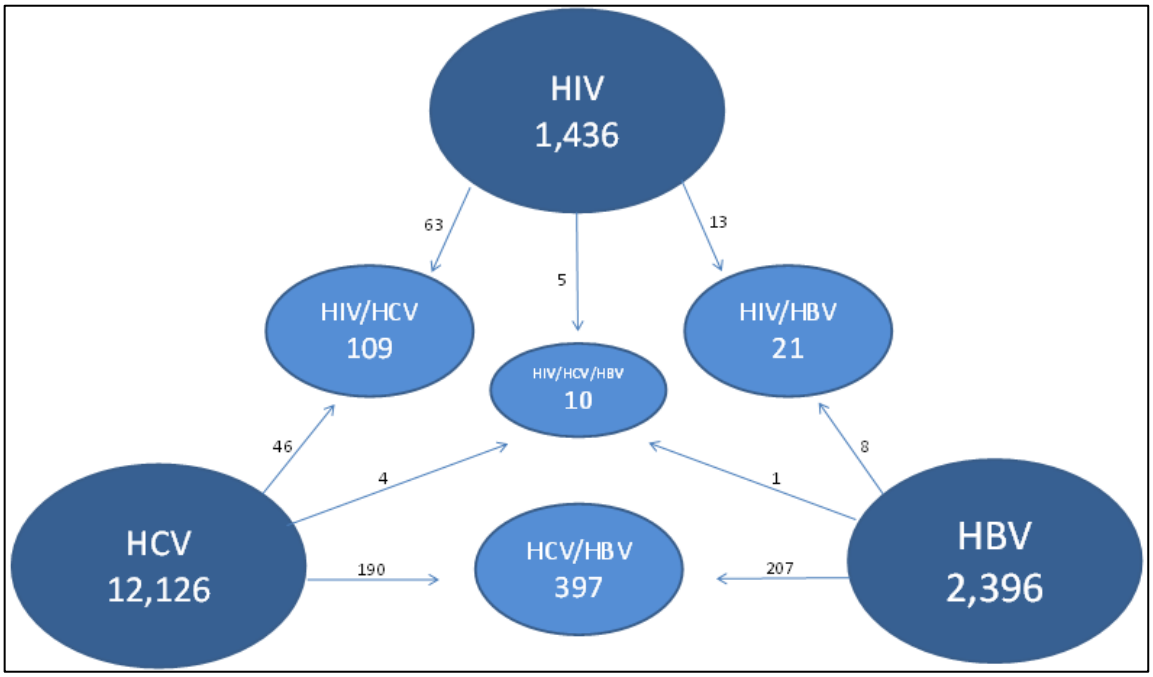


Figure 3. Kaplan-Meier curve of overall survival (in months) by group (mono-infected and multiply-infected).

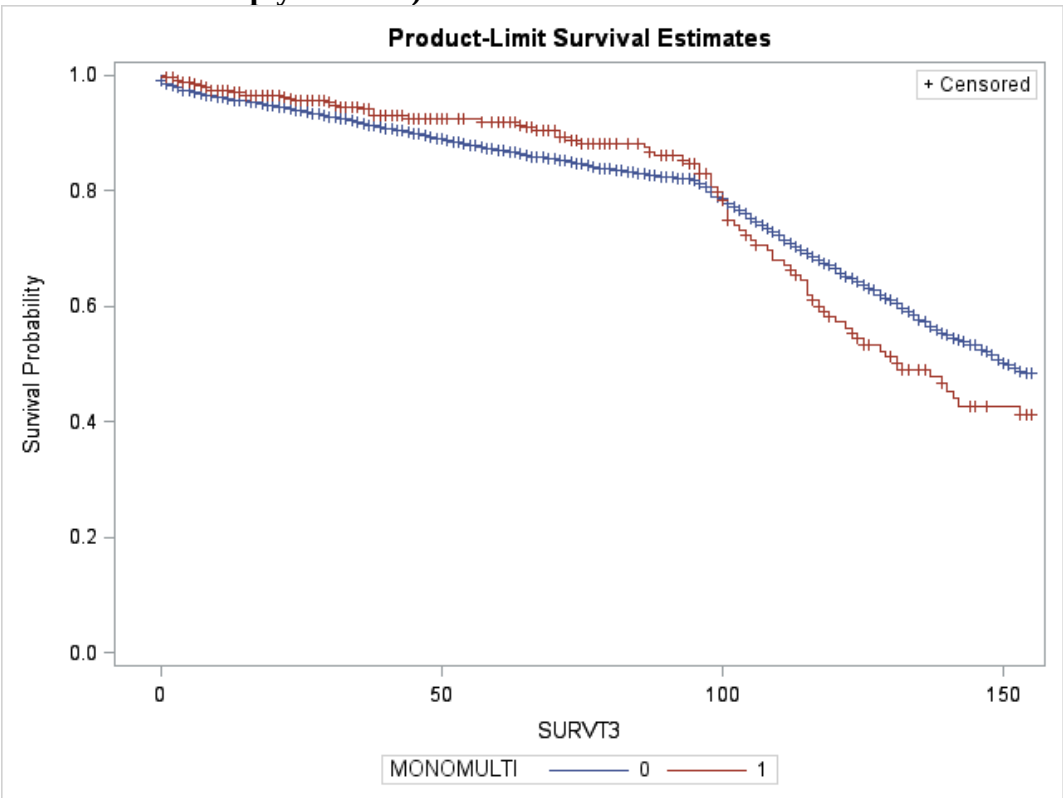


Table 4. Survival in ESRD treatment among all patients, mono-infected, and multiply-infected.

	All patients				All mono-infected patients				All multiply-infected patients			
	Subjects	**Deaths**	**Median Survival (months)**	**Log-rank p-value**	**Subjects**	**Deaths**	**Median Survival (months)**	**Log-rank p-value**	**Subjects**	**Deaths**	**Median Survival (months)**	**Log-rank p-value**
Total	15,958	2,307	28		15,375	2,219	28		537	88	36	
Sex				0.2129				0.127				0.1265
Male	9,391	1,360	27		3,948	1,306	27		161	54	36.5	
Female	6,567	947	29		2,719	913	29		70	34	34.5	
Race				0.5254				0.431				0.7033
White	1,466	427	10		1,431	419	10		35	8	20	
Black	419	122	11		413	121	11		6	1	14	
Multiracial	733	201	9		711	196	9		22	5	22	
Asian	17	3	16		15	2	14		2	1	23	
Indigenous	--	--	--			--	--		--	--	--	
Missing	2,709	1,554	--		4,097	1,481	--		166	73	--	
Age Group				<0.0001				<0.0001				0.0133
10-19	37	4	37		37	4	37		--	--	--	
20-29	266	52	38		259	50	38		7	2	98	
30-39	957	217	86		916	202	85		41	15	98	
40-49	1,709	459	81		1,642	437	80		67	22	96	
50-59	1,900	673	54		1,835	648	53.5		65	25	83	
60-69	1,296	540	44		1,268	529	44		28	11	96	
70-79	567	276	37.5		550	267	37		17	9	63	
80-89	136	75	34.5		131	71	34		5	4	98	
90-98	8	4	74		8	4	74		--	--	--	
Missing	15	7	--		21	7	--		1	--	--	
Region				<0.0001				<0.0001				0.4057
North	238	88	19		230	86	19		8	2	69.5	
Northeast	998	281	27		966	266	26		32	15	47	
Central-West	293	91	31		284	88	31		9	3	19	
Southeast	3,648	1,234	31		3,529	1,186	31		119	48	30	
South	1,721	613	25		1,658	593	24		63	20	40	

Year of Entry				<0.0001				<0.0001			<0.0001
2000	2,204	812	45		2,111	770	44		93	42	43	
2001	107	43	25		98	39	24.5		9	4	51.5	
2002	121	46	26.5		115	43	26		6	3	32	
2003	132	44	8		125	40	8		7	4	49	
2004	134	45	25		127	42	25		7	3	66	
2005	529	198	21		519	197	21		10	1	24	
2006	603	217	20		587	212	20		16	5	42	
2007	214	92	14		206	86	14		8	6	13	
2008	515	212	21		505	206	21		10	6	26.5	
2009	575	214	21		561	208	20		14	6	37	
2010	562	159	21		541	153	21		21	6	25	
2011	580	140	13		564	139	12		16	1	18	
2012	622	85	4		608	84	4		14	1	6	

Table 5. Extended Cox Model for Risk of Mortality by covariate by group (multiply- vs mono-infected)

	Hazard Ratio	95% CI	p-value
Multiple-infection	**1.67**	**(1.34, 2.07)**	**<.0001**
Covariates			
Sex			
Male	0.98	(0.90, 1.07)	0.6306
Female	1	Ref.	--
Age Group			
10-19	--	--	--
20-29	0.49	(0.37, 0.65)	<.0001
30-39	0.52	(0.44, 0.61)	<.0001
40-49	0.62	(0.55, 0.71)	<.0001
50-59	0.93	(0.83, 1.04)	0.2100
60-69	1	Ref.	--
70-79	1.66	(1.43, 1.92)	<.0001
80-89	2.32	(1.82, 2.96)	<.0001
90-98	--	--	--
Region			
North	1.22	(0.98, 1.51)	0.0757
Northeast	0.83	(0.73, 0.95)	0.0059
Central-West	0.90	(0.73, 1.11)	0.3342
Southeast	1	Ref.	--
South	1.12	(1.01, 1.23)	0.0252
Year of Entry			
2000	1	Ref.	--
2001	1.81	(1.33, 2.47)	0.0002
2002	2.69	(1.99, 3.64)	<.0001
2003	4.26	(3.12, 5.83)	<.0001
2004	8.87	(6.43, 12.22)	<.0001
2005	32.02	(25.05, 40.94)	<.0001
2006	42.06	(32.75, 54.02)	<.0001
2007	99.44	(73.69, 134.18)	<.0001
2008	180.76	(139.11, 234.88)	<.0001
2009	208.98	(160.14, 272.73)	<.0001
2010	230.82	(173.99, 306.20)	<.0001
2011	290.30	(216.47, 389.29)	<.0001
2012	283.87	(204.48, 394.10)	<.0001

Race excluded because of high number of missing values

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