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Effects of Hepatitis on Human Immunodeficiency Virus Viral Suppression

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Abstract

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MPH, Morehouse School of Medicine, 2011

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Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Coinfection with human immunodeficiency virus (HIV) and viral hepatitis leads to unfavorable health outcomes, making treatment of HIV difficult and increasing the odds of HIV transmission. The purpose of this study is to assess whether viral hepatitis (B and C) hinders HIV viral suppression and impacts the white blood cell count (CD4) when a person is concurrently infected with both viruses. The syndemics theory guided this study. Two research questions tested whether there was an association between coinfection with viral hepatitis and HIV viral load suppression. The research design was quantitative case-control with secondary data from 65,626 reports of HIV, HBV, and HCV at the Georgia Department of Public Health. Descriptive statistics and measures of association indicated that a coinfection with HBV or HCV was determined to be significantly associated with HIV viral load suppression. Persons coinfected with HBV/HIV were 1.45 times more likely to have achieved HIV viral load suppression than persons who were only infected with HIV (OR= 1.45, 95% CI 1.32-1.59, p= .0001). Those coinfected with HCV/HIV were 1.55 times more likely to have achieved HIV viral load suppression than those only infected with HIV (OR= 1.55, 95% CI 1.44-1.67, p=.0001). Coinfection with HBV was found to have a greater impact on CD4 cell counts, making persons infected with HBV/HIV 1.45 times more likely to be AIDS defining than HCV in individuals infected with HIV (OR= 1.45, 95% CI 1.34-1.67, p= .0001). Positive social change implications may include use of findings to support future prevention and control strategies in the coinfected population aimed at decreasing or controlling the spread of HIV and other sexually transmitted infections in the United States.

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Dedication

I dedicate my research to my loving supporters who pushed and motivated me throughout this journey. Because you believed in me, no matter what the task was, I can proudly say I have successfully accomplished yet another milestone in this journey of life. To my son Carson, let this be a testament that you can accomplish anything your heart desires no matter how long and tough the journey may seem. Mommy loves you forever and a day.

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction to the Study

Introduction

Viral hepatitis is a group of communicable diseases that affects the liver by causing inflammation (CDC, 2014). The most common types of viral hepatitis in the United States are hepatitis A (HAV), hepatitis B (HBV), and hepatitis C (HCV; CDC, 2014]. In the United States, there are between 2.2 and 4.7 million people infected with viral hepatitis, many of whom are not aware they are infected (HHS, 2020).

Currently in 2020, viral hepatitis is the leading cause of liver cancer in the US (HHS, 2020). Liver cancer and other liver-related diseases resulting from long term liver damage secondary to untreated viral hepatitis affect approximately 4.4 million Americans nationwide (CDC, 2014). In the US, certain populations are more affected by viral hepatitis than others (HHS, 2013). Persons living with HIV/AIDS (PLWHA) are among those populations who are disproportionally affected by viral hepatitis (HHS, 2013).

Human immunodeficiency virus (HIV) is a virus that attacks the body's immune system. The infection is known to cause the selective loss of CD4 cells due to virus replication and subsequent cell destruction which causes the body to become more susceptible to other infections or infection-related cancers (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015). CD4 cell count is often used as an important measure of HIV progression and as one of the indications for treatment initiation (WHO, 2013). When the CD4 count drops below 200ml, a person is diagnosed with AIDS. A normal range for CD4 cells is about 500 to 1,500. The higher the CD4 count, the better.

While effective antiretroviral treatment (ART) can significantly increase CD4 cell counts in most patients, there are certain populations who remain at comparatively low CD4 cell count levels (Kaufmann et al., 2013). Factors associated with poor CD4 recovery have been extensively studied; examples of these factors include older age, ongoing HIV replication (Kaufmann et al., 2013), treatment disruption and non-adherence to combined anti-retroviral therapy (cART) (Kaufmann et al., 2011), and late initiation of treatment (Tarwater et al., 2001). Since CD4 level forecasts mortality, and low CD4 cell count is associated with an increased risk of opportunistic infections, it is important to explore all possible factors that hinder immune recovery among HIV infected people (Lewden et al., 2007).

The HIV viral load is a measurement of the amount of HIV circulating in the blood. The goal of HIV therapy is to prevent HIV from replicating in order to bring the viral population down to an undetectable level. When a person living with HIV begins an ART regimen, his/her viral load drops. For almost everyone who adheres to his/her HIV medication as recommended, their HIV viral load will drop to an undetectable level in six months or less. This phenomenon is termed viral suppression. Continuing to take HIV medications as directed is imperative to stay virally undetectable or suppressed. Although a person's viral load is undetectable, HIV is still present in the body. The virus lays dormant inside a small number of cells in the body. However, persons who achieve and maintain viral suppression have effectively no risk of sexually transmitting the virus. The aim of HIV therapy is to sustain viral suppression for many years, which not only preserves future treatment options but reduces the risk of serious illness by 53%. Once

ART is stopped, the virus will return to a detectable level and start replicating again. HIV viral suppression is a powerful predictor of CD4 T-cell gains. HIV viral suppression is also important for people living with HIV to stay healthy, have improved quality of life, and live longer.

Approximately 1.1 million people in the United States are living with HIV, and about 15% of them are not aware of their infection status (Mugavero et al., 2013). HIV and viral hepatitis share common modes of transmission, which include blood (most commonly through injection drug use) and unprotected sexual contact. Because of their common transmission modes, coinfections by these viruses is common (Alter, 2014). Significant proportions of PLWHA are coinfected with HCV, and others are chronically infected with HBV (Soriano et al., 2010). According to the Centers for Disease Control and Prevention (CDC), approximately one-third of HIV infected individuals are coinfected with hepatitis (HHS, 2013). This estimate equates to about 25% having HIV/HCV coinfections and about 10% having HIV/HBV coinfections (HHS, 2013).

Problem Statement

Medical comorbidities resulting in greater risk of liver cancer include obesity, diabetes mellitus, insulin resistance, hepatitis B virus infection and HIV infection (Chopra, 2014). Since persons infected with HIV are immunocompromised, the progression of viral hepatitis is accelerated to end-stage liver disease and hepatocellular carcinoma more than in those who are only infected with hepatitis (Vellozzi et al., 2011).

Evidence suggests that HIV negatively impacts infections of HBV and HCV. Chopra (2014) suggested that when HIV is concurrently present with an HCV infection,

HIV speeds the progression of liver disease. Chun et al. (2012) also suggested that HIV has an adverse impact on HBV liver disease progression as well as an increased risk of liver cirrhosis.

Although an increasing number of HIV-infected persons are taking ART, many do not achieve HIV viral suppression and remain at risk for Acquired Immune Deficiency Syndrome (AIDS) and more likely to transmit HIV. Understanding if HBV or HCV has a potential impact on HIV is limited. Taylor et al. (2012) previously suggested that a coinfection with HIV and viral hepatitis can lead to unfavorable health outcomes, making treatment of HIV difficult and increasing the risk of HIV transmission. However, Taylor et al.'s study did not consider how viral hepatitis impacts HIV CD4 cell counts nor HIV viral load suppression. This study assessed if viral hepatitis leads to unfavorable outcomes in HIV-infected persons by hindering the achievement of HIV viral suppression or by impacting HIV CD4 cell counts.

Purpose of the Study

The purpose of this quantitative, case control study was to assess if viral hepatitis (B and C) hinders HIV viral suppression and impacts CD4 count when a person is concurrently infected with both viruses.

Research Questions

The following are the research questions for this study:

RQ1: Is there an association between coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals?

H_o1: There is no association between coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals.

H_a1: There is an association between coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals.

RQ2: Does the type of viral hepatitis (HBV or HCV) impact the CD4 count of the HIV infection?

H_o2: The type of viral hepatitis (HBV or HCV) does not impact the CD4 count of the HIV infection.

H_a2: The type of viral hepatitis (HBV or HCV) impacts the CD4 count of the HIV infection.

Theoretical Framework

This study was guided by the syndemics theory (Singer & Clair, 2003). The theory is used to understand the synergistic interactions of two or more diseases as they exist within the population with the presence of social and biological conditions. It is a valuable tool in the public health fight against HIV (Douglas-Vail, 2015). There are three constructs to this theory: (a) populations of interest, (b) social contexts shaping disease, and (c) biological synergism. The first construct requires that the two diseases of synergy must cluster in the same population to provide an opportunity for coinfection. The second construct encompasses the social conditions that influence individual and population health. The third construct occurs within the body of the individual when the two diseases are present. According to Singer and Clair (2003), actual biological synergism must occur between the two diseases (HIV and hepatitis), resulting in excess disease burden. There

are seven broad ways in which synergistic diseases interact within the body; they are enhanced contagiousness, accelerated virulence, greater expression of symptoms, physical alterations of the body's immunology, alterations of emotions, and gene assortment between pathogens and iatrogenic interactions (Klein, 2011). This study focused on two of them, accelerated virulence and physical alterations of the body's immunology. The two interactions guided this study by showing how the syndemic interaction of HIV, HBV, and HCV influence HIV viral suppression by increasing the amount of the HIV virus present in the body or by decreasing the CD4 count, thus inhibiting the achievement of HIV viral suppression.

Nature of the Study

This quantitative study had a case-control research design. In a case-control study, the outcome of interest is already known, and the researcher traces back to establish a relationship between the outcome and possible risk factors (Frankfort-Nachmias & Nachmias, 2008). In this study, the data were based on individuals that already have HIV, HIV/HCV, or HIV/HBV and are reported in Georgia's Department of Public Health disease registries. A case-control design was appropriate for this type of study, because it is cost effective and timesaving and does not expose subjects to harm due to intervention effects. Case-control designs are also suitable for the analysis of multiple exposures, and more so in the investigation of rare diseases (Aschengrau & Seage III, 2014).

Definitions of Terms

CD4 cells: a type of white blood cell that fights infection in the body. In HIV infection, the virus destroys CD4 cells, lowering the body's defenses to infection.

Comorbid infection or Coinfection: the presence of multiple infections in a host by multiple infectious agents (Cox, 2001).

Electronic HIV and AIDS Surveillance System (eHARS): a web-based tool supported and developed by the CDC for state and local health departments for HIV/AIDS surveillance.

Hepatitis: inflammation of the liver. The most common causes of viral hepatitis in the US are HAV, HBV, and HCV. HBV and HCV are common among those people who are at risk for or living with HIV (Alter, 2006).

HIV: a virus that causes the HIV infections and over time may cause AIDS.

State Electronic Notifiable Disease Surveillance System (SENDSS): created for the Georgia Department of Public Health (GDPH) for the reporting and surveillance of all notifiable diseases in Georgia.

Viral Load (VL): the amount of HIV in an infected person's blood. The higher the HIV level in the blood, the higher the VL, and the greater the risk the person has of becoming ill due to HIV. It is useful for measuring sustained response to ART (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015).

Viral Suppression: HIV-1 viral load of less than 200 copies on the most recent VL test. Having viral suppression significantly decreases the rate of HIV transmission (Loutfy et al., 2013).

Antiretroviral Therapy (ART): the use of HIV medicines to treat HIV infection. It is recommended for everyone who has HIV. ART helps people with HIV live longer, healthier lives and reduces the risk of HIV transmission.

Highly Active Antiretroviral Therapy (HAART): a form of treatment that uses a combination of three or more drugs to treat HIV infection.

Assumptions

Data collected by the GDPH were used to evaluate the hypotheses. The data set only contained persons living in Georgia at the time of diagnosis with either HIV or hepatitis. Because I did not collect the data, the accuracy of the data can only be assumed. Records cannot be reviewed for accuracy; however, GDPH has quality measures in place to ensure the validity and integrity of the data submitted. Therefore, I assumed that the quality measures in place are accurate and can minimize potential transcription error.

A second assumption was that the data used in this study contained all reports of HIV and hepatitis in Georgia. Because HIV and hepatitis are reportable diseases in Georgia, it is required that all diagnosed diseases are reported to GDPH. Thus, it was assumed that the database contained all known adult disease diagnoses in the state.

Scope and Delimitations

The scope of this study was to compare the CD4 cell counts and HIV VLs of persons coinfected with HIV and HCV/HBV to those of persons who were only infected with HIV to assess whether HCV/HBV affects the achievement of viral suppression as well as to assess which type of hepatitis, B or C, is more virulent to the HIV infection by evaluating CD4 cell counts for a determination of AIDS.

Limitations

One limitation of this study was the data. There may have been missing laboratory data because of inadequate reporting, inadequate processing, or laboratory tests

performed outside of Georgia. All registered are mandated by state law to report laboratory results on HIV-related laboratory test to the Georgia DPH. However, some facilities may not comply or send only some test results and not others. This can result in an underestimation of the coinfected cases in Georgia. Another limitation is that the results of this study may not be generalizable, since the data were only collected from the coinfected population. The results, however, can be used as a reference point to other studies of the same population.

Significance

The goal of this study was to determine if HBV and HCV have an impact on HIV viral suppression and CD4 cell count among HIV/HBV and HIV/HCV coinfected persons. The HIV/viral hepatitis coinfection is a growing and evolving epidemic (Taylor et al., 2012). HBV and HCV are highly prevalent among the HIV infected population (Taylor et al., 2012). People with HIV who are coinfected with either HBV or HCV have an increased risk of life-threatening complications (CDC, 2014). Therefore, it is essential that health professionals be informed on how viral suppression and increased CD4 cell counts can be achieved in coinfected populations. When viral load is controlled (or suppressed), the risk of HIV transmission to others is greatly lowered (Mugavero et al., 2013). This study could potentially be used to support future prevention and control strategies in the co-infected population aimed at decreasing or controlling the spread of HIV and other STIs in the United States. These strategies may increase individual knowledge of HIV, HBV, and HCV statuses, prevent new infections among HIV negative persons, reduce transmission from persons living with HIV, and enhance

response capacity and intensive data-to-care activities to support sustained viral suppression. The results may also provide insight on whether a coinfection with HBV or HCV affects HIV viral suppression in a person infected with HIV, which can be used to improve health outcomes for persons living with HIV through increasing screenings and provide better access to care.

Summary

The purpose of this study was to examine if either or both HBV and HCV affect HIV viral suppression in a person who is infected with HIV. This study used quantitative methodology. Data were extracted from the eHARS and SENDSS databases of the GDPH. The study was grounded by the syndemics theory (Singer & Clair, 2003), which allows researchers to investigate the synergistic interactions of two or more diseases as they coexist within the population alongside social and biological conditions. The results of this study may potentially be used to improve the health outcomes of persons living with HIV/AIDS.

Chapter 2: Literature Review

Introduction

The use of ART has led to great reductions in HIV related morbidity and mortality in HIV infected individuals (Cooper & Cameron, 2014). However, alongside ART's success has been the succeeding emergence of comorbidities, such as STIs. In the presence of an STI, HIV may be transmitted at a rate that is up to five times greater than in a person who does not have an STI (Mehendale et al., 2015).

HCV and HBV, due to their high presence in the HIV positive population, are among the leading causes of morbidity and mortality in the HIV positive population (Matthews et al., 2014). The hepatitis viruses have been known for their potential association with poor HIV health outcomes (Matthews et al., 2014). Coinfection of HIV positive individuals with HBV and HCV is a global problem of increasing concern, despite the availability of successful strategies for both their prevention and treatment. Several studies have examined the impact of HCV and HBV on HIV. While most have found that these viruses have no impact on the HIV virologic response to ART, there are conflicting reports regarding immunologic response.

Literature Search Strategy

I conducted the literature search using the Walden University library's online databases and journal articles from the years 2014 until present. First, I ordered the databases by subject. I searched journals categorized as health sciences and/or nursing. The databases found to be most useful were *Health Sciences: A Sage Full Text Journal*, *MEDLINE,* and *Academic Search Premier*. Other databases searched included *Google*

Scholar, *Health and Medical Complete*, and *Nursing and Allied Health Source*. I searched each of these databases using the same search terms. I reviewed these databases multiple times during the search period to identify newly added articles. Several terms were included in the database searches. *HIV* was used as well as the expanded name of *human immunodeficiency virus*. *AIDS* and its expanded name *acquired immunodeficiency syndrome* were also included. *HIV* and *hepatitis B and hepatitis C* were used individually and in combination. *Comorbid infection* was also searched with *HIV* and *Hepatitis B and C*. This same search was also conducted using *coinfection* as a synonym for comorbid infection. Subsequently, *sexually transmitted disease* and *infection* were also used as search parameters in conjunction with *comorbid illnes*s and *coinfection* to garner some general articles about the effects of coinfection with a sexually transmitted disease (STD) on health.

Organization of the Review

First, I review the theoretical framework for the study. Next, background information on HIV and Hepatitis B and C diseases (treated as separate and unique infections) is presented. The presentation includes relevant statistics and a summary of research studies associated with the infections. Following is a general discussion of HIV/HBV and HIV/HCV coinfection and its associated background, statistics, and studies. Finally, the literature review concludes with a consideration of the impact of this work on society.

Theoretical Framework

The syndemic theory was identified during the mid-1990s by anthropologist Merrill Singer (Klein, 2011). Singer was the first researcher to identify a syndemic in public health research (Wilson et al., 2014). Syndemic refers to the tendency for multiple epidemics to co-occur and interact with one another, with each one worsening the effects of the others (Singer, 2009). Syndemics occur when health-related problems cluster by person, place, or time. Syndemic also focuses on health disparities and the social conditions that affect them. The concept of syndemics represents an acknowledgment of the fact that many diseases and social problems worsen the effects of others already being experienced by their host. Syndemics are prevented by the control of each disease that plays a role in it, as well as the prevention and control of the forces that bound the two diseases together (Singer & Clair, 2003).

The syndemic theory was created in attempts to identify a "big picture" approach in epidemiological and public health thinking. Singer wanted to understand the determinant interconnections among pressing health problems, sufferer and community understandings of the illness(es)/disease(s) in question, the relevant social, political, and economic forces in play, and the environmental conditions that contributed to the development of ill health. The syndemic theory can be conceptualized with the following components: the populations of interest, social contexts shaping diseases, and biological synergism.

The Populations of Interests

The CDC described a syndemic as two or more epidemics in the same population, interacting to create an opportunity for co-infection and synergism which ultimately lead to excess burden of disease (Douglas-Vail, 2015). For example, frequently HIV and Mycobacterium tuberculosis (MTb) are clustered in the same population. When this happens, opportunities for individuals to be coinfected spiral upward due to the presence of both in the same population. Researchers have found that coinfection with HIV and MTb synergically interacts, leading to deadly consequences by lessening the survival time of coinfected individuals compared to individuals with just HIV or MTb (Dye et al., 1999). Another example of a synergistic effect can be seen in individuals who are suffering from asthma, which increases their chances of developing a coinfection with respiratory syncytial virus and influenza A virus, thus resulting in induced asthma attacks of greater severity (Zhoe et al., 2009).

Social Contexts Shaping Disease

The term syndemic goes beyond the idea of disease clustering in a particular location or population. It highlights the importance of the social conditions that influence the health of individuals and populations. Evidence suggests that social conditions are closely related to health outcomes (Currie, 2012). According to Currie (2012), determinants such as socioeconomic status, geographical location, gender, race, ethnicity, age, diet, water, sanitation, residence, access to health care, discrimination, stress, violence, and criminal justice systems are some of the social causes of syndemics. Social contexts outline not only the spread of disease, but also affect access to resources for

coping with disease burdens (Douglas-Vail, 2015). For example, research has shown that the HIV/HBV coinfection interaction can lead to poor health outcomes in the coinfected individual, but Gomez-Gonzalo et al. (2001) underlined that the impact the viruses have on one another is mediated by individual biology and age, nutritional status, and access to medical care of the coinfected individual. Another example of social context would be that individuals living in poverty have an increased likelihood of exposure to TB due to overcrowding in poorly ventilated habitations. Once infected, these individuals would be more likely to develop active TB because they are already weakened from other infections and malnutrition (Douglas-Vail, 2015).

Biological Synergism

The final concept of the syndemic theory is biological synergism. This is described as the interaction that occurs between two diseases within the body of the individual. Biological synergism is not the same as a mere comorbidity or coinfection. A coinfection refers to concurrent diseases without synergistic effects. In order to be defined as syndemic, the two diseases must result in excess burden when present concurrently. Some ways in which syndemic diseases interact in the body include enhanced contagiousness, accelerated virulence, greater expression of symptoms, physical alterations of the body, and gene assortment between pathogens and iatrogenic interactions (Douglas-Vail, 2015). An example of this concept is seen in the interaction between the two viruses HIV and HBV. Research suggests that HIV and HBV may have physical interactions at the cellular level in coinfected individuals (Ockenga et al., 1997).

HBV infects the T-lymphocytes, the primary cellular target of HIV, which in turn contributes to faster HIV replication and a more rapid progression to AIDS.

The full impact of HIV/AIDS stems from its syndemic interaction with various other diseases. The virus works together with a range of pathogens, such as hepatitis, TB, malaria, leishmaniasis, herpes and other STDs. HIV/AIDS also interacts unfavorably with non-infectious diseases and disorders, such as kidney disease, food deficiency, behavioral health problems, and cardiovascular diseases (Singer 2009). A study by Pugliese et al. (2002) showed that a syndemic interaction between human papillomavirus and HIV triggers greater chances of the development of cervical cancer in women when a coinfection by the two viruses is present. In another study, Pugliese et al. (2002) showed that when the effect of the coinfection with HIV and human herpesvirus type 8 was investigated among women, findings suggested that coinfection led to accelerated deterioration of the immune and hematopoietic systems.

The syndemic theory is a valuable tool in the public health fight against HIV. The theory is used to understand the connections between diseases by examining routes of transmission and interrelated health problems which result in excess disease burden (Singer, 2010). Researchers rely on the syndemic theory to understand the forces that tie diseases together. It suggests that medicine and public health should shift focus from individual risk behaviors to relationships, context, and processes (Singer, 2010). One of the greatest strengths of the syndemic theory is its ability to inform prevention and treatment programs. The syndemic approach aims to develop a richer understanding of disease prevention using broad public heath-based initiatives for the creation of programs

to address and lessen the impact of syndemics currently affecting populations and programs designed to predict and prevent the emergence of future syndemics. This study focused on the biological synergism component of the syndemic theory.

Human Immunodeficiency Virus

Originally seen in the 1980s, HIV is the causative agent of AIDS (Sarngadharan et al., 1984). HIV has an attraction for the body's T cells. These are the white blood cells responsible for the cell-mediated immunological response, commonly referred to as CD4 cells. CD4 cells are instrumental in the body's ability to intervene against disease acquisition and are required for the proper functioning of the human immune system. The virus enters these white blood cells via CD4 receptors. The virus then uses mechanisms in the white blood cell to replicate itself and spread throughout the body, slowly killing all the infected person's T cells. Lower CD4 counts mean a higher likelihood of health issues and sometimes death related to HIV, as the infected person's immune system no longer functions to fight off infection. In weakened immune systems, opportunistic infections that would typically not occur in healthy individuals become great threats. These infections become easily acquired and difficult to treat. The infections may often leave an HIV-infected individual severely ill and, if unmanaged, with a high risk of death (CDC, 2016).

HIV resides in white blood cells that can be found in some body fluids, such as blood, semen, breast milk, and vaginal fluid. Thus, one of the primary pathways of acquisition is transmission through sexual intercourse. Other transmission pathways

include intravenous drug use (IDU), vaginal birth, and breast feeding by HIV-positive mothers. There is currently no cure or vaccination for HIV.

As of December 2019, an estimated 38.0 million people globally were living with HIV. 1.7 million became newly infected in 2019, and 690,000 died of an HIV-related illness (UNAIDS, 2020). Although HIV transmission has declined since 2001, more people are living with HIV than ever before due to the use of ART (Platt et al., 2015). In 2018, the CDC estimated 37,968 incident cases of HIV in the United States. Of these cases, 70% were among gay and bisexual men or men who sleep with men (MSM). African Americans, Hispanics and Caucasians were responsible for 44%, 25% and 28.3% of the new infections, respectively (CDC, 2020). Adult women with high-risk heterosexual behavior accounted for 20.0% of the new infections, and men with similar high-risk heterosexual behavior accounted for only 10.3% of new infections. Other risk categories included IDU (10.0%) and a category classified as *other* (0.1%) that included hemophiliacs, blood transfusion recipients, perinatal exposure, or unknown/unreported exposure (CDC, 2020).

The age distribution of all HIV cases in 2018 revealed substantial increases in case numbers beginning at age 20. There were 14,740 new cases of HIV for those between the ages of 20 and 29 years, and 9,943 for those in the age group between 30 and 39 years. Cases began to decline for those between 40 years and 49 years (6,490 new cases), and for persons aged 65 years and older with fewer than 2,000 cases (CDC, 2020). Geographically, the South had the highest incidence rate for HIV in 2018 with 15.6 cases per 100,000 people (CDC, 2020). In the South, Georgia leads with the highest incident

rate of HIV diagnosis, 23.8 cases per 100,000. Disparities in HIV are also found in socioeconomic status, defined in terms of education, income, levels of poverty, educational attainment, and access to care. Poverty is associated with low educational attainment, low income, and reduced access to care. Persons with lower income tend to have lower education, less access to care, and increased HIV incidence (Fenton, 2004). In the United States, rates of HIV among MSM were still the highest among all subgroups (CDC, 2020); this likely explains the large amount of research focusing on MSM.

Hepatitis B Virus

Hepatitis B is a liver infection caused by HBV, which is transmitted through blood, semen, or other bodily fluids through sexual contact; sharing needles, syringes, or other drug-injection equipment; or from mother to baby at birth. For some people, hepatitis B is an acute or short-term illness, but for others, it can become a long-term, chronic infection. Chronic Hepatitis B can lead to serious health issues, like cirrhosis or liver cancer. The best way to prevent Hepatitis B is by getting vaccinated.

In 2018, an estimated 257 million people are living with HBV. In 2018, a total of 3,322 cases of acute HBV in the Unites States was reported to CDC. As of 2018, CDC estimated that almost 862,000 persons in the United States had chronic HBV. The incidence of HBV infection differs significantly by race and ethnicity, with the highest rates being among Blacks, and rates being higher among Hispanics than non-Hispanics. Incidence also varies by age, with the highest rates reported among persons 20-39 years of age. In Georgia, there were 1,421 reported incident cases in 2018. The most common risk factors reported in Georgia were IDU, multiple sex partners, and MSM.

Hepatitis C Virus

HCV is an RNA virus that causes acute and chronic liver infection. In the US, about two- thirds of HCV-infected people become chronic carriers, while the remaining one-third may spontaneously clear the virus without requiring any treatment. HCV infection is the most common chronic blood-borne infection in the United States. In 2005, more than 184 million people were estimated to have been infected with HCV. By 2014, this number had declined to 115 million as a result of improved screening of blood donations and decreased IDU (Platt et al., 2016).

Chronic HCV infection is a major cause of mortality and morbidity across countries. There are an estimated 177 million people infected worldwide (Petruzziello et al., 2016). An estimated 2.7-3.9 million people in the United States have chronic hepatitis C. HCV infection occurs among persons of all ages, but the highest incidence of acute Hepatitis C is found among persons 20-39 years. African Americans and Whites have similar incidence rates of acute disease, with higher rates in persons of Hispanic ethnicity. In Georgia, there were 5,451 reported incident cases in 2018. The most common risk factors reported were IDU, multiple sex partners and MSM.

HIV/HBV Coinfection

The viral diseases of hepatitis and HIV/AIDS are known as the *twin epidemics,* due to their similarities and consequences of coinfection (Highleyman, 2003). A growing body of literature indicates that HIV positive individuals are more likely to be infected with HBV than HIV negative individuals, possibly as a result of shared risk factors (Mallet et al., 2011). There is also evidence that HIV positive individuals who are

subsequently infected with HBV are more likely to become HBV chronic carriers and have a high HBV replication rate. In addition, it is evident that immunosuppression brought about by HIV infection may cause reactivation or re-infection in those previously exposed to HBV. Furthermore, HIV infection exacerbates liver disease in HBV coinfected individuals, and there is an even greater risk of liver disease when HIV and HBV co-infected patients are treated with ART. Complicating matters further, there have been several reports linking HIV infection to "sero-silent" HBV infections, which present serious problems for diagnosis, prevention, and control (Platt et al., 2015) (Marine-Barjoan et al., 2014).

There are several studies that suggest that HIV immunosuppression may reduce liver damage as a result of a less aggressive HBV specific immune response, and this is supported by reports of a reduction in icteric illness in acute HBV infections in HIV positive patients (Highleyman, 2003). However, HIV infection has been found to exacerbate liver disease, with an early study finding death from liver failure in four of five HIV/HBV coinfected individuals compared with two of six HIV negative HBV infected individuals (Matthews et al., 2014).

HIV/HCV Coinfection

Of special concern regarding HIV coinfection is the HCV. Both HIV and HCV are rapidly replicating RNA viruses, and both are transmitted via blood contact. A common route of transmission is multiple sharing syringes by injection drug users (Singer et al., 2000). The prevalence of HCV in HIV-infected populations is highest in

IDU, followed by MSM and pregnant or heterosexually exposed populations (Platt et al., 2015).

Many studies suggest that HIV infection leads to hepatitis infections that are more aggressive than those in individuals not infected with HIV (Singer, 2009). The interaction between HIV and HCV in coinfection affects the transmission and natural history of the HCV infection. HCV transmission proficiency increases in the presence of the HIV infection (Platt et al., 2015). People living with HIV who do not receive ART have reduced chances of naturally clearing the HCV infection, have increased HCV VLs, and experience more rapid HCV disease progression than those without HIV infection (Platt et al., 2015). In HIV/HCV coinfected individuals, successful ART leading to viral suppression of HIV replication is associated not only with lower rates of AIDS-related disorders but also with slower progression of liver fibrosis and lower mortality from liver disease (Marine-Barjoan et al., 2014).

In contrast to HIV negative individuals, HIV positive individuals infected with HCV usually become chronic carriers (Thomas et al., 2000). Among those infected with HCV, approximately 20–45% spontaneously clear the infection without treatment; this proportion is lower in HIV coinfected individuals due to weaker HCV specific immune responses (Moqueet et al., 2015). Although ART has been found to improve HCV outcomes in coinfected patients, the HCV coinfection may complicate HIV treatment. Evidence have suggested an increased risk of drug related hepatoxicity in those receiving ART for HIV infection (Taylor et al., 2012). Such negative outcomes appear to be as a result of the inability of the immune system to contain HCV when under attack from

HIV. Even in cases where it seems that the body has been able to clear HCV, as the immune system deteriorates, HCV replication restarts (Kim et al., 2006).

The question of the impact of HCV on the natural history of HIV disease remains of considerable interest. Prior to the availability of combination ART (pre-1996), increased rates of HIV disease progression largely masked any effects of HCV disease on HIV. Since then, Greub et al. (2014), reported from the Swiss Cohort Study that HCV infection was associated with a 70% increased probability of progression to a new AIDS defining event or death. Some studies have confirmed his findings, such as Bonacini et al. (2004), which found that the hepatitis viruses do in fact have potential associations with poor HIV outcomes, while other studies refute these findings (Kim et al., 2006).

There are many ways that HCV could impact HIV disease progression; for example, liver disease may preclude the use of ART because of hepatotoxicity. Many coinfected individuals, because of sociodemographics or uncontrolled addiction, simply never access ART and die of AIDS. It is also possible that HCV has a direct influence on HIV infection, although the mechanism of action is yet unknown. As people with HIV live longer, HCV related liver disease in coinfected patients is becoming a major cause of morbidity and mortality. However, the burden of HIV/HCV coinfection is poorly understood.

HIV and Viral Suppression

Viral suppression is a measure that indicates a progression along the HIV care continuum. When a person living with HIV begins an ART regimen, his/her HIV VL decreases. For almost everyone who takes his/her HIV medication daily as prescribed, the

HIV VL will decrease to an undetectable level in six months or less. A person's HIV VL is considered undetectable when all VL test results are undetectable for at least six months after the first undetectable test result. Continuing to take HIV medications as directed is imperative for the HIV VL to remain undetectable. Persons living with HIV who take antiretroviral medications daily as prescribed and who achieve and then maintain an undetectable VL, have effectively no risk of sexually transmitting the virus to an HIV negative partner. According to recent data, of the estimated 1.2 million people infected with HIV in the United States, almost 210,000 are virally suppressed (Gardner et al., 2011).

Persons with high initial CD4 counts have a greater likelihood of reaching HIV viral suppression (Yehia et al., 2014). The CD4 cell count is important, because it allows clinicians to monitor how well a person's body is responding to ART and it provides an overall status of the persons's immune system (Brenan et al., 2013). The CD4 cell count is used clinically in determining how quickly ART needs to be initiated and when to start and discontinue prophylaxis for opportunistic infections and is a predictor of disease progression and survival (DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents, 2015). CD4 cell count is also used to monitor ongoing disease progression and severity and to determine stage of HIV infection (Stage 1 is a CD4 count of greater than or equal to 500 cells/μL or a CD4 percentage of total lymphocytes of greater than 26, Stage 2 is a CD4 count of 200- 499 or CD4 percentage of total lymphocytes of 14 – 25, and Stage 3 is a CD4 count of less than 200 or CD4 percentage of total lymphocytes

of less than 14 (Selik et al., 2014). CD4 cell count is a strong predictor of death but is modified by HIV viral suppression and time on ART (Brennan et al., 2013).

Literature Related to the Content

Several studies have investigated the health outcomes of an HIV coinfection with HBV or HCV; however, to date, very few have researched the effects of the CD4 cell count on the coinfection. The data in this area, most published over a decade ago and in both the pre-combination and post-combination ART eras, are mixed in their findings, largely using endpoints of AIDS defining events or death.

A search of the literature showed that there are conflicting reports on the effect of HBV/HCV infection on the natural history of HIV disease. The Swiss HIV Cohort Study for example found that in the first year of initiating ART, HCV infected individuals had smaller increases in CD4 cell counts than HCV negative individuals (Kaufmann et al., 2003). The EUROSIDA study did not find an effect of HCV on HIV disease progression, but there was an increased risk of liver-related deaths among HCV coinfected individuals (Rockstroh et al., 2005).

In Piroth et al. (1998) longitudinal study, immunologic progression was examined in HIV/HCV coinfected persons. One hundred and nineteen HIV infected persons coinfected with HCV, and 119 matched individuals infected with only HIV were included in the cohort. Clinical progression was defined as one or more of the following: a 20% loss of body weight; an AIDS-defining illness (for non-AIDS patients); and/or death (except by accident, suicide or overdose). Immunological progression was defined as a 50% decrease in the initial CD4 T-cell count (for patients with an initial count > 100

x 10(6) cells/l). Effects of HCV coinfection were evaluated using Kaplan-Meier survival analysis, and significance was tested using univariate (log-rank and Peto's tests) and multivariate methods (Cox regression). Clinical progression was more rapid in HIV/HCV coinfected patients than in HIV positive patients not infected by HCV in that CD4 cell counts of more than 600mL declined when HCV was present. This might suggest a greater impact of HCV on HIV disease progression in early HIV infection.

Greub et al. (2014) found that after effective ART, HIV/HCV patients had a modest increased risk of progression to a new AIDS defined illness or death. In this study, 1157 patients (37.2%) were coinfected with HCV. In multivariate Cox regression, the probability of progression to a new AIDS-defining clinical event or to death was independently associated with HCV infection (hazard ratio 1.7 [95% CI 1.26-2.30]). HCV infection was associated with a smaller CD4 cell recovery (hazard ratio for a CD4-cell count increase of at least 50 cells/microL=0.79 [0.72-0.87]).

In a study by Sarkar et al., (2016), 1331 confirmed HIV positive individuals were initiated on ART. Among the participants, 1253 were only infected by HIV, and 78 were HIV/HBV coinfected. All participants, before starting ART, were subjected to baseline mandatory laboratory testing [CD4 count, complete hemogram, liver function tests (LFT), fasting blood sugar, blood urea, serum creatinine, venereal disease research laboratory (VDRL), hepatitis B surface antigen (HBsAg), routine stool and urine analysis and chest X-ray [posterior anterior (PA) view]. HIV/HBV coinfected individuals had more advanced HIV disease (WHO clinical stage 3 and 4) than HIV- only infected

individuals (37.1% vs. 19.9%). CD4 cell count was non-significantly lower in coinfected patients.

A study done by Bani-Sadr et al. (2014), examined the impact of HCV-related characteristics such as genotype, VL or liver fibrosis on the chances of achieving sustained HIV suppression in coinfected patients. Eight hundred ninety-seven patients were examined to determine the relationship between HIV/HCV-related and social behavioral characteristics and HIV sustained viral suppression (SVS). The main outcome variable was HIV SVS, defined as at least two consecutive undetectable HIV VLs. Among the 897 HIV/HCV coinfected patients, 419 (47%) had received HCV therapy at least once, and 103 patients (25%) had experienced an HCV sustained virologic response (SVR). Results showed that HCV SVR was associated with a higher likelihood of achieving HIV SVS.

Van Santen et al. (2019) aimed to assess the effect of incident HCV infection and its timing relative to HIV seroconversion in HIV positive MSM on their subsequent CD4 cell count and HIV VL. HCV/HIV coinfected MSM were matched to HIV only infected MSM by time of HIV infection and combination ART use. Two-hundred fourteen HIV infected and 147 HCV/HIV coinfected MSM were matched to 3954 controls, HIV only infected MSM. The timing of HCV seroconversion relative to HIV seroconversion had no evident effect on HIV VL or CD4 cell count. In the first 2-3 years following HCV infection, CD4 cell counts were lower among HCV/HIV coinfected MSM but became similar to counts in HIV only MSM years later. The authors concluded that regardless of

the duration of HIV infection when HCV is acquired, CD4 cell counts are temporarily lower following HCV, even when on ART.

In a study done by Aibibula et al. (2018), the association between poor HIV viral control and immune recovery among person coinfected with HCV/HIV was examined. A total of 725 participants was enrolled between 2012 and 2015. At baseline, 52% of the participants reported having depressive symptoms, and 75% had an undetectable HIV VL (HIV virally suppressed). Participants experiencing depressive symptoms had 1.32 times (95% CI: 1.07, 1.63) the risk of having detectable HIV VL (not HIV virally suppressed) but had comparable CD4 count to people who did not experience depressive symptoms. The presence of depressive symptoms was thus a risk factor for incomplete, short-term, HIV viral suppression among people co/infected with HIV/HCV.

Aibibula et al. (2018) also examined the impact of food insecurity on HIV viral VL and CD4 cell count among people coinfected with HIV and HCV. There were 725 HIV/HCV coinfected people with 1973 person-visits over 3 years of follow-up in the study. At baseline, 23% of participants experienced moderate food insecurity, and 34% experienced severe food insecurity. The proportion of participants with undetectable HIV viral load was 75%, and the median CD4 count was 460 cells/μL. Participants experiencing severe food insecurity had 1.47 times the risk of having detectable HIV viral load compared with people who were food secure. These findings provide evidence of the negative impact of food insecurity on HIV viral load and CD4 cell count among HIV/HCV coinfected people.

Cescon et al. (2014) compared HIV treatment outcomes and survival between HIV/HCV coinfected individuals with and without IDU history. This study was restricted to 1254 participants with HIV/HCV coinfection and known IDU history. During a median follow-up time of 3.8 years, 217 deaths were reported. In adjusted multivariable analysis, individuals with IDU history were significantly less likely to achieve virologic suppression and CD4 cell count recovery and had a significantly higher risk of mortality.

Despite the adverse clinical consequences of HIV/hepatitis coinfection, the mechanisms by which these two viruses interact at the cellular level remain largely unexplored. At present, the literature suggests that the major contribution of hepatitis to coinfected individuals is accelerated liver disease and increased HIV/AIDS-related complications. A better understanding of the interactions between these two viruses is vital to the development of novel treatment strategies to control HIV/hepatitis coinfections.

Literature Related to Methods

Epidemiological studies may be experimental, quasi-experimental, or observational. Both experimental and quasi-experimental involve manipulation of a study factor, while an observational study observes naturally occurring phenomena to make inferences (Friis & Sellars, 2004,). Research methodologies include qualitative, quantitative and mixed methods. Among the quantitative studies reviewed were retrospective studies, cohort studies, and cross-sectional studies (Rao et al., 1998; Stekler et al., 2005; Shah et al., 2002). Like the proposed research, some of the studies retrospectively examined medical records and charts. An advantage to a medical record

review is that the data are already present and do not have to be collected by the researcher.

In a case-control study in African American women, the researchers evaluated social, behavioral, and epidemiologic risk factors which potentially predispose a person to HIV (Forna et al., 2006). Focus groups were used to gather information regarding HIV behavioral risk factors and recommendations to minimize transmission among African American women. The case-control study design allowed the researcher to evaluate risk factor data as well as presented topics for future investigation as described by the participants.

In a case-control study conducted by Resino et al. (2014), phenotypic and functional parameters of immune restoration were evaluated in 27 HIV-infected patients on HAART. The patients were compared to 11 HIV infected controls that never had less than 500 CD4 cell counts. The participants were followed for 18 months. Results showed that the cases (HAART patients) with a previous state of severe-moderate immunosuppression normalizing their CD4 cells had an incomplete immune reconstruction after HAART.

Skiest et al. (2006), used a case-control methodology to study the impact of comorbidity on the course of HIV disease in older patients as compared to a matched cohort of younger patients. Forty-three HIV infected patients, 55 years and older, were compared to a randomly selected group of 86 patients 45 years old, matched by date of HIV diagnosis. Data were collected on non-HIV-related morbidity, initiator of HIV testing, HIV stage at time of HIV diagnosis (TOHD), AIDS defining diagnoses, AIDS-

related illnesses (ARI), observed AIDS-free interval, survival, and frequency of HIV-related and unrelated hospitalizations. Results showed that older HIV infected patients presented with more advanced disease, which may have been due to lack of HIV awareness in this population, had a shorter survival and had more HIV- and non-HIV-related comorbidity than the younger patients. The more rapid course and decreased survival in the elderly may have been related to possible comorbidity confounders.

Lawrence et al. (2001), performed a case-control study to investigate the impact of early untreated HIV infection on chronic HCV. Medical records were examined for HIV-infected patients who had a medical exam during 1995-1996. Patients were screened for IDU, CD4 cell count, ART, and positive anti-HCV antibody. Thirty-eight eligible HIV-infected patients (cases) and 38 HCV infected patients without HIV (controls) were randomly matched by age, sex and duration of HCV infection. The study found that early treated HIV infection is associated with higher HCV viremia and more severe liver injury in IDUs with chronic HCV.

Ying Yu et al. (2018), used a case-control study to examine the HCV viral loads among IDUs with HCV infection, HCV/HIV coinfection, and HIV/HBV coinfection. Among the 45 IDUs recruited, 27 were HCV mono-infected, 9 were HCV/HIV coinfected; 7 were HCV-HBV coinfected, and 2 were seronegative for HCV, HBV, and HIV infection. A control group of 180 age and gender matched chronic HCV infected non IDU patients was enrolled. Results showed that the HCV RNA levels in IDUs with HCV/HIV coinfection were significantly higher than those in the control group, the IDUs with HCV only infection group, and IDUs with HIV/HBV coinfection group ($P <$

0.001, $P < 0.001$, and $P < 0.001$, respectively). IDUs with HCV/HIV coinfection suffered worse outcomes. Programs for how to block HIV transmission in this group need to focus on the education and routine check- ups of those with risky sexual customs and practices.

A case-control study by Darraj et al. (2018), was performed to characterize the factors associated with decreased immunological response among Manitoba's HIV population. The case-control study included HIV patients with immune reconstitution failure despite suppression of HIV replication by ART. Immune reconstitution failure was defined by CD4 cell count increase from baseline of less than 100 CD4 cells/mm or lack of increase to above 200 CD4 cells/mm within one year of viral suppression. A total of 42 individuals who met the definition of immune reconstitution failure were assigned as cases. Controls were 31 patients comprising a range of ages and CD4 cell counts like those of the cases. Results showed that age and a low CD4 cell count before the start of ART were possible predictors of immune reconstruction failure.

Advanced HIV infection despite sustained viral suppression by HAART is a risk factor for poor immunologic recovery. However, some patients with advanced infection do recover. Kim et al. (2015), examined predictive factors of immunologic recovery in advanced HIV patients showing sustained viral suppression. A case-control study was conducted in HIV-infected adult patients with an HIV diagnosis of 4 years or longer who were receiving HAART. Advanced HIV infection was defined as a baseline CD4 T cell count < 200/mm or AIDS. Immunologic responders were defined as patients showing immunologic recovery (CD4 cell counts ≥ 500/mm at 4 years with HAART). Of 102 eligible patients, 73 had advanced HIV, and 33 showed immunologic recovery. The

median CD4 slopes during 0 to 6 and 0 to 12 months of HAART in the advanced patients were significantly higher in responders than in non-responders. Multivariate analyses showed opportunistic infections at the start of HAART were independently associated with immunologic recovery. Coinfection with HCV and HBV were among the factors that were associated with a poor immunologic response.

Brites-Alves et al. (2015), also used case-control methodology to compare virally suppressed HIV patients according to restoration pattern: adequate response (AR), partial response (PR), and inadequate response (IR). A total of 293 patients, 92 cases and 189 controls, (89 AR, 112 PR, and 92 IR) were evaluated. A previous diagnosis of HCV or Tb was associated with IR. Longer time on ART was associated with a greater chance of AR, but logistic regression identified coinfection by HCV as the main factor associated with abnormal CD4 ratio. They concluded that previous HCV diagnosis significantly increases the risk of abnormal CD4 cell count.

Summary

In the United States, there are between 2.2 and 4.7 million people infected with viral hepatitis (HHS, 2020). Persons living with HIV/AIDS (PLWHA), are among those populations who are disproportionally affected by viral hepatitis (HHS, 2013). HCV and HBV, due to their high prevalence in them, are among the leading causes of morbidity and mortality in the HIV positive populations (Matthews et al., 2014). The literature has revealed that HIV infection leads to hepatitis infections that are more aggressive than those in individuals not infected with HIV, but a focus on the effects of HBV/HCV on HIV viral suppression and CD4 cell counts has not been fully researched. HIV viral

suppression is the goal of ART. People living with HIV who achieve and maintain an undetectable VL have effectively no risk of sexually transmitting the virus to an HIV negative partner. Given that HBV and HCV are heavily prevalent in the HIV population, it is essential to understand if a coinfection by either of these viruses effects the achievement of HIV viral suppression and leads to decreased CD4 cell counts.

Chapter 3: Research Method

Introduction

In this chapter, I describe the research methodology used for this study. The goal of this chapter was to give a description of the study design and secondary data sources. This chapter also includes the data collection procedure and the data analysis plan. This chapter concludes with a summary of the research methods used.

Research Design & Approach

An observational approach was used as opposed to an experimental approach, as variable manipulation in the latter would be both illogical and unethical. The study sample included those with reported HIV and/or hepatitis data available in the GDPH eHARS and SENDSS databases between 2012 and 2016.

The case-control design methodology was used for this study. The case-control methodology allowed me to compare the HIV CD4s and viral loads of persons coinfected with HIV and HBV or HCV with those who are only infected with HIV. The exposure variable of interest and will have three categories: HIV only infection, HIV/HCV infection, and HIV/HBV infection. The outcome variables of interest were HIV viral load suppression and CD4 cell count. After data collection all exposure variables, HIV only, HIV/HCV, and HIV/HBV were evaluated for CD4 cell counts and HIV viral loads.

Population and Sample

The study sample was drawn from reports in the state of Georgia that were reported positive for the HIV infection with and without HBV or HCV between the years

2012 and 2016. The sample only contained persons aged 18 years and older living in Georgia at the time of a positive diagnosis or diagnoses.

This study used quantitative measures. According to Polit and Beck (2012), quantitative research designs often require large samples to increase representativeness and reduce sampling error. The sample size is chosen to maximize the chance of uncovering a specific mean difference that is statistically significant (Polit & Beck, 2012).

Research data collected in public health practice can be primary or secondary (Struwig and Stead, 2001). Secondary data were used for this study.

The study population was drawn from notifiable disease reports received by the GDPH SENDSS and eHARS. Individuals reported to be diagnosed with HBV or HCV between the years of 2012 and 2016 was extracted from the SENDSS database and matched with prevalent HIV cases in eHARS, a database used to collect information on individuals infected with HIV/AIDS.

Based on the G*Power analysis program using the chi-square statistic with a medium effect size of w= 0.30 and an alpha of 0.05, the needed sample size was 94; for a small effect size of w= 0.01, the needed sample size would have been 840; and for a large effect size of w = .50, the needed sample size would have been 34.

Data Collection

The state code grants the GDPH general authority to use surveillance data to investigate preventable disease in the state of Georgia. It also permits the GDPH to collect personal information and health data for the purpose of surveillance that may

prevent and control disease, and it protects the GDPH from civil liability when the data are used as required by law for surveillance. Georgia law allows the GDPH to review and collect the medical records of any medical facility in Georgia for the purpose of disease investigation.

Access to the data for this study was provided by the GDPH. Permission to use the data was granted by the Office of Science, Research, and Academic Affairs in DPH. Upon IRB approval from GDPH and Walden University, the HIV data manager at the GDPH performed an HIV and hepatitis case match between SENDSS and eHARS for the population of coinfected cases. The cases were matched by last name, first name and date of birth. The resulting de-identified dataset of the match was provided for this study. The data were presented as a SAS dataset, which included requested variables, and were transferred securely to the researcher using a password-protected jump drive and were stored in a locked safe at GDPH when not in use.

The request for HBV, HCV, and HIV data collected through December 2016 was submitted to the Georgia DPH in December of 2019. Year-end data of 2016 were the most complete CDC approved data for Georgia at the time of the request. The data request was approved by the GDPH in February 2020, and the data were received from the DPH data submission portal in March 2020. Due to Georgia laws for the protection of human subjects, race/ethnicity data were grouped as White, Black, and other, further de-identifying the data. The dataset was cleaned by deleting all duplicates as well as unknowns such as in gender and race.

Measures and Variables

The information used to create the data set was gathered from disease case reports, field records, laboratory reports, and interview records. The last four most recent VL counts for the all sample participants were also included in the database for assessment of HIV viral suppression. A review of CD4 cell counts was used to understand if viral hepatitis impedes the achievement of HIV viral suppression, which is defined by the HIV care continuum and CDC as the most recent VL count less than 200 copies/mL. The care continuum is important in HIV/AIDS data because it allows for CDC and other public health agencies to monitor how the United States is doing regarding all persons living with HIV, monitor disparities by examining data among sub-groups of the population, and monitor data at the local level to understand local progress and identify additional action steps to meet national level goals. In this study, the care continuum definition of viral suppression, was used as a measure to evaluate if HIV is affected by HBV or HCV.

Data Analysis

Univariate and bivariate analyses were conducted for this study. For all bivariate analyses, an alpha value of 0.05 was used to determine whether the observed outcome for the specified variables differed significantly from the expected outcome. All statistical analyses were carried out using SAS version 9.3.

External Validity

The main threat to the external validity of this study may be the sample being used from a specific location within the US, so the data may only be applicable to

Georgia. The sample will be derived from data reported to the GDPH. Since some persons with disease have not been diagnosed or reported, they will not be present in the data set.

Internal Validity

Possible threats to the internal validity of this study may be the presence of confounders, such as other health related outcomes that may or may not influence HIV viral suppression, such as other STIs or chronic health conditions. Unfortunately, databases which may contain this information are not easily accessible or linked at GDPH, but I do not foresee any major threats to the results of this study because of this issue.

Ethical Protection of Participants

The study proposal was submitted to the Walden GDPH IRB and Walden University IRB for review and approval to ensure the adherence to ethical standards and federal regulations. Additionally, the GDPH required completion of a data request form which also consists of a data use agreement. Identifiers in the data received from GDPH were removed by the agency prior to its releasing. This decreased the likelihood of having a leak of private health information, which would violate HIPPA regulations. Upon completion of the project, the GDPH mandated the return or destruction, by a predetermined method, of all data. These steps ensured the ethical treatment of all participants.

Summary

Observational research was used to determine whether a coinfection with HBV or HCV inhibits HIV viral suppression in an HIV infected individual. All exposure variables will be evaluated for CD4 cell counts and HIV viral loads. The sample included persons 18 years or older who were reported and diagnosed with either HIV, HBV or HCV while living in Georgia. The dataset was created by GDPH and given to the researcher after approval of both DPH and Walden University's IRB. Data analysis were performed using SAS to test the null hypotheses and their associated alternative hypotheses.

Chapter 4: Results

Introduction

This chapter provides the results of a case control study using the data from the GDPH on HIV, HBV, and HCV disease reports through the year ending 2016. The research questions examines the associations between a coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals and assesses the impact of HBV and HCV on CD4 counts in HIV patients. This chapter provides an overview of the demographic, HIV viral suppression, and CD4 characteristics of the study sample, reviews the research questions and hypotheses, reports the statistical analyses, and summarizes the study findings.

Demographic Characteristics and Results of Bivariate Analysis

The study sample included a combined total of 65,626 reports of HIV/HBV (n= 2,034), HIV/HCV (n= 3,321), and HIV only infected (n= 60, 271). The population consisted of 76.3% males and 23.4% females. Age was stratified into five categories: 10.3% were between the ages of 20 years and 29 years; 22% were between the ages of 30 years and 39 years; 22.1% were between the ages of 40 years and 49 years; 28.1% were between the ages of 50 years and 59 years; and 17.5% were aged 60 years and older. Regarding race/ethnicity, 68% of the study population were non-Hispanic African American, 18% were non-Hispanic White, and 14% were defined as Other. The demographic characteristics for each category of the exposure variables (HIV/HBV, HIV/HCV, HIV only) are presented below (Table1).

Table 1

Demographic Characteristics by Disease Status

	HIV/HBV	HIV/HCV	HIV only
Gender			
Males	1,778	2,570	45,203
Females	236	723	14,381
Race			
White	360	609	10,861
Black	1,437	2,302	44,591
Other	237	3,321	8,558
Age (yrs)			
20-29	66	138	6,563
30-39	360	456	13,512
40-49	597	574	13,313
50-59	690	1,109	16,610
≥60	314	1,041	10,071
Risk factor			
*MSM	1486	1654	36,916
*IDU	96	627	3,550

Note. N=65,626 *MSM=Men who have sex with men *IDU= Intravenous drug user

Research Questions and Hypotheses Testing

To answer the research questions, each hypothesis was tested to assess the potential associations between the exposure variable and outcome variables. For each of the hypotheses, a Pearson Chi-square analysis and measure of associations are presented below.

RQ1: Is there an association between coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals?

H_o1: There is no association between coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals.

H_a1: There is an association between coinfection with viral hepatitis and HIV viral load suppression in HIV positive individuals.

Results suggest that people with coinfection (HIV/HBV and HIV/HCV) had more HIV viral suppression than those who were only infected with HIV (Figure 1). Individuals who were coinfected with HIV and HBV were more likely to have achieved HIV viral load suppression than individuals who were only infected with HIV (OR=1.45, 95% CI 1.32-1.59, p= .0001). A similar observation was seen for individuals who were coinfected with HIV and HCV (OR= 1.55 95% CI 1.44-1.67, p= .0001). Therefore, I rejected the null hypotheses which stated that there is no association between coinfection with viral hepatitis and decreased HIV viral load suppression in HIV positive individuals.

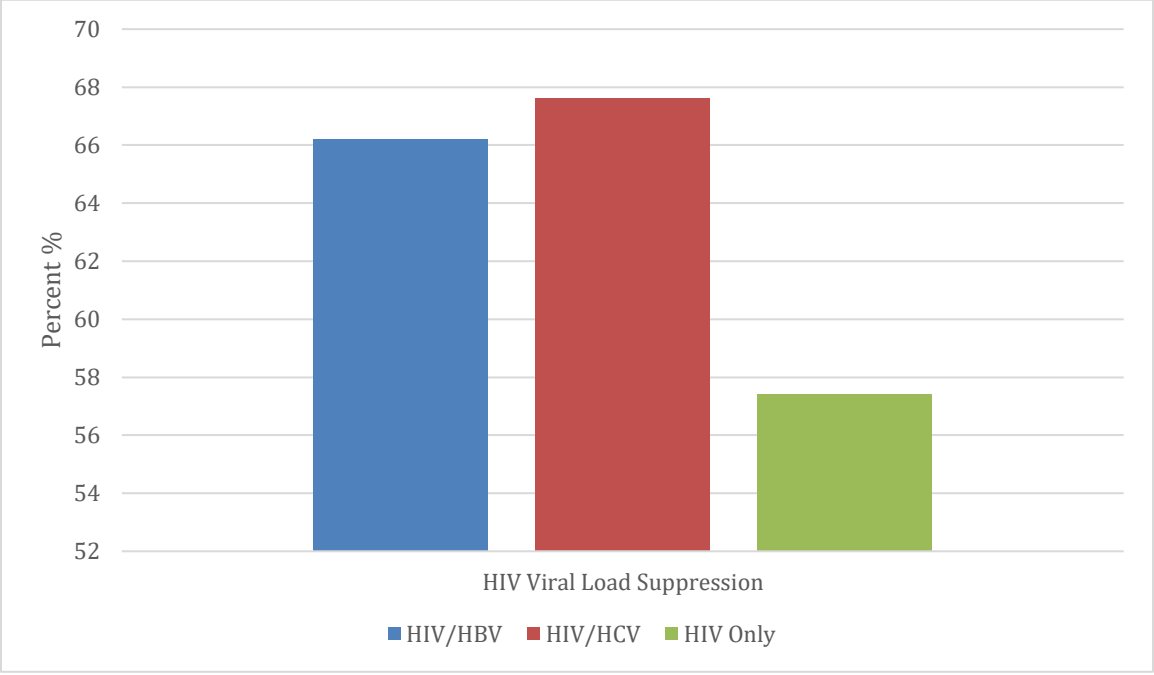

Figure 1. HIV viral load suppression by disease status.

RQ2: Does the type of viral hepatitis (HBV or HCV) impact the CD4 count of the HIV infection?

H_o2: The type of viral hepatitis (HBV or HCV) does not impact the CD4 count of the HIV infection.

H_a2: The type of viral hepatitis (HBV or HCV) impacts the CD4 count of the HIV infection.

HIV/HBV occurrences and HIV/HCV occurrences were evaluated to determine the impact of HBV and HCV on HIV CD4 cell count. HIV CD4 cell count was measured based off the AIDS defining definition, a CD4 cell count which drops below 200 cells/mL. When the three categories HIV/HBV, HIV/HCV & HIV only were compared, the percentage of AIDS defining occurrences, as of year-end December 2016, was greater in individuals coinfected with HIV/HBV and HIV/HCV than those only infected with HIV (Figure 2).

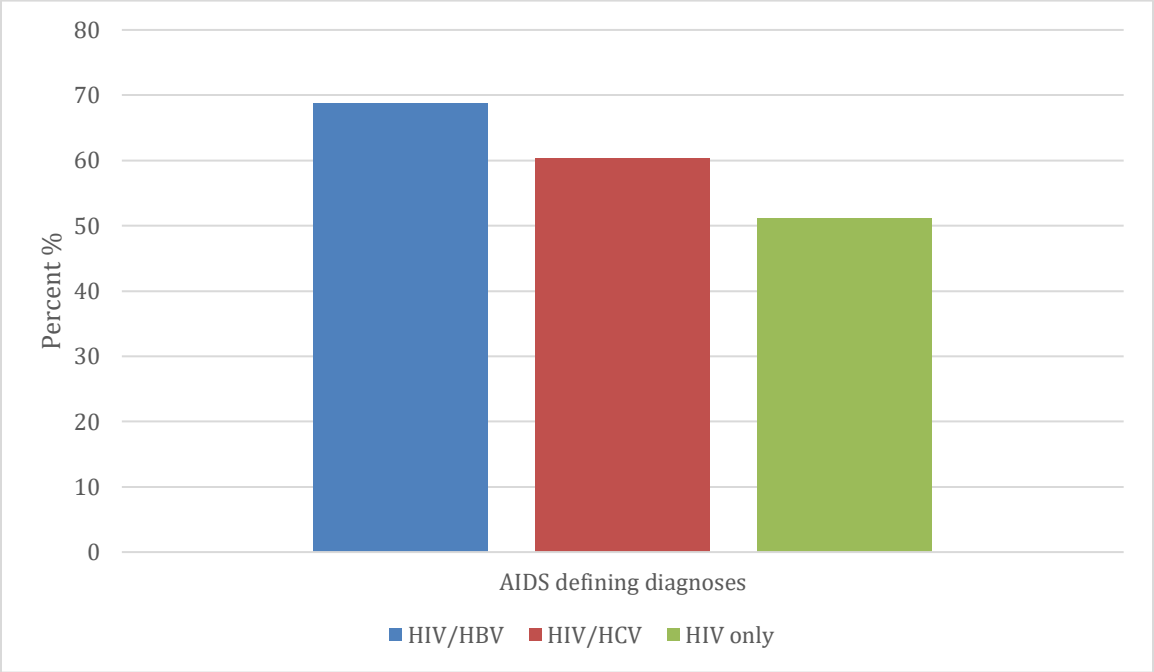

Figure 2. AIDS defining diagnoses by disease status year-end December 2016.

When the CD4 cell counts of HIV/HBV coinfected individuals were compared to the CD4 cell counts of HIV/HCV coinfected individuals using the HIV care continuum time points (3 months after HIV diagnosis, 12 months after HIV diagnosis, and current year-end), there was a significant difference in the amount of AIDS defining cases. At all time frames, HIV/HBV coinfected individuals were more likely to have low CD4 cell counts, (AIDS defining), than HIV/HCV coinfected individuals (Table 2). Therefore, the $H_0$2 null hypothesis which states that the type of viral hepatitis (HBV or HCV) does not impact the CD4 cell count of the HIV infection is rejected.

Table 2

AIDS Defining at Care Continuum Time Points

AIDS (%)	HIV/HBV	HIV/HCV	OR (95% CI)
3 Months			
χ^2= 24.8	20.63	15.32	*1.44(1.23,1.74)
12 Months			
χ^2= 31.1	24.01	17.72	*1.47(1.31,1.71)
Year-end December 2016			
χ^2= 39.1	68.71	60.31	*1.45(1.34,1.67)

Note. * $p < .001$

Summary

The study findings were presented in this chapter. This included a demographic summary of the study population. Both research questions were assessed to determine the variables significantly associated with HIV viral load suppression and HIV CD4 cell counts. In research question one, a coinfection with HBV and HCV was determined to be associated with HIV viral load suppression when compared to individuals only infected with HIV. In research question two, a coinfection with HBV was found to have a greater impact on CD4 cell counts in all time frames of the HIV care continuum than a coinfection with HCV in individuals infected with HIV. Chapter 5 provides a discussion of the findings, limitations of the study, recommendations for future research, as well as implications for social change.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

This study had two major purposes. The first was to assess whether an infection with viral hepatitis B or C hinders HIV viral suppression when present concurrently in individuals. The second was to assess which hepatitis type (HBV or HCV) had a greater impact CD4 cell counts in an HIV infected individual. In this chapter, I describe the results of the study to demonstrate that the purpose was achieved. Chapter 5 includes a discussion of the study findings, recommendations for further, and the conclusion to this study.

Discussion and Interpretation of Findings

A significant finding of this study was that persons who were either coinfected with HBV (OR= 1.45) or HCV (OR=1.55) were more likely to be HIV virally suppressed than those persons who were only infected with HIV. In a study which looked at the relationship of HIV viral load suppression and infection with HCV, persons coinfected with HCV/HIV were two times more likely to have achieved HIV viral load suppression than persons who were only infected with HIV, considering good adherence to HIV treatment (OR= 2.05, 95% CI 1.23-3.43, p= 0.006; Bani-Sadr et al., 2014). Good adherence to HIV treatment, ART, is essential in the HIV infection in that it suppresses the HIV viral load, restore or preserve immunologic function, and improves the infected person's quality of life by reducing the risk of HIV-related morbidity and mortality. The results of this study could be explained by a greater adherence to ART in the HBV and HCV coinfected population. Because persons coinfected with viral hepatitis and HIV are

more likely to have unfavorable health outcomes than persons infected with HIV only, they may be more likely to adhere to HIV therapy guidance due to the presence of more than one infection.

In the current study, persons who were coinfected with HBV (OR= 2.12) or HCV (OR= 1.46) were significantly more likely to have a CD4 cell count below 200cells/ml, AIDS defining, than persons who were infected with HIV only. AIDS defining cases were found in 66.6% of persons coinfected with HIV/HBV, 58.5 % of persons coinfected with HIV/HCV, and 50.5% of persons only infected with HIV. This finding is consistent with those of several studies (Salmon-Ceron et al., (2005); Sherman et al., (2002); Rana et al., 2019). As mentioned, HIV is defined as AIDS when an individual's CD4 cell count drops below 200 cells/ml at any time during the HIV infection. Piroth et al., (1998), Grub et al., (2014), and Van Santen et al., (2019) evaluated the progression of AIDS in persons coinfected with HBV or HCV and observed a decrease in CD4 cells by at least 60% in coinfected persons in compared to persons only infected with HIV. The current study finding may indicate that HBV and HCV negatively impact the HIV infection when concurrently present. This could also explain why persons coinfected with HIV/HBV or HIV/HCV are more likely to be HIV virally suppressed than those infected with HIV only. Persons who are defined as an AIDS case may be more likely to adhere to ART guidance due to the severity of their HIV infection. Without proper treatment adherence, persons diagnosed with AIDS typically have a survival time frame of 3 years.

Those who were HBV/HIV coinfected were significantly more likely to be AIDS defining at all time points of the HIV care continuum than HCV/HIV coinfections. This

could be a result of the high prevalence of men who have sex with men (MSM) among those who are infected with HIV. The proportion of MSM who have HIV is higher than any other group in the US. In 2016, more than half of the HIV infected population identified as being MSM (CDC, 2020). Since HBV is a common coinfection with HIV, MSM are disproportionately affected by HBV, with 15-25% of new infections occurring in this group (Falade-Nwulia et al., 2015). Eskild et al. (2012) looked at the previous and current HBV infection in HIV disease progression and found that the presence of HBV antibodies was associated with more rapid HIV disease progression. MSM who were HBV/HIV infected had a three-time risk of progression to AIDS compared to the individuals who were only infected with HIV. Also, like the current study, Japhet et al. (2016), which investigated HIV viral loads in the presence of HBV, found that although HBV/HIV persons had adequate viral suppression rates, the HBV coinfection was associated with increased progression to AIDS.

Support for the Theoretical Framework

The results of this study indicated that HBV and HCV do not hinder HIV viral load suppression in persons infected with HIV, but the two viruses are associated with more rapid progression to AIDS when a person is concurrently infected with HIV. This finding is important because it highlights how HBV and HCV can cause excess morbidity and mortality in persons infected with HIV. In the syndemic theory, the concept syndemic refers to the tendency for multiple epidemics to co-occur and interact with each other and worsen the others' effects (Singer, 2009). The syndemic theory is a valuable tool in the public health fight against HIV. The theory reveals how important focused

prevention and control measures are for each disease that plays a role in the syndemic as well as the prevention and control of the mechanisms that bring the two diseases together.

The current study provided evidence of the excess burden that HBV and HCV may cause when present with HIV. Given this evidence, there should be more efforts towards the creation of public health initiatives to address and lessen the impact of HBV and HCV in HIV infected individuals.

Limitations

The dataset included information from two databases, SENDSS (HBV and HCV diagnoses) and eHARS (for HIV diagnoses). The two databases contain information on all persons in Georgia who were tested and diagnosed with either HIV or HBV or HCV. While both hepatitis and HIV are reportable diseases under Georgia law, there was no way to guarantee that the data from diagnoses utilizing private insurance and diagnosed with HIV and/or hepatitis had been captured, so they could potentially have been missing from the databases. Additionally, people who were positive for HIV and/or hepatitis but had never been tested were not represented in the dataset. While frequencies of underreporting of HIV and hepatitis diagnoses in Georgia were not available, the GDPH did acknowledge that underreporting may be a limitation of the data available in their databases.

Another limitation included the incompleteness of data on Georgia's HIV reports. When diagnoses are reported by providers, often information regarding gender, risk factors, as well as whether the individual is on ART is missing from the report. This reduces the ability to capture a complete profile of the HIV reports in Georgia. It also

limits the ability to understand how effective ART is on HIV viral suppression. Because scientific data has shown that consistent HIV treatment is key for HIV viral suppression, Georgia can only assume that individuals who were virally suppressed were consistently taking ART.

Because hepatitis data and HIV data are housed in two separate databases, a manual match between the two databases had to be performed to identify the people with coinfections. Because the hepatitis database also experiences underreporting, there were several gaps in identifying cases for inclusion as a coinfected diagnoses. Diagnoses with hepatitis infection and undiagnosed HIV infection would not be included, and diagnoses with HIV infection and undiagnosed hepatitis infection would also not be included in the study database.

Finally, there may have been overlap with successfully treated hepatitis infection and subsequently diagnosed HIV infection. Unlike HIV data, hepatitis data are not continuously reported with updated lab data. So ultimately there is no way to identify if a case which was reported as HBV or HCV positive had been successfully treated and cleared or if the case was not treated and became a chronic hepatitis infection.

Recommendations for Future Research

Due to data limitations, the current study was unable to verify the HIV treatment status of the cases. To assess if the HIV/hepatitis coinfected individuals are more likely to be HIV virally suppressed than individuals infected with HIV only due to their likelihood

of adhering to HIV treatment, future research on ART adherence in this population is recommended.

It is likely that socioeconomic confounders existed among the individuals in the current study that predisposed them to be susceptible to a more rapid progression to AIDS. Such socioeconomic confounders could be education, employment status, occupation, income level, and presence/absence of insurance. These variables are not collected as part of GDPH disease surveillance. Future research should consider collection of such socioeconomic variables to minimize the effects of confounding due to these factors.

Recommendations of Action

Possibly one of the greatest approaches to reduce the incidence of the HBV/HCV/HIV coinfection is screening. HIV infected persons should be screened regularly for HBV and HCV coinfections and advised about prevention, especially in high-risk groups such as MSM and IDUs. Sexual transmission of HBV and HCV should be included in counseling for HIV infected persons. Increased progression rates to AIDS in the coinfected population may require earlier and advanced treatment of both infections.

Implications for Social Change

The current study has shown evidence that HIV viral suppression rates are higher in the HBV/HCV/HIV coinfected population; however, it also revealed that this population is more prone to rapid progression to AIDS. CD4 cell counts, which are used as indicators of AIDS, are relative predictors of mortality in persons infected with HIV,

regardless of how long treatment has been administered or whether a person is currently HIV virally suppressed (Brennan et al., 2013). Data from the current study could be used to support an increase in screening, diagnosis, and access to treatment to properly care for the HIV/HBV/HCV coinfection population.

Conclusion

The HBV/HCV/HIV coinfection has become increasingly common within the HIV population. The coinfection of these viruses increases the morbidity and mortality beyond those caused by either infection alone. The current study has provided insight that the HBV/HCV/HIV coinfected population is at greater risk of progression to AIDS than those only infected with HIV. This alone is a major public health threat. A better understanding of the interactions between these viruses is critical to the development of effective control and prevention of these common syndemic coinfections.

References

Aibibula, W., Cox, J., Hamelin, A. M., Moodie, E. E. M., Anema, A., Klein, M.B., Brassard, P., & Canadian Co-Infection Cohort Investigators (2018). Association between depressive symptoms, CD4 count and HIV viral suppression among HIV/HCV co-infected people. *AIDS Care 30*(5), 643-649. doi: 10.1080/09540121.2018.1431385

Aibibula, W., Cox, J., Hamelin, A. M., Moodie E. E. M., Naimi, A., McLinden, T., Klein, M. B., & Brassard, P. (2018). Food Insecurity may Lead to Incomplete HIV Viral Suppression and Less Immune Reconstitution and HIV/hepatitis C Virus-Coinfected People. *HIV Medicine. 19*(2), 123-131. doi: 10.1111/hiv.12561.

Alter, M. J. (2006). Epidemiology of viral hepatitis and HIV co-infection. *Journal of Hepatology, 44*, S6–S9. doi:10.1016j.jhep.2005.11.004.

Bani-Sadr, F., Loko, M. A., Pambrum, E., Winnock, M., Carrieri, P., Gilbert, C., Duvivier, C., Bouchaud, O., Gervais, A., Dabis, F., Salmon, D., for the ANRS CO HEPAHI Study Group (2014). Correlates of HIV sustained viral suppression in HIV/hepatitis C virus coinfected patients: Possible role of the hepatitis C virus sustained viral response. *AIDS*, 28, 1155-1160.

Bonacini, M., Louie S., Bzowej, N., and Wohl, A. R. (2004). Survival in patients with HIV infection and viral hepatitis B or C: A cohort study. *AIDS, 14*, 2039-45.

Brennan, A. T., Maskew, M., Sanne, I., & Fox, M. P. (2013). The interplay between CD4 cell count, viral load suppression and duration of antiretroviral therapy on mortality in a resource-limited setting. *Tropical Medicine & International Health*,

18(5), 619-631. doi:10.1111 tmi.12079.

Brites-Alves, C., Martins Netto, E., & Brites, C. (2015). Coinfection by hepatitis C Is strongly associated with abnormal CD4/CD8 ratio in HIV patients under stable ART in Salvador, Brazil. *Journal of Immunology Research*. doi: 10.1155/2015/174215.

Burns, N. and Grove, S. K. (2001). *The practice of nursing research, conduct, critique, and utilization.* 4th Edition, W.B. Saunders Company, Philadelphia.

Centers for Disease Control and Prevention. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention. Understanding the HIV Care Continuum (2014). Retrieved from www.cdc.gov Accessed [September 14, 2020]

Centers for Disease Control and Prevention. (2020). *HIV Surveillance Report, 2018 (Updated)*; vol.31. Retrieved from http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published May 2020. Accessed [September 14, 2020].

Ceson, A., Chan., K., Rabound, J. M., Burchell, A. N., Forrest, J. I., Klein, M. B., Loutfy, M. R., Machouf, N., Montaner, J. S., Tsoukas, C., Hogg, R. S., Cooper, C., & CANOC Collaboration. (2014). Significant differences in clinical outcomes between HIV-hepatitis C Virus coinfected individuals with and without injection drug use history. *AIDS, 2*(28), 121-7. doi:10.1097/QAD.0000000000000020

Chopra, S. (2014). Clinical manifestations and natural history of chronic hepatitis C virus. *Infection. Clinical Infectious Diseases, 55*(1), S3-S9.

Chun, H. M., Roediger, M. P., Hullsiek, K. H., Thio, C. L., Agan, B. K., Bradley, W. P., Peel, S. A., Jagodzinski, L. L., Weintrob, A. C., Ganesan, A., Wortmann, G.,

Crum-Cianflone, N. F., Maguire, J. D., Landrum, M. L., and the Infectious Disease Clinical Research Program HIV Working Group. *The Journal of Infectious Diseases, 205*, 185-93.

Cooper, C., and Cameron, D. (2014). Interpretation of undetectable hepatitis C virus RN A levels in HIV-hepatitis C virus co-infection. *AIDS*, *18*(2), 337-8.

Cox, F. E. (2001). Concominant infections, parasites and immune reponses. *Parasitology*. Suppl S23-38.

Currie, C., Zanotti, C., Morgan, A., Currie, D., Looze, M., Roberts, C., Samdal, O. (2012). Social Determinants of Health and Well-being among Young People. World Health Organization Regional Office for Europe. Retrieved from http://www.hbsc.unito.it/it/images/pdf/hbsc/prelims-part1.pdf

Darraj, M., Shafer, L. A., Chan, S., Kasper, K., Keynan, Y. (2018). Rapid CD4 decline prior to antiretroviral therapy predicts subsequent failure to reconstitute despite HIV viral suppression. *Journal of Infection and Public Health, 11*(2), 265-269.

DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. (2015). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Retrieved from http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

Douglas-Vail, M. (2015). Syndemics theory and its applications to HIV/AIDS public health interventions. *International Journal of Medical Sociology and Anthropology*, *4*(1), 81-90.

Dye C., Harries A.D., Maher D., et al. Tuberculosis. In: Jamison D.T., Feachem R.G., Makgoba M.W., et al., editors. Disease and Mortality in Sub-Saharan Africa. 2nd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 13. Retrived from: https://www.ncbi.nlm.nih.gov/books/NBK2285/

Falade-Nwulia O. et al. Incident hepatitis B virus infection in HIV-infected and HIV-uninfected men who have sex with men from pre-HAART to HAART periods: A cohort study. *Ann Intern Med* 2015 Oct 13.

Forna, F., Fitzpatrick, L., Adimora, A., McLellan-Lemal, E., Leone, P., Brooks, J., Greenberg, A. (2006). A case-control study of factors associated with HIV infection among black women. *Journal of the National Medical Association, 98*(11), 1798-1804. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2569785/

Frankfort-Nachmias, C., & Nachmias, D. (2008). Research methods in the social sciences (7th ed.). New York, NY: Worth Publishers

Friis, R.H. and Sellers, T.A. (2004). Epidemiology for Public Health Practice. Jones & Bartlett Publishers Sudbury, Massachusetts

Gardner, E. M., McLees, M. P., Steiner, J. F., Del Rio, C., & Burman, W. J. (2011). The spectrum of engagement in HIV care and its relevance to test-and treat strategies for prevention of HIV infection. *Clinical Infectious Diseases*, *52*(6), 793–800. doi:10.1093cidciq243

Gomez-Gonzalo, M., Carretero, M., Rullas, J., Lara-Pezzi, E., Aramburu, J., Berkhout, B., Alcami, J., and Lopez-Cabrera, M. (2001). The Hepatitis B Virus X Protein Induces HIV-1 Replication and Transcription in Synergy with T-cell Activation Signals: Functional Roles of NF-kappaB/NF-AT and SP1-binding Sites in the HIV-1 Long Terminal Repeat Promoter. The Journal of Biological Chemistry 276(38): 354-43 doi: 10.1074/jbc.M103020200

Greub, G., Ledergerber, B., Battegay, M. (2014). Clinical Progression, Survival, and Immune Recovery during Antiretroviral Therapy in Patients with HIV-1 and Hepatitis C virus Coinfection: The Swiss HIV Cohort Study. *Lancet 356*: 1800-05

Highleyman, L. (2003). HIV and hepatitis coinfection. *Bulletin of Experimental Treatments for AIDS.* Retrieved May 6, 2008, from http://www.thebody.com/content/art2542.html#growing.

Kaufmann G.R., Elzi L., Weber R., et al. Interruptions of cART limits CD4 T-cell recovery and increases the risk for opportunistic complications and death. Aids. 2011; 25(4): 441-451.

Kaufmann G.R., Perrin L., Pantaleo G., Opravil M., Furrer H., Telenti A., Hirschel B., Ledergerber B., Vernazza P., Bernasconi E., Rickenbach M., Egger M., Battegay M., Swiss HIV Cohort Study Group (2013). CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years. Arch Intern Med. 13; 163(18):2187-95 doi: 10.1001/archinte.163.18.2187

Kim, A., Schulze zur Wiesch, J., Kuntzen, T., Timm, J., Kaufmann, D., Duncan, J., et al. (2006). Impaired hepatitis C virus- specific T cell responses and recurrent hepatitis C virus in HIV coinfection. *PLoS Medicine, 3,* e492.

Kim, KH., Yi, J., & Lee, SH. (2015). The CD4 slope can be a predictor of immunologic recovery in advanced HIV patients: A case-control study. *Korean Journal of Internal Medicine 30* (5): 705-713. doi: 10.3904/kjim.2015.30.5.705

Klein, H (2011). Using a Syndemics Theory Approach to Studying HIV Risk Taking in a Population of Men Who Use the Internet to Find Partners for Unprotected Sex. American *Journal of Men's Health* 5 (6): 466-476. doi: 10.1177/1557988311398472

Lewden C., Chene G., Morlat P., et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. Journal of Acquired Immune Deficiency Syndrome. 2007; 46(1): 72-77.

Loutfy, M. R., Wu, W., Letchumanan, M., Bondy, L., Antoniou, T., Margolese, S., Rochon, P. A. (2013). Systematic review of HIV transmission between heterosexual serodiscordant couples where the HIV-positive partner is fully suppressed on antiretroviral therapy. PLoS ONE, 8(2), e55747. doi:10.1371/journal.pone.0055747.

Mallet, V., Vallet-Pichard, A., and Pol, S. (2011). The Impact of Human Immunodeficiency Virus on Viral Hepatitis. Liver International. doi: 10.1111/j. 1478-3231.2010.02394.x

Matthews, P.C., Geretti, A.M., Goulder, P.J.R., & Klenerman, P. (2014). Epidemiology and Impact of HIV Coinfection with Hepatitis B and Hepatitis C viruses in Sub-Saharan Africa. *Journal of Clinical Virology 61*:20-33.

Marine´-Barjoan E., Saint-Paul M.C., Pradier C., Chaillou S., Anty R., Michiels J.F., et al. Impact of antiretroviral treatment on progression of hepatic fibrosis in HIV/hepatitis C virus co-infected patients. *AIDS London England 2004*; 18:2163–2170.

Mehendale, S., Rodrigues, J., Brookmeyer, R., Gangakhedkar, R., Divekar, A., Gokhale, R., Rompalo, A. (2015). Incidence and predictors of human immunodeficiency virus type 1seroconversion in patients attending sexually transmitted disease clinics in India. *Journal of Infectious Diseases, 172*(6), 1486-1491. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7594707.

Mohd, K., Groger, J., Flaxman, AD., and Wiersma, ST. (2013). Global Epidemiology of Hepatitis C virus Infection; New Estimates of Age-Specific Antibody to HCV Seroprevalence. *Hapatology 57*: 1333-42.

Mugavero, MJ., Amico, KR., Horn, T. and Thompson, MA. (2013). The State of Engagement in HIV Care in the United States: From Cascade to Continuum to Control. *Clinical Infectious Diseases, 57*(8), 1164-71.

Moqueet, N., Infante-Rivard, C., Platt, RW., Young, J., Cooper, C., Hull, M., Walmsley, S., Klein, MB. and the Canadian Co-Infection Study Investigators (2015). Favourable IFNL3 Genotypes Are Associated with Spontaneous Clearance and Are Differentially Distributed in Aboriginals in Canadian HIV-Hepatitis C Co-

Infected Individuals. *International Journal of Molecular Sciences 16*, 6496-6512. doi: 10.3390/ijms16036496

Nayak, B. K. (2010). Understanding the relevance of sample size calculation. *Indian Journal of Ophthalmology*, *58*(6), 469–470. doi:10.4103/0301-4738.71673.

Ockenga, J., Tillman, L., Trautwein, C., Stoll, M., Manns, M., and Schmidt, R. (1997). Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *Journal of hepatology*. *27*, 18-24. Retrived from https://www.researchgate.net/publication/13968209 Hepatitis B and C in HIV-infected patients Prevalence and prognostic value.

Petruzziello A., Marigliano S., Loquercio G., Cozzolino A., Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An update of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016; 22(34): 7824-7840.

Piroth L., Duong M., Quantin C., Abrahamowicz M., Michardiere R., Aho L.S., et al. (1998) Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? AIDS 12:381–388.

Platt, L., Easterbrook, P., Gower, E., McDonald, B., Sabin, K., McGowan, C., Yanny, I., Razavi, H., and Vickerman, P (2016). Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infectious Disease 16*, 797-808

Polit, D.F. and Beck, C.T. (2012) Nursing Research: Generating and Assessing Evidence for Nursing Practice. 9th Edition, Lippincott, Williams & Wilkins, Philadelphia.

Pugliese, A., Andronico, L., Gennero , L. , Pagliano , G. , Gallo , G. , & Torre , D. (2002). Cervico - vaginal dysplasia -papillomavirus - induced and HIV - 1 infection: Role of correlated markers for prognostic evaluation. *Cell Biochemistry and Function, 20* (3), 233 – 236.

Pugliese, A., Torre, D., Saini , A. , Pagliano , G. , Gallo , G. , Pietro , G. , et al. (2002). Cytokine detection in HTV - l/ HHV - 8 co - infected subjects. *Cell Biochemistry and Function, 20* (3), 191 – 194.

Rana, U., Driedger, M., Sereda, P. *et al.* Characteristics and outcomes of antiretroviral-treated HIV-HBV co-infected patients in Canada. *BMC Infect Dis* 19**,** 982 (2019). doi: 10.1186s1287901946178.

Rao, V., Iademarco, E., Fraser, V., and Kollef, M. (1998). The impact of Comorbidity on mortality following in-hospital diagnosis of tuberculosis. *Chest, 114*(5), 1244-1252. doi:10.1378/chest.114.5.1244

Resino, S., Rivero, L., Ruiz-Mateos, E., Galan, I., Franco, JM., Munoz-Fernandez, MA., & Leal, M. (2014). Immunity in HIV-1-Infected Adults with a Previous State of Moderate-Severe Immune-Suppression and More than 500 CD4+ T Cell After Highly Active Antiretroviral Therapy. *Journal of Clinical Immunology*, Vol 24, No4.

Rockstroh J.K., Mocroft A., Soriano V., Tural C., Losso M.H., Horban A., Kirk O., Phillips A., Ledergerber B., Lundgren J., EuroSIDA Study Group (2005) Influence of hepatitis C virus infection on HIV-1 disease progression and

response to highly active antiretroviral therapy. *J Infect Dis. 2005 Sep 15; 192(6):992-1002.* doi:10.1086/432762

Salmon-Ceron, D., Lewden, C., Morlat, P., Bévilacqua, S., Jougla, E., Bonnet, F., Héripret, L., Costagliola, D., May, .T, Chêne, G., (2005) Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol, *Journal of Hepatology*, Volume 42, Issue 6, Pages 799-805.

Sarkar, J., Saha, D., Bandyopadhyaym B., Saha, B., Kedia, D., Mazumder, DNG., Chakravarty, R., & Guha, SK (2014). Baseline characteristics of HIV & hepatitis B virus (HIV/HBV) co-infected patients from Kilkata, India. *Indian Journal of Medical Research 143*: 636-642. doi:10.410309715916.187113

Selik, R. M., Mokotoff, E. D., Branson, B., Owen, S. M., Whitmore, S., & Hall, H. I. (2014). Revised surveillance case definition of HIV infection – United States, 89 2014. *Morbidity and Mortality Weekly Report*, *63*(RR03), 1–10. Retrieved from https://www.cdc.gov/mmwr/index.html

Sherman, KE., Rouster, SD., Chung, RT., Rajicic, N., Hepatitis C Virus Prevalence among Patients Infected with Human Immunodeficiency Virus: A Cross-Sectional Analysis of the US Adult AIDS Clinical Trials Group, *Clinical Infectious Diseases*, Volume 34, Issue 6, 15 March 2002, Pages 831–837, https://doi.org/10.1086/339042

Shah, S., McGowan, J., Smith C., Blum, S., & Klein, R. (2002). Comorbid conditions, treatment, and health maintenance in older persons with human

immunodeficiency virus infection in New York City. *Clinical Infectious Diseases, 35*(10), 1238-1243. doi:10.1097/00019048-200208000-00019

Singer, M and Clair, S. (2003). Syndemics and public Health: reconceptualizing disease in bio-social context. *Med Anthropol Q. Dec 1; 17 (4): 423-41*.

Singer, M. (2009). Introduction to syndemics: A systems approach to public and community health. San Francisco, CA: Jossey-Bass.

Singer , M. , Stopka , T. , Siano , C. , Springer , K. , Barton , G. , Khoshnood , K. , et al. (2000). The social geography of AIDS and hepatitis risk: Qualitative approaches for assessing local differences in sterile syringe access among injection drug users. *American Journal of Public Health, 90,* 1049 – 1056.

Skiest, D.J., Rubinstein, E., Carley, N., Gioiella, L., & Lyons R. (2006) The Importance of Comorbidity in HIV-infected patients over 55: A retrospective case-control study. The *American Journal of Medicine Vol 101* pages 605-611.

Soriano, V., Vispo, E., Labarga, P., Medrano, J., & Barreiro, P. (2010). Viral hepatitis and HIV co-infection. Antiviral Research, 85(1), 303–315.

Stekler, J., Bachmann, L., Brotman, R., Erbelding, E., Lloyd, L., Rietmeijer, H. Golden, M. (2005). Concurrent sexually transmitted infections (STIs) in sex partners of patients with selected STIs: implications for patient-delivered partner therapy. *Clinical Infectious Diseases, 4*(6), 787-793. doi:10.1086/428043

Struwig, F. W., & Stead, G. B. (2001). *Planning, designing and reporting research*. Cape Town: Pearson Education South Africa.

Tarwater P.M., Margolick J.B., Jin J., et al. Increase and plateau of CD4 T-cell counts in the 3(1/2) years after initiation of potent antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2001; 27(2): 168-175.

Taylor, L.E., Swan, T., and Mayer, K.H. (2012). HIV Coinfection with Hepatitis C Virus: Evolving Epidemiology and Treatment Paradigms. *Clinical Infectious Diseases* 55 (S1): S33-42.

Thomas D.L., Astemborski J., Rai R.M., et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. *Jama*. 2000; 284(4): 450-456.

UNAIDS (2020, March 03). Global HIV & AIDS statistics - 2020 fact sheet. Retrieved September 15, 2020, from https://www.unaids.org/en/resources/fact-sheet

US Department of Health and Human Services (2013). Action Plan for the Prevention, Care, and Treatment of Viral Hepatitis: Updated 2014-2016

Vellozzi, C., Buchacz, K., Baker, R., Spradling, P.R., Richardson, J., Moorman, A., Tedaldi, E., Durham, M., Ward, J., Brooks, J.T. & the HOPS Investigators. (2011). Treatment of hepatitis C virus (HCV) infection in patients coinfected with HIV in the HIV outpatient study (HOPS). *Journal of Viral Hepatitis 18:* 316-324.

Van Santen, D.K., Van Der H.J.J., Touloumi, G., Panatazis, N., Muga, R., Gunsenheimer-Bartmeyer, B., Gill, M.J., Sanders, E., Kelleher, A., Zangerle, R., Porter, K., Prins, M., Geskus, R.B., and the CASCADE Colloboration within EuroCoord. (2019). Effect of incident hepatitis C infection on CD4+ cell count and HIV RNA trajectories based on a multinational HIV seroconversion cohort.

WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, recommendations for public health approach. Geneva: WHO; 2013 http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. Accessed May 13th, 2018.

Wilson, P.A., Nanin, J., Amesty, S., Wallace, S., Cherenack, E.M., and Fullilove, R. (2014). Using Syndemic Theory to Understand Vulnerability to HIV Infection among Black and Latino Men in New York City. Journal of Urban Health: Bullentin of the New York Academy of Medicine, Vol. 91, No. 5 doi: 10.1007/s11524-014-9895-2

Yehia, B. R., French, B., Fleishman, J. A., Metlay, J. P., Berry, S. A., Korthuis, P. T., … Gebo, K. A. (2014). Retention in care is more strongly associated with viral suppression in HIV-infected patients with lower versus higher CD4 counts: *JAIDS Journal of Acquired Immune Deficiency Syndromes*,*65*(3), 333–339. doi:10.1097/QAI.0000000000000023

Yu, C., Chen, Y.C., Hu, C.C., Chien, C.H., Yeh, C.T., Lin, C.L., & Chien, R.N. (2018). Higher Hepatitis C virus-viral loads and complex sexual partners in hepatitis C virus-human immunodeficiency virus coinfected injection drug users: A case-control study. *Advances in Digestive Medicine 6*: 21-27.

Zhou, H., Hong, X., Jiang, S., Dong, H., Xu, X., & Xu, X. (2009). Analyses of associations between three positionally cloned asthma candidate genes and asthma or asthma-related phenotypes in a Chinese population. *BMC Medical*

Genetics, *10*, 123. doi: org10.11861471-2350-10-123.