EPIDEMIOLOGICAL STUDY OF *NEISSERIA GONORRHEAE* CO-INFECTION AMONG MALES WITH HIV/AIDS RESIDING IN THE STATE OF MICHIGAN

By

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ABSTRACT

EPIDEMIOLOGICAL STUDY OF *NEISSERIA GONORRHEAE* CO-INFECTION AMONG MALES WITH HIV/AIDS RESIDING IN THE STATE OF MICHIGAN

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Background: Epidemiological evidences suggest a synergistic relationship between Human Immunodeficiency Virus (HIV) and *N. gonorrheae* in co-infected individuals. The objectives of this study were; 1) to test whether age at HIV between those with a history of *N. gonorrheae* infection was younger as compared to those with no history of reported *N. gonorrheae* infection, 2) to test whether age at HIV progression event (death or Acquired Immune Deficiency Syndrome (AIDS)) was younger as well as time from HIV diagnosis to HIV progression event was reduced in individuals with a history of *N. gonorrheae* infection as compared to those without, 3) to investigate the geospatial distribution of HIV and *N. gonorrheae* in the State of Michigan, and 4) to investigate the differences in biological markers (CD4 cell count and viral load) in a sub-population of HIV *N. gonorrheae* co-infected individuals.

Methods: A retrospective cohort study from 2005-2011 was conducted in collaboration with Michigan Department of Community Health on Michigan HIV positive males with a history of *N. gonorrheae* infection between 2005-2011 as well as HIV positive males with no history of *N. gonorrheae* infection who were alive at the start of 2005. A sub-group analysis of Michigan HIV positive males with a reported *N. gonorrheae* infection between 2011 and 2013 to investigate biological markers of HIV progression. Spatial, survival, and linear regression analyses were performed on the data to evaluate the objectives of the study.

Results: Mean age at HIV diagnosis was found to be younger in individuals with pre-HIV *N. gonorrheae* infections. On average males with 2 or more pre-HIV *N. gonorrheae* infections were 10.2 years younger than individuals with no *N. gonorrheae* infections, and males with only one pre-HIV *N. gonorrheae* infection were 7.3 years younger at HIV diagnosis. Hazard of AIDS increased in males with post-HIV *N. gonorrheae* infections, with individuals with multiple post-HIV *N. gonorrheae* infections having increase in hazard of progression to AIDS. A longer HIV to AIDS lag time period was observed in males with multiple post-HIV gonorrhea. Geospatial analysis showed that the area around the City of Detroit and the Tri-County area of Oakland, Macomb, and Wayne have the highest burden of disease due to co-infection as well as represent the most likely clusters for HIV *N. gonorrheae* co-infections. CD4 cell count was found to increase in the year during *N. gonorrheae* infection as well as in the years after as compared to pre-gonorrhea levels. Similarly viral load was found to increase in the year during *N. gonorrheae* infection, however, it did not remain elevated as compared to the pre-gonorrhea states.

Conclusion: This study is a first step in documenting the possible synergistic relationship between *N. gonorrheae* infection and HIV. The study found that age at HIV and age at HIV progression event were reduced (younger at event) than in those with no history of gonorrhea. The study also identified areas of concern using geospatial analysis where resources should be focused to try and reduce and disease. Paradoxically the time from HIV to HIV progression event was increased in those with *N. gonorrheae* infections as compared to those without. Finally the study found that CD4 cell count was increased in the time period during and after *N. gonorrheae* infection, and that viral load was increased in the year during *N. gonorrheae* infection, but returned to pre-gonorrhea levels in the years following.

To
My wife Jessica, without whom none of this would have been possible
AMDG

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

KEY TO ABBREVIATIONS

ACHSP	Advisory Committee for HIV & STD Prevention
AIDS	Acquired Immune Deficiency Syndrome
AmIn/AkNat	American Indian, Alaskan Native, non-Hispanic
ART	Antiretroviral Therapy
ARV	Antiretroviral
Asian/HI/PI	Asian/Hawaiian, Pacific Islander non-Hispanic
CCDM	*Control of Communicable Disease Manual*
CCR-5	C-C Chemokine Receptor Type 5
CD4	Cluster of Differentiation 4
CD8	Cluster of Differentiation 8
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
D. C.	District of Columbia
DGI	Disseminated Gonococcal Infection
dL	Deciliter
DNA	Deoxyribonucleic Acid
ESRI	Environmental Systems Research Institute
Fem HCM	Heterosexual intercourse with female
GEE	General Estimating Equation
GIS	Geographic Information Systems
GP	Glycoprotiens
GUD	Genital Ulcerative Diseases
HAART	Highly Active Antiretroviral Therapy

HIPAA	Health Insurance Portability and Accountability Act
HIV	Human-Immunodeficiency Virus
HRadj	Adjusted Hazard Ratio
HR	Hazard Ratio
IDU	Injection Drug User
IRB	Institutional Review Board
JAMA	Journal of the American Medical Association
LC	Langerhas cells
LOS	Lipooligosaccharides
Male HCFR	Male who had sex with a female at risk for HIV
MDCH	Michigan Department of Community Health
MMWR	Morbidity and Mortality Weekly Report
MSM	Men who have sex with men
MSU	Michigan State University
Multi/Unk/Other	Multirace, Unknown, Other, non-Hispanic
N. gonorrheae	*Neisseria gonorrheae*
OR	Odds Ratio
PCP	Pneumocystis carinii pneumonia
PI	Protease Inhibitor
REACH	Reaching for Excellence in Adolescent Care and Health
RH	Relative Hazard
RNA	Ribonucleic Acid
ROR	Relative Odds Ratio
RR	Relative Risk
RSE	Root Mean Square Error

STD	Sexually Transmitted Disease
Std Dev	Standard Deviation
T cell	Thymus cell
TB	Tuberculosis
TLR	Toll-Like Receptors
US	United States
VH	Viral Hepatitis
WHO	World Health Organization
κB	Kappa B
μL	Microliter

Chapter 1.

Background and Objectives

1.1 Human-Immunodeficiency Virus/Acquired Immune Deficiency Syndrome

Natural History

Human-Immunodeficiency Virus (HIV) is a lentivirus, a member of the retroviridae family and is a single stranded RNA virus (1). Retroviruses use an enzyme called reverse transcriptase that is a catalyst that transcribes double-stranded DNA from single-stranded RNA (1). There are two species of HIV, HIV-1 and HIV-2, with HIV-1 being the most common infection and HIV-2 primarily associated with western Africa or cases linked to the area (2). HIV-1 consists of three major groups, M, N, O, with M being the most common and is subdivided into 7 distinct subtypes (2). HIV-2 is thought to have a lower virulence than that of HIV-1 (2). HIV is surrounded by a lipid envelope with transmembrane glycoprotein spikes that mediate viral adsorption to the host cell (1). Two important glycoproteins (GP) located on the viral envelope are GP-120 and GP-41 which are important in attachment of the virus to leukocytes via the CD4 receptors on the cell surface for GP-120 and the CCR-5 receptor of macrophages and CD4 cells for GP-41 (1).

The natural reservoir for HIV is humans and it is thought to have evolved from simian immunodeficiency virus (2). The primary mode of transmission is person-to-person via unprotected sexual intercourse, including penile-vaginal and penile-anal (2). Other modes of transmission include the use of HIV infected needles and syringes, vertical transmission from mother to infant during pregnancy, infant delivery, and by breast feeding (2). A final common transmission mode is via transfusion with infected blood (2). Less common modes of

transmission include transplantation of infected organs, contact of infective secretions on abraded skin or mucosa, as well as documented cases of transmission via pre-chewed food from HIV-infected caregivers (2). The incubation period of HIV varies from case to case. However, the majority of those infected will develop detectable antibodies in less than a month (2). Early symptoms of HIV infection often include flu-like illness or mononucleosis-like illness shortly after infection (2). Other symptoms that occur in the majority of patients include typical viral immune response conditions such as fever, rash, inflammation of lymph nodes, and headaches (2). Due to the flu/mononucleosis like symptoms that manifest shortly after infection, initial infections often unnoticed (2). While the immune system starts to respond to the infection, early clinical symptoms of latent HIV infection may not appear until years after initial infection making it hard to pin point actual time the infection took place (2).

The period of communicability is largely unknown, but is suspected to range from shortly after HIV onset and persists through one's lifetime and is dependent on viral load (2). Viral load and risk of transmission is thought to be the highest during early infection before the onset of immune suppression (2). Use of antiretroviral (ARV) treatment has been shown to reduce viral load in blood and genital secretions. Infected individuals who are on ARV treatment are still considered infectious and are at risk of propagating and disseminating the virus (2).

There are four stages associated with HIV infection and they were introduced by the CDC in 2008 (3,4). One of the most important changes introduced with the implementation of HIV stages is that Acquired Immune Deficiency Syndrome (AIDS) has been relabeled as HIV stage 3 with the goal to eliminate the term AIDS (3). Stage 1, Acute Infection, is defined as when "A case does not have any of the conditions associated with severe HIV infection (called an AIDS-defining condition) and has >=500 CD4 cells/µL" (4). Stage 2, Clinical Latency, is defined as

when “A case has no AIDS-defining conditions, but the level of CD4 cells have fallen to 200-499 cells/μL” (4). Stage 3 which traditionally is referred to as AIDS is defined as “Diagnosis with any one of 26 AIDS-defining conditions which are indicative of a severe immune deficiency, or a laboratory test demonstrating severe immune deficiency: CD4 count <200 cell/μL or CD4 percent <14%” (4). The definition of stage 3/AIDS was last changed in 1993 (2). Stage Unknown is an intermediate stage which is defined as “A case of HIV without information available on CD4 levels or AIDS-defining conditions” (4).

Stage 3 or AIDS positive status was first recognized in 1981 when a series of five cases of Pneumocystis carinii pneumonia (PCP) was identified among assumingly healthy men (5). These index cases were written about in the Morbidity and Mortality Weekly Report (MMWR) describing men in Los Angeles. However, physicians were also seeing cases in San Francisco and New York City (1,5). All of the men in the Los Angeles group were identified as homosexuals and within 18 months epidemiologists and public health officials had identified all major risk factors associated with AIDS (5). Once AIDS was identified the incidence of the disease increased sharply from 1981 and peaked around 1993 (5). After 1993 the incidence of AIDS began to decline with a sharp decline starting around 1996 and continuing through 2013 (5). Early AIDS cases were predominately white males, until 1996 when the trend shifted to African Americans (5). The *Control of Communicable Disease Manual* (CCDM) states that the estimated proportion of untreated HIV infected individuals that will develop AIDS is around 90% (2). In developing countries the estimated time to death after AIDS positive status is 3-5 years making the need for control of HIV progression to AIDS a major topic in reducing the global burden of disease (2).

A study by Nelson et al. investigating the temporal trends of HIV in IDUs found that the relative risk was increased (RR=2.27 CI 1.53-3.38) with the presence of any STD (105). The study also found that MSM had an elevated risk (RR=1.90 CI 1.20-3.13) (105). In those that used intravenous drugs on a nondaily basis but did not have sex the risk of HIV was RR=3.83 (CI 1.69-8.69) and in those that did not have sex but used daily the RR as compared to those that did not have sex or use drugs was found to be RR=4.21 (CI 1.90-9.29) (105).

A 1995 study by O'Brien et al. explored the secular trends in CD4 counts in men and found that from 1984 to 1991 there was no discernable change in the natural history of HIV-1 infections (74). The study looked at the baseline CD4 counts (CD4 count at time of HIV diagnosis), a previous seronegative visit, and scheduled post seroconversion visits and found that year of seroconversion did not change the mean CD4 percent at any time point (74). Pre-seropositive visits had a mean CD4 percent of 44% with a range of mean CD4 percent of 42% in 1990 to 46.7% in 1989 (74). The mean CD4 percent for visits 30 months after seroconversion was 28.3% with a mean CD4 percent range of 23.7% in 1988 to 30.7% in 1986, however, at the 30 month period the seroconversion years only ranged from 1984 to 1989, no 30 month data was collected for 1990 or 1991 (74).

A longitudinal model for AIDS by Boscardin et al. investigated the relationship between HIV viral load and CD4 found that individuals with higher baseline CD4 counts started and ended with lower viral loads over a 12 month period (71). The study also found that in those with higher baseline viral load have lower initial and final CD4 counts after a 12 month period as well as a sharper rate decline (71). A 1994 paper by Zeger and Diggle observed that in the time leading up to seroconversion there is a sudden drop in CD4 count, followed by continued CD4 decay as the disease progresses (73). Zeger and Diggle offered up a model that can be used to

predict an individual's CD4 decay progression by combining the individual's data with the population's curve of CD4 decay (73). A study by Saag et al. found that in a small sample group of 68 adults and 9 children, none of the adults with CD4 cell counts of greater than 400 cells/mm^3 were found to be viremic (80). Of the 17 adults with a CD4 cell count of between 200-400 cells/mm^3 3 adults (~18%) were found to be viremic (80). In individuals with a CD4 count of less than 200 cells/mm^3 15 of 16 were found to be viremic indicating that viral load is elevated when CD4 was reduced (80). There were five children in the study that were either infected in utero or during the perinatal period and all five were found to be viremic (80).

A study published in 1995 looking at the time to AIDS positive status in three groups of HIV infected individuals found that the median time from diagnosis of HIV to AIDS in homosexual males was 63 months, (25^{th} percentile=46 months, 75^{th} percentile=85 months) (62). In homosexuals males the range time to AIDS was found to be 35-114 months (62). The study also found that aside from hemophiliacs, homosexual males had the youngest age of HIV diagnosis with a median age of 29 years old (62). A study published in 1997 by Alcabes et al. found that as time from infection increased the hazard for AIDS positive status also increases with a major jump in hazard at 4 years after seroconversion, and another jump in hazard at around 8 years (63). The study also showed that those who were born before 1951, the older cohort, compared to those born between 1951 and 1962, the younger cohort, had a higher rate of progression to AIDS RH=1.76 (1.08-2.85) (63). These studies show that progression to AIDS is a complex path with many factors that influence the progression of HIV to AIDS. Factors that influenced progression to AIDS were found to be base line CD4, change in CD4, as well as time progression (increase in lag time) from HIV diagnosis.

Epidemiology

A 2007 global HIV review by Kilmarx et al. found that the global rate of HIV was around 1% which accounts for 33 million individuals (54). Kilmarx et al. found that 22 million of the estimated 33 million HIV positive individuals are located in Sub-Saharan Africa up from 20.4 million in 2001 (54). The review also found that there was an estimated 2.7 million newly infected adults and children in 2007 which was lower than the 3 million newly infected reported in 2001 (54). In North America there was an estimated 1.2 million HIV infected individuals with 54,000 new infections in 2007 (54). Kilmarx et al. stated that although there was a rise in HIV positive individuals as well as a rise in the newly infected, rates remained stable in North America (54). The review also stated that in 2006 the estimated incidence per 100,000 in African American men in the US was 115.7, whereas white males in the US have an estimated incidence per 100,000 of 19.6 (54).

The World Health Organization (WHO) estimated in 2012 there were 35.3 million people living with HIV with Sub-Saharan Africa being most affected region (6). In Sub-Saharan Africa it is estimated that 1 in 20 adults in the region are infected with HIV with around 69% of the total population living with HIV (6). The WHO also estimated that in 2012 there were a total of 2.3 million infections and 1.6 million deaths globally due to AIDS related causes (6). Roughly 9.7 million people globally in 2012 were estimated to be on ARV therapy (6). Under the 2013 WHO ARV guidelines there are an estimated 26 million people eligible for therapy leaving a large gap between those that are eligible and those that are receiving ARV treatment (6).

US HIV

As of 2011 the Centers for Disease Control and Prevention (CDC) estimated that there were approximately 1.2 million U.S. citizens 13 years or older living with HIV and over 200,000

undiagnosed cases (7). CDC estimates that in the U.S. there are around 50,000 new cases a year, with an estimated 47,500 new cases in 2010 (7). The majority of infections occur in Men Who Have Sex with Men (MSM) of all racial groups and in African Americans (7, 19, 20, 22). From 2006-2009 the only group to show significant increases in HIV infections were young (13-24 year olds), black MSM, despite white MSM accounting for the largest number of new infections (7). According to the CDC in 2009, MSM accounted for 2% of the U.S. population and make up 61% of all new infections and 49% of the 2008 living U.S. HIV population (7). Heterosexuals in 2008 accounted for 28% of U.S. individuals living with HIV and 27% of the 2009 new HIV infections (7). African Americans in 2010 accounted for 12.6% of the US population and 45% of all new HIV infections in 2010 (16). A study done by Goodenow et al. in 2002 stated that a majority of men diagnosed with AIDS in their 20s or 30s were probably infected in their teens due to the prolonged nature of HIV infections (21). Goodenow et al. also notes that many American youths are sexually active during high school, that heterosexual exclusive males are older than young MSM, and that by age 18 60% of men that identify themselves as bisexual have had an STD (21).

In 2011 the CDC estimated that there were over 32,000 HIV stage 3 (AIDS positive) diagnosed individuals in the U.S. with 24,000 of them being in adult and adolescent males (8). There were over 1.1 million AIDS diagnoses by 2010 in the United States with 487,692 individuals living with AIDS and 15,000 AIDS related deaths in 2010 alone (8). A 2011 study by Hughes et al. estimated that by 2016 half of the US HIV positive population will be over the age of 50 presenting new problems in relation to the understanding of the progression of this disease and other comorbidities (100). The top three states according to number of HIV infections in 2011 were California (n=5,973), Florida (n=5,403), and Texas (n=5,065). The top three states of AIDS

diagnosis were California (n=3,622), New York (n=3,574), and Florida (n=3,440) in 2011 respectively (8,9).

A study by Patrick et al. in 2012 that sought to investigate the risk factors and substance abuse issues related to HIV/AIDS in young adults in the US cited that in 2012 there were roughly 1.2 million individuals in the US with HIV, with around 20% of HIV positive individuals being unaware of the serostatus (99). The study consisted of over 7,000 young adults, 52% female and around 70% white (99). The study found that in US young adults (21-30 years old) 24% of women and 34% of males report more than 5 lifetime sexual partners (99). The study also found that in this age group 55% report that they seldom or never use a condom which has contributed to the increasing prevalence of HIV infection in the younger population (99). The study found that in individuals who used illicit drugs (including marijuana) adherence to condom usage was decreased (99). A study by Karlovsky et al. males 50 years old or older found that few males 50 years or older who are sexually active use condoms or are tested for a sexually transmitted disease (102). The study noted that with the advent of erectile dysfunction medication this group that was traditionally overlooked has become a new risk group for HIV and STD infections and the spread of these diseases (102). The study found that in Florida as well as in the US as a whole the number of HIV infections in males >50 years old has been slowly increasing from 1998 to 2004 (102). The study also found that in both the 55-64 year old age group and the 65+ year old age group that the number of cases of *N. gonorrheae* have been increasing from 1997 to 2002 (102). These findings represent a new risk group, sexually active adults over the age of 50, which have been previously ignored.

Michigan HIV

This study will take place in the State of Michigan where in 2011 ranked 20th in HIV diagnoses and 18th in AIDS diagnoses (9). The January 2014 Annual HIV Surveillance Analysis estimated that there were approximately 19,800 individuals in the state of Michigan who were HIV positive of which an estimated 15,440 (78%) were males (10). Of the 15,440 males with HIV, men who have sex with men make up 55% of prevalent HIV cases between the combine risk groups of MSM and injection drug user (IDU)/MSM in the state of Michigan (10). Heterosexual contacts make up 19% of those with HIV infection, 8% were non-MSM IDU, 1% had a perinatal exposure and 17% had an undetermined source of transmission (10). The most frequent age group for HIV diagnosis was 30-39 year old (33%) with the combined age group of 20-29 at 32% (10). The majority of HIV diagnosis occurred in the Detroit Metropolitan Area (consisting of Lapeer, Macomb, Monroe, Oakland, St. Clair, and Wayne counties) (64%) despite only accounting for 43% of the total Michigan population (10). Males made up the majority of HIV infected individuals with a reported 12,510 cases (10). Within this group 71% are MSM (combined risk groups of MSM and MSM/IDU), 5% are heterosexuals, and 17% have an undetermined mode of transmission (10). As of January 2014 there was an estimated 8,207 stage 3/AIDS positive individuals in the state of Michigan with a reported 428 new stage 3/AIDS positive individuals identified in 2013 (10).

An updated version of the Annual HIV Surveillance Report was released in July 2014 and showed little difference from the Annual HIV Surveillance Analysis released in January 2014. The July 2014 report estimated a slightly lower total prevalence, 19,100 as compared to the January 2014 estimate of 19,800 (10, 111). Males accounted for 78% of HIV infected individuals with MSM (MSM and IDU/MSM) accounting for 55% of total HIV infected individuals, 71% of HIV infected males (111). African Americans had the highest rate of HIV infection

(655/100,000) followed by Hispanics (148/100,000) (111). HIV remained highest in the 30-39 age group with the combined group of 20-29 year olds only slightly behind (33% and 32% respectively) (111). Metropolitan Detroit area geographically had the highest prevalence of HIV infections as well as the highest rate, 238/100,000 (111). The total number of individuals living with AIDS (Stage 3 HIV) increased from 8,207 reported in January to 8,240 in the July 2014 report, with the new 2013 AIDS total at 471 (111). Of all those diagnosed with HIV up to January 2014, 18,794 of 27,407 progressed to AIDS/Stage 3 positive status (111). Among the AIDS positive individuals 35% were diagnosed with AIDS at the same time of their HIV diagnosis, 8% had a "short" lag time (1-12 months after HIV diagnosis) to AIDS positive status, and 26% had a "long" lag period (more than 12 months from HIV diagnosis) (111). Males with HIV had a higher percent AIDS progression than females, 70% of males as compared to 64% of females (111). Within males with HIV 37% were diagnosed as AIDS positive at the time of their HIV diagnosis, 8% had a short lag time, and 25% of males had a long lag time to AIDS positive status (111). In females with HIV the percent of concurrent AIDS diagnosis (HIV and AIDS diagnosis at the same time) was 28%, 8% had a short lag time, and 28% had a long lag time (111).

Acquired Immune Deficiency Syndrome

HIV progression has been studied from a multi-faceted vantage point. Early studies of HIV in homosexual males were modeled on the previous knowledge of the epidemiology of hepatitis B and other well-known Sexually Transmitted Diseases (STDs) (42). Studies like the 1987 Darrow et al. article focused on number of sexual partners, non-steady sexual partners, drug use, and sexual practices (42). A multicenter AIDS cohort study paper published in 1992 looking at white men who have sex with men (MSM) found that immune response rates are predictive of

progression to AIDS positive status (57). The final model reached by Saah et al. included the percent of CD4 cell 5% lower at the first visit had a relative hazard (RH) of 2.08 (1.86-2.31) (57). Other factors that were found to be significant were a decline of 5% in the percent of CD4 between first and second visit [HR= 2.09 (1.80-2.42)], decline of 1 g/dL of hemoglobin between first and second visit [HR=1.21 (1.02-1.44)], and the level of IgA 200 mg/dL higher at first visit [HR=1.91 (1.21-3.00) (57)].

A 1996 study of participants from the Veterans Affairs Cooperative Study on AIDS found that baseline CD4 counts and levels of HIV-1 RNA in the plasma are the main predictors in modeling the risk of AIDS (72). The study found that a 75% decrease in HIV-1 RNA was associated with an unadjusted relative risk (RR) of 0.44 (0.22-0.75) with regard to the progression of AIDS and an adjusted RR of 0.44 (0.23-0.81), model was adjusted for CD4 cell count, $ß_2$-microglobulin, and treatment (72). The study also found that a 10% increase in CD4 count was associated with an unadjusted RR of AIDS progression of 0.45 (0.27-0.77) and an adjusted RR of 0.48 (0.28-0.82) (72). Antiretroviral therapy was found to be significant in the univariate model for protection of AIDS progression with a RR of 0.62 (0.43-0.92) but was not significant in the multivariate model, RR=1.08 (0.66-1.77) (72). The study also looked at the effect of a 15% decrease in $ß_2$-microglobulin. However, it was neither significant in the univariate nor the multivariate model (72). A Kaplan-Meier analysis looking at time to AIDS found that when neither HIV-1 RNA or CD4 changed that the median survival time was around 39 months, whereas when CD4 increased and HIV-1 RNA levels decreased only around 20% of individuals progressed to AIDS over a 5 year (60 month) study period (72). A research letter in JAMA in 2007 captured the percent of variability due to baseline viral load in prediction of time to AIDS and death (HIV progression) as contributing 47% to the time to AIDS and 50% of the time to

death making it the major contributing factor in each (88). The study was done looking at only untreated patients (88). These findings were significant because they show how baseline levels can be used to help to identify individuals with increased risk of AIDS or death.

Miller et al. found that as CD4 cell count decreased the rate of HIV progression events increased (79) Miller et al. also found that when stratifying those with a CD4 cell count of at least 200 cells/mm^3 by previous cell count that those with lower previous recorded cell counts had a greater hazard of having a progression event (79).

Taylor et al. in 1989 published a study that plotted AIDS survival against CD4 percent, absolute CD4 count, and CD4:CD8 ratio (77). The study found that as CD4 percent decreased there was also a decrease in the median time to AIDS positive status (77). The lowest CD4 percent group was from 0-12% and the median time to AIDS was around 9 months (77). The study also found a similar trend when modeling time to AIDS and CD4 count, as the CD4 count decreased (in defined groupings) there was also a reduction in AIDS free time (77). The group with the lowest hazard of AIDS progression was in the greater than or equal to 510 cells/mm^3 group with less than 10% of individuals progressing to AIDS in 3 years (77). A final major finding of this study was that out of the three biological markers studied, CD4 percent may be the best indicator and have the least variability when predicting AIDS progression, however, CD4 count and CD4:CD8 ratio are also useful tools for modeling AIDS progression (77).

Yu et al. found that there is a linear relationship between CD4 count and CD4 percent (76). The study found that a CD4% of 5% corresponds to a CD4 cell count of 45 cells/mm^3 (CI 17-117 cells/mm^3), CD4% of 15% corresponds to a CD4 cell count of 182 cells/mm^3 (CI 64-499), and a CD4% of 30% corresponds to a CD4 cell count of 438 cells/mm^3 (CI 132-1395) (76). The study

also found that among three groups, homosexual/bisexual, injecting drug users, and heterosexuals, homosexual/bisexuals have the highest CD4 cell counts in both AIDS-free and AIDS positive groups (76). In AIDS-free individuals those that are not on zidovudine therapy or PCP prophylaxis have the highest CD4 count in the low CD% grouping (5%) and those that are only on zidovudine have the highest CD4 counts in the high percent grouping (30%) (76). In the AIDS positive group CD4 counts in the 5% CD4 group were highest in those not on any therapy, and in the 30% CD4 group, CD4 counts were highest in the zidovudine only group (76).

In 2010 looked at the risk of death or AIDs between 1979 and 2001 found that the hazard of death or conversion to AIDS positive status remained relatively the same from 1979 to 1993(0.89 in 1979-1990 and 0.90 in 1991-1993) with a drop in the hazard in the time period of 1997 to 2001 to 0.37 when compared to the time period 1994-1996 (56). A UK study published in 1997 found that within 10 years of HIV positive diagnosis 60% of individuals were found to be AIDS positive (59). Within 10 years from HIV diagnosis around 48% of HIV positive males died from any cause and that those diagnosed with HIV at an older age had a faster time to AIDS positive status as well as a shorter survival time (59).

A 1998 study by Yerly et al. of 394 Swiss HIV-1 infected patients found that in unadjusted models Log HIV-1 RNA was significantly associated with an increased in relative hazard (RH) of death (75). As viral load levels rose the risk of death also increased in a dose response fashion. When looking at CD4 cell counts an inverse relationship was found where decreases in CD4 increased the hazard of death in a dose response relationship. While the association remained significant between CD4 count and hazard of death in a multivariate model, viral load was not found to be a significant marker for hazard of death (75). Yerly et al. also found significant association between viral load, CD4 count and $ß_2$-microglobulin in the univariate analysis (75).

A 2009 study looking at risk of death in HIV individuals that deferred treatment was compared to those that started treatment early and found in the 351-500 CD4 cell count group deferral of antiretrovirals resulted in a RR of 1.69 (CI 1.26-2.26) in a model that included sex, age and baseline CD4 count (78). In the group that had a CD4 cell count of over 500, deferral of antiretroviral therapy, however, baseline CD4 count did not (78). In a second model that included viral load found in the 351-500 CD4 cell count group that deferral of antiretroviral therapy increased risk of death, whereas baseline CD4 count [RR=0.74 (CI 0.55-1.00)] and baseline HIV RNA level [RR=1.11 (CI 0.96-1.28)] where not found to be significant risk factors for death (78). The CD4 cell count of more than 500 found similar results with regard to deferral of antiretrovirals, CD4 count and viral load when HIV RNA levels were added (78). A major finding in this study was that longer deferment of antiretroviral therapy was associated with an increase in risk of death, whereas baseline CD4 count and baseline viral load were not found to be associated with risk of death suggestive of the fact that the progression of CD4 count is more important than the baseline level (78).

A 1996 paper by Turner et al found that among those diagnosed with AIDS women had a longer median survival time in months than men as well as the younger age group as defined by those less than 40 years old (70). When AIDS severity (based on judgment by expert panel) was characterized into three categories, based off AIDS-defining diagnosis and complications seen within 3 months of AIDS diagnosis, median time to death decreased as severity increased (70). The administration and use of Zidovudine, a nucleoside analog reverse-transcriptase inhibitor, increased the median time of survival time (70).

A study published in the Lancet in 2000 investigating the mean time to AIDS and death by age of seroconversion found that without treatment as age at HIV infection increased, the time to

AIDS positive status decreased (65). In those infected from ages 15-24 years old the median time to AIDS was 11 years while the time to AIDS in those infected with HIV after 65 years old was 5 years (65). Mortality was also seen to increase with age (65).

Antiretroviral Therapy

Antiretroviral therapy (ART) has been shown in multiple studies to reduce viral load, increase the time to AIDS, and in many cases has been shown to decrease the rate of CD4 destruction and facilitate the resurgence of CD4 counts in the body. An early concern of ART and Highly Active Antiretroviral Therapy (HAART) was that those on the treatment would engage in risky sexual history believing that they were not at risk for transmission (67). A 2012 study by Fu et al. found that those that started HAART treatment have a 75% reduction in unprotected sex (OR=0.25 0.19-0.32) (67). Those that started HAART did not see a reduction in sexual activity, there was however a decrease in the use of injection drugs (67). A negative finding that Fu et al. found was that in some drug users the activity of needle-sharing increased by around 2 fold (OR=1.99 1.57-2.52) (67). Fu et al. also noted that the changes lasted for at least 5 years regardless of adherence to HAART (67). Thus the early concerns of engagement of risky sexual behaviors did not hold true, however, in some injection drug users needle-sharing did increase.

Using patients from the Swiss HIV cohort researchers looked at viremia and progression to AIDS or death in 2674 individuals that started HAART between 1995-1998 (82). The study found that within a year, over 90% of individuals who started treatment during the study period were not viremic (defined as a viral load of less than 400 copies/mL). Individuals on more drugs were less likely to become viremic (82).

Some studies have found that use of protease-inhibitor-containing highly active antiretroviral therapy (HAART) did not guarantee a reduction in viral load with some studies reporting upwards of 49% of individuals on HAART did not have viral suppression (81). Kaufmann et al. showed that while a group of 101 HIV-1 patients on HAART were predominately viremic after at least a 3 month study, that HAART did increase their CD4 counts despite not reducing or suppressing viral load counts (81). Kauffmann et al. point out that while HAART does not easily reduce viral load, which until better drugs become available the benefit of increase in CD4 count should not be over looked (81). A second study by Kaufmann et al. showed that the longer HIV is left untreated, the harder it is to reach normal CD4 cell count level (84). At the end of 4 years nearly all patients reached a cell count of greater than 200 cells/μL and 74% reaching a cell count of greater than 500 cells/μL (84).

A 2001 study from the 1996-1997 Aquitaine cohort found that in patients starting a protease inhibitor during the first 4 months the change in CD4 cell count did not influence the rate of opportunistic infections in participants (87). After the initial 4 month period (120 days) change in CD4 count was found to reduce the rate of opportunistic infections, for every 50 cells/mm^3 there was a reduction in opportunistic infections by 60% (87). The study also found that the median change in CD4 cell count was around 111 cells/mm^3 over 18 months (87). An important finding of the study was that while protease inhibitors increased CD4 cell counts, there is an early delay in the ability of the immune system to reduce opportunistic infections during the initial CD4 cell count ramp up (87).

A 1997 study of eight patients by Autran et al. found that in 3 of 8 patients on HAART viral load was reduced to non-detectable levels over a year period (83). CD4 cell count rose with treatment of HAART during the first 2 weeks of treatment with the remaining year of treatment increasing

CD4 counts at a slower pace (83). A 2003 study published in the Lancet looking at survival and progression to AIDS in those on HAART found 26% of the 7740 participants died from the 22 cohorts looked at (85). Hazard of death was compared to the pre-1997 data, and showed that there was a decrease in hazard of death (HR=0.47 0.39-0.56) in 1997, HAART usage 22%, and a further decrease (HR=0.16 0.12-0.22) in 2001, HAART usage 57% (85). This study along with the one mentioned in the previous paragraphs show the difference in the range of effectiveness of ARV cocktails.

A study looking at HIV care among African Americans found that in the US in 2010 44% of new infections and 44% of those living with HIV are African Americans, despite African Americans only making up 12% of the US population (110). The study also found that around 75% of African Americans who are HIV positive can be linked back to care, 10% shy of the National HIV/AIDS goal mark of 85% (110). The study also found that while 3/4th of those with HIV could be linked to care, only 48% retained care and only 46% were prescribed ART (110). This resulted in only 35% of African Americans achieving viral suppression (110). The study also found that in African Americans less than 25 years old, their levels of care and viral suppression were lower than for African Americans 25 years or older at every stage of the continuum (110). The article concluded by speculating that the reason for the gaps in care of HIV may not be only access to care issues but also barriers due to poverty and social stigma that must be addressed and overcome for public health to make an impact (110).

A study from 1994 modeling the CD4 counts over time in AIDS positive individuals taking the drug zidovudine found that after an early spike in CD4 counts, around week 10 of treatment CD4 counts rapidly decline, obtaining baseline levels by week 20 and reaching an asymptote around week 90 (61). One of the major limitations of the study is that as time progressed, individuals

dropped off due to death and missing observations (61). However, when looking at only survivors the CD4 curves look similar to the total population CD4 curve and show that in the sample AIDS population CD4 counts dropped below 10 cells/μL at around one year (61). A study looking at individuals diagnosed with AIDS in San Francisco from 1993-1996 found that hazard of death after AIDS positive status increased with infection of opportunistic infection (RH=1.97, 1.8-2.2) (64). The use of antiretroviral therapy (ART) was found to be protective of mortality with ART before AIDS diagnosis and post AIDS protease inhibitor (PI) treatment having the greatest impact on survivability (64).

Antiretrovirals are not the only drugs used to treat the progression of HIV to AIDS in positive individuals. A study by Longini et al. looking at the use of zidovudine and aerosolized pentamidine (a common antibiotic used to prevent *Pneumocystis carinii* pneumonia now known as *Pneumocystis jiroveci* pneumonia) found that starting treatment prior to AIDS can increase the time between disease progression stages (higher CD4 counts for longer) and keep individuals out of the AIDS positive category longer (86). The study showed that prompt treatment with zidovudine and antibiotics prolong the time to AIDS positive status (86).

Research shows that not all HAART or ARVs work the same, and it may not be appropriate to group them together (have you ever been on ARVs). There is a need to study the patterns of reduction in HIV progression among those with the disease on the basis of their treatment. This may give insight into variances between treatments in similar individuals.

1.2 *Neisseria gonorrheae*

Natural History

Neisseria gonorrhea is a gram-negative bacterium that is paired, bean-shaped, and has the ability to attach to each other along the flat sides of the cell (1). Gonorrhea is a sexually transmitted disease (STD) and has deep roots in early civilizations easily dating back to ancient Greece (1). The major virulence factor of *N. gonorrheae* is the presence of pili and other surface molecules that facilitate the bacteria attaching to each other and assist in the invasion and infection of host tissue (1). The pili also aid in the defense of the bacteria against macrophages and neutrophils, and *N. gonorrheae* creates a protease that attacks IgA on mucosal surfaces (1).

N. gonorrheae can cause urethritis (inflammation of the urethra), epididymitis (inflammation of the epididymis, tube between the testicles and the vas deferens), proctitis (inflammation of the rectum), cervicitis (inflammation of the cervix), Bartholinitis (formation of a cyst in the Bartholin gland), pelvic inflammatory disease, and pharyngitis (inflammation of the pharynx) (2). In males symptoms start 2-7 days after infection and typically include discharge of pus from the urethra as well as painful urination (dysuria) (2). Rectal infection may include discharge, anal itching, soreness, bleeding, and painful bowel movements, whereas infections of the throat may manifest in sore throat but is typically asymptomatic (11). Although considered rare, some strains of *N. gonorrheae* can also cause arthritis-dermatitis syndrome or gonorrhea arthritis due to what is called Disseminated Gonococcal Infection (DGI) which is the spread of the bacteria to the joints and blood and can be a life threatening condition (2, 11). It is estimated that approximately 10% of males with *N. gonorrheae* are asymptomatic (1).

Sexual contact is the main source of *N. gonorrheae* and incubation is usually 1 to 14 days, but can be longer (2). The period of communicability varies in individuals and is largely dependent on if the individual receives treatment (2). In individuals who do not seek treatment the period of communicability can extend for months, whereas treatment has been shown to end risk of

communicability in hours (2). Untreated gonorrhea in males can develop into epididymitis, inflammation of the tube that connects the testicles and the vas deferens, and can lead to infertility (11). While *N. gonorrheae* infection can be treated with antibiotics, prevention of outbreaks has proven difficult and the spread of drug-resistant strains have introduced a new problem for public health departments (11, 39). While many areas in the U.S. and throughout the globe are experiencing outbreaks of *N. gonorrheae* infections, prevalence of the disease is found to be highest in communities with lower social economic status (2).

Epidemiology

In 2011 WHO estimated that roughly 88 million of the estimated 448 million curable STD infections reported that year were due to *N. gonorrheae* (12). Gonorrhea is one of the most reported infectious diseases in the United States (15). In the United States in 2012, there were over 334,000 gonorrhea cases resulting in an increased rate of 4.1% from the previous year (13). In the U.S. the prevalence among females is greater than males; however, the rate in males is increasing at a higher rate than in women (13). The rates were highest in 2012 among teens and young adults with the highest age group among men 20-24 years, while the highest overall increase was in males 30-34 (13). Where age has been reported, 95% of all gonorrhea fall between 15-44 years old with the age group of 30-34 years having the highest increase in rate from 2011 (13). The only age group to see a decrease in the rate of gonorrhea in 2012 was seen in the 15-19 years age group (13). Manhart el al. found that risk of *N. gonorrheae* infection decreases with age and is increased in African Americans (26). The rate in African Americans in the United States was around 15 times higher than in Caucasians despite an overall decrease in African Americans and a 22% increase in Caucasians (13). The top three states/areas in 2012 for reported gonorrhea cases were Washington D.C. (388.7/100,000), Mississippi (230.8/100,000),

and Louisiana (194.0/100,000) respectively (13). A study published in 2014 that reviewed ciprofloxacin resistance and *N. gonorrheae* infection incidence rates from 1991-2006 and estimated there are 820,000 cases of gonorrhea each year and which have a direct medical cost of $162 million (109).

A study by Weinstock et al. looking at STDs in American youths found that the age group of 15-24 year olds make up a quarter of the sexually active population in the US (48). In 2000 48% of the estimated 19 million STDs occurred in 15-24 year olds (48). The study also found that in 2000 approximately 60% of *N. gonorrheae* infections were in 15-24 year olds (48). A study by Gunn et al. investigating sexual gender preferences found that in San Diego between 1997 and 2003 around 16% of MSM who were tested for *N. gonorrheae* were positive (52).

A geographic study of gonorrheal infections in Baltimore, MD found that over a two year period there were over 6,000 infections of which 9% were those with repeat infections (68). The study found those with reoccurring infections, who were more likely to be younger women in the 15-24 year old age group (68). The study also found that in census tracts with higher infections rates per 1,000 the number of repeat infections was also higher with the center of the city being the area with the highest rates and highest occurrences of re-infections (68). While repeated *N. gonorrheae* infections are not overwhelmingly common, (<10%), this study was able to show that they do occur and they are not equally spread across the city.

As of the 2010 Census, Michigan has the 8th largest population in the US. In 2011 there were over 13,000 cases of gonorrhea reported in the state of Michigan with the highest rate reported in the 20-24 age group (14). The 20-24 age group accounts for 6.7% of the population of Michigan, yet accounts for 34% of all gonorrhea cases (14). The overall rate in African Americans in the

state of Michigan was roughly 24 times higher than the rate in Caucasians (14). Males account for 41% of all 2011 gonorrhea cases in the state of Michigan (14). Of the reported 13,070 gonorrhea cases 2% (n=259) were also HIV positive (14). In 2012 the State of Michigan reported a rate of 127.4/100,000 (13).

1.3 Co-infections

While researchers studying STDs have been aware that there is a significant amount of co-infection periods in those that have a reported infection, the epidemiology and exploration of the possible synergistic relationship that exists before, during and after co-infection has not adequately been investigated (93). It was estimated using 2006 US dollars that the annual direct medical cost of STDs in the US was around $15 billion with over half being spent on the diagnosis and treatment of non-HIV STDs (89). The 1997 Advisory Committee for HIV & STD Prevention (ACHSP) investigated the relationship between HIV and STDs and recommended that the early diagnosis and treatment of treatable STDs should be a major focus of all HIV prevention programs at all levels of public health (24). The committee also stated that in areas where it is believed that STDs assist in the transmission of HIV that screening and treatment programs should be expanded where they currently exist or created where there are gaps (24). The committee also suggested that public health integration between private and public health agencies should take joint responsibility for the implementation and evaluation of the proposed strategies (24). The concluding message that the 1997 committee left with was that a major step in the prevention of HIV is the early diagnosis and treatment of curable STDs (24).

A 1998 study by Chene et al. found that higher CD4 counts were associated with lower rate of opportunistic infections (66). Study participants were prescribed at least one protease inhibitor

and the study found that for each 50% increase of CD4 at baseline the risk of death or opportunistic infection was reduced by 23% (66). A 50% increase in CD4 cell count during the follow-up period (median follow-up time 230 days) was associated with a 9% reduction in the risk of opportunistic infection or death (66). Study participants that increased their CD4 counts at second visit had fewer opportunistic infections than those that decreased in CD4 count (66).

HIV/Non-Gonorrheal STDs

The need to understand the co-infection dynamics of HIV and other STDs is an important aspect in developing and implementing effective outreach and prevention programs (93). In a study by Zhang et al. in 2007 looking at STD co-infections in HIV infected males 94% of study participants had evidence of at least one co-infection, with 50% (8/16) HIV positive MSM being infected with syphilis (25). Another study by Buchacz et al. that found in men during syphilis/HIV co-infection periods viral load increased and CD4+ cell count decreased (49). The study also found that after treatment for syphilis viral concentrations fell and CD4 cell counts rose (49). A 2005 study by Kahn et al. estimated that in adolescents entering juvenile facilities 5.9% of males were infected with chlamydia and 1.3% of males were infected with gonorrhea. Of those infected with *N. gonorrheae* 51% of males were also infected with *Chlamydia trachomatis* (15).

A study done by Huhn et al. using Chicago and Illinois STD/HIV surveillance data found that of the 43,517 patients seen in 2002 around 13% received a positive HIV test (96). The study also found that in 2002 there were 308 new cases of HIV and that within that population the rate of co-infection (STD infection at time of HIV diagnosis) was 23% (96). The study found that the risk of HIV/STD co-infection was highest in MSM and those over the age of 30 (96). The

majority of STD infections were found in males, and when looking at STDs regardless of HIV status the age group with the greatest infection rate was the 20-24 year olds (96). Syphilis had the highest unadjusted OR (11.0 CI 7.7-15.8) for co-STD infection in newly diagnosed HIV individuals, with gonorrhea coming in second with an OR of 2.2 (CI 1.4-3.3) (96).

In a review of HIV/AIDS in Africa Corbett et al. found that a major effect of STD infection was the rise in HIV transmission (94). The review outlines that during co-infection periods HIV can increase the morbidity and fatality rate of the co-infecting pathogen in immunosuppressed individuals (94). There was an increase in the incidence of surrounding pathogens due to the fact that infection more often results in symptomatic presentation of the infection, resulting in more cases coming in for treatment and diagnosis (94). The review also speculates that increased transmission of the non-HIV pathogen may be due to an increase in the virulence of the disease (94). On the other side of the coin, the effect of other pathogens on HIV is that there is a decrease in the survival rate due not only to the elevated virulence of the non-HIV pathogen but also due to the possible acceleration of HIV progression via immune system stimulation (stimulation of immune response offers more targets for HIV infection resulting in a higher viral load) (94). Another effect that STDs have on HIV is that there is an elevated state of infectivity/transmission resulting from the immune response of STDs that cause genital inflammation (94). The authors make a note to point out that unlike counties like the US, the majority of African HIV transmission is through heterosexual encounters, not MSM intercourse (94).

The review goes on to speculate that some of the problems with STDs in Africa can be traced back not only to behavioral factors (condom usage) but also to social factors such as poor health service delivery and that it is really a combination of the two (94). A need for HIV control measures in Africa to include improved STD diagnosis and treatment, with the aim to reduce the

prevalence of STDs in Africa and hopefully thereby reduce the HIV enhancement that can cause higher rates of transmission (94). The review goes on to outline some of the research priorities that need to be considered with regard to HIV and STD prevention. One area is that there is a need for combined intervention practices, mass treatment as well as syndromic treatment, and that these need to be targeted at populations with high rates of curable STDs (94). Another research area that needs to be considered are trials that seek to test interventions on high risk groups, as well as trials aimed at keeping adolescents and young HIV naïve individuals HIV and STD free (94). Other areas for consideration are on increasing STD treatment coverage, monitoring of treatment, development of treatment algorithms, and assessment of herpes treatment options and HIV transmission (94).

HIV/N. gonorrheae

Despite recent multiple outbreaks of *N. gonorrheae* as well as the emergence of antibiotic resistant gonorrhea and the fact that *N. gonorrheae* is one of the most reported diseases in the United States, the relationship between HIV and gonorrhea has yet to be fully explored. Studies show that for many HIV/*N. gonorrheae* co-infected individuals partner service data is not available (33). It has been suggested that HIV and *N. gonorrheae* share an epidemiological synergistic relationship (24). Research shows that in HIV infected males that are co-infected with *N. gonorrheae* viral RNA is increased in the semen roughly 10-fold and drop to pre-gonorrhea infection levels after the start of antibiotic treatment (24). The literature also suggests that there is at least a two-fold increase in the risk of men spreading HIV in their ejaculate who are co-infected with *N. gonorrheae* than in men that are not currently co-infected (31). Mayaurd and McCormick state that among HIV infected males there can be an upwards of an 8-fold increase

in the viral load in and an increase in viral load found in the vaginal secretions of HIV infected women as compared to individuals with no co-infections (40).

Reports show that in the early years of the HIV epidemic *N. gonorrheae* infections were on the decline in the United States until the start of its increase in 1990 in MSM sexual networks (34, 39). A study by Fox et al. reported that in 1998 rates of *N. gonorrheae* infection increased dramatically in 21 states (34). *N. gonorrheae* HIV co-infection in males is documented as peaking in 2005 and by 2007 had returned to levels observed in 1997 (35). Studies show that among HIV infected males the rate of *N. gonorrheae* infection is 20 times higher than those who are HIV negative (35). A 12 year trend in gonorrhea and sexual risks in MSM from 1990 to 2001 found that in HIV infected men the initial gonorrhea increase was between 1995 and 1997, with a brief decline in gonorrhea/HIV co-infections from 1997 to 1998 (37). The second period according to Rietmeijer was from 1999 to 2000 (37).

A multicenter AIDS cohort study of four sites (Chicago, Los Angeles, Pittsburg, Baltimore/Washington DC) in 1987 found that lifetime history of gonorrhea was between 40-67% depending on site with Los Angeles and Chicago having the highest rates (58). The 1987 article also found that the percent of white MSM with HIV was higher in Los Angeles and Chicago (51% and 43%) respectively than in the other two sites (58). A separate study using the multicenter AIDS cohort study published in 1987 found that *N. gonorrheae* infection increased the risk of HIV infection in males (60). The Chmiel et al. study found that risk of HIV infection increases with the frequency of rectal *N. gonorrheae* infection (60). The unadjusted relative odd ratio (ROR) for 1-3 infections was 3.55 and increased to 13.49 in the 4+ *N. gonorrheae* infections (60). The multivariate model showed that the ROR for 1-3 infections was 1.65 (CI 1.39-1.96) and the ROR for 4 or more infections was 3.89 (CI 2.45-6.20) (60). The model also

looked at the grouping of lifetime infection with other STDs which included urethral gonorrhea, syphilis, urethritis, and genital herpes and found an increase in HIV seroconversion that increased with re-occurrence of STD infection (60). The occurrence of one lifetime infection resulted in a multivariate ROR of 1.27 (CI 1.04-1.56) as compared to zero lifetime infections, two infections increased the ROR to 1.48 (CI 1.19-1.83), and three or more infections increased the ROR to 1.93 (CI 1.48-2.52) (60).

Table 1.1 shows the percent urethral and rectal gonorrhea in MSM from a separate AIDS cohort study (55). Average age of sexually activity in MSM was 17 in whites and 15 in Hispanic-whites and African Americans (55). Among whites and Hispanic-whites the rate of individuals who have a history of sexual partners with AIDS was 20% and 23% respectively and lower in African Americans who had lifetime history of partners with AIDS of 13% (55). The study also constructed a multivariate analysis, and odd ratios of HIV seroconversion appear in table 1.2, white males 26-30 year olds had the highest risk of HIV seroconversion, and those with a history of rectal gonorrhea an OR of 1.59 (CI 1.28-1.97). While this study did not look at co-infection status it was able to show that lifetime history of *N. gonorrheae* infection is associated with an increase in risk of HIV seroconversion (55).

A study done in 2001 looking at female HIV positive individuals found that 7% of women with HIV are infected with *N. gonorrheae* (36). In 2005 Stekler et al. found when looking at multiple STIs, partner infections, and co-infection states found that among MSM in those with *N. gonorrheae* 33% of their partners were also co-infected with *N. gonorrheae* and 3% were infected with HIV (41). In heterosexual males that had *N. gonorrheae* around 28% had gonorrhea co-infected partners and no HIV infections were detected (41). A separate study found that in men infected with *N. gonorrheae* 7.9% were co-infected with HIV (48).

A study published in 1997 by Royce et al. that focused on the transmission patterns of HIV found that as early in the research as 1997 gonorrhea (and chlamydia) were seen to increase the risk of HIV infection in males from 60% to 340% (44). The study also reported that local infection which consisted of inflammation or ulceration of the rectum, reproductive track, or mouth was associated with increased viral load in genital secretions, risk of transmission, as well as risk of HIV infection in naïve individuals (44). The study also points out that immune activation in general may increase all three (viral load, transmission, infection) as well although not at the rate of local infection (44).

A study done by Tzeng et al. investigating US HIV positive military personnel showed that 50% of HIV positive individuals also had a STD diagnosis reported (17). Tzeng et al. found that within the HIV positive population who had a history of a STD infection, 32% only had pre-HIV STD infections, 47% only had STD infections after HIV diagnosis, and 20% had both pre and post HIV STD infections (17). Among study participants gonorrhea was the most common pre-HIV infection with 144 individuals having 182 incidents of *N. gonorrheae* infections (17). *N. gonorrheae* incident rate in the 10-year period leading up to diagnosis of HIV were shown to increase and decrease in the 10-year post diagnosis period (17). A study by Torian et al. that investigated risk factors associated with HIV positive diagnosis found that in MSM *N. gonorrheae* was twice as common in HIV positive males as compared to non-seroconverted MSM (18). Increased risk of HIV positive seroconversion with MSM who had a diagnosis of *N. gonorrheae* as well as that MSM who are infected with *N. gonorrheae* were less likely to be tested for HIV than those with other or no reported STDs (18).

A study by Lafferty et al. that looked at *N. gonorrheae* and HIV and found that being HIV positive increased risk of gonorrhea infection (OR=2.3) (23). Gonorrhea was higher in MSM

(11%) than in heterosexuals (6%) and that all but one of 66 males infected with urethral *N. gonorrheae* showed signs of urethritis and 46% of all men with rectal infections presented with symptoms (23). A 2006 review looking at surveillance reports, published studies, and ad hoc publications by Dougah et al. found that in England and Wales 32% of *N. gonorrheae* infected males in 2004 were HIV positive (43). From 1994-1999 in Denmark the rate of gonorrhea was 6 times higher in HIV positive MSM and that in Paris a clinic reported that from 1999-2001 1/3 of patients with gonorrhea were co-infected with HIV (43). In 2004 in 9 US cities the reported rates of gonorrhea in HIV positive MSM was higher than it was in negative or unknown HIV status MSM (43). An article in 1992 by Wasserheit stated that in HIV/*N. gonorrheae* co-infection periods that the presentation of gonorrhea in HIV infected individuals was usually atypical (did not further define atypical), that there was both an increase in pelvic inflammatory disease as well as disseminated gonococcal infection, increased resistance to classical antibiotic treatments resulting in an increase in treatment failures (95).

A 2005 review done by Risbud and the National AIDS Research Institute found that HIV viral shedding is enhanced during STD/HIV co-infection periods by the damaging epithelial cells and causing the accumulation of HIV vulnerable cells (47). The article also notes that STDs are the single major factor in the spread of HIV (47). The review also noted a study done by Wasserheit et al. that found that while both ulcerative and non-ulcerative increase HIV transmission, non-ulcerative STDs infections such as *N. gonorrheae* and may be due to the higher incidence of these infections in the public as compared to ulcerative STDs (47).

A study done in Sweden from 1990 to 2004 found that among MSM in the study infected with gonorrhea, 10% were co-infected with HIV (50). This was a steep decline in the percent of *N. gonorrheae* HIV co-infected MSM from the estimated 50% in 1991 (50). In MSM 13% had

multiple re-infections of *N. gonorrheae* with 5% of re-infections occurring in the same year (50). Of the 10% with co-infections, 25% of those (22 of 88) were concurrently diagnosed (50). While the percent of co-infections decreased from the start of the study, the rate of concurrent infections increased from 11% between 1990 and 1997 to 32% from 1998 to 2004 (50). The study also found that from 1996 to 2004 the rate of gonorrhea in Swedish MSM increased from 2.4 per 100,000 to 6.3 to 100,000 (50).

A study done by Do et al. looking at *N. gonorrheae* and HIV co-infections found that gonorrhea incidence rates were higher in younger adults, MSM, blacks, and those that have not progressed to AIDS yet (51). As age increased there was a significant decrease in risk of *N. gonorrheae* co-infection status from RR=18.2 in 13-19 year olds to RR=3.7 in 25-29 year olds and 1.9 in 35-44 year olds with those 45 years and older as a reference (51). Use of antiretroviral therapy was not found to be significant (51). The Reaching for Excellence in Adolescent Care and Health (REACH) project found that 8.5% of youths were positive for *N. gonorrheae* infection and while the data trended that those with HIV had higher rates of infection it was not statistically significant (53). For males in the REACH project 7.9% of HIV positive individuals were co-infected with *N. gonorrheae* while 6.9% of HIV negative males were infected with *N. gonorrheae* (53).

A Minnesota study by the Minnesota Department of Health found that of the 2,315 HIV positive individuals in the study 1.3% had at least one reported diagnosis of an STD (92). The study found that gonorrhea incidence was higher in the HIV infected individuals as compared to the rest of the MN population (92). Four of the 24 HIV positive individuals (17%) with gonorrhea had 2 or more gonorrhea infections from 1993 to 1994, all of these were male (92). Median time to STD infection from the diagnosis of HIV was 3 years (92). This study is a key paper in

STD/HIV co-infections because it was one of the first (if not the first) to use surveillance data to tract STDs in a HIV positive population and shows that state health departments with limited resources can still conduct meaningful investigations to access the burden of disease in there population using record linkage techniques between existing databases (92). The paper still stands as an important piece as we move to the integration of health based systems for disease tracking, prediction and modeling. The study also points out that an important factor in HIV prevention is the assessment of sentinel events, such as STD infections, as a high risk behavior where intervention may be possible (92).

1.4 Biological Plausibility

There are 4 main types of sexually transmitted diseases which include systemic infections without mucosal disease, genital ulcers, mucosal inflammation (which includes *N. gonorrheae*), and those that cause changes in epithelial cells (29). In men, STDs in the inflammation category cause an increase in HIV viral load in the urethra and in semen and is thought to have a greater effect on viral load than chlamydia (29). Research has shown that the major target cells of an early HIV infection are the CD4 T cells (1, 27, 28). During bacterial infections the immune system releases T cells to help fight off the infection, these T cells can then serve as targets for HIV to infect and replicate resulting in an increased viral load during bacterial co-infection periods (24, 27- 29, 31).

A study looking at host response to co-infection of HIV and *N. gonorrheae* done by Montano et al. states that during periods of co-infection the risk of transmitting or acquiring HIV is increased (30). *N. gonorrheae* infections cause an intense inflammatory response in the host due to the immune response of a bacterial agent and during co-infection periods more genes activated that

are associated with immune response, infection and T-cell stimulation as compared to those with only HIV (30).

Epidemiologic Synergy

A key paper on epidemiologic synergy in HIV and STDs is the 1992 Wasserheit paper entitled "Epidemiological Synergy: Interrelationships between Human Immunodeficiency Virus Infection and Other Sexually Transmitted Diseases". The main premise of the article was the investigation of role of STDs in the transmission and progression of HIV as well as the role of HIV in the natural history of non HIV STDs (95). To paraphrase the article, epidemiological synergy is when two causes of the disease work seemingly together to increase the virulence of both (95). Three key relationships were outlined between HIV and non HIV STDs by Wasserheit (95). The first relationship is that there is a period of increased transmission of HIV during STD co-infection periods (95). The second theorized relationship is that there is an accelerated progression of HIV (shortening of time to AIDS or time to death) during periods of STD co-infection (95). The third key relationship when exploring epidemiological synergy is that there is an alteration in the presentation, diagnosis, and treatment response of the co-infection non HIV STD in individuals who are HIV positive (95).

Due to the nature of transmission of HIV and other STDs being sexual contact or of intravenous drug use, STD infection could also serve as a proxy for the measurement of other know risky behaviors such as use of prostitution or engagement is anonymous sex rather than a definitive causal link to HIV seroconversion (95). Wasshereit points out that the control of these other known risk factors for HIV transmission need to be controlled for to positively identify STDs as a biological risk factor for HIV transmission (95). The author does acknowledge that the

measurement of these other risk factors is often imperfect and heavily dependent self-reported histories and difficult to properly validate (95). A key shift in the article is the acknowledgement of while STDs that cause genital ulcers are more commonly studied, nonulcerative infections such as gonorrhea and chlamydia make up a larger burden of disease and if there exists a synergistic relationship between STDs and HIV that these nonulcerative infections need to be studied as well (95).

Another key point in the Wasserheit article is that there is a hard to define gap between infection with HIV and when HIV is diagnosed (95). This is important to note because it has a great effect on what one would consider the baseline levels of CD4 and viral load to be (95). Those with low baseline levels of CD4 or high baseline levels of viral load concentrations may be in a state of elevated HIV progression due to an unaccounted immune response at time of testing (95).

Working from the original STD synergy papers, Fleming and Wasserheit conclude that non HIV STDs can facilitate the shedding of HIV in the genital tract (increased viral load) which then promotes the transmission of HIV and the infectivity of the genital secretion (97). The review also found that in those that are HIV negative, that STDs increase the susceptibility of HIV by the release of inflammatory cells in the infected area as well as disruption of mucosal barriers via lesions and ulcers which are infection targets for HIV, also found by Rottingen et al. and Mayaud and McCormick (38, 40, 97). The review speculates that *N. gonorrheae* infections most likely promote HIV transmission through the typical immune response to a bacterial infection in the genital area, the release of inflammatory immune cells that are targets for viral entry and reproduction (97). Another finding of the review is that the natural history changes for nonulcerative STDs such as *N. gonorrheae* may be less than those of genital ulcerative diseases (GUD) (97). However, nonulcerative infections may increase the risk in the receptive partner as

opposed to both insertive and receptive partners in those with a GUD (97). The three key points for HIV prevention programs to focus on that the review found were improving access to STD clinical services, promoting STD related health care behaviors, and establishing a joint HIV/STD surveillance system (97).

A review of the synergistic relationships between STDs and HIV by Rottingen et al. explored the possible effects of STDs during possible periods of HIV infection (38). The systemic review also found that in co-infected individuals the risk of HIV transmission was increased and that concurrent HIV/STI co-infection periods decrease the time to AIDS positive status (38). Rottingen et al. also examined the relationship between HIV infection and the epidemiology of STDs (38). The review found in individuals with HIV the risk for acquiring an STD during an infectious encounter is increased as compared to those without HIV as well as that in those who are HIV positive the risk for recurrence from latent infection is greater (38). Mayaud and McCormick state that HIV can modify the duration, severity, and response to treatment of certain STDs, but cite that this is most common in viral infections (40).

Biological Markers of HIV-Progression

An editorial review by Bentwich et al. in 2000 states that since all co-infections will cause immune responses that it is plausible that these co-infection states enhance HIV infection, increase HIV viral load, and increase the rate of progression of disease in those individuals with STD/HIV co-infection states (45). Bentwich et al. diagrams that co-infection starts via activation of cytokines such as tumor necrosis factor-alpha and helper T cells 1 and 2 and activation of chemokines and related receptors co-infections states increase the susceptibility of HIV infection in naïve individuals (45). The review also diagrams that by activation of cytokines and

chemokines as well as cell anergy (inactivation of a lymphocyte following an antigen encounter (46)) and apoptosis (programmed cell death) as well as HIV replication all increase the progression of HIV to AIDS (45). The authors acknowledge that ulcerative infections are associated with increased risk of HIV infection and increased viral load concentrations in those infected with HIV for both men and women but state that inflammation may be the main factor in HIV enhancement in co-infected individuals (45).

A review of co-infection literature by Bafica et al. states that HIVs enhanced viral expression during co-infection states may be due to the microbial-induced immune response that occurs during these periods (90). Bafica et al. also states that when the article was written (2004) toll-like receptors (TLR) were the major innate immune response for microbial infections (90). In most human cells, when stimulated with TLR-2, 4, or 9 that there is an increase in the viral replication of HIV and cytokine-mediated induction of HIV long terminal repeats [long identical sequences of DNA found at the retrotransposons or proviral DNA end and used to insert genes into host (91)] via nuclear factor κB activation occur during co-infection (90).

N. gonorrheae has been shown to attract CD4+ lymphocytes to infective areas disrupting epithelial and mucosal barriers and increasing possible susceptibility to HIV (24). *N. gonorrheae* enhanced HIV infective potential of activated dendritic cells and during co-infective state HIV's ability to replicate in dendritic cells is enhanced and is thought to be due to an interaction between peptidoglycan and TLR-2 (27). Studies also show that *N. gonorrheae* promotes HIV infectivity of CD4+ T cells (27). Ding et al. found that along with peptidoglycan (a TLR2 agonist), Pam_3CSK_4 and Pam_3C-Lip (gonococcus derived synthetic lipopeptide) also increase HIV's ability to infect CD4+ T cells, whereas TRL4 agonists where not shown to increase infection potential (28, 32). Interleukin 2 was also found to be a vital component in the TLR2-

mediated HIV enhancement (28). *N. gonorrheae* enhanced the HIV infection of CD4 cells early infection via TLR-2 activation which not only increased the susceptibility of CD4 infection but also enhanced the viral load associated with HIV infected CD4 cells (28). It has also been shown that when monocytes differentiate into macrophages they become more susceptible to HIV infection (32). Liu et al. also found that lipooligosaccharides (LOS) which are components of the outer membrane of *N. gonorrheae*, have the ability to stimulate TLR4 which has been shown to protect macrophages against HIV infection (32).

A review by Mayer and Venkatesh from 2012 found that individuals with HIV who were also co-infected with an STD were more likely to spread HIV to their partners than those who were only HIV positive (101). The review states that the biological plausibility of bacterial STD enhancement of HIV is largely backed by the fact that during a bacterial co-infection inflammation causes an increase in HIV expression and that this increase in concentration can be seen to decrease by treatment of the bacterial STD (101). After treatment of the bacterial STD, HIV viral levels in the genitals do not return to levels at a pre-bacterial infection state, this is an important concept because it shows that while treatment has the ability to reduce the sudden increase in viral load, treatment does not fully negate the damage done during a co-infection period (101). The review also found that *N. gonorrheae* enhanced HIV infection by activation of TLR-2 which can both increase susceptibility of CD4 cells to HIV infection and enhance HIV replication in those CD4 cells already infected (101). The review also noted that *N. gonorrheae* co-infection periods increased the ability of HIV to infect dendritic cells which then present the virus to other susceptible immune cells (101).

A study by Ghys et al. found that HIV positive women with *N. gonorrheae* co-infection were more likely to shed HIV than in women who were not co-infected (98). Treatment of the STD

was found to decrease shedding within one week (98). The study also found that in co-infected women, not only was there an increase in viral shedding, but the viral load was higher making the risk of transmission greater (98).

A 2004 study by Kaul et al. looking at antibiotic prophylaxis in female HIV naïve Kenyan sex workers and their risk of HIV infection found that while the rate of HIV between those treated and those on a placebo did not differ at the end of 2 years, however, the risk of developing HIV in those with a diagnosed *N. gonorrheae* infection was increased (103). Prophylactic antibiotics were given to female sex workers as prevention against bacterial STDs and to reduce excess risk of HIV infection due to bacterial/HIV interactions. This study is important for multiple reasons. First this study shows that those infected with *N. gonorrheae* have a higher risk of developing HIV then those that are uninfected (103). Second the study shows that prophylactic antibiotic treatments have the ability to reduce the rate of STDs in endemic areas (103). The final key thing that the study found was that despite the reduction in STDs the rate of HIV was unaffected (103). This finding shows that reduction in of the spread of STDs may not be enough and while those on the treatment have protection from bacterial STDs of their partners, their partners could still be infected and therefore have higher viral loads thus increasing the chance of HIV infection (103).

N. gonorrheae has also been shown to induce defensins which have also been show to enhance HIV (104). In a study by Klotman et al. defensins, antimicrobial peptides thought to play a role in mucosal host immune responses, were found to promote HIV during viral entry into the cell (104). Two defensins, 5 and 6, were created during the immune response to *N. gonorrheae* and were found to promote HIV infection of immune cells (104). The study also found that in men with *N. gonorrheae* infection acute urethritis (inflammation of the urethra) is common, which

would lead to the creation of defensins 5 and 6, which in turn would promote HIV infection of susceptible immune cells, as opposed to women who typically have an asymptomatic rate of 50-80% (104).

A study by Ogawa et al. found that Langerhas cells (dendritic cells of the skin and mucosa) are susceptible to HIV infection after sexual intercourse (106). The study found that antagonists of TLR 1/2 [Pam_3CSK_4 and defensins (107)] and TLR 2/6 [Pam_2CSK_4 (108)] enhanced both susceptibility and viral replication in monocytes created from Langerhas cells (LC) (106). The study also looked at other TLR antagonists, but did not find any associations (106). A theory presented by the article to explain the synergistic relationship between *N. gonorrheae* and HIV is that gram positive bacteria such as *N. gonorrheae* may enhance the sexual transmission of HIV by ligation of TLR2 (106). The study also notes that during *N. gonorrheae* infections LC are commonly found in the genital mucosal epithelium and move to the lymph nodes during infections (106).

1.5 Rationale

As of the 2010, Census Michigan has the 8th largest population in the US. It is estimated that in 2012 there were 20,600 persons living with HIV in the state of Michigan, with 63% of HIV cases residing in the Detroit Metro Area. Black males make up the largest group of those living with HIV in the state of Michigan. In 2012, there were 12,770 reported cases of *N. gonorrheae* infections in the state of Michigan, with the highest rate of infected being persons in the age range of 20-24 years old. This age group represents 6.7% of Michigan population but accounts for 1/3 of all gonorrheal infections in the state of Michigan. The rates of infection with N. gonorrheae were higher in African Americans than in Whites (655 per 100,000 vs 68 per

100,000 respectively as of July 2014) and 43% of all cases were males. In 2011, 259 of the 13,000 reported cases were co-infected with HIV.

Evidence suggests that there is a synergistic relationship between HIV-1 and infection with N. gonorrheae resulting in non-classical manifestations of these diseases in co-infected individuals (17, 18, 23, 24, 31, 36, 40, 41, 44, 48, 51, 55, 58, 60, 92). This study aims to explore the possibility of a synergistic relationship between gonorrhea and HIV via reduction in age at HIV diagnosis in those with a history of gonorrhea, reduction in age at AIDS and death in those with a history of gonorrhea, the geospatial distribution of co-infections in Michigan, the change in CD4 cell count (spike during infection then fall to levels lower than pre-gonorrheal state) and the increase in HIV viral load. *N. gonorrheae* infection will be used as a proxy for risky sexual behavior as data on other STDs, bacterial and viral infections during this time period were unavailable. Attention has focused primarily on co-infection with ulcerating STI's in recent years. However, non-ulcerating STI's such as *N. gonorrheae* account for a significant co-infection burden in the HIV/AIDS community and there is a need for research to explore the dynamic relationship between these co-infections. Prevention efforts should be aimed at those with the highest risk for infection or death to reduce the burden of disease. Among its objectives, this study aims to identify the trends associated with time to infection, survival rates, and geographic clustering of the co-infection paradigm between HIV and *N. gonorrheae*.

A retrospective cohort of HIV positive men in Michigan from 2005 to 2011 with *N. gonorrheae* was created by the Michigan Department of Community Health (MDCH). HIV infected men without any reported cases of *N. gonorrheae* between 2005 and 2011 were selected as the control group by MDCH. Males with HIV that had previously been infected with *N. gonorrheae* prior to 2005 were considered ineligible.

There is a need to explore the co-infection relationship between HIV and *N. gonorrheae* and little is known about the impact of *N. gonorrheae* in facilitating acquisition of HIV or about the change in the survival rates in those with histories of *N. gonorrheae* infections. With limited funding and resources available to control the spread of STD's in sexual networks the need for well-structured interventions are required to make the greatest impact. The geographical analysis of STD co-infections will help to identify the spatial patterns of at risk populations where resources should be spent to have the highest chance of success in disrupting the cycle of transmission.

1.6 Objectives

Objective 1: To test whether infection with *N. gonorrheae* increases the hazard (reduces the age at diagnosis) of developing HIV in Michigan males, with *N. gonorrheae* infection being a proxy for engagement in risky sexual practices.

Objective 1.1: Using time to event analysis, test whether individuals with a history of *N. gonorrheae* infections are younger at HIV diagnosis than those with no history of *N. gonorrheae* infections in Michigan males.

Objective 1.2: Using time to event analysis test whether multiple *N. gonorrheae* infections increase the hazard (younger at HIV diagnosis) of HIV infection in Michigan males.

Objective 1.3: Using time to event analysis test whether prior multiple *N. gonorrheae* infections increase the hazard (younger at HIV diagnosis) of HIV infection in Michigan males.

Gonorrhea is a treatable and easily identified STD, if multiple infections reduce the time to HIV+ status then health departments may want to aim intervention resources to educate and reduce STD burden in those individuals in high risk groups. If multiple infections reduce time to HIV+ then intervention should be aimed at the minimum number of infections that will increase the lag time to HIV+ status. From the public health point of view, gonorrhea pre-HIV+ status may indicate possible predictive social behaviors that may be intervened to prevent progression of individual to infection with HIV. These behaviors include non-routine screening of STDs, condom use, multiple partners, or increased frequency of anonymous sexual partners. Infection with *N. gonorrheae* may act as an easily identifiable flag for risky sexual behavior that would reduce the time to HIV positive status in those that have a history of *N. gonorrheae* infections.

Objective 2: To test if *N. gonorrheae* co-infection increases the hazard (younger at event) of an HIV progression event (death or AIDS) due to possible synergistic effects related to co-infection status.

Objective 2.1: Using survival analysis, test whether age at death in HIV infected men that have *N. gonorrheae* infection occurs at a younger age than in those without a recorded incidence of *N. gonorrheae* in the state of Michigan.

Objective 2.2: Using survival analysis, test whether time from HIV diagnosis to death in HIV infected men that have *N. gonorrheae* infection is reduced as compared to those without a recorded incidence of *N. gonorrheae* infection in the State of Michigan.

Objective 2.3: Using time to event analysis test whether history of gonorrhea increases the hazard (younger at AIDS) of AIDS progression in HIV infected males in Michigan.

Objective 2.4: Using time to event analysis, test whether the time from HIV diagnosis to AIDS in those that have *N. gonorrheae* infections is reduced as compared to those with no reported *N. gonorrheae* infections in HIV infected males in Michigan.

Objective 2.5: Using time to event analysis test whether co-infection status increases the hazard (younger at AIDS) of AIDS progression in those with multiple recorded *N. gonorrheae* infections in HIV infected males in Michigan.

Objective 2.6: Using time to event analysis, test whether the time from HIV diagnosis to AIDS is reduced in those with multiple recorded *N. gonorrheae* infections in HIV infected males in Michigan.

Objective 2.7: Test whether hazard of AIDS progression is increased (younger at AIDS) in co-infected individuals with post-HIV *N. gonorrheae* infections in HIV infected Michigan males.

Objective 2.8: Test whether time to AIDS status from HIV diagnosis is reduced in co-infected individuals with post-HIV *N. gonorrheae* infections in HIV infected Michigan males.

Objective 2.9: Test whether the hazard of AIDS progression is increased (younger at AIDS) in co-infected individuals with multiple post-HIV *N. gonorrheae* infections in HIV infected Michigan males.

Objective 2.10: Test whether time to AIDS status from HIV diagnosis is reduced in co-infected individuals with multiple post-HIV *N. gonorrheae* infections in HIV infected Michigan males.

The public health importance of this objective is to test the hypothesized synergistic relationships between *N. gonorrheae* and HIV resulting in a more pathological state in the individual and reducing their life expectancy through progression of the disease, to either death or AIDS positive status. Public health action can then be aimed to educate and inform individuals about the dangers of co-infection states and the need to engage in safe sex practices even after HIV diagnosis and the need for routine screening of STDs.

Objective 3: To identify locations in Michigan where *N. gonorrheae* and HIV co-infections are elevated in order to target future STD intervention.

Objective 3.1: Explore the spatial patterns and clusters of HIV infection in males in Michigan.

Objective 3.2: Explore the spatial patterns and clusters of *N. gonorrheae* infection in HIV infected males in Michigan.

Objective 3.3: Explore the spatial patterns and clusters of multiple *N. gonorrheae* infections in males affected with HIV

Public health importance of this aim to assess if there are geographical boundaries that constitute sexual networks that are statistically more prone to *N. gonorrheae* HIV co-infections in HIV positive males in the state of Michigan from 2005 to 2010. The identification of these sexual networks is crucial to assisting public health agencies to better focus their resources in reducing the burden of disease in these areas. Clusters can be identified as focal points in the effort to reduce the burden of disease due to co-infection in these areas. Public health education can focus on informing HIV+ individuals in these areas about the importance of safe sex to reduce the risk *of N. gonorrheae* co-infection. Areas that have higher occurrences of multiple infections may be of greater public health concern than other areas, and funding for education and prevention programs may be put to better use by being tailored for this population as opposed to a wider sweeping public health message.

Objective 4: To test whether biological markers of HIV progression are altered during co-infection states in HIV infected Michigan males.

Objective 4.1: Characterize the change in HIV viral levels before, during, and after *N. gonorrheae* co-infection.

Objective 4.2: Characterize the change in CD4 cell counts before, during, and after *N. gonorrheae* co-infection.

Objective 4.3: Explore the spatial patterns and clusters of *N. gonorrheae* in those that are infected with HIV in Michigan from 2011-2013.

Change in laboratory markers such as CD4 cell count and HIV viral load are important indicators of HIV disease progression and due to the synergistic relationship of *N. gonorrheae* and HIV may be altered during and after co-infection periods. These changes in the natural history of HIV are important markers in the progression to AIDS or death in the individual. Investigation of these changes may lead to better understanding of the burden that this places on the host during co-infection periods and allow for departments of public health to educate HIV positive individuals on the risk of STDs and the burden to their already overtaxed immune system. This data set also allows for examination of zip code level GIS mapping and the ability to explore ART and its effects on disease progression during co-infection periods.

APPENDIX

Table 1.1: Percent Urethral and Rectal Gonorrhea in MSM, AIDS Cohort Study (55)

Group	Urethral Gonorrhea	Rectal Gonorrhea
White	47%	27%
Hispanic-Whites	57%	34%
African Americans	66%	27%

Table 1.2: HIV Seroconversion Odd Ratios in MSM, AIDS Cohort Study (55)

Group	Urethral Gonorrhea	Rectal Gonorrhea
White	1.83 (95% CI 1.51-2.23)	1.59 (95% CI 1.28-1.97)
Hispanic-Whites	Not Significant	Not Significant
African Americans	Not Significant	2.44 (95% CI 1.07-5.59)

Chapter 2.

Interaction of *N. gonorrheae* and HIV infections in Michigan Males

2.1 Abstract

Introduction

Evidences suggest a synergistic relationship between HIV and *N. gonorrheae* infections resulting in abnormal epidemiological patterns of these diseases in infected individuals. The goal of this study is to investigate the role of age at HIV diagnosis in individuals with and without *N. gonorrheae* co-infection.

Methods

A retrospective cohort study of 19,647 HIV infected males in the state of Michigan from 2005-2011 was designed in collaboration with Michigan Department of Community Health. Cases of *N. gonorrheae* HIV co-infections consisted of males with HIV infection in Michigan with a reported infection with *N. gonorrheae* between 2005 and 2011 and were diagnosed with HIV by 2011. Controls were Michigan males with no history of *N. gonorrheae* infections who were diagnosed with HIV by 2011. Linear regression and Cox proportional hazard models were constructed to assess *N. gonorrheae* and age at HIV diagnosis.

Results

Mean age at HIV diagnosis in males with no history of gonorrhea was 36.8 years old (95% CI 36.6-36.9) whereas there was decrease in mean age at HIV diagnosis of 8.4 years (95% CI 7.8-9.1) in those with a history of gonorrhea. A dose response was seen in the multiple *N. gonorrheae* infections, with one reported gonorrheal infection event having a mean reduction in

age at HIV diagnosis of 7.3 years (95% CI 6.5-8.2), mean reduction of 9.3 years (95% CI 7.8-10.9) in those with two gonorrhea events, a mean reduction of 10.1 years (95% CI 7.8-12.4) in those with three reported gonorrhea events, a mean reduction of 11.8 years (95% CI 8.4-15.2) in those with four *N. gonorrheae* infections, and a mean reduction of 13.9 years (95% CI 10.9-16.8) in those with five or more *N. gonorrheae* infections as compared to those with no history of gonorrhea. Those with only one previous *N. gonorrheae* infection prior to HIV diagnosis had a mean reduction in age at HIV diagnosis of 7.3 years (95% CI 5.7-9.0) as compared to those with no history of gonorrhea, and a mean reduction of 10.2 years (95% CI 7.7-12.7) in those with 2 or more pre-HIV *N. gonorrheae* infections. Resulting median age of HIV diagnosis was 36 for no history of gonorrhea and decreased to 26 (HRadj=2.08 95% CI 1.95-2.23) in individuals with a reported history of gonorrhea from 2005 to 2011 in the state of Michigan. A dose response was also observed with hazard increasing as number of reported *N. gonorrheae* infections increased. The study also found that in those with pre-HIV gonorrhea the median age of HIV diagnosis also decreased. In males with one reported gonorrheal event, the median age of diagnosis was 26 (HRadj=1.85 95%CI 1.57-2.17) and in those with two or more pre-HIV *N. gonorrheae* infections, the median age at HIV diagnosis was 23.5 (HR_{adj}=2.98 95%CI 2.33-3.80).

Conclusion

Michigan males, at HIV diagnosis who had history of *N. gonorrheae* infections were younger than males diagnosed with HIV but without history of *N. gonorrheae* infections. Males with multiple *N. gonorrheae* infections had an increased hazard (lower median age) at HIV diagnosis than those without reported histories of *N. gonorrheae* infections. Recurrent incidents of pre-HIV *N. gonorrheae* infections were associated with a younger age at HIV diagnosis among males in Michigan. HIV prevention efforts need to consider intervention steps aimed at first occurrence of

an STD, in this case *N. gonorrheae*, as an important event in the reduction of HIV infection among populations at risk for the disease.

2.2 Introduction

Evidences suggest that there is a synergistic relationship between HIV and *N. gonorrheae* infections resulting in non-classical manifestations of these diseases in co-infected individuals. Attention has focused primarily on co-infection with ulcerating STI's in recent years. However, non-ulcerating STI's such as *N. gonorrheae* infections account for a significant burden of co-infection in the HIV/AIDS community and therefore the investigation of the dynamic relationship between these co-infections is warranted.

Despite multiple recent outbreaks of *N. gonorrheae* as well as the emergence of antibiotic resistant strains of *N. gonorrheae* and the fact that *N. gonorrheae* is one of the most reported diseases in the United States, the relationship between HIV and gonorrhea has not been fully delineated (15). In 2011, the WHO estimated that roughly 88 million of the estimated 448 million curable STD infections reported that year were due to *N. gonorrheae* (12). In the United States in 2012, there were over 334,000 *N. gonorrheae* cases resulting in an increased rate of 4.1% from the previous year (13).

As of the 2010 Census Michigan has the 8th largest population in the US. In 2012, there were 12,770 reported cases of *N. gonorrheae* infections in the state of Michigan, with the highest rate of infected being persons in the age range of 20-24 years old. This age group represents 6.7% of Michigan population but accounts for 1/3 of all *N. gonorrheae* infections in the state of Michigan. The rates of infection with *N. gonorrheae* were higher in African Americans than in Whites, and 43% of all cases were males. In 2011, 259 of the 13,000 reported cases were co-infected with HIV.

Based on the January 2014 Annual HIV Surveillance Analysis estimates, there were approximately 19,800 individuals in the state of Michigan who were HIV positive. Of this group, an estimated 15,440 (78%) were males (10). Of the 15,440 males with HIV, men who have sex with men accounted for 55% of prevalent HIV cases between the combined risk groups of MSM and injection drug user (IDU)/MSM in the state of Michigan (10). Heterosexual contacts accounted for 19% of those with HIV infection and 17% had an undetermined source of transmission (10). The most frequent age group for HIV diagnosis was 30-39 year old (33%) with the combined age group of 20-29 at 32% (10). The majority of HIV diagnosis was among males in the Detroit Metropolitan Area (64%) despite the fact that the population of Detroit Metropolitan accounts only for 43% of the total Michigan population (10). Males made up the majority of HIV infected individuals with a reported 12,510 cases (10). Within this group 71% are MSM (combined risk groups of MSM and MSM/IDU), 5% are heterosexuals, and 17% have an undetermined mode of transmission (10).

Wasserhiet et al. reported that epidemiological synergy of HIV and STDs occurs "If coinfection with HIV prolongs or augments the infectiousness of individuals with STDs, and if the same STDs facilitate transmission of HIV, these infections may greatly amplify one another" (95). Reported research indicated that the major target cells of an early HIV infection are the CD4 T cells (1, 27, 28). During bacterial infections the immune system releases T cells to help fight off the infection, these T cells can then serve as targets for HIV to infect and replicate resulting in an increased viral load during bacterial co-infection periods (24, 27- 29, 31).

A study done by Huhn et al. using Chicago and Illinois STD/HIV surveillance data found that of the 43,517 patients seen in 2002 around 13% received a positive HIV test (96). Syphilis had the highest unadjusted OR=11.0 (95%CI 7.7-15.8) for co-STD infection in newly diagnosed HIV

individuals, with gonorrhea coming in second with an OR of 2.2 (95%CI 1.4-3.3) (96). In 1987, a multicenter AIDS cohort study of four sites (Chicago, Los Angeles, Pittsburg, Baltimore/Washington DC) found that lifetime history of gonorrhea was between 40-67% depending on site with Los Angeles and Chicago having the highest rates (58). Another early study of HIV and STDs looking at the AIDS cohort sites found that in MSM (defined as homosexual and bisexual males) 47% of whites had a history of urethral gonorrhea and 27% had a history of rectal gonorrhea (55). Among Hispanic-whites, 57% had a history of urethral gonorrhea and 34% had a history of rectal gonorrhea and among African Americans the rate of urethral gonorrhea was 66% and the rate of rectal gonorrhea 27% (55). The study also found that the average age of sexual activity in MSM was 17 in whites and 15 in Hispanic-whites and African Americans (55). The study also constructed a multivariate analysis and found that 26-30 year old white males had the highest risk of HIV seroconversion and those with a history of rectal gonorrhea had an OR of 1.59 (95%CI 1.28-1.97). Those with a history of urethral gonorrhea had an OR of 1.83 (95%CI 1.51-2.23) (55). Among Hispanic-whites, gonorrhea was not found to be significantly associated with HIV seroconversion (55). In African Americans, history of rectal gonorrhea was associated with an OR of 2.44 (95%CI 1.07-5.59) and urethral gonorrhea was not found to be significant (55). While this study did not look at co-infection status, it was able to show that lifetime history of *N. gonorrheae* infection is associated with an increased risk for HIV seroconversion (55).

A separate study using the multicenter AIDS cohort study published in 1987 found that *N. gonorrheae* infection increased the risk of HIV infection in males (60). The Chmiel et al. study found that risk of HIV infection increases with the frequency of rectal *N. gonorrheae* infection (60). The multivariate model showed that the ROR for 1-3 infections was 1.65 (1.39-1.96) and

the ROR for 4 or more infections was 3.89 (2.45-6.20) (60). The model also looked at the grouping of lifetime infection with other STDs which included urethral gonorrhea, syphilis, urethritis, and genital herpes and found an increasing dose response in HIV seroconversion that increased with re-occurrence of STD infection (60).

A study by Royce et al. found that gonorrheal and chlamydial infections increased the risk of HIV infection in males by 60-340% (44). Increased viral load and increased risk of HIV infection in areas where inflammation due to immune response occurred was also seen (17, 30, 38, 44, 97, 106). A study looking at HIV positive US soldiers found that *N. gonorrheae* infection the most common among those with a history of STD infection prior to HIV seroconversion, with some individuals having multiple pre-HIV infections (17).

This study aims to test the hypothesis that *N. gonorrheae* increases the hazard of HIV seroconversion in HIV naïve individuals. Risk of seroconversion is measured primarily in this study by age at HIV diagnosis since there is no way to tell the actual date of HIV exposure. This study also uses *N. gonorrheae* as a proxy for risky sexual behavior. The first objective of this study is to test if those with a history of *N. gonorrheae* (both pre and post HIV diagnosis) between 2005 and 2011 have an increased hazard (younger age at HIV diagnosis) as compared to other HIV infected Michigan males with no reported *N. gonorrheae* infections. The second objective of this study is to assess the dose response associated with multiple reported *N. gonorrheae* infections with the increased hazard in Michigan males. The third and final objective of the study is to assess the relationship between *N. gonorrheae* and HIV when only looking at pre-HIV *N. gonorrheae* infections in HIV positive Michigan males.

2.3 Methods

A retrospective cohort of HIV positive males in Michigan were selected as the study population. Cases of *N. gonorrheae*-HIV co-infection were defined as HIV positive males with a history of reported *N. gonorrheae* between January 1st 2005 and December 31st 2011. HIV infected males with *N. gonorrheae* prior to 2005 were excluded from the study population. All HIV positive males without a history of *N. gonorrheae* during the study time period that were alive as of January 1st 2005 were included in the study as controls. In collaboration with Michigan Department of Community Health (MDCH) a linkage structure between HIV and *N. gonorrheae* data was created for this study. Records with missing first name, last name, or date of birth were excluded from the study population prior to the matching of the data. A total of 19,647 HIV infected males in the state of Michigan were included in this study. Ethical approval was obtained from the Institutional Review Board (IRB) at Michigan State University (MSU) and was reciprocal with the MDCH IRB. To comply with patient confidentiality and privacy a professional employee of HIV Surveillance and Body Art Unit HIV/STD/VH/TB Epidemiology handled the creation of the record linkage structure between HIV datasets and *N. gonorrheae* data sets. The match was conducted between the two registries using LinkPlus. All data used in this study were de-identified according to HIPAA guidelines on public health information. Study staff also did not contact or attempt to contact any participants of the study.

Table 2.1 shows the demographic distributions of study participant. HIV cases were defined according to the CDC case definition of HIV and AIDS defined according to CDC 1993 guidelines. HIV infection was defined as HIV-NA=HIV infection, non-stage 3 and AIDS=stage 3 HIV infection. Acute and Latent, stage 1 and 2, differentiated in this study. Date of birth, date of death, *N. gonorrheae* infection, as well as HIV and AIDS diagnosis were all limited to year of the event. Vital status was coded as 1=alive, 2=deceased, 9=unknown. Ethnicity was classified

into unique non-over lapping groups, 1.White= White non-Hispanic, 2.Black= Black non-Hispanic, 3.Hispanic=Hispanic of any race, 4.Asian/HI/PI=Asian/Hawaiian, Pacific Islander non-Hispanic, 5.Am In /Ak Nat=American Indian, Alaskan Native, non-Hispanic, or 9.Multi/Unk/Other=Multirace, Unknown, Other, non-Hispanic. Due to low rates of Asian/Hawaiian, Pacific Islanders (N=0) and American Indian, Alaskan Native (N=1) in the *N. gonorrheae* group these racial groups were included in the 9.Multi/Unk/Other grouping to avoid analytical complications. Marital status while largely missing was categorized as A=Married and Separated, S=Single and never married, M=Married, N=Not otherwise specified, Missing or U=Unknown, W=Widowed; Risk was condensed and categorized as A.MSM=Male-Male Sex, B.IDU=Injecting Drug Use, C.MSM/IDU=Male-Male Sex and Injecting Drug Use, D. Blood Recipient=Received Blood, E1.(Male HCFR)=Male who had sex with a female at risk for HIV, F. Perinatal=Child exposed by mother (further condensed to risk group G.Unk:Other due to low response, N=3), G.Unk:Other=Unknown/Other. Individual risk categories were also coded and were analyzed as "Yes" and "Not Yes" to handle missing data as suggested by MDCH. In those with perinatal risks mother's HIV status was also coded, although largely missing, as 1=Refused HIV Testing, 2=Known Uninfected after Birth, 3=Know HIV+ before pregnancy, 4=Known HIV+ during pregnancy, 5=Known HIV+ at time of delivery, 6=Known HIV+ sometime before birth, 7=Known HIV+ sometime after birth, 8=HIV+ with time unknown, 9=Unknown and is mainly used for individuals with risk group F. Perinatal where they were infected via the mother.

History of gonorrhea was coded by MDCH as match='N' for no history of gonorrhea and match='Y' for reported history of gonorrhea. The history of gonorrhea model was run using three different strategies to assess possible co-variates included in the data. The initial model used the MDCH defined condensed risk groups and ethnicity. Because MSM was divided into

MSM and MSM/IDU in the MDCH condensed risk group schema, a second model was ran to assess the variable sex with male. This model include history of gonorrhea, ethnicity, sex with male, sex with female, idu, received clotting factor, received a transfusion, received a transplant, heterosexual sex with an IDU, heterosexual sex with a hemophiliac, heterosexual sex with transfusion recipient, heterosexual sex with transplant recipient, heterosexual sex with person living with HIV, and worked in health care setting. A separate final model was ran that created "presumed" sexual orientation groups such as presumed homosexual (yes to sex with male, no to sex with female) presumed bisexual (yes to both males and females). This model also included history of gonorrhea, ethnicity, idu, received clotting factor, received a transfusion, received a transplant, heterosexual sex with an IDU, heterosexual sex with a hemophiliac, heterosexual sex with transfusion recipient, heterosexual sex with transplant recipient, heterosexual sex with person living with HIV, and worked in health care setting.

Number of total gonorrheal events was constructed by count number of years of reported *N. gonorrheae* infections an individual had. The cut point of 5 or more was selected because of the large drop off in individuals with greater than 5 recorded *N. gonorrheae* infections between 2005 and 2011. Kaplan-Meier curves and a cox regression model were analyzed to determine reduction in age at HIV diagnosis in those with multiple *N. gonorrheae* infections. This model included number of gonorrheal infections, ethnicity, and MDCH condensed age groups. Alternative explorations of sexual strategies were not preformed after investigation returned no significant improvement in the history of gonorrhea model.

The variable of pre-HIV gonorrhea was constructed by taking the year of HIV diagnosis and subtracting the year of *N. gonorrheae* infection for each individual's infections. Those that had a result greater than 0 (0 was not included because it could not be determined if gonorrhea was

before, concurrent, or after HIV diagnosis). These were then counted to see how many pre-HIV infections individuals had. The cut point was set at two or more because very few individuals had greater than 2 pre-HIV gonorrhea events.

Statistical analysis of the data was done using SAS 9.3 (SAS Institute, Inc. Cary, North Carolina). Descriptive statistics were preformed to assess distribution of demographic and risk characteristics. Primary analysis was done using general linear model to investigate mean age at HIV diagnosis. Time to event analysis was used to investigate change in age at HIV diagnosis and Kaplan-Meier curves were created to explore unadjusted trends. Event was defined as HIV diagnosis and time was defined as age of HIV diagnosis. Adjusted and unadjusted models were ran for each of the three study objectives.

2.4 Results

History of gonorrhea

Between 2005 and 2011 there were 903 HIV infected males in Michigan with a reported infections with *N. gonorrheae*. Demographic information can be seen in Table 2.1. Of the 903 individuals with gonorrhea, 216 (23.93%) had at least one *N. gonorrheae* infection prior to their diagnosis with HIV. In HIV infected males with a history of gonorrhea, 117 (19.60%) were White, 674 (74.64%) were Black, 23 (2.55%) were Hispanic, 1 (0.11%) was American Indian, and 28 (3.10%) were reported as Multiracial/Unknown/Other. The majority of *N. gonorrheae* cases did not report marital status 889 (98.45%).

In the distribution of MDCH defined risk groups for HIV infected males with a history of *N. gonorrheae* infection, 697 (77.19%) of males were MSM, 21 (2.33%) were IDU, 21 (2.33%) were MSM/IDU, 20 (2.21%) of HIV infected males reported having sex with a female at risk for

HIV, and 144 (15.95%) had other or unknown risks. Of the 903 HIV positive males that had a reported history of *N. gonorrheae* infection 390 (43.19%) progressed to AIDS/Stage 3 HIV positive status and 20 (2.21%) died. Table 2.2 shows the distribution of non-condensed MDCH risk groups.

The mean age at HIV diagnosis in those with no history of gonorrhea was 36.8 years old. Those with any reported history of *N. gonorrheae* infection were 8.4 years younger HIV diagnosis resulting in a mean age of HIV diagnosis of 28.3 years. Three multivariate models were also constructed. Table 2.3 shows the results from the unadjusted and adjusted models. The first model adjusted for ethnicity and MDCH condensed risk groups. History of gonorrhea infection was associated with reduction of age at HIV diagnosis by 7.2 years in the adjusted model. As compared to Whites, Blacks had a reduction in age at HIV diagnosis of 2.3 years, Hispanics by 2.6 years, and those that were grouped in the Multiracial/Unknown/Other saw a reduction of 2.6 years. As compared to MSM condensed risk group, all other risk groups, aside from Blood Recipients were older in age at HIV diagnosis. Blood Recipients had a reduction of 2.2 years as compared to MSMs. Those that fell into the IDU condensed risk group increased age at HIV diagnosis by 6.6 years, those that fell into the MSM/IDU condensed risk group had increased age of 0.9 years, Male who had sex with a female at risk for HIV had an increased age at HIV diagnosis of 3.6 years, and those that fell into the unknown/Other condensed risk group had an increased age at HIV diagnosis of 5.3 years as compared to MSMs.

The second model investigated a different risk group structure than the MDCH condensed risk groups. In the adjusted model, at HIV diagnosis the age of individuals with history of gonorrhea infection was found to be 7.2 years younger than the group without gonorrheal infection. Those who were Black were 2.1 years younger at HIV diagnosis compared to whites, Hispanics were

younger by 2.4 years, and those that were grouped in the Multiracial/Unknown/Other were 2.5 years younger when compared to whites. Individuals with male partners were 4.5 years younger at HIV diagnosis as compared to those who did not have male sex partners. Those that had female sex partners were 0.9 years older at HIV diagnosis as compared to those with who did not have female partners. Those who were identified as IDU were 1.5 years older at HIV diagnosis as compared to the non-IDU group. Those that had sex with a HIV infected female were 2.0 years younger at HIV diagnosis as compared to those who did not have sex with a HIV positive female.

The third model investigated a second sexual orientation structure where presumed sexual orientation was constructed via sex partner data. Orientation groups included presumed homosexual, presumed heterosexual (reference group), presumed bisexual, and unknown. The model also included IDU and sex with HIV infected female. History of gonorrhea infection was found to reduce age at HIV diagnosis by 7.1 years in the adjusted model. As compared to Whites, those who were Black had a reduction in age at HIV diagnosis of 2.1 years, Hispanics by 2.4 years, and those that were grouped in the Multiracial/Unknown/Other saw a reduction of 2.5 years. Presumed bisexuals had a reduction of 4.0 years as compared to presumed heterosexuals, presumed homosexuals had a reduction 5.4 years, and those that had unknown orientation had a reduction of 0.02 years.

Table 2.4 shows the median age at HIV diagnosis as well as the unadjusted hazard ratio for history of *N. gonorrheae* infection. In HIV positive males with a history of gonorrhea (any reported case of gonorrhea from 2005 to 2011 regardless of HIV status at infection time) had a median age of HIV diagnosis of 26. In HIV positive males without a history of reported gonorrhea the median age at HIV diagnosis was 36. Figure 2.1 shows the Kaplan-Meier

unadjusted curves for HIV infected males with a history of *N. gonorrheae* infection and those without a history of infection. There was an increase in hazard, hazard ratio (HR) 2.24 (95%CI 2.09-2.39), in those with a reported history of gonorrhea between 2005 and 2011. This increase in hazard equates to a reduction in the median time to HIV diagnosis in these individuals (26 years of age at diagnosis for those with gonorrhea compared to 36 years of age in those with no history of gonorrhea).

Multivariate models were also analyzed for history of *N. gonorrheae* infection and age at HIV diagnosis. The first model used the MDCH condensed risk groups. No individual fell into more than one risk group and the final model included history of gonorrhea, ethnicity and condensed risk group. The adjusted hazard ratio (HR_{adj}) for history of gonorrhea was 2.08 (95%CI 1.95-2.23). As compared to whites all other reported racial groups had an increase adjusted hazard as seen in Table 2.5. An increase in age of HIV diagnosis (decrease in hazard) was seen in MDCH condensed risk groups of IDU, Blood Recipient, Male who had sex with a female at risk for HIV, and Other/Unknown as compared to the risk group MSM. MSM/IDU was not observed to have a significant reduction in hazard (reduced age at HIV diagnosis) HR_{adj}=0.95 (95%CI 0.90-1.01 p-value=0.08). Two other multivariate models were also tested to look at the effect of reported sexual orientation. The first of these models still consists of history of *N. gonorrheae* infection as well as ethnicity, but the risk groups were not modeled in a condensed version and individuals were able to fall into multiple groups. Variables introduced in this section were sex with males, sex with females, IDU, and heterosexual intercourse with someone with HIV. The main affect, history of *N. gonorrheae* infection remained the same HR_{adj}=2.08 (95%CI 1.95-2.23). Ethnicity was also found to be significant with all groups having elevated hazard as compared to whites. Sex with males was found to increase hazard of HIV infection as well as heterosexual

intercourse with an HIV infected partner. Both IDU and sex with females were found to be protective (increased age of HIV diagnosis). Sex with males and sex with females are not mutually exclusive groups; an individual can belong to either or both. The final multivariate model considered sorted sexual orientation to Presumed Heterosexual, Presumed Homosexual, Presumed Bisexual and Unknown. This analysis also contained history of *N. gonorrheae* infection, ethnicity, IDU, and heterosexual intercourse with HIV infected individual. History of *N. gonorrheae* was again found to be significant, HR_{adj}=2.08 (95%CI 1.94-2.22) and ethnicity was also found to be significant. Presumed Homosexual was found increase hazard, as well as Presumed Bisexual as compared to Presumed Heterosexual males. Unknown status was found to be protective. Since HR_{adj} or mean reduction of age at HIV diagnosis did not change with the reformulation of risk groups, the MDCH condensed risk group structure was deemed to be the most useful model for determining possible co-variates because it allowed for the most parsimonious model.

History of multiple gonorrhea episodes

Mean age at HIV diagnosis in those with no history of gonorrhea was 36.8 years. In those with only one *N. gonorrheae* infection mean age at HIV diagnosis was reduced by 7.3 years, those with two *N. gonorrheae* infections had a reduction in age at HIV diagnosis of 9.3 years, those with three *N. gonorrheae* infections had a reduction in age at HIV diagnosis of 10.1 years, in those with four *N. gonorrheae* infections reduction in age at HIV diagnosis was 11.8 years, and in those with five or more *N. gonorrheae* infections reduction in age at HIV diagnosis was 13.9 years. A multivariate model was also constructed that adjusted for race and MDCH condensed risk group. Results for unadjusted and adjusted models are shown in table 2.6. In those with only one *N. gonorrheae* infection mean age at HIV diagnosis was reduced by 5.1 years, those with

two *N. gonorrheae* infections had a reduction in age at HIV diagnosis of 10.1 years, those with three *N. gonorrheae* infections had a reduction in age at HIV diagnosis of 6.2 years, in those with four *N. gonorrheae* infections reduction in age at HIV diagnosis was 10.0 years, and in those with five or more *N. gonorrheae* infections reduction in age at HIV diagnosis was 10.9 years. As compared to Whites, those who were Black had a reduction in age at HIV diagnosis of 2.2 years, Hispanics by 2.6 years, and those that were grouped in the Multiracial/Unknown/Other saw a reduction of 2.6 years. As compared to MSM condensed risk group all other risk groups aside from Blood Recipient was an increase of age at HIV diagnosis. Blood Recipients was a reduction of 2.2 years as compared to MSMs. Those that fell into the IDU condensed risk group increased age at HIV diagnosis by 6.6 years, those that fell into the MSM/IDU condensed risk group increased age by 0.9 years, Male who had sex with a female at risk for HIV had an increase age at HIV diagnosis of 3.6 years, and those that fell into the unknown/Other condensed risk group had an increase in age at HIV diagnosis of 5.3 years as compared to MSMs.

In those with multiple reported *N. gonorrheae* infections between 2005 and 2011 a dose response with regard to decrease of age at HIV diagnosis was observed. Figure 2.2 shows the Kaplan-Meier curve for individuals with multiple gonorrhea events as compared to those HIV positive males with no reported events. Table 2.7 contains the unadjusted and adjusted HR for multiple *N. gonorrheae* infections and HIV hazard. A logrank p-value of <0.0001 was observed indicating that not only was the reduction in median age of HIV diagnosis significant, the order, 1 vs 2 vs 3 was also significant. In HIV positive males with only one reported gonorrhea event (N=573) the median age of HIV diagnosis was observed to be 27 years old. In those with two reported *N. gonorrheae* infections (N=173) the median age of HIV diagnosis was observed to be 26 years old. In those with 3 reported gonorrhea events (N=76) the median age of HIV diagnosis was 23.5

years old, in those with 4 gonorrhea episodes (N=35) the median age of HIV diagnosis was 22, and in those with 5 or more *N. gonorrheae* infections between 2005 and 2011 the median age of HIV diagnosis was observed to be 21 years old. Hazard also increased as incidence of gonorrhea increased as compared to those with no reported histories of gonorrhea. In those with only one reported infection of *N. gonorrheae* the HR=1.96 (95%CI 1.80-2.13), in those with two reported gonorrhea episodes HR=2.58 (95%CI 2.22-2.99), the hazard ratio in those with three gonorrhea events was 2.72 (95%CI 2.17-3.40), in those with four *N. gonorrheae* infections HR=3.64 (2.61-5.07), and in those HIV positive males with five or more gonorrheal episodes HR=7.26 (5.43-9.70).

A multivariate modeling approach was also used for multiple *N. gonorrheae* infections. Since the previous model testing did not show any benefit to breaking down of sexual history into heterosexual, homosexual, bisexual and unknown, only models including the MDCH condensed risk groups were used. Those with no history of gonorrhea were selected as the reference group. In those with 1 reported *N. gonorrheae* infection the HR_{adj}=1.87 (95%CI 1.72-2.03). The hazard increased to HR_{adj}=2.29 (95%CI 1.97-2.66) in those with a history of 2 *N. gonorrheae* infections. Those with 3 infections had a HR_{adj}=2.30 (95%CI 1.83-2.88), 4 *N. gonorrheae* infections HR_{adj}=3.38 (95%CI 2.43-4.71) and in those with 5 or more reported *N. gonorrheae* infections HR_{adj}=6.34 (95%CI 4.74-8.48). Hazard of HIV diagnosis also increase across ethnicities as compared to Whites. Hazard decreased in all MDCH condensed risk groups as compared to MSM except for in the MSM/IDU group.

Pre-HIV gonorrhea

The study also investigated the hazard of HIV infection associated with only prior *N. gonorrheae* infections. Of the 903 HIV positive males in Michigan that had a history of *N. gonorrheae* infection only 216 had an event prior to their diagnosis with HIV. Of the 216 with a pre-HIV gonorrheal episode 152 (70%) had only one reported infection and 64 (30%) had two or more *N. gonorrheae* infections up to a maximum of 12 pre-HIV reported *N. gonorrheae* infections. A similar dose response was also seen in figure 2.3 when only looking at pre-HIV *N. gonorrheae* infections. Concurrent infections defined as those *N. gonorrheae* infections that happened in the same year as HIV diagnosis were not included in this analysis since only year of infection/year of diagnosis were given.

Mean age at HIV diagnosis in those with no history of gonorrhea was 36.8 years old. In those with only one pre-HIV *N. gonorrheae* infection the mean reduction in age at HIV diagnosis was 7.3 years, and 10.2 years in those with 2 or more pre-HIV *N. gonorrheae* infections. A multivariate model that was adjusted for MDCH condensed risk and race. Table 2.8 shows the results of the unadjusted and adjusted models. After adjusting for MDCH risk groups and race the mean reduction in age at HIV in those with only one pre-HIV *N. gonorrheae* infection was 6.4 years, and 9.0 years in those with two or more pre-HIV *N. gonorrheae* infections. As compared to Whites, those who were Black had a reduction in age at HIV diagnosis of 2.2 years, Hispanics by 2.6 years, and those that were grouped in the Multiracial/Unknown/Other saw a reduction of 2.6 years. As compared to MSM condensed risk group all other risk groups aside from Blood Recipient was an increase of age at HIV diagnosis. Blood Recipients was a reduction of 2.2 years as compared to MSMs. Those that fell into the IDU condensed risk group increased age at HIV diagnosis by 6.6 years, those that fell into the MSM/IDU condensed risk group increased age by 0.9 years, Male who had sex with a female at risk for HIV had an increase age

at HIV diagnosis of 3.6 years, and those that fell into the unknown/Other condensed risk group had an increase in age at HIV diagnosis of 5.3 years as compared to MSMs.

The median age in those with no reported *N. gonorrheae* infections was 36 years old. In those with only one pre-HIV infection the median age at HIV diagnosis was observed to be 26 years old, and in those with two or more gonorrhea events the median age of HIV diagnosis was 23.5 years. Table 2.9 contains the adjusted and unadjusted HR for pre-HIV gonorrhea. The unadjusted HR of one pre-HIV *N. gonorrheae* infection compared to no history was HR=1.89 (95% CI 1.61-2.21). In those with two or more gonorrhea events the unadjusted HR=3.12 (95%CI 2.18-4.47).

A multivariate model was also constructed for multiple pre-HIV *N. gonorrheae* infections. The model included ethnicity and MDCH condensed risk groups. The HR_{adj} for those with one reported *N. gonorrheae* infection was HR_{adj}=1.85 (95%CI 1.57-2.17) and HR_{adj}=2.98 (95%CI 2.33-3.80) for those with two or more pre-HIV *N. gonorrheae* infections. Hazard increased for other racial groups as compared to Whites and decreased in the MDCH condensed risk groups for all group aside from MSM/IDU.

2.5 Conclusion

From 2005 to 2011 there were roughly 19,647 HIV infected males that did not have gonorrhea prior to 2005. Of these HIV infected males 903 (~5%) were diagnosed with gonorrhea during the study period. Blacks accounted for 54% of HIV infected males and 75% of HIV infected males with a history of gonorrhea. Data were collected, coded and linked by MDCH staff. MDCH had pre-constructed risk groups, MSM, IDU, MSM/IDU, Blood Recipient, Perinatal and Other/Unknown. Due to low responses of perinatal exposure, perinatal was included in Other/Unknown. MDCH also supplied a non-condensed version of the collect risk groups. These

were analyzed in the first objective, History of Gonorrhea, and sexual orientation was recoded first by allowing for multiple sex partner responses (male or female) and then by sexual orientation of presumed heterosexual (female partners, no males), presumed homosexuals (male partners, no female), presumed bisexual (male and female partners) and unknown (no males no females). Neither of these explorations of sexual preference added any new insight into the pathway between *N. gonorrheae* and HIV and were later omitted from other models. Ethnicity was also defined by MDCH and recoded due to low values of Asian and American Indians as separate racial groups.

Prevention efforts for gonorrhea including education, screening, and treatment are well established yet not necessarily easily implemented. Evidence suggests that *N. gonorrheae* may share a synergistic relationship with HIV. The co-infection between *N. gonorrheae* and HIV is an understudied relationship that causes these two diseases to express variant epidemiological patterns.

The time to HIV diagnosis, measured by age at diagnosis, was reduced in those with a history of gonorrhea as compared to those that have no history of *N. gonorrheae* infection. History of gonorrhea included any reported infection between 2005 and 2011 independent of current HIV status at time of *N. gonorrheae* infection. This study found that there was an increase in the hazard of HIV diagnosis in those with a history of gonorrhea.

The study observed a 10 year median (8 year mean) difference in the age of HIV diagnosis in those with gonorrhea as compared to those that had no reported history. Ethnicity was also found to significantly increase hazard of HIV diagnosis. Three models were constructed to assess sexual orientation and other risky activities. The first model used MDCH specified risk groups.

In this model an individual only fit into one of the 5 condensed risk groups. MSM was selected as the reference population and hazard was found to decrease in all other groups, aside from MSM/IDU which was found to not be significant. The second model was constructed to better examine the association of MSM individuals and their age at HIV diagnosis. The model showed that those that reported to have sex with men had an increased hazard, and those that reported sex with females had a decrease in hazard. The final model was constructed to gain better understanding of presumed sexual orientation gathered from available data. Individuals were coded as heterosexual if they only responded yes to having sex with females, homosexual if they only responded yes to having sex with males, bisexual if they responded yes to both male and female and unknown if the response was no in both males and females. The model found that both presumed homosexuals and presumed bisexuals had an increase in hazard (lower age of HIV diagnosis) than presumed heterosexual individuals. However, neither of these reformulations of the MDCH condensed risk added any new information to the associations between gonorrhea, MSM, and HIV and due to the amount of unknown orientations, did not respond yes to having sex with men or women, MDCH's condensed risk group structure was deemed to be the most useful.

A possible synergistic relationship between *N. gonorrheae* and HIV was observed in this study. The study also observed that *N. gonorrheae* infection prior to HIV diagnosis significantly increased hazard of diagnosis for males. This relationship was also seen to follow a dose response pattern in both overall history of gonorrhea and in pre-HIV only gonorrhea with multiple *N. gonorrheae* re-infections increasing the hazard, reducing the age at HIV diagnosis. While overall history of gonorrhea allowed for insight into risky sexual behaviors, pre-HIV gonorrhea allowed for better understanding of the temporal relationship. Median age of HIV

diagnosis ranged from 27 years old in those with only one reported *N. gonorrheae* infection to 21 years old to individuals with five or more reported infections. In individuals with one pre-HIV infection the median age of HIV diagnosis was 26, and 23.5 in those with two or more pre-HIV infections as compared to 36 in gonorrhea free males. These increases in hazard represent possible intervention points for HIV reduction strategies. Resources may best be used in focusing on individuals that come in with their first case of gonorrhea and counseling them on safe sex practices aimed not only at reducing their risk of HIV but also aimed at reducing risk of *N. gonorrheae* re-infection. Resources should also be aimed at educating males that every *N. gonorrheae* infection increases their hazard of HIV diagnosis.

The study also found that 37% (N=330) of those with gonorrhea between 2005 and 2011 had more than one occurrence of the infection. This represents a key group to intervene and provide prevention strategies to help to reduce re-infection rates. The study found a 6 year age reduction in age of HIV diagnosis in those with 5 or more infections as compared to those with only one reported infection. In the fight against HIV and AIDS in Michigan, any deferment in the time to HIV or progression to AIDS is a victory. This study showed that risky sexual behavior, as measured by reported gonorrhea, results in a reduction in the time an individual remains HIV free. The study also found that as number of *N. gonorrheae* infections in an individual increases so does their hazard of being diagnosed with HIV.

Limitations of this study include only being able to gain access to data on gonorrhea. Bacterial STDs promote HIV in infecting white blood cells (1, 24, 27-29, 31) and other STDs that were not included could have had an influence on HIV seroconversion. Gonorrhea infection was used as a proxy for risky sexual behavior and a marker for individuals being in sexual networks where STDs were present. Because this study could not control for the effect of other STDs on age of

HIV diagnosis, the resulting synergistic relation is only speculation driven largely by the effect of pre-HIV gonorrhea median age decreases. Another limitation of this study is that both HIV diagnosis and gonorrhea date are reported only in years. *N. gonorrheae* infections that occurred in the same year as diagnosis were excluded from the pre-HIV analysis due to not being able to place them temporally before, at, or after HIV diagnosis. A final limitation is that since it is very hard to pin point the actual date of HIV infection the study really measures the age at diagnosis of HIV and the actual date of infection could be a year or more prior.

N. gonorrheae and other STIs are reportable diseases, and resources should be given to studying their epidemiological patterns in co-infected individuals. Identification of possible risk factors that may allow for intervention are important tools in trying to prevent the spread not only of HIV but other STDs as well. Education and counseling efforts should be focused on those with their first STD as well as those who are HIV naïve and have multiple reported STD infections as a HIV prevention tool. Education and counseling has to walk the fine line between destigmatization of STDs (so individuals get tested and do not feel ashamed if they are positive) and warning individuals about the dangers of these diseases. As individuals within public health we must change the paradigm from “you just have gonorrhea”, to the sexual behaviors that lead to you getting gonorrhea puts you at risk for HIV and other sexually transmitted diseases which may not be curable.

APPENDIX

Table 2.1: Demographic Distribution of 19,647 HIV Positive MI Males (2005-2011)

Variable	**No *N. gonorrheae* history** N=18744	***N. gonorrheae* history** N=903
Ethnicity		
White	7635 (40.73%)	177 (19.60%)
Black	9988 (53.29%)	674 (74.64%)
Hispanic	711 (3.79%)	23 (2.55%)
Asian	62 (0.33%)	-
American Indian	40 (0.21%)	1 (0.11%)
Multiracial/Unknown/ Other	308 (1.64%)	28 (3.10%)
Marital Status		
Married	1317 (7.03%)	2 (0.22%)
Divorced	1268 (6.76%)	2 (0.22%)
Single	4966 (26.49%)	10 (1.11%)
Other/Unknown/ Widower/Missing	11193 (59.72%)	889 (98.45%)
Risk Group		
MSM	11018 (58.78%)	697 (77.19%)
IDU	2675 (14.27%)	21 (2.33%)
MSM/IDU	1338 (7.14%)	21 (2.33%)
Blood Recipient	268 (1.43%)	-
Male HCFR	770 (4.11%)	20 (2.21%)
Other/Unknown	2675 (14.28%)	144 (15.95%)
AIDS Positive	13767 (73.45%)	390 (43.19%)
Deceased	8906 (47.51%)	20 (2.21%)

Table 2.2: MDCH Non-Condensed Risk Group Distribution of HIV Positive MI Males (2005-2011)

Risk Group	**No *N. gonorrheae* history** N=18744	***N. gonorrheae* history** N=903
Sex with Males	12356 (65.92%)	718 (79.51%)
Sex with Females	9192 (49.04%)	412 (45.63%)
Injection Drug Use (IDU)	4013 (21.41%)	42 (4.65%)
Received Clotting Factor	7 (0.04%)	1 (0.11%)
Received a Transfusion	331 (1.77%)	4 (0.44%)
Received a Transplant	10 (0.05%)	-
Heterosexual Sex with an IDU	1372 (7.32%)	26 (2.88%)
Heterosexual Sex with a Hemophiliac	27 (0.14%)	-
Heterosexual Sex with a Transfusion Recipient	36 (0.19%)	-
Heterosexual Sex with a Transplant Recipient	13 (0.07%)	-
Heterosexual Sex with a Person Living with HIV	1610 (8.59%)	58 (6.42%)
Worked in a Health Care Setting	762 (4.07%)	9 (1.00%)

Table 2.3: General Linear Model Adjusted and Unadjusted Means for Age at HIV Diagnosis in Males With and Without Any History of Gonorrhea

N. gonorrheae History	Mean Unadjusted Age at HIV Diagnosis	Change in Adjusted[M1] Mean Age at HIV Diagnosis	Change in Adjusted[M2] Mean Age at HIV Diagnosis	Change in Adjusted[M3] Mean Age at HIV Diagnosis
No Infection/ Baseline	36.8 years old (36.6-36.9)	36.3 years old (36.0-36.5)	40.4 years old (40.0-40.8)	41.1 years old (40.7-41.5)
History of gonorrhea	28.4 years old (27.5-29.1)	¯7.2 years (¯8.5-¯5.9)	¯7.2 years (¯8.5-¯5.8)	¯7.2 years (¯8.4-¯5.8)
Ethnicity				
White	37.1 years old (36.9-37.4)	-	-	-
Black	36.4 years old (35.9-37.0)	¯2.3 years (¯2.6-¯1.9)	¯2.1 years (¯2.4-¯1.8)	¯2.1 years (¯2.4-¯1.8)
Hispanic	35.9 years old (34.9-37.0)	¯2.6 years (¯3.4-¯1.9)	¯2.4 years (¯3.2-¯1.7)	-2.4 years (¯3.2-¯1.7)
Multiracial/Unknown/ Other[*]	35.5 years old (34.3-36.9)	¯2.6 years (¯3.6-¯1.6)	¯2.5 years (¯3.4-¯1.5)	¯2.5 years (¯3.4-¯1.5)
Risk Group				
MSM	34.7 years old (34.5-34.9)	-	-	-
IDU	40.9 years old (40.3-41.5)	6.6 years (6.2-7.0)	-	-
MSM/IDU	35.6 years old (34.8-36.3)	0.9 years (0.3-1.4)	-	-
Blood Recipient	33.7 years old[ǂ] (32.3-34.7)	¯2.2 years (¯3.4-¯1.0)	-	-
Male HCFR[‡]	37.9 years old (37.0-38.9)	3.5 years (2.9-4.3)	-	-
Other/Unknown[†]	39.4 years old (38.8-40.0)	5.3 years (4.8-5.7)	-	-
Sex with Males	34.8 years old (34.2-35.3)	-	¯4.5 years (¯4.9-¯4.2)	-
Sex with Females	37.3 years old (36.8-37.8)	-	0.9 years (0.6-1.3)	-
IDU (Not Condensed)	39.1 years old (38.6-39.6)	-	1.5 years (1.1-1.9)	1.5 years (1.1-1.9)
Sex with HIV Female	35.8 years old (35.2-36.5)	-	¯2.0 years (¯2.5-¯1.5)	¯1.9 years (¯2.5-¯1.4)
Presumed Heterosexual	39.5 years old (39.2-39.7)	-	-	-
Presumed Homosexual	34.5 years old (33.9-35.1)	-	-	¯5.4 years (¯5.8-¯5.0)

Table 2.3 (cont'd)

Presumed Bisexual	35.3 years old (34.6-35.9)	-	-	¯4.0 years (¯4.5-¯3.6)
Unknown Orientation	39.9 years old‡‡ (39.1-40.7)	-	-	¯0.02 years‡‡ (¯0.6-0.5)

[M1] Model 1
[M2] Model 2
[M3] Model 3
[*] Includes Asian/Hawaiian, Pacific Islanders and American Indian, Alaskan Native

[‡] Male who had sex with a female at risk for HIV
[†] Includes Perinatal
‡‡ Not statistically significant

Table 2.4: Median Age at HIV Diagnosis and Unadjusted Hazard of HIV in HIV Positive Males in Michigan 2005-2011

***N. gonorrhea* History**	**Median Age of HIV Diagnosis**	**Unadjusted Hazard Ratio**
No *N. gonorrhea* Infection	36 years old	Reference Group
History of *N. gonorrhea* Infection	26 years old	2.24 (2.09, 2.39)
1 *N. gonorrhea* Infection	27 years old	1.96 (1.80, 2.13)
2 *N. gonorrhea* Infections	26 years old	2.58 (2.22, 2.99)
3 *N. gonorrhea* Infections	23.5 years old	2.72 (2.17, 3.40)
4 *N. gonorrhea* Infections	22 years old	3.64 (2.61, 5.07)
5 or More *N. gonorrhea* Infections	21 years old	7.26 (5.430, 9.70)
1 Pre-HIV *N. gonorrhea* Infection	26 years old	1.90 (1.62, 2.23)
Multiple Pre-HIV *N. gonorrhea* Infections	23.5 years old	3.20 (2.51, 4.09)

Table 2.5: Multivariate Cox Regression Analysis of Hazard of HIV Diagnosis in MI HIV Positive Males with a History of *N. gonorrheae* 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR [M1]	95%CI[MI]	Adjusted HR [M2]	95%CI[M2]	Adjusted HR [M3]	95%CI[M3]
History of *N. gonorrheae*								
No Infection	1		1		1		1	
History of gonorrhea	2.24	2.09-2.39	2.08	1.95-2.23	2.08	1.95-2.23	2.08	1.94-2.22
Ethnicity								
White	1		1		1		1	
Black	1.07	1.04-1.11	1.25	1.21-1.29	1.24	1.20-1.28	1.25	1.21-1.29
Hispanic	1.10	1.02-1.19	1.22	1.13-1.32	1.22	1.13-1.31	1.22	1.13-1.31
Multiracial/Unknown/ Other*	1.17	1.06-1.28	1.27	1.16-1.40	1.27	1.15-1.40	1.27	1.16-1.40
Risk Group								
MSM	1		1		-		-	
IDU	0.64	0.62-0.67	0.60	0.57-0.62	-		-	
MSM/IDU	0.98	0.93-1.04	0.95	0.90-1.01	-		-	
Blood Recipient	0.80	0.70-0.90	0.88	0.78-0.99	-		-	
Male HCFR‡	0.75	0.70-0.81	0.71	0.66-0.76	-		-	
Other/Unknown†	0.65	0.62-0.67	0.62	0.59-0.64	-		-	
Sex with Males	1.51	1.47-1.56	-		1.54	1.49-1.59	-	
Sex with Females	0.85	0.83-0.87	-		0.90	0.87-0.92	-	
IDU (Not Condensed)	0.81	0.79-0.84	-		0.94	0.91-0.98	0.95	0.91-0.99
Sex with HIV Female	1.09	1.04-1.15	-		1.22	1.15-1.28	1.21	1.15-1.27
Presumed Heterosexual	1		-		-		1	
Presumed Homosexual	1.55	1.49-1.60	-		-		1.69	1.63-1.76
Presumed Bisexual	1.39	1.34-1.45	-		-		1.43	1.37-1.49
Unknown Orientation	0.93	0.88-0.98	-		-		0.98	0.93-1.04

Table 2.5 (cont'd)

[M1] Model 1,[M2] Model 2,[M3] Model 3,[*] Includes Asian/HI/PI AmIn/AkNat ,[ǂ] Male who had sex with a female at risk for HIV,[†] Includes Perinatal

Table 2.6: General Linear Model Adjusted and Unadjusted Means for Age at HIV Diagnosis in Michigan Males with Multiple *N. gonorrheae* Infections

Variable	Mean Unadjusted Age at HIV Diagnosis	Change in Adjusted Mean Age at HIV Diagnosis
History of *N. gonorrheae*		
No Infection/ Baseline	36.8 years old (36.6-36.9)	36.2 years old (36.0-36.5)
1 Infection	29.5 years old (28.4-30.4)	¯5.1 years (¯6.9-¯3.2)
2 Infections	27.5 years old (25.7-30.4)	¯10.1 years (¯12.9-¯7.3)
3 Infections	26.7 years old (24.2-29.1)	¯6.2 years (¯10.2-¯2.1)
4 Infections	25.0 years old (21.4-28.5)	¯10.0 years (¯14.4-¯5.5)
5 or More Infections	22.9 years old (19.8-26.0)	¯10.9 years (¯15.6-¯6.2)
Ethnicity		
White	37.1 years old (36.9-37.4)	-
Black	36.4 years old (35.9-37.0)	¯2.2 years (¯2.5-¯1.9)
Hispanic	35.9 years old (34.9-37.0)	¯2.6 years (¯3.4-¯1.9)
Multiracial/Unknown/ Other*	35.5 years old (34.3-36.9)	¯2.6 years (¯3.6-¯1.6)
Risk Group		
MSM	34.7 years old (34.5-34.9)	-
IDU	40.9 years old (40.3-41.5)	6.6 years (6.2-7.0)
MSM/IDU	35.6 years old (34.8-36.3)	0.9 years (0.3-1.4)
Blood Recipient	33.7 years old‡‡ (32.3-34.7)	¯2.2 years (¯3.4-¯1.0)
Male HCFR‡	37.9 years old (37.0-38.9)	3.6 years (2.9-4.3)
Other/Unknown†	39.4 years old (38.8-40.0)	5.2 years (4.8-5.7)

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Table 2.7: Multivariate Cox Regression Analysis of Hazard of HIV Diagnosis in MI HIV Positive Males with a History Multiple of *N. gonorrheae* 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History of *N. gonorrheae*				
No Infection	1		1	
1 Infection	1.96	1.80-2.13	1.87	1.72-2.03
2 Infections	2.58	2.22-2.99	2.29	1.97-2.66
3 Infections	2.72	2.17-3.40	2.30	1.83-2.88
4 Infections	3.64	2.61-5.07	3.38	2.42-4.71
5 or More Infections	7.26	5.43-9.70	6.34	4.74-8.48
Ethnicity				
White	1		1	
Black	1.07	1.04-1.11	1.24	1.20-1.28
Hispanic	1.10	1.02-1.19	1.22	1.13-1.32
Multiracial/Unknown/ Other[*]	1.17	1.06-1.28	1.27	1.16-1.40
Risk Group				
MSM	1		1	
IDU	0.64	0.62-0.67	0.60	0.57-0.62
MSM/IDU	0.98	0.93-1.04	0.95	0.90-1.01
Blood Recipient	0.80	0.70-0.90	0.88	0.78-0.99
Male HCFR[‡]	0.75	0.70-0.81	0.71	0.66-0.76
Other/Unknown[†]	0.65	0.62-0.67	0.62	0.59-0.64

[*] Includes Asian/HI/PI AmIn/AkNat ,[‡] Male who had sex with a female at risk for HIV,[†] Includes Perinatal

Table 2.8: General Linear Model Adjusted and Unadjusted Means of Age at HIV Diagnosis in Michigan Males with Pre-HIV *N. gonorrheae* Infections

Variable	Mean Unadjusted Age at HIV Diagnosis	Change in Adjusted Mean Age at HIV Diagnosis
History of *N. gonorrheae*		
No Infection/ Baseline	36.8 years old (36.6-36.9)	36.2 years old (36.0-36.5)
1 Pre-HIV Infection	29.5 years old (27.6-31.2)	¯6.4 years (¯8.0-¯4.8)
2 or More Pre-HIV Infections	26.6 years old (23.9-29.2)	¯9.0 years (¯11.5-¯6.6)
Ethnicity		
White	37.1 years old (36.9-37.4)	-
Black	36.4 years old (35.9-37.0)	¯2.2 years (¯2.6-¯1.9)
Hispanic	35.9 years old (34.9-37.0)	¯2.6 years (¯3.4-¯1.9)
Multiracial/Unknown/ Other*	35.5 years old (34.3-36.9)	¯2.6 years (¯3.6-¯1.6)
Risk Group		
MSM	34.7 years old (34.5-34.9)	-
IDU	40.9 years old (40.3-41.5)	6.6 years (6.2-7.0)
MSM/IDU	35.6 years old (34.8-36.3)	0.9 years (0.3-1.4)
Blood Recipient	33.7 years old‡‡ (32.3-34.7)	¯2.2 years (¯3.4-¯1.0)
Male HCFR‡	37.9 years old (37.0-38.9)	3.6 years (2.9-4.3)
Other/Unknown†	39.4 years old (38.8-40.0)	5.2 years (4.8-5.7)

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Table 2.9: Multivariate Cox Regression Analysis of Hazard of HIV Diagnosis in MI HIV Positive Males with a History of Pre-HIV *N. gonorrheae* 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History of Pre-HIV *N. gonorrheae*				
No Infection	1		1	
1 Pre-HIV Infection	1.90	1.62-2.23	1.85	1.57-2.17
2 or More Pre-HIV Infections	3.20	2.51-4.09	2.98	2.33-3.80
Ethnicity				
White	1		1	
Black	1.07	1.04-1.11	1.21	1.18-1.25
Hispanic	1.10	1.02-1.19	1.23	1.14-1.33
Multiracial/Unknown/ Other*	1.17	1.06-1.28	1.24	1.12-1.67
Risk Group				
MSM	1		1	
IDU	0.64	0.62-0.67	0.60	0.58-0.63
MSM/IDU	0.98	0.93-1.04	0.96	0.91-1.02
Blood Recipient	0.80	0.70-0.90	0.87	0.77-0.98
Male HCFR‡	0.75	0.70-0.81	0.72	0.67-0.77
Other/Unknown†	0.65	0.62-0.67	0.61	0.59-0.64

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Figure 2.1: Kaplan-Meier Curves for Age at HIV Diagnosis in HIV Positive MI Males with and without History of *N. gonorrheae* (2005-2011).

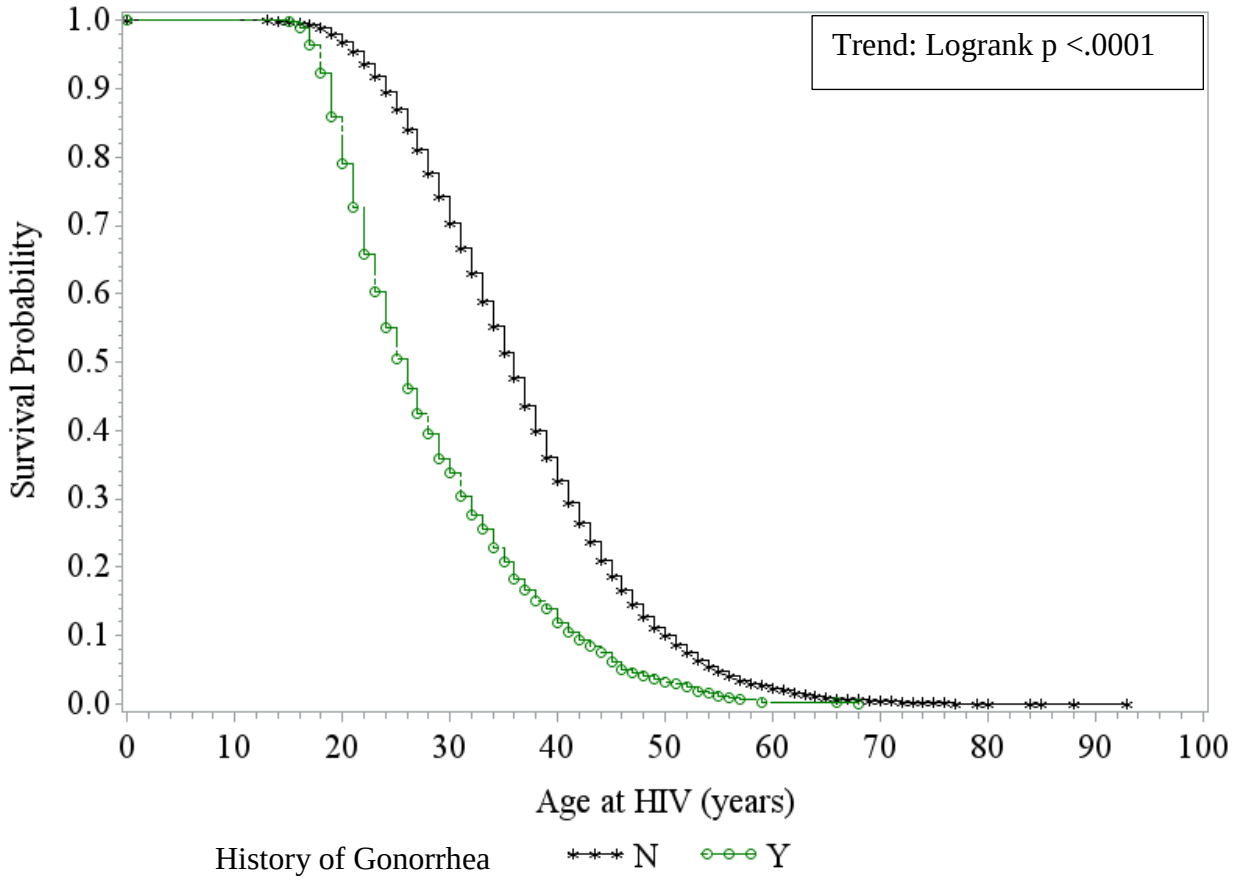


Figure 2.2: Kaplan-Meier Curves for Age at HIV Diagnosis for Multiple *N. gonorrheae* Infections from 2005-2011 in MI HIV Positive Males.

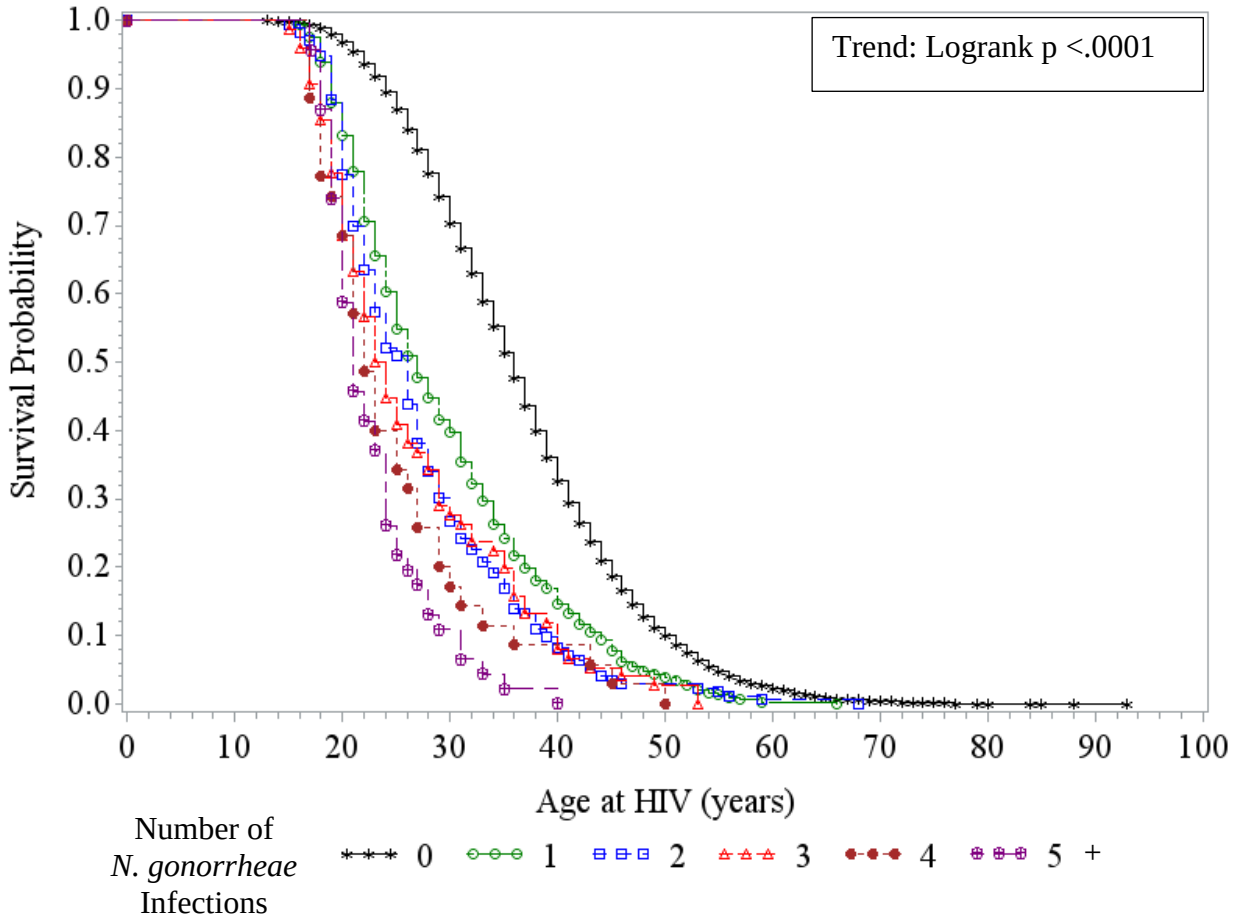
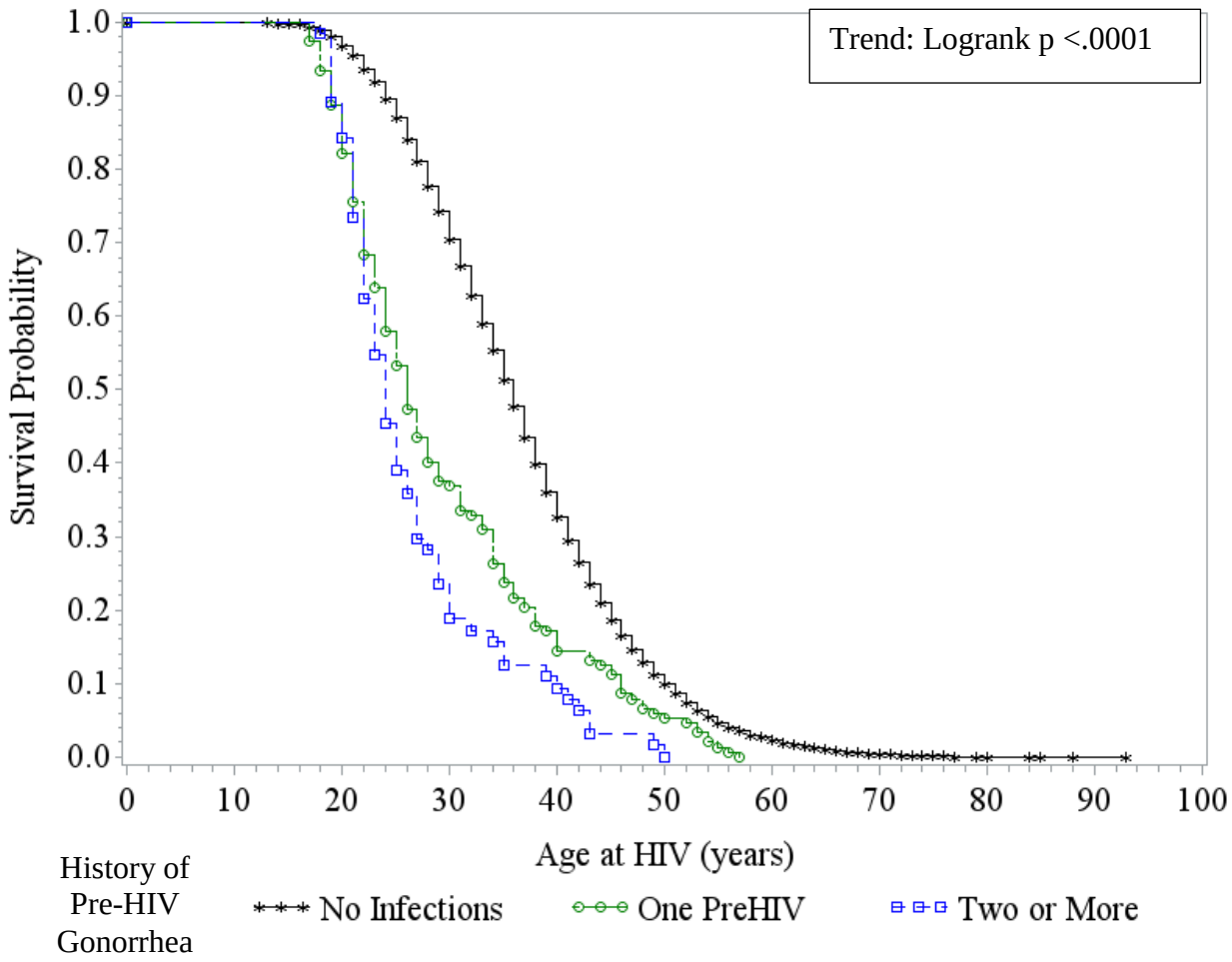


Figure 2.3: Kaplan-Meier Curves for Age at HIV Diagnosis in MI Males with Pre-HIV *N. gonorrheae* Infections 2005-2011



Chapter 3.

Enhancement of HIV Progression by *N. gonorrheae* Co-Infection in Michigan Males

3.1 Abstract

Introduction

Evidence suggests that there is a synergistic relationship between *N. gonorrheae* and HIV with regard to progression of HIV infection, towards AIDS and death. *N. gonorrheae* co-infection in HIV infected individuals has been shown to both increase the hazard associated with progression to AIDS and death. The objective of this study is to test whether *N. gonorrheae* increases the hazard (younger at event) associated with progression to AIDS and death, as well as increases the hazard (shorter lag time) of an HIV progression event from HIV diagnosis.

Methods

A retrospective cohort study of 19,647 HIV infected males in the State of Michigan from 2005-2011 was created through collaboration with Michigan Department of Community Health. Cases consisted of males in Michigan with a reported incidence of *N. gonorrheae* infection between 2005 and 2011 and were diagnosed with HIV by 2011. Controls were Michigan males with no history of *N. gonorrheae* infections who were diagnosed with HIV by 2011. Time to event analysis was used to determine hazard of progression to AIDS and death.

Results

The median age at death in HIV positive males with no history of *N. gonorrheae* infection was found to be 41 years as compared to 38.5 years individuals with a history of gonorrhea. The time period from HIV to death was longer in those with gonorrhea than in those with no history, 5

years and 3 years respectively. The median age at AIDS in individuals with no history of gonorrhea was 38 years as compared to 31 in those with a history of gonorrhea. Those of AIDS positive status with only one reported infection with *N. gonorrheae* had a median age of AIDS positive status of 32 years, 29 years in those with two *N. gonorrheae* infections, 32 years in those with three *N. gonorrheae* infections, 21 years in those with 4 *N. gonorrheae* infections, and 24 years in those with 5 or more *N. gonorrheae* infections. Those with gonorrhea, but no post-HIV gonorrheal episode had a median age of AIDS positive status of 29 years old. In those with a history of post-HIV gonorrhea as well as in those with only one post-HIV *N. gonorrheae* infection the median age of AIDS positive status was 32 years, in those with two post-HIV *N. gonorrheae* infections the median age was 30.5 and those with 3 or more post-HIV infections the median age was 26. Time from HIV to AIDS positive status was longer in those with a history of *N. gonorrheae* as compared to those without. The median time from HIV to AIDS in those with no history of *N. gonorrheae* infection was less than one year. In those with a history of gonorrhea, as well as those with 1-4 *N. gonorrheae* infections the median time from HIV to AIDS was 1 year. In those with 5 or more *N. gonorrheae* infections the median time was 2 years. In individuals with gonorrhea, but no post-HIV gonorrhea the median time between HIV and AIDS was less than one year. In both history of post-HIV gonorrhea as well as in males with 1-2 reported post-HIV *N. gonorrheae* infections the median time from HIV to AIDS was 2 years, and in those with three or more post-HIV infections the median time was 3 years.

Conclusion

A decrease in age at a progression to AIDS or death was observed in individuals with a history of *N. gonorrheae* infection and persisted when looking at post-HIV *N. gonorrheae* infections. An observed increase in the lag time between HIV diagnosis and AIDS positive status was also

found. Infection with *N. gonorrheae* may reduce the hazard of time from HIV to progression event; however, more research is needed to assess possible confounders that may be influencing this potential paradoxical relationship.

3.2 Introduction

Epidemiological evidence suggests that there is a synergistic effect between co-infection with *N. gonorrheae* and infection with HIV resulting in an increase in the progression of HIV in these individuals. Wasserheit (1992) explored the synergistic relationship between STDs and HIV. Wasserheit proposed that there were 3 key relationships between these diseases with the second being the theorized accelerated progression of HIV to AIDS or death in individuals with STD co-infections (95). Wasserheit also noted that STD infection can serve as a useful proxy for difficult to measure variables such as anonymous sex or use of sex workers (95). A review article also focusing on the epidemiological synergistic relationship between STDs and HIV by Rottingen et al. (2001) found that individuals with periods of STD/HIV co-infection have a decrease in time to AIDS positive status. However, while many studies investigated viral load and CD4 cell count during co-infection periods, the actual effect *N. gonorrheae* and other STDs on age of AIDS diagnosis, age at death and time from HIV to one of these progression events has not been well documented. There is a need to study not only laboratory markers of HIV progression in co-infected individuals, but also progression events such as death and AIDS positive status in these individuals.

N. gonorrheae is one of the most reported diseases in the United States with multiple outbreaks of the disease occurring yearly; however, its effect of HIV during periods of co-infection is not fully understood (15). In 2011, WHO estimated that roughly 88 million of the estimated 448 million curable STD infections reported that year were due to *N. gonorrheae* (12). In the United States in 2012, there were over 334,000 *N. gonorrheae* cases resulting in an increased rate of 4.1% from the previous year (13).

The World Health Organization (WHO) estimated in 2012 that there were 35.3 million people living with HIV and a total of 2.3 million infections and 1.6 million deaths due to AIDS related causes (6). Roughly 9.7 million people in 2012 were estimated to be on ARV therapy (6). Under the 2013 WHO ARV guidelines, there are an estimated 26 million people eligible for therapy leaving a large gap between those that are eligible and those that are receiving ARV treatment (6).

In 2011, the CDC estimated that there were over 32,000 HIV stage 3 (AIDS positive) diagnosed individuals in the U.S. with 24,000 of them being in adult and adolescent males (8). There were over 1.1 million AIDS diagnoses by 2010 in the United States with 487,692 individuals living with AIDS and 15,000 AIDS related deaths in 2010 alone (8). The top three states of AIDS diagnosis were California (n=3,622), New York (n=3,574), and Florida (n=3,440) in 2011 respectively (8,9). The state of Michigan in 2011 ranked 20th in HIV diagnoses and 18th in AIDS diagnoses (9).

As of the 2010 Census Michigan has the 8th largest population in the US. In 2012, there were 12,770 reported cases of *N. gonorrheae* infections in the state of Michigan. In 2011, 259 of the 13,000 reported cases were associated with HIV co-infection. The highest rate of *N. gonorrheae* infection occurred in individuals between 20 and 24 years old. This age group represents 6.7% of Michigan population but accounts for 1/3 of all *N. gonorrheae* infections in the state of Michigan. The rates of infection with *N. gonorrheae* were higher in African Americans than in Whites, and 43% of all cases were males.

As of January 2014, there was an estimated 8,207 Stage 3/AIDS positive individuals in the State of Michigan with a reported 428 new Stage 3/AIDS positive individuals identified in 2013 (10).

The total number of individuals living with AIDS (Stage 3 HIV) increased from 8,207 reported in January to 8,240 in the July 2014 report, with the new 2013 AIDS total at 471 (111). Of all those diagnosed with HIV up to January 2014, 18,794 of 27,407 progressed to AIDS/Stage 3 positive status (111). Among the AIDS positive individuals 35% were diagnosed with AIDS at the same time of their HIV diagnosis, 8% had a "short" lag time (1-12 months after HIV diagnosis) to AIDS positive status, and 26% had a "long" lag period (more than 12 months from HIV diagnosis) (111). Males with HIV had a higher percent AIDS progression than females, 70% of males as compared to 64% of females (111). Within males with HIV, 37% were diagnosed as AIDS positive at the time of their HIV diagnosis, 8% had a short lag time, and 25% of males had a long lag time to AIDS positive status (111). In females with HIV the percent of concurrent AIDS diagnosis (HIV and AIDS diagnosis at the same time) was 28%, 8% had a short lag time, and 28% had a long lag time (111).

N. gonorrheae infections were thought to be on a decline at the early start of HIV in the US (circa 1986), however, gonorrhea started its re-emergence in the MSM population around 1990 and reached its peak in 2005 (34). Rietmeijer et al. note that *N. gonorrheae* infection of HIV positive males can be broken into two time periods with a decline between them (37). The first increase in HIV positive males occurred between 1995 and 1997 with a decline between 1997 and 1998 (37). This was then followed in 1999 by a second period of *N. gonorrheae*/HIV co-infections that lasted until 2000 (37).

A study conducted to study HIV and STDs in US military personnel of around 2,000 HIV positive individuals, found that among HIV positive personnel, 50% also had a history of a STD (17). The study found that of those with a history of STD infection, 47% were reported to only have had a STD infection after HIV diagnosis and 20% having both pre and post HIV STD

infections (17). Syphilis was the most common post-HIV STD infection while *N. gonorrheae* accounted for 24% (N=157) of post-HIV STD infections (17). The study also found that individuals had multiple gonorrhea events with a total of 186 reported *N. gonorrheae* infections in 157 individuals (17). A study by the Minnesota Department of Health found that of 1.3% of HIV positive individuals in the study had at least one reported diagnosis of an STD (92). Among MN HIV positive individuals, gonorrhea incidence was higher than it was in the HIV negative population (92). 17% of HIV positive individuals with gonorrhea had 2 or more *N.* gonorrheae infections from 1993 to 1994, all of which were male (92). Other studies have reported as high as a 20 fold increase in gonorrhea in HIV infected men than in those that are HIV negative (35).

In a review of the synergistic relationship between STDs and HIV Rottingen et al. suggest that along with susceptibility of the HIV infection in naïve individuals the HIV/STD co-infection period decreases the time to AIDS positive status (38). A study by Mayaud and McCormick also found that STDs both ulcerative and inflammatory effect the progression of HIV to AIDS (40). An editorial review by Bentwich et al. also states that during HIV co-infections the activation of cytokines and chemokines, anergy and apoptosis, as well as increased HIV replication all influence the progression of HIV to AIDS (45).

3.3 Methods

A retrospective cohort of HIV positive males in Michigan were selected as the study population. Cases were defined as HIV positive males with a history of reported *N. gonorrheae* between January 1st 2005 and December 31st 2011. HIV infected males with *N. gonorrheae* prior to 2005 were excluded from the study population. All HIV positive males without a history of *N. gonorrheae* during the study time period that were alive as of January 1st 2005 were included in

the study as controls. A linkage structure between HIV and *N. gonorrheae* data for this study was created in collaboration with Michigan Department of Community Health (MDCH). Records with missing first name, last name, or date of birth were excluded from the study population prior to the matching of data. A total of 19,647 HIV infected males in the state of Michigan were included in this study. Ethical approval was obtained from the Institutional Review Board (IRB) at Michigan State University (MSU) and was reciprocal with the MDCH IRB. An MDCH employee at the HIV Surveillance and Body Art Unit HIV/STD/VH/TB Epidemiology created the record linkage structure between HIV datasets and *N. gonorrheae* data sets to comply with patient confidentiality and privacy. The match was conducted between the two registries using LinkPlus. All data used in this study were de-identified according to HIPAA guidelines on public health information. Study staff also did not contact or attempt to contact any participants of the study.

HIV infection was defined as HIV-NA=HIV infection, Non-Stage 3 and AIDS=Stage 3 HIV infection. Acute and Latent, Stage 1 and 2, differentiated in this study. Date of birth, date of death, *N. gonorrheae* infection, as well as HIV and AIDS diagnosis were all limited to year of the event. Vital status was coded as 1=alive, 2=deceased, 9=unknown. Ethnicity was classified into unique non-over lapping groups, 1.White= White non-Hispanic, 2.Black= Black non-Hispanic, 3.Hispanic=Hispanic of any race, 4.Asian/HI/PI=Asian/Hawaiian, Pacific Islander non-Hispanic, 5.Am In /Ak Nat=American Indian, Alaskan Native, non-Hispanic, or 9.Multi/Unk/Other=Multirace, Unknown, Other, non-Hispanic. Due to low rates of Asian/Hawaiian, Pacific Islanders (N=0) and American Indian, Alaskan Native (N=1) in the *N. gonorrheae* group these racial groups were included in the 9.Multi/Unk/Other grouping to avoid analytical complications. Marital status while largely missing was categorized as A=Married and

Separated, S=Single and never married, M=Married, N=Not otherwise specified, Missing or U=Unknown, W=Widowed; Risk was condensed and categorized as A.MSM=Male-Male Sex, B.IDU=Injecting Drug Use, C.MSM/IDU=Male-Male Sex and Injecting Drug Use, D.Blood Recipient=Received Blood, E1.(Male HCFR)=Male who had sex with a female at risk for HIV, F.Perinatal=Child exposed by mother (further condensed to risk group G.Unk:Other due to low response, N=3), G.Unk:Other=Unknown/Other. Individual risk categories were also coded and were analyzed as "Yes" and "Not Yes" to handle missing data as suggested by MDCH. Mothers HIV status was also coded, although similar to marital status largely missing as 1=Refused HIV Testing, 2=Known Uninfected after Birth, 3=Know HIV+ before pregnancy, 4=Known HIV+ during pregnancy, 5=Known HIV+ at time of delivery, 6=Known HIV+ sometime before birth, 7=Known HIV+ sometime after birth, 8=HIV+ with time unknown, 9=Unknown and is mainly used for individuals with risk group F. Perinatal where they were infected via the mother. Table 3.1 shows the descriptive statistics for HIV positive males in MI from 2005-2011.

Statistical analysis of the data was performed using SAS 9.3 (SAS Institute, Inc. Cary, North Carolina). Descriptive statistics were preformed to assess distribution of demographic and risk characteristics. Time to event analysis was used to investigate change in age at AIDS diagnosis as well as time from HIV to AIDS and Kaplan-Meier curves were created to explore unadjusted trends. Event was defined as AIDS diagnosis and time was defined as age of AIDS diagnosis. Adjusted and unadjusted models were run time from HIV to event models. Only unadjusted models were constructed for age at HIV progression event. Survival analysis and Kaplan-Meier curves were created to investigate age at death as well as time from HIV diagnosis to death in those with and without a history of *N. gonorrheae* infection.

As stated above death was coded by two variables, the first variable was vital status, yes/no/unknown, and year of death for those that died. The variable of time from HIV diagnosis to death was constructed by taking the year of death and subtracting the year of HIV diagnosis. Due to low numbers of deaths in gonorrhea positive HIV males in this study population, no multiple *N. gonorrheae* infection models were ran on the data. Gonorrhea was coded as match='N' for no history of gonorrhea and match='Y' for reported history of gonorrhea by MDCH.

Current Diagnostic Status was coded as HIV-NA=HIV infection, Non-Stage 3 and AIDS=Stage 3 HIV infection and only year of diagnosis was recoded for HIV and AIDS. History of gonorrhea was ran as match='N' for no history of gonorrhea and match='Y' for reported history of gonorrhea and a model looking at multiple *N. gonorrheae* infections was also constructed. Number of total gonorrhea events was constructed by count number of years of reported *N. gonorrheae* infections an individual had. The cut point of 5 or more was selected because of the large drop off in individuals with greater than 5 recorded *N. gonorrheae* infections between 2005 and 2011. Post-HIV gonorrhea events were constructed by taking the year of gonorrhea and subtracting the year of HIV diagnosis, positive values constituted post-HIV infections, 0 indicated same year of diagnosis, and negative numbers indicated pre-HIV gonorrhea. All concurrent years (where HIV diagnosis and *N. gonorrheae* infection were equal) were not included in the Post-HIV variable. Post-HIV infections were tabulated and a cut point of 3 or more was used for analysis.

3.4 Results

In Michigan from 2005-2011, there were 903 HIV positive males that had a reported history of *N. gonorrheae* infection. Of these individuals, 390 (43%) progressed to AIDS positive status by 2011. Of the remaining HIV positive males in Michigan that were alive as of January 1st 2005, who had no reported gonorrhea, 13,767 (73%) progressed to AIDS positive status by 2011 and 48% died as compared to only 2% in those with a reported history of gonorrhea. Demographic distributions are shown in Table 3.1. MDCH supplied both a condensed single variable to determine high risk sexual behavior as well as individual binary components. In HIV positive males that had no history of *N. gonorrheae* infection 59% identified themselves as MSM and 7% identified as MSM as well as an injection drug user (IDU). Presumed heterosexual IDU accounted for 14% of the gonorrhea free HIV males. 4% of gonorrhea free HIV males were males that have had sex with a female that was HIV positive and the remaining 14% were categorized as other or unknown. In HIV positive males with a history of gonorrhea, 77% identified themselves as MSM with another 2% identifying themselves as MSM/IDU. 2% of HIV positive males with gonorrhea were IDU, 2% were males that have had sex with a HIV positive female, and 16% were other or unknown.

Table 3.2 shows the demographic distributions for those who have progressed to AIDS positive status compared to those that have not progressed to AIDS as of 2011. Of those HIV positive males in MI that have progressed to AIDS positive status, 40% were White, 54% were Black and about 4% were Hispanic. Most individuals did not give marital status (51%), of those that did the majority were single. In the MDCH condensed sexual risk groups MSM accounted for 60% of AIDS positive males with 7% identifying themselves as MSM/IDU and 15% as only IDU. 2% identified themselves as blood recipients, 4% of AIDS positive males had sex with a female that was positive for HIV, and 12% fell into the other or unknown risk group. In HIV positive males

that had not progressed to AIDS positive status by 2011 39% were White, 55% were Black and 4% were Hispanic. The majority of individuals did not report marital status (89%) and of those that did the majority were single. In the MDCH condensed risk groups 60% of non-AIDS positive HIV males were MSM with 6% identifying themselves as MSM/IDU, and 10% identifying themselves as only IDU. 4% were males that have had sex with a HIV infected female and 20% fell into the other or unknown risk group.

The non-condensed distribution of high risk factors by AIDS status can be seen in Table 3.3. Of the total study population 14,157 of 19,647 HIV positive males in Michigan progressed to AIDS positive status by 2011. Individuals may fall into multiple categories of the non-condensed risk groups as opposed to the MDCH condensed grouping, which only allows for an individual to exist in one hierarchical category. Of these individuals who progressed to AIDS positive status 67% had sex with men, 51% had sex with women, and 23% were IDU. A total of 5 individuals who progressed to AIDS received clotting factor, 10 received a transplant, and 287 (2%) received a transfusion. 7% of AIDS positive males identified themselves as having heterosexual intercourse with an IDU and 9% reported that they have heterosexual intercourse with a person living with HIV. Approximately 4% worked in a health care setting and 390 (2.75%) had a history of *N. gonorrheae* between 2005 and 2011. In those that had not yet progressed to AIDS positive status 65% reported they had sex with males, 44% reported they had sex with females, and 16% were IDU. None of the non-AIDS positive HIV males received a transplant, 3 received clotting factors and less than 1% received a transfusion. 6% reported that they have had heterosexual intercourse with an IDU and 8% reported having heterosexual intercourse with a female living with HIV. Of the non-AIDS positive HIV males less than 3% were health care workers and 513 (9%) had a history of *N. gonorrheae* infection reported to the state. Table 3.4

shows the median age of progression event (AIDS or death) and the median time from HIV diagnosis to a progression event.

Time to Death

Figure 3.1 shows the Kaplan-Meier curve for the survival rate of those with and without a history of *N. gonorrheae* infection. Only 20 of those with gonorrhea died between 2005 and 2011 as compared to 47.51% of those with no reported *N. gonorrheae* infections. The study found that those with no history of *N. gonorrheae* infection had a median age at death of 41 years old as compared to 38.5 years old in those with reported gonorrhea. Despite the low number of death events in the gonorrhea group a multivariate analysis was ran to determine hazard of death in those with gonorrhea. Table 3.4 shows the unadjusted hazard ratios for death in those with and without a history of N. gonorrheae infection. Unadjusted HR for those with gonorrhea as compared to those with no history of gonorrhea was HR=0.01 (95% CI 0.06-0.15) as compared to those with no history of gonorrhea. Time from HIV diagnosis to death was also analyzed.

Figure 3.2 shows the Kaplan-Meier survival curve for time from HIV diagnosis to death in those with and without a history of gonorrhea. The median time form HIV diagnosis to death was 3 years in those with no history of gonorrhea and 5 years in those who have had gonorrhea. Table 3.6 shows the unadjusted and adjusted HR for time from HIV diagnosis to death. The multivariate model consisted of history of *N. gonorrheae* infection, ethnicity, MDCH condensed risk group, and age at HIV diagnosis categorized by less than 20 years old, 20-29, 30-39, 40-49, and 50 years old and older. History of a reportable *N. gonorrheae* infection was seen to have a protective effect of death with a HR_{adj}=0.06 (95% CI 0.04-0.09). The only racial grouping to have an increasing effect was black with an increase in hazard of HR_{adj}=1.05 (95% CI 1.00-1.10)

as compared to Whites. Both Hispanic and Multiracial/Other/Unknown had HR_{adj}= 0.83 (95% CI 0.74-0.95) and HR_{adj}=0.63 (95% CI 0.52-0.75) respectively. Those that identified as MSM/IDU, IDU, or a blood recipient all had increased hazard of death as compared to MSM. IDU had a HR_{adj}=1.56 (95% CI 1.47-1.65), MSM/IDU condensed risk group individuals had a HR_{adj}=1.23 (95% CI 1.14-1.33) and those that fell into the blood recipient condensed risk group had an increase in HR_{adj}=2.28 (95% CI 1.98-2.62). Both males that had heterosexual intercourse with a female living with HIV and those that fell into the other/unknown condensed risk group had HR_{adj}=0.75 (95% CI 0.67-0.84) and HR_{adj}=0.78 (95% CI 0.73-0.84) respectively. Age of HIV diagnosis was also found to be a significant predictor of time to death. In those that were diagnosed with HIV in their 20s as compared to those diagnosed before they turned 20 HR_{adj}=2.17 (95% CI 1.72-2.73), those that were diagnosed in their 30s had a HR_{adj}=2.86 (95% CI 2.27-3.60), those that were diagnosed in their 40s had a HR_{adj}=3.33 (95% CI 2.64-4.20) and those that were diagnosed at 50 years or older had an increased HR_{adj}=4.43 (95% CI 3.50-5.61) as compared to those diagnosed with HIV prior to turning 20.

Time to AIDS Positive Status

Figure 3.3 shows the Kaplan-Meier time-to-event curve for age at AIDS positive status in those with and without a reported history of *N. gonorrheae* infection. Median age at AIDS positive diagnosis was seen to be 38 years old in those with no reported history of gonorrhea, and 31 years old in those with a history of *N.* gonorrheae infection. Table 3.7 shows the unadjusted HR for age at AIDS positive status in those with and without *N. gonorrheae* infection. Unadjusted HR of AIDS for males with a history of *N. gonorrheae* was HR=1.17 (95% CI 1.06-1.30) as compared to those with no history of gonorrhea. Time from HIV diagnosis to AIDS positive status was also analyzed.

Time from HIV to AIDS positive status in those with and without a history of *N. gonorrheae* infection was also analyzed. The median time from HIV diagnosis to AIDS positive status was less than 1 year in those with no history of gonorrhea and 1 year in those with gonorrhea. Figure 3.4 shows the Kaplan-Meier time-to-event curve for time from HIV diagnosis to AIDS positive status in those with and without gonorrhea. A multivariate model was constructed to analyze time from HIV diagnosis to AIDS positive status and includes history of gonorrhea, ethnicity, MDCH condensed risk groups, and age at HIV diagnosis. Table 3.8 shows the unadjusted and adjusted HR for progression to AIDS from time at HIV diagnosis. History of *N. gonorrheae* infection was seen to be protective with a HR_{adj}=0.63 (95% CI 0.57-0.70). Being Black as compared to White slightly increased hazard of AIDS progression, HR_{adj}=1.06 (95% CI 1.02-1.10). Only blood recipient was found to increase hazard as compared to falling into the MSM condensed group, HR_{adj}=1.26 (95% CI 1.10-1.43). Both risk groups of males who have had sex with a HIV positive female and the group other/unknown were found to be protective as compared to MSM, with HR_{adj}=0.85 (95% CI 0.78-0.93) and HR_{adj}=0.82 (95% CI 0.77-0.86) respectively. Age at HIV diagnosis was also found to increase the hazard of AIDS progression from HIV diagnosis with a similar dose-response relationship that was seen in the time from HIV to death analysis. In those that were diagnosed with HIV in their 20s as compared to those that were diagnosed before they turned 20, the HR_{adj}=1.31 (95% CI 1.15-1.49), in those that were diagnosed in their 30s HR_{adj}=1.68 (95% CI 1.47-1.91), in those diagnosed in their 40s HR_{adj}=1.78 (95% CI 1.56-2.04) and in those that were diagnosed with HIV at age 50 or over HR_{adj}=1.97 (95% CI 1.71-2.26).

Time to AIDS Positive Status and Multiple N. gonorrheae Infections

History of multiple *N. gonorrheae* infections was also analyzed in relation to age AIDS positive status. Figure 3.5 shows the Kaplan-Meier time-to-event curve for those with multiple *N. gonorrheae* infections and progression to AIDS. Median age of AIDS positive status was seen to be 38 years old as reported in the previous section. Those with only one reported *N. gonorrheae* infection between 2005 and 2011 had a median age of AIDS positive progression of 32 years, in those with two reported *N. gonorrheae* infection the median age was observed to be 29 years, those with three *N. gonorrheae* infections the median age of AIDS positive status was 32 years old, in those with four reported *N. gonorrheae* infections the median age of AIDS positive status was 21, and in those with 5 or more *N. gonorrheae* infections the median age was observed to be 24 years old. Table 3.9 shows the unadjusted HR for multiple *N. gonorrheae* infections and age at AIDS positive status. Unadjusted HR for one gonorrheal infection was HR=1.01 (95% CI 0.89-1.15), in males with two *N. gonorrheae* infections HR=1.45 (95% CI 1.17-.181) as compared to those with no history of gonorrhea. In HIV positive males with three *N. gonorrheae* infections HR=1.55 (95% CI 1.11-2.16), in males with four *N. gonorrheae* infections HR=2.16 (95% CI 1.30-3.59), and in HIV positive males with five or more *N. gonorrheae* infections HR=2.47 (95% CI 1.54-3.97) as compared to those with no history of gonorrhea. Time from HIV to AIDS in those with multiple *N. gonorrheae* infections was also modeled.

Time from HIV diagnosis to AIDS positive status was also looked at in those with a history of multiple *N. gonorrheae* infections. Figure 3.6 shows the Kaplan-Meier time-to-event curve for time from HIV diagnosis to AIDS positive status in individuals with a history of multiple *N. gonorrheae* infections. The median time from HIV diagnosis to AIDS positive status in those males without a reported history of gonorrhea was less than one year. In those with only one reported event of gonorrhea the median time to AIDS positive status was 1 year, as was the

median time from HIV diagnosis to AIDS positive status in those with 2, 3, and 4 reported *N. gonorrheae* infections. In those that had 5 or more *N. gonorrheae* infections the median time from HIV diagnosis to AIDS positive status was 2 years. Table 3.10 shows the unadjusted and adjusted HR for time from HIV diagnosis to AIDS in those with a history of multiple *N. gonorrheae* infections. A multivariate model was constructed that included number of *N. gonorrheae* infection, ethnicity, condensed risk group, and age of HIV diagnosis. In those with only one *N. gonorrheae* infection the HR_{adj}=0.60 (95% CI 0.53-0.68), in those with two *N. gonorrheae* infections HR_{adj}=0.68 (95% CI 0.54-0.85), those that had three *N. gonorrheae* infections had a HR_{adj}=0.71 (95% CI 0.51-0.99), in those with four reported *N. gonorrheae* infections had a HR_{adj}=0.72 (95% CI 0.44-1.20), and in those with five or more reported *N. gonorrheae* infections the HR_{adj}=0.58 (95% CI 0.36-0.94) as compared to those with no history of gonorrhea. Blacks had a slightly higher HR than Whites, HR_{adj}=1.06 (95% CI 1.02-1.10). As compared to MSM only blood recipients had a higher HR, HR_{adj}=1.26 (95% CI 1.10-1.43). There was no statistical difference between IDU or MSM/IDU when compared to MSM, HR_{adj}=0.96 (95% CI 0.91-1.01) and HR_{adj}=0.96 (95% CI 0.90-1.03) respectively. Male HCFR and those that were categorized into the other/unknown risk group had a HR_{adj}=0.85 (95% CI 0.78-0.93) and HR_{adj}=0.82 (95% CI 0.77-0.86) respectively. Age was found to follow a dose response with time. In those that were diagnosed in their 20s as compared to those that were diagnosed before age 20 the HR_{adj}=1.31 (95% CI 1.15-1.50), in those that were diagnosed with HIV in their 30s the HR_{adj}=1.68 (95% CI 1.47-1.92), in those diagnosed with HIV in their 40s HR_{adj}=1.79 (95% CI 1.56-2.04) and in those that were diagnosed in their 50s or above the HR_{adj}=1.97 (95% CI 1.72-2.26).

Post-HIV N. gonorrheae Time to AIDS

The study was also able to look at those who had post-HIV *N. gonorrheae* infections and analyze the hazard of development to AIDS. Figure 3.7 shows the Kaplan-Meier time-to-event curve for individuals with post-HIV gonorrhea and their time to AIDS positive status. The median time to AIDS positive status in those individuals that did not have a post-HIV gonorrhea event (pre or concurrent with HIV diagnosis only) was 29 years old. In those with a history of post-HIV gonorrhea the median age of AIDS was 32 years old. Those that did not have a reported *N. gonorrheae* infection had a median age at AIDS positive diagnosis of 38 years old. Table 3.11 shows the unadjusted HR for individuals with and without a post-HIV gonorrhea event. Unadjusted HR in those with any history of post-HIV *N. gonorrheae* was HR=1.26 (95% CI 1.13-1.41) as compared to those with no history of gonorrhea.

Time from HIV diagnosis to AIDS positive status was also analyzed in those with and without a post-HIV *N. gonorrheae* infection. Figure 3.8 shows the Kaplan-Meier time-to-event curve for time from HIV to AIDS in those with a post-HIV *N. gonorrheae* infection. The median time from HIV diagnosis to AIDS positive status in those with post-HIV gonorrhea was 2 years as compared to less than 1 year for both those with no post-HIV gonorrhea and those without a reported *N. gonorrheae* infection. Table 3.12 shows the unadjusted and adjusted HR for time from HIV diagnosis to AIDS positive status in those with a reported post-HIV *N. gonorrheae* infection. A multivariate model that adjusted for ethnicity, MDCH condensed risk group and age of HIV diagnosis. As compared to those with no history of gonorrhea those with a post-HIV *N. gonorrheae* infection had a HR_{adj}=0.68 (95% CI 0.61-0.77). Blacks had a slightly higher hazard than Whites, HR_{adj}=1.05 (95% CI 1.01-1.09). As compared to those in the MSM condensed risk group, blood recipients had a HR_{adj}=1.27 (95% CI 1.11-1.45). There was no statistical significance between MSM and those that either identified themselves as IDU or those that

identified as both MSM and IDU. Males that had sex with HIV positive females had a HR_{adj}=0.86 (95% CI 0.78-0.93) as compared to MSMs, and those that fell into the other/unknown had a HR_{adj}=0.82 (95% CI 0.77-0.86). Similar to the other time from HIV diagnosis to AIDS positive status, there was a dose response with regard to age at HIV diagnosis. In those that were diagnosed in their 20s as compared to those that were diagnosed with HIV pre 20s, the HR_{adj}=1.34 (95% CI 1.17-1.53), in those that were diagnosed in their 30s the HR_{adj}=1.73 (95% CI 1.52-1.97), in those that were diagnosed in their 40s the HR_{adj}=1.84 (95% CI 1.61-2.10), and in those that were diagnosed at 50 years of age or older the HR_{adj}=2.03 (95% CI 1.77-2.33).

Time to AIDS Positive Status and Multiple Post-HIV N. gonorrheae Infections

The study also looked at multiple post-HIV *N. gonorrheae* and hazard of progression to AIDS. Figure 3.9 shows the Kaplan-Meier time-to-event curve for those with a history of multiple post-HIV *N. gonorrheae* infections and age of AIDS positive status. The median age of AIDS positive status in those with no history of *N. gonorrheae* infection was 38 years old. In those with gonorrhea, but no post-HIV *N. gonorrheae* infections the median age of AIDS positive status was 29 years old. Those that had only one occurrence of post-HIV gonorrhea had a median age of AIDS positive status of 32 years, in those with 2 post-HIV *N. gonorrheae* infections the median age of AIDS positive status was 30.5 years, and in those with 3 or more post-HIV *N. gonorrheae* infections the median age of AIDS positive status was 26 years. Table 3.13 shows the unadjusted HR for multiple post-HIV *N. gonorrheae* infections and hazard of AIDS progression from time of HIV diagnosis. Unadjusted HR in males with a history of gonorrhea, but no post-HIV gonorrhea was HR=0.95 (95% CI 0.77-1.17) as compared to those with no history of gonorrhea. Unadjusted HR in males with only one post-HIV *N. gonorrheae* infection

was HR=1.10 (95% CI 0.95-1.27), in those with two post-HIV *N. gonorrheae* infections HR=1.55 (95% CI 1.22-1.97), and in those with three or more post-HIV *N. gonorrheae* infections HR=2.06 (95% CI 1.51-2.79) as compared to those with no history of gonorrhea. Time from HIV to AIDS in those with multiple post-HIV gonorrheal infections was also analyzed.

The study also looked at multiple post-HIV *N. gonorrheae* and hazard of time from HIV infection to AIDS. Figure 3.10 shows the Kaplan-Meier time-to-event curve for those with a history of multiple post-HIV *N. gonorrheae* infections and the time from diagnosis of HIV to AIDS positive status. The median time to AIDS positive status from HIV diagnosis in individuals with no history of *N. gonorrheae* was less than 1 year. In individuals with gonorrhea, but who did not have post-HIV *N. gonorrheae* infections the median time from HIV diagnosis to AIDS positive status was also less than 1 year. For HIV positive males with one or two post-HIV *N. gonorrheae* infections the median time to AIDS from HIV diagnosis was 2 years, and in those who had 3 or more post-HIV *N. gonorrheae* infections the median time was 3 years. Table 3.14 shows the unadjusted and adjusted HR for multiple post-HIV *N. gonorrheae* infections and hazard of AIDS progression from time of HIV diagnosis. A multivariate model was constructed adjusting for ethnicity, MDCH condensed risk group, and age of HIV diagnosis. Those who had no history of post-HIV gonorrhea had a HR_{adj}=0.51 (95% CI 0.41-0.63) as compared to those with no history of gonorrhea. In those with only on post-HIV *N. gonorrheae* infection HR_{adj}=0.64 (95% CI 0.55-0.74), HR_{adj}=0.77 (95% CI 0.60-0.97) in those with two post-HIV *N. gonorrheae* infections, and in those with 3 or more post-HIV *N. gonorrheae* infections HR_{adj}=0.72 (95% CI 0.53-0.98). Blacks had an increase in hazard as compared to Whites, HR_{adj}=1.06 (95% CI 1.02-1.09). Hispanics as compared to Whites had a HR_{adj}=1.07 (95% CI 0.98-1.17) and those in the Multiracial/Unknown/Other ethnic grouping had a HR_{adj}=0.94 (95%

CI 0.84-1.06). As compared to MSMs those in the Blood Recipient risk group had a HR_{adj}=1.26 (95% CI 1.10-1.43). Both Male HCFR and those in the Other/Unknown risk groups were found to have a protective effect (increase lag time from HIV diagnosis to AIDS positive status) as compared to MSMs, HR_{adj}=0.85 (95% CI 0.78-0.93) and HR_{adj}=0.82 (95% CI 0.77-0.86) respectively. Both IDU and MSM/IDU were not found to be significant as compared to MSMs, HR_{adj}=0.96 (95% CI 0.91-1.01) and HR_{adj}=0.96 (95% CI 0.90-1.03) respectively. Age of HIV diagnosis was found to follow a similar dose-response pattern as it did in previous analysis. As compared to those that were diagnosed before they turned 20 years old, those diagnosed in their 20s had a HR_{adj}=1.31 (95% CI 1.15-1.50), in those that were diagnosed with HIV in their 30s the HR_{adj}=1.68 (95% CI 1.48-1.92), in those diagnosed in their 40s HR_{adj}=1.79 (95% CI 1.57-2.04), and in those that were diagnosed at 50 years of age or older with HIV HR_{adj}=1.97 (95% CI1.72-2.26).

3.5 Conclusion

Among the 903 HIV infected males in MI from 2005-2011 that were included in this study, 43.19% progressed to AIDS positive status by 2011 and only 2.21% died. In those that had no history of gonorrhea, by 2011 73.45% progressed to AIDS positive status and 47.51% had died.

Time to Death

The median age of death in those that had no history of gonorrhea was 41 years old as compared to 38.5 years old in those who had a reported *N. gonorrheae* infection between 2005 and 2011. When looking at the unadjusted model history of gonorrhea seems to be protective with regard to death even though the median age (in those that died) was lower in the gonorrhea group. However, far more individuals that never had gonorrhea died (48%) than in those with a history

of gonorrhea (2%). The median time from HIV diagnosis to death in those with no history of gonorrhea was 3 years as compared to those with a history of gonorrhea who had a median time from HIV diagnosis to death of 5 years. This seemingly protective effect of *N. gonorrheae* infection was also observed in the multivariate model. One of the most likely causes of this paradox to the epidemiological synergistic model proposed by other researchers is that those with reported *N. gonorrheae* infections may have had more exposure to the health care system, and less time between seeing a medical provider than those who did not have any reportable *N. gonorrheae* infections. This may possibly explain why in each time from HIV diagnosis analysis having a history seemingly extends time to AIDS positive status, even though age at AIDS is reduced in all versions of gonorrhea history. The study was able to show that one of the largest factors in time from HIV diagnosis to death was age of HIV diagnosis, and that in all models it has a dose-response effect of increasing hazard as age increases.

Blacks had a marginal increase in hazard (reduction in time from HIV diagnosis to death) as compared to Whites. Both ethnic groups of Hispanic and those that fell into the Multiracial/Unknown/Other had reductions in hazard (longer lags from HIV diagnosis to death) as compared to Whites. Using the MDCH condensed risk group of MSM as the reference group those that fell into the IDU, MSM/IDU, and Blood Recipients all had reduced lag times from HIV to death. Those that fell into the Male HCFR and those in the Other/Unknown risk groups had an increase in lag time from HIV diagnosis to death as compared to the reference group of MSM.

Time to AIDS Positive Status

The median age of AIDS positive status in those that had no history of gonorrhea was 41 years as compared to the median age in those with a history of *N. gonorrheae* infection which was 38.5 years old. The unadjusted hazard model also found that history of *N. gonorrheae* infection increased hazard of AIDS. The median time from HIV diagnosis to AIDS positive status in those with no history of gonorrhea was less than one year as compared to those with a history of gonorrhea who had a median time between HIV diagnosis and AIDS positive status of one year. Those of Black ethnicity were found to have an increase in hazard as compared to Whites. Both Hispanic and Multiracial/Other/Unknown were not statistically significant with Hispanic trending toward increase in hazard of AIDS positive status and Multiracial/Other/Unknown trending toward a decrease in hazard as compared to Whites. Neither IDU nor MSM/IDU were found to be statistically significant as compared to MSM, however, both trended toward reduction in hazard. Blood Recipients were found to have an increase in hazard, and Male HCFR and those in the Other/Unknown risk group were found to reduce hazard (increase age at AIDS positive status) as compared to MSM. Age again was found to increase hazard of a progression event, in this case AIDS positive status. There was a significant increase in hazard with each increase of age at HIV diagnosis as compared to those who were diagnosed with HIV before they turned 20.

Time to AIDS Positive Status and Multiple N. gonorrheae Infections

The median age at AIDS positive status in those with no history of *N. gonorrheae* infection was observed to be 38 years old. Those with a single reported history of gonorrhea had a median age of AIDS positive status of 32 years old which is 6 years earlier than in those without a history of gonorrhea. Median age in those with two *N. gonorrheae* infections is 29, in those with three *N. gonorrheae* infections the median age is 32 years, in those with 4 *N. gonorrheae* infections the

median age of AIDS positive status is 21 years and 24 years in those with 5 or more *N. gonorrheae* infections. This trend in reduction in age of AIDS positive status shows that there is a possible increase in the virulence of HIV in these males due to the presence of having *N. gonorrheae* infections. Each infection may cause a spike in antibody production leading to increase sites for HIV replication. Each *N. gonorrheae* infection represents a possible intervention opportunity to get individuals to be aware that they are at risk for progressing to AIDS positive status and an opportunity to determine where their viral load and CD4 levels are.

The unadjusted hazard analysis also showed that there was an increase in hazard of progression to AIDS in individuals as their re-infection with *N. gonorrheae* increases. Time from HIV diagnosis to AIDS positive status had similar results as it did with the binary history of *N. gonorrheae* infection model, with there being a reduction in risk with the increase of *N. gonorrheae* infections. Median time from HIV diagnosis to AIDS positive status in those with no history of gonorrhea was less than 1 year as compared to those with 1-4 *N. gonorrheae* infections having a median time to infection of 1 year and in those with 5 or more the median time from HIV diagnosis to AIDS positive status was 2 years. The multivariate model also found similar results with hazard decreasing in a linear trend with the increase of *N. gonorrheae* infections. Blacks were found to have increased hazard of AIDS as compared to Whites. Neither IDU nor MSM/IDU were found to significantly decrease hazard as compared to MSM. Those that fell into the Blood Recipient group were found to have an increase in hazard of AIDS progression as compared to MSM. Both Male HCFR and those in the Other/Unknown risk groups were found to have reductions in hazard. As seen in the previous time from HIV models hazard increased with increase in age of HIV diagnosis meaning that there was a shorter time from HIV to AIDS in

those that were diagnosed at an older age with HIV as compared to those that were diagnosed at a younger age.

Post-HIV N. gonorrheae Time to AIDS

The median age of AIDS positive status in those that had no history of gonorrhea was 38 years old as compared to those with post-HIV gonorrhea who had a median age of AIDS positive status of 32 years. The unadjusted hazard model also showed an increase in hazard in those with a history of post-HIV gonorrhea. For time from HIV to AIDS positive status those with no history of gonorrhea had a median time from HIV diagnosis to AIDS positive status of less than 1 year as compared to those with a post-HIV *N. gonorrheae* infection who had a median time from HIV to AIDS positive status of 2 years. The multivariate model shows this seemingly protective relationship as well with hazard decreasing in those with a post-HIV *N. gonorrheae* infection as compared to those with no history of infection. Blacks have a slight increase in hazard as compared to Whites and Blood Recipients have an increase in hazard as compared to MSMs. Neither IDU nor MSM/IDU were found to statistically reduce hazard as compared to MSMs. Both Male HCFR and those in the Other/Unknown risk group had decreases in hazard. A similar dose-response with regard to hazard and age of HIV diagnosis was also found in the model with hazard increasing as age of HIV diagnosis increased.

Time to AIDS Positive Status Multiple Post-HIV N. gonorrheae Infections

The median age of AIDS positive status in those that had no history of gonorrhea was 38 years old, and in those with a history of gonorrhea, but no history of post-HIV gonorrhea (gonorrhea reported after HIV diagnosis) the median age of AIDS positive status was 29 years old, almost a 10 year difference. In those with a history of post-HIV *N. gonorrheae* the median age of AIDS

positive status does increase as compared to those with no post-HIV gonorrhea, but decreases (increase in hazard) as compared to those with no reported history of *N. gonorrheae* infection. The median age of AIDS positive status in those with only one post-HIV gonorrhea infection is 32 years, in those with 2 post-HIV infections the median age is 30.5 years old and in those with 3 or more post-HIV infections the median age of AIDS positive status is 26 years old, a 12 year difference from those that remained gonorrhea free.

The unadjusted hazard model also showed an increase in hazard in those with post-HIV gonorrhea. Hazard increased with occurrence of post-HIV *N. gonorrheae* infections as compared to those with no history of *N. gonorrheae* infection. The median time from HIV diagnosis to AIDS positive status in those with no history of gonorrhea was less than one year as well as in those with a history of gonorrhea, but no post-HIV gonorrhea. The median time from HIV diagnosis to AIDS positive status in those with one or two post-HIV *N. gonorrheae* infections was 2 years and the median time between HIV and AIDS positive status in those with 3 or more post-HIV *N. gonorrheae* infections was 3 years. The multivariate model also shows a reduction in hazard for the increase in post-HIV *N. gonorrheae* infections. There was a slight increase in hazard in Blacks as compared to Whites as well as in those that were in the risk group Blood Recipients as compared to MSMs. Neither IDU nor MSM/IDU was found to be statistically significant, and Male HCFR and those in the Other/Unknown were found to have a reduction in hazard as compared to MSMs. Again a dose-response with hazard and age of HIV diagnosis was seen in this model as well, with hazard increasing as age of HIV diagnosis increased.

Limitations

One of the major limitations of this study in that the interval of time limited the number of deaths as well as the number of individuals that progressed to AIDS in the *N. gonorrheae* group. This was most seen in the time to death modeling. Another limitation that hampered statistical analysis was that all dates were only recorded as years. This had the greatest impact on time from HIV diagnosis to AIDS positive status, but also did not allow us to use con-current HIV/gonorrhea diagnoses in the data (HIV and gonorrhea reported in the same year). The use of actual dates would have allowed for time from HIV to AIDS to be modeled in days not years which may have given better distinction between the different break downs of history of gonorrhea. Another major limitation is that the data available did not allow for the adjustment of other bacterial or viral STDs during the progression to AIDS positive status. While this study is a first step in understanding co-infection paradigms and in acknowledging that STDs, especially HIV do not occur in vacuums to one another, this study did not have information on the frequency of other STDs in the progression to AIDS or death.

It is also important to note that the data used in this study was obtained from a system designed to collect data on reportable diseases, such as STDs and HIV and that it was not a study that was expressly designed to capture the difference in time between HIV and AIDS. Surveillance data is a very useful tool but it does have its limitations as compared to a true retrospective cohort study or a case-control study. Data on ARV was not included in this section of the study, but was included in a subgroup study done on HIV positive males with *N. gonorrheae* co-infection between 2011 and 2013 in chapter 5. In this subgroup the question ever been on ARV, along with the date range was reported and linked. Only 8% of individuals responded in the positive (ever having been on ARV treatment) and among them 71% started the same year or after their *N. gonorrheae* infection which may account for some of the paradoxical findings presented in

this study. It is also important to note that absence of a positive response does not constitute a definite no (never having been on ARV treatment) and the data dictionary instructed to analyze as “Yes” and “Not Yes”. This is an important distinction from an epidemiologic view because it expresses that not all the missing or not “yes” are actually no (individuals who have never been on ARV). While in the GEE models presented in chapter 5 ARV was never found to be significant, it did have a major influence over both CD4 cell count and HIV viral load, two key components of HIV disease progression.

The final major limitation is that we do not know how long a *N. gonorrheae* infection lasted in an individual. Since these are all reported cases, we only capture *N. gonorrheae* infections caught on a screening or due to treatment of symptoms that forced the male to get test, we have no way of knowing the actual rate of *N. gonorrheae* infections in the population. This is true for most STDs as they often, in men go undiagnosed and untreated.

Conclusion

This study was able to find that there was an increase in hazard (progression event at younger ages) in those with a history of *N. gonorrheae* infection as compared to those with no reported history. The study also found that despite a younger age of progression even, the time between HIV diagnosis and a progression event (death or AIDS) was longer in those that had a history of *N. gonorrheae* than in those with no history. The study also found that these relationships were modified by repeated *N. gonorrheae* infections, and multiple *N. gonorrheae* infections were found to both decrease the age of a progression event, and increase the time between HIV diagnosis and a progression even such as AIDS or death. The study found that as multiple *N. gonorrheae* infections, both total and post-HIV, occurred in an individual their hazard of AIDS

increased. Multiple *N. gonorrheae* infections also increased the lag time (reduced hazard) between the diagnosis of HIV in an individual and their diagnosis as being AIDS positive. A possible explanation may be that those with gonorrhea have more visits to a health care professional and therefore may have better management over their HIV compared to individuals that have HIV and then only are possibly seen at routine screenings. The data did not have the reported usage of ART or HAART which may have also influenced the results.

More research is needed, especially looking into ARV rates in Michigan, as well as mechanisms to increase or those that decrease the time from HIV to AIDS positive status. The chapter 5 subgroup, which only consisted of HIV positive males with a history of co-infection, did not allow for testing of number of laboratory tested performed on an individual as a proxy for access to health care due to these being no controls (HIV males with no history of *N. gonorrheae* co-infection. Further research using dates, aside from years is also need to better understand the progression of laboratory markers of HIV progression pre, during, and post *N. gonorrheae* infection.

APPENDIX

Table 3.1: Demographic Distribution of 19,647 HIV Positive MI Males (2005-2011)

Variable	**No *N. gonorrheae* history** N=18744	***N. gonorrheae* history** N=903
Ethnicity		
White	7635 (40.73%)	177 (19.60%)
Black	9988 (53.29%)	674 (74.64%)
Hispanic	711 (3.79%)	23 (2.55%)
Asian	62 (0.33%)	-
American Indian	40 (0.21%)	1 (0.11%)
Multiracial/Unknown/ Other	308 (1.64%)	28 (3.10%)
Marital Status		
Married	1317 (7.03%)	2 (0.22%)
Divorced	1268 (6.76%)	2 (0.22%)
Single	4966 (26.49%)	10 (1.11%)
Other/Unknown/Widower/Missing	11193 (59.72%)	889 (98.45%)
Risk Group		
MSM	11018 (58.78%)	697 (77.19%)
IDU	2675 (14.27%)	21 (2.33%)
MSM/IDU	1338 (7.14%)	21 (2.33%)
Blood Recipient	268 (1.43%)	-
Male HCFR	770 (4.11%)	20 (2.21%)
Other/Unknown	2675 (14.28%)	144 (15.95%)
AIDS Positive	13767 (73.45%)	390 (43.19%)
Deceased	8906 (47.51%)	20 (2.21%)

Table 3.2: Distribution of HIV Positive MI Males with and without AIDS in 2005-2011

Variable	**HIV (Non-Stage 3)** N=5490	**AIDS Positive** N=14157
Ethnicity		
White	2134 (38.87%)	5678 (40.11%)
Black	3002 (54.68%)	7660 (54.11%)
Hispanic	217 (3.95%)	517 (3.65%)
Asian	21 (0.38%)	41 (0.29%)
American Indian	17 (0.31%)	24 (0.17%)
Multiracial/Unknown/ Other	99 (1.8%)	237 (1.67%)
Marital Status		
Married	93 (1.69%)	1226 (8.66%)
Divorced	115 (2.09%)	1155 (8.16%)
Single	365 (6.65%)	4611 (32.57%)
Other/Unknown/Widower/Missing	4917 (89.57%)	7165 (50.64%)
Risk Group		
MSM	3285 (59.84%)	8430 (59.55%)
IDU	547 (9.96%)	2149 (15.18%)
MSM/IDU	305 (5.56%)	1054 (7.45%)
Blood Recipient	38 (0.69%)	230 (1.62%)
Male HCFR	234 (4.26%)	556 (3.93%)
Other/Unknown	1081 (19.69%)	1738 (12.28%)

Table 3.3: Risk Group Distribution of HIV Positive and AIDS Positive MI Males (2005-2011)

Risk Group	**HIV (No Progression to AIDS)** N=5490	**AIDS Positive** N=14157
Sex with Males	3590 (65.39%)	9484 (66.99%)
Sex with Females	2417 (44.03%)	7187 (50.77%)
Injection Drug Use (IDU)	852 (15.52%)	3203 (22.62%)
Received Clotting Factor	3 (0.05%)	5 (0.04%)
Received a Transfusion	48 (0.87%)	287 (2.03%)
Received a Transplant	-	10 (0.07%)
Heterosexual Sex with an IDU	338 (6.16%)	1060 (7.49%)
Heterosexual Sex with a Hemophiliac	5 (0.09%)	22 (0.16%)
Heterosexual Sex with a Transfusion Recipient	6 (0.11%)	30 (0.21%)
Heterosexual Sex with a Transplant Recipient	3 (0.05%)	10 (0.07%)
Heterosexual Sex with a Person Living with HIV	432 (7.87%)	1236 (8.73%)
Worked in a Health Care Setting	143 (2.60%)	628 (4.44%)
History of *N. gonorrheae*	513 (9.34%)	390 (2.75%)

Table 3.4: Median Age and Time from HIV Diagnosis to HIV Progression Events

***N. gonorrheae* History**	**Median Age of Progression Event**	**Median Time from HIV Diagnosis to Progression Event**
Death		
No *N. gonorrheae* History	41 years old	3 years
N. gonorrheae History	38.5 years old	5 years
AIDS Positive Status		
No *N. gonorrheae* History	38 years old	<1 year
N. gonorrheae History	31 years old	1 year
1 *N. gonorrhea* Infection	32 years old	1 year
2 *N. gonorrhea* Infections	29 years old	1 year
3 *N. gonorrhea* Infections	32 years old	1 year
4 *N. gonorrhea* Infections	21 years old	1 year
5 or More *N. gonorrhea* Infections	24 years old	2 years
No Post HIV gonorrhea	29 years old	< 1 year
Post HIV gonorrhea	32 years old	2 years
2 Post HIV *N. gonorrheae* infections	30.5 years old	2 years
3 or more Post HIV *N. gonorrheae* infections	26 years old	3 years

Table 3.5: Unadjusted Analysis of Hazard of Death in MI Males from 2005-2011

Variable	Unadjusted HR	95% CI
History *N. gonorrheae*		
No Infection	1	
History of gonorrhea	0.10	0.06-0.15
Ethnicity		
White	1	
Black	1.13	1.08-1.18
Hispanic	0.90	0.79-1.02
Multiracial/Unknown/ Other*	0.68	0.57-0.82
Risk Group		
MSM	1	
IDU	1.27	1.20-1.34
MSM/IDU	1.25	1.16-1.35
Blood Recipient	1.75	1.52-2.01
Male HCFR‡	0.70	0.62-0.79
Other/Unknown†	0.62	0.58-0.67

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Table 3.6: Multivariate Analysis of Hazard of Time from HIV to Death in MI Males with and without a History of *N. gonorrheae* 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History *N. gonorrheae*				
No Infection	1		1	
History of gonorrhea	0.05	0.03-0.07	0.06	0.04-0.09
Ethnicity				
White	1		1	
Black	1.05	1.00-1.09	1.05	1.00-1.10
Hispanic	0.82	0.72-0.93	0.83	0.74-0.95
Multiracial/Unknown/ Other[*]	0.58	0.49-0.70	0.63	0.52-0.75
Risk Group				
MSM	1		1	
IDU	1.88	1.78-1.98	1.56	1.47-1.65
MSM/IDU	1.30	1.21-1.40	1.23	1.14-1.33
Blood Recipient	2.00	1.74-2.29	2.28	1.98-2.62
Male HCFR[ǂ]	0.83	0.74-0.93	0.75	0.67-0.84
Other/Unknown[†]	0.86	0.80-0.92	0.78	0.73-0.84
Age Group (Age of HIV Diagnosis)				
Less than 20 Years Old	1		1	
20-29 Years Old	2.17	1.72-2.72	2.17	1.72-2.73
30-39 Years Old	3.10	2.74-3.89	2.86	2.27-3.60
40-49 Years Old	3.82	3.04-4.80	3.33	2.64-4.20
Over 50 Years Old	4.89	3.88-6.16	4.43	3.50-5.61

[*] Includes Asian/HI/PI AmIn/AkNat ,[ǂ] Male who had sex with a female at risk for HIV,[†] Includes Perinatal

Table 3.7: Unadjusted Analysis of Hazard of AIDS Positive Status in MI Males with and without a History of *N. gonorrheae* 2005-2011

Variable	Unadjusted HR	95% CI
History *N. gonorrheae*		
No Infection	1	
History of gonorrhea	1.17	1.06-1.30
Ethnicity		
White	1	
Black	1.06	1.03-1.10
Hispanic	1.10	1.01-1.21
Multiracial/Unknown/ Other*	1.01	0.90-1.13
Risk Group		
MSM	1	
IDU	0.73	0.69-0.76
MSM/IDU	0.95	0.89-1.01
Blood Recipient	1.07	0.94-1.22
Male HCFR‡	0.75	0.68-0.81
Other/Unknown†	0.62	0.59-0.66

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Table 3.8: Multivariate Analysis of Hazard of Time of HIV Diagnosis to AIDS Positive Status in MI Males with and without a History of *N. gonorrheae* 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History *N. gonorrheae*				
No Infection	1		1	
History of gonorrhea	0.56	0.50-0.62	0.63	0.57-0.70
Ethnicity				
White	1		1	
Black	1.00	0.96-1.03	1.06	1.02-1.10
Hispanic	1.02	0.93-1.11	1.07	0.98-1.17
Multiracial/Unknown/ Other*	0.88	0.79-0.99	0.94	0.84-1.06
Risk Group				
MSM	1		1	
IDU	1.09	1.04-1.15	0.96	0.91-1.01
MSM/IDU	1.01	0.94-1.07	0.96	0.90-1.03
Blood Recipient	1.51	1.01-1.31	1.26	1.10-1.43
Male HCFR‡	0.91	0.84-1.00	0.85	0.78-0.93
Other/Unknown†	0.87	0.83-0.92	0.82	0.77-0.86
Age Group (Age of HIV Diagnosis)				
Less than 20 Years Old	1		1	
20-29 Years Old	1.33	1.17-1.52	1.31	1.15-1.49
30-39 Years Old	1.73	1.52-1.96	1.68	1.47-1.91
40-49 Years Old	1.82	1.60-2.08	1.78	1.56-2.04
Over 50 Years Old	1.99	1.74-2.28	1.97	1.71-2.26

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Table 3.9: Unadjusted Analysis of Hazard of AIDS Positive Diagnosis in MI Males with and without Multiple *N. gonorrheae* Infections 2005-2011

Variable	Unadjusted HR	95% CI
History *N. gonorrheae*		
No Infection	1	
1 *N. gonorrhea* Infection	1.01	0.89-1.15
2 *N. gonorrhea* Infections	1.45	1.17-1.81
3 *N. gonorrhea* Infections	1.55	1.11-2.16
4 *N. gonorrhea* Infections	2.16	1.30-3.59
5 or More *N. gonorrhea* Infections	2.47	1.54-3.97

Table 3.10: Multivariate Analysis of Hazard of Time from HIV Diagnosis to AIDS in MI Males with and without a History of Multiple *N. gonorrheae* Infections 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History *N. gonorrheae*				
No Infection	1		1	
1 *N. gonorrhea* Infection	0.54	0.48-0.62	0.60	0.53-0.68
2 *N. gonorrhea* Infections	0.60	0.48-0.74	0.68	0.54-0.85
3 *N. gonorrhea* Infections	0.60	0.43-0.83	0.71	0.51-0.99
4 *N. gonorrhea* Infections	0.61	0.37-1.01	0.72	0.44-1.20
5 or More *N. gonorrhea* Infections	0.48	0.30-0.77	0.58	0.36-0.94
Ethnicity				
White	1		1	
Black	1.00	0.96-1.03	1.06	1.02-1.10
Hispanic	1.02	0.93-1.11	1.07	0.98-1.17
Multiracial/Unknown/ Other[*]	0.88	0.79-0.99	0.94	0.84-1.06
Risk Group				
MSM	1		1	
IDU	1.09	1.04-1.15	0.96	0.91-1.01
MSM/IDU	1.01	0.94-1.07	0.96	0.90-1.03
Blood Recipient	1.51	1.01-1.31	1.26	1.10-1.43
Male HCFR[‡]	0.91	0.84-1.00	0.85	0.78-0.93
Other/Unknown[†]	0.87	0.83-0.92	0.82	0.77-0.86
Age Group (Age of HIV Diagnosis)				
Less than 20 Years Old	1		1	
20-29 Years Old	1.33	1.17-1.52	1.31	1.15-1.50
30-39 Years Old	1.73	1.52-1.96	1.68	1.47-1.92
40-49 Years Old	1.82	1.60-2.08	1.79	1.56-2.04
Over 50 Years Old	1.99	1.74-2.28	1.97	1.72-2.26

[*] Includes Asian/HI/PI AmIn/AkNat ,[‡] Male who had sex with a female at risk for HIV,[†] Includes Perinatal

Table 3.11: Unadjusted Analysis of Hazard of AIDS in MI Males with and without Histories of Post-HIV *N. gonorrheae* Infections 2005-2011

Variable	Unadjusted HR	95% CI
History *N. gonorrheae*		
No Infection	1	
Post-HIV History of gonorrhea	1.26	1.13-1.41

Table 3.12: Multivariate Analysis of Hazard of Time from HIV Diagnosis to AIDS in MI Males with and without a History of Post-HIV *N. gonorrheae* Infection 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History *N. gonorrheae*				
No Infection	1		1	
Post-HIV History of gonorrhea	0.60	0.54-0.68	0.68	0.61-0.77
Ethnicity				
White	1		1	
Black	1.00	0.96-1.03	1.05	1.01-1.09
Hispanic	1.02	0.93-1.11	1.06	0.97-1.17
Multiracial/Unknown/ Other[*]	0.88	0.79-0.99	0.94	0.84-1.05
Risk Group				
MSM	1		1	
IDU	1.09	1.04-1.15	0.97	0.92-1.02
MSM/IDU	1.01	0.94-1.07	0.97	0.91-1.03
Blood Recipient	1.15	1.01-1.31	1.27	1.11-1.45
Male HCFR[‡]	0.91	0.84-1.00	0.86	0.78-0.93
Other/Unknown[†]	0.87	0.83-0.92	0.82	0.77-0.86
Age Group (Age of HIV Diagnosis)				
Less than 20 Years Old	1		1	
20-29 Years Old	1.33	1.17-1.52	1.34	1.17-1.53
30-39 Years Old	1.73	1.52-1.96	1.73	1.52-1.97
40-49 Years Old	1.82	1.60-2.08	1.84	1.61-2.10
Over 50 Years Old	1.99	1.74-2.28	2.03	1.77-2.33

[*] Includes Asian/HI/PI AmIn/AkNat ,[‡] Male who had sex with a female at risk for HIV,[†] Includes Perinatal

Table 3.13: Unadjusted Analysis of Hazard of Age at AIDS in MI Males with and without a History of Multiple *N. gonorrheae* Infections 2005-2011

Variable	Unadjusted HR	95% CI
History *N. gonorrheae*		
No Infection	1	
No Post HIV gonorrhea	0.95	0.77-1.17
Post HIV gonorrhea	1.10	0.95-1.27
2 Post HIV *N. gonorrheae* infections	1.55	1.22-1.97
3 or more Post HIV *N. gonorrheae* infections	2.06	1.51-2.79

Table 3.14: Multivariate Analysis of Hazard of Time from HIV Diagnosis to AIDS in MI Males with and without Multiple *N. gonorrheae* Infections 2005-2011

Variable	Unadjusted HR	95% CI	Adjusted HR	95%CI
History *N. gonorrheae*				
No Infection	1		1	
No Post HIV gonorrhea	0.45	0.37-0.55	0.51	0.41-0.63
Post HIV gonorrhea	0.60	0.50-0.67	0.64	0.55-0.74
2 Post HIV *N. gonorrheae* infections	0.67	0.53-0.85	0.77	0.60-0.97
3 or more Post HIV *N. gonorrheae* infections	0.60	0.44-0.81	0.72	0.53-0.98
Ethnicity				
White	1		1	
Black	1.00	0.96-1.03	1.06	1.02-1.09
Hispanic	1.02	0.93-1.11	1.07	0.98-1.17
Multiracial/Unknown/ Other*	0.88	0.79-0.99	0.94	0.84-1.06
Risk Group				
MSM	1		1	
IDU	1.09	1.04-1.15	0.96	0.91-1.01
MSM/IDU	1.01	0.94-1.07	0.96	0.90-1.03
Blood Recipient	1.15	1.01-1.31	1.26	1.10-1.43
Male HCFR‡	0.91	0.84-1.00	0.85	0.78-0.93
Other/Unknown†	0.87	0.83-0.92	0.82	0.77-0.86
Age Group (Age of HIV Diagnosis)				
Less than 20 Years Old	1		1	
20-29 Years Old	1.33	1.17-1.52	1.31	1.15-1.50
30-39 Years Old	1.73	1.52-1.96	1.68	1.48-1.92
40-49 Years Old	1.82	1.60-2.08	1.79	1.57-2.04
Over 50 Years Old	1.99	1.74-2.28	1.97	1.72-2.26

* Includes Asian/HI/PI AmIn/AkNat ,‡ Male who had sex with a female at risk for HIV,† Includes Perinatal

Figure 3.1: Kaplan-Meier Curves for Survival Rate in MI Males with and without *N. gonorrheae* Infection 2005-2011

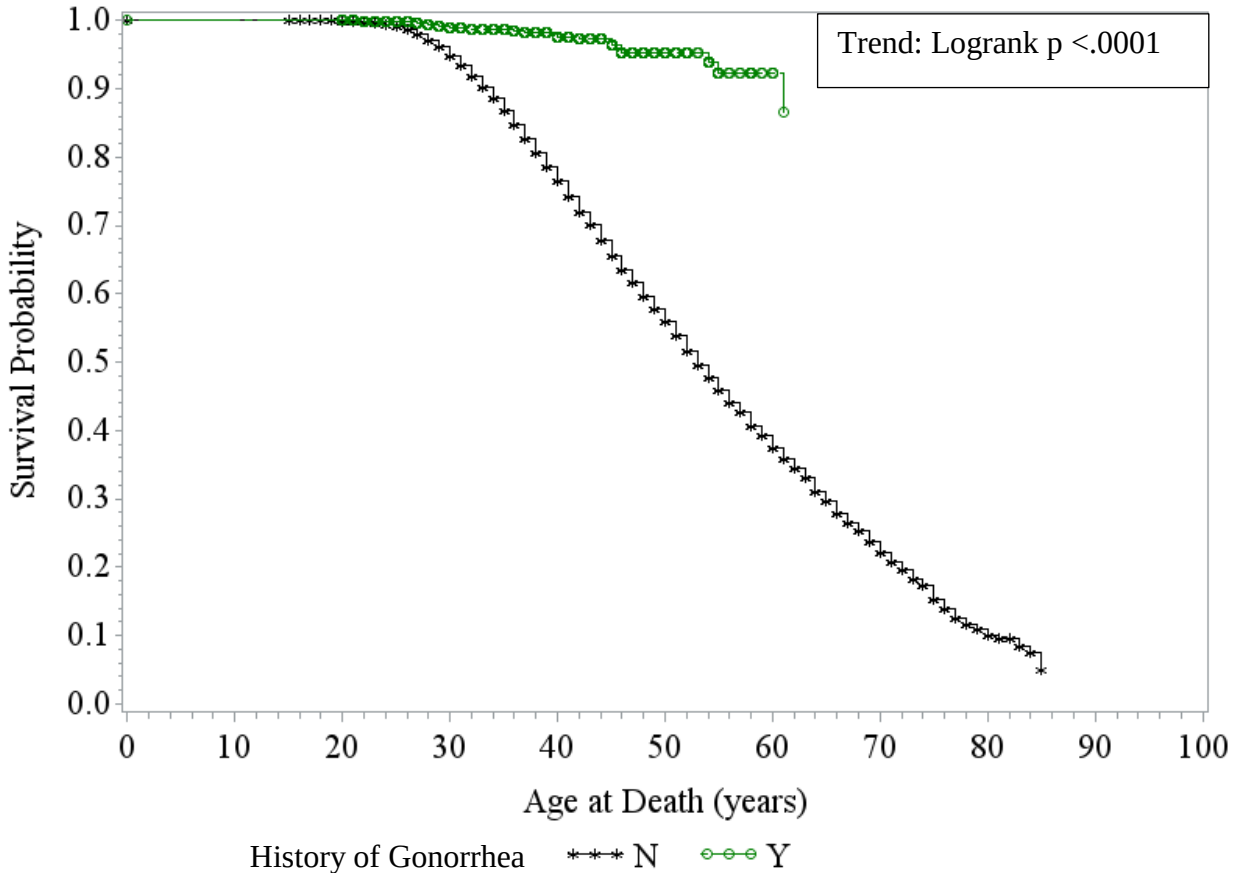


Figure 3.2: Kaplan-Meier Curves for Survival from Time of HIV Diagnosis in MI Males with and without a History of *N. gonorrheae* 2005-2011

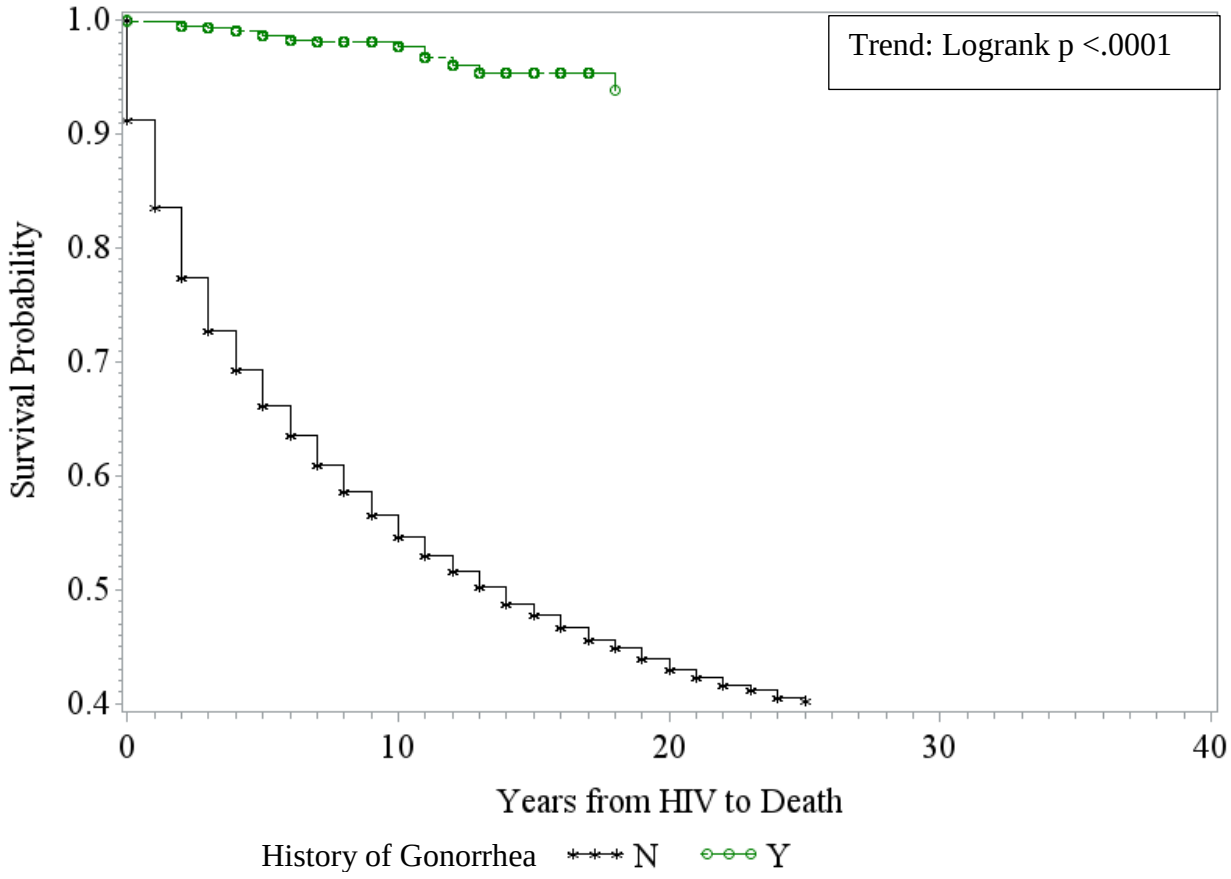


Figure 3.3: Kaplan-Meier Curves for Age of AIDS Positive Status in MI Males with and without *N. gonorrheae* 2005-2011

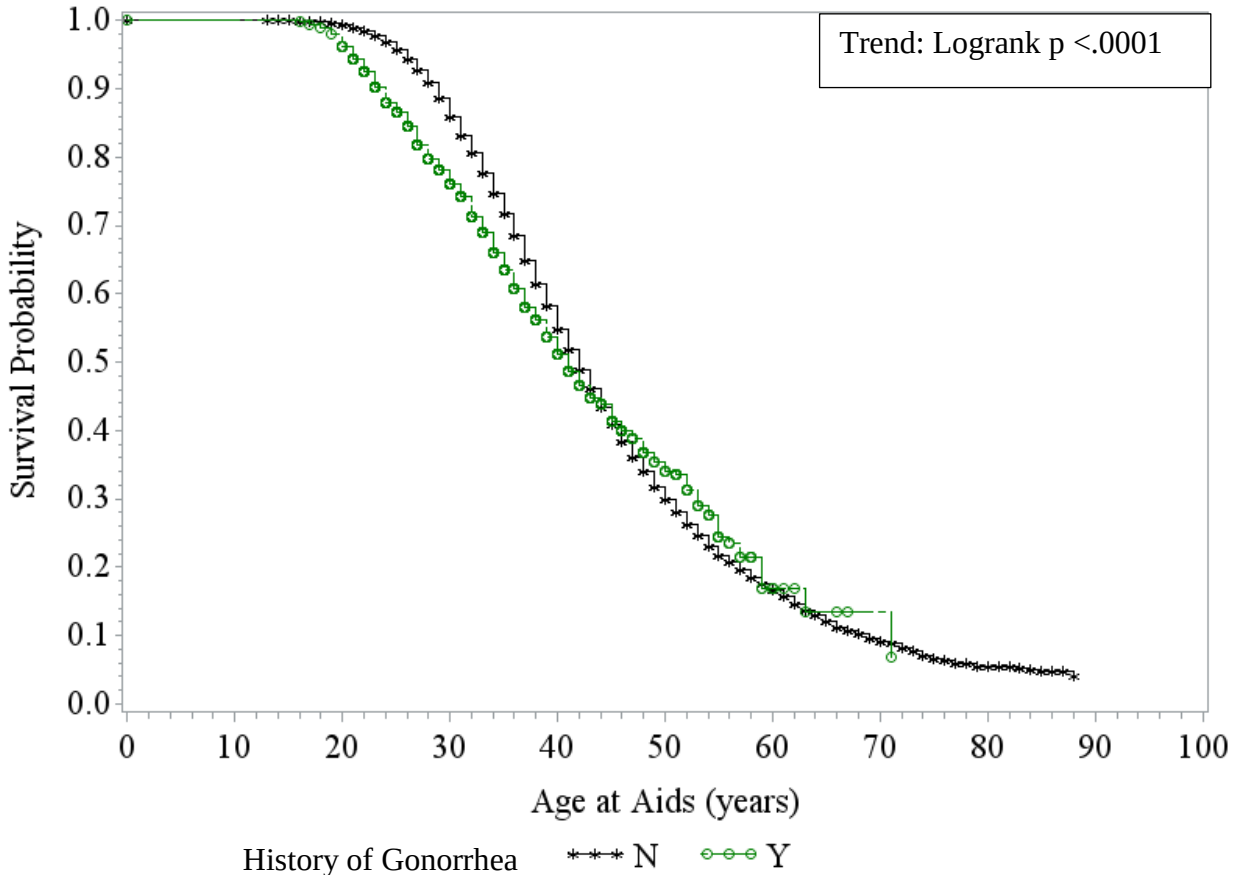


Figure 3.4: Kaplan-Meier Curves for Time from HIV Diagnosis to AIDS Positive Status in MI Males 2005-2011

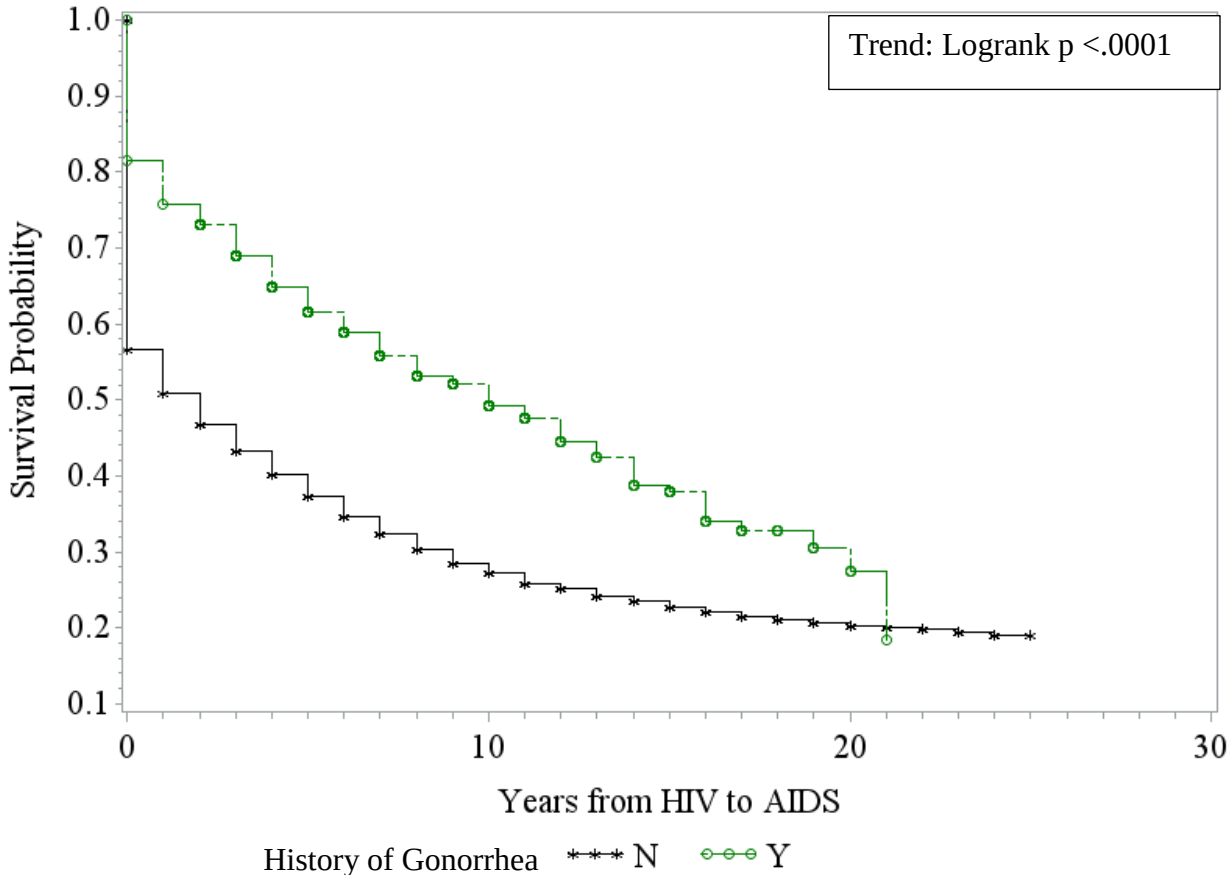


Figure 3.5: Kaplan-Meier Curves for Age of AIDS Positive Diagnosis in MI Males with Multiple *N. gonorrheae* Infections 2005-2011

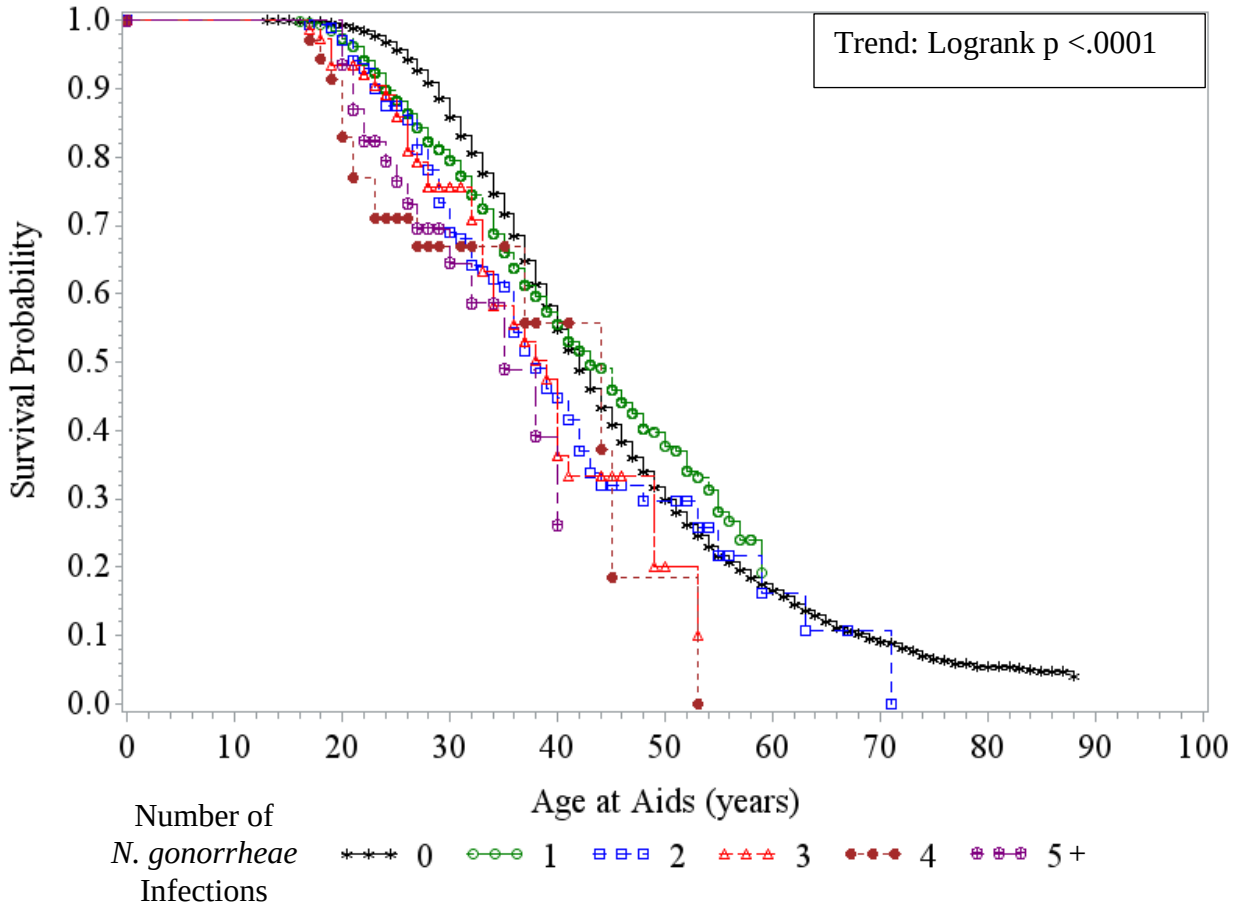


Figure 3.6: Kaplan-Meier Curve for Time from HIV Diagnosis to AIDS Positive Status in MI Males with a History of Multiple *N. gonorrheae* Infections 2005-2011

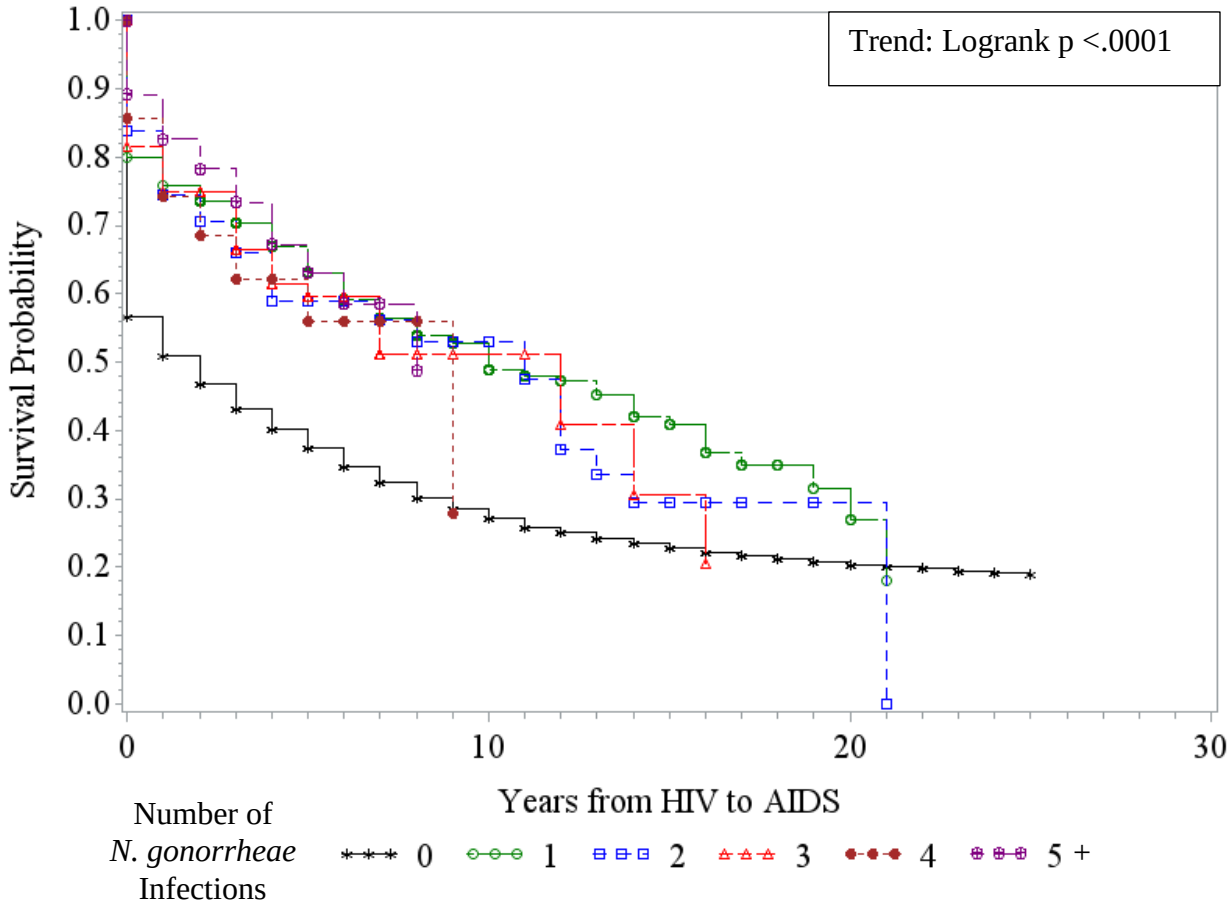


Figure 3.7: Kaplan-Meier Curves for Age at AIDS Positive Diagnosis in MI Males with Histories of Post-HIV *N. gonorrheae* Infections 2005-2011

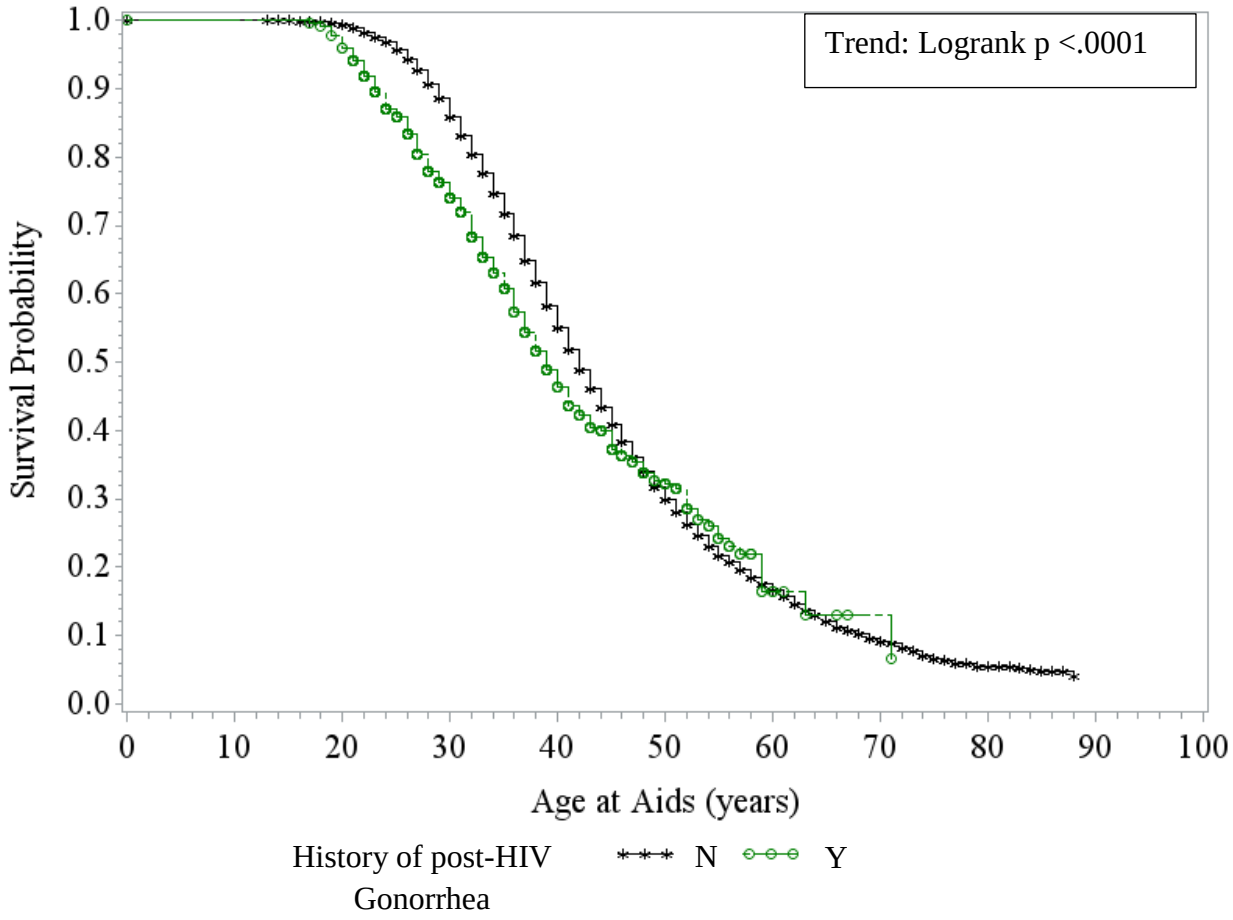


Figure 3.8: Kaplan-Meier Curves for Time from HIV Diagnosis to AIDS Positive Status in MI Males with a History of Post-HIV *N. gonorrheae* Infection 2005-2011

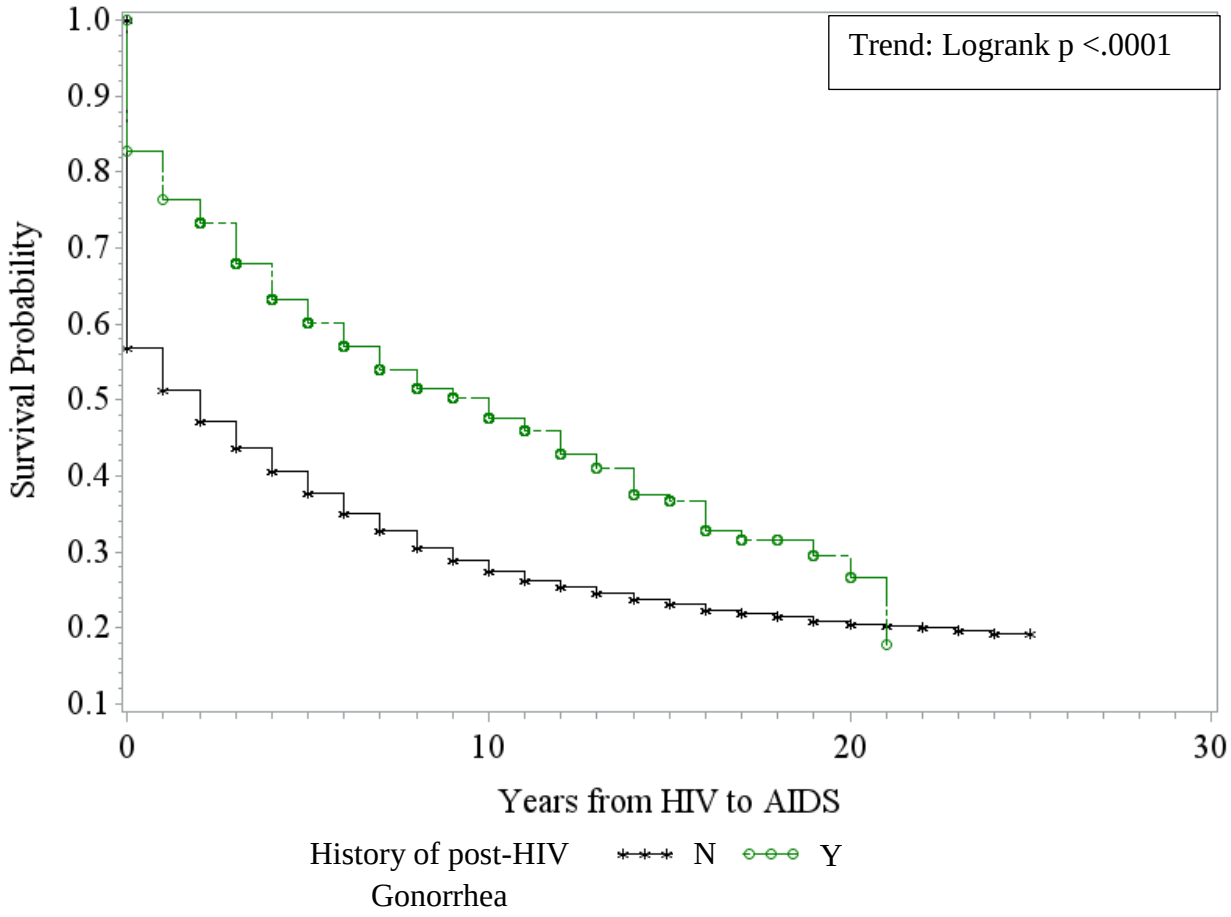


Figure 3.9: Kaplan-Meier Curves for Age at AIDS Positive Diagnosis in MI Males with a History of Multiple Post-HIV *N. gonorrheae* Infections 2005-2011

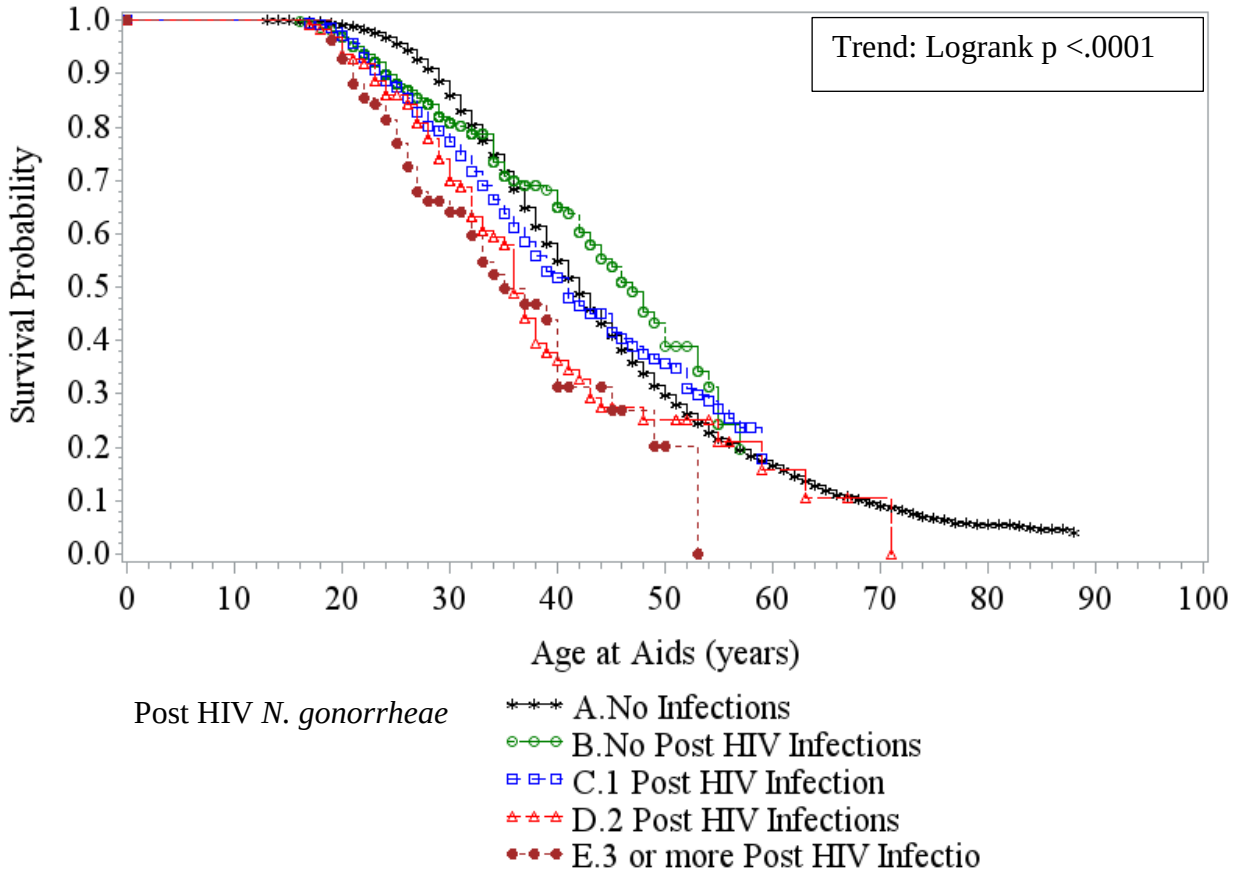
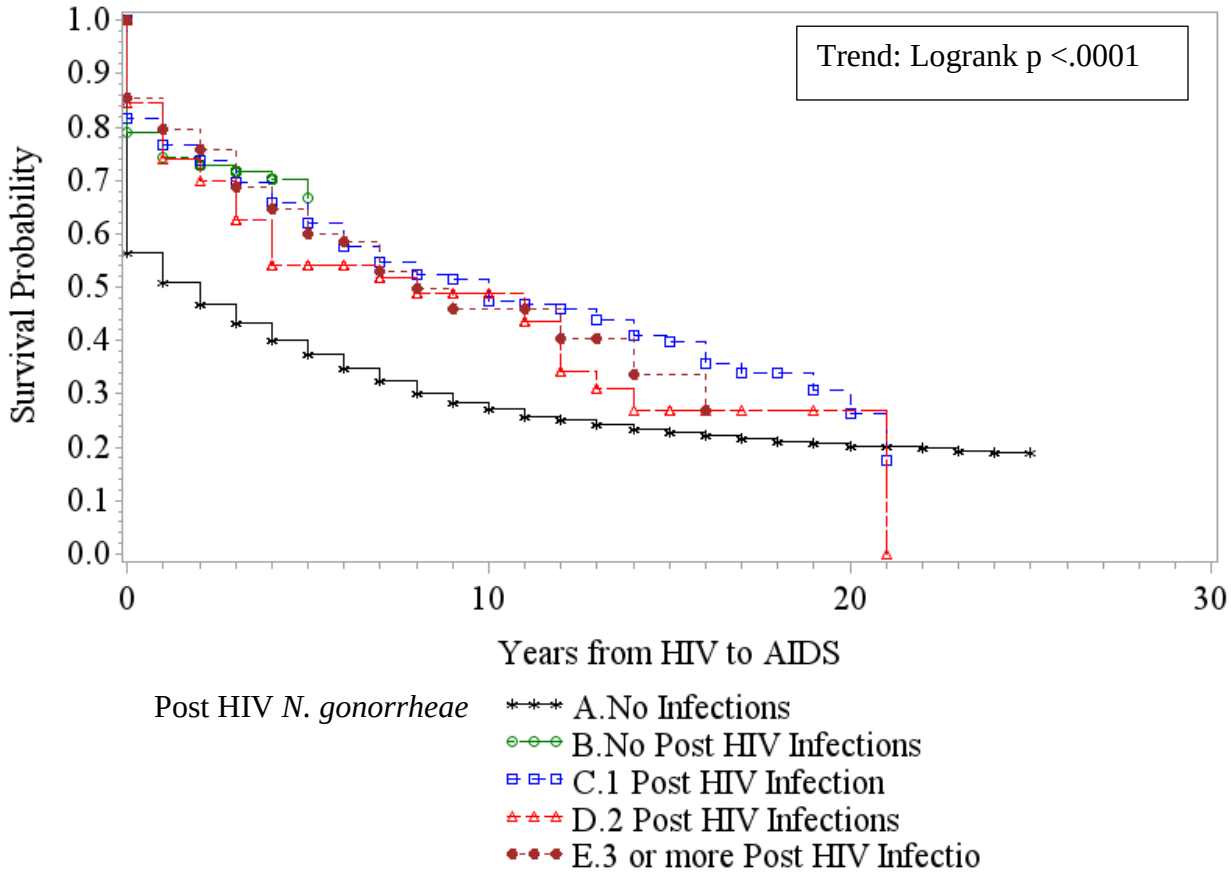


Figure 3.10: Kaplan-Meier Curves for Time from HIV Diagnosis to AIDS Positive Status in MI Males with Multiple Post-HIV *N. gonorrheae* Infections 2005-2011



Chapter 4.

Geospatial Analysis of HIV associated *N. gonorrheae* Infections in Michigan Males 2005-2011

4.1 Abstract

Introduction

Sexual networks are a key factor in understanding the proliferation of sexually transmitted diseases. The purpose of this study is to identify geographic boundaries and clusters at the county level of HIV infected individuals with *N. gonorrheae* co-infection in Michigan from 2005-2011. In order for public health to most effectively use its resources, prevention efforts must be targeted at locations with the highest burden of disease.

Methods

A retrospective cohort of 19,647 HIV infected Michigan males from 2005-2011was linked to *N. gonorrheae* infection data through collaboration with the Michigan Department of Community Health. Geospatial analysis of HIV prevalence and *N. gonorrheae* incidence was constructed to determine areas with increased burden of disease. Spatial clusters of *N. gonorrheae*, HIV, and HIV/*N. gonorrheae* co-infection areas were also analyzed using both Bernoulli and Poisson models.

Results

Detroit and the tri-county area of Macomb, Wayne, and Oakland were identified as potential hot spots of *N. gonorrheae* infected HIV positive males. Bernouilli high rate detection analysis identified Oakland County as the most likely cluster with a RR=1.44 (p-value=0.007). The

analysis also identified the secondary high rate cluster of the city of Detroit, Huron, Macomb, Sanilac, and Lapeer counties had a RR=1.26 (p-value=0.036) as opposed to the rest of the state. The final cluster consisted of cases in Gratiot and Clinton counties, RR=2.22 but was not found to be statistically significant (p-value=0.974).

Conclusion

The identification of Detroit and the surrounding counties as hot spots for *N. gonorrheae* infected HIV positive males suggests that the burden of disease due to the co-infection of these two STDs is not distributed equally across the state of Michigan. These hotspots represent potential areas for intervention and prevention programs to have the potential for greatest impact on disease reduction in the state.

4.2 Introduction

Sexually transmitted diseases (STDs) do not exist in a vacuum in relation to each other. Epidemiologic evidence suggests that there is a synergistic relationship between *N. gonorrheae* and HIV causing atypical progression of the diseases in co-infected individuals. It is important from a disease control standpoint identify areas that have higher than expected rates of co-infected individuals and to aim intervention efforts at these locations to help to prevent the possible increase in disease burden due to individuals having both diseases. While geospatial analysis is still an under-utilized epidemiologic tool for tracking and preventing the spread of STDs, geographic boundaries have played an important role in our understanding of STDs. From dating back to 1546 when Fracastoro wrote a poem that gave rise to calling the "French disease" syphilis after the shepherd in the poem who insulted Apollo and was cursed with the disease to the first MMWR on HIV that pointed out the initial cases being in Los Angeles with physicians also seeing the disease in New York and San Francisco geography has played a vital role in understanding STD transmission patterns (112, 1, 5). Geospatial analysis is an important tool in understanding the geographic underpinnings of where diseases occur and where to focus prevention and intervention efforts.

Despite the fact that *N. gonorrheae* is one of the most reported diseases in the United States, the relationship between HIV and gonorrhea has yet to be fully explored and little attention has been given to the geospatial relationship between the two diseases (15). In 2011 WHO estimated that roughly 88 million of the estimated 448 million curable STD infections reported that year were due to *N. gonorrheae* (12). In the United States in 2012, there were over 334,000 *N. gonorrheae* cases resulting in an increased rate of 4.1% from the previous year (13). As of the 2010 Census Michigan has the 8th largest population in the US. The January 2014 Annual HIV Surveillance

Analysis estimated that there were approximately 19,800 individuals in the state of Michigan who were HIV positive of which an estimated 15,440 (78%) were males (10). The majority of HIV diagnosis occurred in the Detroit Metropolitan Area (64%) despite only accounting for 43% of the total Michigan population (10). Areas that are affected by poverty and that lack health infrastructure are at a greater risk for spread of HIV and STDs, as well as have worse outcomes associated with these diseases (31).

In a geospatial study investigating chlamydia clusters in networks of STDs, researchers acknowledged that STDs are a behavior-based disease and that clusters represented distinct transmission networks (unique chlamydial genotypes) within larger sexual networks (113). The study found a total of 10 geographic clusters within the Canadian province of Manitoba (113). Researchers found that clusters were characterized by the socioeconomic factors attributed to the area with little to no geographic overlap of chlamydial genotypes (113). The study showed that even within larger sexual networks, distinct sexual networks existed characterized by their unique chlamydia genotype (113). A HIV study by Tanser et al. in 2009 found that in the rural population of KwaZulu-Natal, South Africa that there was variation in local rates of HIV, with the highest rates attributed to a three cluster zone along the National Road, with lower rate clusters being located inland away from the National Road (114). The study is important because it was able to show that in an area where HIV was believed to be "ubiquitous" there actually existed localized epidemics that shared a unique geographic characteristic, their proximity to the National Road (114). The authors go on to state that there needs to be a shift in the paradigm of interventions aimed at rural South African communities, focusing not on entire population but on targeted high risk socio-geographic communities (114).

A separate article by Wand and Ramjee also looking at KwaZulu-Natal, South Africa found similar results when looking at sexually active women (116). The study area was slightly south of the study area used in the Tanser et al. paper and found that hotspot of HIV tend to border major roadways in the area, aside from the lowest cluster (RR of excess HIV=2.4) which occurred in a more outlying area (116). This study along with Tanser et al. shows that even in areas where disease is considered endemic, hotspots of disease occur and it takes proper use of geographic spatial analysis to detect where resources need to be focused to reduce the burden of disease in these areas (116).

A 2010 article by Westercamp et al. found opposite results when studying sexual risk behaviors in young Kenyan men (115). The study did not find clusters, nor did it find an association between residency and risk behavior (115). Results showed that STDs were evenly distributed among urban and rural communities in the Kisumu district of Kenya (115). Even distribution of STDs means that prevention strategies should be aimed at centralized areas as well as areas where individuals are most likely gather. Like the Tanser et al. article this paper is important because it shows that STD distribution is not a one size fits all paradigm and that in order to understand the geospatial distribution of STDs in a community, researchers need to map disease patterns and not rely on previous assumptions.

A study by Jennings et al. that mapped gonorrhea in Baltimore, MD states that STIs (STDs) are not equally distributed across a population, for example the city of Baltimore and thus mapping of disease clusters may give insight into disease trends that extend past sexual orientation, age and race, and help to identify geographic boundaries associated with the disease after controlling for race/ethnicity (69). The purpose of the study was to identify high risk transmission areas and hopefully interrupt the transmission of the disease in these high risk areas (69). The study found

that in Baltimore the highest burden of disease occurred in the African American population and that sexual networks in the Baltimore areas were heavily segregated based on race/ethnicity (69). The study also found that *N. gonorrheae* infections tended to be focused around the center of the city, and eight high transmission clusters were identified in the city, indicating that risk of *N. gonorrheae* infection can be varied across geographic boundaries (69).

In another study of gonorrhea in Baltimore researchers focused on cases counts, rates, and percent of repeaters in the Baltimore area and found that of the 6,108 gonorrhea cases recorded in the 2 year study period, 9% were in individuals with multiple *N. gonorrheae* infections (68). These individuals tended to be younger females, and the study found that those labeled as repeaters tended to cluster geographically closer to each other than those that only had one reported *N. gonorrheae* infection in the study period (68). Similar geospatial trends were found in this study as were found in the Jennings et al paper, with the highest burden of disease focused toward the center of the city (68).

There is a current need to explore the relationship between HIV and *N. gonorrheae* co-infections. With the limited funding and resources available to control the spread of STI's in sexual networks the need for well-structured interventions are required to make the greatest impact. The geographical analysis of STI co-infections will help to identify high risk populations where resources should be spent to have the highest chance of success in disrupting the cycle of transmission. This study aims to investigate the geographical distribution of clusters of male individuals diagnosed with HIV with and without gonorrhea residing in the state of Michigan between 2005 and 2011.

4.3 Methods

The Michigan Department of Community Health (MDCH) constructed a retrospective cohort of HIV infected males in Michigan from 2005 to 2011. Records of reported *N. gonorrheae* infections were linked by MDCH staff using LinkPlus. An employee of HIV Surveillance and Body Art Unit HIV/STD/VH/TB Epidemiology created the record linkage structure between the HIV datasets and the *N. gonorrheae* data sets to comply with patient confidentiality and privacy (HIPPA 2014). All data used in this study were de-identified according to HIPAA guidelines on public health information. Study staff also did not contact or attempt to contact any participants of the study. All data collected by county and state employees prior to the start of the study. Ethical approval was obtained from the Institutional Review Board (IRB) at Michigan State University (MSU) and was reciprocal with the MDCH IRB.

Cases were defined as HIV positive males with a history of reported *N. gonorrheae* between January 1st 2005 and December 31st 2011. HIV infected males with *N. gonorrheae* prior to 2005 were excluded from the study population. Controls were defined as all HIV positive males without a history of *N. gonorrheae* during the study time period that were alive as of January 1st 2005. Records with missing first name, last name, or date of birth were excluded from the study population prior to the matching of the data. A final dataset of 19,647 HIV infected males in the State of Michigan were included in this study.

HIV infection was defined as HIV-NA=HIV infection, non-stage 3 and AIDS=stage 3 HIV infection. Acute and Latent, stage 1 and 2, were not differentiated in this study. Ethnicity was classified into unique non-over lapping groups, 1.White= White non-Hispanic, 2.Black= Black non-Hispanic, 3.Hispanic=Hispanic of any race, 4.Asian/HI/PI=Asian/Hawaiian, Pacific Islander

non-Hispanic, 5.Am In /Ak Nat=American Indian, Alaskan Native, non-Hispanic, or 9.Multi/Unk/Other=Multirace, Unknown, Other, non-Hispanic. Due to low rates of Asian/Hawaiian, Pacific Islanders (N=0) and American Indian, Alaskan Native (N=1) in the *N. gonorrheae* group these racial groups were included in the 9.Multi/Unk/Other grouping to avoid analytical complications associated with extremely small numbers. Marital status while largely missing was categorized as A=Married and Separated, S=Single and never married, M=Married, N=Not otherwise specified, Missing or U=Unknown, W=Widowed; Risk behaviors were condensed and categorized as A.MSM=Male-Male Sex, B.IDU=Injecting Drug Use, C.MSM/IDU=Male-Male Sex and Injecting Drug Use, D.Blood Recipient=Received Blood, E1.(Male HCFR)=Male who had sex with a female at risk for HIV, F.Perinatal=Child exposed by mother (further condensed to risk group G.Unk:Other due to low response, N=3), G.Unk:Other=Unknown/Other.

Descriptive statistics were preformed to assess the distribution of demographic and risk characteristics using SAS 9.3 (SAS Institute, Inc. Cary, North Carolina). The MDCH provided dataset did not contain any cases or controls from Keweenaw County. The geospatial analysis was performed using the 83 counties in the State of Michigan as well as the city of Detroit. Data collected from MDCH also contained individuals who were either unknown or labeled as "prison" diagnosed. These unknown and prison diagnosed were removed from the geospatial analysis (n=1,097). The State of Michigan has over 30 state level prisons located in various counties throughout the state and one federal prison in the City of Milan. Chloropleth maps (map that uses colors, shading, or symbols within geographic boundaries to represents differences between areas) were created for frequency of *N. gonorrheae*, rate of HIV per 100,000; rate of *N. gonorrheae* per 1,000 and percent multiple gonorrhea, using ArcGIS v.10.2 (Environmental

Systems Research Institute (ESRI) 2014). The rates per 100,000 and 1,000 were calculated using the 2006-2008 American Community Survey (ACS) data where available, and 2012 Demographic and Housing data when counties were not included in the ACS. The population of Wayne County was adjusted by removing people who resided in the City of Detroit so both geographies could be mapped independently. Spatial cluster-analyses were performed using two methods: 1) Getis-Ord statistics to access global and local High and Low clusters of prevalence rates in ArcMap 10; and 2) Bernouilli (0/1) and Poisson distributed methods using SaTScan V9.1.1 to detect high and low prevalence rates. Getis-Ord Gi Hot Spot analysis is a cluster detection analysis that measures each area in context to its neighbors. If a map unit (county or Detroit) has high values that are contiguous to its adjoining neighbors then the area constitutes a 'hot spot'. The cluster is then compared to all map units and a Z score is calculated. Clusters with higher rates of disease will have higher Z scores and clusters with lower than average rates of disease have lower Z scores. The GiZ scores were mapped at the county level along with the city of Detroit. A GiZ score of 0 represents a map unit that does not differ from the overall mean. An increase in GiZ score represents greater distance from the overall mean (increase in *N. gonorrheae*/HIV co-infection). A negative GiZ score represents areas with a lower than average rate of *N. gonorrheae*/HIV co-infection.

In SaTScan the Bernouilli method cases were defined as HIV positive males with a history of *N. gonorrheae* infection between 2005 and 2011 and controls were defined as HIV positive male between 2005 and 2011 with no reported history of *N. gonorrheae* infections. Bernouilli high only analysis was conducted to best identify areas with the greatest need for prevention efforts which include screening, treatment and education. For the Poisson method the cases were defined as described for the Bernoulli method and population data were gathered from the 2006-

2008 American Community Survey (ACS) data where available, and 2012 Demographic and Housing data when counties were not included in the ACS (available online at http://factfinder2.census.gov/faces /nav/jsf/pages /index.xhtml) at the county level. Coordinate data was constructed using ArcGIS via the "Calculate Geometry" function, and mapped as latitude and longitude. Bernouilli and Poisson cluster-detection methods consist of a gradually scanning window that moves across the study frame (county and city of Detroit centroids) calculating the number of observed and expected observations (cases) inside the scanning window of each map unit. Maximum likelihood estimates are calculated to determine areas where clustering was least likely (p-value less than 0.05) to be due to chance. SaTScan has the ability to document and rank multiple possible clusters of high rates.

County population data was adjusted for males 0-65 years old from the 2006-2008 American Community Survey (ACS) data where available, and 2012 Demographic and Housing data when counties were not included in the ACS. (available online at http://factfinder2.census.gov/faces /nav/jsf/pages /index.xhtml). HIV positive males with a history of gonorrhea before 2005 were excluded from the study as well as those with missing first name, last name, or date of birth due to record linkage issues. Geospatial analysis of HIV and *N. gonorrheae* clusters were done using Poisson method scanning for high rate areas. No time precision options were used and map areas were scanned for high rates with no clusters centered over other clusters.

4.4 Results

Between 2005 and 2011 903 HIV positive males in the State of Michigan had a reported *N. gonorrheae* infection. This accounted for 1,588 total *N. gonorrheae* infections in the study period. Females were not included in the study due to low rates of HIV positive females with a

history of *N. gonorrheae* between 2005 and 2011 in the State of Michigan. Demographic information for both HIV males with and without gonorrhea can be seen in Table 4.1. In HIV infected males with a history of gonorrhea, 117 (19.60%) were White, 674 (74.64%) were Black, 23 (2.55%) were Hispanic, 1 (0.11%) was American Indian, and 28 (3.10%) reported as Multiracial/Unknown/Other. The majority of *N. gonorrheae* cases did not report marital status 889 (98.45%). In the distribution of MDCH defined risk groups for HIV infected males with a history of *N. gonorrheae* infection 697 (77.19%) of males were MSM, 21 (2.33%) IDU, 21 (2.33%) were MSM/IDU, 20 (2.21%) of HIV infected males reported having sex with a female at risk for HIV, and 144 (15.95%) had other or unknown risks. Of the 903 HIV positive males that had a reported history of *N. gonorrheae* infection 390 (43.19%) progressed to AIDS/Stage 3 HIV positive status and 20 (2.21%) died. 37% of HIV positive men in Michigan with gonorrhea had more than one *N. gonorrheae* infection from 2005-2011.

There were 18,744 HIV positive males that were alive at the start of 2005, or diagnosed between 2005 and 2011 that did not have a reported case of gonorrhea. In HIV positive males with no history of *N. gonorrheae* infection 7,635 were White (40.73%), 9,988 were Black (53.29%), 711 were Hispanic (3.79%), 62 identified as Asian (0.33%), 40 identified as Native American (0.21%) and 308 (1.64%) were grouped into the Multiracial/Missing/Unknown ethnicity category. Response rate for marital status was slightly higher than in HIV men with gonorrhea, with 1,317 (7.03%) responding as married, 1,268 (6.76%) as Divorced, 4,966 (26.49%) as Single and 11,193 (59.72%) falling into the Other/Unknown/Widower/Missing Marital status category. The distribution of MDCH condensed risk groups showed that MSM account for the majority (58.78%) of HIV positive males with no history of gonorrhea. There were 2,675 individuals that identified as IDU (14.27%) and 1,338 that identified as both MSM and IDU (7.14%). Males that

have had sex with a female living with HIV accounted for 4.11% of HIV positive males with no history of gonorrhea and there were a total of 268 (1.43%) Blood Recipients and 2,675 (14.28%) that fell into the Unknown/Other MDCH condensed risk group.

Figure 4.1 shows the geospatial distribution of the rate of HIV infected males per 100,000 in the State of Michigan between 2005 and 2011. Areas with the highest rates of infection (82-1,032 per 100,000) tend to be in the southern part of the state with the exception of Baraga County in the northern part of the Upper Peninsula. Detroit along with the tri-county area that surrounds it all fall into the highest rate per 100,000 group for HIV infected males. Other high counties include Genesee (Flint, MI), Saginaw County, Ingham, Kent and Washtenaw counties. Rates tend to fall off further north in the state and become unstable. County population data was adjusted for males 0-65 years old from the 2006-2008 American Community Survey (ACS) data where available, and 2012 Demographic and Housing data when counties were not included in the ACS. 47 counties were found to have unstable rates, cases less than 20 or population less than 50.

Figure 4.3 shows the geospatial distribution of gonorrhea cases in HIV positive males in the State of Michigan from 2005 to 2011. No data was available (either no cases or missing) for Keweenaw county in the Northern tip of the Upper Peninsula. While this chloropleth map does not show clusters, the areas with the highest frequency of gonorrhea cases in HIV positive males are the City of Detroit, Oakland County, and Wayne County (minus Detroit). Other high frequency counties are Macomb, Genesee, Washtenaw, Ingham and Kent. A slightly different trend emerges in Figure 4.4 that maps gonorrhea/HIV positive males per 1,000. Rate per 1,000 shows the highest counties to Oakland, Ogemaw, Roscommon, Mecosta, Gratiot, Clinton, Eaton, and Sanilac. Detroit and Macomb County fell into the 45-58 per 1,000 along with 6 other

counties. 24 counties were found to have unstable rates, cases less than 20 or population less than 50.

The next series of maps display the rates of repeated *N. gonorrheae* infection in HIV positive male between 2005 and 2011. Figure 4.6 shows the percent of HIV individuals with *N. gonorrheae* who had multiple re-infections of the bacteria between 2005 and 2011. While Detroit and the tri-county area have some of the highest counts of HIV positive males infected with *N. gonorrheae* they do not fall into the highest division of percent of repeatedly infected HIV males. Low incident counties like Grand Traverse, Lenawee, Calhoun, Clinton, and Gratiot have fewer individuals getting infected with *N. gonorrheae*, but these individuals are more prone to being re-infected. While Detroit, Macomb, Wayne, and Oakland do not fall into the highest infection rate group, it is important to note that their number of individuals of repeat *N. gonorrheae* cases are higher. This represents two distinct pathways to intervention. In counties with low total gonorrhea, but high reinfection rates prevention strategies aimed at improvement of partner services may have the greatest impact, where as in areas with high incidence of gonorrhea and mid to high re-infection rates, prevention strategies may need to target sexual networks and focus on partner tracking methods. Figure 4.7 shows the rate of multiple *N. gonorrheae* infections in HIV positive males. This map shows that the overall percent of HIV infected males who are multiple *N. gonorrheae* infections is low with most counties that have re-infected individuals at less than 3% of total HIV infected males.

Cluster analysis was done in multiple phases using three different techniques to try and isolate potential hotspots of HIV/*N. gonorrheae* co-infections. The first cluster analysis performed used Getis-Ord Gi Hot Spot detection to identify areas of HIV/*N. gonorrheae* co-infections. Figure 4.8 shows the standard deviation of Getis-Ord GiZ scores for *N. gonorrheae* infected HIV positive

males. Four counties had GiZ scores whose standard deviations greater than 2.58 which were St. Clair, Shiawassee, Clinton and Gratiot. Areas that had standard deviations between 1.96 and 2.58 included Macomb, Oakland, Lapeer, Isabella, and Midland represent the second set of hot spots. The standard deviation grouping included the city of Detroit, Wayne, Ingham, Saginaw, Montcalm, Gladwin, and Iosco counties which had standard deviations between 1.65 and 1.96. Two distinct clusters were detected, one consisted of eight counties around Gratiot and Clinton, and the other being located around Detroit and the Tri-County area. No areas of low *N. gonorrheae* infections in HIV positive males were detected using the Getis-Ord GiZ scores.

The second stage consisted of independently mapping HIV and *N. gonorrheae* clusters using the discrete Poisson method. Figure 4.9 shows the Poisson cluster analysis of HIV positive males in Michigan. This cluster analysis used high onlyrate analysis, with a limit radius of 20 miles (32.2km) and a maximum spatial cluster size of 50% of the population at risk. Detroit was found to be the most likely cluster and had an increase in relative rate (RR=10.26 p-value <0.0001). The City of Detroit represented the only high risk cluster identified. Figure 4.10 shows the Poisson cluster analysis of *N. gonorrheae* in HIV infected males in Michigan from 2005 to 2011. A similar high only rate Poisson analysis was performed for *N. gonorrheae*. Detroit represented the most likely cluster and as with the HIV cluster analysis the only area with an increased relative risk was Detroit, RR=12.66 (p-value <0.0001).

The final cluster analysis performed used Bernouilli methods of *N. gonorrheae* infected HIV males in Michigan. Figure 4.11 shows the high only Berouilli analysis of *N. gonorrheae* infected HIV males in Michigan. Oakland County represented the most likely cluster with a RR=1.44 (p-value=0.007). A secondary cluster consisted of the city of Detroit, Huron, Macomb, Sanilac, and Lapeer county had a RR=1.26 (p-value=0.036) and was also statistically significant. A third

cluster consisting of Clinton and Gratiot counties was also detected but was not found to be statistically significant (p-value=0.974).

4.5 Conclusion

Geospatial analysis at the county level shows that most of the burden of disease of HIV is centered around Detroit and the tri-county area of Macomb, Wayne, and Oakland counties. HIV rates per 100,000 were also elevated across the southern part of the state with a high rate per 100,000 extending from Detroit and the tri-county area to Allegan, Kent, and Kalamazoo counties on the Western edge of the state. There was also a high rate county, Baraga, located in the Upper Peninsula.

HIV cluster analysis using the Poisson methods shows that the only real hotspot in the state is the City of Detroit when using high only rate detection methods. The use of two geospatial analysis techniques, rate and cluster detection, allow for epidemiologists and public health officials to address the HIV problem at multiple fronts. While the City of Detroit represents the only hot spot in the state for HIV, HIV rates are increased in multiple other counties including the surrounding tri-county area and across the Southern part of the state. These counties represent areas of concern and intervention efforts should be targeted at the county level as well as in the City of Detroit.

The frequency of HIV positive men with a history of *N. gonorrheae* infection is highest in Detroit and the tri-county area and decreases as it moves toward the center and Western part of the state. This may be largely due to the higher population of HIV infected males in the area and may not represent a complete picture of burden of disease in these areas. *N. gonorrheae* infected per 1,000 in HIV positives males gives a slightly better picture of where the real burdens of

disease occur in Michigan. The *N. gonorrheae* infected per 1,000 HIV positive males shows that while Detroit had some of the highest occurrences of gonorrhea in the state, it does not have the corresponding highest rate. Rates of *N. gonorrheae* HIV infected males decrease as they move west from Detroit and the tri-county area and are noticeably low in the northern part of the state aside from Roscommon and Ogemaw counties.

Rates of multiple *N. gonorrheae* were analyzed by those that had at least one reported *N. gonorrheae* infection between 2005 and 2011 and by total number of HIV positive males. Both maps show relatively similar results with Detroit and the tri-county area being lower than expected for rates of multiple *N. gonorrheae* infections. These maps are interesting for a number of reasons, mainly that while Detroit, Wayne County, Macomb County, and Oakland County fall in the middle of the rate distributions some of the smaller counties like Gratiot, Clinton, and Lenawee have high rates of individuals with repeat *N. gonorrheae* infections. These areas represent where there may be greatest potential and need for partner based services to try and prevent individuals from being re-infected.

Figure 4.3 along with Figure 4.4 show that one of the major areas of concern when investigating *N. gonorrheae*/HIV co-infections in MI males is the tri-county area and the City of Detroit due to their increased frequency of *N. gonorrheae* infection as well as their increased rates of *N. gonorrheae*/HIV positive males. These two maps offer different ways of looking the gonorrhea/HIV problem from a public health stand point. While areas like Detroit and Wayne County have some of the highest raw numbers of HIV positive males with a history of gonorrhea, other counties have higher rates of the disease and may see their need for prevention funding as great as Detroit and Wayne County.

Geospatial analysis and cluster detection show that the City of Detroit and the tri-county area represent high risk areas of HIV/*N. gonorrheae* co-infections. Using three different cluster detection approaches this study was able to identify possible hot spots of HIV/*N. gonorrheae* co-infections in the State of Michigan. As stated previously Poisson based cluster detection found that there was only one true hot spot for *N. gonorrheae*/HIV co-infections in MI males. From this analysis prevention should be focused on Detroit and counties in close proximity to the City of Detroit. A second cluster technique used Getis-Ord GiZ scores to determine where there was an increase in rate of co-infections and found that there appeared to be another possible grouping that was not flagged on the Poisson method approach. The Getis-Ord approach revealed that similar to the Poisson approach that Detroit, the tri-county area, and counties in close proximity to Detroit all had increased rates as seen by their GiZ score, but the analysis also revealed that there may be another smaller cluster near the center of the state focusing around Clinton, Gratiot, and Shiawassee counties. This is important because it shows that the burden of disease is not just limited to Detroit and the surrounding areas, that there are increased rates of *N. gonorrheae*/HIV co-infections in other parts of the state as well forming their own unique little cluster.

The final cluster detection approach was the Bernouilli method. In the Bernouilli analysis, using only high rate detection three hot spots were identified. Oakland County again had its own high rate cluster, but the secondary cluster of Detroit, Macomb, Lapeer, Sanilac, and Huron counties was statistically significant this time representing a unique cluster as compared to Oakland and the rest of the state. The final cluster detected that was not found to be statistically significant was that of Gratiot and Clinton county which were two of the counties identified in the Getis-Ord technique that gave each individual map unit a GiZ score as compared to the Poisson and Bernouilli approaches that relied on neighbor level data as well.

These maps show that there is unequal distribution across Michigan with regard to *N. gonorrheae* infection among HIV positive males and this is primarily centralized among Detroit and the neighboring counties. The purpose of this study was to identify areas where there is an increase in *N. gonorrheae* among HIV infected males since it has been hypothesized that risk of transmitting both diseases is increased in those with co-infections. This study identifies possible clusters in the state of Michigan and helps both epidemiologists and public health officials plan targeted interventions to stop the spread of these diseases.

Limitations

A major limitation was that only county of diagnosis, Detroit, Prison, or Unknown were reported so all inferences are applied to the county level, even though the entire county may not be at the same risk. Further studies should seek to gain smaller geographical units, such as zip codes or census block level data to explore the possibility of unequal distribution among the counties, specifically among those in the hot spots. This would require alternate approaches to analysis including automated zone mapping to censor units with low numbers. Prisons could also be mapped to represent their locations. Given the high number of prison diagnosed HIV cases, it would be important to know if there is equal distribution across all prisons in the system, or if prisons have the same rates as the county they are located in. Another limitation is that location can only be reported as location of residence at time of diagnosis, and not residence at time of infection or location at infection. Due to the nature of STDs, their social underpinnings, and the difficulties in not only identifying from whom an infection may have spread, but when infection occurred, only residence at diagnosis can be measured by public health. It also remains a key limitation in not only the spatial analysis of STDs, but also in the epidemiological study of them as well. A final limitation of this study is that *N. gonorrheae* is often asymptomatic in males and

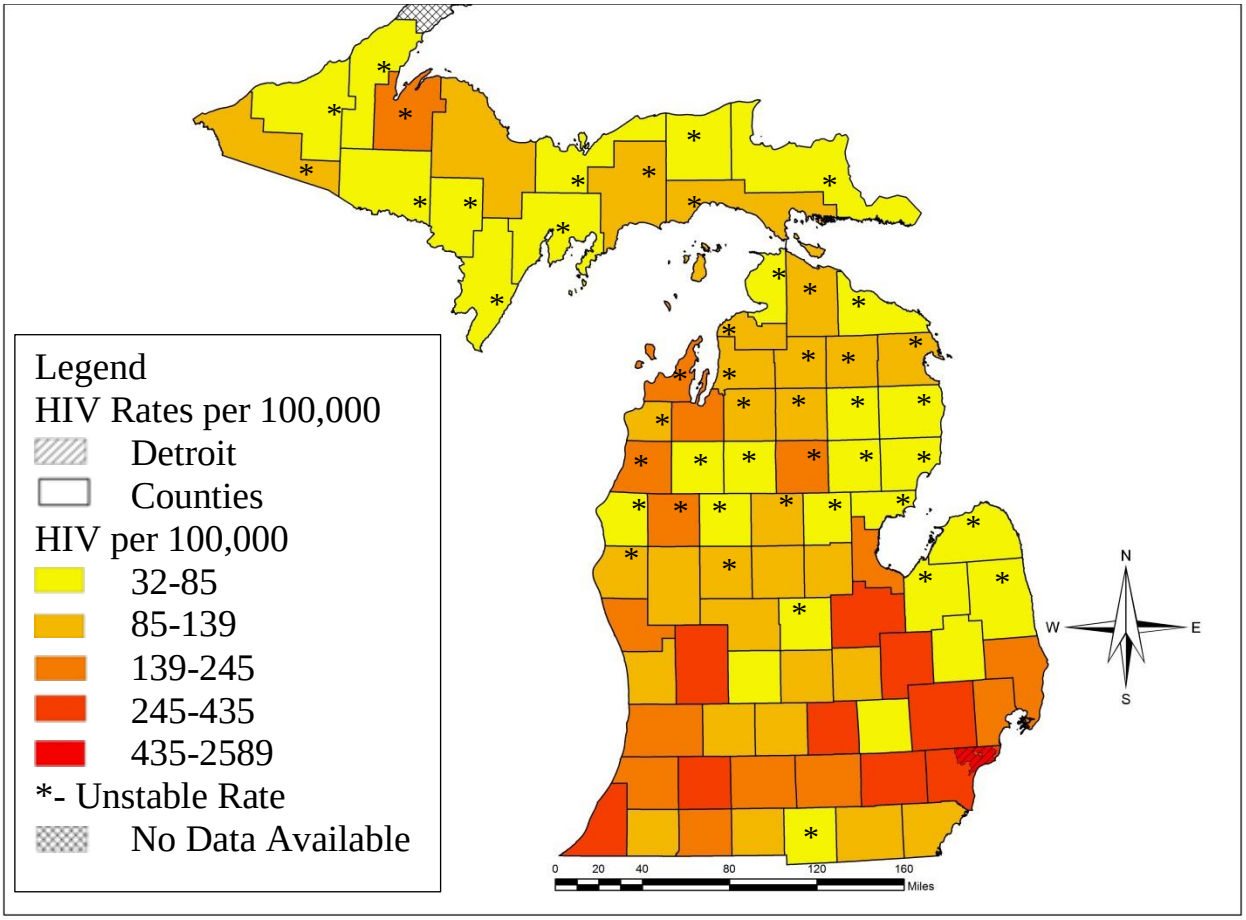
aside for a handful of strains that develop into systemic infections, Disseminated Gonococcal Infection (DGI), infections can resolve without treatment (1, 2, 11). Due to this there is a possibility that some *N. gonorrheae* infections go undiagnosed and unreported skewing the actual rate and rate of re-infections to be lower than they truly are in a community. This could possibly be negated with an increase in men's health initiatives aimed at routine testing for all sexually active males especially in males who fall into high risk groups.

APPENDIX

Table 4.1: Demographic Distribution of 19,647 HIV Positive MI Males (2005-2011)

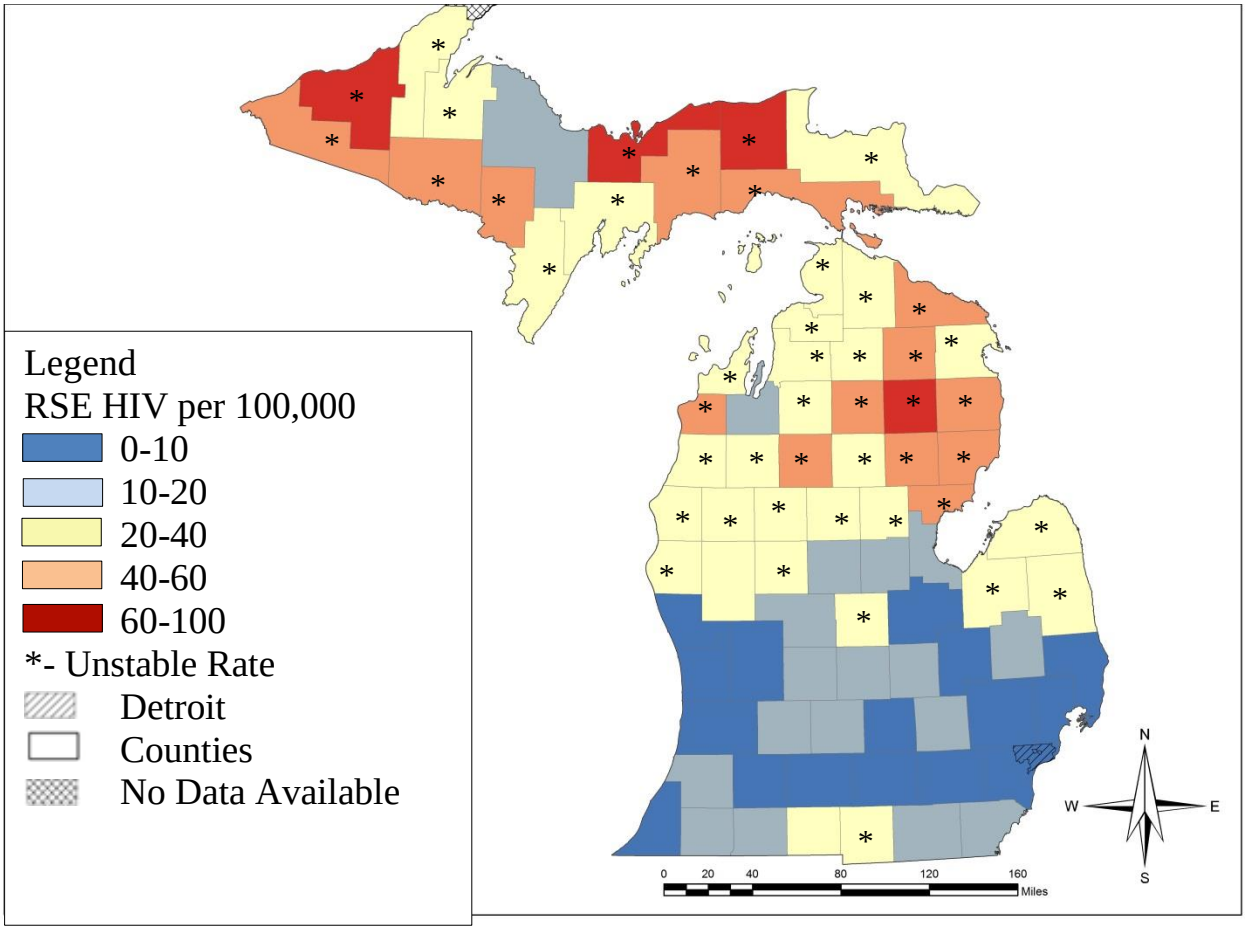
Variable	**No *N. gonorrheae* history** N=18744	***N. gonorrheae* history** N=903
Ethnicity		
White	7635 (40.73%)	177 (19.60%)
Black	9988 (53.29%)	674 (74.64%)
Hispanic	711 (3.79%)	23 (2.55%)
Asian	62 (0.33%)	-
American Indian	40 (0.21%)	1 (0.11%)
Multiracial/Unknown/ Other	308 (1.64%	28 (3.10%)
Marital Status		
Married	1317 (7.03%)	2 (0.22%)
Divorced	1268 (6.76%)	2 (0.22%)
Single	4966 (26.49%)	10 (1.11%)
Other/Unknown/Widower/Missing	11193 (59.72%)	889 (98.45%)
Risk Group		
MSM	11018 (58.78%)	697 (77.19%)
IDU	2675 (14.27%)	21 (2.33%)
MSM/IDU	1338 (7.14%)	21 (2.33%)
Blood Recipient	268 (1.43%)	-
Male HCFR	770 (4.11%)	20 (2.21%)
Other/Unknown	2675 (14.28%)	144 (15.95%)
AIDS Positive	13767 (73.45%)	390 (43.19%)
Deceased	8906 (47.51%)	20 (2.21%)

Figure 4.1: Map of Number HIV Positive Males per 100,000 in the State of Michigan, 2005-2011



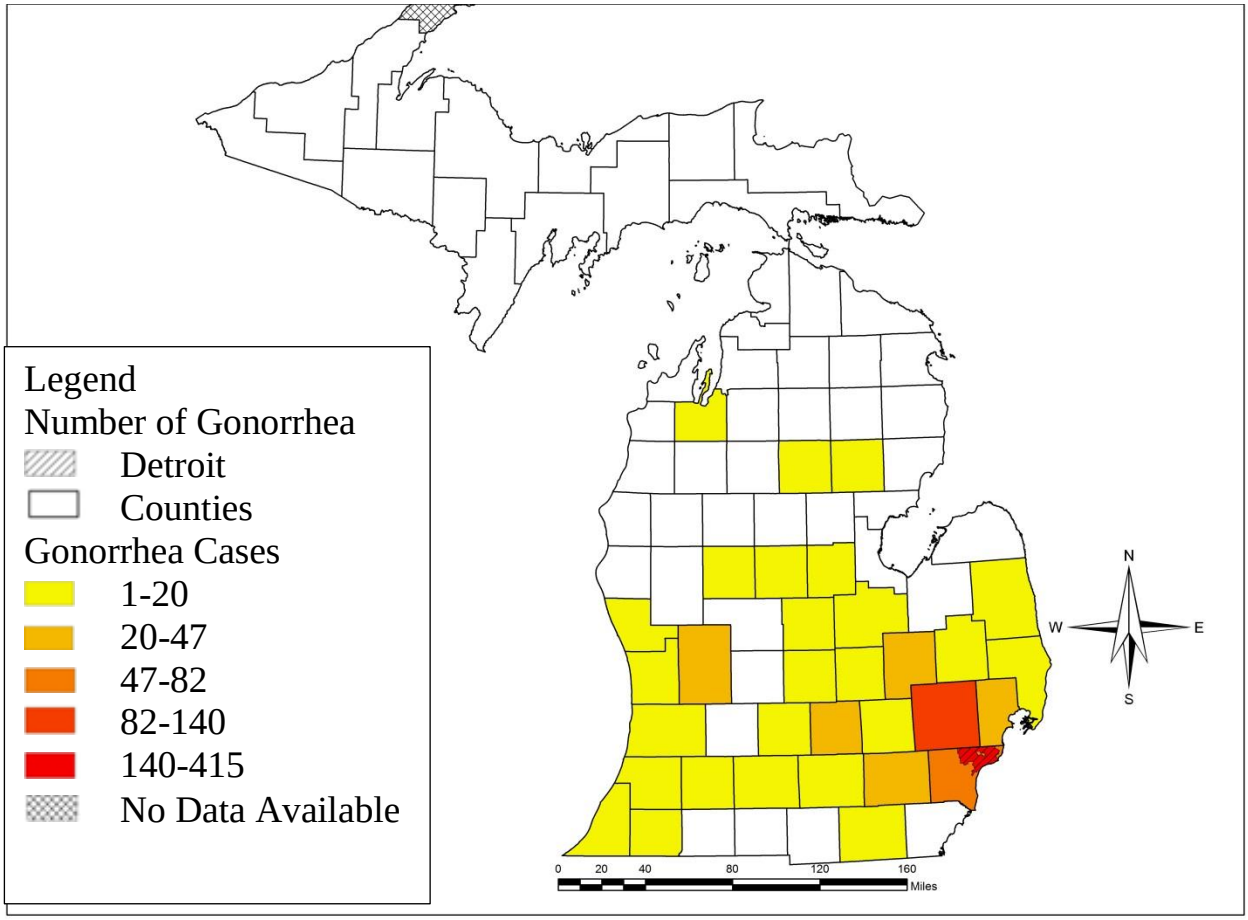
HIV rate per 100,000 was calculated from 2006-2008 ACS and 2012 Demographic and Housing estimates: http://factfinder2.census.gov/faces/nav/jsf/pages /index.xhtml. County population was adjusted for males 0-65 years old. Detroit and the tri-county area of Macomb, Wayne, and Oakland, along with most of the counties in the lower half of the state all have relatively high rates of HIV, as compared to the northern section of the Lower Peninsula and the Upper Peninsula, with the exception of Baraga County (however rate is considered unstable). Counties marked with an "*" represent areas with unstable rates (less than 20 cases of HIV or population less than 50). A total of 18,550 HIV positive males were able to be geocoded at the county level.

Figure 4.2: RSE (Root Mean Square Error) of Number HIV Positive Males per 100,000 in the State of Michigan, 2005-2011



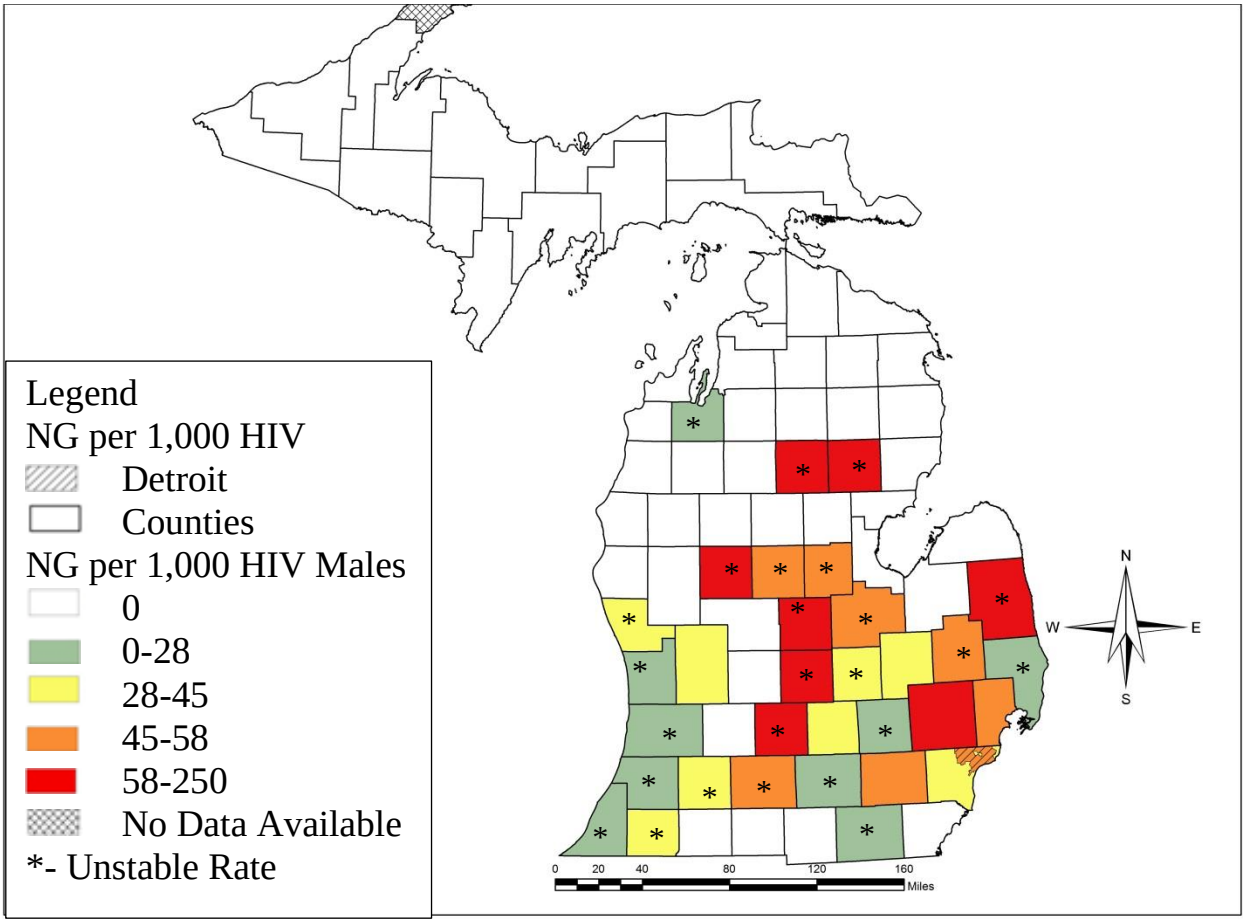
Root Mean Square Error (RSE) of rate of HIV per 100,000. Calculated from 2006-2008 ACS and 2012 Demographic and Housing estimates: http://factfinder2.census.gov /faces/nav/jsf /pages /index.xhtml. County population was adjusted for males 0-65 years old. RSE was calculated by Standard Error/Rate*100, Standard Error=Rate/Square Root (Cases). Counties marked with an "*" represent areas with unstable rates (less than 20 cases of HIV or population less than 50).

Figure 4.3: Map of the Number *N. gonorrheae* cases in HIV Positive Males from 2005-2011 in the State of Michigan.



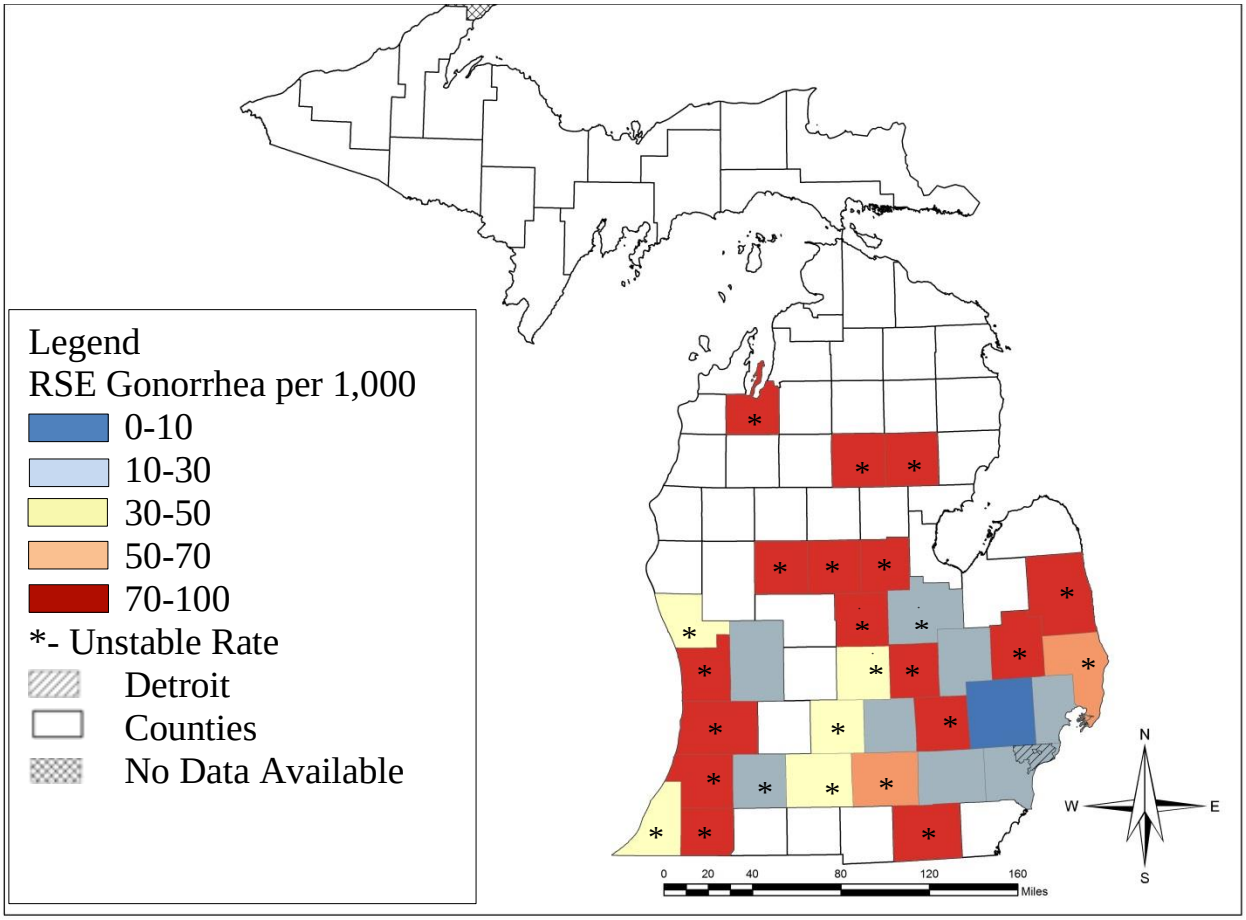
Number of *N. gonorrheae* represents individuals and not unique infections of *N. gonorrheae*. Detroit and the tri-county area of Macomb, Wayne, and Oakland all have increased HIV positive *N. gonorrheae* infected individuals than the rest of the state. The majority of cases seem to be located near Detroit, with numbers of individuals reducing the further away from Detroit a county is. A total of 879 HIV positive males with gonorrhea were able to be geocoded

Figure 4.4: Map of Rate of *N. gonorrheae* per 1,000 in HIV Infected Males in the State of Michigan 2005-2011 Adjusted Population Density



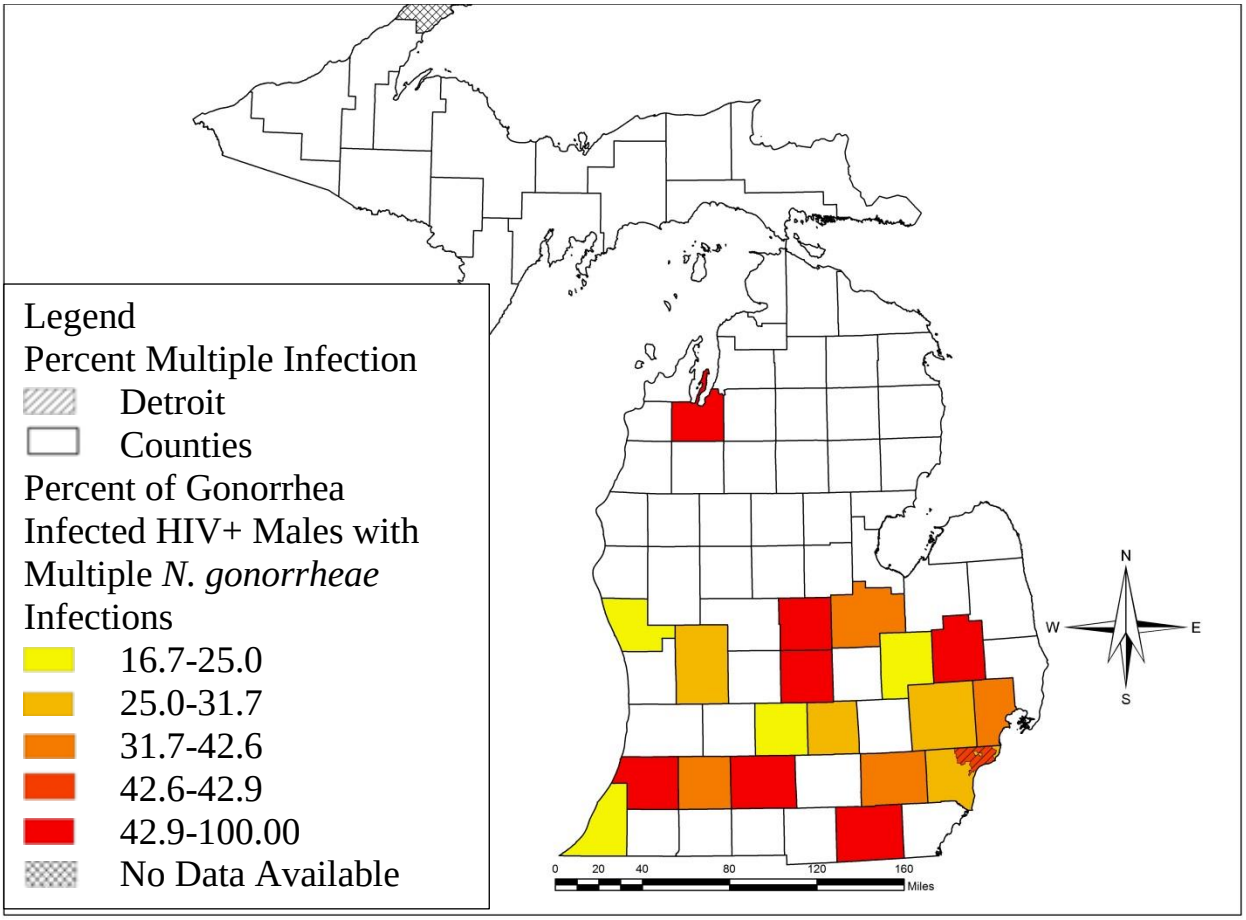
Rate of *N. gonorrheae* in HIV positive males was calculated using the 2010 US census at: http://factfinder2.census.gov/faces/nav/jsf/pages /index.xhtml. Oakland County, along with several others appears to have the highest rates of HIV/*N. gonorrheae* co-infected males. The city of Detroit and Macomb County, despite having higher than most occurrences of co-infected males do not fall into the highest group. Counties marked with "*" represent unstable rates (less than 20 cases or population less than 50). A total of 879 HIV positive males with gonorrhea were able to be geocoded.

Figure 4.5: Root Mean Square Error of *N. gonorrheae* per 1,000 in HIV Infected Males in the State of Michigan 2005-2011 Adjus Population Density



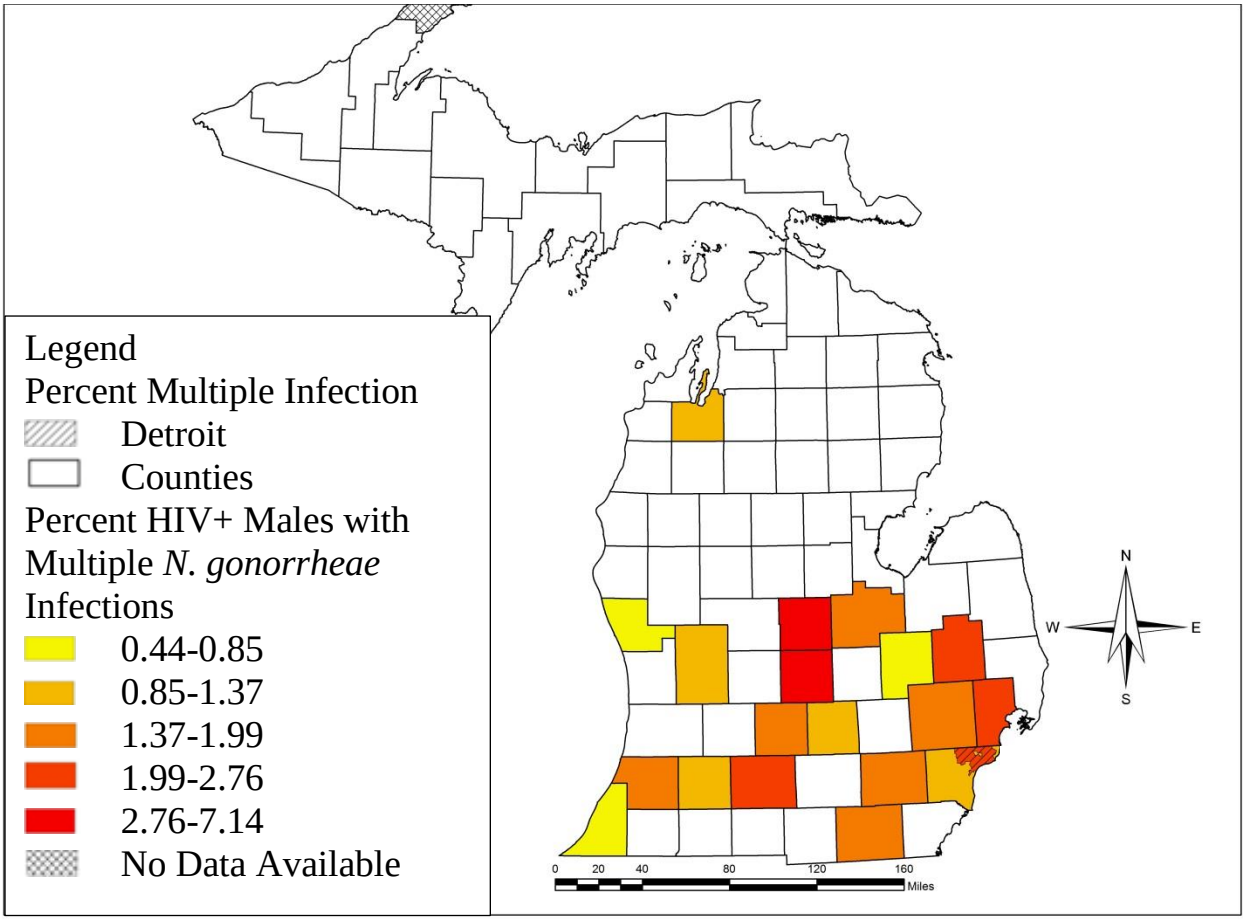
Root Mean Square Error (RSE) of rate of gonorrhea per 1,000 HIV positive males. Calculated from 2006-2008 ACS and 2012 Demographic and Housing estimates: http://factfinder2.census.gov /faces/nav/jsf /pages /index.xhtml. County population was adjusted for males 0-65 years old. RSE was calculated by Standard Error/Rate*100, Standard Error=Rate/Square Root (Cases). Counties marked with an "*" represent areas with unstable rates (less than 20 cases of HIV or population less than 50).

Figure 4.6: Percent of Gonorrhea Infected HIV Positive Males with Multiple *N. gonorrheae* Infections in the State of Michigan, 2005-2011



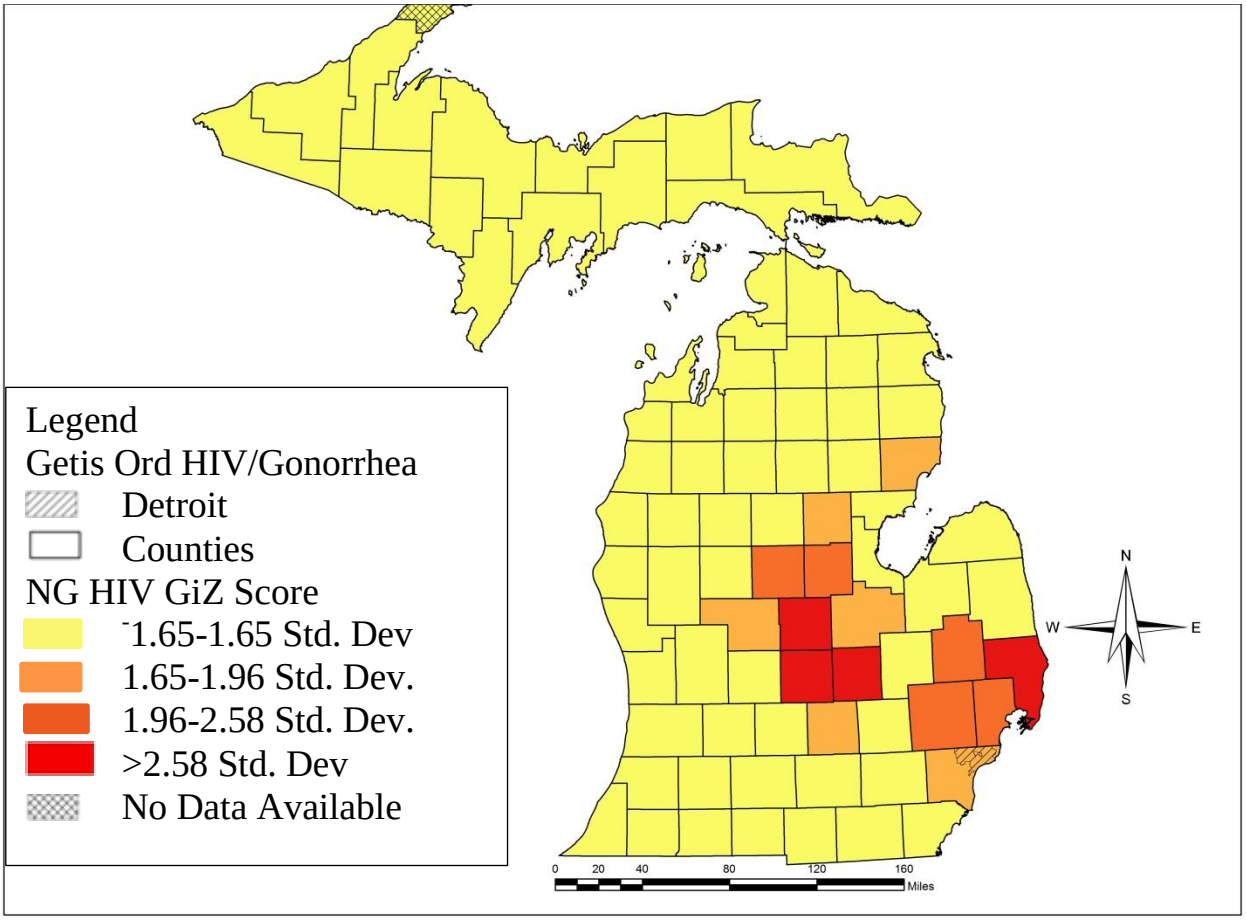
Highest rates of repeated infections in HIV males with a history of *N. gonorrheae* infections do not occur in the city of Detroit or in the tri-county area, but rather in counties with lower populations of HIV infected males such as Gratiot, Clinton, and Lenawee counties. Detroit, Wayne County, Oakland County, and Macomb County all still have relatively high rates of HIV positive males with a history of *N. gonorrheae* having multiple *N. gonorrheae* infections. A total of 879 HIV positive males with gonorrhea were able to be geocoded.

Figure 4.7: Map of Percent of HIV Infected Males with Multiple *N. gonorrheae* Infections in the State of Michigan, 2005-2011



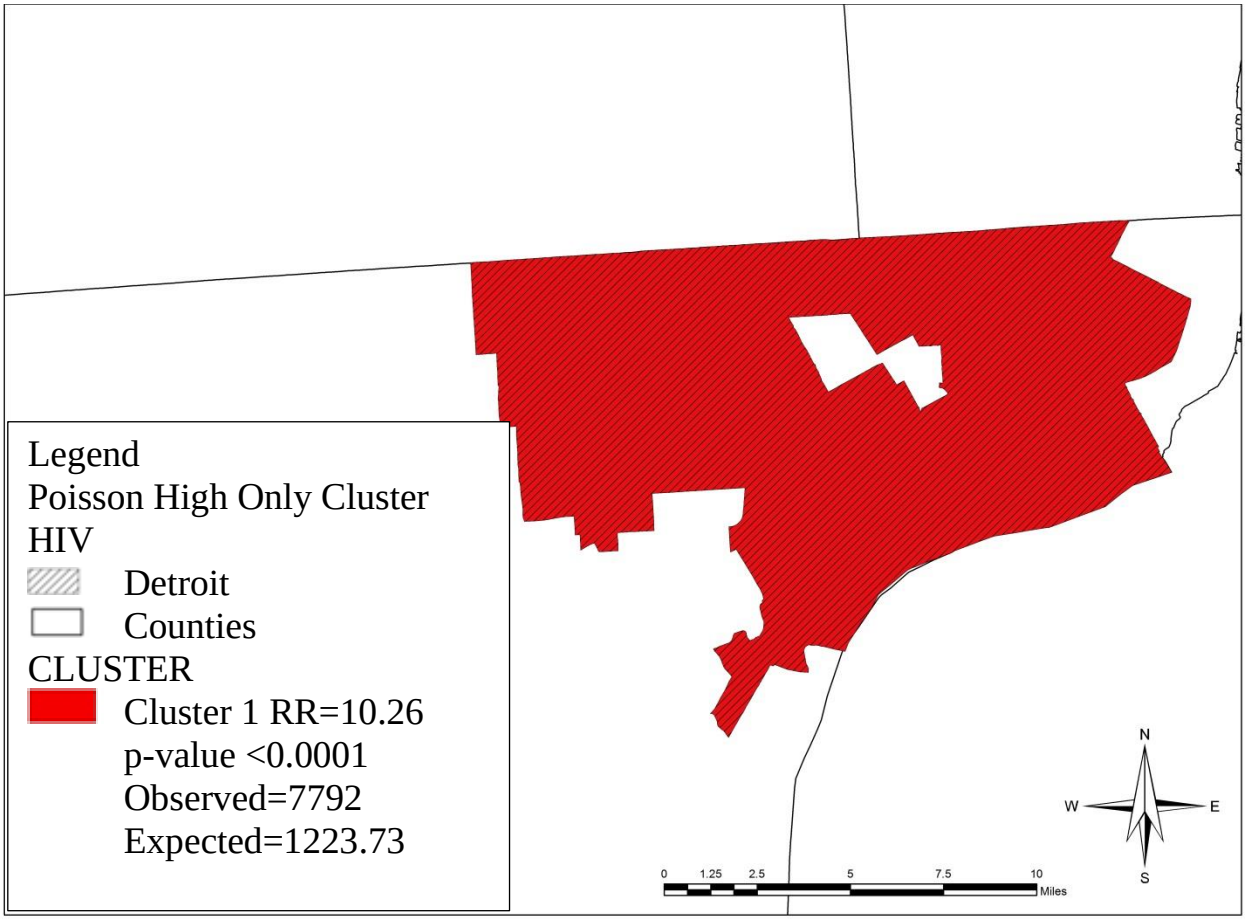
Gratiot and Clinton counties have the highest rates of HIV positive males with multiple *N. gonorrheae* infections. Detroit and the tri-county area also have increased rates of HIV positive males with multiple *N. gonorrheae* infections. A total of 327 individuals with repeated *N. gonorrheae* infections were able to be geocoded.

Figure 4.8: Getis-Ord GiZ score Cluster Analysis of *N. gonorrheae* Infected HIV Positive Males in the State of Michigan, 2005-2011



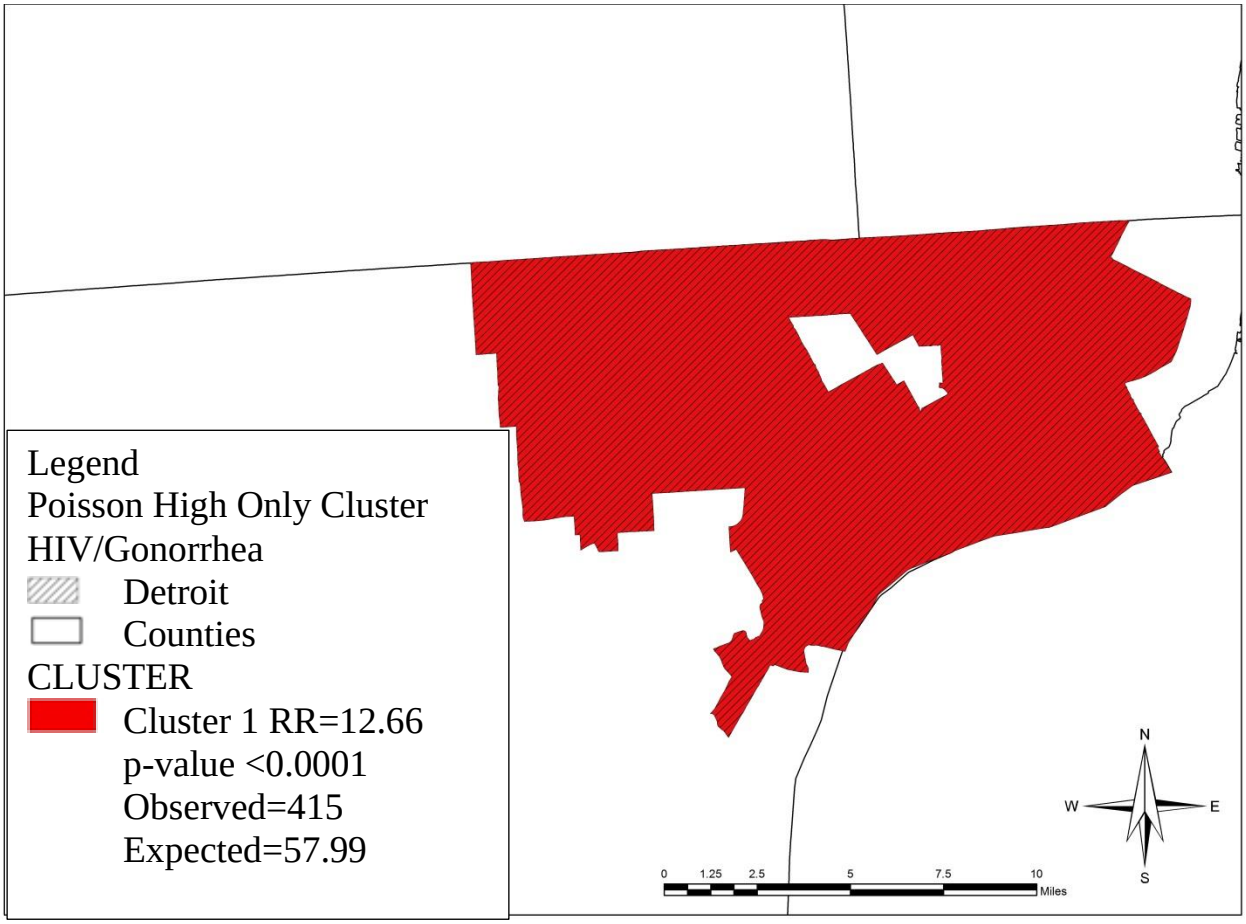
Getis-Ord GiZ score found that counties located near the city of Detroit (Oakland, Wayne, Macomb, Lapeer and St. Clair have higher rates of HIV positive males with a history of *N. gonorrheae* as well as a select group of counties near Gratiot, Clinton and Shiawassee counties. Counties and areas in the orange to red range are considered to be hot spots and represent a GiZ score of greater than or equal to 1.65 standard deviations above the average rate. A total of 18,550 HIV positive males were able to be geocoded at the county level.

Figure 4.9: Poisson High Only Rate Cluster Detection Method of HIV Positive Males in the State of Michigan, 2005-2011



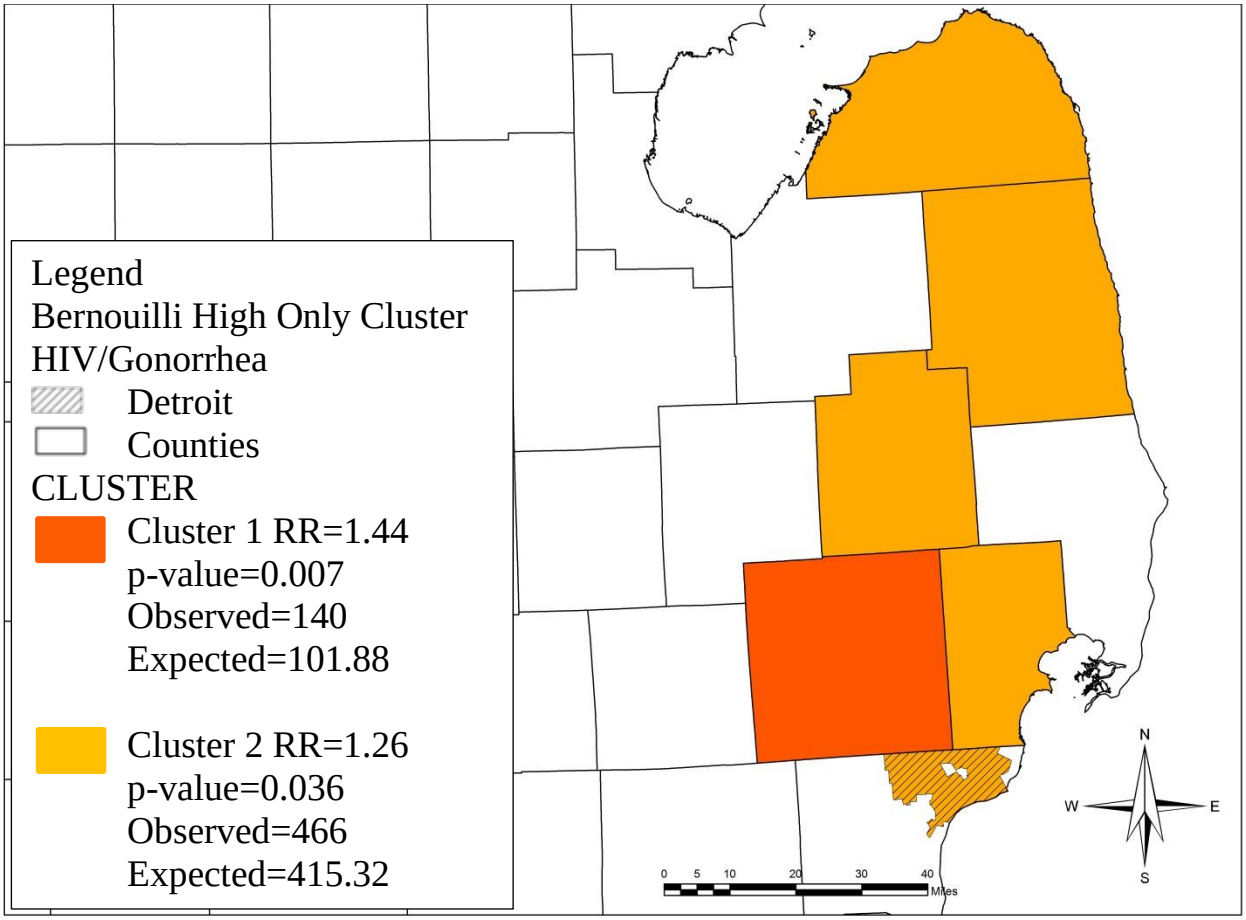
Poisson high only rate cluster detection of HIV clusters found that Detroit was the most likely cluster with a RR=10.26 (p-value <0.0001). The observed number of cases in Detroit was 7,792 whereas the expected number of cases for the city was 1,223.73. A total of 18,550 HIV positive males were able to be geocoded at the county level.

Figure 4.10: Poisson High Only Rate Cluster Detection Method of *N. gonorrheae* Infected HIV Positive Males in the State of Michigan, 2005-2011



Poisson method high only cluster detection found Detroit was the most likely cluster with a RR=12.66 (p-value <0.0001). Observed number of HIV males with gonorrhea was 415 whereas the expected number was 57.99. A total of 879 HIV positive males were able to be geocoded.

Figure 4.11: Bernouilli High Rate Only Cluster Analysis of *N. gonorrheae* Infected HIV Positive Males in the State of Michigan, 2005-2011



Bernouilli analysis was performed investigating only high rate clusters. Oakland County represented the most likely cluster with a RR=1.44 (p-value=0.007). A secondary cluster consisted of the city of Detroit, Huron, Macomb, Sanilac, and Lapeer county had a RR=1.26 (p-value=0.036) A third cluster consisting of Clinton and Gratiot counties was also detected, RR=2.22, but was not found to be statistically significant (p-value=0.974). Cases consisted of 879 HIV positive males with a history of gonorrhea, and controls consisted of 18,550 HIV positive males that were able to be geocoded at the county level.

Chapter 5.

Biological Markers and Geospatial Analysis of Michigan Males with HIV and *N. gonorrheae* Co-Infections from 2011 to 2013

5.1 Abstract

Introduction

Epidemiological evidence suggests that there is a synergistic relationship between HIV and *N. gonorrheae* with regard to changes in the natural history of these diseases in individuals who are co-infected. This study aims to investigate the changes in biological markers, CD4 cell count and HIV viral load, during co-infection periods. Geospatial analysis was also done in order to investigate areas with high rates of co-infections at the zip code level.

Methods

A retrospective study of 743 males in the State of Michigan from 2011-2013 with a history of HIV and *N. gonorrheae* was created in collaboration with the Michigan Department of Community Health. Laboratory data extending back to time of HIV diagnosis were linked to HIV and STD datasets, and longitudinal analysis was preformed to assess changes in CD4 cell count and viral load due to *N. gonorrheae* infection. Geospatial cluster analysis at the zip code level was also performed using Getis-Ord GiZ score as well as Poisson high only cluster detection method.

Results

Both CD4 cell count and HIV viral load were found to be increased during the year time period in which a *N. gonorrheae* infection was reported by MDCH. There was low overall reporting of

antiretroviral (ARV) usage, however, in those that did report ever being on ARV treatment, 71% started in the same year or after their *N. gonorrheae* infection. Cluster analysis showed that there is not equal geographic distribution of gonorrhea/HIV co-infections in the State of Michigan within counties or in the City of Detroit. Poisson cluster analysis showed that Detroit based zip codes had a RR=12.71 (p-value<0.0001), and that zip codes from the surrounding counties also had increased in risk, Wayne and Northern Monroe RR=3.65 (p-value<0.0001) and Oakland, Livingston, and Washtenaw RR=2.71 (p-value<0.0001).

Conclusion

Infection with *N. gonorrheae* during HIV positive status causes a change in both CD4 cell count as well as in viral load, however, without better knowledge of ARV treatment, total individuals ever receiving ARV, ARV cocktail usage, and length of time on ARV, these estimates only serve as stepping stones to investigating the change in laboratory indicators of HIV progression in co-infected individuals. Geospatial cluster analysis showed that there is not uniform distribution of co-infected individuals in the State of Michigan within counties and the State of Detroit. Public Health and Epidemiology need to target areas with the highest risk to make the most of the limited resources available to preventing the spread and acquisition of HIV and other preventable STDs.

5.2 Introduction

Evidence suggests that there is a synergistic relationship between HIV and infection with *N. gonorrheae* resulting in non-classical manifestations of these diseases in co-infected individuals. Attention has focused primarily on co-infection with ulcerating STI's in recent years. However, non-ulcerating STI's such as *N. gonorrheae* account for a significant co-infection burden in the HIV/AIDS community and there is a need for research to explore the changes in laboratory level data, such as CD4 cell count and viral load, in those who are co-infected (45, 47).

Despite multiple recent outbreaks of *N. gonorrheae* as well as the emergence of antibiotic resistant gonorrhea and that *N. gonorrheae* is one of the most reported diseases in the United States, the relationship between HIV and gonorrhea has yet to be fully explored (15). In 2011 WHO estimated that roughly 88 million of the estimated 448 million curable STD infections reported that year were due to *N. gonorrheae* (12). In the United States in 2012, there were over 334,000 *N. gonorrheae* cases resulting in an increased rate of 4.1% from the previous year (13).

As of the 2010 Census Michigan has the 8th largest population in the US. In 2011 there were over 13,000 cases of gonorrhea reported in the State of Michigan with the highest rate reported in the 20-24 age group (14). The 20-24 age group accounts for 6.7% of the population of Michigan, yet accounts for 34% of all gonorrhea cases (14). The overall rate in African Americans in the State of Michigan was roughly 24 times higher than the rate in Caucasians (14). Males account for 41% of all 2011 gonorrhea cases in the State of Michigan (14). Of the reported 13,070 gonorrhea cases 2% (n=259) were also HIV positive (14).

The January 2014 Annual HIV Surveillance Analysis estimated that there were approximately 19,800 individuals in the State of Michigan who were HIV positive of which an estimated

15,440 (78%) were males (10). Of the 15,440 males with HIV, men who have sex with men make up 55% of prevalent HIV cases between the combine risk groups of MSM and injection drug user (IDU)/MSM in the State of Michigan (10). Heterosexual contacts make up 19% of those with HIV infection and 17% had an undetermined source of transmission (10). The most frequent age group for HIV diagnosis was 30-39 year old (33%) with the combined age group of 20-29 at 32% (10). The majority of HIV diagnosis occurred in the Detroit Metropolitan Area (64%) despite only accounting for 43% of the total Michigan population (10). Males made up the majority of HIV infected individuals with a reported 12,510 cases (10). Within this group 71% are MSM (combined risk groups of MSM and MSM/IDU), 5% are heterosexuals, and 17% have an undetermined mode of transmission (10).

Wasserhiet et al. states that epidemiological synergy of HIV and STDs occurs "If coinfection with HIV prolongs or augments the infectiousness of individuals with STDs, and if the same STDs facilitate transmission of HIV, these infections may greatly amplify one another" (95). A second point the article makes is that there is a hard to define gap between infection with HIV and when HIV is diagnosed (95). This is important to note because it has a great effect on when baseline levels of CD4 and viral load would be collected (95). Those with low baseline levels of CD4 or high baseline levels of viral load concentrations may be in a state of elevated HIV progression due to an unaccounted immune response at time of testing (95). The article also notes that while there is value in testing the presence of absence of a given STD and its influence on HIV, the number of infections for each STD may also be an important risk factor, that at the time of the article were being overlooked (95).

Another key paper in the epidemiological synergy literature between HIV and STDs is the 1999 Fleming and Wasshereit paper that reviewed the scientific data on these co-infections (97). The

article found that non HIV STDs can facilitate the shedding of HIV in the genital tract (increased viral load) which then promotes the transmission of HIV and the infectivity of the genital secretion (97). Mayaud and McCormick state that HIV can modify the duration, severity, and response to treatment of certain STDs, but cite that this is most common in viral infections (40). The article also states that STDs can influence the risk of HIV transmission in naïve individuals as well as enhance the viral load of those infected with HIV (40). The article states that among HIV infected males there can be an upwards of an 8-fold increase in the viral load in semen as compared to the control group, as well as an increase in viral load found in the vaginal secretions of HIV infected women (40).

A review of co-infection literature by Bafica et al. states that HIVs enhanced viral expression during co-infection states may be due to the microbial-induced immune response that occurs during these periods (90). Bafica et al. also states that when the article was written (2004) toll-like receptors (TLR) were the major innate immune response for microbial infections (90). The review also found that in most human cells, when stimulated with TLR-2, 4, or 9 that there is an increase in the viral replication of HIV (90). The review goes on to state that another key component of HIV enhancement during co-infection periods may be due to cytokine-mediated induction of HIV long terminal repeats [long identical sequences of DNA found at the retrotransposons or proviral DNA end and used to insert genes into host (91)] via nuclear factor κB activation which occurs during times of co-infection (90).

N. gonorrheae infection has been shown to attract CD4+ lymphocytes to infective areas disrupting epithelial and mucosal barriers and increasing possible susceptibility to HIV (24). A study by Ding et al noted that *N. gonorrheae* infection enhanced the HIV infection of CD4 cells early infection via TLR-2 activation which not only increased the susceptibility of CD4 infection

but also enhanced the viral load associated with HIV infected CD4 cells (28). An editorial review by Bentwich et al. in 2000 states that since all co-infections will cause immune responses, that it is plausible that these co-infection states enhance HIV infection, increase HIV viral load, and increase the rate of progression of disease in those individuals with STD/HIV co-infection states (45). Bentwich et al. diagrams that co-infection starts via activation of cytokines such as tumor necrosis factor-alpha and helper T cells 1 and 2 and activation of chemokines and related receptors co-infections states increase the susceptibility of HIV infection in naïve individuals (45). Bentwich also states that non-ulcerative bacterial infections such as *N. gonorrheae* are more prevalent in HIV positive individuals than genital ulcerative bacterial infections such as *Haemophilus ducreyi* and *Treponema pallidum* more commonly referred to as syphilis (45). The authors acknowledge that ulcerative infections are associated with increased risk of HIV infection and increased viral load concentrations in those infected with HIV for both men and women but state that inflammation may be the main factor in HIV enhancement in co-infected individuals (45). The review goes on to state that gonorrhea may increase HIV transmission by recruitment of CD4+ cells at that infected site and that treatment of the co-infecting STD will reduce the transmission potential of HIV (45).

A review by Mayer and Venkatesh from 2012 found that even after treatment of the bacterial STD, HIV viral levels in the genitals do not return to levels at a pre-bacterial infection state, this is an important concept because it shows that while treatment has the ability to reduce the sudden increase in viral load, treatment does not fully negate the damage done during a co-infection period (101). The review also found that *N. gonorrheae* enhanced HIV infection by activation of TLR-2 which can both increase susceptibility of CD4 cells to HIV infection and enhance HIV replication in those CD4 cells already infected (101). The review also noted that *N. gonorrheae*

co-infection periods increased the ability of HIV to infect dendritic cells which then present the virus to other susceptible immune cells (101).

A conflicting study found that in HIV infected males that are co-infected with *N. gonorrheae* viral RNA is increased in the semen roughly 10-fold and drop to pre-gonorrhea infection levels after the start of antibiotic treatment (24). The literature also suggests that there is at least a two-fold increase in the risk of men spreading HIV in their ejaculate who are co-infected with *N. gonorrheae* than in men that are not currently co-infected (31). A 2005 review done by Risbud and the National AIDS Research Institute found that HIV viral shedding is enhanced during STD/HIV co-infection periods by the damaging epithelial cells and causing the accumulation of HIV vulnerable cells (47). The article also notes that STDs are the single major factor in the spread of HIV (47). The review also noted a study done by Wasserheit et al. that found that while both ulcerative and non-ulcerative increase HIV transmission, non-ulcerative STDs infections such as *N. gonorrheae* and may be due to the higher incidence of these infections in the public as compared to ulcerative STDs (47).

A study modeling the CD4 counts over time in AIDS positive individuals taking the drug zidovudine found that after an early spike in CD4 counts, around week 10 of treatment CD4 counts rapidly decline, obtaining baseline levels by week 20 and reaching an asymptote (part of a curve line where the distance between the curve and the line approaches zero as both move toward infinity) around week 90 (61). One of the major limitations of the study is that as time progressed, individuals dropped off due to death and missing observations (61). However, when looking at only survivors the CD4 curves look similar to the total population CD4 curve and show that in the sample AIDS population CD4 counts dropped below 10 cells/μL at around one year (61).

Yu et al. found that there is a linear relationship between CD4 count and CD4 percent (76). The study found that a CD4% of 5% corresponds to a CD4 cell count of 45 cells/mm^3 (CI 17-117 cells/mm^3), CD4% of 15% corresponds to a CD4 cell count of 182 cells/mm^3 (CI 64-499), and a CD4% of 30% corresponds to a CD4 cell count of 438 cells/mm^3 (CI 132-1395) (76). The study also found that among three groups, homosexual/bisexual, injecting drug users, and heterosexuals, homosexual/bisexuals have the highest CD4 cell counts in both AIDS-free and AIDS positive groups (76). In AIDS-free individuals those that are not on zidovudine therapy or pneumocystis carinii pneumonia (PCP) prophylaxis have the highest CD4 count in the low CD% grouping (5%) and those that are only on zidovudine have the highest CD4 counts in the high percent grouping (30%) (76). In the AIDS positive group CD4 counts in the 5% CD4 group were highest in those not on any therapy, and in the 30% CD4 group, CD4 counts were highest in the zidovudine only group (76). Zidovudine works well in keeping CD4 cell counts elevated, however, in individuals who are in the lowest CD4 grouping, the drug does not seem as effective.

5.3 Methods

A retrospective cohort of HIV positive males in Michigan with a history of *N. gonorrheae* between 2011 and 2013 were selected as the study population. Through collaboration with Michigan Department of Community Health (MDCH) a linkage structure between HIV and *N. gonorrheae* datasets was created for this study. Records with missing first name, last name, or date of birth were excluded from the study population prior to the matching of the data. Laboratory data for these individuals was also obtained through MDCH and included all CD4 cell count/percent and viral load data available for an individual. An employee of HIV Surveillance and Body Art Unit HIV/STD/VH/TB Epidemiology created the record linkage

structure between HIV datasets, *N. gonorrheae* datasets and laboratory datasets to comply with patient confidentiality and privacy. The matches were conducted between the registries using LinkPlus. All data used in this study were de-identified according to HIPAA guidelines on public health information. Study staff also did not contact or attempt to contact any participants of the study. Ethical approval was obtained from the Institutional Review Board (IRB) at Michigan State University (MSU) and was reciprocal with the MDCH IRB.

HIV cases were defined according to the CDC case definition of HIV and AIDS according to CDC 1993 guidelines. HIV infection was defined as HIV-NA=HIV infection, non-stage 3 and AIDS=stage 3 HIV infection. Acute and Latent, stage 1 and 2, were not differentiated in this study. Date of birth, date of death, *N. gonorrheae* infection, as well as HIV and AIDS diagnosis were all limited to year of the event. Vital status was coded as 1=alive, 2=deceased, 9=unknown. Ethnicity was classified into unique non-over lapping groups, 1.White= White non-Hispanic, 2.Black= Black non-Hispanic, 3.Hispanic=Hispanic of any race, 4.Asian/HI/PI=Asian/Hawaiian, Pacific Islander non-Hispanic, 5.Am In /Ak Nat=American Indian, Alaskan Native, non-Hispanic, or 9.Multi/Unk/Other=Multirace, Unknown, Other, non-Hispanic. Due to low rates of Asian/Hawaiian, Pacific Islanders (N=0) and American Indian, Alaskan Native (N=1) in the *N. gonorrheae* group these racial groups were included in the 9.Multi/Unk/Other grouping to avoid analytical complications. Marital status while largely missing was categorized as A=Married and Separated, S=Single and never married, M=Married, N=Not otherwise specified, Missing or U=Unknown, W=Widowed; Risk was condensed and categorized as A.MSM=Male-Male Sex, B.IDU=Injecting Drug Use, C.MSM/IDU=Male-Male Sex and Injecting Drug Use, D. Blood Recipient=Received Blood, E1.(Male HCFR)=Male who had sex with a female at risk for HIV, E2. (Fem) HCM=Heterosexual contact with a female, F. Perinatal=Child exposed by mother, G.

Unk:Other=Unknown/Other. For CD4 analysis MDCH risk groups were condensed to A.MSM=MSM and MSM/IDU and G. Unk:Other=All other risk groups due to low numbers in the other groups. For viral load analysis F. Perinatal was analyzed as its own group along with MSM, and Other/Unknown.

The dataset also contained limited information on antiretroviral (ARV) therapy. A binary variable indicating if ARV were ever taken was coding as 'Y' and 'U' and was analyzed as yes and not yes. Along with this were two variables that indicated date of ARV start and date of ARV end. While most of the data for individuals who had responded yes to ever taken ARV was complete, day month and year, there were 5 individuals with missing information on ARV start date. Four individuals were missing the day of the month that they started ARV therapy. In these individuals start date was set to the last day of that month. This was done to allow for usage of the ARV information in the longitudinal analysis of the data while trying to adjust for bias caused by assigning a day to the unknown field. One individual only had year of ARV start, ARV start date was set to December 31st of that year. Two individuals were missing days of the month for ARV end dates, end dates were set to the first of the month. In individuals with perinatal exposure to HIV, no date of HIV positive status was recorded. For these individuals year of HIV positive status was set to birth year.

Biological marker data included date of collection (MM/DD/YYYY), collection day (DD), collection month (MM), and collection (YY) as four distinct variables. Result data was captured using several variables as well. Results were mainly numeric data (aside for "UNDET") stored as character data, which was transformed to numeric data using SAS 9.3. A variable label results_units was the main identifier of what type of laboratory data the result was. PCT=Percent CD4 count, CNT=CD4 Cell Count, and C/ML=Viral Copies per mL. Lab data also contained a

result interpretation variable that identified results as < (below limit), = (within limit) and > (above limit). The final variables that captured results data were VL=Viral load (collected as character, converted to numeric), CD4=CD4 cell count (collected as character, converted to numeric) and CD4PCT=CD4 percent (collected as character, converted to numeric). Biological marker data also contained *N. gonorrheae* infection year for study participants.

Age at HIV was a constructed variable that approximated age at HIV by using year of HIV diagnosis and year of birth. A flag variable for time on ARV treatment was also created for this study. The flag variable was constructed so ARV would only equal 1 while the individual was actually on treatment, as opposed to the MDCH ARV indicator that only measured if someone had ever been on ARV treatment. ARV flag was constructed by using data of lab collection (date the viral load/CD4 cell count was collected) and was equal to 0 if collection occurred before start of ARV treatment, after the end of ARV treatment, or where individuals did not have start or end dates, ARV='U', from the MDCH dataset. ARV flag was set to 1 when collection date occurred on or between the ARV start and end date, and when it occurred after ARV start and no end date was recorded. As stated before *N. gonorrheae* infection was limited to only the year of infection and analyzed for viral load as *N. gonorrheae* during collection year=1 and not during collection year=0. This variable was constructed using collection year, all data where collection year was equal to year of *N. gonorrheae* infection, gonorrhea=1, else gonorrhea=0. For CD4 cell count, longitudinal analysis was able to capture before, during, and after *N. gonorrheae* infection so gonorrhea was coded as 0=collected before *N. gonorrheae* infection, 1= same year as *N. gonorrheae* infection, and 2=collected in the year/s after *N. gonorrheae* infection.

Longitudinal analysis was run using SAS 9.3 (SAS Institute, Inc. Cary, North Carolina). Descriptive statistics were performed to assess distribution of demographic and risk

characteristics. Primary analysis was done using general estimating equation (GEE) with repeated subject adjustment to investigate change in CD4 and viral load in HIV positive males with a history of *N. gonorrheae* infection between 2011 and 2013. Adjusted (collection date, ethnicity, MDCH condensed risk group, age at HIV, and ARV usage) and unadjusted models were ran for each of the biological marker variables.

Spatial cluster-analyses were performed using two methods: 1) Getis-Ord statistics to access global and local High and Low clusters of prevalence rates in using ArcGIS v.10.2 (Environmental Systems Research Institute (ESRI) 2014).; 2) Poisson distributed methods using SaTScan V9.1.1 to detect high prevalence rates. Getis-Ord Gi Hot Spot analysis is a cluster detection analysis that measures each area in context to its neighbors. If a map unit (zip code) has high values that are contiguous to its adjoining neighbors then the area constitutes a 'hot spot'. The cluster is then compared to all map units and a Z score is calculated. Clusters with higher rates of disease will have higher Z scores and clusters with lower than average rates of disease have lower Z scores. The GiZ scores of were mapped at the zip code level. A GiZ score of 0 represents a map unit that does not differ from the overall mean. An increase in GiZ score represents greater distance from the overall mean (increase in *N. gonorrheae*/HIV co-infection). A negative GiZ score represents areas with a lower than average rate of *N. gonorrheae*/HIV co-infection.

Coordinate data was constructed using ArcGIS via the "Calculate Geometry" function, and mapped as latitude and longitude. Poisson cluster-detection methods consist of a gradually scanning window that moves across the study frame (Michigan zip codes) calculating the number of expected and observed observations (cases) inside the scanning window of each map unit. Cases were Michigan HIV positive males with a history of *N. gonorrheae* infection between

2011 and 2013. Maximum likelihood estimates are calculated to determine areas where clustering is least likely (p-value less than 0.05) to be due to chance. SaTScan has the ability to document and rank multiple possible clusters of both high and low rates. Geospatial analysis of HIV and *N. gonorrheae* clusters were done using Poisson method scanning for high only rate areas. No time precision options were used and map areas were scanned for high only rates with no clusters centered over other clusters. A maximum radius of 20 miles (32.2 km) was used as well as the limitation of no more than 50% of population at risk in a cluster. Zip code populations were taken from the 2008-2012 American Community Survey 5-year Estimate available at the US Census website (http://factfinder2.census.gov/faces/tableservices /jsf/pages/productview.xhtml?pid=ACS_12_ 5YR_S0101&prodType=table). Zip code populations were adjusted for age (0-65) and sex (males only) using the estimated percent for 5 year age group blocks.

5.4 Results

Table 5.1 shows the demographic distribution for the 743 HIV positive males in the State of Michigan with a reported history of *N. gonorrheae* infection between 2011 and 2013. Blacks represent the largest ethnic group, accounting for 78% of co-infected individuals, with Whites accounting for 15%, Hispanics accounting for 2% and Multiracial/Unknown/Other accounting for 4%. In HIV positive males who had a *N. gonorrheae* infection between 2011 and 2013 around 66% progressed to AIDS positive status by 2013, with only 1 death in co-infected participants. MDCH condensed risk group showed that MSM accounted for the majority of the population, 77%. Other MDCH risk group categories had relatively low numbers. Only 6 individuals (<1%) fell into the IDU category, 5 (<1%) were categorized as MSM/IDU, 1 individual was grouped in the Blood Recipient group, 15 (2%) males identified as having

heterosexual intercourse with a woman living with HIV, and 45 (6%) identified themselves as heterosexual. There were 31 individuals in the study population with perinatal exposure to HIV (4%). The mean age at HIV diagnosis was 25 years old.

CD4 Cell Count

CD4 cell count was modeled using a longitudinal approach that accounted for repeated measures in study participants. Table 5.2 shows both the collection date adjusted and multivariate change in CD4 cell count. A multivariate model was constructed using *N. gonorrheae* infection as a discrete variable with 3 levels, collection date prior to *N. gonorrheae* infection, collection date occurring in same year as *N. gonorrheae* infection, and collection date after *N. gonorrheae* infection. The multivariate model was also adjusted for race, MDCH risk group (MSM vs Other), age at HIV diagnosis and ARV usage at time of collection. ARV usage was not found to be a statistically significant predictor of CD4 cell count in this group, however, due to what is known about the relationship between CD4 and ARV usage, ARV was retained in the model. The model observed that as date of collection progressed forward in time there was a mean reduction in CD4 cell count of -0.06 (p-value=0.005). As compared to the reference state of CD4 collected prior to *N. gonorrheae* infection, CD4 collected during the same year saw a mean increase in cell count by 110 cells (p-value <0.0001), and collections that occurred in the years after a *N. gonorrheae* infection saw a mean increase in difference of 138 cell as compared to the reference state (p-value =0.0001).

As compared to MSM (MSM and MSM/IDU) HIV infected males that fell into one of the other condensed risk groups had a mean increase in CD4 cell count of 90 (p-value=0.011). Blacks were the only ethnic group to have a statistically significant change in mean CD4 cell count as

compared to Whites. Blacks had a reduction in CD4 cell count of 64 (p-value=0.036) as compared to the reference group of Whites. Hispanics also had a reduction in CD4 cell count, but this was not statistically significant when compared to Whites. Age of HIV diagnosis reduced CD4 cell count by 5 per year increase in age (p-value=0.002).

Viral Load

Viral load was modeled using a longitudinal approach that accounted for repeated measures in study participants. Table 5.3 shows both the adjusted and unadjusted change in viral load. A multivariate model was constructed using *N. gonorrheae* infection as a discrete variable with 2 levels, collection date occurring in same year as *N. gonorrheae* infection, and collection date prior/after *N. gonorrheae* infection. The multivariate model was also adjusted for race, MDCH risk group (MSM, Perinatal and Other), age at HIV diagnosis and ARV usage at time of collection. ARV usage was not found to be a statistically significant predictor of viral load in this group, however, due to what is known about the relationship between viral load and ARV usage, ARV was retained in the model. The model observed that as date of collection progressed forward in time there was a mean decrease in viral load of -1.13 copies/mL (p-value=0.001). As compared to the reference state of viral load collected in years with no *N. gonorrheae* infection, viral load copies/mL collected during the same year saw a mean increase in copies/mL by 1631 copies/mL (p-value <0.033).

As compared to MSM, those that were placed in the perinatal MDCH condensed risk group had a reduction in mean viral load of 16,374 (p-value<0.0001), those in the Unknown/Other group did not have a statistically different mean viral load than MSM. Age at HIV diagnosis had a mean reduction of 260 copies/mL (p-value<0.0001). As with CD4 cell count only those in the

Black ethnicity group had a statistically significant change in viral load as compared to Whites. Despite ARV being not statistically significant there was a decreasing viral load trend for measurements taken during their reported treatment time. The estimated mean reduction due to ARV treatment was 2,038 copies/mL (p-value=0.306)

Zip Code Cluster Analysis

The State of Michigan consists of approximately 900 unique zip codes according to the 2010 US census. Figure 5.1 shows the map of the Getis-Ord GiZ score of HIV/gonorrhea co-infections between 2011 and 2013 in males in the State of Michigan. Using GiZ score cluster analysis two "hot spots" were detected, both in close proximity to the City of Detroit. Figure 5.2 is a zoomed in view of the 2 "hot spots" identified by the Getis-Ord GiZ score analysis. The main cluster consists of around 48 zip codes that account for most of Detroit as well as the Northern adjacent zip codes. This primary cluster is largely situated within the North East corner of Wayne County, but extends north to the Southern Edges of Oakland and Macomb counties. The second cluster that was detected by Getis-Ord GiZ score analysis is situated slightly east of center of the county of Oakland, a relatively short distance from the primary cluster.

A second cluster analysis was performed using Poisson high only cluster analysis techniques. Maximum spatial cluster size was set to 50.0% of the population at risk as well as in a circle with a 32.2 km (20 miles) radius. Figure 5.3 shows the 5 clusters detected in the Poisson cluster analysis and Figure 5.4 shows a zoomed in version of this map. The most likely cluster includes zip codes that constitute the City of Detroit as well as a number of zip codes to the north that extend into parts of Oakland and Macomb counties. Table 5.4 shows the RR and respective p-value of Poisson identified clusters. Cluster 1 consists of 44 zip codes with a RR=12.71 (p-

value<0.0001). A secondary cluster consisting of 38 zip codes located in Wayne and northern Monroe counties and had a RR=3.65 (p-value<0.0001). Cluster 3 is located in Washtenaw, Livingston, and Oakland as well as 5 zips in the North West corner of Wayne County and consists of 49 total zip codes with a RR=2.71 (p-value<0.0001). Cluster 4 consists of 3 zip codes in Kalamazoo with a RR=3.02 which was found to not be statistically significant (p-value=0.971). The final cluster that was detected using Poisson high only analysis was located Genesee County and consisted of 2 zip codes in the center of the county, cluster 5 had a RR=2.78 and was not found to be statistically significant (p-value=0.998).

5.5 Conclusion

CD4 Cell Count

This study found that there is an increase in CD4 cell count in the year during a *N. gonorrheae* infection as well as in the years following gonorrheal infection as compared to the time from HIV diagnosis to first *N. gonorrheae* infection. The study also found that there was an overall decrease in CD4 count as time progressed in the study population which is characteristic of being HIV positive. Using the MDCH condensed risk group categories, those that were MSM (MSM and MSM/IDU) had a lower CD4 cell count as compared to the rest of the population. The study also found there is a lower CD4 count in those that are diagnosed with HIV at an older age as compared to those that are younger, which may help to explain why time from HIV to AIDS is so dependent on the age of the individual, with those that are diagnosed with HIV at an older age typically having a shorter time to AIDS positive status as seen in Chapter 3. The study also found that while both those that identified their ethnicity as Black or Hispanic had a reduction in mean CD4 cell count, only Blacks were statistically significant.

Finally, ARV usage was not a statistically significant factor in CD4 progression, which may be largely due to two reasons. First, there were very few individuals in the study population that reported that they had ever been on ARV treatment, and not all of these individuals remained on ARV treatment to the end of the study. Second, ARV data is not defined as yes and no, it has to be analyzed as yes and not yes. Individuals that did not have a "Y" for ARV are actually unknown and may be on ARV treatment. Without knowing if individuals are on ARV treatment and for how long they have been on treatment ARV as a measurement will remain incomplete. Despite this ARV was included in the model because of the known relationship between taking ARV and changes in CD4 cell count.

These findings may help to shine light on a previous seemingly paradoxical relationship between *N. gonorrheae* infection and time from HIV to AIDS positive status. In a previous chapter, Chapter 3, there was a greater lag time between HIV and AIDS in individuals with a history of *N. gonorrheae* infection as compared to those without a history of gonorrhea. This spike in CD4 cell count during and after *N. gonorrheae* infection may play a role in that paradoxical relationship and may represent a possible intervention time in the natural history of an individual's disease progression, however, it would also increase the number of CD4 cells HIV could infect. Since this data was collected from MDCH reportable disease database, individuals that had a confirmed *N. gonorrheae* infection would have gotten treatment for the infection and thus brought back into medical care; where as those without a history of *N. gonorrheae* infection may not have the same access to medical care. This is speculation and there is need for subgroup analysis in both the initial HIV/gonorrhea study population (2005-2011) as well as the laboratory subgroup (HIV/gonorrhea 2011-2013) population. There is also a need for further research into all STDs and reported infections an individual had from onset of HIV to assess the change in

CD4 due to various bacterial, viral, parasitic, and fungal infections. Finally there is a need to gain better information on ARV usage in this population and address any barrier to ARV access or compliance.

Viral Load

Viral load (copies/mL) increased in the year during *N. gonorrheae* infection as compared to the time periods before and after *N. gonorrheae* infection. This coincides with what other studies have found and what researchers like Wasshereit and Flemming have outlined in the STD synergistic papers (24, 28, 40, 45, 90, 95, 97, 101). This finding is also biologically supported by the finding in the previous section in that during the year of a *N. gonorrheae* infection there is also an elevation of CD4 in the body, these CD4 act as replication sites for HIV allowing the virus to have more host cells in which to make viral copies.

The study also found that Blacks had a statistically significant increase in viral load as compared to Whites. The study also observed that in the multivariate model viral load decreased with collection date, representing a decreasing trend in viral load as time progressed for these individuals. Being older at age of HIV diagnosis was also found to reduce the mean viral load in individuals. This study was unable to investigate the cause of these findings, but they may be due to ARV treatment or HAART in these individuals. As with CD4 cell count ARV was not found to be a statistically significant predictor of viral load, but was included in the model because of its known ability to facilitate in the regulation of viral load in HIV positive individuals. The study also found that 42 of 59 (71%) individuals that reported they were ever on ARV started in the same year or after their *N. gonorrheae* infection. While ARV reported usage was low in this study (~8%) it is important to note that lack of a positive response is not the same as a no, and

that in fact some of these individuals may have been on ARV treatment. The fact that 71% of those that responded that they were ever on ARV having started ARV in the same year or after a *N. gonorrheae* infection may help to explain some of the seemingly paradoxical observations found in this study, such as CD4 cell count not returning to baseline or lower level in the years after a *N. gonorrheae* infection and the increased lag time from HIV to AIDS seen in Chapter 3.

Zip Code Cluster Analysis

This subgroup of HIV/gonorrhea co-infected individuals represented a unique opportunity to investigate spatial patterns of disease at the zip code level, and to better identify areas in the State of Michigan were efforts to reduce *N. gonorrheae* infections and disrupt HIV transmission should be targeted. Both cluster techniques found that the City of Detroit represented the most likely "hot spot" with regard to HIV/gonorrhea co-infections. Both techniques also found that there was an area in the proximity of central Oakland County that also had elevated risk of HIV/*N. gonorrheae* co-infection as compared to the rest of the state. These maps reflect what was also seen at the county level of geospatial analysis and aid in confirming that the City of Detroit and neighboring areas need to be the primary target for interventions aimed at stopping the spread of STDs, specifically *N. gonorrheae* and *N. gonorrheae*/HIV positive males.

The Getis-Ord GiZ score analysis showed that the areas with the highest standard deviation from the mean of the state was located in and around the City of Detroit with a small subcluster being located just right of center in Oakland County. This analysis was able to show that these areas have higher than average rates and that intervention services may have the most impact in these areas. The Poisson cluster analysis method was also able to show that the area around the City of Detroit was a "hot spot", it unlike the Getis-Ord analysis, the Poisson analysis was able to

visually show how the rates of disease seem to diffuse from the primary cluster (Detroit) and spread to other areas, such as Wayne, Oakland, and parts of Livingston and Washtenaw counties.

These maps as with the maps in the previous chapter show that the burden of HIV/gonorrhea co-infection is not even distributed among the state, and by using zip code level data, the study found that it is not evenly distributed among or within the tri-County area of Macomb, Wayne, and Oakland. The use of zip codes allows for epidemiologists and public health officials to consider where the best area for intervention and prevention efforts should be placed in the city as well as across the affected counties.

Limitations

The data for this study were collected for surveillance purposes and not primarily for epidemiological or biostatistical analysis. There is a certain level of missing/incomplete data that is inherent in using data not specifically designed for the research question as opposed to designing a study to specifically capture key variables. The lack of information on ARV is a key limitation of this study and a key area to focus on to make these data more meaningful. Obtaining better response rates on ARV treatment will allow for better modeling of key laboratory factors such as viral load and CD4 cell count, allowing epidemiologists and public health officials to model the actual disease progression in an individual by adjusting for a treatment that is designed to reduce viral load and there by either maintain or improve CD4 cell count. Another key limitation is that *N. gonorrheae* infection was only recorded as year of infection, and no data such as history of other STDs or other bacterial reportable disease during HIV was collected. The lack of information of other STDs is important when looking at spikes in CD4 and viral load in the period of time prior to *N. gonorrheae* infection. This again is a

limitation to using surveillance data and should be considered when developing future integrated models. A final limitation of the study was that only data on co-infected individuals was collected. The study was not able to model the change in CD4 and viral load in individuals with only HIV infections as compared to those with a history of *N. gonorrheae* infection. Having a control group may have allowed for better inferences from the data as well as a way to control for potential bias due to other STD or reportable infections individuals may have had in the time leading up to their *N. gonorrheae* infection.

APPENDIX

Table 5.1: Demographic Distribution of 743 HIV/Gonorrhea Co-Infected Michigan Males from 2011-2013

Variable	**HIV/*N. gonorrheae* Co-Infected** N=743
Ethnicity	
White	109 (14.67%)
Black	583 (78.47%)
Hispanic	18 (2.42%)
Multiracial/Unknown/ Other	33 (4.44%)
ARV Treatment Status (Ever Been on)	
Yes	59 (7.94%)
Unknown	684 (92.06%)
Risk Group	
MSM	569 (76.58%)
IDU	6 (0.81%)
MSM/IDU	5 (0.67%)
Blood Recipient	1 (0.13%)
Male HCFR	15 (2.02%)
Fem HCM	45 (6.06%)
Perinatal	31 (4.17%)
Other/Unknown	71 (9.56%)
AIDS Positive	246 (33.11%)
Deceased	1 (0.13%)
Mean Age at HIV (Std Dev)	25.35 (9.59)

Table 5.2: Multivariate General Estimating Equation (GEE) with Repeated Subjects Model of CD4 Cell Count in HIV Positive Males with *N. gonorrheae*

Variable	Mean Collection Date Adjusted CD4 Cell Count	Mean Multivariate Adjusted CD4 Cell Count
Gonorrhea		Baseline: 1818.9 (937.4-2700.4)
Pre-Gonorrhea Period	1843.2 (898.2-2788.2)	Reference
During Gonorrhea Period	1967.1 (1904.4-2029.7)	109.9 (56.0-163.8)
Post Gonorrhea Period	1998.0 (1917.2-2078.8)	137.9 (68.4-207.5)
Ethnicity		
White	1273.247 (550.6-1995.9)	Reference
Black	1253.8 (1197.1-1310.4)	ˉ64.4 (ˉ124.7-ˉ4.1)
Hispanic	1253.7 (1153.9-1353.6)	ˉ40.6 (ˉ133.4-52.2)
Multiracial/Unknown/ Other*	1353.7 (1240.2-1467.2)	78.6 (ˉ36.7-193.8)
Risk Group		
MSM	1201.3 (523.9-1878.7)	Reference
Other/Unknown	1296.5 (1221.7-1371.3)	90.4 (20.9-159.9)
Age at HIV Diagnosis	Baseline: 1338.1 (610.4-2065.9)	
Per Unit Increase	ˉ4.4 (ˉ7.7-ˉ1.2)	ˉ4.9 (ˉ8.1-ˉ1.8)
ARV		
Unknown/Not Yes	1284.1 (557.0-2011.1)	Reference
Yes	1317.8 (1202.9-1432.7)	47.3 (ˉ84.7-179.4)
Collection Date		
Per Unit Increase		ˉ0.06 (ˉ0.11-ˉ0.02)

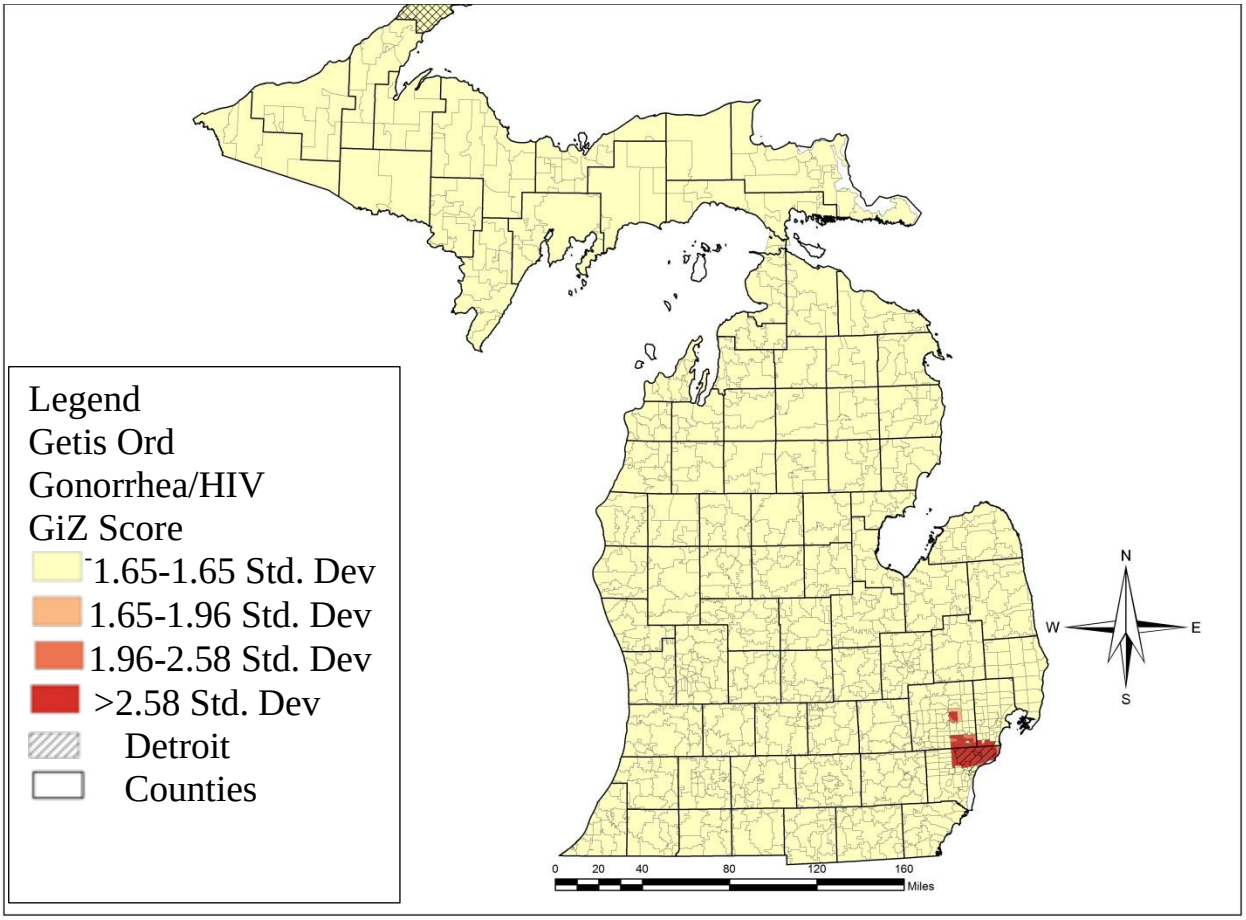
Table 5.3: Multivariate General Estimating Equation (GEE) with Repeated Subjects Model of Viral Load (copies/mL) in HIV Positive Males with *N. gonorrheae*

Variable	Mean Collection Date Adjusted Viral Load (copies/mL)	Mean Multivariate Adjusted Viral Load (copies/mL)
Gonorrhea		Baseline: 36441.7 (22845.7-500376)
Pre/Post Gonorrhea	23029.0 (9339.7-36718.3)	Reference
During Gonorrhea	24624.4 (23124.4-26124.7)	1630.8 (129.8-3131.8)
Ethnicity		
White	18509.9 (4740.2-32279.6)	Reference
Black	22347.2 (20298.8-24395.5)	2181.6 (59.6-4303.6)
Hispanic	20563.7 (17121.1-24089.7)	¯759.6 (¯5153.1-3633.8)
Multiracial/Unknown/ Other*	20563.7 (17121.1-24006.4)	799.3 (¯2532.7-4131.2)
Risk Group		
MSM	23206.4 (10214.1-36198.7)	Reference
Perinatal	14629.0 (11953.1-17301.8)	¯16374.4 (¯20152.1-¯12596.6)
Other/Unknown	23055.1 (20661.7-25448.6)	719.6 (¯1685.8-3125.0)
Age at HIV Diagnosis	Baseline: 26056.3 (10068.8-42043.8)	
Per Unit Increase	¯195.3 (¯299.5-¯91.0)	¯260.0 (¯351.8-¯168.2)
ARV		
Unknown/Not Yes	19005.0 (5559.2-32450.8)	Reference
Yes	16647.2 (12627.8-20666.5)	¯2037.61 (¯5940.2-1865.0)
Collection Date		
Per Unit Increase		¯1.1 (¯1.8-¯0.4)

Table 5.4: Poisson Analysis of Gonorrhea/HIV Co-Infected Clusters in Michigan Males, 2011-2013

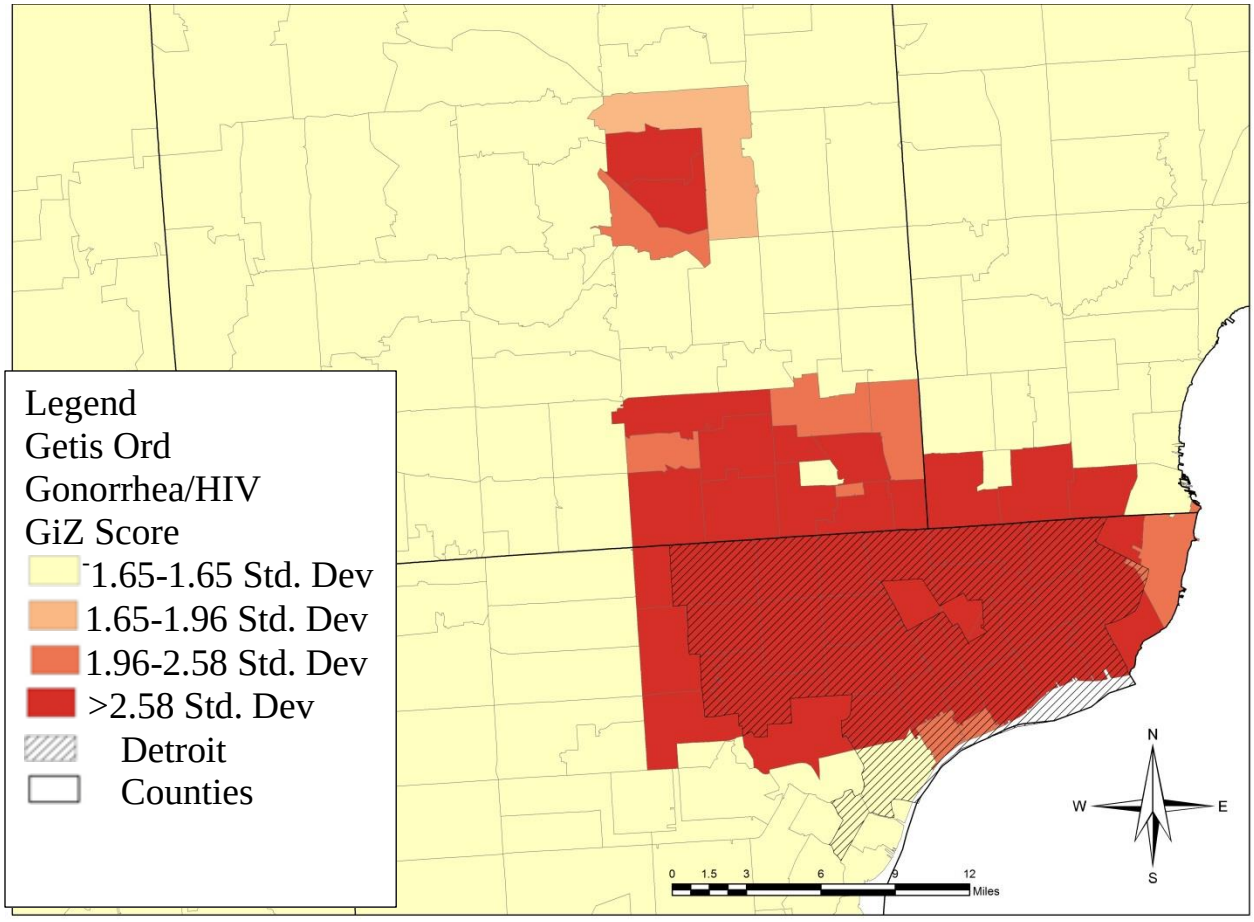
Cluster ID	Geographic Description	Relative Risk (RR)	p-value
1	Detroit, Southern Oakland and Macomb	12.71	<0.0001
2	Wayne and Monroe	3.65	<0.0001
3	Oakland, Livingston, Washtenaw	2.71	<0.0001
4	Kalamazoo	3.02	0.971
5	Genesee	2.78	0.998

Figure 5.1: Getis-Ord GiZ Score Cluster Analysis of *N. gonorrheae*/HIV Co-Infected Michigan Males 2011-2013



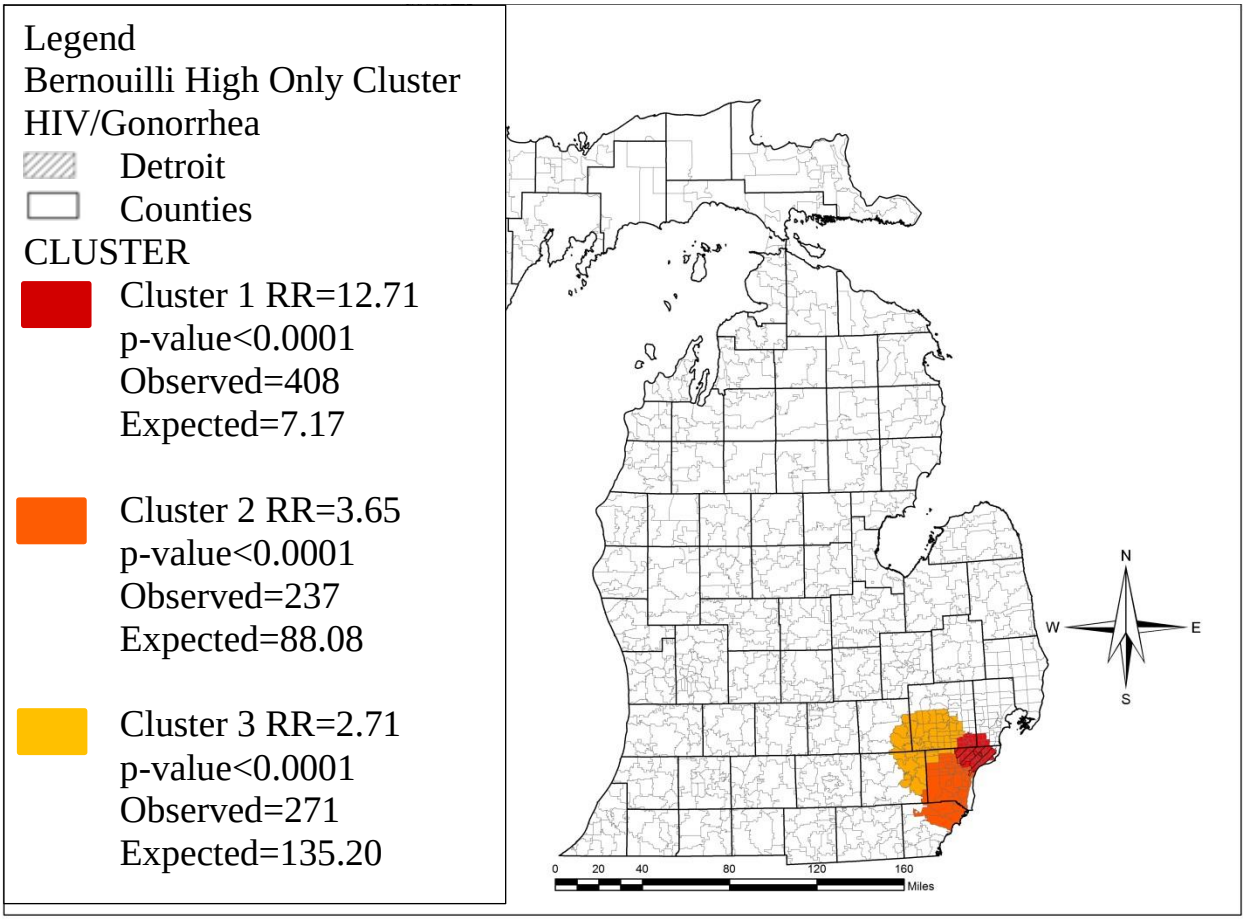
Getis-Ord GiZ Score found that the zip codes representing the City of Detroit had higher rates of *N. gonorrheae*/HIV co-infected males than the rest of the state. This "hot spot" extends in to the lower zip codes of Oakland and Macomb counties. There is a second "hot spot" located in the zip codes that make up the center right area of Oakland County. A total of 700 HIV positive males with gonorrhea were able to be geocoded.

Figure 5.2: Getis-Ord GiZ Score Cluster Analysis of *N. gonorrheae*/HIV Co-Infected Michigan Males 2011-2013 Detroit and Tri-County Area



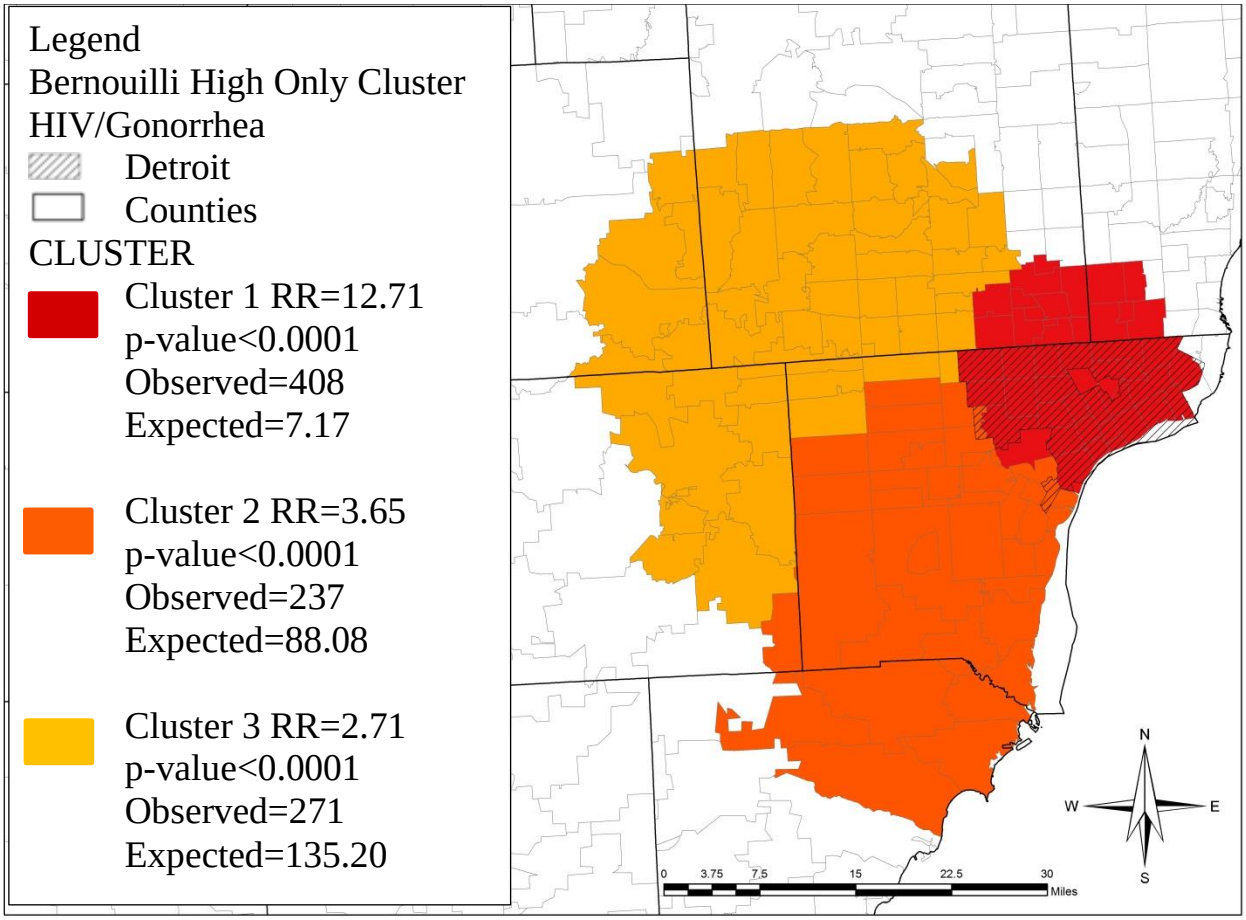
Getis-Ord GiZ Score distribution zoomed in to show "hot spot" located in the City of Detroit that extends into the Southern parts of Oakland and Macomb counties. The map also shows a secondary "hot spot" located just east of the center of Oakland County. The City of Detroit is represented by the shaded region in the North East Corner of Wayne County. A total of 700 HIV positive males with gonorrhea were able to be geocoded.

Figure 5.3: Poisson Cluster Analysis of Gonorrhea/HIV Co-Infections in Michigan Males from 2011 to 2013



Poisson cluster analysis of Michigan gonorrhea/HIV infected males from 2011 to 2013. Cluster 1 which is mainly made up of the zip codes comprising the City of Detroit as well as zip codes in the Southern adjacent edges of Oakland and Macomb counties represents the most likely cluster with a RR=12.71 (p-value<0.0001). Cluster 2 represents another elevated risk area, RR=3.65 (p-value=<0.0001) which is located in the remaining zip codes of Wayne County as well as in the Northern part of Monroe County. Cluster 3 is comprised of the lower half of Oakland County, parts of Livingston and Washtenaw counties and has a RR=2.71 (p-value<0.0001). Cluster 4 is located in the middle of Kalamazoo County, between Van Buren and Calhoun counties, and has a RR=3.02, however, this was not found to be statistically significant (p-value=0.971). Cluster 5 is located in Genesee County and has a RR=2.78 (p-value=0.998) which was not statistically significant. A total of 700 HIV positive males with gonorrhea were able to be geocoded.

Figure 5.4: Poisson Cluster Analysis of Gonorrhea/HIV Co-Infections in Michigan Males from 2011 to 2013 Detroit and Tri-County Area



Poisson cluster analysis, zoomed into to focus on Cluster 1-3 which are mainly located in the Detroit and Tri-County area, as well as extending into Livingston, Washtenaw, and Monroe counties and represent areas of increased risk of gonorrhea/HIV infection. Clusters 4 and 5, located in Kalamazoo and Genesee counties respectively were not found to have statistically significant elevations in gonorrhea/HIV co-infections. A total of 700 HIV positive males with gonorrhea were able to be geocoded.

Chapter 6.

Conclusion

6.1 Age at HIV Positive Diagnosis

The co-infection between *N. gonorrheae* and HIV may cause these two diseases to express variant epidemiological patterns and therefore warrants further evaluation. Prevention efforts for gonorrhea including education, screening, and treatment are well established yet not necessarily easily implemented. In this dissertation, age at HIV diagnosis, age at AIDS, time from HIV to AIDS, the geospatial patterns, and the change in biological markers were investigated in Michigan males with and without a history of gonorrhea.

A synergistic relationship between *N. gonorrheae* and age at HIV diagnosis was observed. The study found that when looking at individuals with a reported history of gonorrhea between 2005 and 2011 had a lower age at HIV diagnosis than males with no reported history of gonorrhea, 29.1 years old (in the adjusted model) compared to 36.3 years old in those with no *N. gonorrheae* infection. This represents a possible opportunity to intervene and attempt to prevent HIV by reaching out to males with *N. gonorrheae* infections in populations. Tracking *N. gonorrheae* reported infections may lead to a window of opportunity for identifying males in high risk sexual networks before they are exposed to HIV and become infected. *N. gonorrheae* infection is a useful marker for risky sexual behaviors for various reasons including the short incubation time (2-7 days in males (2)) as well as well-known symptoms including dysuria and discharge of pus from the urethra (2).

The study also found that when looking at an individual's complete reported *N. gonorrheae* infection history between 2005 and 2011 there was a dose response with regard to number of *N.*

gonorrheae infection in the time period and reduction of age at HIV diagnosis. This finding was important for several reasons. These findings again show that a useful addition to the techniques used in HIV surveillance may be the identification of other STDs including bacterial infection as markers for high risk groups. The dose response also shows that reducing the number if infections as well as interrupting the infection of treated individuals by members of their sexual network is important in not only controlling the burden of disease cause by gonorrhea but also HIV as the more *N. gonorrheae* infections an individual has the younger they are when they are diagnosed with HIV. Individuals with only one reported *N. gonorrheae* infection were found to have a mean reduction in age of HIV diagnosis of 5.1 years (31.1 years old 95% CI 29.3-33) in the adjusted model as compared to males with no reported history of *N. gonorrheae* infection (36.2 years old), and age at HIV diagnosis was reduced by 10.9 years (25.3 years old 95% CI 20.6-30.0) in those with a reported history of 5 or more *N. gonorrheae* infections between 2005 and 2011. These findings are important because they show that intervening early in someone's STD history, at someone's first *N. gonorrheae* infection as opposed to their fifth would may help in increasing the age at when they may be diagnosed with HIV by almost 5 years. The study also found that 37% (N=330) of those with gonorrhea between 2005 and 2011 had more than one occurrence of the infection. This represents a key group to intervene and provide prevention strategies to help to reduce re-infection rates.

The study also modeled pre-HIV only gonorrhea and the age at HIV diagnosis and found a similar trend as compared to looking at any *N. gonorrheae* infection regardless of their state of HIV. In those with no history of any *N. gonorrheae* infection (neither pre or post HIV infection) the mean age at HIV diagnosis was 36.2 years old (in the adjusted model) and in those with only one pre-HIV *N. gonorrheae* infection there was a reduction of 6.4 years (29.8 95% CI 28.2-31.4)

and in those with 2 or more pre-HIV *N. gonorrheae* infections the mean reduction in age at HIV diagnosis was 9 years (26.2 years old 95% CI 24.7-29.6). This along with the two previous analysis show that intervening in areas with *N. gonorrheae* outbreaks, or the STD is common help aid in reducing the burden of disease due to HIV in those communities. These pre-HIV infections represent real opportunities to intervene when individuals come in with their first infection. Education and HIV prevention services should target at risk males defined as those males with their first *N. gonorrheae* infection, or even their first reported STD infection.

6.2 Time to HIV Progression Event

Very few deaths in HIV positive males with a history of *N. gonorrheae* between 2005 and 2011 were observed in the State of Michigan. In individuals with no history of *N. gonorrheae* infection the median age at death was 41 years old and the median time from HIV diagnosis to death was observed to be 3 years. In individuals with a *N. gonorrheae* infection the median age at death was observed to be 38.5 years, 2.5 years younger, however the median time from HIV diagnosis to death was observed to be 5 years, 2 years longer than those with no history of *N. gonorrheae* infection. This paradox, younger at age of event with longer time to event from HIV diagnosis was observed in time to AIDS as well and may be related to the findings in the laboratory markers of HIV progression where information on CD4 cell count, viral load, and ever being on ARV treatment were analyzed. Results from that analysis showed that while only around 8% of individuals reported that they ever were on ARV treatment, over 70% were observed to start ARV treatment in the same year or after their infection with *N. gonorrheae*. This may have led to the increase in the time from HIV infection to HIV progression event; however, more research is needed to understand the rate of ARV usage, length of ARV

treatment, variances in ARV cocktails on laboratory markers of HIV progression and any barriers to ARV and medical access Michigan HIV positive males may face.

Age at AIDS positive status as well as time from HIV to AIDS was also analyzed in this study. The study found when looking at any reported history of *N. gonorrheae* infection that individuals with no *N. gonorrheae* infection had a median age of AIDS positive status of 38 years old, with a median time from HIV to AIDS of less than 1 year. In individuals with any history of *N. gonorrheae* infection between 2005 and 2011 the median age at AIDS positive status was observed to be 31 years old (HR=1.17 95% CI 1.06-1.30) with a median time from HIV to AIDS positive status of 1 year (HR_{adj}=0.63 95% CI 0.57-0.70). A dose response similar to that found in age of HIV diagnosis was also observed in individuals with multiple *N. gonorrheae* infection. The median age of AIDS positive status in individuals with only one *N. gonorrheae* infection was 32 years old while the median age of AIDS positive status in individuals with 5 or more *N. gonorrheae* infections was 24 years old. HR=1.01 (95% CI 0.89-1.15) for one *N. gonorrheae* infection as compared to those with no gonorrhea and HR=2.47 (95% CI 1.54-3.97) in those with 5 or more *N. gonorrheae* infections. A minor inverse dose response was found when looking at time from HIV diagnosis to AIDS positive status. Those with only one infection had a median time from HIV to AIDS of 1 year and those with 5 or more infections had a median time of 2 years. The adjusted HR also showed a minor inverse dose response with one *N. gonorrheae* infection HR_{adj}=0.60 (95% CI 0.53-0.68) as compared to those with no *N. gonorrheae* infection history and HR_{adj}=0.58 (95% CI 0.36-0.94) in those with 5 or more *N. gonorrheae* infections. While the biological markers of HIV progression may help to understand these paradoxical findings, more complete data on medical history is needed to fully understand the increase in time from HIV to AIDS and death.

The study also modeled post-HIV *N. gonorrheae* infections and age at AIDS positive status as well as the time from HIV diagnosis to AIDS positive status. In individuals who had a *N. gonorrheae* infection, but did not have a post-HIV *N. gonorrheae* infection the median age at AIDS positive status was 29 years old (HR=0.95 95% CI 0.77-1.17) as compared to 38 years old in those with no *N. gonorrheae* infection history showing that post-HIV gonorrhea may have a more significant impact on HIV progression than pre-HIV infections. In those with only one post-HIV *N. gonorrheae* infection the median age of AIDS positive status was 32 years old (HR=1.10 95% CI 0.95-1.27). In those with two post-HIV *N. gonorrheae* infections the median age of AIDS positive status was 30.5 years (HR=1.55 95% CI 1.22-1.97) and in those with three or more post-HIV *N. gonorrheae* infection the median age was 26 years old (HR=2.06 95% CI 1.51-2.79). Again a seemingly paradoxical finding with regard to time from HIV to AIDS was observed with 1-2 post-HIV *N. gonorrheae* infections having a time from HIV to AIDS of 2 years as opposed to less than one year in those with no post or no history of reported *N. gonorrheae* infections and 3 years in those with 3 or more post-HIV *N. gonorrheae* infections. Such observations may be attributed, in part, to: i) the fact that individuals with gonorrhea are frequently treated with antimicrobials that can delay or slow the impact of infections that are commonly end fatally in AIDS patients and ii) infection with N. gonorrheae may elicit a type immune response that can slow the progression of the HIV infection. Additionally, as stated previously this may be driven by what is happening with the laboratory markers for HIV progression as well as by the finding that in those that reported being on ARV, 71% started within the same calendar year or in the years after their *N. gonorrheae* infection.

6.3 County Level Geospatial Analysis

A chloropleth map of HIV rate per 100,000 in Michigan males age 0-65 was constructed and showed that the areas with the highest rate per 100,000 in Michigan were Detroit as well as the Tri-County area and a select handful of counties such as Genesee, Ingham, and Kalamazoo. This map is important because it gives us a basis for the underlying distribution of HIV in the State of Michigan males. The study was then able to map the number of *N. gonorrheae* infections per county and show the underlying distribution of *N. gonorrheae* in HIV infected males. Again Detroit and the Tri-County area have the highest number of *N. gonorrheae* infections. While these two maps are very useful they do not show the complete picture of HIV/*N. gonorrheae* co-infections in Michigan males.

A map of gonorrhea per 1,000 in HIV positive males was also constructed to see if counties that had a high rate of HIV per 100,000 as well as elevated number of *N. gonorrheae* infections also had high rates of *N. gonorrheae* infections in HIV positive males. The study found that while Detroit and the Tri-County area had high rates, such as Oakland that had one of the highest, other counties with low HIV rates and fewer over all *N. gonorrheae* infections the rate of *N. gonorrheae* in HIV males was elevated. This map shows that while overall numbers may be low, in some counties there is a high rate of co-infected individuals which is an area of concern, as well as possible opportunities for education and intervention. The study was also able to map the percent of HIV/*N. gonorrheae* co-infected individuals with multiple *N. gonorrheae* infections in the State of Michigan. This map presents an opportunity to investigate which counties may need to focus on partner therapy to reduce the burden of disease on individuals how have had multiple *N. gonorrheae* infections within the study period of 2005 to 2011. While Detroit and the Tri-County area have mid to high levels of repeated infections smaller counties like Calhoun, Van Buren, and Lapeer have a higher percentage of individuals that may be at risk for re-occurring

infections. A similar map looking at percent of HIV positive males with a history of multiple *N. gonorrheae* infections was also created. This showed similar results to that of the percent of HIV/*N. gonorrheae* co-infected individuals with multiple *N. gonorrheae* infections. Counties like Gratiot and Clinton have the highest percent of HIV men with multiple *N. gonorrheae* infections, and Detroit and the Tri-County area also have mid to high rates. These maps show that while Detroit and the Tri-County area is an important area to focus on treatment and prevention, other counties may also have problems and need to evaluate how to control and prevent males from having re-occurring infections.

Both Poisson high only cluster analysis of HIV as well as the high only cluster analysis of HIV/*N. gonorrheae* co-infections show that only Detroit had an increase in relative risk, RR=10.26 and RR=12.66 respectively, as well as being the most likely cluster. A second method of cluster or "hot spot" analysis, Getis-Ord GiZ scoring, showed that there are two distinct "hot spots" in the state with regard to HIV/*N. gonorrheae* co-infections. Getis-Ord analysis detected a cluster group of Detroit, Wayne, Macomb, Oakland, Lapeer and St. Clair as well as a separate cluster representing a group of counties near Gratiot, Clinton and Shiawassee counties. The Getis-Ord analysis offers a different way to detect clusters that uses the surrounding neighbors as reference points to detect "hot spots".

The third and final cluster analysis that was used was the Bernoulli high only cluster analysis. In the Bernoulli high only analysis three distinct high RR clusters were detected. Both the previous clusters of Oakland and the cluster of Detroit, Huron, Macomb, Sanilac and Lapeer counties were found to be statistically significant and together present one of the "hot spots" detected by the Getis-Ord approach. The third cluster detected using Bernoulli high only consisted of Gratiot

and Clinton counties, similar to the second Getis-Ord “hot-spot”, but was not found to be statistically significant.

Geospatial analysis of disease distribution and detection of disease clusters is an important tool in understanding the underlying distribution and proliferation of the disease in a given community. This study was able to show that there is not uniform co-infection of HIV individuals with *N. gonorrheae*, and offers some insight into where education and prevention programs should be aimed to gain the most benefit. Using this data it is clear that Detroit and the Tri-County area are the “hot spots” for HIV/*N. gonorrheae* co-infections, but as the other maps show, such as the Getis-Ord and Bernoulli maps, there are other counties and areas where while the overall number of individuals may not be as high as a place like Detroit, there is still an important population that is co-infected and needs to be addressed.

The previous findings from age at HIV diagnosis and age at AIDS positive status show that in male with a history of *N. gonorrheae* the age of HIV and eventually AIDS is reduced as compared to individuals who remain *N. gonorrheae* free. These maps offer important insight into where *N. gonorrheae* interventions should be placed to reduce the number of HIV infected males with gonorrhea, as well as where these individuals are more likely to have multiple infections thus increasing their hazard for HIV and AIDS.

6.4 Zip Code Level Geospatial Analysis

In order to better determine where education and prevention services should be targeted the study was also able to do geospatial analysis at the zip code level using a separate population of HIV positive males who had a *N. gonorrheae* infection between 2011 and 2013. Population level data on the zip codes were adjusted for a male only population and for an age range of 0-65 years old

using the 2008-2012 American Community Survey 5-year Estimates from the US Census. Two cluster detection techniques were used, Getis-Ord and Poisson. The Getis-Ord GiZ Score analysis found two "hot spots" one being the City of Detroit and some of the zip codes that bordered the Northern edge of the city and extended into Oakland and Macomb counties and a separate distinct "hot spot" located in the center of Oakland County. These findings matched up well with the previous Getis-Ord county findings, but were able to identify at the zip code level where in a county like Oakland the burden of disease due to HIV/*N. gonorrheae* co-infections is located. The Poisson analysis found 5 distinct clusters with the most likely cluster being the City of Detroit and the Northern zip codes, closely approximating what was found using the Getis-Ord approach. A second cluster was also detected that consisted of Wayne and Monroe county zip codes and was found to have a statistically significant increase in RR. A third cluster which included Oakland, Livingston, and Washtenaw counties was also identified and had a statistically significant increase in relative risk. Two other clusters, which included zip codes in Kalamazoo County and Genesee County had an increase in relative risk, but were not found to be statistically significant. Zip code level analysis allowed for better detection of possible clusters as well as visually represented the reduction in HIV/*N. gonorrheae* co-infection as the distance from Detroit increases. Working at the zip code level will allow for epidemiologists and public health officials to better target at risk areas with prevention and education strategies.

6.5 Biological Markers

CD4 cell count was found to increase in the year of *N. gonorrheae* infection as well as remain higher than pre-gonorrhea states in the years after. A rise in CD4 cell count in HIV positive males during the year that coincided with *N. gonorrheae* infection would most likely be due to the CD4 cell response of a bacterial STD. CD4 remaining elevated from pre-gonorrheal state

may be due to a number of factors including re-entry into public health/access to health care as well as starting ARV therapy. The study found that among the 8% that reported ever being on ARV treatment, 71% started in the same year or after their *N. gonorrheae* infection. This finding may also help shed light on the seemingly paradoxical findings of increased time from HIV diagnosis to HIV progression event (AIDS or death) as seen in Chapter 3. This increase and lack of decrease in the years after may be an important factor in understanding the progression of the disease as well as how re-occurring reported infections, and thus re-occurring contact with public health or a health care provider may alter the natural history of HIV.

Viral load was also found to increase sharply in the year of a *N. gonorrheae* infection, but did not remain elevated in the years post. This again may be related to access to medical care or the initiation of ARV treatment post infection. This finding does however show that in the year during a *N. gonorrheae* infection there is increased viral load in an individual making them at a higher risk for transmitting the disease to others. This is an important finding because it shows there in HIV positive males; HIV is enhanced during the time period surrounding co-infection.

More research is needed and there is a need to run these types of models with either the date of onset of gonorrhea symptoms, or the date gonorrhea was confirmed and reported to gain a better understanding of the rise and fall of Laboratory markers such as CD4 cell count and HIV viral load in the time period leading up to *N. gonorrheae* infection, during treatment, and post infection. There is also a need to collect better data on ARV usage and when individuals start and end. Finally since ARV treatment relies on a cocktail of drugs, it is also important to know what series of drugs individuals are on to assess if there are variances in ARV treatment around co-infection periods.

6.6 Conclusions

This study showed that risky sexual behavior, as measured by reported gonorrhea, results in a reduction in the time an individual remains HIV free. The study also found that as number of *N. gonorrheae* infections in an individual increases so does their hazard of being diagnosed with HIV. The study also showed that this trend persisted when looking at pre-HIV gonorrhea, as well as when looking at age of death and AIDS positive status. A seemingly paradoxical finding of increased time from HIV diagnosis to HIV progression event was also observed. This finding along with the increase and lack of decrease in CD4 cell count in the laboratory markers analysis may represent possible unmeasured confounding most likely due to the lack of individuals reporting if they are or have been on ARV treatment. These findings could also be influenced by the re-entry into HIV care as represented by reporting of a *N. gonorrheae* infection. It should be noted that for time from HIV diagnosis to HIV progression event all time was measured as the year an event occurred and the difference in times was around 1 year. Using full dates, mm/dd/yyyy for this type of analysis in the future and calculating days instead of years, along with better information on ARV treatment status may help to better define this time window. The study also found that during the year of *N. gonorrheae* infection was recorded viral load increased representing a time period of increased risk for spreading the disease.

Finally the study was able to map out possible clusters and "hot spots" at the county and in a smaller population at the zip code level. These maps show that the major area of concern for HIV/*N. gonorrheae* co-infections in the state of Michigan in males from 2005-2013 is in the Detroit and Tri-County areas, with a few small (non -statistically clusters in other counties). These maps along with the information gained in the previous chapters allow for better placement of intervention efforts in high risk areas.

6.7 Limitations

Limitations of this study include only being able to gain access to data on gonorrhea. Bacterial STDs promote HIV in infecting white blood cells (1, 24, 27-29, 31) and other STDs that were not included could have had an influence on HIV seroconversion. Gonorrheal infection was used as a proxy for risky sexual behavior and a marker for individuals being in sexual networks where STDs were present. Because this study could not control for the effect of other STDs on age at HIV diagnosis, time from HIV to AIDS, age at AIDS, or changes in laboratory markers the resulting synergistic relationship is only the start of exploring HIV and STD co-infections. Another limitation of this study HIV diagnosis, AIDS positive status, *N. gonorrheae* infection and death were all only coded as year of event. In analysis such as time from HIV to HIV progression event using days or weeks may have been more appropriate. A final limitation regarding the non-spatial analysis sections is that HIV diagnosis is not a proxy for HIV infection, and other than HIV screening tests, there is little data to determine length of time an individual may be been incubating HIV and not aware of their infection status.

A major limitation in the geospatial analysis section is that locations represent where the individual was living and may not reflect where they were infected with either HIV or *N. gonorrheae*. While the study set 20 mile windows for cluster analysis individuals may travel much further distances and become infected out of their zip code of residency or even out of their county of residence. Another limitation is that a number of infections were diagnosed in the prison system, but this does not necessarily mean infection happened in prison, and therefore place of residence would have been an acceptable substitute for prison diagnosed. A final limitation of the geospatial analysis only a small subset of the data had zip code level data. While county level data is a great tool, the study was able to show that similarly to state level, co-

infections are not equally distributed across a county. Having more years of zip code level data may have been able to give a time series analysis of the trends in co-infections over the last decade or half decade.

N. gonorrheae and other STIs are reportable diseases, and resources should be given to studying their epidemiological patterns in co-infected individuals. Identification of possible risk factors that may allow for intervention are important tools in trying to prevent the spread not only of HIV but other STDs as well. Education and counseling efforts should be focused on those with their first STD as well as those who are HIV naïve and have multiple reported STD infections as a HIV prevention tool. Education and counseling has to walk the fine line between destigmatization of STDs (so individuals get tested and do not feel ashamed if they are positive) and warning individuals about the dangers of these diseases. As individuals within public health we must change the paradigm from "you just have gonorrhea", to the sexual behaviors that lead to you getting gonorrhea puts you at risk for HIV and other sexually transmitted diseases which may not be curable.

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