THE EPIDEMIOLOGY OF HEPATITIS B AND C CO-INFECTION AMONG HIV INFECTED INDIVIDUALS IN MICHIGAN

By

Zahid Ahmad Butt

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSPHY

Epidemiology

2011

ABSTRACT

THE EPIDEMIOLOGY OF HEPATITIS B AND C CO-INFECTION AMONG HIV INFECTED INDIVIDUALS IN MICHIGAN

By

Zahid Ahmad Butt

Background: AIDS (Acquired immune deficiency syndrome) is a global public health issue affecting millions of individuals. HIV (Human immunodeficiency virus) infected individuals commonly acquire hepatitis B and C viral infections through shared transmission routes. In order to evaluate the effect of hepatitis co-infection on HIV infected individual, the objectives of our study were ; 1) to investigate the geographic distribution of HIV-hepatitis co-infection, 2) to estimate the prevalence of hepatitis co-infection and associated factors, and 3) to estimate the mortality and identify factors associated with mortality; among HIV-hepatitis co-infected individuals residing in Michigan during the years 2006 to 2009.

Methods : We conducted a retrospective cohort study from January 1, 2006 to December 31, 2009 using data from the Michigan Department of Community Health. HIV infected individuals were matched to hepatitis B and C cases for the same time period by establishing a record linkage. Spatial, logistic and survival regression analyses were performed on the data to evaluate the objectives of the study.

Results : The Bernoulli cluster analysis of HIV-hepatitis B or C co-infection identified a most likely cluster with a significant relative risk (RR = 1.75) in the northeast Lower and Upper

peninsulas. Poisson cluster analysis identified a most likely cluster with a significant RR of 2.93 in the northwest Lower Peninsula. Multivariable logistic regression analysis revealed a significant association between co-infection and being male and of Black race (Odds Ratio (OR) =2.0, 95% Confidence Interval (CI): 1.2-3.6) and male and of Other race (OR=3.5, 95% CI: 1.7-7.0) as compared to White race. Co-infection was associated with risk categories of blood products, IDU (Injecting drug user) and MSM/IDU (Males having sex with males) and two interactions; sex and current HIV status and current HIV status and age at HIV diagnosis. The final Cox regression model indicated a decreased survival; among individuals of Other (Hazards Ratio (HR) =2.2, 95% CI: 1.4-3.2) and Black (HR=1.3, 95% CI: 1.1-1.6) races compared to White race, and IDU, MSM/IDU, individuals with undetermined risk, heterosexual practices, and older age at HIV diagnosis in addition to an interaction between current HIV status and co-infection status.

Conclusions: This study identified localized clusters of HIV-hepatitis co-infection in counties outside of Michigan's urban areas where HIV is more prevalent. Overlapping counties indicate 'hotspots' for co-infection in the Upper Peninsula and upper portion of the Lower Peninsula. The relatively high prevalence of co-infections and mortality suggests the existence of a continuing public health problem. Our study aimed to address the changing epidemiology of HIV-hepatitis co-infections in order to implement preventive measures and interventions to reduce prevalence and mortality among the HIV infected individuals.

DEDICATION

To

my mother, Safia, my wife, Faiza, and daughter, Minha

ACKNOWLEDGEMENTS

I am grateful and indebted to my guidance committee, Dr. Mahdi Saeed, Dr. Melinda Wilkins, Dr. Joseph Gardiner and Dr. David Todem, for their continuous and unfailing support, help and guidance during various aspects of my research and writing process of my dissertation.

I am greatly indebted to my advisor and mentor, Dr. Mahdi Saeed who is a wonderful professor, and has guided me through every step of my graduate studies. Your support, time, guidance and faith in me has directed and kept me on the right path towards the completion of my project and achievement of my degree.

I gratefully acknowledge the staff of Communicable Disease Division, Michigan Department of Community Health for their support. In particular, I would like to thank Elizabeth Hamilton (HIV/AIDS Epidemiology Specialist) and Dr. Kim Kirkey (Adult Viral Hepatitis Epidemiologist) for providing study related logistical support as well as important insights for the project at MDCH.

I am also thankful to The Graduate School, the College of Human Medicine, and the Department of Epidemiology for providing financial support in the form of a dissertation completion fellowship.

I am grateful to the United States Educational Foundation in Pakistan, the Institute for International Education and the Fulbright program for providing financial support in the form of a Fulbright scholarship and enabling me to study in the United States and complete my PhD degree. I am also grateful to Ms. Mary Gebbia-Portice, our international student advisor, who was always there to lend a helping hand and listen to my problems over the years as a graduate student.

Finally, I would also like to thank my family, the foundation of who I am, for always being there for me, keeping me in their prayers and my faith strong, and their encouragements for me.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ASD	Adult and Adolescent Spectrum of Disease
HIV	Human immunodeficiency virus
CI	Confidence Interval
CDC	Centers for Disease Control and Prevention
eHARS	enhanced HIV/AIDS Reporting System
HAART	Highly Active Anti-retroviral Therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IDU	Injecting Drug User
LHDs	Local health departments
MDCH	Michigan Department of Community Health
MDSS	Michigan Disease Surveillance System
OR	Odds Ratio
US	United States
WHO	World Health Organization

CHAPTER 1.

BACKGROUND AND OBJECTIVES

1.1 Background

Acquired immune deficiency syndrome (AIDS) is a continuing global public health problem affecting millions of individuals. Globally, by the end of 2009; 33.3 million people were living with (Human immunodeficiency virus (HIV) infection, of these, 30.8 million were adults including 15.9 million women and 14.9 million men. Two and a half million were children under the age of 15 years. In, 2009, 2.6 million individuals were newly infected with AIDS (1). Among these, 2.2 million were adults whereas 370,000 were children under the age of 15 years. About 1.8 million deaths were reported in 2009; 1.6 million among adults and 260,000 in children under 15 years of age (1).

In the United States (US) during 2006, 35,314 new cases of HIV/AIDS in adults, adolescents, and children were diagnosed in the 33 states with long-term, confidential name-based HIV reporting (2). In another study in 2008, serum specimens from newly diagnosed HIV patients during 2006 residing in 22 states in the US were tested with the BED HIV-1 capture enzyme immunoassay to categorize infections as recent or long-standing. According to extrapolations from the data, the estimated number of new infections in the US during 2006, was 56,300 while the estimated incidence rate was 22.8 per 100,000 population (3). By the end of 2009, an estimated 1.2 million people were living with AIDS in the US while approximately 17,000 AIDS related deaths were reported in the same year (4). An estimated 54,000 adults and children were newly diagnosed with HIV in 2009 (1). According to the Michigan Department of

Community Health (MDCH), there are an estimated 19,500 people currently living with HIV/AIDS in Michigan, of these, 14,895 were reported by January 2011 (5).

Viral hepatitis is caused by an infection with any of the five distinct hepatitis viruses (6). The three most commonly identified in the US are hepatitis A, hepatitis B and hepatitis C viruses. However, in terms of morbidity and mortality, hepatitis B and hepatitis C viruses are the most important. Around 2 billion people worldwide have been infected with the hepatitis B virus whereas about 350 million currently have chronic infection. About 600,000 persons die each year from acute or chronic sequelae of hepatitis B. Hepatitis B virus (HBV) is endemic in China and other parts of Asia. The majority of infections with HBV occur during childhood. In these areas, 8% to 10% of the adults suffer from chronic infection with HBV. Chronic infection rates are also high in the Amazon region and the southern parts of eastern and central Europe. Approximately 2% to 5% of the general population is chronically infected in the Middle East and Indian sub-continent. In comparison, less than 1% of the population in Western Europe and North America suffers from chronic infection with HBV (7).

According to the World Health Organization (WHO), there are about 180 million people infected with hepatitis C virus (HCV) amounting to 3% of the world's population. Among these, 130 million are chronic HCV carriers at risk of developing liver cirrhosis and or liver cancer. Approximately, 3 to 4 million individuals are newly infected each year, 70% of whom will develop chronic hepatitis. HCV is implicated in 50–76% of all liver cancer cases, and two thirds of all liver transplants in the developed world. HCV prevalence is low (< 1%) in Australia, Canada and northern Europe. It is about 1% in countries such as the US and most of Europe, and

high (>2%) in many countries in Africa, Latin America and Central and South-Eastern Asia. The prevalence in these countries ranges from 5% to 10% (8).

The Centers for Disease Control (CDC) reported 4,519 cases of acute hepatitis B in the US in 2007. The overall incidence of reported acute hepatitis B was 1.5 per 100,000 population. As many HBV infections are either asymptomatic or never reported, the actual number of new infections is estimated to be nearly tenfold higher or approximately 43,000 persons in the US in 2007. The incidence is highest among adults; particularly males aged 25 to 44 years (9). In the US, there are an estimated 800,000 to 1.4 million persons suffering from chronic HBV infection. In Michigan, there were 142 cases of acute HBV in 2008 while the number of confirmed cases of chronic hepatitis B was 1,340 in the same year (10, 11).

During 2007, 849 cases of confirmed acute hepatitis C were reported in the US. However, the CDC estimates that approximately 17,000 new HCV infections occurred that year, taking into account asymptomatic infection and underreporting. As individuals newly infected with HCV are usually asymptomatic, so acute hepatitis C is rarely identified or reported. There are approximately 3.2 million persons in the US with chronic HCV infection (12). In 2008, there were 125 cases of acute hepatitis C and 7,167 confirmed cases of chronic hepatitis C in the state of Michigan (13, 14).

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) co-infections are commonly acquired by individuals infected with HIV/AIDS because of shared transmission routes. In sub-Saharan Africa, a review of 60 studies on HIV-hepatitis co-infection reported prevalence rates of

15% for mean HBsAg and 7% for mean anti-HCV (15). The reported prevalence for HIV-HCV co-infection was 4.4% in Brazil (16), 7.8% in Thailand (17), 16% in Denmark (18), and 24.3% in France (19). For HIV-HBV co-infection, the reported prevalence was 6% in Denmark (20), 7% in France (19) and, 8.7% in Thailand (17). The reported prevalence for HIV-HBV-HCV co-infection was 1.6% in France (19) whereas for Brazil, it was 4.4% (21). A study on IDUs (Injecting Drug Users) along the China-Myanmar border region reported a HIV-HBV co-infection prevalence of 20.1% among Chinese IDU's and 11.3% among Burmese IDUs (22). In the same study, the prevalence of HIV-HCV co-infection was 31.8% among Chinese IDUs and 23.9% among Burmese IDUs whereas HIV-HBV-HCV co-infection prevalence was 19.1% among Chinese IDUs and 10.4% among Burmese IDUs.

In Michigan, the Adult and Adolescent Spectrum of Disease (ASD) surveillance project collected data from the medical records of HIV patients at two major medical centers in Detroit, between 1990 and 2004. Based on this surveillance project, hepatitis C was the most common hepatitis co-infection among HIV-infected individuals. Out of the 1,790 individuals in care and in ASD in 2001-2003, 353 (20 %) were diagnosed with HCV infection at some time during ASD follow-up, while 207 (12 %) were diagnosed with hepatitis B (HBV) infection (23).

Immunologically, it has been observed that after HIV seroconversion, there is an increase in HCV RNA load which remains at a higher level as compared to HCV only infected individuals during the course of chronic infection. A study on hemophiliacs reported a 58 fold increase of HCV RNA load in HIV and HCV co-infected patients as compared to a 3 fold increase in HIV negative patients (24). A Dutch study on IDUs observed that HCV RNA levels

increased significantly immediately after HIV seroconversion (25). In addition, the study found an inverse association between CD4 cell counts and HCV RNA levels. In another study, each 10 fold increase in HCV viral load was found to be associated with an increased risk of clinical progression to AIDS and AIDS related mortality (26). HIV infection also modifies the natural history of HBV infection in HIV and hepatitis B co-infected individuals by increasing the proportion of HBsAg carriers (27). Furthermore, HIV and hepatitis B co-infected individuals have elevated HBV DNA polymerase activity, lower alanine aminotransferase levels, lower rate of loss of serum HbeAg, and lower serum albumin levels. The lower rate of loss of serum HbeAg indicates that HIV-HBV co-infection may lengthen the period of infectivity (27). Another important finding in co-infected patients is a higher rate of HBV replication due to HIV mediated immune impairment concomitant with less severe liver damage and less effective immune response to HBV (28). Additionally, the quality of the HBV specific T cell response is compromised in the HIV and hepatitis B co-infected individuals (29).

With the recent decline in opportunistic infections due to advances in anti-retroviral therapy (30), HBV and HCV co-infections have emerged as major contributors to morbidity and mortality among HIV/AIDS patients. There is also evidence to suggest that HCV infection may negatively affect the course of HIV infection leading to a rapid progression to AIDS and death (31). However, the association between HBV or HCV co-infection and increased mortality has not been consistently identified. Several studies in different settings have shown no association between hepatitis co-infection and mortality. Studies conducted in the US (32) and South Africa (33) did not show an association between co-infection and mortality. However, other studies

which did not identify an association between HIV-HCV infection and mortality did report an association between AIDS and mortality (34, 35).

Although these studies did not identify an association between HIV-hepatitis co-infection and mortality, other studies have observed an increased liver related mortality with co-infection. HCV associated end-stage liver disease is now a predominant cause of death among people living with HIV/AIDS (36, 37, 38). Additionally, HIV-HBV co-infected patients are at increased risk for developing chronic infection which can lead to an elevated risk for liver-related morbidity and mortality (39). Prospective cohort studies conducted on HIV and hepatitis (HBV or HCV) co-infection have identified a significant association between co-infection and liver related mortality (40-43). However, among these, two studies also reported an increased risk for all-cause mortality and co-infection (40, 42).

Several studies focusing upon hepatitis B and C co- infections have identified an association between co-infection and mortality which is not liver related. A clinic- based study on HIV infected patients reported a decreased survival in AIDS patients co-infected with HBV or HCV (44). The Swiss HIV cohort study reported an increased progression to new AIDS defining event and death among HIV-1 infected patients with HCV co-infection (45). Another prospective cohort study identified HIV-HCV co-infection among IDUs as a significant contributor to mortality in the HAART era (46). HIV and chronic hepatitis B co-infected patients were also found to have an increased risk of death after initiation of Highly Active Anti-retroviral Therapy HAART (47). Another cohort study on HIV infected patients reported decreased durations of survival from time to diagnosis of HIV infection and AIDS among HIV-HCV co-infected

patients (48). A cohort study on HIV-HCV co-infected veterans observed an increased risk of death due to co-infection even after controlling for exposure to HAART and response to HAART (49). The Danish cohort study, found a significantly increased overall mortality in addition to mortality from liver related and AIDS related causes in HIV-HCV co-infected (18) and HIV-HBV co-infected patients on HAART (20). A study on mortality related to chronic hepatitis B and C in France also observed an increased frequency of deaths among HIV/HBV and HIV/HCV co-infected individuals (50). HIV and chronic hepatitis B co-infected patients in a multicenter cohort study showed an increased mortality which was mainly due to liver disease in spite of being on HAART, in addition to an increased risk of AIDS related death (51). A meta-analysis of 11 studies on HIV-HBV co-infection reported a significant effect of co-infection on overall mortality. This increased rate of death among HBV co-infected individuals was present in studies conducted before and after starting HAART (52). Another meta-analysis of studies on HIV-HCV co-infection found an increased risk for overall mortality among HIV-HCV co-infected individuals during the HAART era (53).

The majority of studies on HIV infection focus on either the prevalence or mortality experience of infected individuals and often do not take into consideration the spatial variation in disease or risk factors for HIV/AIDS to identify high-risk areas for public health prevention and health care intervention programs. Studies of hepatitis, HIV and other sexually transmitted diseases have looked either at the spatial clustering of HIV infection by applying scan statistics such as the Bernoulli (54) and Poisson (55) methods or sexually transmitted infections by applying the Bernoulli (56) method in SaTScan™ (57). Other studies have looked at the spatial clustering of gonorrhea cases using *k*-function techniques and SaTScan's Poisson model (58, 59)

and hepatitis C using spatial filtering and SaTScan's Poisson models (60) in urban and rural settings. One of the challenges of cluster analytical techniques for relatively rare diseases such as HIV and hepatitis are that large geographic areas with low population density can overshadow the geographical heterogeneity of the disease(s), which might lead to misinterpretation of the underlying geographic distribution (54). In this respect, the spatial scan statistic used in SaTScan™ (57) has been widely applied to identify disease clusters in a variety of geographic settings, scales and for rare events (54, 61-66). The spatial scan statistic also has good power to detect localized clusters and can also account for multiple testing in the data (67). Therefore in addition to the study of prevalence and mortality among HIV-hepatitis co-infected individuals, spatial analysis of HIV data can serve as an important tool to identify areas with high prevalence of HIV-hepatitis co-infection.

1.2 Rationale

As co-infection with HBV and HCV are associated with an increased morbidity and mortality among HIV/AIDS patients, it is essential that the magnitude of the co-infection and its concomitant risk factors are studied among the HIV/AIDS population in the state of Michigan. This would enable better prevention and control of these infections among the HIV/AIDS infected individuals.

However, it is also important to study the impact of this co-infection on HIV infected individuals in this population which can be measured by the mortality among these individuals. Previous studies conducted on mortality among HIV infected individuals have been inconsistent in identifying hepatitis co-infection as a major contributor to mortality with most studies having

smaller sample sizes (33, 34, 35, 37,47, 48, 51), shorter duration of follow-up (33) and focusing mainly on hospital or clinic based populations (32, 34, 48). Therefore, keeping this in view, another aim of our study was to estimate the mortality and identify the factors associated with mortality among HIV-hepatitis co-infected individuals in Michigan. The findings from this aspect of the study can be used for planning and implementing interventions to reduce mortality among the vulnerable population of HIV infected individuals. In addition, it is also important to know the geography of HIV-hepatitis co-infection which would provide valuable knowledge for public health epidemiologists, programmatic and policymakers and health managers of where to plan and implement interventions and allocate resources.

Therefore, our study is an effort to look at different aspects of the influence of HBV and HCV viruses on HIV infected individuals with emphasis on the geographic distribution, prevalence and mortality among the HIV-hepatitis co-infected individuals. In an attempt to encompass these three different aspects of HIV-hepatitis co-infection, we planned and conducted a retrospective cohort study in Michigan from January 1, 2006 to December 31, 2009 utilizing data from the Michigan Department of Community Health (MDCH). For this purpose, HIV/AIDS infected individuals of all age groups residing in the state of Michigan were matched to hepatitis B and hepatitis C cases from the same time period. The HIV/AIDS data were obtained from the enhanced HIV/AIDS Reporting System (eHARS) maintained by the HIV/STD/VH/TB Epidemiology Section whereas the hepatitis B and C data were obtained from the Michigan Disease Surveillance System (MDSS) maintained by the Surveillance and Infectious Disease Epidemiology Section of the MDCH for the study period (68). These datasets were linked together to enable matching of hepatitis B and C and HIV/AIDS cases to the same

individual. To enable the different analyses, the data were edited according to the specifications required for each analysis.

The primary objectives of our study, therefore, were threefold focusing on the geographic distribution, prevalence and survival of the HIV-hepatitis co-infected individuals.

1.3 Objectives

GIS (Spatial) study

1. To investigate the geographic distribution of HIV-hepatitis co-infection among HIV infected individuals residing in the state of Michigan during the years 2006 to 2009.

Prevalence study

1. To estimate the prevalence of hepatitis co-infection among HIV infected individuals residing in the state of Michigan during the years 2006 to 2009.

2. To identify the factors associated with hepatitis co-infection among HIV infected individuals residing in the state of Michigan during the same time period.

Survival study

1. To estimate mortality and identify the factors associated with mortality among HIV-hepatitis co-infected individuals in the state of Michigan during the years 2006 to 2009.

CHAPTER 2.

SPATIAL EPIDEMIOLOGY OF HIV-HEPATITIS CO-INFECTION IN THE STATE OF MICHIGAN

2.1 Abstract

Background

Acquired immunodeficiency syndrome (AIDS) is a continuing global public health threat affecting millions of individuals. In 2009, 33.3 million people worldwide were living with HIV infection. HIV infected individuals are at an increased risk of acquiring hepatitis B and hepatitis C viral infections because of shared transmission routes. The purpose of this study is to investigate the geography of HIV and HIV-hepatitis co-infection in Michigan.

Methods

Retrospective data on HIV infected individuals were matched to all hepatitis B and C cases in Michigan's counties during the period of January 1, 2006 through December 31, 2009. A prevalence rate map of HIV infection was created and spatial clusters of HIV-hepatitis B or C co-infection were detected using SaTScan's Bernoulli and discrete Poisson models.

Results

The Bernoulli cluster analysis of HIV-hepatitis B or C co-infection identified a most likely cluster with a significant relative risk (RR) = 1.75 in the northeast lower and upper peninsulas. The Poisson cluster analysis identified a most likely cluster with a significant RR of 2.93 controlling for sex, age and HIV vs. AIDS status in the northwest lower peninsula of the state.

Conclusions

This study identified localized clusters of HIV-hepatitis B or C co-infection in counties outside of Michigan's urban areas where HIV is more highly prevalent. Overlapping counties identified by both methods indicate 'hotspots' for HIV-hepatitis co-infection in counties of the Upper Peninsula and upper portion of the Lower Peninsula. The findings from this study may be used to guide future public health policy and health care interventions in these areas.

2.2 Introduction

In 2009, 33.3 million people worldwide were living with HIV (Human immunodeficiency virus) (1). Of these, approximately 2.6 million (7.8%) individuals had newly acquired HIV infections (1). In 2009, an estimated 1.2 million people were living with AIDS in the United States with about 17,000 AIDS-related deaths (4). According to the Michigan Department of Community Health (MDCH), there are an estimated 19,500 people currently living with HIV/AIDS in the state, and of these, 14,895 were reported in the surveillance system through January 2011 (5). These figures demonstrate the continued need to monitor and implement HIV/AIDS public health prevention and health care intervention strategies in Michigan and the United States.

Individuals infected with HIV are at an increased risk of developing opportunistic infections, because of their immunodeficiency. In addition to opportunistic infections, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are common in individuals infected with HIV/AIDS because of the shared infectious disease transmission routes. In sub-Saharan Africa, a review of 60 studies on HIV and hepatitis co-infection reported prevalence rates of 15.0% for mean HBsAg and 7.0% for mean anti-HCV in HIV positive populations (15). In Brazil, studies from 2000 to 2007 on HIV and hepatitis co-infection reported a prevalence of 4.4% for HIV and HCV+ HBV co-infection (21) and 4.4% for HIV and HCV co-infection (16). Prospective cohort studies conducted in Denmark estimated a prevalence of 6.0% for HIV and chronic HBV co-infection (20) and 16.0% for HIV and HCV co-infection (18). Two studies conducted in the United States on HIV and hepatitis co-infection reported a prevalence of 7.6% during 1998 to 2001 (69) and 11.0% for HIV and chronic HBV from 1998 to 2008 (70).

The majority of HIV studies focus on the prevalence or mortality experience of infected individuals and often do not take into account the spatial variation in disease or risk factors for HIV/AIDS to identify high-risk areas for public health prevention and health care intervention programs. Studies of hepatitis, HIV and other sexually transmitted diseases s have looked either at the spatial clustering of HIV infection by applying scan statistics such as the Bernoulli (54) and Poisson (55) methods or sexually transmitted infections by applying the Bernoulli (56) method in SaTScan™ (57). Other studies have looked at the spatial clustering of gonorrhea cases using *k*-function techniques and SaTScan's Poisson model (58, 59) and hepatitis C using spatial filtering and SaTScan's Poisson models (60) in urban and rural settings. One of the challenges of cluster analytical techniques for relatively rare diseases such as HIV and hepatitis are that large geographic areas with low population density can overshadow the geographical heterogeneity of the disease(s), which might lead to misinterpretation of the underlying geographic distribution (54). In this respect, the spatial scan statistic used in SaTScan™ (57) has been widely applied to identify disease clusters in a variety of geographic settings, scales and for rare events (54, 61-66). The spatial scan statistic also has good power to detect localized clusters and can also account for multiple testing in the data (67).

The Adult and Adolescent Spectrum of Disease (ASD) surveillance project focusing on HIV and hepatitis co-infection in Michigan reported that 20.0% of HIV infected individuals were also diagnosed with HCV infection, whereas 12.0% of HIV infected persons were diagnosed with HBV infection (23). However, no study has looked at the spatial structure of hepatitis B and C co-infection among HIV infected individuals using spatial scan statistics. Therefore, the purpose of this study is to evaluate the likelihood of hepatitis clusters among HIV-infected

individuals in Michigan. Identification of the spatial patterns of HIV and hepatitis co-infection in Michigan would provide valuable knowledge for public health epidemiologists, programmatic and policymakers and health managers of where to plan and implement interventions and allocate resources. To the best of our knowledge, this is the first study to investigate the geographic distribution of HIV and hepatitis co-infection among HIV/AIDS infected individuals in the state of Michigan using data from a statewide population based surveillance system.

2.3 Methods

Study Area

The study was conducted in the state of Michigan at the county level (n=83). Michigan is the 11th largest state of the 50 states with an area of 96,810 square miles (mi^2). Out of this area, 56,809 mi^2 are land areas whereas 40,001 mi^2 are covered by water (71). Michigan is 490 miles long and 240 miles wide and comprises of two separate peninsulas into the Great Lakes. The Upper Peninsula is bounded on the north by Lake Superior, on the south by Lake Michigan and Lake Huron, and on the west by Wisconsin. The Lower Peninsula is bounded on the west by Lake Michigan, on the east by Lake Huron and Lake Erie, and on the south by Indiana and Ohio. The state has a population of 9,883,640 residents according to the 2010 census (72) most of which reside in urban areas in the lower half of Michigan's Lower Peninsula.

Data

For this study, HIV/AIDS infected individuals of all ages residing in Michigan's counties were included and matched with all hepatitis B virus (HBV) and hepatitis C virus (HCV) cases in the period of January 1, 2006 through December 31, 2009 using a common identifier. Data were

retrospectively obtained for the study period from the enhanced HIV/AIDS Reporting System (eHARS) maintained by the HIV/STD/VH/TB Epidemiology Section and the Michigan Disease Surveillance System (MDSS), which is the statewide communicable disease reporting system maintained by the Surveillance and Infectious Disease Epidemiology Section of MDCH.

Ethical approval was obtained from the Institutional Review Board (IRB) at Michigan State University and MDCH. An employee of the HIV/STD/VH/TB Epidemiology Section performed the record linkage to ensure confidentiality and privacy of the participants. De-identification of the study participant data was done according to HIPAA guidelines on public health information. In addition, no participants were interviewed or contacted. For this study, HIV/AIDS cases were defined using the Center for Disease Control's (CDC) 1993 revised classification system of HIV (73). The outcome variable was 'Co-infection' which was recoded into 'co-infected' = 1 and 'not co-infected' = 0. An HIV/AIDS individual was categorized as co-infected if he or she had been concomitantly infected with confirmed Hepatitis B or Hepatitis C virus (acute and chronic) based on the CDC case definition (74-78) and residing in the state of Michigan during the period 2006 through 2009. Any HIV/AIDS infected individuals who had a diagnosis of acute or chronic hepatitis B or C before 2006 were not included in this study. Additionally, HIV/AIDS positive individuals infected with both hepatitis B and C were excluded from the analysis, as they constituted a very small proportion (< 1%) of the cohort. The characteristics of HIV infected and co-infected individuals utilized in this research included sex, race and current HIV status (status through December 2009). The variable sex was categorized as dichotomous, male = 1 and female = 2; race was classified into White = 1, Black = 2,

Hispanic = 3 and Other = 4; and current HIV status was dichotomized into HIV without AIDS = 1 and AIDS = 2.

Methodology

A map of HIV prevalence by county was created for the state by using information on HIV cases from 2006 to 2009 based upon the administrative boundaries of MDCH using information from MDCH (5). Descriptive analysis of the HIV and hepatitis B or C data were performed in SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). The co-infected and not co-infected individuals were compared using the Pearson chi-square statistic or t-test depending on the type of variable analyzed. Spatial cluster analyses were performed using SaTScan version 9.0 (57) and Bernoulli and discrete Poisson methods (79, 80) were implemented. Scan statistics are used for the detection and evaluation of clusters by applying a scanning window across the study area (i.e., the centroids of each county across Michigan). Within the window at each location, the number of observed and expected cases of HIV co-infected individuals is calculated and a likelihood function is estimated depending on the method used (81). The window with the maximum likelihood is the most likely cluster, that is, the cluster that is least likely to have occurred by chance. Secondary clusters are also identified and ordered by the program according to the likelihood ratio test statistic. The Bernoulli model uses cases (HIV-HCV or HIV-HBV co-infection) and controls (HIV only) at each location to determine if there is significant clustering of HIV-co-infection as compared to HIV only in relation to location (81). The discrete Poisson model assumes that the number of cases in each location is Poisson distributed. The null hypothesis for the model is that the expected number of cases in each scanning window is proportional to its population size (81). For both models, the significance of the likelihood ratio was tested using 999 Monte Carlo simulations. In this study, a

circular window was used and the maximum circle size included up to 50% of the population being analyzed. A significant p-value was considered to be less than 0.05. In addition, for each probability model, a purely spatial analysis was performed.

The data for both the Bernoulli and Poisson methods were aggregated at the county level using SAS version 9.2. For the Bernoulli model the files were then exported to an excel file and the case (n=578) and control (n=13,358) files were created for each county location. Counties that had missing data for cases or controls were removed from the input dataset. In the situation where both cases and controls were missing, no changes were made to the dataset (81). If there were very few cases as compared to controls (< 10%) a discrete Poisson model was used because it was a very good approximation for the Bernoulli model (81). In this study, there were fewer cases as compared to controls (< 5%), therefore, a Poisson discrete analysis was performed in addition to the Bernoulli analysis. For Poisson discrete analysis, a case and a population file for each location was created with the addition of the covariates sex, race, and current HIV status. For both Bernoulli and discrete Poisson models a coordinates file containing the latitude and longitude at the centroid of each county was used to define the locations for analysis.

2.3 Results

Table 2.1 shows that a total of 13,936 individuals were reported to be infected with HIV/AIDS during the study period. The prevalence of HIV-hepatitis B or C co-infection among these individuals was 4.2% (n=578). The majority of HIV infected individuals had AIDS (68.0%), were males (80.6%), and Black (66.0%). There was a significant difference between co-infected and not co-infected individuals in regards to the sex (p-value = 0.007), race (p-value < 0.0001)

and current HIV status (p-value < 0.0001) of individuals. The HIV prevalence in Michigan by county of residence at time of diagnosis is provided in Figure 2.1 (5). This map shows a higher prevalence of HIV infection in the urban areas of Lower Michigan, particularly in southeastern Michigan and the city of Detroit. In addition, a higher HIV prevalence was also observed in the counties of Luce, Alger, Mackinac and Schoolcraft.

The Bernoulli cluster analysis of HIV-hepatitis co-infection identified two spatial clusters; the first most likely cluster with a significant relative risk (RR) = 1.75 (p-value = 0.005) and the second cluster was non-significant, RR = 0.73 (Table 2.2). The most likely cluster consisted of 46 counties in the northeast Lower and Upper Peninsulas namely Presque Isle, Montmorency, Alpena, Cheboygan, Otsego, Oscoda, Alcona, Emmet, Crawford, Charlevoix, Antrim, Iosco, Ogemaw, Chippewa, Kalkaska, Mackinac, Roscommon, Arenac, Missuake, Grand Traverse, Gladwin, Leelanau, Clare, Wexford, Luce, Bay, Huron, Benzie, Osceola, Midland, Schoolcraft, Manistee, Isabella, Lake, Tuscola, Mecosta, Saginaw, Sanilac, Gratiot, Mason, Alger, Delta, Montcalm, Newaygo, Lapeer and Genesee (Figure 2.2.a). The secondary cluster consisted of 12 counties in Lower Michigan, specifically Hillsdale, Branch, Jackson, Lenawee, Calhoun, Washtenaw, St. Joseph, Ingham, Eaton, Kalamazoo, Monroe, and Livingston (Figure 2.2.a).

The Poisson cluster analysis also identified two spatial clusters (Table 2.3). The first most likely cluster had a significant RR of 2.93 (p-value = 0.05) after adjusting for sex, race and current HIV status. The secondary cluster was non-significant (RR: 1.76, p-value = 0.13) after adjustment. The most likely cluster was located along the northwest side of the state, including

the 5 counties Leelanau, Lake, Newaygo, Allegan, and Benzie. The secondary cluster included only Genesee County located in the middle of the state in Lower Michigan (Figure 2.2.b).

2.4 Discussion

This study identified localized clusters of HIV-hepatitis B or C co-infection in counties of the Upper Peninsula, north, west and northwestern Michigan and adjacent counties in addition to a few non-significant counties in the southern portion of the state. Although HIV, HBV and HCV share common transmission routes, which include parenteral, perinatal and sexual transmission (82), the elevated clusters identified in the Bernoulli and Poisson models were not in counties in Southeast Michigan where elevated HIV prevalence rates were identified (Figure 1). It is conceivable that the geography of HIV-hepatitis co-infection is different from the geography of HIV prevalence as shown in the unadjusted HIV prevalence map because of other factors not explained in the HIV prevalence map. Additionally, there could be some unobserved factors that might influence the transmission of hepatitis infection among HIV infected individuals that are different from the transmission of HIV infection among the normal population. It is also possible that the transmission dynamics of hepatitis infection among HIV infected individuals are different from the transmission dynamics of HIV infection in the normal population. The Poisson clusters were found in certain counties that had significant clustering of HIV-hepatitis co-infection after adjustment for sex, race and current HIV status. There is also a non-significant cluster in Genesee County that had a high prevalence of HIV infection. It is important to note that geographic analyses of incidence or prevalence should take into account characteristics that are significantly associated with prevalence to delineate the underlying spatial structure.

Comparison of the Bernoulli and Poisson methods revealed significant overlapping counties. The overlapping counties (Allegan, Newaygo Lake, Benzie, Leelanau) indicated that these areas may be 'hotspots' for HIV-hepatitis co-infection that require further investigation. It is likely that the counties that showed significant clustering of HIV-hepatitis co-infection by both methods have certain characteristics that complement the HIV infected population. There may also be a lack of available or accessible health services in the counties with significant HIV and hepatitis co-infection clustering. In this regard, enumeration of the health facilities revealed that most of these counties had a limited number of hospitals as compared to other more densely populated counties (83). According to the health facility atlas (83), Leelanau, Lake, Newaygo, and Benzie counties had one hospital each whereas Allegan County had two hospitals. Future research should investigate the relationship between HIV co-infection and the number of hospitals or other health services, which could affect access to health care and early treatment and diagnosis. Another reason could be that these counties are areas where injection drug use is common. Data from MDCH indicates that 29.0% of all injecting drug users living with HIV in Michigan reside in counties with significant co-infection clustering (23). Additionally, Traverse City, which borders Leelanau County, has a Traverse City Michigan syringe exchange program. Existence of syringe exchange programs in a locality have been shown to be a proxy indicator for substantial injection drug use in a study conducted on Hepatitis C (60). Furthermore, Allegan County has been designated as a High Intensity Drug Trafficking area (HIDTA) in Michigan by the Office of the National Drug Control Policy (ONDCP) (84). HIDTAs are areas which are deemed as centers of drug production, manufacturing, importation, or distribution or where; state and local law enforcement agencies have committed resources to respond to the drug trafficking problem or drug related activities are harmful to the rest of the country and substantial Federal

resources are required to respond to drug related activities (85). It is therefore conceivable that IDU as well as other high risk behaviors are much more common in this county as a result of drug related activities which may lead to a high prevalence of HIV and hepatitis co-infection.

Limitations

One of the limitations of the study is that there is a possibility of under-reporting and under detection of HBV and HCV cases as the MDSS is based on a passive surveillance system. Additionally, the HIV surveillance system in Michigan is based on data for those persons who have been confidentially reported by name. Data for infected individuals who have not been tested, have been tested only anonymously, or have been tested by name but not reported, are not included which could lead to under reporting of HIV cases (23). However, in spite of the limitations, the strength of our study is that it is population based including all the statewide data detected by the surveillance system on almost all HIV/AIDS infected individuals as well as persons having hepatitis B and C co-infection residing in the state of Michigan

Conclusions

This study identified significant clusters of HIV-hepatitis B and C co-infection in counties that would not be considered high risk because of low population density and low HIV prevalence. In this respect, spatial cluster analysis serves as an important tool to delineate infectious disease clusters, which could be missed by other analytic methods that do not consider geography. The results from this study can guide policy makers and health managers to target interventions and disease control measures towards these areas. In addition, efficient allocation of resources to these areas can be considered as a means to obtain maximum benefit from any measures undertaken to prevent spread of hepatitis infection among the high risk population of HIV infected individuals. Future research should focus upon identifying risk factors that are

associated with clustering of HIV-hepatitis co-infection in these counties as well as modifiable factors that tend to prevent these infections.

Table 2.1. Comparative analysis of HIV-hepatitis B or C co-infected and not co-infected individuals by sex, race and current HIV status in Michigan, through January 2011.

Variable	Co-infected (578), *n*(%)	Not co-infected (13358), *n*(%)	P-value*
Sex			
Female	112 (19.4)	3235 (24.2)	0.007
Male	466 (80.6)	10123 (75.8)	
Race			
White (non-Hispanic)	161 (27.9)	4797 (35.9)	< 0.0001
Black (non-Hispanic)	381 (66.0)	7710 (57.7)	
Hispanic	13 (2.3)	557 (4.2)	
Other†	23 (3.9)	294 (2.2)	
Current HIV status			
HIV (not AIDS)	185 (32.0)	6040 (45.2)	< 0.0001
AIDS	393 (68.0)	7318 (54.8)	

*Chi-square test

†Other= Multiracial, Asian, Hawaiian & Pacific Islander, Alaskan Native, American Indian

Table 2.2. HIV-hepatitis B or C co-infection spatial clusters with high and low rates identified by SaTScan Bernoulli method, Michigan 2006-2009.

Cluster	HIV Population No.	Observed Cases No.	Expected Cases No.	Relative Risk*	Log-Likelihood Ratio	P-value
Most Likely cluster	1,052†	74	44.83	1.75	9.19	0.005
Secondary Cluster	1,642‡	53	69.98	0.73	2.63	0.88

*Relative Risk = observed/expected

†Cluster includes 46 counties

‡Cluster includes 12 counties

Table 2.3. HIV-hepatitis B or C co-infection spatial clusters with high or low rates identified by SaTScan discrete Poisson method, Michigan 2006-2009.[*]

Cluster	HIV/AIDS Population No.	Observed Cases No.	Expected Cases No.	Relative Risk[†]	Log-Likelihood Ratio	P-value
Most Likely cluster	125[‡]	14	4.85	2.93	5.75	0.05
Secondary clusters	538[§]	38	22.22	1.76	4.83	0.13

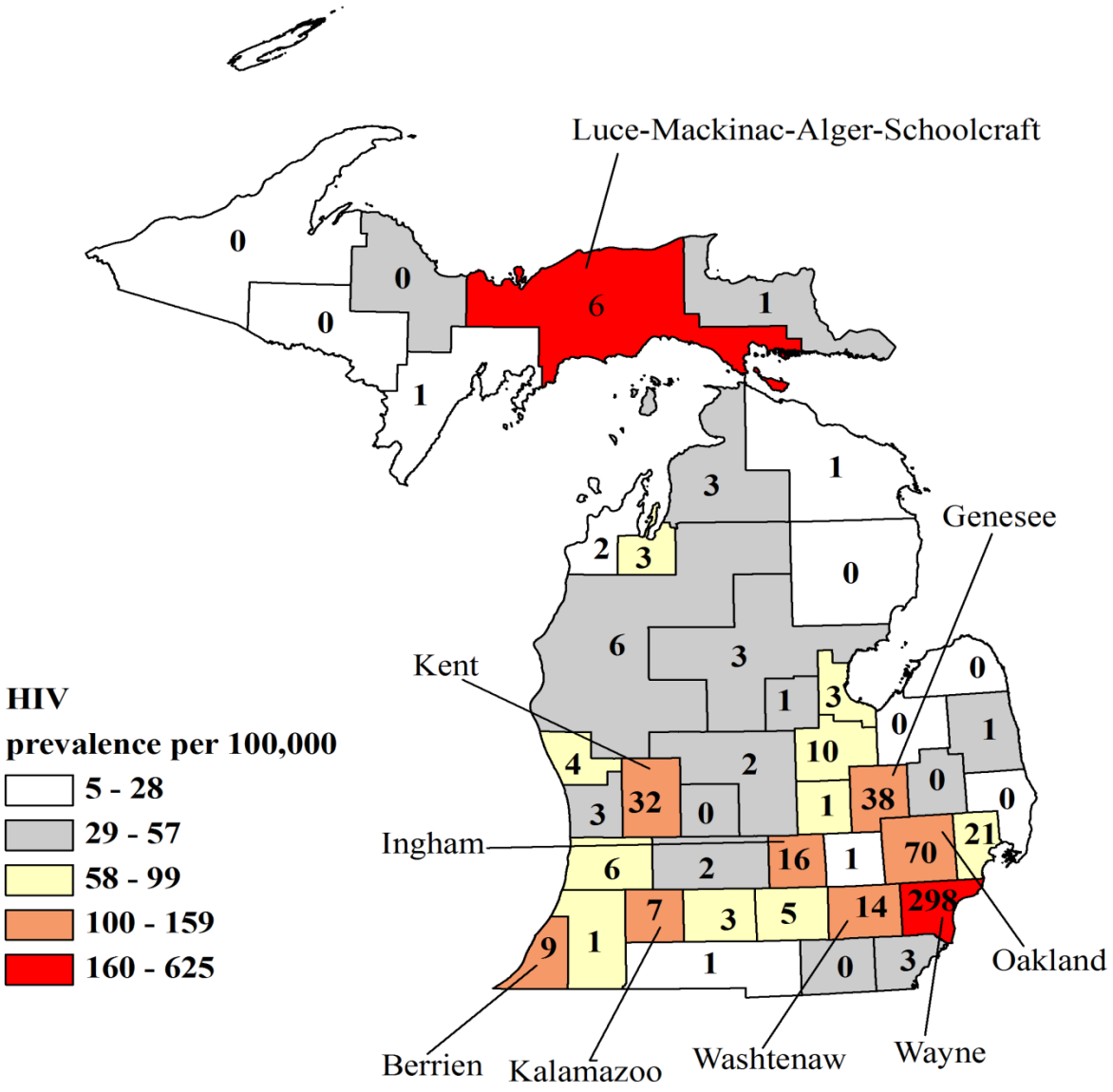
[*]Controlling for sex, race and current HIV status

[†]Relative Risk = observed/expected

[‡]Cluster includes 5 counties

[§]Cluster includes 1 county

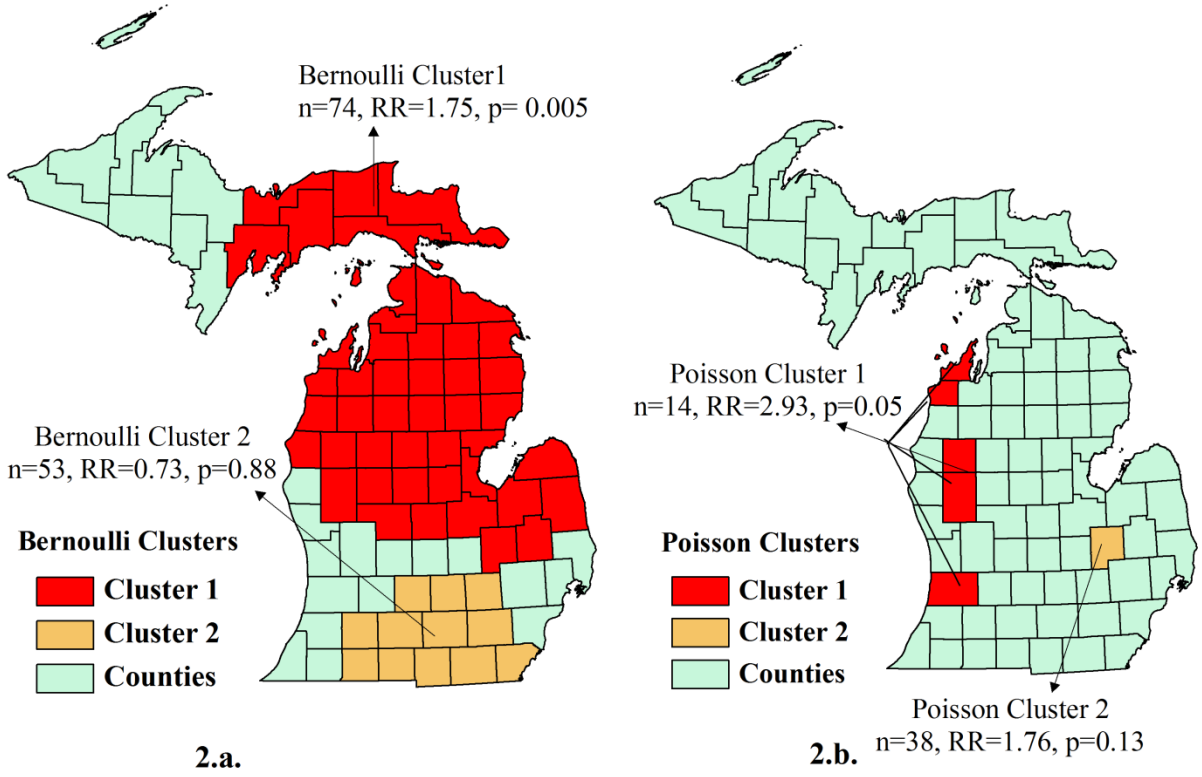
Figure 2.1. Map of Michigan showing HIV prevalence and hepatitis co-infection cases per county, 2006 to 2009 (Numbers inside counties denote hepatitis B or C cases).



Note: To mitigate the effect of small numbers of cases, reported HIV prevalence in multi-county health departments are listed for the health department as a whole and not the individual counties.

For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation.

Figure 2.2. Michigan with counties showing clustering of HIV and hepatitis co-infection identified with Bernoulli (2.2.a) and Poisson (2.2.b) methods



Note: n=number of cases; RR=Relative Risk; p=p-value

CHAPTER 3.

HEPATITIS B AND HEPATITIS C CO-INFECTION IN HIV/AIDS POPULATION IN THE STATE OF MICHIGAN

Abstract

Background

Hepatitis B and C virus infections are commonly acquired by HIV infected individuals due to shared transmission routes. Therefore, the purpose of this study was to estimate the prevalence of hepatitis co-infection and associated factors among HIV infected individuals in the state of Michigan.

Methods

A retrospective cohort study was carried out from January 1st, 2006 through December 31st, 2009 in Michigan utilizing data from the Michigan department of community health. All HIV infected individuals were matched with all hepatitis B and C cases during the study period. Logistic regression analysis was used to assess factors associated with the outcome of co-infection.

Results

The prevalence of HIV and hepatitis co-infection among HIV infected individuals was 4.1%. Multivariable analysis revealed a significant association between co-infection and being male and of Black race (Odds Ratio (OR) =2.0, 95% Confidence Interval (CI): 1.2-3.6) and male and of Other race (OR=3.5, 95% CI: 1.7-7.0) compared to Hispanic race. A significant association was found between co-infection and risk categories of blood products (OR=11.1, 95% CI: 6.2-20.2), IDU (OR=3.6, 95% CI: 2.7-4.8) and MSM/IDU (OR=3.4, 95% CI: 2.4-4.9) in addition to

two interactions; one between sex and current HIV status and the other between current HIV status and age at HIV diagnosis.

Conclusions

The relatively high prevalence of HIV and hepatitis co-infections in Michigan identifies a continuing public health problem. This study is an effort to document the changing epidemiology of HIV-hepatitis co-infections in order to implement preventive measures and interventions to reduce the prevalence of hepatitis co-infections.

3.1. Introduction

AIDS (Acquired immune deficiency syndrome) reached a pandemic level by the end of 2009; 33.3 million people were living worldwide, with HIV (Human immunodeficiency virus), of these, 30.8 million were adults including 15.9 million women and 14.9 million men. Two and a half million were children under the age of 15 years. There were 2.6 million individuals newly infected with AIDS in 2009 (1). Among these, 2.2 million were adults whereas 370,000 were children under the age of 15 years. About 1.8 million deaths were reported in 2009; 1.6 million among adults and 260,000 in children under 15 years of age (1).

In the United States (US) in 2006, 35,314 new cases of HIV/AIDS in adults, adolescents, and children were diagnosed in the 33 states with long-term, confidential name-based HIV reporting (2). In another study in 2008, serum specimens from newly diagnosed HIV patients during 2006 residing in 22 states in the US were tested with the BED HIV-1 capture enzyme immunoassay to categorize infections as recent or long-standing. According to extrapolations from the data, the estimated number of new infections for the US in 2006 was 56,300 while the estimated incidence rate was 22.8 per 100,000 population (3). By the end of 2009, an estimated 1.2 million people were living with AIDS in the US while approximately 17,000 AIDS related deaths were reported in the same year (4). An estimated 54,000 adults and children were newly diagnosed with HIV in 2009 (1).

The Michigan Department of Community Health (MDCH) estimates that there are 18,200 people currently living with HIV/AIDS in Michigan, of these, 14,871 were reported by October

2010 (86). According to a recent review of HIV trends in Michigan from 2004 to 2008, the rate of new HIV diagnosis decreased from 9.0 per 100,000 in 2004 to 8.5 per 100,000 in 2008 with an average decrease of 2% per year (87).

Viral hepatitis is caused by an infection with any of the five distinct hepatitis viruses. The three most commonly identified in the US are hepatitis A, hepatitis B and hepatitis C viruses. However, in terms of morbidity and mortality, hepatitis B and hepatitis C viruses are the most important. Around 2 billion people globally have been infected with the hepatitis B virus while about 350 million live with chronic infection. Approximately 600,000 persons die each year from acute or chronic sequelae of hepatitis B. Hepatitis B virus (HBV) is endemic in China and other parts of Asia. The majority of infections with HBV occur during childhood. In these areas, 8% to 10% of the adults suffer from chronic infection with HBV. Chronic infection rates are also high in the Amazon region and the southern parts of eastern and central Europe. Approximately 2% to 5% of the general population is chronically infected in the Middle East and Indian sub-continent. In comparison, less than 1% of the population in Western Europe and North America suffers from chronic infection with HBV (7).

According to the World Health Organization (WHO), there are about 180 million people infected with hepatitis C virus (HCV) amounting to 3% of the world's population. Among these, 130 million are chronic HCV carriers at risk of developing liver cirrhosis and or liver cancer. Approximately, 3 to 4 million individuals are newly infected each year, 70% of whom will develop chronic hepatitis. HCV is implicated in 50–76% of all liver cancer cases, and two thirds of all liver transplants in the developed world. HCV prevalence is low (< 1%) in Australia, Canada and northern Europe. It is about 1% in countries such as the US and most of Europe, and

high (>2%) in many countries in Africa, Latin America and Central and South-Eastern Asia. The prevalence in these countries ranges from 5% to 10%. Currently, there are 3.9 million individuals in the US with chronic HCV, with prevalence as high as 8 to10% in Blacks. Nearly 90% of new HCV infections are due to injection drug use, which remains the main route of transmission globally (8).

According to the CDC, there were 4,519 cases of acute hepatitis B in the US in 2007. The overall incidence of reported acute hepatitis B was 1.5 per 100,000 population. As many HBV infections are either asymptomatic or never reported, the actual number of new infections is estimated to be nearly tenfold higher or approximately 43,000 persons in the US in 2007. The incidence is highest among adults; particularly males aged 25 to 44 years (9). In the US, there are an estimated 800,000–1.4 million persons suffering from chronic HBV infection. In Michigan, there were 142 cases of acute HBV in 2008 while the number of confirmed cases of chronic hepatitis B was 1,340 in the same year (10, 11).

In 2007, 849 cases of confirmed acute hepatitis C were reported in the US. However, the CDC estimates that approximately 17,000 new HCV infections occurred that year, taking into account asymptomatic infection and underreporting. As individuals newly infected with HCV are usually asymptomatic, so acute hepatitis C is rarely identified or reported. There are approximately 3.2 million persons in the US with chronic HCV infection (12). In 2008, there were 125 cases of acute hepatitis C and 7,167 confirmed cases of chronic hepatitis C in the state of Michigan (13, 14).

In the US, the estimated prevalence of HCV ranges from 15 to 30% among people living with HIV/AIDS and as high as 50 to 90% among people living with HIV/AIDS who acquired HIV infection through injecting drug use (IDU). HCV associated end-stage liver disease is currently a major cause of death among people living with HIV/AIDS (36-38). It is also one of the most important causes of chronic liver disease in the US and HCV infection progresses more rapidly to cause liver damage in HIV-infected persons. HCV infection may also influence the course and management of HIV infection. Furthermore, HIV infected persons who become infected with HBV are at increased risk for developing chronic HBV infection. This co-infection can have serious medical complications, including an increased risk for liver-related morbidity and mortality (39).

Rationale

With the recent decrease in many common opportunistic infections in HIV/AIDS patients, other infections have become very important from the public health viewpoint. Among these infections, HBV and HCV co-infection among HIV/AIDS patients have emerged as major contributors to morbidity and mortality. HIV-HCV co-infection leads to an accelerated progression to symptomatic liver disease and cirrhosis. Additionally, highly active anti-retroviral therapy (HAART) may be limited by either HCV- related liver disease or hepatotoxicity of the medications used in viral liver disease (88, 89). There is also evidence to suggest that HCV infection may negatively affect the course of HIV infection by accelerated progression to both AIDS and death (31).

HIV infection may also modify the natural history of HBV infection among HIV-hepatitis co-infected individuals. Individuals with HIV are found to have higher rates of HBV

chronicity, higher HBV replication, lower ALT levels and lower rates of seroconversion to anti-HBe and anti-HBs (90). HIV- infected adults progress to chronic hepatitis B at a rate approximately five times higher than HIV-uninfected adults (chronic hepatitis B developed among seven of 31 HIV-infected adults versus two of 46 HIV-uninfected adults following acute infection, p=0.026) (91, 92). In HIV/HBV co-infected individuals, both HBV DNA and HBe antigenaemia are increased, which may be the reason for the 18-fold increased risk of mortality from liver disease in HIV/HBV co-infected men compared with only HBV infected men in a US study (40).

In Michigan, the Adult and Adolescent Spectrum of Disease (ASD) surveillance project collected data from the medical records of HIV patients at two major medical centers in Detroit, between 1990 and 2004. Based on this surveillance project, hepatitis C was the most common hepatitis co-infection among HIV-infected individuals. Out of the 1,790 individuals in care and in ASD in 2001-2003, 353 (20 %) were diagnosed with HCV infection at some time during ASD follow-up, while 207 (12 %) were diagnosed with hepatitis B (HBV) infection (23).

As co-infection with HBV and HCV are associated with an increased morbidity and mortality among HIV/AIDS patients, it is imperative that the magnitude of the co-infection is estimated among the HIV/AIDS population in the state of Michigan along with the concomitant risk factors for co-infection. This would allow for better prevention and control of these infections among the HIV/AIDS population.

Objectives

1. To estimate the prevalence of hepatitis co-infection among HIV infected individuals residing in the state of Michigan in the years 2006 to 2009.

2. To identify the factors associated with hepatitis co-infection among HIV infected individuals residing in the state of Michigan during the above mentioned period.

3.2. Methods

Michigan is the 10th largest state in the US with a population of 9,938,444 according to the 2000 census (93). The state of Michigan has 83 counties, served by 45 local health departments (LHDs). In most cases, each county has a LHD but in the less populated areas of the state, LHDs may include more than one county (68). A retrospective cohort study was carried out from January 1st, 2006 through December 31st, 2009 in the state of Michigan to meet the objectives of the study. Information on the participants was obtained from the enhanced HIV/AIDS Reporting System (eHARS) maintained by the HIV/STD/VH/TB Epidemiology Section and the Michigan Disease Surveillance System (MDSS) which is the statewide communicable disease reporting system maintained by the Surveillance and Infectious Disease Epidemiology Section of the Michigan Department of Community Health (MDCH) (68). The information on HIV infected individuals was obtained from eHARS while information on HBV and HCV infections was gathered from the Michigan Disease Surveillance System. To enable analysis of HBV and HCV infections among HIV/AIDS individuals, a record linkage was established between the HIV/AIDS surveillance database and the MDSS. For our study individuals of all ages, infected

with HIV/AIDS, from all the counties of Michigan, were included in the dataset and matched with all HBV and HCV cases during the study period to obtain a prevalence estimate, and the factors associated with HBV/HCV/HIV/AIDS co-infections were identified. As information on all hepatitis cases in this HIV/AIDS population was obtained, no sampling was performed.

Ethical approval was sought from the Institutional Review Board (IRB) at Michigan State University and MDCH. To ensure confidentiality and privacy of the participants, an employee of the HIV/STD/VH/TB Epidemiology Section performed the record linkage. The resulting database was de-identified according to HIPAA guidelines on public health information (there were no interviews or contact with the participants). Information on a number of characteristics of the individuals was collected from eHARS and MDSS. For this study, variables included were sex, race, age at HIV diagnosis, current HIV status (status through December 2009) and risk for transmission of HIV. The outcome variable was a binary indicator for 'Coinfection'. An HIV/AIDS individual was categorized as co-infected if he or she had been concurrently infected with confirmed hepatitis B or hepatitis C virus (acute and chronic) based on the CDC case definition (74-78) and residing in the state of Michigan during the period 2006 through 2009. The rationale for creating the co-infection variable was based on the fact that the three diseases share similar routes of transmission (94, 21). Any HIV/AIDS case which had a diagnosis of acute or chronic hepatitis B or C before 2006 was excluded from the study. In addition, doubly co-infected HIV/AIDS (Hepatitis B & C together) cases were excluded from the analysis as they constituted a very small proportion (<1%) of the cohort. The HIV/AIDS case definition was based on the CDC's 1993 revised classification system of HIV (73). Statistical analysis was performed in SAS software version 9.2 (SAS Institute, Inc., Cary, North Carolina). Descriptive

statistics were generated to examine the distribution of characteristics. Logistic regression was used to assess factors associated with the outcome of co-infection. Univariable analyses provided the unadjusted association of factors with co-infection and the corresponding odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Multivariable analysis was conducted to evaluate the association of factors with co-infection while adjusting for confounding effects of other variables. All possible interactions were checked and entered into the final model based on statistical significance and or biological plausibility. For interpretation, adjusted ORs ($_{adj}$OR) and their respective 95% CIs were utilized.

3.3. Results

A total of 13,936 individuals were found to be infected with HIV/AIDS during the study period. Approximately 76% were male. The race/ethnicity distribution was Black (58.1%), White (35.5%), Hispanic (4.1%), multiracial (1.5%), Asian/Hawaiian/Pacific islander (0.5%), and American Indian/Alaskan Native (0.3%). The prevalence of HIV-hepatitis co-infection among these individuals was 4.1% (n=578) (Table 3.1). The majority of co-infected cases were either chronic hepatitis B (n=250, 1.8%) or chronic hepatitis C (n=307, 2.2%). For HIV transmission risk categories, the majority of HIV/AIDS infected individuals were Men who have sex with men (MSM) (48.9%) followed by high risk heterosexual (HRH) (12.9%), injecting drug user (IDU) (9.8%), heterosexual male (8.6%), unknown risk (8.5%), heterosexual female (5.7%), MSM/IDU (3.9%), perinatal (1.1%) and blood products (0.6%). With respect to age at HIV diagnosis, most HIV/AIDS infected individuals were in the age groups of 30-39 (34.7%)

followed by 40-49 (21.3%), 25-29 (16.2%), and 20-24 (12.6%). With respect to current HIV status, there were more individuals with AIDS (55.3%) compared to only HIV (44.7%).

For univariable analysis, the variable HIV transmission risk was reclassified into blood products, heterosexual, IDU, MSM/IDU, MSM, perinatal and undetermined (86) (Table 3.2). The variable race was categorized into Black, White, Hispanic and Other whereas age at HIV diagnosis (years) was reclassified into < 20, 20-29, 30-39, 40-49, and 50 and over (23). Those individuals who were co-infected were more likely to be male, of other race followed by black and white race and predominantly having AIDS (Table 3.2). They were also more likely to have had a transmission risk through blood products, MSM/IDU and IDU. Furthermore, HIV diagnosis at an older age showed a significant association with hepatitis co-infection (Table 3.2). The multivariable analysis was based upon statistical significance and biological plausibility of the variables. After adjusting for all other variables in the model, there was a significant association between co-infection and being male and of Black race (OR=2.0, 95% CI: 1.2-3.6) and male and of Other race (OR=3.5, 95% CI: 1.7-7.0) compared to Hispanic race. In addition, a significant association was found between co-infection and transmission risk categories of blood products (OR=11.1, 95% CI: 6.2-20.2), IDU (OR=3.6, 95% CI: 2.7-4.8) and MSM/IDU (OR=3.4, 95% CI: 2.4-4.9) after adjustment. The final model also included two interactions; one between sex and current HIV status and the other between current HIV status and age at HIV diagnosis (Table 3.2). The first interaction shows that the effect of gender differs if the individual's current HIV status is AIDS (OR: 1.9) or HIV positive (OR: 1.0) in relation to co-infection. The second interaction indicates that the effect of current HIV status among males as compared to females differs across different age groups at HIV diagnosis in relation to co-infection (Table 3.2).

3.4. Discussion

In this study, about 4% of HIV/AIDS infected individuals were co-infected with hepatitis viruses. Although this prevalence estimate consists of both hepatitis B and C cases, it is lower than the estimate reported in other studies on chronic hepatitis B in the US (69, 70). However, these studies were focused upon hospital (prevalence 7%) (37) or military (prevalence 11%) populations (70). A cross-sectional analysis of the US Adult AIDS clinical trials group data estimated a prevalence of 16.1% for HIV-HCV co-infection (36) whereas another study reported a prevalence of 31.6% for this co-infection (48). Although these studies reported a higher prevalence than our study, it should be noted that one study was clinic based (48) while the other was conducted on a relatively small sample from a cohort (36).

A systematic review of HIV-hepatitis co-infection in sub-Saharan Africa reported a prevalence of 15% for HBV and 7% for HCV (15). A study conducted in Brazil on HIV, HCV and HBV co-infection reported a prevalence of 4.4% which is comparable to our study (21). The majority of HIV/AIDS-hepatitis co-infected individuals were male (69, 95) and of Black or Other race groups which is consistent with findings of other studies (69, 94). In our study, Other race which included multiracial groups, Asian, Hawaiian and Pacific Islanders along with Alaskan native and American Indians had a stronger association with co-infection than the Black and White populations. This association needs to be explored further to identify racial subgroups which might be at a higher risk for hepatitis co-infections.

Co-infected individuals were more likely to be associated with a HIV transmission risk of blood products followed by IDU and MSM/IDU. These findings are similar to others reported in a study in Georgia which identified blood transfusion as a significant contributor to HIV-hepatitis co-infection (96). It is important to note that in spite of improved testing of viral pathogens in blood, transmission through blood products still remains a major source of infection (97). A study conducted in Brazil identified heterosexual transmission as a major risk factor (16) whereas other studies have identified IDU as a significant factor (94, 19, 98, 99). Our study also identified IDU and MSM/IDU as significant factors contributing to co-infection (100). Older age at HIV diagnosis showed a significant association with co-infection which is consistent with other studies conducted in the US (70, 101). It is quite likely that these individuals had HIV infection earlier on but were diagnosed later and additionally, had more chances of acquiring hepatitis infection through similar transmission routes because the duration of exposure to viral hepatitis is more likely to be higher in older individuals (21). Another explanation could be that they are more immunologically compromised when they are infected with HIV at an older age as compared to a younger age making them more likely to develop chronic hepatitis infection.

Individuals currently having AIDS were more likely to be associated with co-infection which could mean that infection with hepatitis could have led to rapid progression from HIV to AIDS status (102). Additionally, there may be other factors specific to AIDS which could lead these individuals to acquire hepatitis B or C infections. It is also possible that AIDS status contributed to development of chronic hepatitis infections (103). To our knowledge, interactions between sex and current HIV status and sex, current HIV status and age at HIV diagnosis in relation to co-infection are documented for the first time in this study. Based on these results,

males currently having AIDS were more likely to be co-infected with hepatitis B or C than females. It is possible that there could be some risk factors more prevalent in males having AIDS as compared to females which could result in them acquiring hepatitis infection more commonly than females. A survey on adolescent males reported that bisexually active adolescent males were more likely to engage in AIDS related risk behaviors such as having multiple sex partners, unprotected intercourse, sexually transmitted disease, and injection drug use (104). Conversely, it is also quite likely that females practice more protective behaviors like needle exchange use and carrying clean syringes compared to males as reported by a study on female IDUs (105) which might lead to them having a lower prevalence of HIV/AIDS and or co-infection. Additionally, when this relationship was stratified by age at HIV diagnosis, males currently having AIDS were more likely to be co-infected at age of 39 years or below and age of 50 or above. This association indicates that co-infection is more likely among males having AIDS at a younger age than females of comparable groups. It is conceivable that certain high risk behaviors or practices associated with the younger age groups could lead to a higher prevalence of co-infection compared to older age groups. However, males currently having AIDS who were 50 years or older at HIV diagnosis were also found to be associated with co-infection. It is quite likely that some of the high risk behaviors or practices at a younger age that are identified with these men make them more likely to acquire hepatitis co-infections that persists with the group at an older age. Additionally, as the duration of exposure to viral hepatitis is more likely to be higher in older individuals and persons with AIDS as compared to younger individuals with HIV infection only, these factors could interact with high risk behaviors or practices specific to male gender leading to a significant association with co-infection as observed in this study.

Limitations

One of the limitations of conducting a retrospective cohort study is the dependence on the available information. We were not able to obtain complete information on anti-retroviral therapy among HIV/AIDS infected individuals. Additionally, tests for CD4 counts were not routinely done on most HIV cases which limited our analysis. However, a study conducted in US did not identify either CD4 counts or HIV RNA level as a significant predictor of HIV-HCV co-infection (101).

As the reporting of HBV and HCV infection through the MDSS is based on a passive surveillance system, there is a high likelihood of under reporting and under detection of cases. However, the issues with the current hepatitis surveillance system are not limited to Michigan but have been identified nationwide. According to a report from the Institute of Medicine in 2010, the current hepatitis surveillance systems do not provide accurate estimates of current disease burden and are not contributing enough to program planning and evaluation (106). In addition, the HIV surveillance system in Michigan is based on data for those persons who have been confidentially reported by name. Data for infected individuals who have not been tested, have been tested only anonymously, or have been tested by name but not reported, are not included which could lead to under reporting of cases (23). However, the strength of our study lies in the fact that it is a population based study encompassing most if not all HIV/AIDS infected individuals as well as persons having hepatitis B and C co-infection residing in the state of Michigan.

Conclusion

Although the prevalence of HIV/AIDS- hepatitis co-infections in Michigan are not higher than the national average, it does represent a public health problem especially when considering the vulnerability of the immunocompromised HIV/AIDS infected population. Furthermore, this study identified males of different races as well as of Black race to be at a higher risk of hepatitis co-infections. The majority of studies indicated that individuals of Black race are at a higher risk of HIV/AIDS as well as for hepatitis co-infection, however, our results indicate that other races might be at a higher risk for hepatitis co-infections. Currently having AIDS and being of older age at diagnosis were found to be important predictors of hepatitis co-infection. An important finding was the correlation of transmission through blood products with co-infection which indicates that additional measures should be taken to address this issue. Other high risk populations identified in this study were IDUs and MSM/IDU. The study also demonstrated interactions between current HIV status, sex and age at HIV diagnosis. The importance of these findings needs to be explored further in order to implement preventive measures and interventions to reduce the prevalence of hepatitis co-infections. Finally, future studies should be conducted keeping in mind the changing epidemiology of HIV-hepatitis co-infections and the urgent need to prevent co-morbidities in an already high risk immune-compromised population of HIV/AIDS infected individuals.

Table 3.1. Distribution of basic characteristics of the HIV/AIDS infected individuals in Michigan (*n*=13,936)

Variable	Frequency (%)
Coinfection	
Coinfected*	578 (4.1)
Not coinfected	13358 (95.8)
Sex	
Male	10589 (76.0)
Female	3347 (24.0)
Race	
White (non-hispanic)	4958 (35.5)
Black (non-hispanic)	8091 (58.1)
Hispanic	570 (4.1)
Asian/HI/PI †	72 (0.5)
American Indian/Alaskan native (non-hispanic)	42 (0.3)
Multi Race/Unknown/ Other (non-Hispanic)	203 (1.5)
HIV transmission Risk ‡	
Blood products	85 (0.6)
High risk heterosexual	1796 (12.9)
Presumed Heterosexual (PH)-male	1203 (8.6)
Presumed Heterosexual (PH)- female	793 (5.7)
IDU	1363 (9.8)
MSM	6810 (48.9)
MSM/IDU	539 (3.9)
Perinatal	156 (1.1)
Unknown	1191 (8.5)
Age at HIV diagnosis (years)	
0 - 12	178 (1.3)
13 - 19	638 (4.6)
20 - 24	1753 (12.6)
25 - 29	2260 (16.2)
30 - 39	4836 (34.7)
40 - 49	2976 (21.3)
50 - 59	1044 (7.5)
60 and over	248 (1.8)
Missing	3 (0.0)
Current HIV status	
AIDS	7711 (55.3)
HIV-NA (not AIDS)	6225 (44.7)

*Coinfection=Any HIV infected individual that is infected by hepatitis B and C virus (acute and chronic), †Asian/Hawaiian, Pacific Islander, non-Hispanic, ‡Heterosexual female=Female who denies IDU and has had sex with a man, MSM= Male-male sex, IDU=Injecting drug user

Table 3.2. Multivariable analysis of different factors associated with co-infection among HIV infected individuals in the state of Michigan

Variable	Co-infected (578) *N* (%)	Not co-infected (13358) *N* (%)	Crude OR	95% CI for OR	Adjusted OR	95% CI for $_{adj}$OR
Sex						
Female	112 (19.4)	3235 (24.2)	1			
Male	466 (80.6)	10123 (75.8)	1.3	1.1-1.6		
Race						
White (non-hispanic)	161 (27.9)	4797 (35.9)	1.4	0.8-2.6	1.3	0.7-2.4
Black (non-hispanic)	381 (65.9)	7710 (57.7)	2.1	1.2-3.7	2.0	1.2-3.6
Hispanic*	13 (2.3)	557 (4.2)	1		1	
Other†	23 (3.9)	294 (2.2)	3.4	1.7- 6.7	3.5	1.7-7.0
Age at HIV diagnosis , years						
< 20	22 (3.8)	794 (5.9)	1			
20 - 29	134 (23.2)	3879 (29.0)	1.3	0.8-2.0		
30 - 39	215 (37.2)	4621 (34.6)	1.7	1.1-2.6		
40 - 49	130 (22.5)	2846 (21.3)	1.7	1.0-2.6		
50 and over	77 (13.3)	1215 (9.1)	2.3	1.4-3.7		
Current HIV status						
HIV-NA (not AIDS)	185 (32.0)	6040 (45.2)	1			
AIDS	393 (68.0)	7318 (54.8)	1.8	1.5-2.1		
HIV transmission Risk						
Blood products	20 (3.5)	65 (0.5)	9.1	5.3- 15.8	11.1	6.2-20.2
Heterosexual‡	58 (10.0)	2531 (18.9)	0.7	0.5-1.0	0.8	0.6-1.2
IDU	144 (24.9)	1219 (9.1)	3.5	2.6- 4.7	3.6	2.7-4.8
MSM	218 (37.7)	6592 (49.4)	0.9	0.8-1.3	1.0	0.8-1.3
MSM/IDU	59 (10.2)	480 (3.6)	3.7	2.6-5.2	3.4	2.4-4.9
Perinatal	1 (0.2)	155 (1.2)	0.2	0.03- 1.4	0.3	0.03-2.3
Undetermined§	78 (13.5)	2316 (17.3)	1		1	
Interactions						
Male vs Female						
AIDS					1.9	1.3-2.6
HIV-NA					1.0	0.7-1.5

Table 3.2. (cont'd).

Variable	Co-infected (578) *N* (%)	Not co-infected (13358)*N* (%)	Crude OR	95% CI for OR	Adjusted OR	95% CI for $_{adj}$OR
AIDS vs HIV-NA for Female						
< 20 yrs					1.6	0.6-4.2
20 - 29 yrs					1.3	0.8-2.2
30 - 39 yrs					1.2	0.7-1.9
40 - 49 yrs					0.5	0.3-0.9
50 and over					0.9	0.5-1.7
AIDS vs HIV-NA for Male						
< 20 yrs					2.9	1.2-7.1
20 - 29 yrs					2.4	1.6-3.5
30 - 39 yrs					2.1	1.5-2.9
40 - 49 yrs					1.0	0.7-1.4
50 and over					1.7	1.0-2.8

* Based on lowest risk (Kellerman et al. *J Infect Dis*. 2003;188(4):571-577.)

† Other= Multiracial, Asian, Hawaiian & Pacific Islander, Alaskan Native, American Indian

‡ Heterosexual= Presumed Heterosexual (PH)- female and HRH, § Undetermined=Unknown (Males and Females with no identified risk) and Presumed Heterosexual (PH)- male

CHAPTER 4.

MORTALITY AMONG HIV-HEPATITIS CO-INFECTED INDIVIDUALS IN THE STATE OF MICHIGAN

Abstract

Background

AIDS is one of the most devastating diseases the world is currently facing in terms of morbidity and mortality. In 2009, there were 1.8 million deaths due to HIV/AIDS globally. HIV infected individuals are commonly infected by hepatitis B and C virus because of shared transmission routes. The purpose of this study was to estimate mortality and associated factors among HIV-hepatitis co-infected individuals in Michigan.

Methods

A retrospective cohort study was conducted in Michigan during the period of January 1, 2006 to December 31, 2009 in which HIV infected individuals were matched to all hepatitis B and C cases. The mortality was ascertained from vital records and Cox proportional hazards regression analysis was conducted to assess the association of variables with mortality.

Results

A total of 727 HIV/AIDS infected individuals died during the follow-up period of four years. In the final model, individuals of Other (Hazards Ratio (HR)=2.2, 95% Confidence Interval (CI): 1.4-3.2) and Black (HR=1.3, 95% CI:1.1-1.6) race had decreased survival as compared to White race. Age at HIV diagnosis showed an increased mortality with increasing age. Similarly, IDU (HR=2.1, 95% CI: 1.6-2.6), MSM/IDU (HR=1.5, 95% CI: 1.1-2.2), individuals with undetermined risk (HR=1.5, 95% CI: 1.2-1.9) and, heterosexual (HR=1.4, 95% CI: 1.1-1.8)

practices had decreased survival as compared to MSM. Additionally, an interaction was found between current HIV status and co-infection status.

Conclusions

Mortality among HIV infected individuals with hepatitis co-infection remains a continuing problem in the HAART era. The associations identified by this study can be used for planning and implementing interventions to reduce mortality among the vulnerable population of HIV infected individuals.

4.1. Introduction

AIDS (Acquired immune deficiency syndrome) is one of the most devastating diseases the world is currently facing in terms of morbidity and mortality. By the end of 2009, 33.3 million people were living with HIV (Human immunodeficiency virus) infection globally with an estimated 2.6 million individuals newly infected with HIV (1). There were 1.8 million deaths due to HIV/AIDS in 2009; 1.6 million among adults and 260,000 in children under 15 years of age (1). In 2009, an estimated 1.2 million people were living with AIDS in the US (United States) while about 17,000 AIDS related deaths were reported in the same year (4). According to the Michigan Department of Community Health (MDCH), there are an estimated 19,500 people currently living with HIV/AIDS in Michigan, of these, 14,895 were reported by January 2011 (5).

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) co-infections are relatively common in individuals infected with HIV/AIDS because of shared transmission routes. In sub-Saharan Africa, a review of 60 studies on HIV-hepatitis co-infection reported prevalence rates of 15% for mean HBsAg and 7% for mean anti-HCV (15). The reported prevalence for HIV-HCV co-infection was 4.4% in Brazil (16), 7.8% in Thailand (17), 16% in Denmark (18), and 24.3% in France (19). For HIV-HBV co-infection, the reported prevalence was 6% in Denmark (18), 7% in France (19) and, 8.7% in Thailand (17). The reported prevalence for HIV-HBV-HCV co-infection was 1.6% in France (19) whereas for Brazil, it was 4.4% (21).

Studies conducted on chronic hepatitis B in the US report a prevalence of 7.6% (69) and 11% (70) in two different populations with HIV. Hepatitis C was the most common hepatitis co-

infection among HIV-infected individuals reported by the Adult and Adolescent Spectrum of Disease surveillance project conducted in Michigan. This project was based upon data from the medical records of HIV patients at two major medical centers in Detroit, Michigan between 1990 and 2004. Out of the 1,790 individuals in care and in ASD in 2001-2003, 20% were diagnosed with HCV infection, while 12% were diagnosed with HBV infection (23).

Hepatitis B and hepatitis C virus co-infections have emerged as major contributors to morbidity and mortality among HIV/AIDS patients. There is also evidence to suggest that HCV infection may negatively affect the course of HIV infection leading to a rapid progression to AIDS and death (31). However, the association between HBV or HCV co-infection and increased mortality has not been consistently identified. Several studies in different settings have shown no association between hepatitis co-infection and mortality. Studies conducted in the US (32) and South Africa (33) did not show an association between co-infection and mortality. However, other studies which did not identify an association between HIV-HCV infection and mortality did report an association between AIDS and mortality (34, 35).

Although these studies did not identify an association between HIV-hepatitis co-infection and mortality, other studies have observed an increased liver related mortality with co-infection. HCV associated end-stage liver disease is now a predominant cause of death among people living with HIV/AIDS (36-38). Additionally, HIV-HBV co-infected patients are at increased risk for developing chronic infection which can lead to an elevated risk for liver-related morbidity and mortality (39). Prospective cohort studies conducted on HIV and hepatitis (HBV or HCV) co-infection have identified a significant association between co-infection and liver related

mortality (40-43). However, among these, two studies also reported an increased risk for all-cause mortality and co-infection (40, 42).

Other studies focusing upon hepatitis B and C co-infection identified an association between co-infection and mortality which is not liver related. A clinic based study on HIV infected patients reported a decreased survival in AIDS patients co-infected with HBV or HCV (44). The Swiss HIV cohort study reported an increased progression to new AIDS defining event and death among HIV-1 infected patients with HCV co-infection (45). Another prospective cohort study identified HIV-HCV co-infection among injecting drug users (IDU) as a significant contributor to mortality in the HAART era (46). HIV and chronic hepatitis B co-infected patients were also found to have an increased risk of death after initiation of HAART (47). Another cohort study on HIV infected patients reported decreased durations of survival from time to diagnosis of HIV infection and AIDS among HIV-HCV co-infected patients (48). A cohort study on HIV-HCV co-infected veterans observed an increased risk of death due to co-infection even after controlling for exposure to HAART and response to HAART (49). The Danish cohort study, found a significantly increased overall mortality in addition to mortality from liver related and AIDS related causes in HIV-HCV co-infected (18) and HIV-HBV co-infected patients on HAART (20). A study on mortality related to chronic hepatitis B and C in France also observed an increased frequency of deaths among HIV/HBV and HIV/HCV co-infected individuals (50). HIV and chronic hepatitis B co-infected patients in a multicenter cohort study showed an increased mortality which was mainly due to liver disease in spite of being on HAART, in addition to an increased risk of AIDS related death (51). A meta-analysis of 11 studies on HIV-HBV co-infection reported a significant effect of co-infection on overall mortality. This

increased rate of death among HBV co-infected individuals was present in studies conducted before and after starting HAART (52). Another meta-analysis of studies on HIV-HCV co-infection found an increased risk for overall mortality among HIV-HCV co-infected individuals during the HAART era (53).

Although these studies reported an increased mortality among HIV-hepatitis co-infected individuals as compared to only HIV infected individuals, other studies have noted no effect on mortality with co-infection or have attributed mortality to mostly liver related causes. With the exception of a few studies (18, 20, 45, 46, 49), most studies had smaller sample sizes (33-35, 44, 47, 48, 51), shorter duration of follow-up (33) and focused mainly on hospital or clinic based populations (32, 44, 48). Therefore, the objectives of our study were to estimate the mortality and identify the factors associated with mortality among HIV-hepatitis co-infected individuals in the state of Michigan using a statewide population based surveillance system.

4.2. Methods

This study was conducted in the state of Michigan which is the 10th largest state of the United States with a population of 9,938,444 individuals (93). A retrospective cohort design was utilized to attain the objectives of the study. HIV/AIDS infected individuals of all age groups residing in the state of Michigan during the period of January 1, 2006 to December 31, 2009 were matched to hepatitis B and hepatitis C cases from the same period. The HIV/AIDS data were obtained from the enhanced HIV/AIDS Reporting System (eHARS) maintained by the HIV/STD/VH/TB Epidemiology Section whereas the hepatitis B and C data were obtained from the Michigan

Disease Surveillance System (MDSS) maintained by the Surveillance and Infectious Disease Epidemiology Section of the Michigan Department of Community Health (MDCH) for the study period (68). These datasets were linked together to enable matching of hepatitis B and C and HIV/AIDS cases to the same individual.

Ethical approval for the study was obtained from the Institutional Review Board (IRB) at the Michigan State University and MDCH. To safeguard the privacy and confidentiality of the participants, an employee of the HIV/STD/VH/TB Epidemiology Section performed the record linkage. HIPAA (Health Insurance Portability and Accountability Act) guidelines on public health information were followed to de-identify subjects included in the study. Information on a number of socio-demographic characteristics and laboratory tests of the HIV/AIDS infected individuals was obtained. Independent variables included in the analysis were sex, race, age at HIV diagnosis, current HIV status (status through December 2009), risk for transmission of HIV, and a binary indicator for co-infection. An HIV/AIDS individual was categorized as co-infected if he or she had been concurrently infected with confirmed HBV or HCV (acute and chronic) based on the CDC case definition (73-78) and residing in the state of Michigan during the years 2006 through 2009. The rationale for creating the co-infection status variable was based on the fact that the three diseases share similar routes of transmission (21, 94). Any HIV/AIDS infected individual who had a diagnosis of acute or chronic hepatitis B or C before 2006 was not included in the study. Additionally, HIV/AIDS individuals infected with both hepatitis B and C were excluded from the analysis as they constituted a very small proportion (<1%) of the cohort. The HIV/AIDS case definition was based on the CDC's 1993 revised classification system of HIV (73).

The mortality was ascertained from vital records by using the entry date as January 1, 2006 when the study was started and December 31, 2010 the date used when the study was concluded. Only HIV/AIDS-hepatitis co-infected individuals that were diagnosed during 2006 to 2009 and HIV/AIDS not co-infected individuals were included in the analysis. To allow for additional time to follow-up, the study was concluded in 2010. The duration of survival of the HIV/AIDS-hepatitis co-infected individuals as well as the HIV/AIDS not co-infected individuals was calculated from the time (number of days) spent in the study till the date of death. Those alive at the end of the study were considered censored.

The Kaplan-Meier method was utilized to construct survival curves for the co-infected and not co-infected group. For comparison of survival curves the log rank test was used. The Cox proportional hazards regression analysis was conducted to assess the association of variables with mortality using hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs). All possible interactions were checked and entered into the final model based on statistical significance and or biological plausibility. Statistical analyses were performed in SAS statistical software version 9.2 (SAS Institute, Inc., Cary, North Carolina).

4.3. Results

The total number of individuals infected with HIV/AIDS during the study period was 13,930. The prevalence of HIV-hepatitis co-infection among these individuals was 4.1% (Table 4.1) with chronic hepatitis B in 1.8% and chronic hepatitis C in 2.2% (data not shown). There were proportionately more males (76%) infected with HIV/AIDS as compared to females (24%). The

race/ethnicity distribution was Black (58.1%), White (35.6%), Hispanic (4.1%), Multiracial (1.4%), Asian/Hawaiian/Pacific islander (0.5%), and American Indian/Alaskan Native (0.3%). Among HIV transmission risk categories, HIV/AIDS infected individuals were predominantly males having sex with males (MSM) (48.9%) followed by High Risk Heterosexual (HRH) (12.9%), Injecting Drug User (IDU) (9.8%), heterosexual male (8.6%), Unknown risk (8.5%), heterosexual female (5.7%), MSM/IDU (3.9%), perinatal (1.1%) and blood products (0.6%). With respect to age at HIV diagnosis, the distribution was: 30-39 (34.7%), 40-49 (21.3%), 25-29 (16.2%), and 20-24 (12.6%). There were more individuals with AIDS (55.3%) compared to HIV only (44.7%).

A total of 727 HIV/AIDS infected individuals died during the follow-up period. The total number of deaths was proportionately more among hepatitis co-infected individuals (10%) as compared to not co-infected individuals (5%) (data not shown). Survival in the HIV-hepatitis co-infected group was significantly lower as compared to the not co-infected group (log rank test p-value < 0.0001, Figure 4.1). The variable HIV transmission risk was categorized as blood products, heterosexual, IDU, MSM/IDU, MSM, perinatal and undetermined (86) (Table 4.2). Race was categorized as Black, White, Hispanic and Other and age at HIV diagnosis was reclassified into age groups < 20, 20-29, 30-39, 40-49, and 50 and over (23). From univariable Cox regression analysis, co-infected individuals had a decreased survival (HR=2.4, 95% CI: 1.8-3.2) as compared to not co-infected individuals. Females compared to males had an increased mortality (HR=1.2, 95% CI: 1.0-1.4). Compared to White race the mortality risk was higher in Blacks (HR=1.5, 95% CI: 1.3-1.8) and individuals belonging to the Other race category (HR=2.3, 95% CI: 1.5-3.4) (Table 4.2). For age at HIV diagnosis, a gradual increase in mortality

with increasing age was observed and individuals who were 50 years and over had the shortest survival (HR=9.0, 95% CI: 5.0-16.1). Individuals currently having AIDS showed a decreased survival as compared to only HIV infected individuals (Table 4.2). For HIV transmission risk categories, injecting drug users (IDU) had a decreased survival (HR=2.8, 95% CI: 2.3-3.4) followed by MSM/IDU (males having sex with males) (HR=1.8, 95% CI: 1.2-2.5), individuals with undetermined risk (HR=1.7, 95% CI: 1.4-2.1) and, heterosexual practices (HR=1.4, 95% CI: 1.2-1.8).

Variable selection for the adjusted model was based upon statistical significance of the variables from the univariable analysis and biological plausibility. In the final model, individuals of Other and Black race had decreased survival as compared to White race adjusting for all other variables in the model (Table 4.2). Age at HIV diagnosis showed an increased mortality with increasing age after adjustment. Similarly, IDU, MSM/IDU, individuals with undetermined risk and, heterosexual practices had decreased survival as compared to MSM after adjusting for all other variables in the model (Table 4.2). The final model also included an interaction between current HIV status and co-infection status which indicates that the effect of having AIDS as compared to HIV only differs if the individual is co-infected (HR=2.4, 95% CI: 1.2-4.8) or not co-infected (HR=5.9, 95% CI: 4.6-7.4) in relation to mortality (Table 4.2).

4.4. Discussion

In this study, mortality among HIV-hepatitis B and C co-infected individuals was nearly twice that of HIV infected individuals. There were no liver related deaths recorded in the cohort during

the follow-up period of four years. Being co-infected with either HCV or HBV resulted in an increased risk for mortality, a finding which is consistent with several studies (17, 18, 44-53). It is conceivable that there may be factors other than liver disease or treatment related hepatotoxicity that might lead to this increased risk of mortality. Another factor could be that the HIV-HCV co-infected patients were less likely to receive HAART than non-HCV infected patients as identified by an earlier cohort study (48). This could be due to the fact that increased mortality among HIV-HCV co-infected individuals is causing the decreased use of HAART. A study on mortality among siblings of HIV-HCV co-infected patients reported a higher mortality among HIV-HCV co-infected patients as compared to siblings of only HIV infected patients or siblings of control subjects (107). The authors attributed this excess mortality to probable differences in family background and socio-economic factors like shared socioeconomic disadvantage or family history of IDU. Another study by the same authors focusing on causes of death revealed an increased mortality among siblings of HIV/HCV co-infected patients to be related to substance abuse mainly alcohol or drug abuse (108). It is quite likely that other factors like lack of access to care, non-compliance with treatment, alcohol or drug related morbidity or postponement of treatment for co-infection by physician's due to underlying fears of hepatotoxicity could also play an important role in the increased mortality observed among HIV-hepatitis co-infected individuals.

A study in Brazil attributed the higher mortality in AIDS cases co-infected with HCV to the receipt of less antiretroviral therapy among these patients (109). The authors speculated that this discrepancy in treatment could be due to the knowledge of physician's that HAART may be hepatotoxic, inability of patients to tolerate antiretroviral treatment or physician's belief's that

injecting drug users are non-compliant. Similarly, HIV-HCV co-infection might be a proxy for some other types of high risk behaviors that lead to an increased mortality related to non AIDS related causes among co-infected individuals (110).

Females were also found to have an increased mortality. A study focusing on gender differences in HIV-HCV co-infected patients identified females as having a reduced survival as compared to males while on HAART (111). However, the association did not remain significant after adjustment in our study. An increased mortality was observed among individuals of Black and Other race as compared to White race, a finding which might be related to the fact that a lower interferon-alpha response resulting in a slower viral decline has been observed in HIV-HCV co-infected Blacks (112). It is conceivable that a similar mechanism may be operating in co-infected Blacks on HAART. However, an even higher mortality as compared to Blacks was observed among individuals belonging to Other races which included multiracial groups, Asian, Hawaiian and Pacific Islanders along with Alaskan native and American Indians. It is possible that there might be certain high risk behaviors or practices that make these populations more vulnerable to an increased risk for mortality, however, this relationship needs to be explored further to identify such practices or behaviors. It is also likely that some of the populations in the Other race group include individuals coming from countries which have decreased immunization rates or unsafe injection practices; although this association cannot be fully addressed in this study.

A gradual increase in mortality was observed with increasing age and individuals diagnosed with HIV at 50 years or above had the highest predisposition for mortality. Other

studies have reported similar findings (48, 49). Individuals currently having AIDS had a decreased survival as compared to HIV only infected individuals, a finding which is consistent with other studies (18, 35, 113). A higher propensity for mortality was also observed among IDU's followed by MSM/IDU's, individuals with undetermined risk and heterosexuals. IDU has been identified as a major contributor to mortality in other studies as well (45, 46). It is possible that non-compliance to treatment among IDU's could be factor as well as physician's belief that IDU's are non-compliant. Other factors related to IDU or pharmacological interactions between illicit drugs and antiretroviral therapy could have led to the decreased survival as well. It is also important to note that the effect of IDU was apparent in the category of MSM who also have history of IDU (MSM/IDU). This observation indicates that MSM's who are already vulnerable to developing HIV or AIDS have additional risk if they are in the practice of injecting drugs. Our study also found a decreased survival among individuals with undetermined risk which includes presumed heterosexual males as well as heterosexuals which indicate that as a group heterosexual transmission does confer an additional risk for mortality.

The final model after adjustment showed a significantly increased mortality; among HIV-infected individuals belonging to Black and other races, older age at HIV diagnosis, IDU's, MSM/IDU's, individuals with undetermined risk and heterosexuals as well as a significant interaction between current HIV status and co-infection. To our knowledge, this is the first study that documents an interaction between current HIV status and co-infection. Based on these results, individuals who currently have AIDS and are not co-infected are at a significantly decreased survival as compared to individuals having AIDS who are co-infected. It is possible that individuals who are diagnosed with AIDS and are not co-infected do not get the extra care

and treatment that may be given to AIDS patients who are co-infected with hepatitis viruses. It is also likely that these individuals tend to die earlier before they get infected with hepatitis viruses. Additionally, individuals with AIDS having hepatitis related morbidity may be diagnosed earlier because of the co-morbidity and are then put on appropriate therapy for co-infection which increases their duration of survival. Also, as identified in a study of mortality among HIV-HCV infected individuals, HAART decreased the mortality rate among HIV-HCV co-infected individuals (114) which could partially explain the relatively decreased, albeit significant, risk observed among AIDS infected individuals with co-infection.

Limitations

We were not able to obtain complete information on anti-retroviral therapy among HIV/AIDS infected individuals. However an analysis of the subset of HIV/AIDS infected individuals which were on anti-retroviral therapy in our study yielded similar results as our multivariate analysis. No significant difference in mortality was found among HIV infected individuals or HIV-hepatitis co-infected individuals on antiretroviral therapy as compared to those not on antiretroviral therapy. Additionally, tests for CD4 counts were not routinely done on all HIV cases which restricted our analysis. However, limited analysis of data containing CD4 counts among HIV infected as well as HIV-hepatitis co-infected individuals did not identify any association between CD4 counts and mortality. As the reporting of HBV and HCV infection is based on a passive surveillance system, there is a high likelihood of under reporting and under detection of hepatitis cases. Additionally, the HIV surveillance system in Michigan includes data only for persons who have been confidentially reported by name. Data for infected individuals who have not been tested, have tested only anonymously, or have tested by name but were not reported, are not included which could lead to under reporting of cases (23). However, in spite of

the limitations, the strength of our study lies in the fact that it is a population based study which includes all the statewide data detected by the surveillance system on almost all HIV/AIDS infected individuals as well as persons having hepatitis B and C co-infection residing in the state of Michigan all of which assists in reducing selection bias. Furthermore, our study had a relatively sufficient follow-up period of four years, an adequate sample size, along with a representative group of persons including minorities with HIV infection.

Conclusions

With the advent of HAART, there has been an increased survival among HIV/AIDS patients; however, challenges for treatment still remain because of other co-morbidities like hepatitis B and C infection. This population based study indicates that mortality among HIV/AIDS infected individuals with hepatitis co-infection is a continuing problem even after the availability of HAART. Our study identified certain high risk populations like individuals of Black and Other race which were at a higher risk for mortality. It is particularly concerning that individuals belonging to other races were also at a higher risk. Currently having AIDS conferred a higher risk of mortality which highlights the importance of early diagnosis and treatment of AIDS. An increased risk of death was observed with increasing age at HIV diagnosis which was more apparent after 30 years of age whereas the highest risk was seen among individuals who were 50 years and older. For HIV transmission risk categories, IDU remains a major contributor to mortality, a finding consistent with earlier studies, whereas additionally, MSM/IDU, and heterosexual transmission were important predictors for mortality.

The study also demonstrated an interaction between current HIV status and co-infection, a finding which underscores the importance of complex relationships between different factors

which are associated with mortality. There is a need to further explore these associations in order to plan and implement interventions to reduce mortality among this vulnerable population of HIV infected individuals. Future research studies should focus upon the impact of early initiation of antiretroviral therapy for HIV co-infected individuals and the advantages of early screening of all HIV/AIDS infected individuals for co-morbidities like hepatitis along with identification of additional high risk behaviors or practices that may be present specifically in HIV-hepatitis co-infected individuals.

Figure 4.1. Kaplan-Meier curves showing mortality among HIV/AIDS infected individuals, stratified by co-infection status.

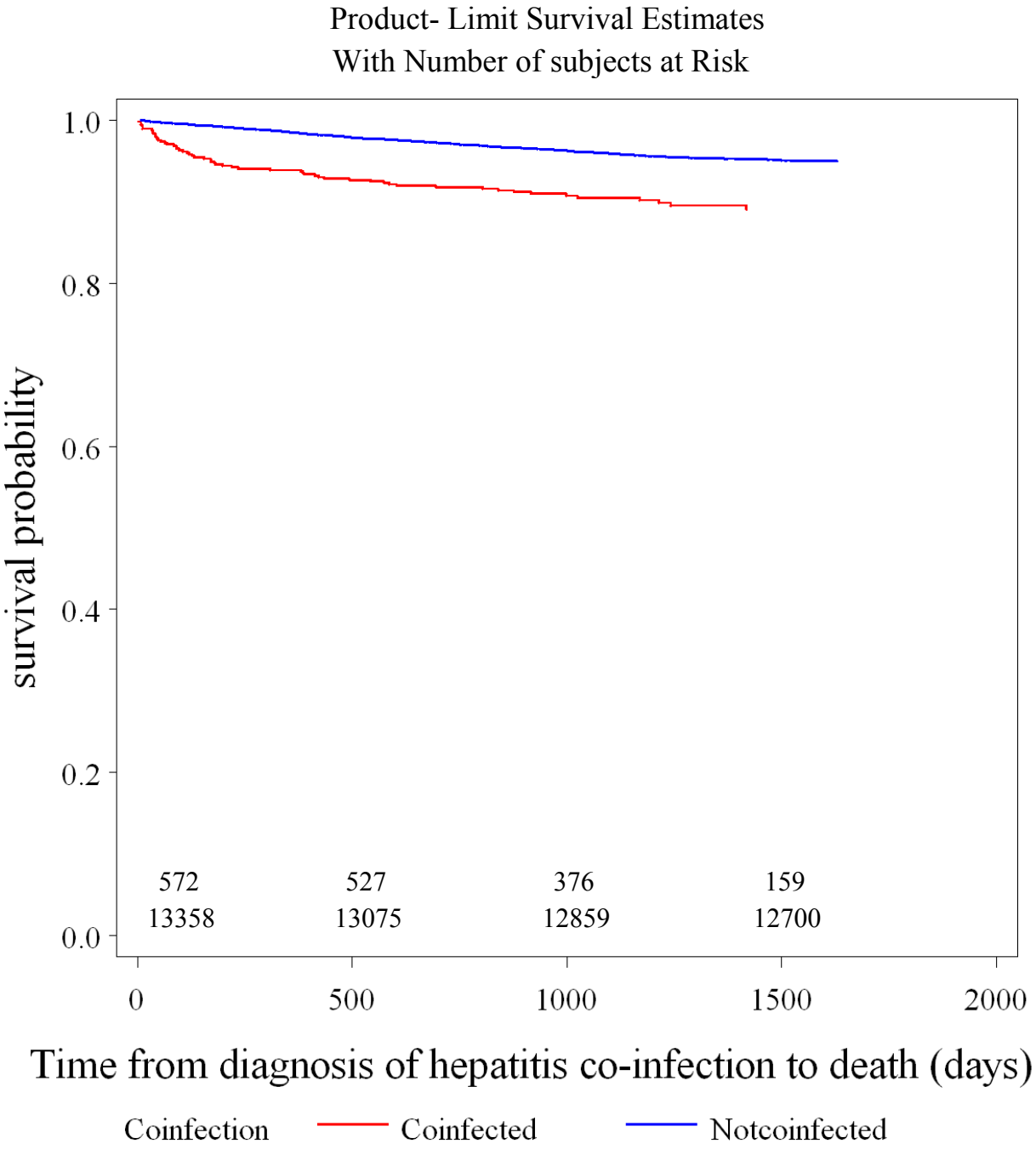


Table 4.1. Distribution of basic characteristics of the HIV/AIDS infected individuals in Michigan (*n*=13,930)

Variable	Frequency (%)
Coinfection	
Coinfected*	572 (4.1)
Not coinfected	13358 (95.9)
Sex	
Male	10584 (76.0)
Female	3346 (24.0)
Race	
White (non-Hispanic)	4956 (35.6)
Black (non-Hispanic)	8088 (58.1)
Hispanic	569 (4.1)
Asian/HI/PI †	72 (0.5)
American Indian/Alaskan native (non-Hispanic)	42 (0.3)
Multi Race/Unknown/ Other (non-Hispanic)	203 (1.4)
HIV transmission Risk ‡	
Blood products	85 (0.6)
High risk heterosexual	1796 (12.9)
Presumed Heterosexual (PH)-male	1201 (8.6)
Presumed Heterosexual (PH)- female	793 (5.7)
IDU	1362 (9.8)
MSM	6807 (48.9)
MSM/IDU	539 (3.9)
Perinatal	156 (1.1)
Unknown	1191 (8.5)
Age at HIV diagnosis (years)	
0 - 12	178 (1.3)
13 - 19	638 (4.6)
20 - 24	1753 (12.6)
25 - 29	2260 (16.2)
30 - 39	4833 (34.7)
40 - 49	2974 (21.3)
50 - 59	1044 (7.5)
60 and over	247 (1.8)
Missing	3 (0.0)
Current HIV status	
AIDS	7707 (55.3)
HIV-NA (not AIDS)	6223 (44.7)

*Coinfection=Any HIV infected individual that is infected by hepatitis B and C virus (acute and chronic) †Asian/Hawaiian, Pacific Islander, non-Hispanic, ‡Heterosexual female=Female who denies IDU and has had sex with a man, MSM= Male-male sex, IDU=Injecting drug user

Table 4.2. Multivariable Cox regression analysis of factors associated with survival among HIV/AIDS infected individuals in the state of Michigan

Variable	Crude HR	95% CI for HR	Adjusted HR	95% CI for Adjusted HR
Coinfection				
Not coinfected	1			
Coinfected	2.4	1.8-3.2		
Sex				
Male	1		1	
Female	1.2	1.0-1.4	0.9	0.8-1.2
Race				
White (non-Hispanic)	1		1	
Black (non-Hispanic)	1.5	1.3-1.8	1.3	1.1-1.6
Hispanic	1.1	0.7-1.7	1.0	0.6-1.5
Other *	2.3	1.5-3.4	2.2	1.4-3.2
Age at HIV diagnosis (years)				
< 20	1		1	
20 - 29	2.4	1.3-4.4	1.7	0.9-3.1
30 - 39	3.1	1.8-5.6	1.8	1.0-3.3
40 - 49	4.6	2.6-8.2	2.5	1.4-4.5
50 and over	9.0	5.0-16.1	4.7	2.6-8.6
Current HIV status				
HIV-NA (not AIDS)	1			
AIDS	5.9	4.8-7.4		
HIV transmission Risk				
MSM	1		1	
Blood products	1.3	0.5-3.5	1.4	0.5-3.7
Heterosexual†	1.4	1.2-1.8	1.4	1.1-1.8
IDU	2.8	2.3-3.4	2.1	1.6-2.6
MSM/IDU	1.8	1.2-2.5	1.5	1.1-2.2
Perinatal‡	-	-	-	-
Undetermined§	1.7	1.4-2.1	1.5	1.2-1.9
Interaction				
Current HIV status x coinfection				
AIDS vs HIV-NA				
Coinfected			2.4	1.2-4.8
Not coinfected			5.9	4.6-7.4

* Other= Multiracial, Asian, Hawaiian & Pacific Islander, Alaskan Native, American Indian

[†]Heterosexual= Presumed Heterosexual (PH)- female and HRH (High risk heterosexual), [‡] Some cells have zero counts, [§]Undetermined=Unknown (Males and Females with no identified risk) and Presumed Heterosexual (PH)-male

CHAPTER 5.

SUMMARY AND CONCLUSIONS

Spatial study

This spatial study identified localized clusters of HIV-hepatitis B or C co-infection in counties of the Upper Peninsula, north, west and northwestern Michigan and adjacent counties in addition to a few non-significant counties in the southern portion of the state. However, the high risk clusters identified in the Bernoulli and Poisson models were not in counties in Southeast Michigan where there is high HIV prevalence and high population density. It is possible that the geography of HIV-hepatitis co-infection prevalence is different from the geography of HIV prevalence. This could be due to the presence of some unobserved factors that might influence the transmission of hepatitis infection among HIV infected individuals that are different from the transmission of HIV infection among the normal population. The Poisson clusters were found in certain counties that had significant clustering of HIV-hepatitis co-infection after adjustment for sex, race and current HIV status. Therefore, it is essential that the geographic analyses of incidence or prevalence should take into account characteristics that are significantly associated with prevalence to delineate the underlying spatial structure. In this respect, spatial cluster analysis serves as an important tool to delineate infectious disease clusters, which could be missed by other analytic methods that do not consider geography.

Comparison of the Bernoulli and Poisson methods revealed significant overlapping counties. The overlapping counties namely Allegan, Newaygo Lake, Benzie, and Leelanau indicated that these areas may be ‘hotspots’ for HIV-hepatitis co-infection that require further

investigation. It is likely that the counties that showed significant clustering of HIV-hepatitis co-infection by both methods have certain characteristics that complement the HIV infected population. It is possible that there could also be a lack of available or accessible health services in the counties with significant HIV and hepatitis co-infection clustering. Future research should investigate the relationship between HIV co-infection and the number of hospitals or other health services, which could affect access to health care and early treatment and diagnosis. Additionally, these counties could be areas where injection drug use is common.

The results from this geographic study can guide policy makers and health managers to target interventions and disease control measures towards these areas. In addition, efficient allocation of resources to these areas can be considered as a means to obtain maximum benefit from any measures undertaken to prevent spread of hepatitis infection among the high risk population of HIV infected individuals. Future studies should focus upon identifying risk factors that are associated with clustering of HIV-hepatitis co-infection in these counties as well as modifiable factors that tend to prevent these infections.

Prevalence study

Although the prevalence of HIV- hepatitis co-infections in Michigan was not higher than the other studies conducted in the US on the same topic, it does represent a public health problem especially when considering the vulnerability of the immunocompromised HIV infected population. An important finding in our study was the identification of males of different races as well as of Black race to be at a higher risk of hepatitis co-infections. The majority of studies on

HIV and hepatitis co-infection indicated that individuals of Black race are at a higher risk of HIV/AIDS as well as for hepatitis co-infection, however, our results indicate that other races might be at a higher risk for hepatitis co-infections. This association needs to be explored further to identify racial subgroups which might be at a higher risk for hepatitis co-infections. Possible reasons could be inadequate immunization coverage for hepatitis B, cultural practices, poor access to health care, or risk factors specific to some racial subgroups.

Currently having AIDS and being of older age at diagnosis were found to be important predictors of hepatitis co-infection. It is likely that being co-infected with hepatitis could have led to rapid progression to AIDS or there may be other factors specific to AIDS which could lead these individuals to acquire hepatitis B or C infections. It is conceivable that older individuals had HIV infection earlier on but were diagnosed later. It is also likely that these individuals had more chances of acquiring hepatitis infection through similar transmission routes because the duration of exposure to viral hepatitis is more likely to be higher in older individuals. Another possibility could be that they are more immunologically compromised when they are infected with HIV at an older age as compared to a younger age making them more likely to develop chronic hepatitis infection.

An important finding was the correlation of transmission through blood products with co-infection which points to the continuing issue of screening blood, and blood products and indicates that additional measures should be taken to address this issue. Other high risk populations identified in this study were IDUs and MSM/IDU which is consistent with previous studies. The study also demonstrated for the first time interactions between current HIV status,

and sex and current HIV status, sex, and age at HIV diagnosis. According to the results, males currently having AIDS were more likely to be co-infected with hepatitis B or C than females. It is likely that there could be some risk factors more prevalent in males having AIDS as compared to females which could result in them acquiring hepatitis infection more commonly than females. Additionally, the interaction between current HIV status, sex, and age at HIV diagnosis indicated that males currently having AIDS and at a younger age were more likely to be co-infected, in addition to males who had AIDS and were above 50 years of age. The importance of these findings needs to be explored further in order to implement preventive measures and interventions to reduce the prevalence of hepatitis co-infections. Finally, future studies should be conducted keeping in mind the changing epidemiology of HIV-hepatitis co-infections and the urgent need to prevent co-morbidities in an already high risk immune-compromised population of HIV/AIDS infected individuals.

Survival study

The initiation of HAART as an effective form of anti-retroviral therapy has resulted in an increased survival among HIV/AIDS patients. However, challenges for treatment still prsist because of other co-morbidities like hepatitis B and C infection. This study points to the fact that mortality among HIV/AIDS infected individuals with hepatitis co-infection is a continuing problem even after the availability of HAART. Our study identified certain high risk populations like individuals of Black and Other race which were at an increased risk for mortality. It is particularly concerning that individuals belonging to other races were at a higher risk for death which could indicate a shift in the mortality profile of HIV and hepatitis co-infected individuals.

Currently having AIDS was associated with a higher risk of mortality which underscores the importance of early diagnosis and treatment of AIDS. An elevated risk of death was observed with increasing age at HIV diagnosis which was more apparent after 30 years of age whereas the highest risk was seen among individuals who were 50 years and older. For HIV transmission risk categories, IDU remains a major predictor for mortality, a finding consistent with earlier studies. Additionally, MSM/IDU, and heterosexual transmission were important contributors to mortality.

Our study also demonstrated an interaction between current HIV status and co-infection. It is important to note that individuals who currently have AIDS and are not co-infected are at a significantly decreased survival as compared to individuals having AIDS who are co-infected. Possible reasons could be an early mortality among AIDS patients before diagnosis of hepatitis infections, extra care and treatment that may be given to AIDS and hepatitis co-infected patients or early diagnosis and treatment of AIDS and hepatitis co-infected patients.

The findings from this study highlight the importance of complex relationships between different factors which are associated with mortality. It is essential to further explore these associations in order to plan and implement interventions to reduce mortality among HIV infected individuals. Future research should emphasize upon the impact of early initiation of antiretroviral therapy for HIV co-infected individuals and the benefits of early screening of all HIV or AIDS infected individuals for co-morbidities like hepatitis. Furthermore, identification of additional high risk behaviors or practices that may be present specifically in HIV-hepatitis co-

infected individuals could also serve to be an important point for prevention and control of hepatitis co-infections.

REFERENCES

REFERENCES

1. Global Report. UNAIDS report on the Global AIDS Epidemic 2010. (http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en.pdf). (Accessed January 24, 2010).

2. HIV/AIDS in the United States. (http://www.cdc.gov/hiv/resources/factsheets/us.htm). (Accessed April 6, 2008).

3. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA*. 2008;300(5):520-529.

4. United states of America. HIV and AIDS estimates 2009. (http://www.unaids.org/en/regionscountries/countries/unitedstatesofamerica/). (Accessed January 24, 2010).

5. Quarterly HIV/AIDS report, Michigan. January 2011. (http://www.michigan.gov/documents/mdch/Jan_2011_344131_7.pdf). (Accessed February 24, 2011).

6. Viral Hepatitis. (http://www.cdc.gov/hepatitis/index.htm). (Accessed May 8, 2011).

7. Hepatitis B. (http://www.who.int/mediacentre/factsheets/fs204/en/). (Accessed October 30, 2009).

8. Hepatitis C: Disease burden. (http://www.who.int/vaccine_research/diseases/viral_cancers/en/index2.html). (Accessed October 30, 2009).

9. Hepatitis B: FAQs for health professionals: Overview and statistics. (http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#overview). (Accessed October 28, 2009).

10. 2008 Acute Hepatitis B Surveillance Summary. (http://www.michigan.gov/documents/mdch/Acute_Hepatitis_B_Surveillance_Summary_2008_289340_7.pdf). (Accessed November 10, 2009).

11. 2008 Chronic Hepatitis B Surveillance Summary. (http://www.michigan.gov/documents/mdch/Chronic_Hepatitis_B_Surveillance_Summary_2008_289337_7.pdf). (Accessed November 10, 2009).

12. Hepatitis C:FAQs for health professionals: Overview and statistics. (http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1). (Accessed October 28, 2009).

13. 2008 Acute Hepatitis C Surveillance Summary. (http://www.michigan.gov/documents/mdch/Acute_Hepatitis_C_Surveillance_Summary_2008_289339_7.pdf). (Accessed November 10, 2009).

14. 2008 Chronic Hepatitis C Surveillance Summary. (http://www.michigan.gov/documents/mdch/Chronic_Hepatitis_C_Surveillance_Summary_2008_289342_7.pdf). (Accessed November 10, 2009).

15. Barth RE, Huijgen Q, Taljaard J, et al. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. [electronic article]. *Int J Infect Dis*. 2010;14(12):e1024-1031.

16. Victoria MB, Victoria Fda S, Torres KL, et al. Epidemiology of HIV/HCV coinfection in patients cared for at the Tropical Medicine Foundation of Amazonas. *Braz J Infect Dis*. 2010 ;14(2):135-40.

17. Sungkanuparph S, Vibhagool A, Manosuthi W, et al. Prevalence of hepatitis B virus and hepatitis C virus co-infection with human immunodeficiency virus in Thai patients: a tertiary-care-based study. *J Med Assoc Thai*. 2004;87(11):1349-1354.

18. Weis N, Lindhardt BO, Kronborg G, et al. Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. *Clin Infect Dis*. 2006;42(10):1481-1487.

19. Larsen C, Pialoux G, Salmon D, et al. Prevalence of hepatitis C and hepatitis B infection in the HIV-infected population of France, 2004. *Euro Surveill*. 2008;13(22):1-4.

20. Omland LH, Weis N, Skinhøj P, et al. Impact of hepatitis B virus co-infection on response to highly active antiretroviral treatment and outcome in HIV-infected individuals: a nationwide cohort study. *HIV Med*. 2008;9(5):300-306.

21. Portelinha Filho AM, Nascimento CU, Tannouri TN, et al. Seroprevalence of HBV, HCV and HIV co-infection in selected individuals from state of São Paulo, Brazil. *Mem Inst Oswaldo Cruz*. 2009;104(7):960-963.

22. Zhou YH, Liu FL, Yao ZH et al. Comparison of HIV-, HBV-, HCV- and Co-Infection Prevalence between Chinese and Burmese Intravenous Drug Users of the China-Myanmar Border Region [electronic article]. *PLoS One*. 2011;6(1):e16349.

23. 2010 Epidemiologic Profile of HIV/AIDS in Michigan. (http://www.michigan.gov/documents/mdch/2010_EPI_PROFILE_ENTIRE_335483_7.pdf). (Accessed January 24, 2010).

24. Eyster ME,Fried MW,Di Bisceglie AM,Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs:relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. Blood 1994; 84: 1020‑1023.

25. Beld M,Penning M, Lukashov V, et al. Evidence that both HIV and HIV-induced immunodeficiency enhance HCV replication among HCV seroconverters.Virology 1998; 244: 504‑512.

26. Daar ES,Lynn H,Donfield S, et al. Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. J Infect Dis 2001; 183: 589‑595.

27. Gilson RJ,Hawkins AE,Beecham MR, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. AIDS 1997; 11: 597–606.

28. Stanojevic M,Zerjav S,Jevtovic DJ,Markovic LJ. HBsAg as the antigen component of circulatingimmune complexes in HIV-infected patients. Biomed Pharmacother 2000; 54: 163–167.

29. Chang JJ, Sirivichayakul S, Avihingsanon A, Thompson AJ, Revill P, Iser D, Slavin J, Buranapraditkun S, Marks P, Matthews G, Cooper DA, Kent SJ, Cameron PU, Sasadeusz J, Desmond P, Locarnini S, Dore GJ, Ruxrungtham K, Lewin SR. Impaired quality of the hepatitis B virus (HBV)-specific T-cell response in human immunodeficiency virus type 1-HBV coinfection J Virol. 2009 Aug;83(15):7649-58

30. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD; HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr. 2006 Sep;43(1):27-34.

31. Sabin CA, Telfer P, Phillips AN, et al. The association between hepatitis C virus genotype and human immunodeficiency virus disease progression in a cohort of hemophilic men. *J Infect Dis*. 1997; 175:164–168.

32. Sulkowski MS, Moore RD, Mehta SH, et al. Hepatitis C and progression of HIV disease. *JAMA*. 2002;288(2):199-206.

33. Hoffmann CJ, Charalambous S, Martin DJ, et al. Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program. *Clin Infect Dis*. 2008;47(11):1479-1485.

34. Riley ED, Bangsberg DR, Guzman D, et al. Antiretroviral therapy, hepatitis C virus, and AIDS mortality among San Francisco's homeless and marginally housed. *J Acquir Immune Defic Syndr*. 2005;38(2):191-195.

35. Macías J, Pineda JA, Leal M, et al. Influence of hepatitis C virus infection on the mortality of antiretroviral-treated patients with HIV disease. *Eur J Clin Microbiol Infect Dis*. 1998;17(3):167-170.

36. Sherman KE, Rouster SD, Chung RT, et al. Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis*. 2002;34:831-837.

37. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med*. 2003;138(3):197-207.

38. Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology*. 2002;36(5 suppl 1):S201S-209S.

39. HIV/AIDS and Viral Hepatitis. (http://www.cdc.gov/hepatitis/Populations/hiv.htm). (Accessed October 30, 2009).

40. Thio CL, Seaberg EC, Skolasky R Jr, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926.

41. Bonacini M, Louie S, Bzowej N, et al. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. *AIDS*. 2004;18(15):2039-2045.

42. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS*. 2005;19(6):593-601.

43. Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis*. 2005;192(6):992-1002.

44. Ockenga J, Tillmann HL, Trautwein C, et al. Hepatitis B and C in HIV-infected patients. Prevalence and prognostic value. *J Hepatol*. 1997;27(1):18-24.

45. Greub G, Ledergerber B, Battegay M, et al. 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*. 2000;356(9244):1800-1805.

46. Voirin N, Trépo C, Miailhes P, et al. Survival in HIV-infected patients is associated with hepatitis C virus infection and injecting drug use since the use of highly active antiretroviral therapy in the Lyon observational database. *J Viral Hepat*. 2004;11(6):559-562.

47. Sheng WH, Chen MY, Hsieh SM, et al. Impact of chronic hepatitis B virus (HBV) infection on outcomes of patients infected with HIV in an area where HBV infection is hyperendemic. *Clin Infect Dis*. 2004;38(10):1471-1477.

48. Anderson KB, Guest JL, Rimland D et al. Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. *Clin Infect Dis*. 2004;39(10):1507-1513.

49. Backus LI, Phillips BR, Boothroyd DB, et al. Effects of hepatitis C virus coinfection on survival in veterans with HIV treated with highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2005;39(5):613-619.

50. Marcellin P, Pequignot F, Delarocque-Astagneau E, et al. Mortality related to chronic hepatitis B and chronic hepatitis C in France: evidence for the role of HIV coinfection and alcohol consumption. *J Hepatol*. 2008;48(2):200-207.

51. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. *AIDS*. 2009;23(14):1881-1889.

52. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clin Infect Dis*. 2009;48(12):1763-1771.

53. Chen TY, Ding EL, Seage Iii GR, et al. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin Infect Dis*. 2009;49(10):1605-1615.

54. Tanser F, Bärnighausen T, Cooke GS, et al. Localized spatial clustering of HIV infections in a widely disseminated rural South African epidemic. *Int J Epidemiol*. 2009;38(4):1008-1016.

55. Wand H, Ramjee G. Targeting the hotspots: investigating spatial and demographic variations in HIV infection in small communities in South Africa. *J Int AIDS Soc*. 2010;13:41.

56. Westercamp N, Moses S, Agot K, et al. Spatial distribution and cluster analysis of sexual risk behaviors reported by young men in Kisumu, Kenya. *Int J Health Geogr*. 2010 May 22;9:24.

57. Kulldorff M. and Information Management Services, Inc. SaTScan™ v9.0: Software for the spatial and space-time scan statistics. http://www.satscan.org/, 2009.

58. Jennings JM, Curriero FC, Celentano D, et al. Geographic identification of high gonorrhea transmission areas in Baltimore, Maryland. *Am J Epidemiol*. 2005;161(1):73-80.

59. Bernstein KT, Curriero FC, Jennings JM, et al. Defining core gonorrhea transmission utilizing spatial data. *Am J Epidemiol*. 2004;160(1):51-58.

60. Trooskin SB, Hadler J, St Louis T, et al. Geospatial analysis of hepatitis C in Connecticut: a novel application of a public health tool. *Public Health*. 2005;119(11):1042-1047.

61. Haque U, Hashizume M, Sunahara T, et al. Progress and challenges to control malaria in a remote area of Chittagong hill tracts, Bangladesh. *Malar J*. 2010;9:156.

62. Mirghani SE, Nour BY, Bushra SM, et al. The spatial-temporal clustering of Plasmodium falciparum infection over eleven years in Gezira State, The Sudan. *Malar J*. 2010;9:172.

63. Haque U, Huda M, Hossain A, et al. Spatial malaria epidemiology in Bangladeshi highlands. *Malar J*. 2009;8:185.

64. Ageep TB, Cox J, Hassan MM, et al. Spatial and temporal distribution of the malaria mosquito Anopheles arabiensis in northern Sudan: influence of environmental factors and implications for vector control. *Malar J*. 2009;8:123.

65. Klassen AC, Kulldorff M, Curriero F. Geographical clustering of prostate cancer grade and stage at diagnosis, before and after adjustment for risk factors. *Int J Health Geogr*. 2005;4(1):1.

66. Osei FB, Duker AA. Spatial dependency of V. cholera prevalence on open space refuse dumps in Kumasi, Ghana: a spatial statistical modelling. *Int J Health Geogr*. 2008;7:62.

67. Song C, Kulldorff M. Power evaluation of disease clustering tests. *Int J Health Geogr*. 2003 ;2(1):9.

68. Complete 2006 Epidemiologic Profile of HIV/AIDS in Michigan. (http://michigan.gov/mdch/0,1607,7-132-2944_5320_5331-36307--,00.html). (Accessed April 6, 2008).

69. Kellerman SE, Hanson DL, McNaghten AD, et al. Prevalence of chronic hepatitis B and incidence of acute hepatitis B infection in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003;188(4):571-577.

70. Chun HM, Fieberg AM, Hullsiek KH, et al. Epidemiology of Hepatitis B virus infection in a US cohort of HIV-infected individuals during the past 20 years. *Clin Infect Dis*. 2010;50(3):426-436.

71. Geography of Michigan. (http://www.netstate.com/states/geography/mi_geography.htm). (Accessed January 23, 2010).

72. 2010 Census Data for Michigan. (http://www.michigan.gov/cgi/0,1607,7-158-54534-252541--,00.html). (Accessed March 29, 2011).

73.1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults.[No authors listed] *MMWR Recomm Rep*. 1992;41(RR-17):1-19.

74. Hepatitis B, acute. (http://www.cdc.gov/ncphi/disss/nndss/casedef/hepatitisb2000.htm). (Accessed October 28, 2009).

75. Chronic Hepatitis B Virus.
(http://www.cdc.gov/ncphi/disss/nndss/casedef/hepatitisbcurrent.htm). (Accessed October 28, 2009).

76. Hepatitis C virus infection, acute.
(http://www.cdc.gov/ncphi/disss/nndss/casedef/hepatitiscacutecurrent.htm). (Accessed October 28, 2009).

77. Hepatitis C Virus Infection, Past or Present.
(http://www.cdc.gov/ncphi/disss/nndss/casedef/hepatitisccurrent.htm). (Accessed October 28, 2009).

78. Michigan Department of Community Health: Health care professionals' guide to the Michigan communicable disease rules (Version 2006.1).
(http://www.michigan.gov/documents/hlth_care_prof_guide_167371_7.pdf). (Accessed April 6, 2008).

79. Kulldorff M. A spatial scan statistic. *Commun. Statist. Theory Meth*. 1997; 26:1481-1496.

80. Kulldorff M, Nagarwalla N. Spatial disease clusters: Detection and inference. *Stat Med*. 1995 ;14(8):799-810.

81. Kulldorff M. SaTScan™ User Guide for version 9.0. 2010;1-107.

82. Heymann DL ed. *Control of Communicable Diseases Manual*. 19th ed. Washington, DC: American Public Health Association; 2008.

83. 2010 Health Facilities Atlas. (http://www.michigan.gov/mdch/0,1607,7-132-2945_5106-63274--,00.html). (Accessed March 31, 2011).

84. Michigan HIDTA. (http://www.whitehousedrugpolicy.gov/hidta/mich.html). (Accessed May 24, 2011).

85. The High Intensity Drug Trafficking Area Program: An Overview. (http://www.ncjrs.gov/ondcppubs/publications/enforce/hidta2001/overview.html#4). (Accessed May 24, 2011)

86. Quarterly HIV/AIDS report, Michigan. October 2010. (http://www.michigan.gov/documents/mdch/Oct_2010_335648_7.pdf). (Accessed 01/02/2011).

87. Annual review of HIV trends in Michigan (2004-2008). (http://www.michigan.gov/documents/mdch/MIReport_Final_325200_7.pdf). (Accessed January 1, 2011).

88. Eyster ME, Diamondstone LS, Lien JM, et al. Natural history of hepatitis C virus infection in multitransfused hemophiliacs: effect of coinfection with human immunodeficiency virus.The Multicenter Hemophilia Cohort Study. *J Acquir Immune Defic Syndr.* 1993; 6:602–610.

89. Benhamou Y, Bochet M, DiMartino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. *Hepatology*. 1999; 30:1054–1058.

90. Puoti M, Airoldi M, Bruno R, et al. Hepatitis B Virus Co-infection in Human Immunodeficiency Virus-infected Subjects. *AIDS Rev*. 2002;4(1):27-35.

91. Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B carrier state. *J Infect Dis*. 1991; 163: 1138–1140.

92. Shukla NB, Poles MA. Hepatitis B virus infection: co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus. *Clin Liver Dis*. 2004; 8: 445–460.

93. Michigan in Brief. Information about the state of Michigan. (http://www.michigan.gov/documents/hal_lm_MiB_156795_7.pdf). (Accessed January 17, 2011).

94. Kim JH, Psevdos G, Suh J, et al. Co-infection of hepatitis B and hepatitis C virus in human immunodeficiency virus-infected patients in New York City, United States.*World J Gastroenterol*. 2008;14(43):6689-6693.

95. Otegbayo JA, Taiwo BO, Akingbola TS, et al. Prevalence of hepatitis B and C seropositivity in a Nigerian cohort of HIV-infected patients. *Ann Hepatol*. 2008;7(2):152-156.

96. Kuniholm MH, Mark J, Aladashvili M, et al. Risk factors and algorithms to identify hepatitis C, hepatitis B, and HIV among Georgian tuberculosis patients. *Int J Infect Dis*. 2008;12(1):51-56.

97. Dwyre DM, Fernando LP, Holland PV. Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century.*Vox Sang*. 2011;100(1):92-98.

98. Reuter S, Oette M, Wilhelm FC, et al. Prevalence and characteristics of hepatitis B and C virus infections in treatment-naïve HIV-infected patients. *Med Microbiol Immunol*. 2011 ;200(1):39-49.

99. Vibhagool A, Manosuthi W, Kiertiburanakul S, et al. Prevalence of hepatitis B virus and hepatitis C virus co-infection with human immunodeficiency virus in Thai patients: a tertiary-care-based study. *J Med Assoc Thai*. 2004;87(11):1349-1354.

100. Lincoln D, Petoumenos K, Dore GJ, et al. HIV/HBV and HIV/HCV coinfection, and outcomes following highly active antiretroviral therapy. *HIV Med*. 2003;4(3):241-249.

101. Tedaldi EM, Hullsiek KH, Malvestutto CD, et al. Prevalence and characteristics of hepatitis C virus coinfection in a human immunodeficiency virus clinical trials group: the Terry Beirn Community Programs for Clinical Research on AIDS. *Clin Infect Dis*. 2003;36(10):1313-1317.

102. Dorrucci M, Valdarchi C, Suligoi B, et al. The effect of hepatitis C on progression to AIDS before and after highly active antiretroviral therapy. *AIDS*. 2004;18(17):2313-2318.

103. Romeo R, Rumi MG, Donato MF, et al. Hepatitis C is more severe in drug users with human immunodeficiency virus infection. *J Viral Hepat*. 2000;7(4):297-301.

104. Goodenow C, Netherland J, Szalacha L. AIDS-related risk among adolescent males who have sex with males, females, or both: evidence from a statewide survey. *Am J Public Health.* 2002;92(2):203-210.

105. Montgomery SB, Hyde J, De Rosa CJ, et al. Gender differences in HIV risk behaviors among young injectors and their social network members. *Am J Drug Alcohol Abuse*. 2002;28(3):453-475.

106. Institute of Medicine. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Colvin H, Mitchell A, eds; Committee on the Prevention and Control of Viral Hepatitis Infections, 2010.

107. Hansen AB, Gerstoft J, Kronborg G, et al. Mortality in siblings of patients coinfected with HIV and hepatitis C virus. *J Infect Dis*. 2007;195(2):230-235.

108. Hansen AB, Lohse N, Gerstoft J, et al. Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus [electronic article]. *PLoS One*. 2007;2(1):e738.

109. Marins JR, Barros MB, Machado H, et al. Characteristics and survival of AIDS patients with hepatitis C: the Brazilian National Cohort of 1995-1996. *AIDS*. 2005;19(Suppl 4):27S-30S.

110. Jain MK. Mortality in patients coinfected with hepatitis B virus and HIV: could antiretroviral therapy make a difference?. *Clin Infect Dis*. 2009;48(12):1772-1774.

111. Emery J, Pick N, Mills EJ, et al. Gender differences in clinical, immunological, and virological outcomes in highly active antiretroviral-treated HIV-HCV coinfected patients. *Patient Prefer Adherence*. 2010;4:97-103.

112. Rozenberg L, Haagmans BL, Neumann AU, et al. Therapeutic response to peg-IFN-alpha-2b and ribavirin in HIV/HCV co-infected African-American and Caucasian patients as a function of HCV viral kinetics and interferon pharmacodynamics. *AIDS*. 2009;23(18):2439-2450.

113. Rosenthal E, Poirée M, Pradier C, et al. Mortality due to hepatitis C-related liver disease in HIV-infected patients in France (Mortavic 2001 study). *AIDS*. 2003;17(12):1803-1809.

114. Tedaldi EM, Baker RK, Moorman AC, et al. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2003;36(3):363-367.