RISK FACTORS ASSOCIATED WITH GONORRHEAL INFECTION AMONG MALE HIV/AIDS POPULATION IN MICHIGAN

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ABSTRACT

RISK FACTORS ASSOCIATED WITH GONORRHEAL INFECTION AMONG MALE HIV/AIDS POPULATION IN MICHIGAN

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Infection of human immunodeficiency virus (HIV) continues to be a major global public health issue. Many individuals who are diagnosed with HIV are later diagnosed with other diseases, including *Neisseria gonorrhoeae* [NG], a bacterium that is transmissible from one person to another during vaginal, anal, and oral sex. A retrospective cohort study was conducted to investigate the risk factors associated with gonorrhea infection after HIV infection among the HIV-positive male population in Michigan. METHODS: Descriptive statistics were used to illustrate the differences between the gonorrhea-diagnosed case and non-diagnosed control populations. Results are presented using univariable, fully-parameterized multivariable and best-fit multivariable logistic regression models. RESULTS: Among the 10,721 HIV-positive individuals that were included in the study, 739 (6.9%) were diagnosed with gonorrhea at some point after their HIV diagnosis. HIV-positive males that were ever diagnosed with gonorrhea were six years younger at HIV diagnosis when compared to those where were never diagnosed with gonorrhea. Older age is positively associated with NG-positive diagnosis when compared to the age 20-24 reference category. Conversely, those in younger age groups had increased odds of having a NG-positive outcome. Individuals identifying themselves as white (OR=0.56, 95% CI [0.46, 0.68]) or Hispanic (OR=0.45, 95% CI [0.31, 0.7]) were less likely to be associated with a positive NG outcome when compared to a black reference group. DISCUSSION: HIV- and gonorrhea-infected individuals share similar risk factors. Public health programs must be expanded to reduce barriers for testing of sexually transmitted diseases.

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KEY TO SYMBOLS

AIDS – Acquired immunodeficiency syndrome

DNA – Deoxyribonucleic acid

HCW_RISK – Men who work in the health care industry

HIV – Human immunodeficiency virus

HIV+ – HIV-positive

IDU – Men who have ever used intravenous drugs

MSB – Men who have ever had sex with both men and women

MSF – Men who have ever had sex with women

MSM – Men who have ever had sex with men

NG – *Neisseria gonorrhoeae* (gonorrhea)

NG+ – Gonorrhea-positive case group

NONE – Men who have reported none of the risk factors

PID – Pelvic inflammatory disease

REF – Reference group

RNA – Ribonucleic acid

SEX_HEMO – Men who have ever had sex with a hemophiliac individual

SEX_HIV – Men who have ever had sex with a person who was infected with HIV

SEX_IDU – Men who have ever had sex with an intravenous drug user

SEX_TRANSFUSION – Men who have ever had sex with a person who has had a blood transfusion

STD – Sexually transmitted disease

CHAPTER 1
INTRODUCTION

Human immunodeficiency virus (HIV), having claimed more than 25 million lives worldwide over the past 30 years, continues to be a major global public health issue. In 2011, approximately 34 million people were living with HIV infection, the highest number of individuals living with HIV ever reported (World Health Organization [WHO], 2014). Due to the increased use of anti-retroviral therapies and other treatments, a significant number of people who are diagnosed with HIV are living longer lives, and therefore are more likely to be infected and subsequently die of other infectious diseases. Such co-infections include gonorrhea caused by *Neisseria gonorrhoeae* (NG), a bacterium that is transmissible from one person to another during vaginal, anal, and oral sex. While an HIV infection is not curable and therefore permanent, a gonorrheal infection can be cured by appropriate antimicrobials. However, those who are infected with NG do not exhibit long-lasting immunity and thus NG infection may occur multiple times over the lifetime of an individual. NG infection can spread to the blood or joints and can be life-threatening if left untreated or if the infected individual is immunocompromised. Thus, it is important to investigate how gonorrheal infection among the HIV-infected population may be influenced by exposure- and demographic-related factors, which could lead to future clinical and public health interventions. We hypothesize that various demographic and exposures may impact the frequency of gonorrhea infection among those already infected with HIV. The proposed study is designed to investigate the relationship between the incidence of gonorrheal infection, environmental exposure and demographic variables among the HIV-positive male population in Michigan.

CHAPTER 2
BACKGROUND

Human Immunodeficiency Virus (HIV)

The following is a description of human immunodeficiency virus (HIV), including the biological mechanisms of the virus, recent prevalence and incidence rates, factors associated with incidence of HIV infection, and current methods of prevention.

Biology. HIV is a round-shaped lentivirus (i.e. single-strand, positive-sense, enveloped ribonucleic acid (RNA) viruses) and a member of the family retroveridae (Weiss, 1993). HIV is considered a retrovirus given that its primary method of reproduction is via reverse transcription of RNA into double-helix deoxyribonucleic acid (DNA) that is transported to the nucleus, where it integrates into the host cell DNA. When the host cell DNA is replicated, viral DNA is replicated, transcribed, and translated (NIH, 2008).

HIV infection reduces the number and function of many system cells, most frequently and specifically infecting the "helper" T-cell subgroup of lymphocytes. T cells once matured may express the surface protein CD4 and thus become CD4+ T cells. These mature cells are considered "helper cells" given that they aid other cell types through a combination of cell-to-cell interactions and through the use of humoral regulator cytokine proteins (Alberts et al., 2002; NIH, 2008).

Infection by the HIV virus impacts the frequency of CD4+ T cells in three ways. First, the HIV virus leads to the reduction in cell size, cell nucleus fragmentation, chromatin condensation and chromosomal DNA fragmentation, in process known as apoptosis. In addition to apoptosis, HIV may directly kill other cells via lysis. Finally, HIV may reduce the number of CD4+ T cells by inhibiting production of CD4 needed for maturation and function of CD8 cells (Garg, Mohl, & Joshi, 2012).

HIV is comprised of two pathogenic strains, delineated HIV-1 and HIV-2, the latter of which is distinguished by its reduced virulence and longer clinical latency period. In addition to the two strains, both HIV-1 and HIV-2 strains are comprised of several strain groups (Romagnani, 1992; Sharp & Hahn, 2011). The most prevalent strain group combination is HIV-1 group 'M' (for major), the subtypes of which are believed to be associated with 90% of all HIV infections (Romagnani, 1992).

AIDS. Once many CD4+ T cells are destroyed, cell counts will be reduced in blood tests. When the CD4+ T count falls below 200 total per uL, or when the individual is diagnosed with co-occurring infection, the individual is diagnosed with acquired immunodeficiency syndrome (AIDS) (Centers for Disease Control and Prevention [CDC], 1992). The transition from HIV infection to AIDS occurs in three phases: the initial phase, which may last between 2-4 weeks and includes symptoms such as influenza- or mononucleosis-like symptoms; a phase of clinical latency, which may last anywhere between 3 years for untreated individuals and up to 20 years for treated or those who are untreated but considered long-term non-progressors (LTNP); and fully-matured AIDS, a period in which the individual is most susceptible to co-infection and will most commonly develop pneumocystis pneumonia, cachexia, esophageal candidiasis and respiratory tract infection as a result of co-infection (U.S. Department of Health and Human Services [HHS], 2013).

Prevalence and incidence of HIV infection. HIV infection is considered a pandemic. According to the Central Intelligence Agency (CIA) world factbook, approximately 34 million people worldwide were living with HIV in 2011. Although HIV is present on all continents, the African continent continues to have the highest per capita rate of HIV infection, including the countries with the highest rates of Uganda (7.2% of population), Kenya (6.2%), Tanzania

(5.6%), and Gabon (5%). The countries with the highest total infected individuals were South Africa (N=5.6 million) and Nigeria (N=3.3 million). India is the third-highest population of HIV-infected individuals (N=2.4 million) (CIA, 2011).

In the United States, an estimated 1,148,200 persons aged 13 and older were living with HIV as of 2009. This includes an estimated 207,600 (18.1%) persons who are likely infected but whose infections had not been diagnosed (CDC, 2012a). Approximately 50,000 people in the United States are newly infected with HIV each year. In 2010, there were an estimated 47,500 new HIV infections (CDC, 2012b). HIV infection is most prevalent in the states of California (N=5,973 new infections in 2011), Florida (N=5,403), Texas (N=5,065), and New York (N=4,560) (CDC, 2013).

Mortality and recent trends. Worldwide, HIV infection has claimed more than 25 million lives over the past 30 years (CDC, 2013). In 2010, approximately 1.8 million people died from complications due to HIV infection which led to AIDS–associated infections with several microbial agents. However, mortality rates trended downward in 2011 to approximately 1.7 million deaths, due in large part to prevention and effective treatment techniques including Highly Active Anti-Retroviral Treatments (HAART) (WHO, 2014).

Factors associated with exposure. HIV is a blood-borne disease. As such, it may be spread through both intravenous methods (e.g. intravenous drug use and blood transfer) as well as through sexual transmission (CDC, 2012a). The strongest predicting factor for acquiring HIV is men who have reported that they have had sex with men (MSM). In a 2010 U.S. study, young MSM accounted for more than 70% of HIV incidence among all individuals aged 13 to 24, and 30% of new infections among all MSMs. At the end of 2010, 56% of persons living with an HIV diagnosis in the U.S. were MSM (N=489,121). HIV infected MSM individuals are

predominantly white. As of 2011, 47% percent of MSM living with an HIV diagnosis were white, 31% were black/African American, and 19% were Hispanic/Latino in the United States (CDC, 2012b).

Intravenous drug use (IDU) is the second leading risk category among HIV cases in developed countries. In a 2011 survey, an estimated 2,220 males that were infected with HIV reported injection drug use out of 49,273 total infections for the year. While this represents roughly 10% of the total of MSM subjects, it is a well-represented associated factor. In 2011, among 216,966 female subjects infected with stage 3 AIDS, over 25% of the incidence was attributed to IDU compared to 13% of males (CDC, 2012b).

Demographics. HIV is also prevalent in African American individuals. In 2009, African Americans accounted for an estimated 44% of HIV incidence despite accounting for only 14% of the US population. HIV is most prevalent in black men, which constituted 70% of the total black infected US population and 30.8% of all US HIV incidence. In a 2009 study of US men, an African American individual was more than 8 times more likely to be diagnosed with HIV compared to a white individual within the same age group. If this trend continues, it would mean that at any point in their lifetime an estimated 1 in 16 black men and 1 in 32 black women will be diagnosed with HIV infection (CDC, 2013).

The increase in prevalence compared to whites can be attributed mainly to the lower socioeconomic status among black men and women, which contributes to reduced access to quality care and education concerning HIV and increased stigma for infection with the disease (CDC, 2013). Alcohol use and smoking are not associated with the incidence of HIV when controlled for other socioeconomic factors. Indeed, this is true even when controlling for race. In a 2008 study, an individual living below the economic threshold for poverty was 2 times more

likely to be infected with HIV when compared with those above the threshold (OR=2.1, CI=[1.3,3.2]) (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2008).

Prevention and treatment. The use of latex condoms is a highly effective method of preventing HIV infection. A condom that is used correctly effectively creates a nearly impermeable barrier, interrupting the contact between the blood, anal, urethral or vaginal secretion and mucosal surfaces. According to a 2001 report by the National Institutes of Health (NIH), the use of latex condoms consistently reduces the rate of HIV transmission by 85% when compared to no condom use. This equates to a seroconversion rate of 0.9 conversions per 100-person years, compared to 6.7 seroconversion rate per 100 person-years for those who do not use condoms (NIH, 2008). Other studies found similar rates of seroconversion rates for both condom and non-condom users (Davis & Weller, 1999).

The progression of HIV to AIDS may be slowed by the use of HAART. In a 2011 study of 1763 African couples, wherein one was infected with HIV and the other was HIV-free, only 1 subject in the early-intervention HAART group was found to be infected with HIV versus 28 new subjects in the control group (Cohen et al., 2011).

Neisseria Gonorrhoeae

The following is a description of *Neisseria gonorrhoeae,* including a description of its biological mechanisms, recent prevalence and incidence rates of gonorrheal infection, factors associated with incidence of gonorrheal infection, and current methods of preventing the infection.

Biology. *Neisseria gonorrhoeae* [NG] is a bean-shaped bacterium that is the necessary and sufficient cause of gonorrheal infection in the human host. NG is a fastidious bacterium given that it has a complex nutritional requirement that is necessary for survival and replication. NG are facultative anaerobic organisms, meaning that they can grow in the presence or absence

of oxygen. NG bacteria typically grow in pairs as diplococci. NG are considered motile bacteria, meaning that the bacteria are able to use hair-like pili for motility. In this case, the bacteria use type IV pili for motility by adhering to vascular surfaces. This would typically mean that the pili adhere to, and pull against, vascular tissue (i.e. noncilliated epithelial cells) and other cellular objects in the blood stream (Mattick, 2002).

NG may replicate using one of two methods. First, NG may duplicate using DNA replication methods. Throughout the life cycle of the bacterium, each organism replicates in a process similar to cellular division. Second, NG may use bacterial conjugation methods to duplicate, wherein the bacteria may transfer genetic material in the form of cellular plasmid between bacterial cells by cell-to-cell contact. Using this method, both cells build a bridge-like connection using F-plasmid episome protein and transfer genetic material in a process that takes approximately 100 minutes to complete (Holmes & Jobling, 1996).

NG is characterized by its ability to escape an immune response by "masking" its surface structure by the use of antigenic variation, wherein NG is able to create a variety of antibody binding sites. Other virulence factors include pili, opacity and porin surface proteins (Stern, Brown, Nickel, & Meyer, 1986). Additionally, the body is also unable to produce "memory" cells, making it difficult for the human immune system to defend against the bacteria. This means that the human body may be infected multiple times by the same species and strain (Cahoon & Seifert, 2011).

While there are 11 species of Neisseria bacteria, only two, *N. gonorrhoeae* [NG] and *N. Meningitidis*, are considered pathogens harmful to the human body. NG bacteria release outer membrane fragments, dubbed "blebs", during its typical process of cellular growth. Blebs contain lipooligosaccharide (LOS) capsules, basal oligosaccharide lipid structures without

repeating O-antigen subunits. LOS, combined with *IgA* protease, an enzyme responsible for breaking down the proteins in nearby biologic matter, are important components of its pathogenicity (Todar, 2008-2012).

Like HIV, gonorrhea is a sexually transmitted infection (STI). As such, gonorrhea may be spread via vaginal, oral and anal sexual activities. Approximately 10% of males and 80% of females are asymptomatic. For those who present symptoms, such symptoms include pus-like discharge from genitalia, which may be foul smelling. Additionally, both sexes may experience inflammation redness, swelling, and dysuria. More serious symptoms may also include pharyngitis, conjunctivitis, proctitis, urethritis, prostatitis, and orchitis. In women, untreated genital gonorrheal infections may result in Pelvic Inflammatory Disease (PID), the result of which could be infertility. Nearly 15% of women with PID as a result of gonorrhea infection may become infertile due to the infection (American College of Obstetricians and Gynecologists [ACOG], 1999).

Prevalence and incidence of gonorrhea infection. Globally, it is estimated that the incidence of gonorrhea is 62 million infected people annually (WHO, 2014). In a 2001 WHO report, the area of highest incidence worldwide was determined to be South and Southeast Asia, which is estimated to have had 29.11 million incident cases in 1999. This is followed by Sub-Saharan Africa (N=15.67 million), and Latin America and Caribbean areas (N=7.12 million). This may be due in large part to the challenges in determining and preventing the disease in these regions, given that the diagnosis of NG typically needs equipment more sophisticated than that which is typically available in these regions. In the report, world regional rates were evenly distributed between sexes (WHO, 2001).

Gonorrhea is the second most commonly reported sexually transmitted disease (STD) in the United States, second only to human papillomavirus (HPV). In a CDC report of gonorrheal infection in the US, a total of 321,849 cases of gonorrhea were reported for 2011, yielding a rate of 104.2 cases per 100,000 in the US population (CDC, 2012c). Rates varied widely by state: rates per 100,000 ranged from 7.7 in Vermont to 202.3 in Louisiana. The five states with the highest incidence rates were Louisiana (202.3 per 100,000), Mississippi (195.9), Alabama (191.1), North Carolina (183), and South Carolina (180.5). In 2011, the Southern region of the US was determined to have the highest rate of gonorrheal infection (135.5 cases per 100,000 population), followed by the Midwest (111.2), Northeast (85.8), and West (62.2) (CDC, 2012c).

Factors associated with exposure. Gonorrhea is a blood-borne STD, similar to HIV. As such, it is possible that it may be spread through both intravenous methods (e.g. intravenous drug use and blood transfer), although it is more frequently transmitted via sexual activity, including vaginal, oral and anal sex (CDC, 2012c). Aside from demographic associated factors, the exposure central to the incidence of gonorrhea is the rate and method of sexual activity. In a 1998 study that distinguished sexual activity frequency among women in the US population, gonorrhea morbidity rates for consistently sexually active women were 123% higher when compared to crude rates for women who were sexually experienced but not currently active among the same age groups (Aral et al., 1999).

A recent study showed that, although injection drug use was associated with infection of Chlamydia it was not associated with gonorrhea infection. Although there is a difference in incidence rates between Chlamydia and gonorrhea within injection drug users, the biological mechanics that can be attributed to the difference in frequency is not yet known (Creighton, Tenant-Flowers, Taylor, Miller, & Low, 2003).

Demographics. Gonorrhea infection is more frequently found in women than in men. In a 2011 report of US gonorrhea incidence, 108.9 females per 100,000 were determined to be infected versus 98.7 per 100,000 males. While it is true that female infections are more prevalent, the incidence of gonorrhea is increasing faster in men than in women (3.1% and 5.1%, respectively.) Additionally, infected males aged 30 and over outnumber infected females in the same age group. However, US infections were most prevalent under 30 years of age. Overall, persons aged 15-44 years accounted for 94.6% of US reported gonorrhea cases (CDC, 2012c). In addition to associations in sex and age, gonorrhea has been shown to be associated with socioeconomic factors related to unprotected sexual activity and lack of adequate prevention and treatment techniques. Such socio-demographic factors include race/ethnicity, education, income, and proximity to metropolitan areas. Gonorrhea rates were highest among blacks (427.3 per 100,000), the rate of which was determined to be 17 times the rate of infection among whites (25.2 per 100,000). This was also true among those that identified themselves as American Indian/Alaskan Native and of Hispanic ethnicity (115.7 and 53.8 per 100,000, respectively) (CDC, 2012c).

Mortality and recent trends. Gonorrhea is not considered to be a life-threatening disease in adults. Thus, the risk of mortality is mainly due to complications incident during pregnancy, including ectopic pregnancies and stillbirths as a result of gonorrhea-related pelvic inflammatory disease (PID). In 1999, 108 U.S. reported deaths occurred due to PID, although it is unclear how many were caused by NG infection (ACOG, 1999). Worldwide mortality rates due to gonorrhea-related PID are unknown.

While the US experienced its lowest incidence rate on record in 2009 (98.1 cases per 100,000), incidence rates have increased between 2009 and 2011. In the between 2010 and 2011,

US gonorrhea rates increased across racial groups, including whites (7.7% increase), American Indians/Alaska Natives (7.7%), Asian/Pacific Islanders (4.9%), and Blacks (0.3%). This is also true for those who had identified themselves as Hispanic ethnicity across race groups (12.3%). The US geographic region with the greatest increase during this period was the US Northeast (10.9% increase), followed by 6.5% in the west, 2.7% in the Midwest, and 2.1% in the Southern US. While most age groups experienced an increase, the most pronounced increase was a 6.9% increase among those aged 30-34 years. The gonorrhea rate decreased among those aged 15-19 years during the 2010-2011 period, which experienced a 0.1% decline (CDC, 2012c).

Prevention and treatment. Similar to HIV, the secondary method of preventing gonorrheal infection (after abstinence) is through the use of latex prophylactics such as latex condoms. Because latex creates a near impermeable layer, gonorrheal infection rates drop to near zero when latex condoms are used (CDC, 2014).

Recently, vaccines have been developed that could be used to prevent gonorrheal infection. Such vaccines that have been shown to be efficacious by affecting the type IV motor pili function of the bacteria. As of this writing, no such vaccines have met FDA requirements for broad use in humans (Liu, Egilmez, & Russell, 2013; Schoolnik, Tai, & Gotschilich, 1983).

In terms of social programs aimed at prevention, much of the decline in the 2009 period can be attributed to the national gonorrhea control program. After the initiation of the program in 1972, the national gonorrhea rate declined 74%. Currently, the challenge for such programs is the development of resistance to antibiotics and social and cultural change in clinical research and prevention methods (Fleming & Wasserheit, 1999).

Gonorrhea, having been treated with antibiotics for the last 70 years, is considered a curable disease. For those who have symptoms, a clinic bacteria isolation test may be conducted

using culture in Thayer-Martin or other chocolate agar with carbon dioxide or similar culture method. Recently, non-culture methods, including real-time PCR, have been used to quickly and effectively determine the species of infection. Although PCR methods have been determined to be cost-effective over the long term in rapid diagnosis of other STIs, culture methods continue to be used in many clinics due to the reduced initial expense of such methods (Scherer et al., 2009).

Once it is determined that the patient is infected with gonococcal bacteria, patients are treated using antibiotics. Historically, oral penicillin-based antibiotic treatments such as amoxicillin and tetracycline have been used. However, an increasing problem in gonorrhea infection treatment has been the evolutionary development of antimicrobial resistance. Due to this, many penicillins, tetracyclines, and macrolides are limited in their utility in treating recent infections. Only very few treatments, including third-generation cephalosporins, most notably ceftriaxone, have retained their efficacy in treating the disease. Antimicrobial resistance in gonorrhea may be attributed to the over-prescribing and over-reliance on antibiotic treatments as a disease control measure, high disease rates and poor control of antibiotic prescribed usage (Tapsall, 2005).

HIV and Gonorrhea Co-infection Synergy

There is evidence that HIV and gonorrhea may have synergistic qualities in individuals who are co-infected. Specifically, individuals who are infected with gonorrhea may be particularly susceptible to infectious bacteria. This is because genital ulcers caused by other infectious diseases such as syphilis, herpes, or chancroid may break the skin and create a portal of entry for HIV. Additionally, non-ulcer producing infections such as gonorrhea and chlamydia increase the concentration of cells in genital secretions that serve as target for HIV, such as CD4+ T cells. It is because of this added concentration of CD4+ T cells in genital secretions that

may also cause increased susceptibility among those that are infected (Fleming & Wasserheit, 1999). A research study has shown that the median concentration of HIV in semen may be 10 times higher in men who are infected with both HIV and gonorrhea when compared to HIV-only infected males. This increases the likelihood considerably that the infected individual's sex partner will be infected with HIV (Wasserheit, 1992).

CHAPTER 3
STUDY HYPOTHESIS, AIMS, AND OBJECTIVES

In this study, I hypothesize that various demographic and exposure risk factors may impact the frequency of gonorrhea infection among those already infected with HIV. The study is designed to investigate the relationship between the incidence of gonorrheal infection, sexual activity risk factor, other exposures (e.g. intravenous drug use, health care work, etc.) and demographic variables among the Michigan HIV-positive male population.

Specifically, the study aims are the following:

1. Describe the demographics and risk factors of the MI population of HIV-positive males within the study period (2005-2012)
2. Use quantitative methods to compare demographic, sexual activity, and other exposure risk factors of those who have been diagnosed with gonorrhea with those who have never been diagnosed with gonorrhea within the HIV-positive male population in Michigan
3. Describe potential public health solutions based on the results of the comparison of gonorrhea vs. non-gonorrhea demographics and risk-factors

The study methodology is designed to explore the study objectives and is as follows:

CHAPTER 4
METHODS

Study Population

The study population consists of 10,721 males living within the state of Michigan and diagnosed with HIV between 1988 and 2012. All subjects included in the study were aged 16-65 at the time of HIV diagnosis and were alive during the 2005-2012 study period.

Data Collection and Linkage

HIV and gonorrhea are reportable infections. As such, they are tracked by the state of Michigan. Once diagnosed with either HIV or NG, patients are asked to be interviewed to collect required information (e.g. personally identifiable information (PII)) and optional information (e.g. sexual activity, intravenous illicit drug use, etc.). All HIV information is reported using the Michigan Adult HIV-AIDS Confidential Case Report Form or the gonorrhea Case Investigation Report.

The information collected on both forms includes federally mandated data collection information regarding the dates of the infection and the address of the patient. The patient has the option of answering questions in the voluntary portion of both forms. The voluntary portion of the form includes other demographic information (e.g. race/ethnicity, education, employment, income, etc.) and history of co-infection, including gonorrhea, syphilis, and chlamydia data. HIV and NG infection data were linked using a temporary dataset of matched records. Matching was conducted at the Michigan Department of Community Health (MDCH) by using a deterministic-matching algorithm based on PII. Specifically, the first three letters of the patient's last name, the first two letters of the patient's first name, and the month, day, and year of birth were used to determine which subjects match between data sources.

The datasets are housed at, and obtained from, MDCH, specifically by the MDCH HIV Surveillance & Body Art Unit HIV/STD/VH/TV Epidemiology and the MDCH Bureau of Epidemiology. The linked HIV/NG dataset was obtained for analysis by Dr. A. Mahdi Saeed at the Michigan State University (MSU) Department of Epidemiology and Biostatistics.

Data Transfer and Preparation

HIV subject data were obtained for the study period from the enhanced HIV/AIDS Reporting System (eHARS), a system maintained by the HIV/STD/VH/TB Epidemiology Section. Gonorrhea infection data were obtained using the Michigan Disease Surveillance System (MDSS), a statewide communicable disease reporting system maintained by the Surveillance and Infectious Disease Epidemiology Section of MDCH. An employee of the HIV/STD Epidemiology section performed the record linkage to ensure confidentiality and privacy of the participants. HIV/AIDS cases were defined using the CDC 1993 revised classification system for HIV infection, wherein one is considered to have AIDS if the individual's CD4+ T-cell count falls below 200 total per uL (CDC, 1992). The outcome variable of 'co-infection' was coded as a dichotomous variable, wherein any presence of gonorrhea infection was coded to 'co-infected' = 1 and 'not co-infected' = 0 (ANY_GC). An HIV/AIDS subject was categorized as co-infected if the subject had been diagnosed with gonorrhea at or after HIV diagnosis.

All risk variables (e.g. IDU, MSM, etc.) were dichotomized by combining an explicit "Yes" answer in a true category and all explicit "No" answers and missing values in a False category. The Michigan County of Residence variable was grouped into 6 groupings: Upper Peninsula, Upper Michigan, West Michigan, Mid-Michigan, Southeast Michigan (Non-Detroit),

Thumb, Detroit City, and Unknown/Missing. The age of each subject was calculated by subtracting the birth year of the subject from the year of HIV diagnosis.

Case Definition

Subjects were considered cases for the purpose of this study if they were diagnosed with NG infection any time between 2005 and 2012. All cases must also be diagnosed with NG infection at least once after HIV-positive diagnosis.

Human Subjects Protection

Study datasets were de-identified according to Health Information Portability and Accountability Act (HIPAA) guidelines on public health information. Specifically, names, addresses, geo-location data, and other potentially identifying data were removed from the dataset prior to transfer from MDCH to MSU. Only authorized personnel were able to see any identifiable information from subjects, and only on an as-needed basis. No participants were interviewed or contacted for the study.

Statistical Analysis

Statistical analysis was performed using SAS v9.3 (SAS Institute Inc., Cary, North Carolina).

Descriptive analysis was conducted. Distribution and proportion of variables were reported using the frequency procedure in SAS (PROC FREQ). SAS Output Delivery System (ODS) function was used for table union and formatting.

Logistic regression analysis was conducted for the event of the outcome variable ANY_GON, according to the logistic model as displayed in the following equation:

$$\pi(x) = \frac{e^{\beta_0+\beta_1 x}}{e^{\beta_0+\beta_1 x}+1} = \frac{1}{1+e^{-(\beta_0+\beta_1 x)}}$$

where β represents the coefficient for each covariate. Univariable logistic models were estimated using a single covariate in the logistic model. Chi-square results including the point estimate odds ratios and 95% confidence intervals were reported for each covariate.

Multivariable analysis was conducted using SAS PROC LOGISTIC. Stepwise backward elimination methods were used, wherein a fully parameterized model is first used. At each stage of testing, the least statistically significant variable is eliminated from the model and the more-parsimonious model is executed anew. The best-fitting model was produced when all non-significant variables are eliminated, leading to a parsimonious model (wherein the -2 Log L statistic or SAS "score" statistic) is not appreciably improved by removing further covariates.

For the analysis of categorical variables as covariates, the most populous categorical group will be used as reference category unless otherwise noted. Goodness-of-fit of the selected model was assessed by the Hosmer-Lemeshow statistic, using the following equation:

$$\chi^2_{HL} = \sum_{g=1}^{G} \frac{(r_g - n_g \bar{\pi}_g)^2}{n_g \bar{\pi}_g (1 - \bar{\pi}_g)}$$

Where r_g = observed number of events in the *g*-th group, n_g = number of individuals in the *g*-th group, and $\bar{\pi}_g$ = average of the predicted probability of the event in the *g*-th group.

Under the null hypothesis that the adopted model is correct, χ^2_{HL} has a chi-square distribution with *p-q* degrees of freedom, where p and q are the number of covariates in the original and comparison model, respectively.

Stepwise Backward Elimination Technique

Stepwise technique was used to assess the most parsimonious model using the available covariates and ANY_GON outcome variable. Specifically, backward elimination techniques

will be used, wherein all covariates will be included in the model and are assessed for elimination from the parsimonious model.

The analysis will be conducted in a series of steps. To begin, all two-level interaction variables are included in the model. Starting with the least significant (i.e. highest p-value) covariate, the variable will be assessed for elimination by comparing the model with and without the covariate. To compare the two models, log likelihood (-2 Log L) statistical tests will be used. For each covariate removed from the model, models will be compared by creating a standard likelihood ratio (LR) test, wherein the difference between the two log-likelihood (-2 Log L) statistics is taken:

$$LR = (-2 \text{ Log } L)_p - (-2 \text{ Log } L)_q$$

The LR test will be conducted with p-q degrees of freedom (df) and be assessed at the alpha .05 level. If LR is significant at the alpha .05 level, the covariate will be removed from the model and the model will be re-assessed. If the LR statistical test is not significant at the .05 level, the variable will remain in the model and the next covariate with least significance (i.e. highest p-value) will be considered for removal. If an interaction variable is eliminated from the model, the interaction terms will be added individually to the model and the model will be executed with all remaining terms plus the individual covariate terms.

CHAPTER 5
RESULTS

10,721 males were diagnosed with HIV. Among the 10,721 individuals that were included in the study, 739 (6.9%) were diagnosed with gonorrhea at some point after their HIV diagnosis. Table 1 lists the frequency of each study classification and the distribution of subjects to each demographic and risk factor exposure variable. Figure 1 illustrates the proportional distribution of age between the NG+ case group and the entire HIV+ study population. Whereas the distribution of the entire male HIV+ population tended to be older than 35 (Median=36 years), the age distribution of HIV+ males that were ever NG+ tended to be younger (Median=30 years). 739 (97.8%) of the NG+ males had an unknown marital status and 10,705 (99.9%) of the subjects in the NG- control group were unknown, therefore marital status was removed from the study. Table 1 displays the frequency and proportions of race/ethnicity in the study population, and Figure 2 displays the proportions visually. While both the NG+ cases and NG- controls identified themselves more often as black, the overall population of HIV+ males was more distributed between black and other races when compared to NG+. Likewise, the NG+ group was more frequently reported in Detroit when compared to the overall HIV+ male population, and less disproportionately low in the West Michigan and Upper Michigan areas (Figure 3). Figure 4 illustrates the proportion of risk factors for NG+ and NG- groups. 81.1% of NG+ subjects had identified as MSM during their lifetime compared with 69.4% of the HIV-positive study population. Conversely, fewer NG+ males indicated that they had sex with females when compared to the overall HIV-positive study population (45.3% vs. 48.5%, respectively), or had used intravenous drugs (12.8% of the overall HIV+ population vs. 4.7% in the NG+ group).

The three-stage logistic regression analysis results are displayed in Table 2 and are graphically displayed in the forest plots in Figures 5 and 6. In both the fully parameterized

model and the best-fit model, all covariates were used to control for potential confounding effects in displayed results. All age groups were found to be statistically associated with NG infection. However, older age is protective against a NG-positive diagnosis when compared to the age 20-24 reference category. Conversely, those in younger age groups had increased odds of having a NG-positive outcome. Individuals identifying themselves as white (OR=0.56, 95% CI [0.46, 0.68]) or Hispanic (OR=0.45, 95% CI [0.31, 0.7]) were less likely to be associated with a positive NG outcome when compared to a black reference group.

A residency of West Michigan (OR=0.63, 95% CI [0.48, 0.82), and the Thumb (OR=0.36, 95% CI [0.16, 0.82], $p<.05$) were associated with a NG-positive outcome in the best-fit model. Unknown residency was found to be associated with the outcome and found to have a protective effect against the outcome (best-fit OR=0.62, 95% CI [0.44, 0.87], $p<.05$). While a univariate test found a significant association between living in Southeast Michigan and NG-positive diagnosis, the introduction of other covariates as control factors (e.g. race/ethnicity) in the fully-parameterized and best-fit model eliminated the association.

While the MSM risk factor was associated with NG-positive outcome in all models, (best-fit OR=1.42, 95% CI [1.19, 1.69], $p<.05$) those who had sex with intravenous drug users (SEX_IDU) had reduced odds of being associated with a positive outcome in univariate models (OR=0.76, 95% CI [0.59, 0.97], $p<.05$). No other risks factors were associated with NG-positive outcome in the best-fit model.

CHAPTER 6
DISCUSSION

There are several findings in this study that may impact our understanding of gonorrhea and HIV co-infection among the male HIV-positive population in Michigan. For instance, the younger age of those that are NG-diagnosed vs. those that are not indicates that HIV diagnosis occurs earlier in those with NG diagnosis post-HIV infection. A possible explanation is that, in individuals co-infected with NG and HIV, the symptoms of NG made it necessary to receive care. At the time that the individual receives care for NG, the individual is often asked to complete a test for HIV. Thus, receiving care for NG may increase the odds of diagnosis of other STD infections including HIV. In a sense, contracting NG may increase the odds of detection of HIV, given that the obvious symptoms of NG cause individuals to seek care leading to the detection of the asymptomatic infection of HIV. This may also be true of individuals who have other health issues or of advice related to risk behaviors (e.g. MSM sexual activity, intravenous drug use, clean needles for IDUs, etc.) This may compel younger individuals who do not have access to care or who are less inclined to seek routine care to be screened for HIV and other STDs closer to contracting both infections. This relates to both the increased frequency of individuals in younger age groups as well as the increased ORs of the NG outcome in younger individuals; it is reasonable to expect that those individuals in the younger age groups are more likely to be diagnosed with NG infection given that younger age groups are more likely to conduct risky sexual behavior, while older individuals are less likely to conduct such behavior (CDC, 2012c).

As discussed in the background section, MSMs are a known risk factor for NG infection, and the results of this study are no different. While intravenous drug use is unlikely to spread NG infection, the IDU risk factor, in addition to the other protective-effect risk factors (e.g. those

who have sex with a known HIV-positive individual and those who work in the health care industry) are statistically significant effects even after controlling for the frequently indicated MSM variable. While the risky behaviors associated with the NG outcome are unlikely to directly infect the individuals with NG, the NG-positive individual may be more likely to seek treatment for NG, use preventative measures to avoid NG-infection, and receive treatment for other conditions directly related to each risk factor.

Study Limitations

While the study has several strengths, including a large control-group sample size and population-wide comprehensive sample, it has several limitations. Here is a list of those limitations and how they may be overcome in future clinical research studies.

- The study effectively "joins" two data sources into a single data source for analysis. While the procedure used to join the two datasets is a frequently used standard for joining such data sources, it is possible that some error in joining subjects by their identifiable data was introduced during the "match" process. Unfortunately, it is unlikely that this could be improved unless the public infrastructure was changed to link health records to individuals using a single identifier (e.g. social-security number or some other state- or federally-created subject identifier.)
- When the individual is diagnosed with NG infection, information about sexual activity is collected. However, NG is a bacterial infection and thus is it may be contracted multiple times. The study may be strengthened if it included information about the frequency of infection and recent sexual activity, particularly sexual risk behaviors conducted between NG infection diagnoses.

- The study may also be strengthened to include temporal relationships of multiple NG-infections over time. Currently, the study only considers any NG infection during or after HIV diagnosis.

The study could benefit from lengthening the study period, either extending earlier than 2005 or later than 2012. The shortness of the study period could exhibit cohort effects. It is recommended that the study be lengthened in order to draw conclusions not only to a specific cohort but to represent as closely as possible the entire HIV+ population represented in the examined dataset.

All of the risk factors are dichotomous variables and a single subject can select more than one. As such, it is important to note that the risk factor variables may interact with one another. It is possible that subjects who indicated one risk factor might be more likely to select more risk factors, especially in the case of sexual activity risk factors, each of which may be highly associated with each other. Future studies should investigate the likelihood that subjects indicated more than one risk factor and possibly consider creating a derived "risk" group depending on the cluster of responses for risk factors in both HIV and gonorrhea interview forms.

Public Health Impact

The racial and ethnic distribution of the HIV-positive population demonstrated in this study is in stark contrast with the racial and ethnic distribution of the state of Michigan in its entirety. As of the 2010 census, 80.8% (N=7,803,120) of the population of the state of Michigan had identified themselves as white, whereas 14% (N=1,400,362) of the state had identified themselves as black. The black-white counts within the male HIV-positive population during the study period present a different picture: 40% of the population had identified

themselves as white and 53% as black. The results are intensified when looking at the proportions of those who are diagnosed with HIV and gonorrhea, as nearly 75% of those who are diagnosed with both have identified themselves as black and 19% identified themselves as white. While it is important to note that race/ethnicity is significantly associated with both HIV and gonorrhea diagnosis, race/ethnicity are so highly associated with socioeconomic factors including income, education, and geographic region that a derived variable of sociodemographic status that includes these covariates must be considered as one whole. For a public health strategy to cost-effectively reduce incident infections of either agent, the strategy must consider a targeted approach for factors highly associated with the outcome. Such factors would include MSM, black race, age less than 24, and proximity to Southeast Michigan urban areas.

Finally, the demographic factors and risk behaviors are often very similar between those infected with NG and those infected with HIV. An effective public health program would be to expand the standard of care for NG infected individuals to include an HIV test. The median age of HIV diagnosis in the state of Michigan is 36 years of age. For those who have ever been diagnosed with NG infection, the median age of HIV diagnosis is 30 years of age. This represents a 6-year age difference between those who have ever been infected with NG versus those who have not. Given this fact, it becomes important to maximize the frequency of HIV testing among those who have been infected with sexually transmitted bacterial agents. There is, however, a series of barriers that individuals may encounter when attempting to be diagnosed or treated for a series of STDs. For example, if an individual arrives at the clinic complaining of symptoms that may be perceived as STD symptoms, the individual may be tested for bacterial STDs using urine tests but may not necessarily be tested for HIV. Often, the cost of HIV tests may be covered by the state, but STD testing for gonorrhea and chlamydia testing may not

necessarily be covered either by the state or by insurance providers. The testing methods between HIV (blood or saliva testing) and gonorrhea (urine sample) are different. Thus, for an individual to be diagnosed with both, two tests are required. While these may seem like insignificant barriers to outsiders, the barriers may often be enough for individuals to be tested only for most-likely STDs while postponing or ignoring the need for the series of tests. If the barriers were reduced or eliminated, incidence rates would temporarily increase. However, the long-term impact of increased HIV testing may decrease future incidence of HIV due to earlier diagnosis and intervention among the affected population.

Conclusion

There are several risk factors associated with gonorrhea infection after HIV infection. Thus, we are able to refute the null hypothesis that the incidence of gonorrhea is not impacted by risk factors. The investigator hopes that the results of this study will enhance and support public health solutions that involve the HIV-positive male population in the state of Michigan.

APPENDICES

APPENDIX A

Tables

Table 1. Frequency and proportion of demographics and risk-factors across gonorrhea+ and gonorrhea- men among the HIV+ male population in Michigan during study period (2005-2012)

		ALL HIV+			HIV+ and gonorrhea+	
		N	%		N	%
Age at HIV diagnosis (years)						
	Undefined	203	1.9		49	6.6
	<18	107	1.0		31	4.2
	18-19	114	1.1		32	4.3
	20-24	1,404	13.1		229	31.0
	25-29	1,785	16.6		141	19.1
	30-34	1,966	18.3		95	12.9
	35-39	1,888	17.6		68	9.2
	40-44	1,413	13.2		47	6.4
	>=45	1,841	17.2		47	6.4
	TOTAL	10,721	100.0		739	100.0
Marital status	Divorced	<10	0.0		<10	0.0
	Married	<10	0.0		<10	0.0
	Single (never married)	13	0.1		<10	0.0
	Unknown	10,705	99.9		739	100.0
	Widowed	<10	0.0		<10	0.0
	TOTAL	10,721	100.0		739	100.0
Race/ethnicity	White, non-Hispanic	4,214	39.3		138	18.7
	Black, non-Hispanic	5,734	53.5		567	76.7
	Hispanic of any race	462	4.3		14	1.9
	Asian/Hawaiian, Pacific Islander, non-Hispanic	48	0.4		<10	0.0
	American Indian, Alaskan Native, non-Hispanic	24	0.2		<10	0.1
	Multi-race, Unknown, Other, non-Hispanic	239	2.2		19	2.6
	TOTAL	10,721	100.0		739	100.0
Residency	Unknown	653	6.1		22	3.0
	Upper Michigan	177	1.7		<10	0.5
	Upper Peninsula	52	0.5		<10	0.0
	West Michigan	1,354	12.6		51	6.9
	Mid-Michigan	1,069	10.0		59	8.0
	Thumb	107	1.0		<10	0.4
	Southeast Michigan (non-Detroit)	3,542	33.0		237	32.1
	Detroit (City)	3,767	35.1		363	49.1
	TOTAL	10,721	100.0		739	100.0

Table 1 (cont'd)

		ALL HIV+			HIV+ and gonorrhea+	
		N	%		N	%
Risk factors						
	MSM	7,443	69.4		599	81.1
	MSF	5,203	48.5		335	45.3
	MSB	2,785	26.0		237	32.1
	IDU	1,370	12.8		35	4.7
	SEX_IDU	586	5.5		21	2.8
	SEX_HEMO	17	0.2		<10	0.0
	SEX_TRANSFUSION	14	0.1		<10	0.0
	SEX_HIV	985	9.2		51	6.9
	HCW_RISK	341	3.2		<10	1.2
	NONE	663	6.2		39	5.3

Legend

ALL HIV+ = All subjects in datasets (includes cases and controls)
HCW_RISK = Men who work in the health care industry
HIV = Human immunodeficiency virus
HIV+ = HIV-positive
IDU = Men who have ever used intravenous drugs
MSB = Men who have ever had sex with both men and women
MSF = Men who have ever had sex with women
MSM = Men who have ever had sex with men
N = Total number of subjects
NONE = Men who have reported none of the risk factors above
REF = Reference category
SEX_HEMO = Men who have ever had sex with a hemophiliac individual
SEX_HIV = Men who have ever had sex with a person who was infected with HIV
SEX_IDU = Men who have ever had sex with an intravenous drug user
SEX_TRANSFUSION = Men who have ever had sex with a person who has had a blood transfusion

Table 2. Odds ratio point estimates and 95% confidence intervals for chi-square, fully parameterized and best-fit logistic regression models for comparison of gonorrhea+ and gonorrhea- men among the HIV+ male population in Michigan during study period (2005-2012)

	Univariate			Fully parameterized			Best fit (stepwise)		
	PE	Lower	Upper	PE	Lower	Upper	PE	Lower	Upper
Age at HIV diagnosis (years)									
Undefined	**1.63**	**1.13**	**2.35**	**1.52**	**1.04**	**2.20**	**1.51**	**1.04**	**2.19**
<18	**2.45**	**1.57**	**3.82**	**2.44**	**1.55**	**3.84**	**2.44**	**1.55**	**3.84**
18-19	**2.05**	**1.31**	**3.21**	**1.84**	**1.17**	**2.89**	**1.83**	**1.16**	**2.88**
20-24 (REF)	REF	REF	REF	REF	REF	REF	REF	REF	REF
25-29	**0.49**	**0.39**	**0.62**	**0.56**	**0.45**	**0.71**	**0.56**	**0.45**	**0.71**
30-34	**0.34**	**0.27**	**0.43**	**0.40**	**0.32**	**0.51**	**0.40**	**0.32**	**0.51**
35-39	**0.29**	**0.23**	**0.37**	**0.36**	**0.28**	**0.46**	**0.36**	**0.28**	**0.46**
40-44	**0.28**	**0.21**	**0.37**	**0.34**	**0.26**	**0.45**	**0.34**	**0.26**	**0.45**
>=45	**0.23**	**0.18**	**0.30**	**0.29**	**0.22**	**0.38**	**0.29**	**0.22**	**0.38**
Marital status									
Divorced	0.78	0.17	3.58	*****	*****	*****	*****	*****	*****
Married	0.75	0.17	3.45	*****	*****	*****	*****	*****	*****
Single (never married) (REF)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Unknown	*****	*****	*****	*****	*****	*****	*****	*****	*****
Widowed	*****	*****	*****	*****	*****	*****	*****	*****	*****
Race/ethnicity									
White, non-Hispanic	**0.45**	**0.38**	**0.52**	0.57	0.47	0.69	**0.56**	**0.46**	**0.68**
Black, non-Hispanic (REF)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Hispanic of any race	**0.37**	**0.25**	**0.55**	0.46	0.31	0.70	**0.46**	**0.31**	**0.69**
Asian/Hawaiian, Pacific Islander, non-Hispanic	*****	*****	*****	*****	*****	*****	*****	*****	*****
American Indian, Alaskan Native, non-Hispanic	*****	*****	*****	*****	*****	*****	*****	*****	*****
Multi-race, Unknown, Other, non-Hispanic	**0.64**	**0.39**	**1.04**	0.70	0.42	1.14	0.69	0.42	1.14

Table 2 (cont'd)

	Univariate			Fully parameterized			Best fit (stepwise)		
	PE	Lower	Upper	PE	Lower	Upper	PE	Lower	Upper
Residency									
Unknown	**0.50**	**0.36**	**0.69**	0.61	0.43	0.86	0.62	0.44	0.87
Upper Michigan	**0.43**	**0.23**	**0.79**	**0.69**	**0.36**	**1.32**	**0.69**	**0.36**	**1.32**
Upper Peninsula	*****	*****	*****	*****	*****	*****	*****	*****	*****
West Michigan	**0.43**	**0.34**	**0.55**	**0.63**	**0.48**	**0.82**	**0.63**	**0.48**	**0.82**
Mid-Michigan	**0.57**	**0.44**	**0.74**	0.77	0.59	1.01	0.77	0.59	1.02
Thumb	**0.25**	**0.11**	**0.56**	**0.35**	**0.15**	**0.81**	**0.36**	**0.16**	**0.82**
Southeast Michigan (non-Detroit)	**0.65**	**0.55**	**0.76**	0.90	0.75	1.09	0.90	0.75	1.09
Detroit (City) (REF)	REF	REF	REF	REF	REF	REF	REF	REF	REF
Risk factors									
MSM	**1.63**	**1.39**	**1.91**	1.41	1.05	1.89	**1.42**	**1.19**	**1.69**
MSF	0.92	0.80	1.06	1.03	0.75	1.42	@@@	@@@	@@@
IDU	**0.69**	**0.49**	**0.96**	1.02	0.70	1.49	@@@	@@@	@@@
SEX_IDU	*****	*****	*****	*****	*****	*****	*****	*****	*****
SEX_HEMO	*****	*****	*****	*****	*****	*****	*****	*****	*****
SEX_TRANSFUSION	**0.90**	**0.70**	**1.15**	0.95	0.73	1.23	0.96	0.75	1.24
SEX_HIV	**0.65**	**0.42**	**1.00**	0.70	0.45	1.09	0.70	0.45	1.09
HCW_RISK	**1.63**	**1.39**	**1.91**	1.41	1.05	1.89	**1.42**	**1.19**	**1.69**

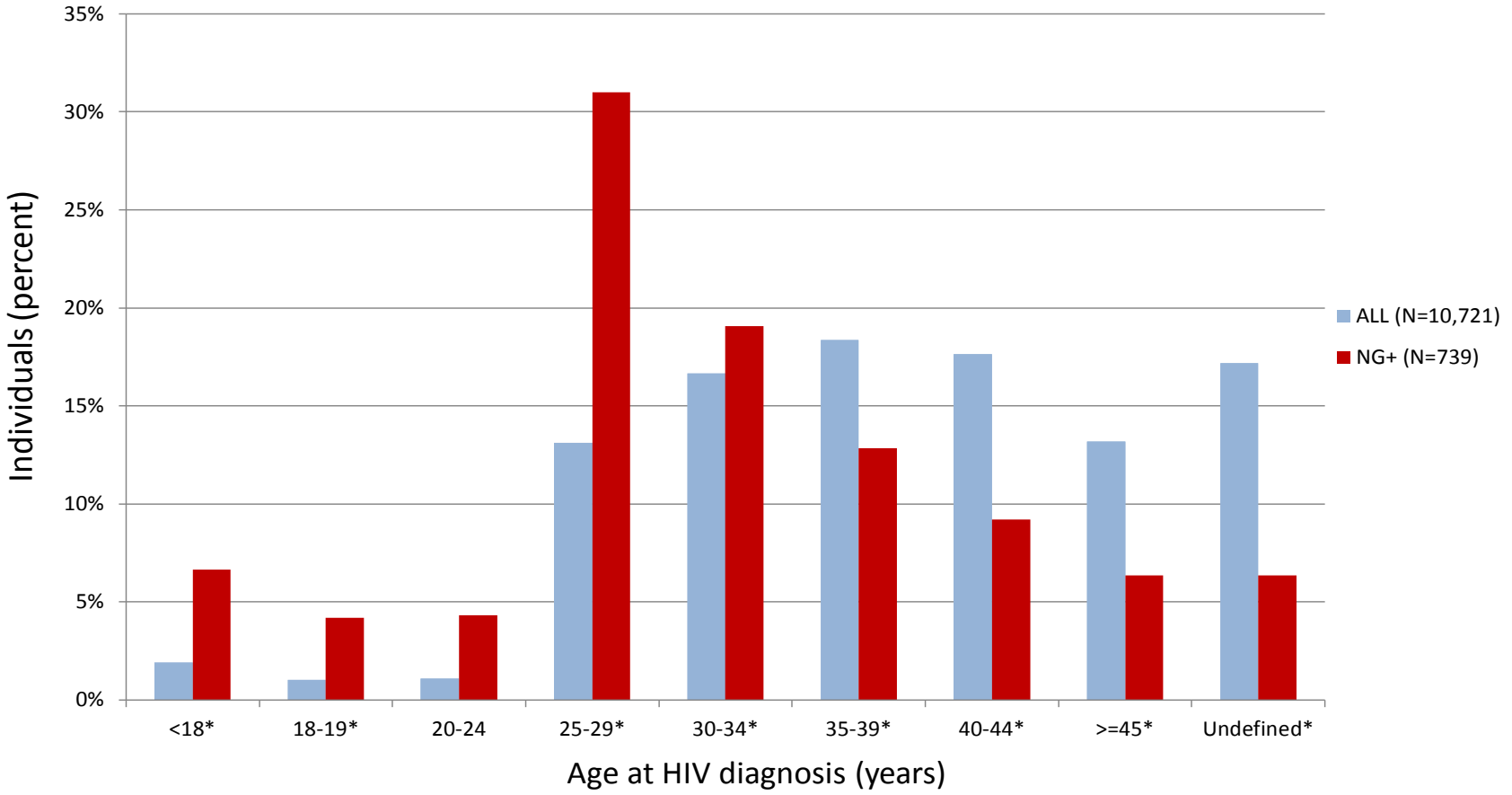
Legend

@@@ = Covariate was eliminated from the best-fit model
***** = Covariate has insufficient sample size to analyze
Bold = Statistically significant
HCW_RISK = Men who work in the health care industry
IDU = Men who have ever used intravenous drugs
LOWER = Lower limit of the 95% confidence interval
MSB = Men who have ever had sex with both men and women
MSF = Men who have ever had sex with women
MSM = Men who have ever had sex with men
PE = Odds ratio point estimate
REF = Reference category
SEX_HEMO = Men who have ever had sex with a hemophiliac individual
SEX_HIV = Men who have ever had sex with a person who was infected with HIV
SEX_IDU = Men who have ever had sex with an intravenous drug user
UPPER = Upper limit of the 95% confidence interval

APPENDIX B

Figures

Figure 1. Proportional distribution of age of all HIV+ males and gonorrhea+ cases within the HIV+ male population in Michigan during study period (2005-2012)



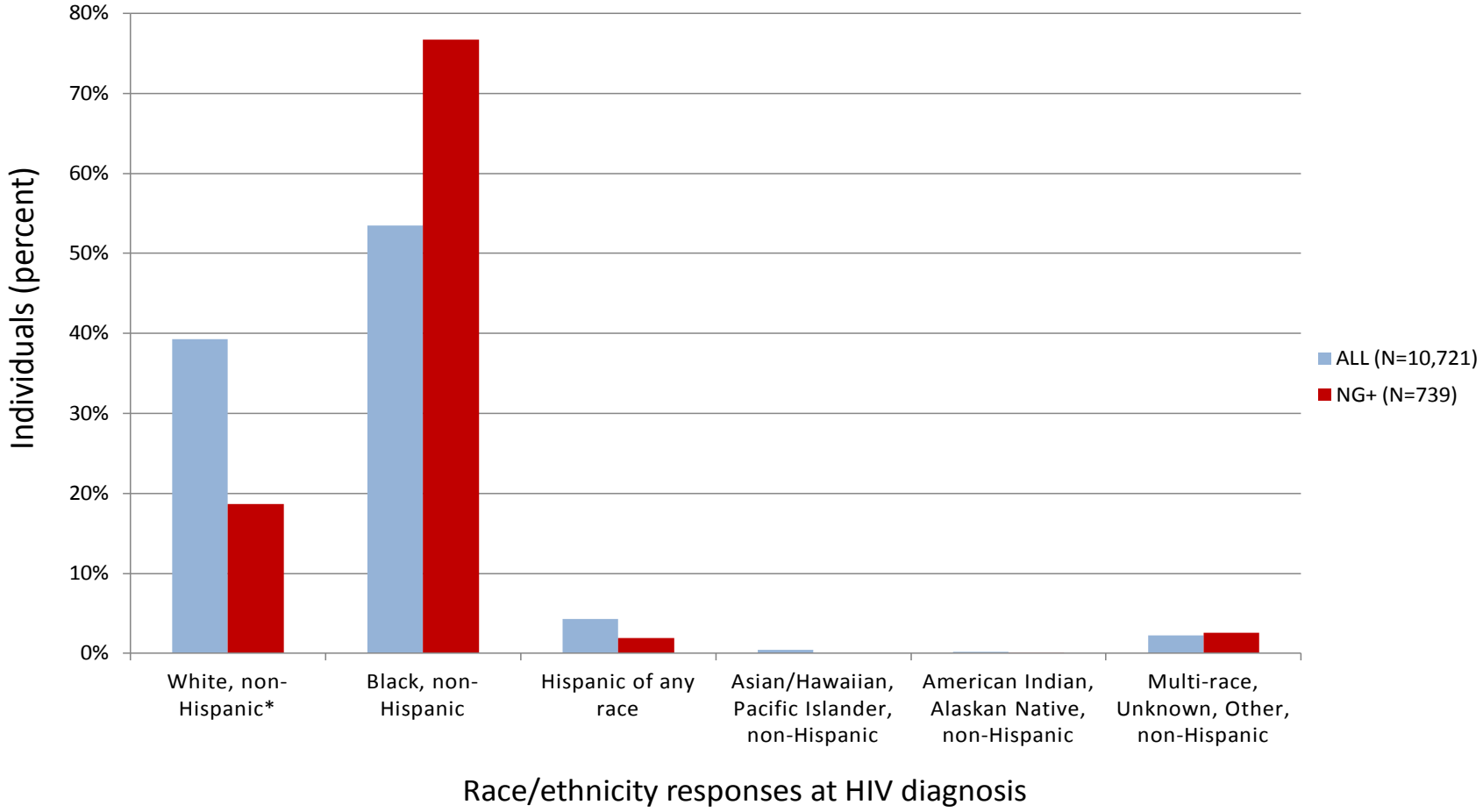
Legend

* = Statistically significant (p<.05) in univariate model (univariate model compares gonorrhea+ cases to gonorrhea- controls [Table 2])

ALL = All subjects in datasets (includes cases and controls)

NG+ = Gonorrhea cases only

Figure 2. Proportional distribution of race/ethnicity of all HIV+ males and gonorrhea+ cases within the HIV+ male population in Michigan during study period (2005-2012)



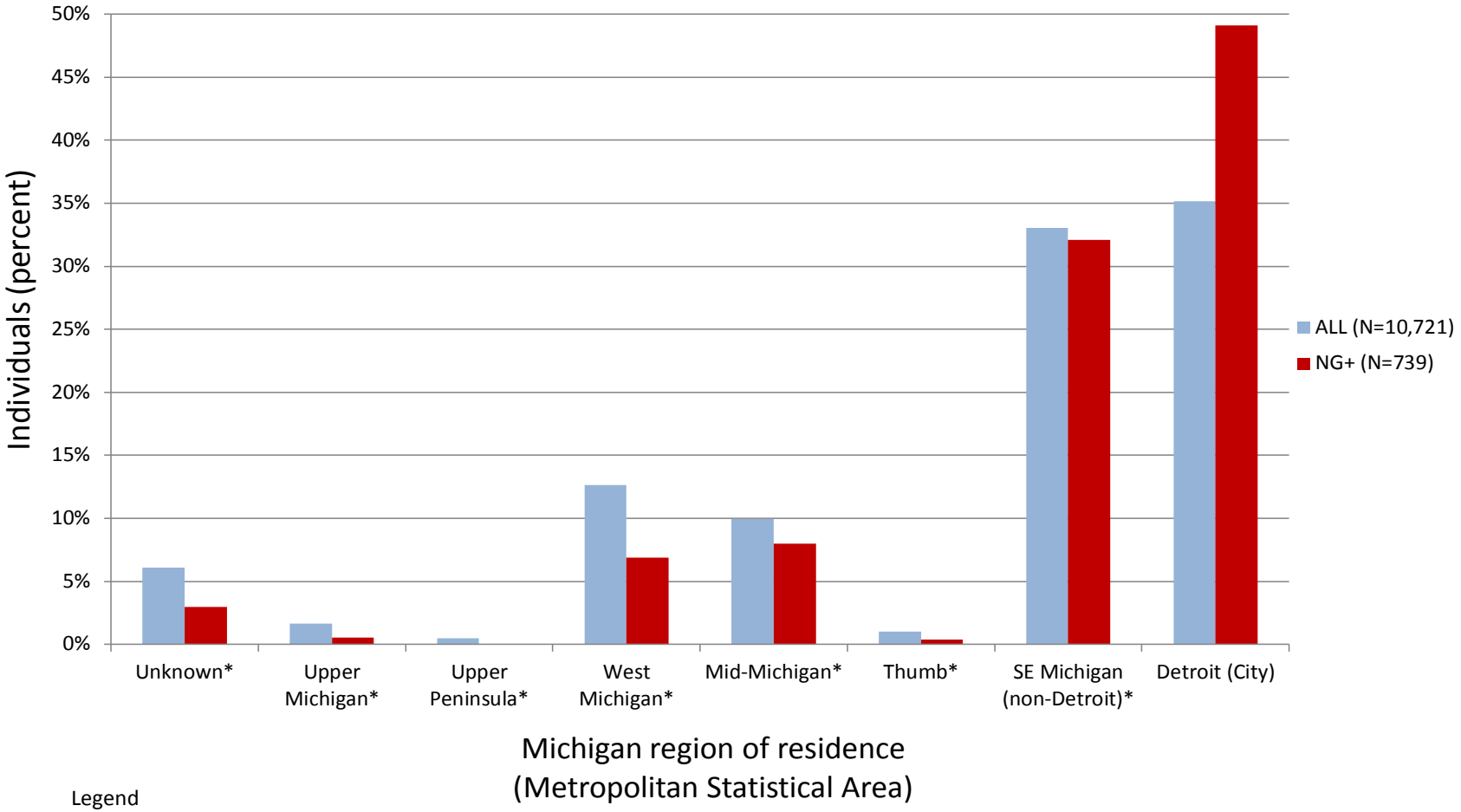
Legend

* = Statistically significant (p<.05) in univariate model (univariate model compares gonorrhea+ cases to gonorrhea- controls [Table 2])

ALL = All subjects in datasets (includes cases and controls)

NG+ = Gonorrhea cases only

Figure 3. Proportional distribution of regions of residence of all HIV+ males and gonorrhea+ cases within the HIV+ male population in Michigan during study period (2005-2012)

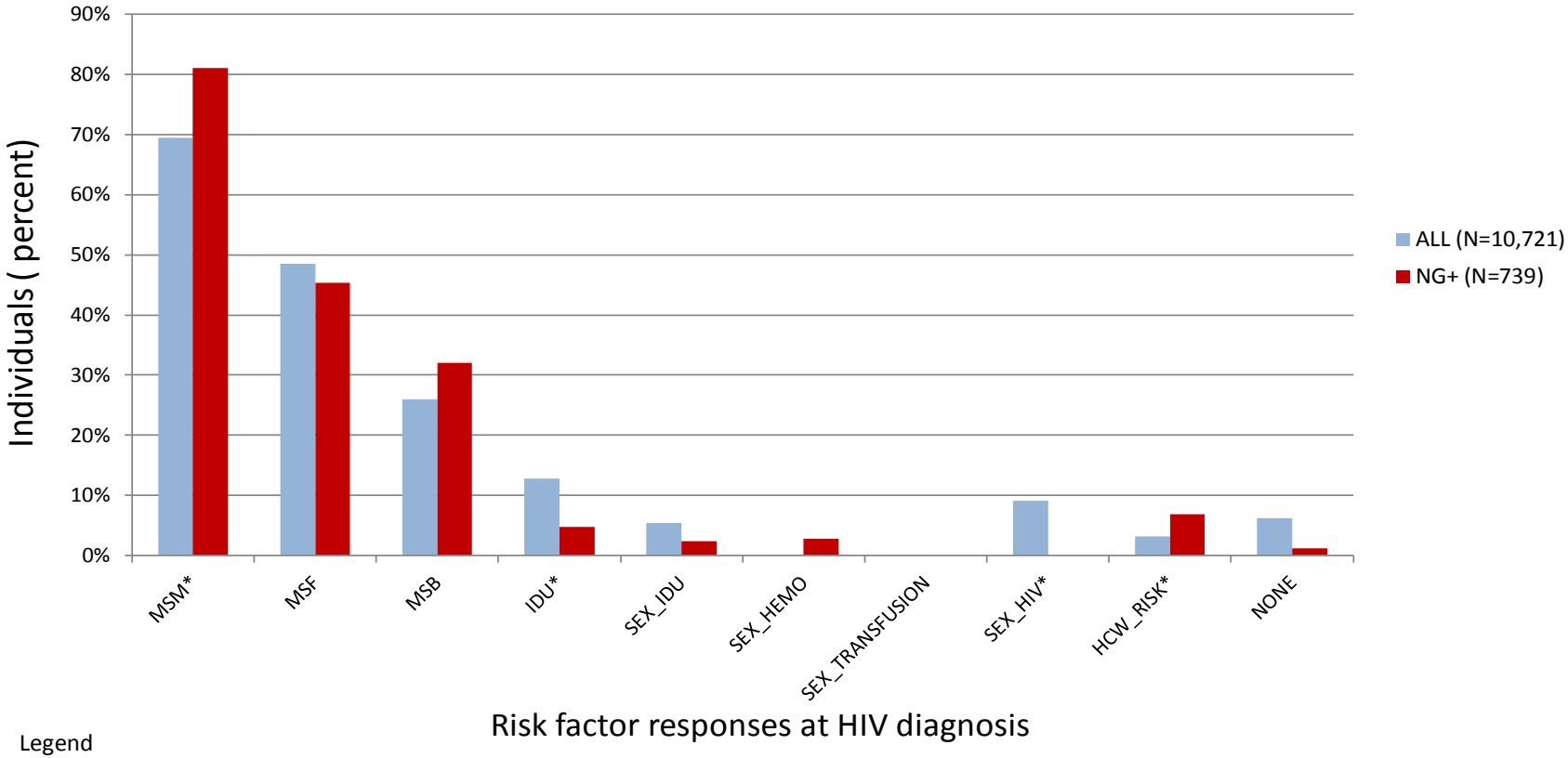


Legend

* = Statistically significant (p<.05) in univariate model (univariate model compares gonorrhea+ cases to gonorrhea- controls [Table 2])

ALL = All subjects in datasets (includes cases and controls)
NG+ = Gonorrhea cases only

Figure 4. Proportional distribution of sexual activity and other exposure risk factors of all HIV+ males and gonorrhea+ cases within the HIV+ male population in Michigan during study period (2005-2012)



Legend

* = Statistically significant (p<.05) in univariate model (univariate model compares gonorrhea+ cases to gonorrhea- controls [Table 2])

ALL = All subjects in datasets (includes cases and controls)
HCW_RISK = Men who work in the health care industry
IDU = Men who have ever used intravenous drugs
MSB = Men who have ever had sex with both men and women
MSF = Men who have ever had sex with women
MSM = Men who have ever had sex with men
NG+ = Gonorrhea cases only
NONE = Men who have reported none of the risk factors above
SEX_HEMO = Men who have ever had sex with a hemophiliac individual
SEX_HIV = Men who have ever had sex with a person who was infected with HIV
SEX_IDU = Men who have ever had sex with an intravenous drug user
SEX_TRANSFUSION = Men who have ever had sex with a person who has had a blood transfusion

Figure 5. Forest plot of odds ratios and point estimates for demographic and risk factor covariates in fully parameterized logistic model for comparison of gonorrhea+ and gonorrhea- men among the HIV+ male population in Michigan during study period (2005-2012)

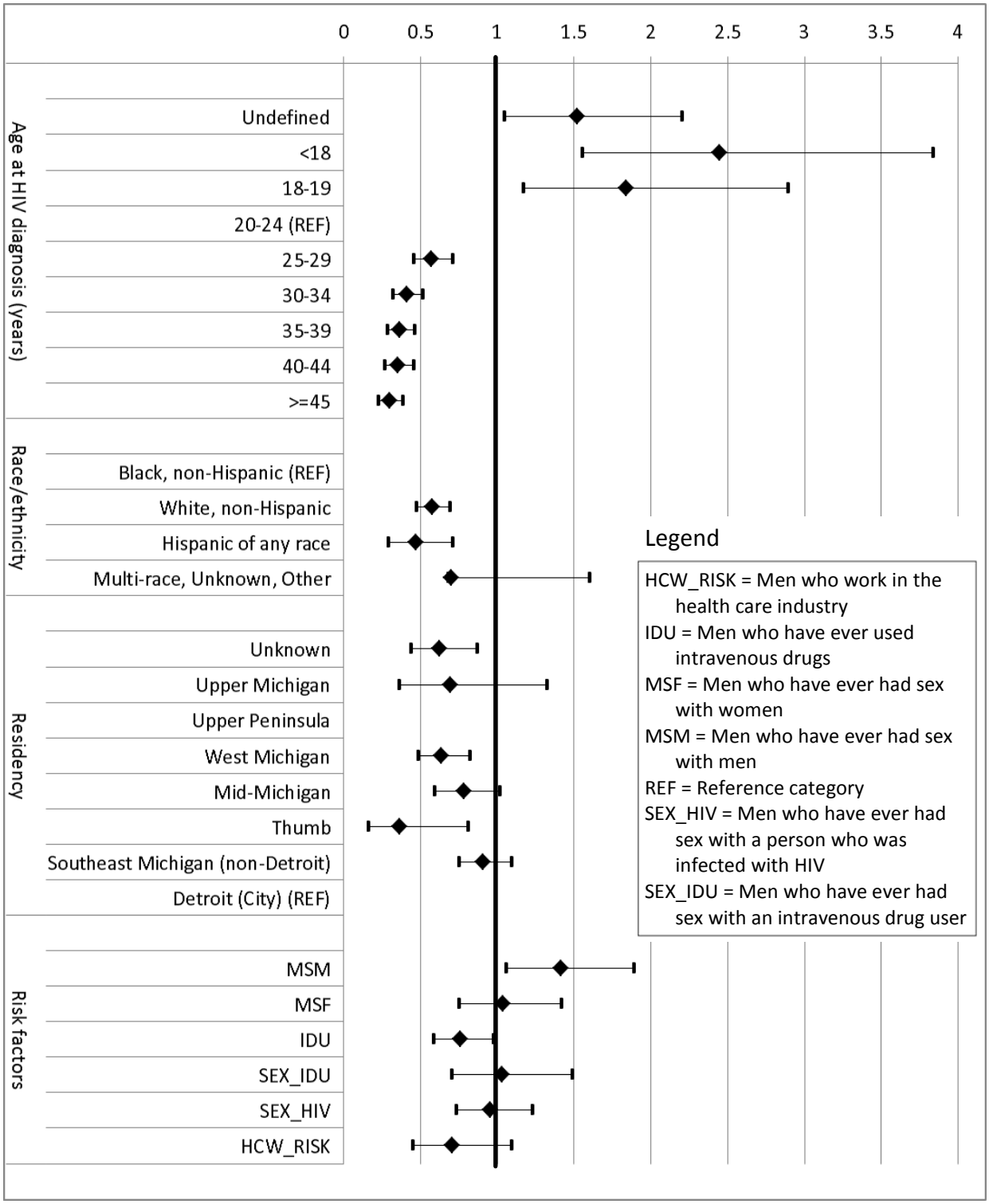
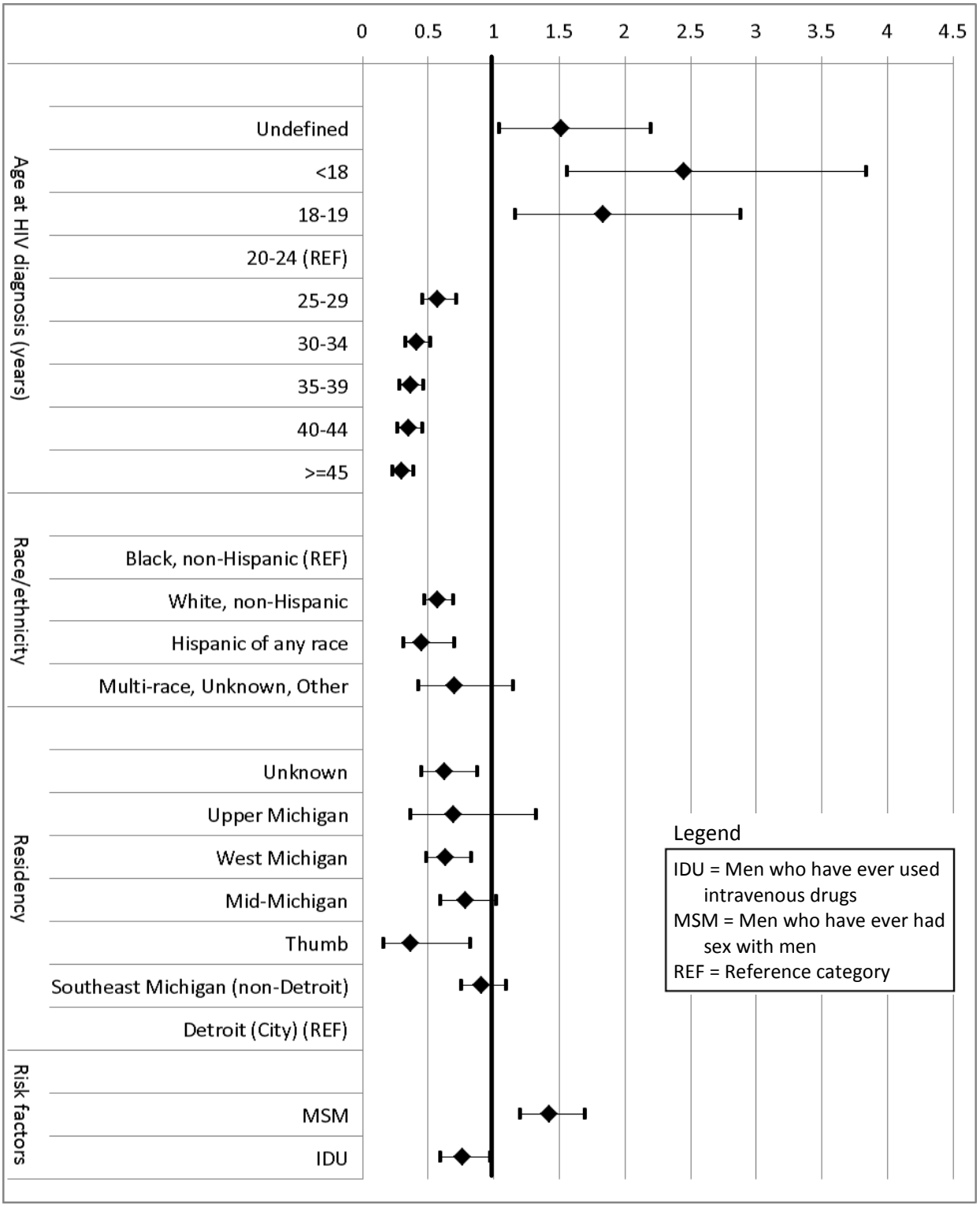


Figure 6. Forest plot of odds ratios and point estimates for demographic and risk factor covariates in best fit logistic model for comparison of gonorrhea+ and gonorrhea- men among the HIV+ male population in Michigan during study period (2005-2012)



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