ASSESSMENT OF HIV TRANSMISSION AND DIAGNOSIS PATTERNS IN NORTH CAROLINA

Anna Barry Cope

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Epidemiology in the Gillings School of Global Public Health.

Chapel Hill
2014

Approved by:

William C. Miller

Michael E. Emch

Peter A. Leone

Kimberly A. Powers

Marc L. Serre

ABSTRACT

Anna Barry Cope: Assessment of HIV transmission and diagnosis patterns in North Carolina
(Under the direction of William C. Miller)

Diagnosis, presentation to care, and initiation of antiretroviral therapy during the early stages of HIV have substantial individual and public health benefits. However, current estimates of the HIV care continuum, or care cascade, indicate that most HIV-infected persons in the US are diagnosed late in the course of their disease and even more do not achieve viral suppression. The purpose of this dissertation was to characterize the cascade-related behaviors of persons participating in active transmission networks and examine the geographic barriers to early diagnosis. Using data collected as part of the North Carolina (NC) Screening and Tracing of Active Transmission Program, we assessed the HIV status and if HIV-infected, the diagnosis, care, treatment and viral suppression status of named partners of persons acutely-infected with HIV (index AHI case) between 2002 and 2013. More than one-third of all traceable partners were HIV-infected. Most observed transmission events appeared attributable to previously-diagnosed partners (77.4%, 95% confidence interval 69.4-85.3%), of whom only 23.2% (14.0-32.3%) were in care and on treatment near the index AHI case diagnosis. Among phylogenetically-linked cases and partners, 60.6% of partners were previously diagnosed (43.9-77.3%).

Using HIV surveillance data from a 52-county region in central NC, we mapped new diagnosis rates by stage of disease (early, chronic, and AIDS) and testing period (2005-2007, 2008-2010, 2011-2013). Maps were standardized and the percent overlap of high rate diagnoses (top 10^{th}, 25^{th} and 50^{th} percentile) by disease stage and testing period were assessed. We identified a definite, underlying core area of HIV as represented by disproportionately high overlap in the top 25^{th} and 50^{th} percentiles by disease stage and testing period. The identification of early infection varied geographically over time, suggesting changes in testing behaviors or the epidemic itself. Relatively high rates of AIDS diagnoses persisted over time in the southeastern part of the study area. Finally, we assessed the association of distance to a publicly-funded testing site with stage of disease at diagnosis. Traveling longer distances to the testing site of diagnosis, particularly when a closer testing site was available, increased the prevalence of post-early stage diagnoses (prevalence ratio=1.09, 1.03-1.16).

For the people of North Carolina living with HIV

ACKNOWLEDGEMENTS

From the beginning idea to the final dissertation push, and everything in between, this effort would not have been possible without the help and support of many smart people. First, I must recognize my advisor and mentor, Bill Miller. His patience, insight, creativity, and ability to multi-task never ceases to amaze me. His expertise is far-reaching and I am grateful to have had the opportunity to learn from him over the past 3 years. Working with Bill has made me a better writer and thinker. Peter Leone is truly an advocate for people living with HIV in North Carolina. His ideas are inspiring and I am lucky to have worked with someone so passionate about public health. Mike Emch and Marc Serre provided key geospatial perspectives to this research. Mike's comments and questions helped me think through my ideas and strengthened the final draft of my dissertation. Marc patiently re-taught me BME methods and reviewed many preliminary versions of my mapping results. His guidance helped me translate my results into an epidemiologically meaningful story. Kim Powers might be the most thoughtful faculty member I have come across. From her willingness to meet at a drop of the hat to the thoroughness of her reviews of my manuscripts, Kim has been incredibly generous with her time and has taught me so much in the relatively short time I have known her.

I would like to thank Brian Pence for helping through the proposal process and providing useful feedback on my work. I am also grateful to Philip McDaniel who taught me how to geocode in ArcGIS and to Veronica Escamilla for helping me think through the spatial methods used in this dissertation.

I am immensely grateful to the North Carolina Division of Public Health for providing

me with the datasets necessary to complete this dissertation and supporting me every step along the way. Aaron Fleischauer, Heidi Swygard, Vicki Mobley, Evelyn Foust, Del Williams, Bill Jones, and Janet Alexander provided the necessary institutional support to execute this project. I am especially grateful to Lynne Sampson and John Barnhart who spent hours helping me understand the intricacies of the HIV surveillance data and to Steve Beagle for explaining the ins and outs of DIS work.

I am fairly certain that this work would not have come to fruition if not for my involvement with the STAT program and the Acute HIV group at UNC and Duke. Aside from providing funding for my PhD, this position provided experience working with some of the best minds in HIV research. Thank you to Cindy Gay, Joe Eron, and David Margolis for teaching me everything I know about acute HIV, providing me with opportunities to conduct my own research and keeping me on, even when the CHAVI money ran dry! And to JoAnn Kuruc, thank you for hiring me back in 2010 and introducing me to the world of Acute HIV research. You have been a true collaborator and friend over the past 4 years and for that, I am forever grateful.

Better than most. I can think of no better phrase to describe my experience as a student in the Epidemiology Department at UNC. Nancy Colvin, Carmen Woody, and Valerie Hudock in the Student Services Office were key in helping me navigate the life (and paperwork) of a graduate student at UNC.

I literally do not know epidemiology without Jessica Rinsky. From UK to UNC, Jess has taught me so much about what it means to be a good student, epidemiologist and friend. I am also so very thankful for the expertise, camaraderie, and laughter provided by so many of my other classmates, including Monita Patel, Rushina Cholera, Nicole Davis, Liz Yanik, Sabrina Zadrozny, Anne Butler, Cathy Panozzo, Kumi Smith, Katie Lesko, and Kristen Hampton.

I would not be where I am today without the love and support of my Mom and Dad. Early on, they instilled the importance of education and have been there every step of the way as I moved from one basketball school to another…to another!

Finally, words cannot express how thankful I am for my husband, Matt Cope. He consistently kept me positive and well fed throughout the dissertation process as only a Cope can do. He kept me sane and always entertained. I would not be here without Matt.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADAP	AIDS Drug Assistance Program
Ag	Antigen
AHI	Acute HIV Infection
ART	Antiretroviral Therapy
BME	Bayesian Maximum Entropy
BMEGUI	Bayesian Maximum Entropy Graphical User Interface
CDC	Centers for Disease Control and Prevention
CHAVI-001	Center for HIV/AIDS Vaccine Immunology 001 Study
CHI	Chronic HIV Infection
CI	Confidence Interval
CTR	Counselling and Testing Report
DIS	Disease Intervention Specialist
DPH	Division of Public Health
eHARS	Electronic HIV/AIDS Reporting System
EHI	Early HIV Infection
EIA	Enzyme Immunoassay

EMM	Effect Measure Modification
GEE	Generalized Estimating Equations
Ig	Immunoglobulin
MSM	Men who have sex with men
NAAT	Nucleic Acid Amplification Technology
NC	North Carolina
NC EDSS	North Carolina Electronic Disease Surveillance System
RHI	Recent HIV Infection
SAS	Statistical Analysis Software, Cary, NC
SOD	Standard Optical Density
STARHS	Serologic Testing Algorithm for Recent HIV Seroconversion
STAT	Screening and Tracing of Active Transmission
STI/STD	Sexually Transmitted Infection/Sexually Transmitted Disease
UMBME	Uniform Model Extension of Bayesian Maximum Entropy
UNC	University of North Carolina
VL	Viral Load

CHAPTER ONE: SPECIFIC AIMS

Diagnosis, presentation to care, and treatment during the early stages of HIV have substantial individual and public health benefits.[1-6] Antiretroviral therapy (ART) results in dramatically higher life expectancies and lowers the probability of HIV acquisition in uninfected sexual partners.[1,6,7] These benefits require early HIV diagnosis, followed by entry into and continued engagement in HIV care. This series of steps has been formalized into a framework commonly referred to as the "HIV treatment cascade."[8]

Losses along the HIV treatment cascade represent substantial numbers of missed opportunities to optimize health and limit HIV transmission.[8,9] Efforts have been made to estimate the number of HIV-infected persons in each stage.[8] However, the contribution of each stage on HIV transmission depends not only on its size, but also on the behaviors and infectiousness of persons in the stage. Current models indicate that persons unaware of their HIV infection account for the majority of transmission.[10,11] Geographic barriers, including rurality and distance, often exacerbate delays in diagnosis, impacting morbidity and transmission.[12,13] However, the transition to opt-out testing in 2007 may have had implications on when HIV-infected people test in the US.[14] Empirical estimates of the contribution of each stage of the cascade to transmission can improve the accuracy of transmission models, while a more developed understanding of the geographic barriers to early diagnosis allow for effective targeting of limited HIV prevention resources.[15]

The HIV treatment cascade provides a useful framework for assessing the potential

impact of the HIV testing and care system on transmission. Unlike many other states, the North Carolina (NC) Division of Public Health (DPH) has the capacity to classify stage of disease in all new HIV diagnoses. The NC DPH maintains demographic and clinical data on all persons diagnosed with HIV or AIDS in NC in eHARS (electronic HIV/AIDS Reporting System).[16] Recent HIV diagnoses (cases identified within 6 months of infection) have been estimated through the serologic testing algorithm for recent HIV seroconversion (STARHS) assessment since 2005.[17,18] Persons diagnosed with acute HIV (AHI) and their sexual and needle-sharing partners are tracked via the Screening and Tracing of Active Transmission (STAT) program.[16] Taken together, data from these surveillance systems provide a unique opportunity to explore the diagnosis, care, and treatment status of HIV-infected persons in active transmission networks and assess the contribution of geographic location to delays in diagnosis and possible HIV transmission. This assessment can direct future resources for HIV testing and care towards persons at greatest risk for acquiring and transmitting HIV. Specifically, we aim to:

AIM 1: Estimate the relative contributions of persons with AHI, previously undiagnosed established infection, and diagnosed established infection (in care vs. out of care, treated vs. untreated, virally suppressed vs unsuppressed) to ongoing transmission in NC.

Hypothesis: We hypothesize that the majority of suspected transmitting partners will be unaware of their disease status.

Overview: We will use disease intervention specialist (DIS) interviews of persons with AHI to identify reported sexual and needle-sharing contacts that have been cross-matched in surveillance databases to allow identification of their HIV status, and for HIV-infected contacts, their diagnosis (newly- or previously-diagnosed), care, treatment and viral suppression status.

These data about the sources of incident HIV infection will provide preliminary information about the transmission contributions of people in each cascade stage.

AIM 2: Assess spatial clustering and patterns of HIV diagnoses by stage of disease both before and after opt-out HIV testing was implemented in NC.

Hypothesis: We hypothesize that acutely and recently diagnosed persons will cluster near urban centers in NC, while persons diagnosed with chronic HIV and AIDS will display a more dispersed spatial pattern.

Overview: We will aggregate all newly diagnosed persons coming out of publicly-funded testing sites in central NC between 2005 and 2012 at the census tract level. Stage of disease will be determined by data provided by the STAT program, HIV Incidence Surveillance project, and eHARS. Bayesian Maximum Entropy (BME) and SaTScan will be used to evaluate differences in clustering by stage of disease at diagnosis over the entire time period, as well as before (2005-2008) and after (2008-2010 and 2011-2013) the implementation of routine, opt-out testing.

AIM 3: Examine the relationship between stage of disease at diagnosis and proximity to both the closest publicly-funded testing site as well as the testing site where diagnosed with HIV.

Hypothesis: We hypothesize that cases diagnosed with chronic disease or AIDS will live farther away from publicly-funded testing sites than cases diagnosed with acute or recent HIV.

Overview: For all patients identified in Aim 1, we will use log-binomial regression models that account for clustering at the neighborhood level to assess the effect of geographic distance from both 1) the actual site of diagnosis and 2) the closest publicly funded testing site to the case's address on the stage of disease at diagnosis.

CHAPTER TWO: BACKGROUND AND SIGNIFICANCE

Epidemiology of HIV/AIDS in the Southern United States

In the United States, the 16 states plus the District of Columbia that make up the American South experience a disproportionate burden of HIV morbidity and mortality in the United States (US). The South accounted for 46% of all new HIV infections, while only representing 37% of the population in 2010.[19] The estimated proportion of AIDS diagnoses in the South increased from the third highest percentage in 1981 (15.8%) to the highest percentage in 2010 (44.6%).[19,20] While still comparatively high, recent trends indicate a slight decrease in both the number of persons living with HIV and the rate of new diagnoses between 2007 and 2010 in the South.[19]

The elevated level of HIV-related morbidity in the South is due to a multitude of factors related to demographics, economics, and infrastructure. As compared to the rest of the country, this region is comprised of a higher percentage of Black persons and a greater concentration of persons living in poverty areas (defined by the US Census Bureau as a census tract with poverty rates of 20% or more). Additionally, the South is markedly less urban in nature, with more than 40% of the population living outside of an urban area, versus 30.8% in the rest of the US.[21]

The regional burden of disease in the US is largely consistent with the demographic distribution of the population,[19] with HIV primarily concentrated in ethnic minorities in the

South.[22,23] The highest rates of HIV are among black persons (57.2%), women (23.8%), and those reporting heterosexual risk (15.0% for males and 88.5% for females).[19] Persons living with HIV and reside in a rural or suburban areas is disproportionately high in the South.[19]

As observed in other parts of the US, the South is currently experiencing increases in both the rate and number of new HIV diagnoses among young men between the ages of 13 and 29 years.[18,19] Men who have sex with men (MSM) are also disproportionately affected by HIV/AIDS in the South; only 34% of self-reported MSM lived in the South in 2007,[24] but 43% of AIDS cases in MSM live in the region.[25] The South was the only region in the US where black MSM living with HIV outnumbered white MSM.[26] High rates of sexually transmitted infections (STIs) and the presence of concurrent partnerships in affected populations in the South increase the likelihood of HIV acquisition and transmission in this region.[27,28]

Persons living in the South experience worse outcomes after an HIV diagnosis compared to other regions. Southerners have higher case-fatality rates[29] and experience poorer 36-month survival rates.[19] Persons living in the South have a higher likelihood of experiencing HIV-related morbidity as compared to persons residing in other parts of the country, particularly among non-whites.[30] These poor outcomes have been linked to problems with access to HIV testing and care that are exacerbated by a history of distrust in the health care system, inadequate HIV and STI care infrastructure, distance to care services, and stigma surrounding HIV.[31-34]

The Epidemiology of HIV in North Carolina: Approximately 1500 new cases of HIV are diagnosed annually in North Carolina (NC). The absolute number of new HIV diagnoses has decreased since a peak in 2008. In 2009, NC was ranked 8th in terms of new HIV diagnoses in the US, with a rate of 23.8 per 100,000 which was slightly higher than the national average of

21.1 per 100,000. Trends observed over the entire region classified as the American South are similar to those seen in NC, where HIV is disproportionately represented among minorities and the economically disadvantaged. The 2010 rate of new HIV diagnoses for blacks (59.7 per 100,000) was more than nine times greater than that of whites (6.5 per 100,000). The diagnosis rate for Hispanics was almost four times higher than that of whites. The male-to-female ratio of new diagnoses has risen from 2.5 in 2006 to 3.2 in 2010. In males, 75% of the new diagnoses were attributed to MSM risk behaviors in 2010. That same year, in females, heterosexual sex accounted for 95% of HIV diagnoses. Urban areas account for the majority of HIV prevalence in NC, with over 50% of new HIV cases being diagnosed in 5 of NC's 100 counties (Mecklenburg, Wake, Durham, Guilford, and Cumberland). In 2006, the CDC reported that NC had the highest number of reported cases in rural areas for both AIDS and HIV in the US.[16]

The HIV Treatment Cascade

Antiretroviral therapy (ART) has led to dramatic improvements in HIV-related morbidity and mortality. Test-and-treat strategies for HIV prevention suggest that expanded testing and earlier treatment of HIV has the potential to significantly decrease ongoing HIV transmission, and therefore limit the HIV epidemic.[35] A test-and-treat strategy cannot be effective without stressing the importance of linkage and retention in care. Successful establishment of HIV treatment requires that a diagnosis of HIV is followed by timely linkage to care, prompt initiation of ART, and subsequent adherence to prescribed medications. In July 2010, the U.S. National HIV/AIDS Strategy set as one of its main priorities to increase access to care and improve health outcomes for people living with HIV/AIDS.[36] To fully benefit from ART, patients must progress through the HIV Treatment Cascade [Figure 2.1] while remaining engaged in uninterrupted HIV clinical care.[3,8,37-39]

Unrecognized HIV Infection: In the US, approximately 20% of HIV-infected persons are unaware of their disease status.[40] These persons cannot engage in HIV care and treatment, tend to participate in riskier behaviors, and may have a higher risk contributing to ongoing transmission of disease.[10,11,40-42] Mathematical models have estimated that between 50-70% of all new infections are attributable to people who are unaware of their HIV serostatus.[10,11,43] These models are based on a combination of empirical data and difficult-to-verify assumptions when empirical data was unavailable.[10,11,43] Additional empirically collected data about the care and treatment status and risk behaviors of the transmitting partners could improve the validity of these estimates.

Among the persons newly diagnosed with HIV infection in the US, 35%-45% have AIDS within 1 year after diagnosis.[8] In 2010, 49% of all AIDS diagnoses in NC were made at the same time or within six months of their HIV diagnosis.[16] Late-stage diagnoses are generally more common among persons who are not perceived or who do not perceive themselves to be at high risk for infection, among those not actively offered HIV testing, and among marginalized groups[44] In a 2003 report, persons tested late in the course of their disease were more likely to be black or Hispanic and to have been exposed through heterosexual contact.[9] These results prompted the Centers for Disease Control (CDC) to launch the "Advancing HIV Prevention Initiative" in 2003, whereby simpler testing procedures were adopted. Pretest counseling was eliminated and testing recommendations were expanded to persons with risk factors in low prevalence settings.[45] This initiative was followed by further recommendations in late 2006 to adopt routine, voluntary HIV screening for patients in all health care settings. The 2006 recommendations aimed to enhance earlier detection of HIV infection, identify and counsel

persons with unrecognized HIV infection and link them to clinical and prevention services, and continue to reduce perinatal HIV transmission.[14]

Many healthcare professionals have endorsed routine HIV testing in all healthcare settings as a way to de-stigmatize the testing process and facilitate access to clinical care for newly diagnosed persons[14,46-48] Additionally, streamlining the HIV testing process may make it easier for health care providers to conduct HIV testing.[49] Approximately 54% of U.S. adults, aged 18 to 64, have reported ever being tested for HIV, including 21% who reported being tested within the past year.[22] Critics of the CDC's 2006 recommendations are concerned that the non-targeted HIV-screening policy might involve inefficient over-testing of low risk populations. The results of mathematical modeling evaluations of the cost-effectiveness of these recommendations in the general population are mixed.[50-52]

Delays in Presentation for Medical Care: Delays in linkage to HIV medical care are associated with greater likelihood of progression to AIDS and increased risk of transmission.[4] Between 69%-90% of persons diagnosed with HIV in the US are linked to an HIV care provider,[5,8] with greater evidence of linkage within the past decade.[5] Approximately three-quarters of persons linked to care, enter care within 4 months of diagnosis.[5] Data suggests that persons diagnosed at emergency and urgent care departments that are located on the same premises as HIV medical care have a higher likelihood of being linked to care than persons diagnosed at testing-only sites such as health departments or community-based organizations.[5] Additional factors associated with earlier linkage to care include male sex, older age, white race, no history of intravenous drug use, having insurance, positive social interaction, being diagnosed with AIDS, use of case management services, mental health services, substance abuse treatment at the time of diagnosis, being diagnosed at the time of first HIV test, having a regular source of medical care before the

diagnosis, the presence of symptoms, and access to transportation.[13,31,53-61] Short-term case management interventions at testing sites that help patients navigate the HIV care landscape improve both the number of people linked to HIV care and shorten the time between diagnosis and entry into care.[54,62]

Most HIV-infected persons do not present for HIV testing near the time of infection.[63] Persons presenting at an advanced stage of immunosuppression are at high risk of adverse clinical events and death. These persons are also more likely to respond poorly to treatment.[64] The median CD4 count at first presentation for HIV care has increased annually over the past decade,[65,66] suggesting improvements in testing and linking patients to care at an earlier stage of disease. However, a high proportion of patients first present to care at CD4 counts less than 350 cells/mm^3, the level at which ART initiation was recommended in the US between 2008 and 2010.[67] Because a recommended CD4 threshold for ART initiation no longer exists,[68] earlier entry into care and initiation of treatment has to the potential to be even more beneficial to the long-term health and survival of both the HIV-infected person and their partners.

Retention in Care: Sustained high-quality HIV care maximizes treatment outcomes in patients.[36] A successful "test-and-treat" prevention strategy is dependent upon efficient and effective means of entering and retaining patients in care.[69] The US Department of Health and Human Services recommends that most HIV patients have medical visits for monitoring CD4 cell count and viral load (VL) every 3-4 months. Patients who are adherent to ART regimens with sustained viral suppression and a stable clinical status may extend the time between visits and be asked to return every 6 months.[67]

It is estimated that between 40%-50% of patients aware of their HIV status are not engaged in regular care.[5,8,70] Missed visits within the first year of HIV care have been associated with decreased likelihood of receiving ART, higher rates of ART failure, increased HIV transmission risk behavior, increased hospitalization rates, and reduced long-term survival.[3,71-75] Younger age, black race, female sex, less advanced HIV disease, few or no HIV co-morbidities, greater distance to care, lack of health insurance, lower socioeconomic status (SES), rural residence, and shorter time for entry into HIV care have been associated with poorer engagement and retention in care.[70,76] Additionally, psychological factors including, acceptance of HIV diagnosis, substance use, mental health issues, perceived stigma, lack of an external support system, capability of overcoming systematic barriers such as housing or transportation, and previous poor experiences with health care providers have been listed as obstacles to engaging in and being retained in HIV care.[76,77]

Antiretroviral Therapy: Successful HIV treatment suppresses HIV to undetectable levels, increasing long-term survival, reducing disease-related morbidity, and decreasing ongoing transmission.[1,2,78] HIV-infected persons actively engaged in care have four main barriers to successful treatment with ART: 1) delay or failure to initiate ARTs, 2) discontinuation of therapy due to adverse effects or other competing priorities, 3) poor adherence to therapy, and 4) viral resistance to ARTs. Under current recommendations in the US, all HIV-infected persons in care are eligible for treatment; however 25% are not receiving therapy.[8,68]

The HIV Treatment Cascade and Ongoing Transmission: The HIV treatment cascade is an effective tool to monitor the HIV epidemic in the US. The contribution of each stage to HIV transmission depends not only on its size, but also the behaviors and infectiousness of persons in the stage. Based on previous analyses, ongoing transmission may be more likely to be attributed

to persons who have yet to be diagnosed, persons diagnosed but out of care, or persons in care with unsuppressed vial loads.[1,10,11] Accurate estimation of the relative contribution of each cascade stage to HIV transmission is critical to optimize HIV prevention strategies.

Considerations about HIV Diagnosis and Care in the South

Most research assessing predictors of delayed HIV diagnosis and presentation to medical care in the US come from studies based in large urban centers, primarily on the East and West coasts. These predictors may not be generalizable to the South. The tax-base of Southern state governments is lower than states from other parts of the US, limiting their ability to provide optimal disease prevention and treatment.[79] In general, there are fewer providers experienced in HIV-care in the South, resulting in a health infrastructure that is less equipped to identify and handle the epidemic.[19,27,79] While the South has made improvements in prevention efforts in recent years, with reductions in both the number and rate of new HIV diagnoses,[19] much work remains to increase both testing and care services for HIV-infected persons.

Surveys of local HIV testing sites in the South indicate that the overwhelming majority of HIV testing is conducted at health departments, suggesting testing services are available and accessible in most rural counties in the region.[34] However, sites that provide HIV care and treatment are less common,[34] potentially inhibiting the receipt of quality HIV care and treatment in the South.[34] Case managers identify major barriers to care in the South as the perception of stigma against people living with HIV/AIDs, lack of housing for person with HIV/AIDS, a lack of accessible transportation for clients, distance to care facilities, inadequate service infrastructure, and a distrust of privacy and confidentiality in the healthcare system in the South.[34,80] Health department providers tend to report that their clients travel longer distances from the health department to the nearest treatment facility, while providers at treatment facilities

have indicated travel time to be much shorter.[34] Providers at these treatment facilities may base their opinions about access to care and distance traveled on their current clients, many of whom are referred to care because they live nearby the treatment facility. These facilities may be less likely to see patients who live in remote parts of the region and experience difficulties related to accessing, linking to, and engaging in care.[34]

Poverty and lack of health insurance make it difficult for many Southerners secure adequate health care.[79] The South includes 9 of the 10 states with the highest proportion of people living in poverty in the US.[21] The high levels of poverty in the South limit both the ability of the person to access care and also the ability of the states to allocate the resources necessary to provide adequate testing and care services to HIV-infected persons.

Many HIV-infected persons rely on Medicaid, Medicare, disability insurance, the Ryan White Comprehensive AIDS Resource Emergency Act, and the AIDS Drug Assistance Program (ADAP) to receive necessary care and treatment in the South.[31,70] However, Medicaid and disability eligibility is more restrictive in Southern states, and even if a person qualifies, benefits tend to be lower in Southern states.[81,82] Approximately one-quarter of all HIV-infected persons in NC receive funding from Ryan White Part B and/or ADAP.[16] Many Southern states contribute less than the national average of 16% of the state's ADAP funding[83] During the recent recession, many states cut ADAP benefits and capped enrollment, leaving some HIV-infected persons waiting for ART. In 2011, 90% of HIV-infected persons on ADAP waiting lists lived in Southern states.[84] These delays can be expected to increase morbidity, mortality, and HIV transmission.

Prevention and treatment of HIV/AIDS are further complicated in the South by the high prevalence of HIV-infected persons living in rural areas.[79] The wide geographic dispersion of rural residents adds to the complexity of planning and delivering HIV testing and treatment services. Rural residents are less likely to be tested for HIV and are more likely to be diagnosed at a later stage of disease than urban residents.[12,85] At entry into care, rural residents are more likely to have more advanced disease and decreased 2 year survival than urban residents.[13] However, overall survival has improved for both urban and rural residents alike over the past decade.[13,66] Data suggest that most rural residents living with HIV seek medical care in nearby urban settings, primarily because of a perceived lack of adequate medical infrastructure and a perceived lack of confidentiality among community members, including family, friends, providers, and pharmacists.[79,86] Additionally, greater stigma related to HIV infection has been identified in rural areas further complicating efforts to provide HIV/STI prevention and treatment.[27,86]

The failure to utilize testing and care services is not a unique phenomenon to the American South. However, the reasons for delayed testing and non-engagement in care are distinct. The dispersed geography of the region has resulted in greater distances between testing sites and care providers. High levels of poverty in the South have made it difficult for both the person to access and the states to provide appropriate HIV care. Deep-rooted cultural norms influence the perception of disease risk and stigma, reducing the likelihood of early testing. In order for potential test-and-treat prevention strategies to succeed in the South, structural improvements in testing and linkage to care may be warranted.

Testing and HIV Staging

Diagnosing persons with HIV within months of acquisition is of increasing interest to researchers. The events in the first few months of infection predict the course of the disease in the individual,[87-89] making methods to identify early stage infection important. Persons with early stage infection have a higher risk of transmitting the disease than persons with chronic infection[90] due to elevated virus in the blood.[91] Detecting early infection can help public health officials and healthcare providers intervene and reduce the potential for future onward transmission. Early stage disease can be divided into Acute HIV (AHI) and Recent HIV (RHI).

Detection of Acute HIV Infection: Acute HIV (AHI) is defined as the 3 to 4 week period from HIV acquisition until seroconversion[92] where HIV RNA is present before the patient has developed anti-HIV antibodies. The p24 antigen (Ag) is also usually detectable within a few days of the onset of viremia. As the host's immune system initiates a response, levels of both the virus and the p24 Ag fall.[93] HIV RNA remains detectable after the early stages of HIV infection, but usually at levels that are much lower than during the acute phase. Conversely, the p24 Ag usually becomes undetectable until the degradation of the host immune system associated with late-stage disease, typically around 10 years post-infection.[94] The initial immune response begins with a virus-specific Immunoglobulin (Ig) M response that is highly variable in both intensity and duration.[94] The IgM response generally peaks within 1-2 weeks after infection and falls to background levels 1-2 weeks later. At the same time, a high-titer IgG response develops.[94] [Figure 2.2]

Transmission risk is high during AHI due to elevated virus in the blood and genital secretions.[95-97] AHI is often characterized by a set of flu-like symptoms that are often too vague

or nonspecific to lead to a diagnosis.[98] AHI also may go unrecognized because antibodies are not present for traditional serological tests to detect.[99,100]

HIV RNA can be detected in the blood within a few days of infection.[91] Nucleic acid amplification technology (NAAT) testing is the most sensitive test for diagnosing AHI.[94] Pooled NAAT screening is a cost-effective method for detecting HIV RNA during the acute stages of disease. In 2002, the NC Division of Public Health (DPH) was one of the first health departments in the US to implement NAAT pooling through the Screening and Tracing Active Transmission (STAT) program, a state-wide strategy of screening for AHI at all public HIV testing sites.[101] Between 2002 and 2013, all antibody-negative specimens were tested for HIV RNA using pooled NAAT screening per STAT program protocol. Positive NAAT pools were further divided until HIV RNA is detected in a single sample and the person with AHI can be identified. Using this methodology, 1.2 per every 10,000 HIV tests in NC were identified as having AHI and 3.3% of all positive diagnoses in the state were diagnosed with AHI.[102] This methodology for detecting AHI has been implemented in other areas, both domestic and international.[100,101,103-107]

Alternative strategies to identify HIV include 3rd generation antibody tests, p24 enzyme immunoassay (EIA) antibody tests, and other developmental nucleic acid tests. Third generation EIA tests can detect IgM anti-HIV-1 antibodies.[98] In the past, tests for p24 antigen have been highly specific, but only exhibited moderate sensitivity (70-80%) for preseroconversion HIV. Newer 4th generation EIA tests can simultaneously detect viral p24 antigen and antiviral antibodies.[98] These tests may detect HIV within three days of the first detection by NAAT testing.[98] In November 2013, 4th generation testing was implemented in NC. A diagnosis of AHI was re-defined as a positive 4th generation EIA and negative multi-spot rapid test in the presence

of HIV RNA. It is anticipated that a rapid point-of-care test will be developed in the future to diagnose AHI.[91,98]

Detection of Recent HIV Infection in NC: Persons with RHI have already experienced seroconversion, but are still early in their infection. The exact time period cut-off for recent infection varies from study to study and can be anywhere from 3 to 9 months after infection.[108-111] A general consensus emerged among researchers that the ideal time period defining RHI was around 6 months.[94] In general, during RHI, the concentration of HIV in blood remains somewhat elevated as compared to chronic infection, though not as high as during AHI.[91]

The BED IgG-Capture Enzyme Immunoassay (BED assay) is the most frequently applied test to identify recent HIV infection.[112] The BED assay measures the ratio of specific anti-HIV IgG for HIV-1 subtype B, E, and D to total IgG in a sample. The smaller the ratio, the more likely the person was recently infected. The result is reported as a standard optical density (SOD), a continuous measure that describes the relative concentration of anti-HIV IgG. The period of time during which the SOD is below a threshold predetermined to define "long-standing" infection is termed the recency period.[18,94,109] The BED assay lacks specificity, with a proportion of persons with long-standing infection, severe immunosuppression, or on antiretroviral therapy being misclassified as a RHI.[112,113] AIDS is characterized by a failed immune system, which is associated with a decline in anti-HIV antibody levels, impacting the specificity of the BED assay.[112] It has been estimated that the misclassification rate due to AIDS diagnoses is 2-3%.[114] It is not fully understood why infected persons on ART are misclassified as recent, but it is thought to be related to the suppression of viral replication by ART which results in the removal of the chronic stimulus to the humoral immune response and leads to a decline in anti-HIV antibody titer.[94]

To correct for potential misclassification individual level information pertaining to ART use, previous HIV testing and AIDS diagnoses are used to identify non-recent samples and exclude samples from BED assay testing. If RHI identified by BED testing will be used for estimating incidence at the population level, correction estimators can be used to account for the imperfect specificity of the BED assay.[17,18,112] A recently published approach, the multiassay algorithm, uses several data sources (BED-assay, an antibody avidity assay, HIV VL, and CD4 cell count) to estimate a more sensitive measure of incidence in the population.[110,115,116]

The Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) combines diagnostic testing (confirmed HIV antibody-positive) and testing for recent infection using the BED assay to identify RHI to create incidence estimates in the population. Since 2004, the CDC has identified 25 jurisdictions, including NC, to conduct HIV incidence surveillance. The NC HIV Incidence Surveillance project team works in collaboration with the CDC to estimate RHI in NC using STARHS methodology. Currently 50-60% of all newly positive HIV blood samples from NC are forwarded to CDC labs for STARHS testing.[117]

Detection of Chronic HIV and AIDS: Chronic HIV (CHI) can be defined as the time period between RHI and AIDS. Most persons with a confirmed HIV antibody-positive test as their first HIV test are considered to have CHI. Only those tests identified through the BED assay and STARHS to have a SOD below the recency period threshold would be reclassified from CHI to RHI. AIDS is classified as late stage HIV and is characterized by a damaged immune system that has difficulty fighting diseases and certain cancers. A diagnosis of AIDS occurs with a laboratory confirmation of HIV infection and at least one of the following: 1) CD4 cell count of less than 200 cells/mm3, 2) CD4 count that is less than 14 percent of all lymphocytes, or 3) a diagnosis of one or more AIDS-defining illness.[118] [Table 2.1]

Surveillance Data and the HIV Treatment Cascade

HIV surveillance systems collect demographic data, as well as testing, clinical, laboratory, and vital status information on all HIV case reports. Originally, information was only collected at the time of diagnosis. As of 2009, 38 of 50 states and the District of Columbia required reporting of either all CD4 cell counts or all HIV VL. The remaining states either did not require any reporting of CD4 cell counts and HIV VLs, or required reporting within a specified range of values.[118,119] Prior to July 2013, NC required CD4 cell counts <200 cells/mm^3 or <14% and all detectable VLs (>20 copies/mL) be reported to the NC DPH.[117]

When using surveillance systems for research purposes, it is preferred that high-quality surveillance data with complete capture of HIV-related laboratory results be used.[120] However, data can be missing in many surveillance systems. Reports of new HIV diagnoses and their clinical lab values may be delayed or incomplete, thus affecting the real-time tracking of testing and care patterns in a population. As more health departments move towards electronic reporting of testing and clinical lab values, this should become less of a limitation. Incomplete reporting of deaths and migration out of a jurisdiction distorts estimates of the total number of HIV-infected persons in a place and makes the estimation of their care and treatment status difficult.[121]

CD4 and HIV VL tests have been used as a proxy for the receipt of medical care in a number of epidemiologic studies.[5,53,59,60,119,120,122-126] Studies have suggested that state databases such as eHARS (electronic HIV/AIDS Reporting System) generate the lowest estimates of entry and retention in care as compared to studies utilizing patient self-report or clinic medical record searches.[5,121] Further, it has been demonstrated that using a single VL or CD4 measurement as a proxy for receipt of HIV care may overestimate the number of people currently in care.[122] Linkage across HIV surveillance databases and with for-profit data warehouses containing

current residential information could improve the accuracy in estimating the care status of HIV-infected persons in a specific jurisdiction.[121]

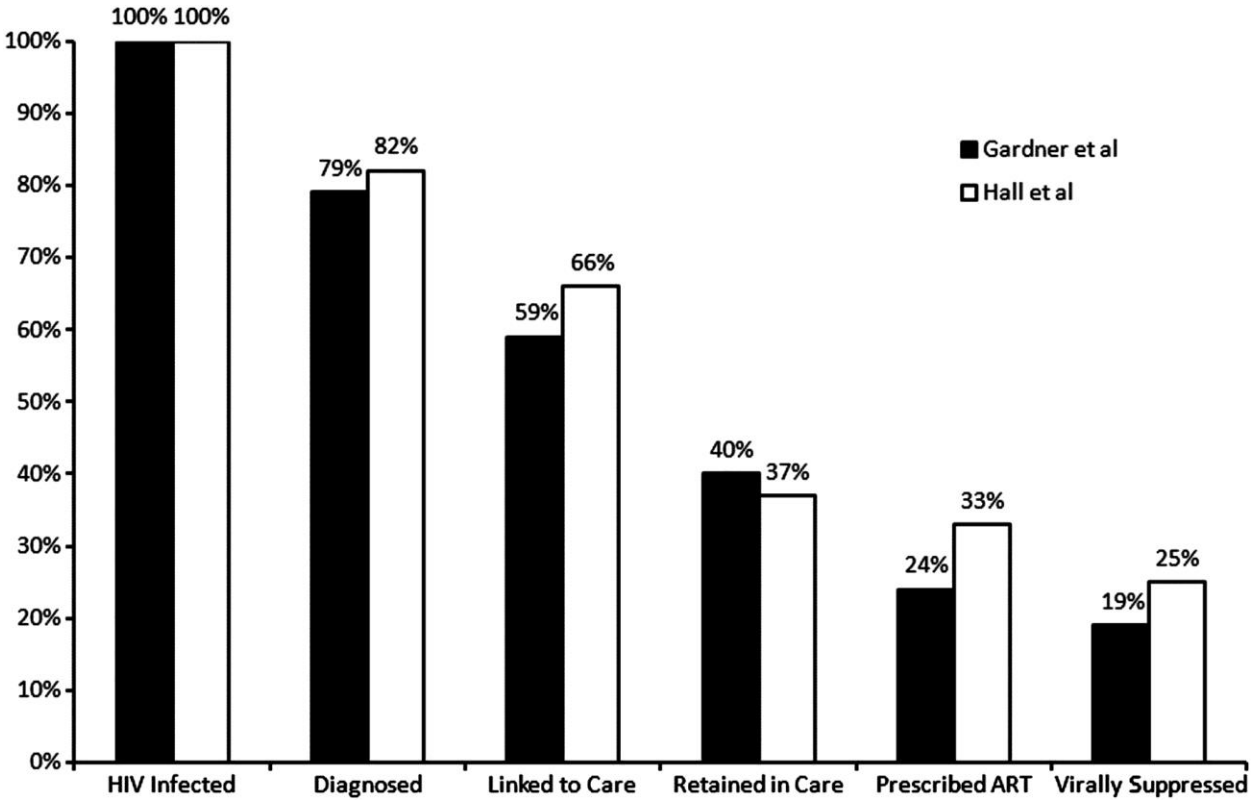
Despite its limitations, surveillance records reflect real-world, care-seeking and treatment behaviors that are unmodified by study monitoring. The limitations of HIV surveillance systems should be considered and noted when analyzing data originating from these sources. Active surveillance can increase the number of CD4 and HIV VL tests reported and consequently, increase the number of HIV-infected persons identified as receiving HIV care.[124]

Summary

Ensuring timely access to HIV testing, care, and treatment is challenging. Understanding the context and settings in which transmission risk is increased may lead to more robust and effective prevention interventions. It is anticipated that the findings from this dissertation, will improve the identification of at-risk populations in NC and the allocation of resources towards the areas and populations most likely to be affected by HIV. Improvements in preventative services to overcome discrepancies in undiagnosed HIV infection and inadequate engagement in HIV care among persons involved in active transmission networks could have a tremendous impact on HIV incidence in this and similar settings.

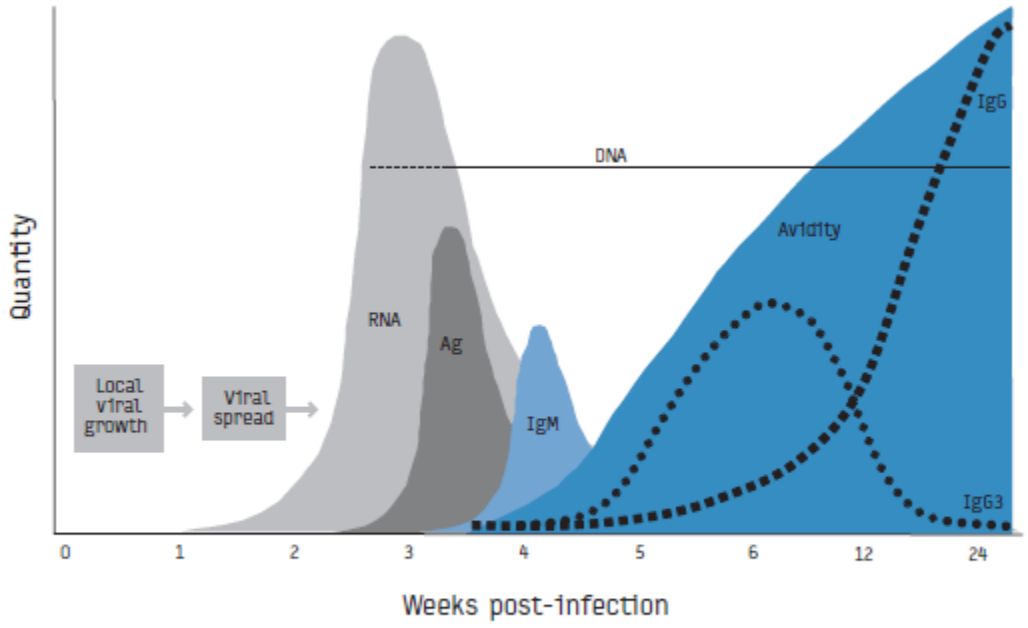
Tables and Figures

Figure 2.1 The HIV treatment cascade in the United States



Courtesy of Mugavero, 2011[39]

Figure 2.2 Evolution of key viral and serological markers during the first weeks after HIV-1 infection



Viral markers: RNA, Ribonucleic acid; DNA, Desoxyribonucleic acid; Ag, Antigen.
Immunological markers: IgM/IgG, Immunoglobulin M/G antibodies.

Courtesy of Murphy, 2008.[94]

Table 2.1 AIDS-defining Illnesses

- Bacterial infections, multiple or recurrent
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi sarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis* of any site, pulmonary,disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

CHAPTER THREE: DESCRIPTION OF DATA SOURCES

The Counselling and Testing Report Database:

Persons requesting an HIV test from a publicly-funded testing site in NC, including local health departments, complete a counselling and testing report (CTR) form at the time of testing [Appendix 1]. Demographics, testing history, zip code, transmission risk factors, and site of testing are captured on the CTR forms are linked to HIV test results processed by the NC state laboratory of public health by a de-identified barcode number. Data for both HIV-infected and HIV-negative tests is entered in the CTR database maintained by the NC Division of Public Health (DPH). All HIV-positive cases in the CTR system are linked to electronic HIV/AIDS Reporting System (eHARS) through an eHARS identification number.

The Electronic HIV/AIDS Reporting System:

The DPH monitors all persons either diagnosed with HIV in NC or diagnosed with HIV in another state and now living in NC in eHARS. Data collected and entered in eHARS includes basic demographic and risk factor information, date of HIV and AIDS diagnosis, residence at HIV and AIDS diagnosis, and HIV or AIDS diagnosis site and address. Selected laboratory values, including CD4 cell counts <200 cells/mm^3, and detectable viral loads, are included in eHARS.

Results from Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) testing is also stored in eHARS. STARHS is a 2 test algorithm in which the first test is used to determine whether a person is HIV-positive on standard EIA tests. The EIA test is followed by

the BED capture enzyme immunoassay which measures the ratio of specific anti-HIV immunoglobulin G (IgG) for HIV-1 subtype B, E, and D to total IgG in a sample. The lower the ratio, the more likely a person was infected within the past 6 months can be classified as recently infected. The result is reported as a standard optical density (SOD), a continuous measure that describes the relative concentration of anti-HIV IgG. The period of time during which the SOD is below a threshold predetermined to define "long-standing" infection (approximately 156 days from infection), is termed the recency period. Since 2005, the NC DPH has collected and sent remnant samples of confirmed HIV antibody-positive serum from the NC state laboratory to the CDC STARHS designated laboratory for BED-assay testing. STARHS results are returned to the NC DPH and entered into eHARS.

The Screening and Tracing Active Transmission Database:

The Screening and Tracing Active Transmission (STAT) program is a collaboration between the University of North Carolina (UNC) and NC DPH to identify persons diagnosed with acute HIV (AHI) at the state laboratory via nucleic acid amplification test (NAAT) pooling procedures for all negative or indeterminate HIV antibody tests.[100,127] Positive NAAT pools are subdivided until HIV RNA is detected in a single sample and a person with AHI can be identified. This process typically takes between 10-14 days before results are released and the person is notified of their disease status.[117] AHI cases screened and identified via "community" testing facilities (e.g. emergency departments, urgent care centers, student health centers, or primary care clinics) are also tracked by the STAT program. In the community settings, AHI was defined by a negative or indeterminate antibody test and reproducibly detectable HIV RNA or a positive antibody test with seronegative documentation within the preceding 30 days of the positive test date.

Disease Intervention Specialists (DIS) contact all persons newly-diagnosed with AHI (index AHI) within 72 hours of release of HIV test results and perform an initial interview, conduct confirmatory HIV testing, and make referrals to HIV care providers, as necessary. In addition to standard information about the testing sites, reasons for HIV testing, demographics, HIV testing history and risk factors, DIS also collect detailed information about acute retroviral symptoms, risk behavior, and sexual and needle-sharing partnerships within 8 weeks of the original HIV diagnosis date for all acute cases. DIS attempt to find, counsel, and provide HIV testing for all named sexual and needle-sharing partnerships within 8 weeks of the index AHI diagnosis date for the STAT program. DIS search the Sexually Transmitted Disease Management Information System (2002 to November 2012) or the NC Electronic Disease Surveillance System (NC EDSS) (November 2012-present) to identify partners who have been previously-diagnosed and verify HIV diagnosis dates and most recent clinical lab values (VL and CD4). For previously-diagnosed partners reporting current HIV care, DIS follow-up with providers to classify the care and treatment status of partners in the 6 months prior to transmission. Prior to 2013, index AHI cases were also required to sign a HIPAA form for DIS to report detailed testing and sexual behavior with named partners as part of the STAT program.

De-identified data collected about all index AHI cases and their partners are reported on a biweekly conference call with state officials and researchers at UNC. DIS complete three STAT forms for each AHI: the STAT log form to summarize testing and referral to care, the STAT Symptoms and STI form, and the STAT Partner log [Appendix 2]. Completed forms are faxed to the STAT data manager at UNC for entry into the STAT database.

CHAVI-001:

Between 2006 and 2011, all suspected and confirmed AHI cases via the STAT program were referred for evaluation at UNC or Duke University, and offered enrollment in the Center for HIV/AIDS Vaccine Immunology 001 Study: Acute HIV Infection Prospective Cohort Study (CHAVI-001), a longitudinal study examining the HIV-1 virus, host response, genetic factors that determine HIV transmission, and viral set point.[128]

In addition to the basic demographic and testing information collected by the DIS, laboratory data, including VL and CD4 cell count were collected for all CHAVI-001 patients at the time of enrollment. All sexual or needle-sharing partners within 12 weeks of the index AHI diagnosis date who were located by either a DIS or the CHAVI-001 field coordinator were also offered enrollment in CHAVI-001, regardless of HIV status. HIV-uninfected partners received HIV testing and counseling at each study visit during follow-up, while VL and CD4 were collected at enrollment and each study visit for HIV-infected partners on CHAVI-001. Data collected via CHAVI-001 was maintained in a separate database through Duke University by the Statistical Center for HIV/AIDS Research and Prevention.

CHAPTER FOUR: RESEARCH DESIGN AND METHODS

Aim 1: HIV transmission in NC

Study Design

For this aim, we estimated 1) the cascade landscape of all named partners and 2) the relative contribution of persons unaware versus aware of their HIV infection to ongoing transmission in NC. If aware, the care, treatment and viral suppression status of potential transmitting partners were also considered. This cross-sectional assessment relied on named sexual and needle-sharing partner information of acutely-diagnosed cases (index AHI case) collected as part of the STAT program. A complementary cross-sectional analysis of phylogenetically-linked partnerships identified via CHAVI-001 was also conducted.

Study Population

Persons 16 years of age or older, diagnosed with AHI in NC between November 2002 and June 2013 and identified via the STAT program were included in the main analysis. Additionally, all sexual and needle-sharing partners named by the index AHI case in the 8 weeks prior to their diagnosis were included.

For the complementary analysis among CHAVI-001 data, all index AHI cases identified via the STAT program who enrolled on study between May 2006 and December 2011 and their named sexual and needle-sharing partners within the past 12 weeks were included for analysis.

Data for named partners could not be linked between the STAT program and CHAVI-001, therefore the number of partners and their characteristics may be different between data sources.

Exposure Assessment

All named partners were initially classified as identifiable or anonymous. Anonymous partners were not pursued by DIS because identifying information provided by the index AHI case was absent or incomplete. For identifiable partners, the index AHI case provided enough information for DIS to identify the partner and classify as previously-diagnosed or undiagnosed. Undiagnosed partners who were unlocatable or unwilling to be tested were classified as "Unknown." The remaining partners were tested for HIV and were subsequently classified as "HIV-uninfected," "New AHI," or "New chronic HIV infection (CHI)." Among partners not diagnosed with AHI or AIDS at the time of the index AHI case diagnosis, Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) testing results were used to approximate recent (≤6 months) from longstanding infection (>6 months) at the time of transmission using a normalized optical density cut-point of <0.8 on the BED assay. Care and treatment status of previously-diagnosed partners was confirmed by DIS, to classify partners as "in care" (visit with an HIV provider during the 6 months prior to AHI diagnosis) or "on ART" (receipt of ART or VL below the detectable limits of the reported test during the 6 months prior to the index AHI case diagnosis).

Diagnosis status (new AHI, new CHI, or previously-diagnosed) was assigned to all HIV-infected partners. For previously-diagnosed partners for whom complete HIV care and treatment data were reported by DIS, we assigned care and treatment status at the time of the index AHI case diagnosis (not in care, in care and not on ART, in care and on ART). Because quantitative VLs are not collected as part of the STAT program, we extracted all partner VLs reported in

eHARS between 6 months before to 2 months after the index AHI case diagnosis date. To assess viral suppression (<200 copies/ml) status near transmission, we considered only the closest VL to the index AHI case's diagnosis date. If VLs for previously-diagnosed partners were identified both before and after the index AHI case diagnosis date, the earlier VL was used to assess viral suppression near transmission.

Between May 2006 and December 2011, all index AHI cases identified via the STAT program were referred for evaluation at the University of North Carolina at Chapel Hill (UNC-CH) or Duke University, and offered enrollment in CHAVI-001. Blood samples were collected from patients at the time of enrollment in addition to basic demographics and HIV testing history. The HIV status for all partners within 12 weeks of the diagnosis date of each index AHI case was collected by the CHAVI-001 field coordinator in a method similar to that described with the STAT program. Locatable partners were offered enrollment in CHAVI-001, regardless of HIV status and blood samples were collected for HIV-infected partners at enrollment.

Cell-free blood plasma was extracted from blood samples provided by index AHI cases and HIV-infected partners enrolled in CHAVI-001 to isolate viral RNA using the QIAMP Viral RNA Mini Kit (Qiagen). For each sample, approximately 10,000 to 20,000 viral RNA copies were extracted and eluted. Single genome amplification of the *env* gene was performed using a limiting dilution, as previously described.[129-138] Additionally, bulk sequences of *pro-pol* amplicons were derived from Genosure® or the TRUGENE® HIV-1 assay (Siemens Healthcare Diagnostics, Tarrytown, NY).

DNA sequence alignments on either full length *env* or *pro-pol* amplicons were performed using Clustal W 2.0.7.[136] Phylogenetic trees were generated using a neighbor-joining method

(MEGA 4.0) with inclusion of random subtype B sequences.[137] Transmission pairs were confirmed by co-clustering on phylogenetic trees with high bootstrap values (>95%). Pairwise DNA distances computed using MEGA 4.0 and Highlighter plots (www.hiv.lanl.gov) were visualized to confirm transmission pairs had identical or nearly identical sequences.

Once a phylogenetically-linked transmission pair was identified, Bayesian analysis was used to distinguish the donor from the recipient in the pair based on the date of the blood sample and contact dates reported during the field investigation. Markov Chain Monte Carlo simulation was used to estimate the time of divergence from the most recent common ancestor in Bayesian Evolutionary Analysis by Sampling Trees (version 1.4.8), as previously described.[139]

Statistical Analysis

Each index AHI case was classified according to the pattern of information collected about the HIV status of named partners [Table 4.1]: A) the HIV status of all partners is known and only one is HIV-infected, B) >1 HIV-infected partner (with or without additional unknown/anonymous partners) or one HIV-infected partner with additional unknown/anonymous partners, C) only partners of unknown/anonymous status and D) no HIV-infected or partners of unknown/anonymous partners status.

Diagnosis status and when available, care and treatment status, were estimated for the most likely HIV-infected transmitting partner named by index AHI cases. For index cases naming only 1 HIV-infected partner with the status of all other partners known (Type A), this partner was assumed to be the most-likely transmitting partner. The proportion of HIV-infected partners and 95% confidence intervals (CI) by HIV diagnosis, care and treatment status were estimated.

For index AHI cases naming >1 potential transmitting partner (HIV-infected and/or anonymous/unknown status) as part of the STAT program investigation, we were less certain of the most likely-transmitting partner. To provide a reasonable estimate of the diagnosis, care, and treatment characteristics of the most likely transmission source among named HIV-infected partners for these index AHI cases (Type B), we repeatedly, randomly sampled HIV-infected partners 1000 times with replacement. The repeated sampling allows for an accurate estimate of diagnosis, care, and treatment status to be made among multiple HIV-infected partners are named.[140] The proportion and 5th and 95th percentiles of sampled HIV-infected partners by HIV diagnosis, care, and treatment status were then reported. For index AHI cases naming 1 HIV-infected partner (Type B1), the probability of selection was 1, while the probability of selection for index AHI cases naming >1 HIV-infected partners (Types B2 and B3) was 1/(number of named HIV-infected partners). Index AHI cases naming only potential transmitting partners of unknown status (Type C) were not included in the repeated sampling analysis as HIV diagnosis, care and treatment status were unspecified and the most likely transmission source could not be estimated.

Among phylogenetically-linked cases identified via CHAVI-001, the proportion and 95% Confidence Intervals (CI) of new AHI, new CHI, and previously-diagnosed partners was estimated. Treatment status was estimated based on the partner's reported ART history at enrollment. HIV care status could not be estimated for partners identified via CHAVI-001 because this information was not collected as part of the study and data collected via the STAT program could not be linked to these partners.

All statistical analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC).

Aim 2: Spatial assessment of early and late stage HIV diagnoses in NC

Study Design

In Aim 2, we assessed the spatiotemporal clustering of new diagnoses in NC by stage of disease as determined by HIV testing results. Using a case-only design within the context of an ecological framework, we aimed to determine if and how high rate clustering by disease stage at diagnosis has changed in NC over time. We used surveillance data maintained by 3 different NC Division of Public Health (DPH) sources: 1) the NC Counselling and Testing Report (CTR) database, 2) the NC STAT program, and 3) the NC electronic HIV/AIDS Reporting System (eHARS). The use of data collected for surveillance purposes represents real-world HIV testing behaviors that have not been modified by study monitoring.

Study Population

All persons aged 16 years and older and newly-diagnosed with HIV in a publicly-funded testing site [Table 4.2] between July 2005 and June 2013 and residing within a 52-county study area in central NC [Figure 4.1] were considered for analysis. We geocoded all cases to their self-reported address at the time of diagnosis as recorded in eHARS using an ESRI (Redlands, CA)-supplied NC street basemap and the testing population to their self-reported zip code at the time of diagnosis as recorded in the CTR database to a population-weighted random location in a ESRI NC zip code basemap using ArcGIS (version 10.1, ESRI). Persons whose testing was conducted at a correctional facility were excluded from analysis as their motivation for testing may be different.

To estimate the underlying testing population at a publicly-funded testing site, we deduplicated HIV tests reported in the CTR system based on recorded name, date of birth, race,

and gender using The Link King Program (version 7.1.21, Camelot Consulting Olympia, Washington). Spelling and data entry errors were not uncommon in this dataset, so we relied on both deterministic and probabilistic linkages generated by The Link King Program.

Probabilistic linkage occurs through statistical analysis of the similarity between data elements record-pairs. Weights and scaling factors based on the available data are used to generate a score for each record pair. Weights reflect the relative importance of specific data elements in predicting a match and scaling factors adjust the weights based on the frequency with which that specific data value occurs in the data being analyzed. Cut-points for the score are derived to identify definite matches, possible matches and non-matches.[141]

In deterministic linkage, criteria used to indicate a match between records are set outside of and known prior to the linking process. The Link King Program allows for some discrepancy in the deterministic linking process through the incorporation of "less certain" equivalence algorithms.[141]

The sensitivity and positive predictive value of linkages produced by The Link King Program have been found to be >90%, when using reviewers' decision as the gold standard.[141] We used the default settings to indicate a match between records in all instances except for the following: 1) no minimum disagreement weight was set for zip codes (i.e. zip codes could be different and the records could still match) and 2) we did not pre-specify the minimum weight for probabilistic linkages.

Using The Link King, we generated 2 estimates of the testing population in which we deleted non-exact matches (conservative estimate) or kept non-exact matches (liberal estimate) categorized in the lowest linkage certainty categories (4, 6, and 7) by the Link King program

(version 6.4). The testing population based on the conservative estimate was used to calculate testing rates for the main analysis.

Exposure Assessment (Stage of Disease at Diagnosis)

Using a 3-step process, we assigned all new diagnoses a stage of disease at diagnosis (AHI, RHI, Chronic HIV Infection (CHI), and AIDS) based on STAT, STARHS, and standard HIV testing results [Figure 4.2]. First, STAT cases were linked to eHARS to identify all cases diagnosed with AHI. Next, all cases diagnosed with AIDS in eHARS (as defined by either a CD4 cell count <200 cells/mm^3, a CD4 count < 14% of all lymphocytes, or a diagnosis of one or more AIDS-defining illnesses) at the time of or within 6 months of an HIV diagnosis were identified. For the remaining cases, STARHS results were used (when available) to approximate recent (≤6 months) from longstanding infection (>6 months), based on a normalized optical density cut-point of <0.8 on the BED assay.[17] All other diagnoses were classified as CHI. If non-AHI, non-AIDS cases did not have STARHS testing, their disease stage could not be determined. These cases were therefore excluded from analysis. Since diagnosis during AHI is rare in NC,[102] AHI and RHI were considered together as one stage of disease, Early HIV infection (EHI) for Aim 2.

Outcome Assessment (HIV diagnosis rate by stage of disease and testing period):

All geocoded cases were aggregated to the 2010 census tract boundaries to maintain confidentiality while still exhibiting variability in space.[142] The study area contains 1597 (73.1%) of the census tracts in NC in 2010. Some census tract boundaries changed when the results of the 2010 census were released. A difference in clustering due to these changes was expected to be minor.[143]

Each case was assigned a testing period of diagnosis based on when they were diagnosed in relation to the release of the CDC recommendations for opt-out testing in September 2006. Assuming a slight delay between the release of the recommendations and the implementation of opt-out testing in practice, we classified cases diagnosed between July 2005 and December 2007 as being diagnosed before CDC recommendations (Period 1). Cases diagnosed between January 2008 and December 2010 were classified as being diagnosed immediately after the CDC recommendations (Period 2). Finally, cases diagnosed between January 2011 and June 2013 were classified as being diagnosed after the recommendations with some delay (Period 3).

To compare disease maps across multiple time periods, we assigned HIV diagnosis rates [number of cases tested per tract/(number of people testing in each tract*time)] by stage of disease and testing period to the geographic center (centroid) of each census tract for subsequent analysis, estimation, and mapping.

Statistical Analysis:

BME: Bayesian Maximum Entropy (BME), specifically the uniform model extension of BME (UMBME), was used to describe the changes in spatial distribution of HIV diagnosis rates by stage of disease in each testing period. BME is a geostatistical technique in which disease rates can be estimated for a given interval by using the surrounding observations in both space and time.[144-146] The main output of this method is a series of spatially-dependent maps. For relatively rare diseases, such as HIV, calculating crude rates from routinely collected surveillance data indexed at a small geographical resolution poses statistical problems due to the sparse nature of the data.[147-150] Error due to sampling variability introduces observational noise into the map that may obscure and therefore lead to incorrect inferences about HIV diagnosis patterns in NC.

BME is a useful tool in the evaluation of rates because it is able to separate this noise from actual disease patterns to provide an accurate picture of disease clusters.[151]

In BME methodology, a spatiotemporal random field $X(s,t)$ is used to assign probabilities to a set of possible distributions that describe the disease in space, s, and time, t. These probabilities provide the basis for the prior ("total") knowledge that is known about the disease.

Total knowledge is divided into the general knowledge base, G, and the site-specific knowledge base, S. The general knowledge base includes theories, laws, covariance structures, and mean trends. This information is processed using the maximum entropy principle and yields a prior probability density function model for the spatiotemporal disease map. The site-specific knowledge refers to measured data over the spatiotemporal random field, $X(s,t)$. Data measured with low error and high certainty are referred to as "hard data," and data measured with high error and low certainty are referred to as "soft data". This stage is a generalized form of the likelihood stage in traditional Bayesian methods.[146]

A posterior pdf of the disease outcome at each estimation point is generated using a Bayesian conditionalization rule to update the prior pdf with the site-specific data. This results in a series of smoothed maps that are temporally dependent if the composite spatiotemporal BME approach was applied. Error maps associated with the disease estimates are also generated at this stage [Figure 4.3].

In UMBME, measurement error is assumed to be distributed uniformly around the observed rate in an interval the size of 1/testing population. Therefore, observed diagnosis rates are treated as probabilistic ("soft") data with measures of uncertainty as defined by the uniform distribution interval. BMEGUI (version 3.0.1, Chapel Hill, North Carolina), the computer

software used to implement the BME approach, was used to conduct the composite space-time analyses and mapping.

Once a smoothed map was created for each of the 3 disease stages during the 3 testing periods under consideration, maps were normalized to the same scale to assess percent overlap of high diagnosis rate areas. A cut-off point at the top 10^{th} percentile on this normalized scale was used to dichotomize diagnosis rates in each pixel as high versus low rates. The proportion of "high rate" pixels on one map that were also "high rate" on another map was assessed 1) across each testing period within each disease stage and 2) across each disease stage within each testing period.

We varied the cut-off point used to define "high-rate" clusters in sensitivity analyses to the top 25^{th} and 50^{th} percentiles to evaluate the effect of the definition of "high rate" on our conclusions.

Kulldorff's Spatial Scan Statistic: The Kulldorff spatial scan statistic (SaTScan software, Information Management Services, Inc., Silver Spring, Maryland) was applied to identify the presence and location of clusters by disease stage and testing period using census tract diagnosis rates. High-rate clusters were identified as areas where the observed number of cases was greater than the expected number of cases based on spatial randomness.

The Kulldorff's spatial scan statistic uses a Poisson model where the observed number of cases is compared to the background population data and the expected number of cases in each census tract is proportional to the size of the population at risk (i.e. the estimated testing population) [74]. The null hypothesis for the Kulldorff spatial scan statistic states that the probability of being a case is the same in all parts of the map, while the alternative hypothesis

states that the probability of being a case inside the window (p) is greater than the probability of being a case outside the window (q).[152] The alternative hypothesis suggests a significant degree of spatial clustering is present inside the window.

A likelihood ratio test statistic was calculated for each potential cluster:

$$L(z)=Lp>q/\ Lp=q$$

The maximum likelihood ratio (L(z)max) value is evaluated first by performing a log-likelihood ratio test. This test determines the approximate p-value for the L(z)max cluster using Monte Carlo simulation which randomly allocates cases in the study area. Potential clusters with a corresponding observed likelihood ratio test statistic within the upper 5% tail of the corresponding simulated (expected) distribution will be classified as statistically significant at the 0.05 level.

The percent overlap of high-rate clusters identified via the Kulldorff spatial scan test statistic by disease stage-time period categories was calculated, as described in the BME analysis. Briefly, "high-rate" census tracts are those that the Kulldorff spatial scan statistic estimated to be included in a statistically-significant cluster. The percent overlap of census tracts identified as being involved in "high-rate" clustering by each disease stage-testing period category will be calculated.

Aim 3: Distance to a testing site and stage of disease at diagnosis

Study Design:

The underlying research question for Aim 3 is whether increased distance to a publicly-funded testing site is associated with HIV diagnosis at later stages of disease. Because both the outcome (stage of disease at diagnosis) and the exposure (distance to testing site) will be

collected a single time point, this analysis will be cross-sectional in nature. Using the home addresses of all newly diagnosed persons that were collected for standard surveillance purposes by the NC DPH and geocoded in Aim 2, we calculated the geographic (i.e. road network) distance between the home address and the both the 1) the HIV testing site of diagnosis and 2) nearest publicly-funded HIV testing site.

In this analysis, we assumed people living near one another were more similar than those living farther apart from one another in terms of socioeconomic status, access to transportation, education, and employment and would exhibit similar HIV test-seeking behaviors. Therefore, we used census tract as a proxy for one's neighborhood in log binomial models with generalized estimating equations to account for these second-level characteristics. These models produce a population averaged estimate of the risk of late stage diagnosis across the entire study areas that could be useful for public health officials and policymakers when deciding how and where to allocate resources.

Study Population:

The eligibility criteria and study population for Aim 2 is identical to that used to identify newly-diagnosed cases for Aim 2.

Exposure Assessment:

Residential addresses of all new HIV cases were geocoded to an ESRI-supplied NC street basemap using ArcGIS, as described in Aim 2. Census tract at diagnosis was assigned based on the geocoded residential address.

All publicly-funded HIV testing sites that provide samples to the state lab of public health for processing were geocoded to their physical address using the same method used to geocode the residential addresses of new HIV cases. The network distance (miles) between each case's residential address and both 1) the testing site of diagnosis and 2) the closest publicly-funded testing site were calculated in ArcGIS using the Network Analyst extension.

We assessed the most appropriate form for the continuous distance variables to model the association between distance and the risk for late stage diagnosis. To determine the most appropriate form, distance was coded continuously, as a categorical variable, and using upper and lower tail restricted quadratic spline variables. Risk of late stage disease and 95% confidence intervals were calculated and plotted for each form of the distance variables and p-values for trend and confidence limit ratios were assessed to determine the precision and accuracy of each coding method. Because the dose-response relationship increased until mile 5 and then plateaued, we decided to dichotomize both distance variables ($\leq$ 5 miles versus >5 miles) to increase precision and parsimony.

Outcome Assessment:

The main outcome under analysis is the stage of disease at diagnosis. All cases were assigned a stage of disease at diagnosis as described in Aim 2 (Figure 4.2). We dichotomized stage of disease into early (AHI and RHI) diagnoses and post-early (CHI and AIDS) diagnoses for all analyses for Aim 3.

Statistical Analysis:

Because place frames a person's behavior, we assessed the presence of spatial autocorrelation between the geocoded addresses of early and post-early diagnoses with the global Moran's *I* statistic in ArcGIS.

Moran's *I* is defined as:

$$I = \frac{N}{\sum_i \sum_j w_{ij}} \frac{\sum_i \sum_j w_{ij}(X_i - \bar{X})(X_j - \bar{X})}{\sum_i (X_i - \bar{X})^2}$$

Where *N* is the number of spatial units indexed by *i* and *j*. *X* is post-early stage disease, $\bar{X}$ is the mean of *X*, and w_{ij} is an element of a matrix of spatial weights.

The global Moran's *I* evaluates whether diagnoses are clustered, dispersed or random in space by stage of disease.[152] Because the global Moran's *I*, was not statistically significant (p=0.5), the cases were assumed to be distributed randomly in space by disease stage and it was not necessary to account for spatial autocorrelation in any further statistical modeling.

Binomial risk models (log link and binomial distribution) using generalized estimating equations and a compound symmetry correlation matrix, were fit to estimate prevalence ratios (PR) and robust 95% confidence intervals (CI) for late stage diagnoses and by distance (closest site and site of diagnosis). Census tracts, which served as a proxy for unobserved characteristics (e.g. education, income, and employment), were used to account for the clustering of the outcome at the neighborhood level.

Generalized estimated equations (GEE) are used to estimate the parameters of a generalized linear model with possible unknown correlation between outcomes.[153] The main

purpose of GEE models is to estimate the average response over the population rather than subject (or in this case, census tract) specific responses. Our model took the following form:

$$\ln(P(D_{ij}=1|X_{ij})) = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots$$

Where D is post-early stage diagnosis and X represents the set of all exposure variables for subject *i* within census tract *j*.

GEE produces unbiased standard errors even if the working correlation matrix is slightly misspecified through the use of robust or "sandwich" variance estimation.[153] Because we are working with hierarchical data (HIV cases within a census tract), it is unlikely that the correlations vary within a cluster. Furthermore, some census tracts include up to 27 cases. Therefore, to maintain parsimony, a compound symmetry working correlation matrix was used during all modeling with GEE. Compound symmetry assumes variation between census tracts is greater than variation within subjects and requires that only 1 parameter be estimated.

Effect measure modification (EMM) was assessed using likelihood ratio testing. An interaction term was maintained in the model if the difference between the full model (interaction term present) and the reduced model (no interaction term) was statistically significant at an a priori level of $p>0.15$. In this case, the null hypothesis that the interaction term equals 0 was rejected and variable was classified as an EMM. No variables under consideration (age, race/ethnicity, gender, time period, risk group, rurality, and testing site) were considered EMMs based on these methods.

For all variables not considered to be EMMs, we used change-in-estimate methods to assess confounding of the exposure-outcome relationship in the covariates listed above. Change-in-estimate ($|\ln(CoOR)|$) was calculated by comparing the full model to a reduced model with the

potential confounder removed. This was repeated for all potential confounders. All variables that change the prevalence ratio estimate by less than 10% when removed should be dropped from the final model.

Using these methods, no covariate was classified as a confounder. However, a review of the literature and construction of a directed acyclic graph [Figure 4.4] suggest the minimally sufficient adjustment set included race/ethnicity, rurality, and testing period. Therefore, these confounders were considered in all adjusted models. Because census tract was used to account for clustering of the outcome and was also used to determine urban/rural status, we did not directly adjust the models for rurality.

Tables and Figures

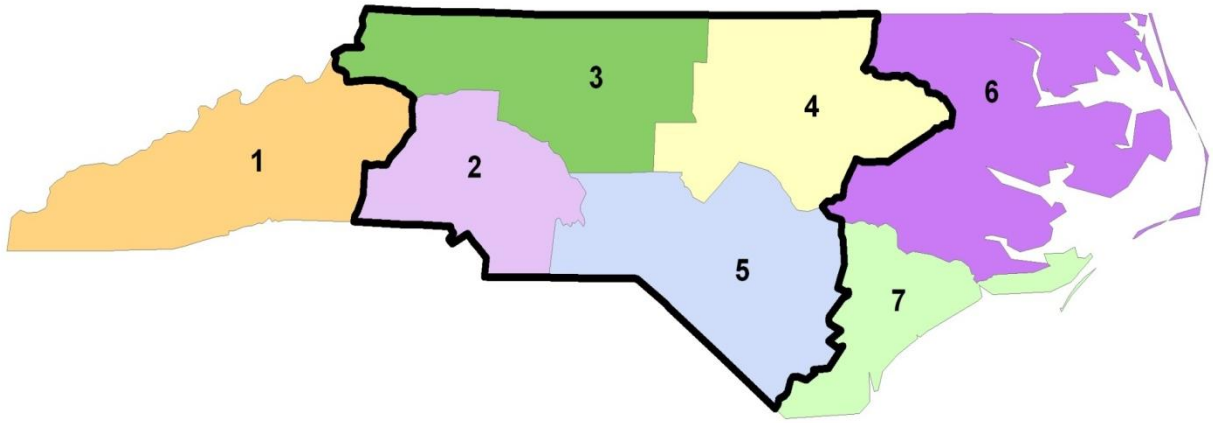
Table 4.1 Pattern of Partner Status

Type	Number of known HIV-infected partners	Number of known HIV-uninfected partners	Number of unknown status partners
A	1	≥0	0
B			
B1	*>1*	*≥0*	*0*
B2	*1*	*≥0*	*≥1*
B3	*>1*	*≥0*	*≥1*
C	0	0	≥1
D			
D1	*0*	*0*	*0*
D2	*0*	*≥1*	*0*

Table 4.2 Publicly-Funded Testing Sites in North Carolina

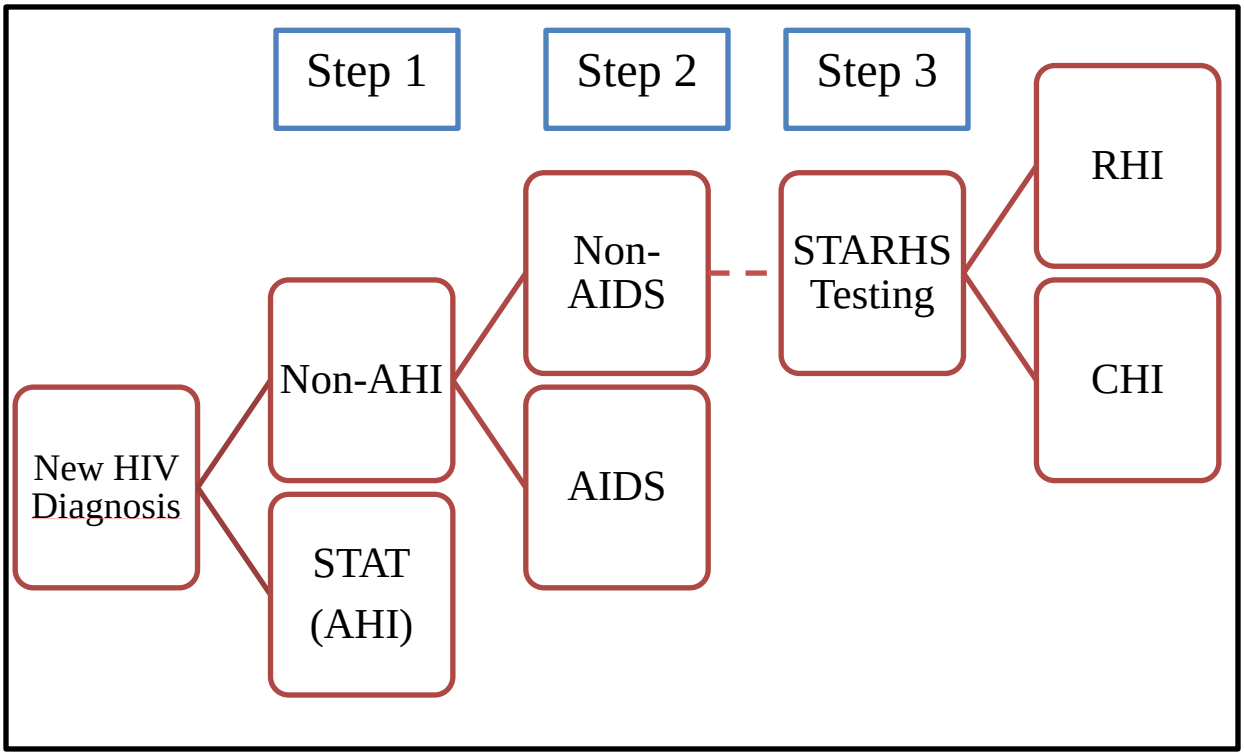
1. HIV Counseling and Testing Services (CTS)
2. Sexually Transmitted Disease Clinic
3. Drug Treatment Clinic
4. Family Planning Clinic
5. Prenatal/Obstetrics Clinic
6. TB Clinic
7. Community Health Center
8. Prison/Jail
9. Field Visits
10. Outreach Testing
11. Hospital/Private Medical Doctor

Figure 4.1 Study Area in Central North Carolina



CAPTION: 52-county study area in central North Carolina roughly corresponds to the North Carolina Division of Public Health Field Services Unit Regions 2 (Charlotte), 3 (Winston-Salem/Greensboro), 4 (Raleigh), and 5 (Fayetteville).

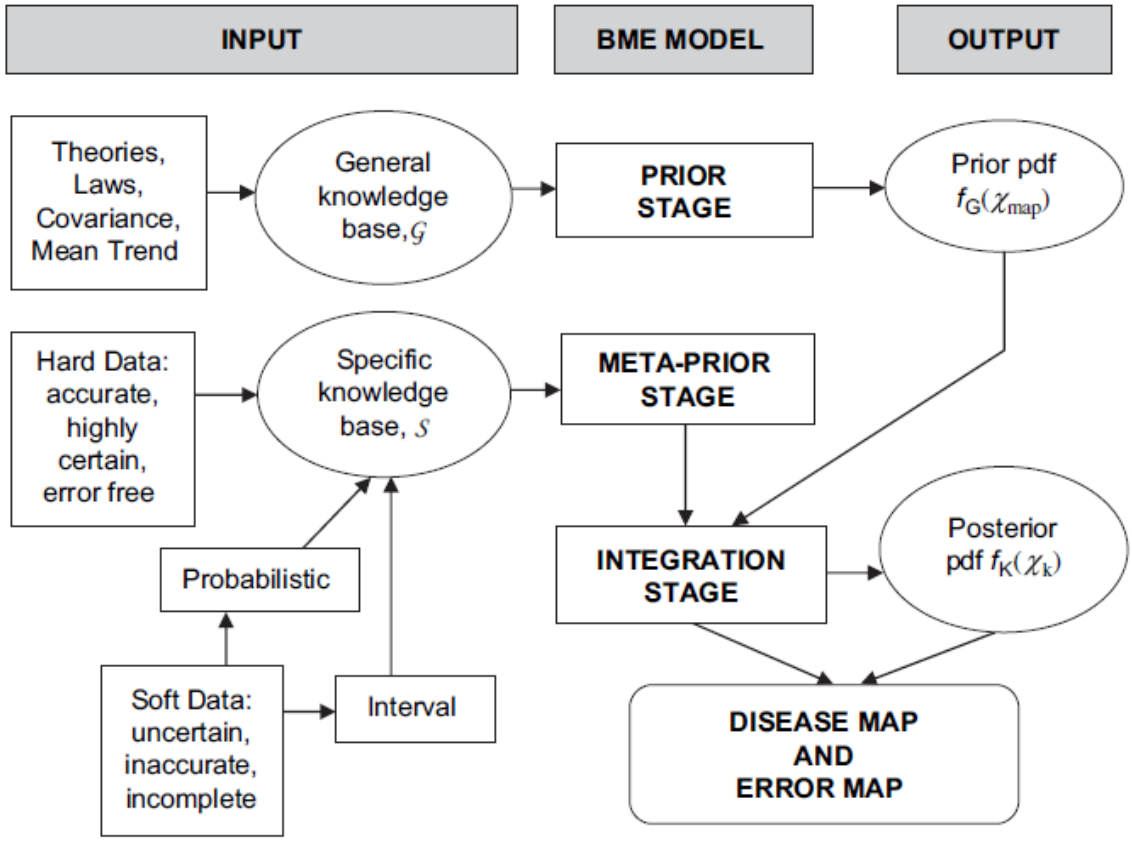
Figure 4.2 Three-Step Algorithm based on HIV testing results reported to the North Carolina Communicable Disease Branch used to determine stage of disease



*AHI=Acute HIV infection; RHI=Recent HIV Infection; CHI=Chronic HIV Infection

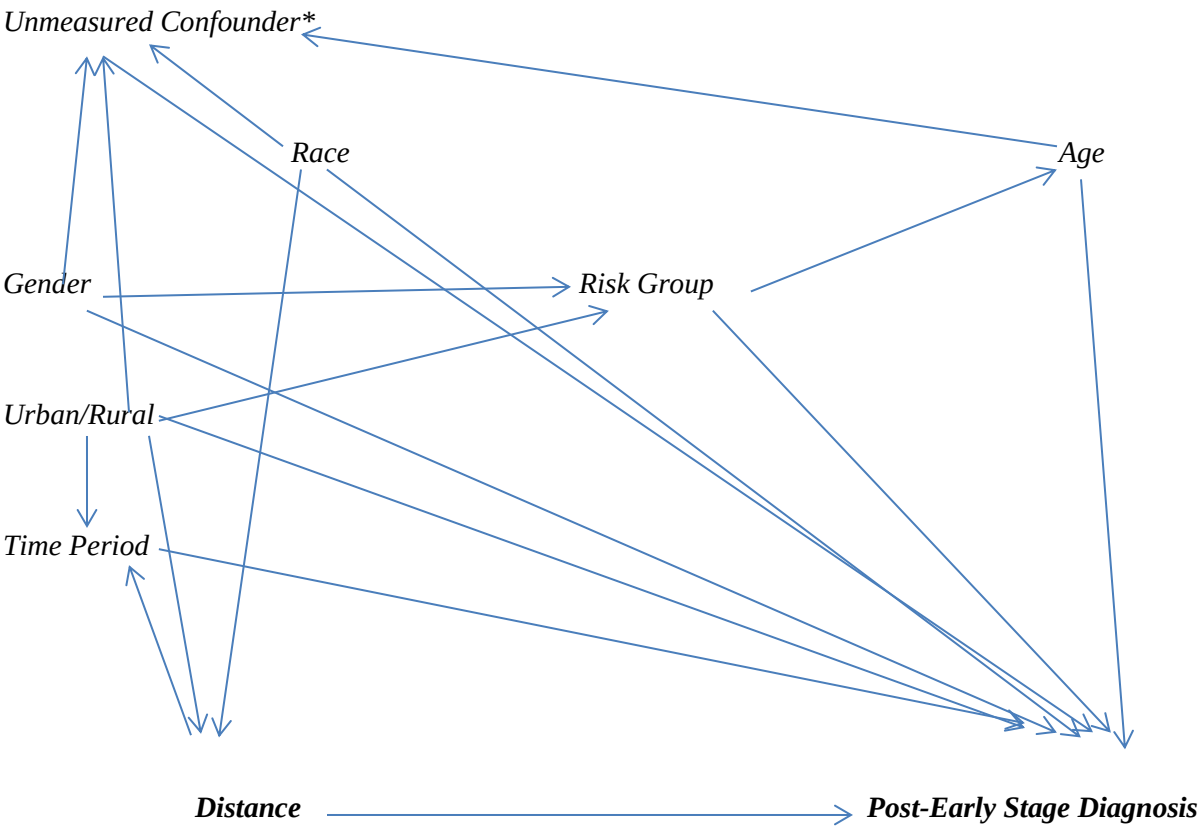
CAPTION: From the pool of all persons newly-diagnosed at a publicly-funded testing site, we first classified all Acute HIV infection identified by the STAT (Screening and Tracing of Active Transmission) program. Next, we used AIDS diagnosis dates reported in eHARS (electronic HIV/AIDS reporting system) to classify AIDS cases. Among the remaining cases with STARHS (Serologic Testing Algorithm for Recent HIV Seroconversion) testing reported in eHARS, we were able to classify Recent from longstanding infection.

Figure 4.3 Conceptual model of the Bayesian maximum entropy (BME) approach



CAPTION: Conceptual model of the Bayesian Maximum Entropy Approach, courtesy of Gesink Law, 2006.[145] Briefly, BME incorporates general knowledge in the form or theories, laws, mean trends, and covariance plots with site specific information that can be either highly accurate ("hard data") or probabilistic ("soft data") to create a posterior probability distribution function (*pdf*) of the disease outcome at each estimation point in a spatiotemporal random field, $X(s,t)$.

Figure 4.4 Directed Acyclic Graph illustrating the association between Distance to a Testing Site and Stage of Diagnosis



*Unmeasured confounder includes income, insurance, and education

CAPTION: Directed Acyclic Graph (DAG) assessing the relationship between distance to a testing site and post-early stage diagnosis, accounting for measured and unmeasured confounders.

CHAPTER FIVE: ONGOING HIV TRANSMISSION AND THE HIV CARE CONTINUUM IN NORTH CAROLINA

Abstract:

Objective: HIV transmission is influenced by status awareness and receipt of care and treatment. We analyzed these attributes of named partners of persons with acute HIV infection (index AHI cases) to characterize the transmission landscape in North Carolina (NC). **Design:** Secondary analysis of programmatic data. **Methods:** We used data from the NC Screening and Tracing of Active Transmission Program (2002-2013) to determine HIV status (uninfected, AHI, or chronic HIV infection [CHI]), diagnosis status (new or previously-diagnosed), and care and treatment status (not in care, in care and not on treatment, in care and on treatment) of index AHI cases' named partners. We developed an algorithm identifying the most likely transmission source among known HIV-infected partners to estimate the proportion of transmissions arising from contact with persons at different HIV continuum stages. We conducted a complementary analysis among a subset of index AHI cases and partners with phylogenetically-linked viruses. **Results:** Overall, 358 index AHI cases named 932 partners, of which 218 were found to be HIV-infected (162 (74.3%) previously-diagnosed, 11 (5.0%) new AHI, 45 (20.6%) new CHI). Most transmission events appeared attributable to previously-diagnosed partners (77.4%, 95% confidence interval 69.4-85.3%). Among these previously-diagnosed partners, 23.2% (14.0-32.3%) were reported as in care and on treatment near the index AHI case diagnosis date. In the subset study of 33 phylogenetically-linked cases and partners, 60.6% of partners were previously diagnosed (43.9-77.3%). **Conclusions:** A substantial proportion of HIV transmission in this

setting appears attributable to contact with previously-diagnosed partners, reinforcing the need for improved engagement in care after diagnosis.

Introduction:

Antiretroviral treatment (ART) reduces the probability of HIV transmission by suppressing plasma viral load (VL) to undetectable levels.[1,2,78] However, current estimates of the HIV care continuum, or cascade, indicate that most HIV-infected persons in the US are not achieving viral suppression. [8,154] Undiagnosed persons and those diagnosed but not in care, on treatment, and virally suppressed, are potential sources of ongoing transmission and high-priority targets for maximizing HIV prevention.

Current estimates of the transmission contributions made by persons aware and unaware of their HIV status are based on mathematical models.[10,11,43] Empirical estimates to compare to modeling studies are difficult to obtain, as they require information at the time of HIV acquisition about newly infected persons' transmitting partners. However, few people are diagnosed near the time of HIV transmission,[100,104,126,155-157] and many do not know with certainty from whom they acquired HIV.

The North Carolina (NC) Screening and Tracing of Active Transmission (STAT) program has detected persons with acute HIV infection (AHI) since 2002, providing a unique opportunity to characterize the partners of newly infected persons near the time of transmission.[100,127] The primary objective of this secondary analysis of STAT data is to classify the HIV status and diagnosis, care, treatment, and viral suppression status of a) all traceable partners and b) the most likely transmission source among identified HIV-infected partners for acutely-infected persons (index AHI cases) diagnosed in NC between 2002 and 2013. The first

analysis characterizes the overall continuum-related landscape in a network where HIV incidence is known to be actively occurring; the second describes the continuum attributes of persons specifically deemed the most likely transmission source for incident cases. The overarching goal of this analysis is to provide information for designing, modeling, and targeting HIV care and treatment services.

Methods:

For each index AHI case aged ≥16 years and diagnosed between November 2002 and June 2013 in NC, we assessed the HIV status and diagnosis, care, and treatment status (if available) of sexual and needle-sharing partners he/she named at the time of diagnosis. Data for the main analyses originated from the STAT program, a NC Division of Public Health (DPH) effort to identify persons with AHI. In a complementary analysis, we used data from the Center for HIV/AIDS Vaccine Immunology 001 Study: Acute HIV Infection Prospective Cohort Study (CHAVI-001), an observational study examining factors related to HIV transmission.[128]

STAT Program

The STAT program identifies index AHI cases through testing at health departments and in community settings (e.g. private providers).[100,127] AHI is defined as: a) a negative or indeterminate antibody test and reproducibly detectable HIV RNA, or b) a positive antibody test with seronegative documentation within 30 days.

Disease intervention specialists (DIS) contact index AHI cases within 72 hours of release of HIV test results and perform an initial interview, conduct confirmatory HIV testing, and make referrals to HIV care providers. DIS also attempt to find, counsel, and provide HIV testing for all named partners during the 8 weeks prior to the index AHI case's diagnosis date. Before 2012, the

NC DPH required index AHI cases to sign a Health Insurance Portability and Accountability Act form for DIS to report detailed demographic and testing information about named partners for the STAT program.

Partner HIV Status Determination

All partners were classified as identifiable or anonymous. Anonymous partners were not pursued by DIS because identifying information provided by the index AHI case was absent or incomplete. For identifiable partners, the index AHI case provided enough information for DIS to identify the partner and classify him/her as "previously-diagnosed" or "undiagnosed" based on a search of electronic HIV surveillance databases. Undiagnosed partners who were not located or not willing to be tested were classified as "Unknown." The remaining undiagnosed partners were tested for HIV and classified as "HIV-uninfected," "New AHI," or "New chronic HIV infection (CHI)." For all HIV-infected partners not diagnosed with AHI or AIDS within 6 months of the index AHI case diagnosis, results of the Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) were used (when available) to approximate recent (≤6 months) and longstanding (>6 months) infection at the time of transmission, based on a normalized optical density cut-point of <0.8 on the BED assay.[17]

Partner Diagnosis, Care, Treatment, and Viral Suppression Status

Per STAT program protocol, DIS investigate care-seeking and treatment behaviors of previously-diagnosed partners in the 6 months before the index AHI case's diagnosis for classification as "in care" (HIV provider-confirmed visit and/or 1 clinical lab present in surveillance databases) and/or "on ART" (HIV provider-confirmed receipt of ART and/or a VL below the detectable limits of the reported test in surveillance databases).

We classified the diagnosis status (new AHI, new CHI, or previously-diagnosed) of all HIV-infected partners and the reported care and treatment status at the time of the index AHI case diagnosis (not in care, in care and not on ART, in care and on ART, unclassified care and treatment) of all previously-diagnosed partners. Because quantitative VLs are not collected as part of the STAT program, we extracted all partner VLs reported in the NC electronic HIV/AIDS reporting system between 6 months before to 2 months after the index AHI case diagnosis date. To assess viral suppression (<200 copies/ml) status near transmission, we considered only the closest VL to the index AHI case's diagnosis date. For previously-diagnosed partners with VLs before and after the index AHI case diagnosis date, the closest VL before diagnosis was used to assess viral suppression near transmission.

Likely Transmission Source Identification

Each index AHI case was classified according to the HIV status pattern of named partners (first four columns of Table 5.1): A) the HIV status of all partners was known and only one was HIV-infected, B) >1 HIV-infected partner (with or without additional unknown/anonymous partners) or one HIV-infected partner with additional unknown/anonymous partners, C) only partners of unknown/anonymous status, and D) no HIV-infected or unknown/anonymous partners.

For index cases naming only 1 HIV-infected partner with the status of all other partners known (Type A), this single HIV-infected partner was assumed to be the most likely transmitting partner. For index AHI cases naming >1 potential transmitting partner (i.e., known HIV-infected or status-unknown partner) with at least one confirmed HIV-infected partner (Type B), we assumed that the likely transmitting partner was among those partners named. We repeatedly,

randomly sampled the known HIV-infected partners 1000 times with replacement to identify the most likely transmitting partner. For index AHI cases naming 1 HIV-infected partner (Type B2), the probability of selecting that partner was 1, while the probability of selection for each partner of index AHI cases naming >1 HIV-infected partner (Types B1, B3) was 1/(number of named HIV-infected partners). Index AHI cases not naming any HIV-infected partner (Types C and D) were excluded from these analyses. For these cases, the diagnosis, care and treatment status for the most likely transmission source among identified partners could not be estimated because all partners were HIV-uninfected or of unknown status.

HIV Care Continuum Analyses

To describe the overall transmission landscape in this network, we calculated the proportion of all HIV-infected partners with each diagnosis, care, and treatment status. To describe the putative transmission contributions of the various continuum stages, we calculated these proportions only among the persons identified as the most likely transmission source for each incident case. Although no single sample from our repeated sampling approach captures all transmitting partners, the combination of the samples provides a reasonable estimate of the range of plausible values for the diagnosis, care, and treatment status of the most-likely transmitting partner among named HIV-infected partners.[140]

CHAVI-001

Between 2006 and 2011, all index AHI cases identified via the STAT program were referred for evaluation at the University of North Carolina at Chapel Hill (UNC-CH) or Duke University, and offered enrollment in CHAVI-001. Study investigators collected basic demographics for each enrolled index AHI case (representing a subset of the STAT index AHI

cohort) and data for all partners within 12 weeks of their diagnosis date. Locatable partners were offered enrollment in CHAVI-001, regardless of HIV status.

Upon enrollment, cell-free plasma was extracted from samples provided by index AHI cases and HIV-infected partners to isolate viral RNA using the QIAMP Viral RNA Mini Kit (Qiagen). DNA sequence alignments, phylogenetic tree generation, and transmission pair confirmation were performed on either full length *env* genes resulting from single genome amplification or *pro-pol* amplicons derived from bulk sequencing as previously described.[129-138] The donor was distinguished from the recipient among all phylogenetically-linked transmission pairs, using Bayesian Evolutionary Analysis by Sampling Trees (BEAST) v.1.4.8, as previously described.[129,139]

CHAVI-001 Data Analysis

The HIV status of partners named by index AHI cases enrolled in CHAVI-001 was assigned based on CHAVI-001 field investigation and the proportion of phylogenetically-linked partners with each diagnosis status was estimated. We based treatment status of phylogenetically-linked partners on reported ART history collected at enrollment. Partner care status was not collected for study purposes and therefore not assigned. Data from the STAT program could not be linked to CHAVI-001 partners for reasons of confidentiality.

All statistical analyses were conducted in SAS version 9.3 (Cary, NC). The study was approved by the UNC-CH Institutional Review Board.

Results:

STAT

Index AHI cases

Between November 2002 and June 2013, 358 index AHI cases were identified via the STAT program. Index AHI cases were predominantly Black (70.1%), male (83.0%) and self-identified as men who have sex with men (MSM) (66.5%). Nearly one-quarter of cases had been diagnosed with a sexually transmitted infection within 2 month of their AHI diagnosis (24.3%) [Table 5.2].

Partner Overview

Overall, 932 sexual partners (4 of whom were also needle-sharing) were reported by index AHI cases in the 8 weeks prior to their diagnosis (per-index median=2; range 0-27). Index AHI cases provided detailed information for 656 partners (70.4%) as part of the STAT program [Figure 5.1a]. Most partners with detailed information were male (85.8%) and Black (62.7%), with a median age of 28 years (IQR 23-37) [Table 5.2].

Of the 656 partners with detailed information, 218 (33.3%) were HIV-infected. Of these, 162 (74.3%) were previously-diagnosed and 56 (25.7%) were newly-diagnosed (11 AHI and 45 CHI). An additional 210 partners (32.1%) were HIV-uninfected (antibody and HIV RNA negative) at DIS follow-up. The HIV status for 228 partners (34.8%) remained undetermined after the DIS investigation (78 anonymous, 31 counseling-and-testing refusals, 48 testing-only refusals, 71 unlocatable or unclassified based on DIS reports) [Figure 5.1a].

Recent HIV infection could be assessed for 171 (82.6%) HIV-infected partners not diagnosed during AHI (145 previously-diagnosed and 26 newly-diagnosed). Ten (38.5%) new diagnoses and 8 (5.5%) partners previously-diagnosed in the 6 months before the index AHI case had STARHS testing indicative of recent HIV infection at the time of their diagnosis. Only 3 (37.5%) of the 8 previously-diagnosed, recently-infected partners had entered care between their diagnosis and the index AHI case diagnosis; one had initiated ART. Including new AHI diagnoses, a total of 29 (13.3%) HIV-infected partners were estimated to have been infected within 1 year of the index AHI case.

Among all 162 previously-diagnosed partners, 26 (16.0%) were not in care, 51 (31.5%) were in care but not on ART, and 48 (29.6%) were in care and on ART at the time of the index AHI case diagnosis [first bar of Figure 5.2/Supplemental Table A3.1]. Care and treatment status was left undetermined after DIS investigation for the remaining 37 (22.8%) previously-diagnosed partners.

Overall, 40 (18.3%) previously-diagnosed partners had a VL reported in a NC surveillance database 6 months before to 2 months after the index AHI case diagnosis; 19 (33.9%) newly-diagnosed partners had a VL in the 2 months after the index AHI case diagnosis. An additional 31 (14.2%) partners had a VL reported more than 6 months before the index AHI case diagnosis, suggesting potential loss from care. The partners' median VL near the time of the index AHI case diagnosis was higher in newly-diagnosed (55,698 copies/ml [range 1,521-10,000,000]) as compared to previously-diagnosed partners (27,153 copies/ml [range 19-3,402,708]) [Figure 5.3]. Among the 40 previously-diagnosed partners in care and with an available VL, 30 (75.0%) were unsuppressed in the period 6 months before to 2 months after the index AHI case diagnosis. Of the 10 virally suppressed partners at the time of their most recent

VL, 4 had detectable VLs in the year surrounding the index AHI case diagnosis, indicating unsustained suppression.

Likely Transmitting Partner Estimates

A total of 106 index AHI cases named only 1 potential HIV-infected transmitting partner with all other partners testing negative (Type A), 68 named >1 potential transmitting partner with at least one confirmed HIV-infected partner (Type B), and 127 named only potential transmitting partners of unknown status (Type C). The remaining index AHI cases either did not name any partners during the 8 weeks prior to their diagnosis (N=38) or only named HIV-uninfected partners (N=19) (Type D) [Table 5.1].

Among index AHI cases naming only one HIV-infected partner with all other partners testing negative (Type A), over three-quarters of transmission events appeared attributable to contact with previously-diagnosed partners (77.4%, 95% confidence interval (CI) 69.4-85.3%) [2nd bar of Figure 5.2/Supplemental Table A3.1]. Among previously-diagnosed partners (N=82), the proportion of partners reportedly not in care (23.2%, 95% CI 14.0-32.3%), in care and not on ART (26.8%, 95% CI 17.2-36.4%), in care and on ART (23.2%, 95% CI 14.0-32.3%), and with unclassified care/treatment status (26.8%, 95% CI 17.2-36.4%) were roughly equivalent. Of the 38 previously-diagnosed partners with a VL near the time of the index AHI case diagnosis, 94.7% were unsuppressed (N=36, 95% CI 87.6-100.0%)

Repeated sampling methods resulted in similar diagnosis, care, and treatment status estimates among index AHI cases naming >1 potential transmitting partner with at least one confirmed HIV-infected partner (Type B) [3rd bar of Figure 5.2/Supplemental Table A3.1] and

when combining these two groups (Types A and B) [4th bar of Figure 5.2/Supplemental Table A3.1].

CHAVI-001

Overall, 55.5% (N=117) of all index AHI cases identified by the STAT program between May 2006 and December 2011 enrolled in CHAVI-001 and were considered in the complementary analysis [Table 5.2]. As observed by the STAT program, most index AHI cases were male (87.2%), Black (65.0%) and young (median age=25 years, IQR 21-36).

Index AHI cases reported 367 partners as a part of the CHAVI-001 investigation (per-index median=3; range 0-14), of whom 119 (32.4%) were HIV-infected. Compared to STAT investigations, a smaller proportion of HIV-infected partners identified via the CHAVI-001 study were previously-diagnosed (82 (68.9%) previously-diagnosed, 26 (21.8%) new CHI, and 11 (9.2%) new AHI) [Figure 5.1b]. An additional 126 (34.3%) partners were HIV-uninfected. The status of 122 (33.2%) partners remained unknown (78 anonymous, 44 unlocated or refused testing). Demographics of partners reported during the CHAVI-001 investigation were similar to those observed by the STAT program [Table 5.2]. Seventy (59.8%) index AHI cases named ≥1 HIV-infected partner; only 47 index AHI cases had ≥1 HIV-infected partner enroll on study and provide samples for phylogenetic analysis. The transmitting partner for 33 (70.2%) of these index AHI cases was phylogenetically verified. One additional phylogenetic linkage was identified between 2 index AHI cases diagnosed 2 years apart. Because neither index AHI case named the other during the CHAVI-001 investigation, we could not rule out a shared or intermediary transmitting partner and excluded this pair from further analysis.

Most of the 33 partners phylogenetically-linked to index AHI cases in CHAVI-001 had been previously-diagnosed (60.6%, 95% CI 43.9-77.3%) [4th bar in Figure 5.2/Supplemental Table A3.1], although the contribution is smaller than observed in STAT data. Three linkages were attributable to AHI–to-AHI transmission (9.1%, 95% CI 0.0%-18.9%). All phylogenetically-linked partners were unsuppressed. The median VL of linked partners at transmission was 123,928 copies/ml (range 123,928-2,346,147) for new AHI partners, 62,493 copies/ml (range 2,771-148,042) for new CHI partners, and 72,084 copies/ml (range 10,957-507,795) for previously-diagnosed partners. Although two phylogenetically-linked partners with recognized infection reported a history of ART, neither were on treatment at the time of the index AHI case diagnosis. One partner stopped treatment within 1 month of contact with the index AHI case.

Discussion:

Most observed transmission events in North Carolina appear attributable to contact with previously-diagnosed partners. Roughly one-quarter of these previously-diagnosed partners were reported to be in care and on ART in the 6 months before the index AHI case diagnosis. However, only a small proportion of transmission events were estimated to be a result of previously-diagnosed partners confirmed to be virally suppressed.

These transmission events occur because many previously-diagnosed persons continue to engage in high-risk behaviors with uninfected persons, as seen in our analyses of the transmission landscape incorporating all identified partners. Over one-third of these identifiable partners were HIV-infected; most were aware of their status prior to the index AHI case diagnosis. Consistent condom use was reported with only 16.7% of previously-diagnosed

partners (data not shown). Moreover, previously-diagnosed partners were uncommonly on treatment at the time of contact with the index AHI case, increasing the likelihood of onward transmission.[158,159] In line with observed HIV infection trends in the South,[18,160-162] these active transmission networks, as represented by index AHI cases and their partners, were disproportionately populated by young, Black MSM. Engaging this population in care and ensuring receipt of ART is certain to lessen the disease burden in these high-prevalence settings.

The relative contribution of previously undiagnosed partners to onward transmission in this study was lower than estimated in other settings. Model-based estimates predicted 50-75% of all new HIV infections are due to partners unaware of their infection,[10,11,43] which is approximately 10-50% higher than the 22%-38% estimates we obtained in this study.

Our empirical work is limited by a distinct set of biases related to difficult-to-verify assumptions and missing information, as compared to modeling studies. Perhaps most importantly, we had phylogenetic analyses on only a small proportion of the population. The transmission source cannot be verified in partnerships where phylogenetic testing was not done, even if the status of all partners was known and only one was HIV-infected. Furthermore, approximately half of the index AHI cohort named at least one status-unknown or anonymous partner, and over one-third named only unknown/anonymous partners. Undoubtedly, some unknown/anonymous partners transmitted HIV. Status-unknown partners have no record of a positive test in NC surveillance databases under the name provided by the index AHI case and either refused HIV testing or could not be located. HIV infection may be more prevalent among persons refusing HIV testing.[163] If HIV-infected, status-unknown partners are undiagnosed, misnamed by the index AHI case, or were diagnosed outside NC. Anonymous partners did not

have any identifiable information, and may be more likely to engage in riskier behaviors and less likely to test for HIV or enter care than identifiable partners.

Partner services for index AHI cases identified by the STAT program occur close to the transmission event, decreasing the likelihood of recall bias and increasing the accuracy in naming potential transmitting partners and assessing their diagnosis, care, and treatment status. However, diagnosis during AHI is relatively uncommon in NC,[63] making it difficult to assess any heterogeneity in partner continuum stages that might have existed over the 11 years under analysis.

The contribution of AHI to ongoing transmission is not easily assessed with these data. The duration of AHI is short and partners transmitting during this stage may not be tested until they reach CHI. Approximately one-third of newly-diagnosed partners with available STARHS testing data were classified as having recent infection, suggesting these partners were unaware of their HIV status for a short period of time, with some potentially representing AHI-to-AHI transmission. When both the index case and the partner are diagnosed with AHI, the direction of transmission is difficult to determine, even if phylogenetically linked,[139] leaving open the possibility that the index AHI case transmitted disease to at least some newly-diagnosed partners unaware of their HIV status.

Partner viral suppression status at the time of transmission is difficult to assign. Only half of the previously-diagnosed partners had an available VL in surveillance databases near the time of the index AHI case diagnosis and approximately 20% of these partners were virally suppressed. The relatively low levels of viral suppression observed among previously-diagnosed partners may be a result of more restrictive treatment guidelines in place prior to 2009.[67] If

partners are truly virally suppressed, HIV transmission is known to be unlikely.[1,164] Sexually transmitted co-infection, treatment non-adherence or resistance provide possible explanations for potential rebound in virus in the period between the last suppressed VL and contact with the index case.[165-167]

Engagement (and re-engagement) in care and early initiation of treatment should remain a high priority to prevent HIV transmission. In both surveillance data from the STAT program and phylogenetic data collected via the CHAVI-001 study, a substantial proportion of HIV transmission appears attributable to contact with previously-diagnosed partners. Interventions to find previously-diagnosed persons not in care and facilitate receipt of consistent care and immediate treatment should have a tremendous impact on improving health and reducing HIV incidence in this and similar settings.

Tables and Figures

Table 5.1. Index AHI cases by pattern of partner HIV status

Type	Number of known HIV-infected partners	Number of known HIV-uninfected partners	Number of unknown status partners	Number of index AHI cases with partner HIV status pattern	
				N	%
A	1	≥0	0	**106**	**(29.6)**
B				**68**	**(19.0)**
B1	*>1*	*≥0*	*0*	*12*	*(3.4)*
B2	*1*	*≥0*	*≥1*	*38*	*(10.6)*
B3	*>1*	*≥0*	*≥1*	*18*	*(5.0)*
C	0	0	≥1	**127**	**(35.5)**
D				**57**	**(15.9)**
D1	*0*	*0*	*0*	*38*	*(10.6)*
D2	*0*	*≥1*	*0*	*19*	*(5.3)*

Table 5.2. Demographics of Index AHI and Named Partners

	STAT Program* *(Inclusive of CHAVI cases)*				CHAVI-001**			
	Index AHI (N=358)		Named Partners^ (N=656)		Index AHI (N=117)		Named Partners (N=367)	
	Median	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**	**Median**	**(IQR)**
Age at Diagnosis	26	(21-36)	28	(23-37)	25	(21-36)	27	(22-35)
Number of Named Partners	2	(1-3)	--	--	3	(2-4)	--	--
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Reporting Location								
State Laboratory (NAAT Pooling)	255	(71.2)	--	--	--	--	--	--
Community Setting	103	(28.8)	--	--	--	--	--	--
Gender								
Female	61	(17.0)	85	(13.0)	15	(12.8)	40	(10.9)
Male	297	(83.0)	563	(85.8)	102	(87.2)	326	(88.8)
Sex Risk								
Female	61	(17.0)	85	(13.0)	15	(12.8)	40	(10.9)
Heterosexual Male	39	(10.9)	95	(14.5)	13	(11.1)	26	(7.1)
MSM	238	(66.5)	468	(71.3)	89	(76.1)	300	(81.7)
Unknown Risk Male	20	(5.6)	--	--	--	--		
Race[#]								
Black	251	(70.1)	411	(62.7)	76	(65.0)	237	(64.6)
White, Non-Hispanic	82	(22.9)	160	(24.4)	35	(29.9)	106	(28.9)
White, Hispanic	20	(5.6)	43	(6.6)	6	(5.2)	8	(2.2)
Other	3	(0.8)	2	(0.3)	--	--	--	--
STI in 8 weeks prior to AHI Diagnosis								
Yes	87	(24.3)	--	--	20	(17.1)	--	--
No	271	(75.7)	--	--	97	(82.9)	--	--

*The North Carolina Screening and Tracing of Active Transmission Program

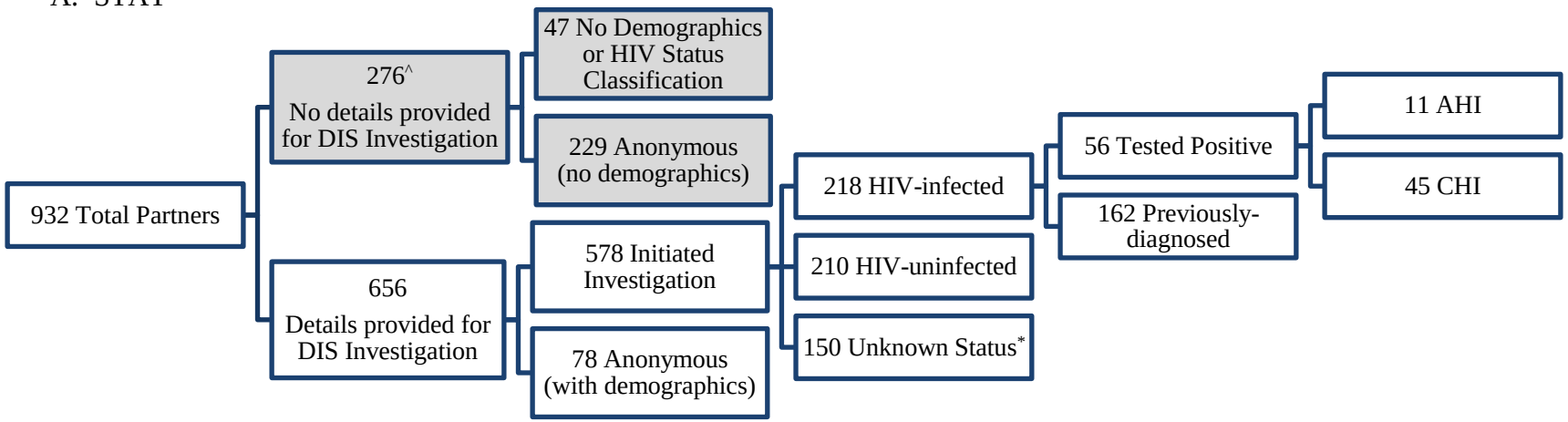
** Center for HIV/AIDS Vaccine Immunology 001 Study: Acute HIV Infection Prospective Cohort Study

^ 932 partners were named by Index AHI cases during the STAT investigation. Index AHI cases refused to provide detailed demographic information for the STAT Program for a total of 276 partners, leaving 656 with detailed demographic information.

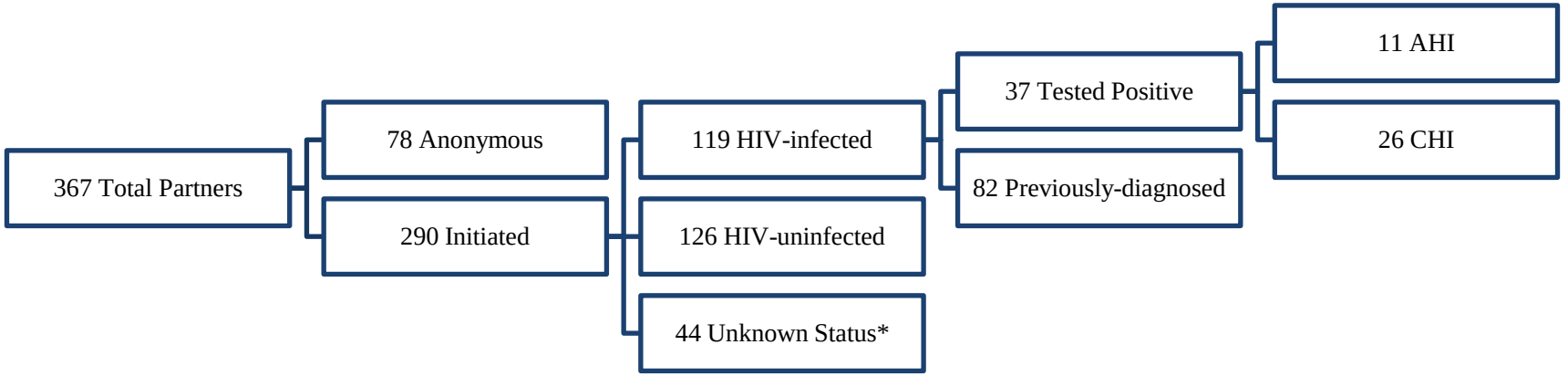
[#]Missing Race not included in table.

Figure 5.1 HIV Status of sexual and needle-sharing partners reported by index AHI cases

A. STAT



B: CHAVI-001

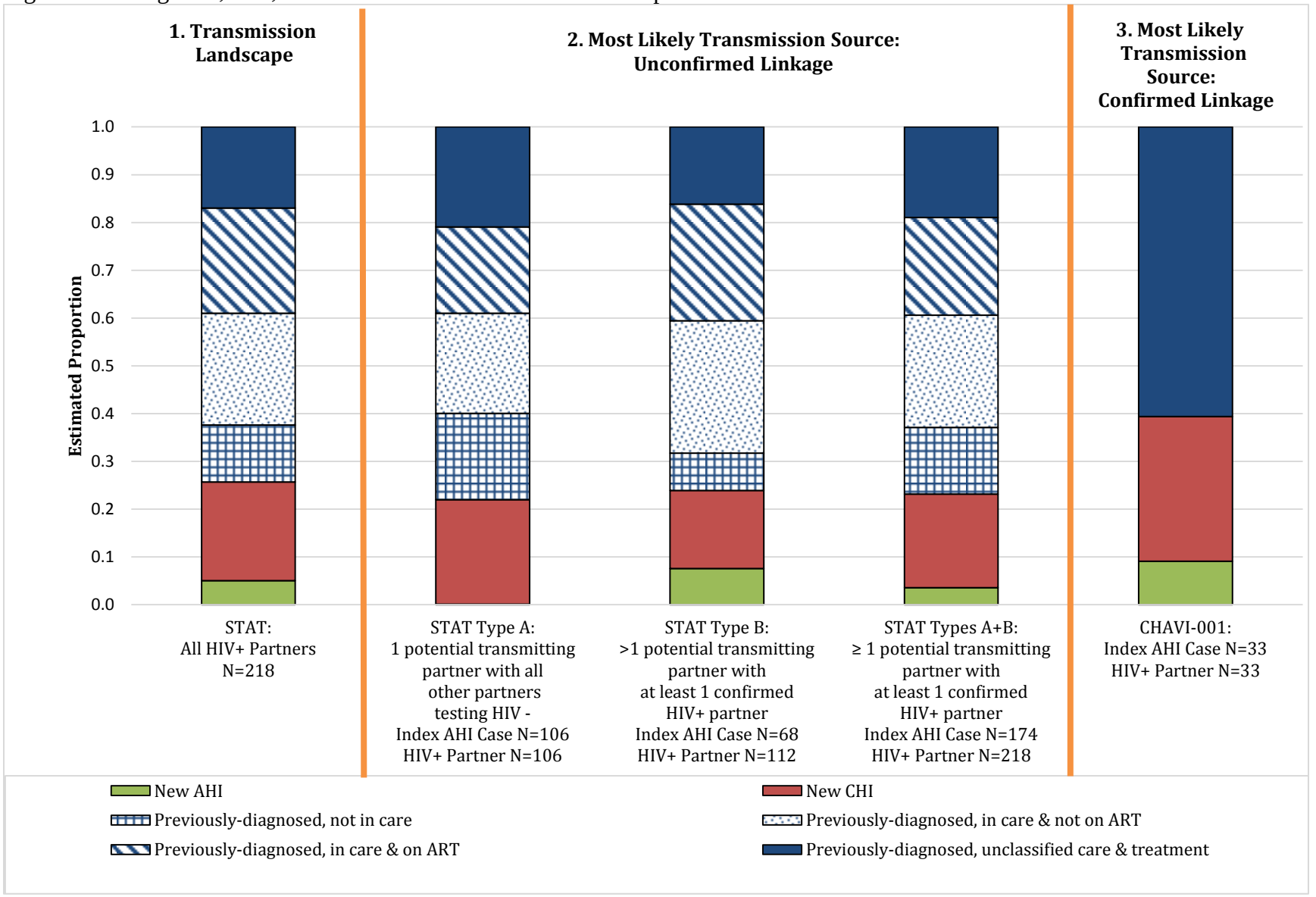


^ 932 partners were named by Index AHI cases during the STAT investigation. Index AHI refused to provide detailed testing information for the STAT Program on a total of 276 partners, leaving 656 with detailed demographic information.

*STAT "Unknown" status includes 31 (20.7%) refusing counselling and testing, 48 (32.0%) refusing testing only, 61 (40.7%) unable to locate and 10 (6.7%) who could not be classified. Reason for unknown status could not be identified among CHAVI-001 partners.

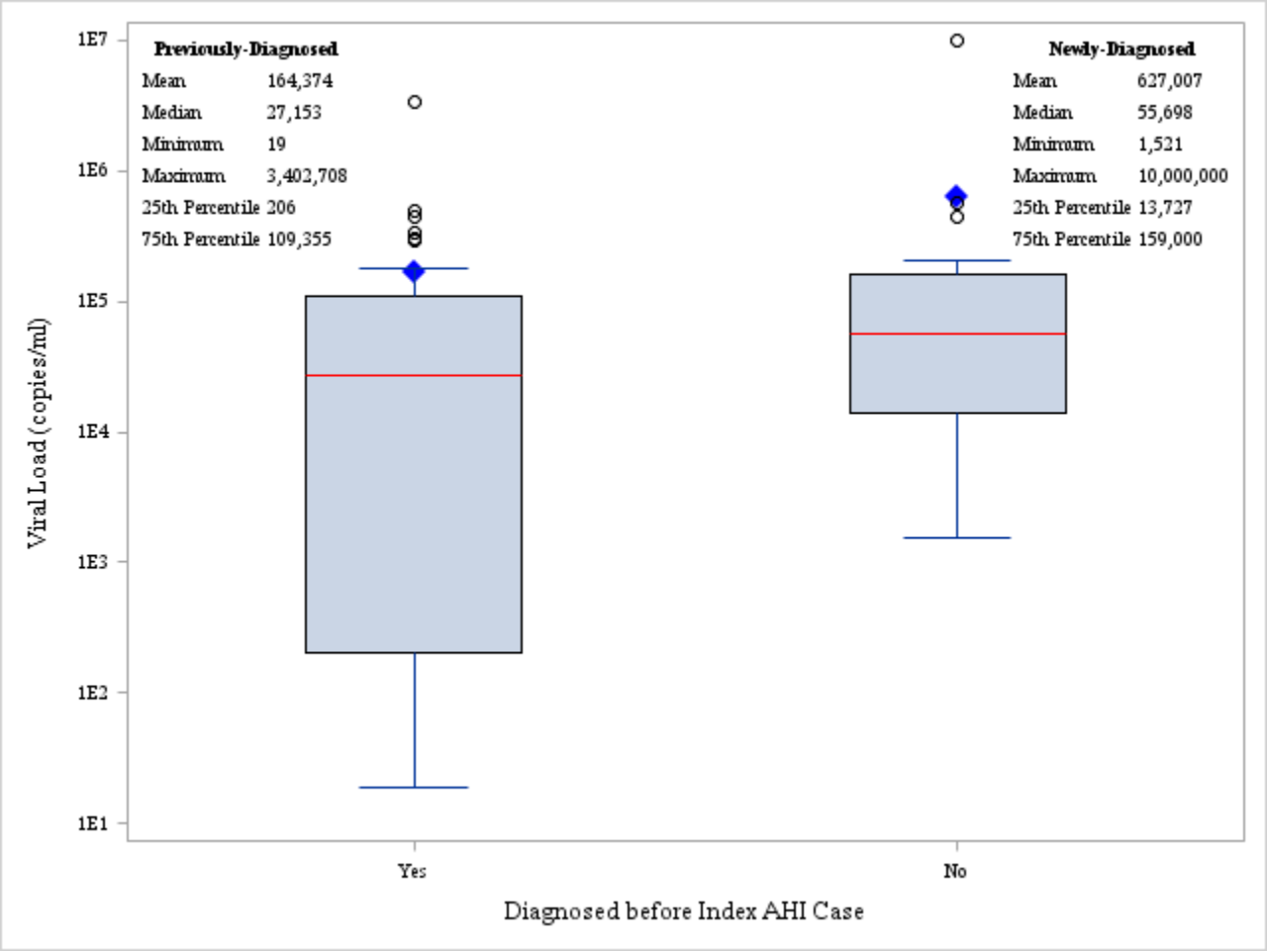
CAPTION: Figure 5.1A displays the HIV status of partners of index AHI cases identified via the STAT program between November 2002 and June 2013. Figure 5.1B displays the HIV status of partners reported by index AHI cases enrolled in CHAVI-001 between May 2006 and June 2011.

Figure 5.2: Diagnosis, care, and treatment status for HIV-infected partners



CAPTION: In Figure 5.2, the diagnosis, care, and treatment status are presented for 1) all HIV-infected partners named by the index AHI cohort and identified by the STAT program, 2) the most likely transmission source among identified HIV-infected partners presented by the pattern of HIV-infected, uninfected, and status-unknown partners reported to the STAT program and 3) phlyogenetically-linked partners identified via the CHAVI-001 study. For estimates of the most likely transmission source where >1 potential transmitting partner was named, repeated random sampling was used to estimate diagnosis, care, and treatment status of the partner. NOTE: Potential transmitting partner refers to any partner reported in the 8 week period prior to the index AHI diagnosis date who was not classified as HIV-uninfected (e.g. HIV-infected and status-unknown partners). NOTE: Potential transmitting partner refers to any partner reported in the 8 week period prior to the index AHI diagnosis date who was not classified as HIV-uninfected (i.e. HIV-infected and status-unknown partners).

Figure 5.3 HIV-infected partner viral load (VL) at the time of the Index AHI case diagnosis by diagnosis status.



CAPTION: Figure 5.3 displays the closest VL within 6 months before to 2 months after the index AHI diagnosis date extracted from NC surveillance databases for HIV-infected partners and dichotomized by status-unaware versus status-aware partners.

CHAPTER SIX: SPATIAL AND TEMPORAL PATTERNS OF EARLY AND LATE HIV DIAGNOSES IN NORTH CAROLINA FROM 2005 TO 2013

Abstract:

Background: HIV test-seeking behaviors may be a function of both time and space. We assessed spatial patterns of high rate HIV diagnoses in North Carolina (NC) both before and after the adoption of the CDC's recommendations for routine testing. **Methods:** Using surveillance data from a 52-county region in central NC, we mapped diagnosis rates by disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS) and testing period (2005-2007, 2008-2010, 2011-2013). Bayesian Maximum Entropy smoothed maps were standardized and the percent overlap of the top 10^{th}, 25^{th} and 50^{th} percentile of diagnosis rates were assessed. We conducted a complementary analysis of census tracts involved in high rate clusters identified via SaTScan. **Results:** Overall, 3216 persons were diagnosed with HIV (1060 (33%) EHI, 1659 (52%) CHI, and 497 (16%) AIDS) at publicly-funded testing sites [crude rate 60.5 per 100,000 person-years]. Estimated diagnosis rates were highest prior to opt-out testing (2005-2007). An underlying, "core" area for HIV diagnosis was observed across each testing period and disease stage, as represented by disproportionately high overlap in the top 25^{th} and 50^{th} percentiles. EHI identification has geographically changed over time, as indicated by minimal overlap at high diagnosis rates (10^{th} percentile). AIDS diagnoses displayed consistent overlap in the southeastern part of the study area. High rate EHI and CHI clusters were concentrated in urban centers.

Conclusions: High rate diagnoses appear to be spatially dynamic across time and disease stage, suggesting possible shifts in the testing activity and/or the epidemic itself over time.

Introduction:

Initiation of antiretroviral therapy (ART) increases the life expectancy of HIV-infected persons and reduces the probability of HIV transmission by suppressing plasma viral load (VL) to undetectable levels.[1,2,7] However, late stage HIV diagnoses postpones receipt of care and limits treatment effectiveness.[9] Over one-third of HIV-infected persons in the United States receive an AIDS diagnosis within one year of their HIV diagnosis.[9] In an effort to identify and link HIV-infected persons to care earlier during their infection, the Centers for Disease Control (CDC) recommended that providers adopt routine, opt-out HIV testing.[14]

The impact of the CDC's recommendations for routine, opt-out testing has been inconclusive. While acceptability of the recommendations is high,[168,169] the effectiveness of the recommendations in terms of case detection and identification of recent infection have been mixed.[52,169-175] Geography may be a factor in understanding testing behaviors of both providers and patients. Persons living in rural areas are less likely to be tested for HIV[12,176] and more likely to test later during the course of their disease than urban residents.[85]

North Carolina (NC) is representative of the HIV epidemic in the Southeastern United States and provides a unique setting to assess stage of HIV at diagnosis. Over the past decade, the NC Division of Public Health (DPH) has tracked acute HIV infection (AHI) recent HIV infection (RHI) (cases identified within approximately 6 months of infection), and AIDS cases, allowing for the classification of stage of disease based on testing results.

In this analysis, we aimed to assess spatial clustering of HIV diagnoses by stage of disease in NC both before and after the CDC recommended routine, opt-out HIV testing. Enhanced understanding of the relationship between residence and the timing of HIV testing both before and after the CDC recommendations for routine, opt-out testing provides evidence into the effectiveness of these recommendations and identifies the areas in NC that would most benefit from additional resources to identify early infection.

Methods:

Data Sources

We performed a cross-sectional analysis using data collected from 3 different surveillance mechanisms at the NC DPH: Counselling and Testing Report (CTR) data, electronic HIV/AIDS Reporting Service (eHARS), and the Screening and Tracing of Active Transmission (STAT) Program.

A CTR form is completed for all persons requesting a test at a publicly-funded testing site in NC to capture personal identifiers, demographics, risk factors, testing site, and residential zip code. Data from the CTR form are linked to specific blood samples submitted to the NC state laboratory of public health for HIV testing.

All HIV-positive tests in the CTR system are linked to eHARS, a state-run database that maintains demographic, risk factor, and HIV/AIDS diagnosis dates for regular surveillance reporting to the CDC. eHARS also collects case addresses at the time of both HIV and AIDS diagnosis and Serologic Testing Algorithm for Recent HIV Seroconversion (STARHS) testing results.

Since 2002, the STAT program has identified persons diagnosed with acute HIV (AHI) in NC through nucleic acid amplification test (NAAT) pooling procedures for all negative HIV antibody tests at the state laboratory.[100,177] The STAT program defines AHI as a negative or indeterminate antibody test followed by reproducibly detectable HIV RNA. All persons diagnosed with AHI and identified by the STAT program were linked to their case report in eHARS for this analysis.

Study Area

We restricted this analysis to a 52-county (1597 census tracts) study area in central North Carolina (NC) that represents both urban and rural areas and accounts for approximately 80% of all new HIV diagnoses and 74% of the population in the state[178] [Figure 6.1]. The remaining 48 NC counties contain a substantial proportion of census tracts with zero-case counts that could interfere with the stability of spatial models used to assess clustering of disease. Therefore, cases diagnosed in these counties were excluded from our analysis.

Study Population:

We classified cases as any person aged 16 years or older diagnosed at a publicly-funded testing site between July 2005 and June 2013 in the 52-county study area. This represents approximately 40% of all new HIV diagnoses in in the study area.

To estimate the underlying testing population at a publicly-funded testing site, we deduplicated HIV tests reported in the CTR system based on recorded name, date of birth, race, gender, and zip code using The Link King Program (version 7.1.21, Camelot Consulting Olympia, Washington). This program uses a combination of probabilistic and deterministic algorithms to determine linkages.[141] The sensitivity and positive predictive value of linkages

produced by The Link King program have previously been found to be >90%, when using reviewers' decision as the gold standard.[141] We used the default program settings in all instances except for the following: 1) no minimum disagreement weight was set for zip codes (e.g zip codes could be different and the records could still match) and 2) we did not pre-specify the minimum weight for probabilistic linkages.

We generated 2 estimates of the testing population in which we deleted non-exact matches (conservative estimate) or kept non-exact matches (liberal estimate) classified to linkage certainty categories 4, 6, and 7 by the Link King program. The testing population based on the conservative estimate was used to calculate testing rates for this analysis.

Testing Period:

We classified both cases and the testing population to a testing period based on both the date of their HIV test and estimated date of implementation of the CDC's recommendations for expanded testing. Revised recommendations were made in September 2006.[14] However, we estimated a year lag for statewide implementation and categorized all cases and testers as occurring: at or before (Period 1: July 2005- December 2007), immediately after (Period 2: January 2008- December 2010), or after with some delay (Period 3: January 2011- June 2013).

HIV-Stage Assignment:

Using a 3-step process, we assigned all new diagnoses a stage of disease at diagnosis (AHI, RHI, Chronic HIV Infection (CHI), and AIDS) based on STAT, STARHS, and standard HIV testing results. First, STAT cases were linked to eHARS to identify all cases diagnosed with AHI. Next, all cases diagnosed with AIDS in eHARS (as defined by either 1) CD4 cell count <200 cells/mm^3, 2) CD4 count < 14 percent of all lymphocytes, or 3) a diagnosis of one or more

AIDS-defining illnesses) at the time of or within 6 months of an HIV diagnosis were identified. For the remaining cases with STARHS results, we approximated recent (RHI, ≤6 months) from longstanding infection (CHI, >6 months) based on a normalized optical density cut-point of <0.8 on the BED assay.[17] Non-AHI and non-AIDS cases without available STARHS testing were excluded from analysis. Due to the small numbers of AHI diagnoses each year, AHI and RHI were combined for the remainder of this analysis and considered as early HIV infection (EHI).

Geocoding:

Residential addresses of all new HIV cases were geocoded to an ESRI (Redlands, California)-supplied NC street basemap using ArcGIS (version 10.1, ESRI). Persons with an address that could not be geocoded or who did not provide a full address were geocoded to a population-weighted, random point in their zip code (if reported). New HIV diagnoses were aggregated in space to the tract level and in time by the testing period to preserve confidentiality. Cases with residential addresses outside the geographic boundary of the 52-county study area were excluded.

The entire deduplicated testing population at publicly-funded testing sites were also geocoded to a population-weighted, randomly-assigned point in the zip code provided on the CTR form. If a person reported more than 1 zip code at subsequent testing events, a zip code was selected at random for analysis. Geocoded zip codes for persons testing for HIV at publicly-funded testing sites were then aggregated to estimate the testing population in each census tract.

Spatial Analysis:

To compare disease maps across multiple time periods, we assigned HIV diagnosis rates [number of cases tested per tract/(number of people testing in each tract*time)] by stage of

disease and testing period to the geographic center (centroid) of each 2010 census tract for subsequent analysis, estimation, and mapping. The study area contains 1597 (73.1%) of the census tracts in NC in 2010. Some census tract boundaries changed when the results of the 2010 census were released. A difference in clustering due to these changes was expected to be minor.[143]

Bayesian Maximum Entropy

Bayesian Maximum Entropy (BME), specifically the uniform model extension of BME (UMBME), was used to describe the changes in spatial distribution of HIV diagnosis rates by stage of disease in each testing period. In UMBME, measurement error is assumed to be distributed uniformly around the observed rate in an interval the size of 1/testing population.[144] Therefore, observed diagnosis rates are treated as probabilistic ("soft") data with measures of uncertainty as defined by the uniform distribution interval. BMEGUI (version 3.0.1, Chapel Hill, North Carolina), the computer software used to implement the BME approach, was used to conduct this composite space-time analyses and mapping.[146]

Once a smoothed map was created for each of the 3 disease stages during the 3 testing periods under consideration, maps were normalized to the same scale to assess percent overlap of high diagnosis rate areas. A cut-off point at the highest 10^{th} percentile on this normalized scale was used to dichotomize diagnosis rates in each pixel as high versus low rates. The proportion of "high rate" pixels on one map that were also "high rate" on another map was assessed for each disease stage-time period combination. We varied the cut-off point used to define "high-rate" clusters to the top 25^{th} and 50^{th} percentiles in sensitivity analyses.

Cluster Detection:

In a complementary analysis, the Kulldorff spatial scan statistic (SaTScan software, Information Management Services, Inc., Silver Spring, Maryland) was applied to identify the presence and location of clusters by disease stage and testing period using crude census tract diagnosis rates. High-rate clusters were identified as areas where the observed number of cases was greater than the expected number of cases based on spatial randomness. A likelihood ratio test statistic was calculated for each potential cluster and *p*-values corresponding to the test statistic were calculated using Monte-Carlo simulation. The percent overlap of census tracts involved in high-rate clusters identified via the Kuldorff spatial scan test statistic by disease stage-time period categories was calculated, as described in the BME analysis.

The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Results:

Between July 2005 and June 2013, 1,620,781 samples were tested for HIV at publicly-funded testing sites in NC. After deduplication using a conservative linking definition, 853,900 unique persons were tested for HIV. A total of 664,695 (77.8%) of this testing population reported a zip code within the 52-county study area and could be geocoded.

A total of 10,690 persons had a positive HIV test reported to the NC DPH during this period in the study area, with 4893 (45.77%) testing in publicly-funded testing sites. Previous diagnoses (N=763), persons <16 years of age (N=14), and persons whose reported address at the time of HIV diagnosis was a correctional facility (N=90) were excluded. Of the 4023 remaining cases, 3621 (90.0%) were geocoded to the address provided at the time of HIV diagnosis. An

additional 388 cases could be geocoded to a random location within the provided zip code, resulting in a total of 4009 (99.7%) cases whose residential address or zip code at the time of HIV testing was geocoded. Of these, 3216 (80.2%) had enough information to classify disease stage at diagnosis (RHI, CHI, or AIDS), representing the study population for this analysis.

Of the 3216 newly-infected cases, most were male (76.4%), black (70.4%), and self-identified as a man who has sex with men (MSM) (53.2%). The median age of participants was 29 years (IQR 23-41). HIV diagnoses occurred most often in HIV counselling sites (72.0%). The HIV testing population was less likely to male (37.6%), black (44.2%), or MSM (2.9%) [Table 6.1]. Using testing results reported to the NC DPH, participants could be classified by stage of disease at diagnosis: 1060 (33%) EHI (156 AHI and 904 RHI), 1659 (51.6%) CHI, and 497 (15.5%) AIDS cases [Table 6.1].

The overall crude HIV testing rate in the study area was 60.5 cases per 100,000 person-years. The rate varied by stage of disease: 19.9 EHI cases, 31.2 CHI cases, and 9.3 AIDS cases per 100,000 person-years. Given the exclusions we used to define our study population, this is likely an underestimate of the true diagnosis rates in this area. The individual census tract crude HIV diagnosis rates ranged from 0 to 3571.4 cases per 100,000 person-years, with over one-third of the tracts with a rate of zero (N=565; 35.4%). When we removed the spatial mean trend for covariance modeling and BME estimation, rates were more normally distributed for each disease stage.

UMBME Analysis

The covariance plots used in UMBME estimation suggest that the diagnosis rates for EHI, CHI, and AIDS in the study area exhibit differing levels of spatial dependence

[Supplemental Figure A4.1]. The spatial range for CHI cases was longer than that of both EHI and AIDS cases (4 km for CHI versus 1 km for both EHI and AIDS). While relatively short (1 km), the spatial range for AIDS cases is not entirely smooth, suggesting potential movement in space after infection but before diagnosis. The temporal lag for each disease stage was long (6 years for EHI and CHI; 2.5 years for AIDS).

UMBME estimated diagnosis rates were highest during Period 1 (2005-2007) when opt-out testing was not yet adopted [Table 6.2]. However, the absolute number of cases identified was lowest during this period. Diagnosis rates during CHI were highest across all 3 periods compared to other disease stages. The lowest diagnosis rates were observed among AIDS cases during each of the testing periods. An increase in diagnosis rates from Period 2 (2008-2010) to Period 3 (2011-2013) was observed for both EHI and AIDS diagnoses. However, AIDS diagnoses had a larger relative increase from Period 2 (2008-2010) to Period 3 (2011-2013) compared to EHI diagnoses.

Overlap

Relatively little overlap at the highest rates (top 10 percentile) was observed across disease stage and time period [Table 6.3a and b/Figure 6.2/Supplemental Figure A4.2 and A4.3]. However, disproportionately higher amounts of overlap at lower rates (top 25 and top 50 percentiles) were observed by disease stage and testing period, suggestive of an underlying core area of HIV diagnosis, and consequently, transmission in central NC.

The overlap of EHI and CHI diagnoses at the highest rates (top 10 percentile) was relatively constant in terms of both quantity and location [Table 6.3a/Figure 6.2/Supplemental Figure A4.2]. Between Period 1 (2005-2007) and Period 2 (2008-2010), an increase in the

number of overlapping high rate (top 10 percentile) areas was observed between CHI and AIDS diagnoses, possibly indicating cases that would have been diagnosed during AIDS were being found earlier and diagnosed during CHI in these areas. Most of the increase in overlap was observed in the southeastern part of the study area.

Minimal testing period overlap at the highest rates (top 10 percentile) was observed within each disease stage [Table 6.3b/Figure 6.2/Supplemental Figure A4.3]. At lower rates (top 25 and 50th percentiles), significant overlap was observed providing further evidence for a background, "core" area. Overlap of high rate EHI diagnoses across time was spatially dynamic, indicating EHI was consistently diagnosed across the study area and the location of high rate EHI diagnoses changed over time. Overlap of high rate AIDS diagnoses was highest across all 3 testing periods [Table 6.3b] and was geographically prominent in the southeastern part of the study area.

Kulldorf Spatial Scan Statistic

In the complementary analysis, the number of statistically significant ($p<0.05$) high rate clusters identified by the Kulldorff spatial scan statistic varied by disease stage and study period [Figure 6.3/Supplemental Table 6.1]. During Period 1 (2005-2007), high rate clusters for each disease stage were concentrated in the major urban centers located in the study area. In Period 2 (2008-2010), the high rate clusters remained in roughly the same location, with several AIDS clusters disappearing or shrinking, possibly because these persons were being identified earlier during the course of their disease. During Period 3 (2011-2013), a large AIDS cluster was identified in the southeastern part of the study area.

Overlap of census tracts involved in high rate clusters was highest between EHI and CHI during all time periods, with Period 2 (2008-2010) displaying the most overlap [Table 6.4a]. Overlap of high rate EHI and CHI clusters was only observed in urban centers [Figure 6.3a].

Across testing periods, CHI clusters displayed the most overlap, which was concentrated in urban centers. High rates AIDS clusters displayed the least amount of overlap, with no single census tract being involved in high rate clusters across all three time periods [Figure 6.3b/Table 6.4b].

Discussion:

A core HIV diagnosis area was observed across each testing period and disease stage, but only at lower diagnosis rates. In these areas, stage of disease does not appear to be heavily influenced by location or the adoption of the CDC's testing recommendations. Areas with high rates of HIV diagnosis by disease stage and testing period were more spatially dynamic, with minimal overlap observed by disease stage and testing period. This could indicate shifting trends in the underlying epidemic in the central NC.

Recognition of EHI is important to fully realize the benefits of HIV care and treatment and to follow trends in active transmission across the study period. In our analysis, EHI diagnoses appeared to be clustered in urban centers, with small pockets of high rate EHI in rural areas. Areas with high rates of early diagnosis during one testing period were unlikely to experience high rates of early testing in a different period in this analysis. This could be due to a shift in the epidemic or a change in testing activity (partially explained by the CDC's recommendations for routine, opt-out testing). Due to high levels of infectiousness during EHI, improved diagnosis, linkage to care, and initiation of ART in areas with high rates of EHI

diagnosis could have a major impact on transmission particularly if the spatial patterns of the epidemic truly are shifting in North Carolina.

High rate EHI/CHI overlap remained relatively constant across all testing periods in terms of quantity and location in both the UMBME and SaTScan analyses. This suggests EHI and CHI diagnoses occur in comparable risk populations with similar test-seeking behaviors. As a result, targeting resources for HIV testing and care to areas with high rates of CHI diagnoses may be an effective strategy to identify early stage HIV infection.

Overlap of high rate AIDS diagnoses across each time period was consistently high and concentrated in the southeastern part of the study area. This part of NC represents a rural part of the state that is highly impoverished.[179] Perceived risk, stigma against HIV-infected persons, and accessibility may all factor in the HIV test-seeking behaviors of persons living in this part of the state.[44] Alternatively, testing sites in this part of the state may not have fully adopted routine, opt-out HIV testing practices, resulting in increased rates of late stage diagnoses.[180]

As observed in other settings[169,170,172-175] the CDC's recommendations for routine, opt-out testing resulted in an increase in the absolute number of HIV-infected persons identified, some of whom would have likely been missed under targeted or diagnostic testing approaches. However, the number of tests to identify one new positive also increased, resulting in lower overall rates after the adoption of the CDC's recommendations. Early HIV infection diagnosis rates remained lower than CHI diagnoses during each testing period, suggesting routine, opt-out testing may not be the most effective strategy to identify early HIV over a sustained period of time in this setting.

We present a novel method to classify stage of disease based on testing results. Disease stage is traditionally based on CD4 cell counts,[181] which requires a newly-diagnosed person to

have contact with the HIV care system and a lab value be reported to the NC DPH. Because care reporting standards varied across the study period, we developed a disease stage classification algorithm that relied only on testing results collected in eHARS. This algorithm is not without bias. The BED assay used for STARHS testing is a nonspecific test, with AIDS diagnoses or persons on antiretroviral therapy (ART) sometimes classified as a recent infection.[112,113] We assumed this misclassification was minor since our study population included only newly-diagnosed persons who were not likely to have a history of ART use and we removed all persons diagnosed with AIDS prior to the assignment of recent infection. However, it is possible that the observed overlap of high rate EHI and AIDS diagnoses represents some expected misclassification.

UMBME smoothing models provide an accurate prediction of the underlying diagnosis rate in an area by effectively imputing disease rates to areas where data are missing. This smoothing process can result in the addition of "noise" in the estimated rates.[144] Therefore some of the high rate areas may be an artifact of the smoothing process used in UMBME estimation. To address this, we aggregated cases to the census tract level and three-year testing periods because rare diseases, such as HIV, tend to be more spatially correlated when measured over larger areas and time periods, improving the smoothing of UMBME models.[144] However, these larger units of aggregations do mask some sub-unit variation and could result in misinterpretation of true underlying spatiotemporal patterns.[182]

Using crude diagnosis rates, the SaTScan cluster analysis identified areas of high diagnosis rate clustering in central NC. While we are unable to directly compare the results from the SaTScan cluster analysis based on crude census tract rates with the smoothed rates from UMBME estimation, both methods are useful tools to assess spatial patterns in diagnosis rates at

a local level. Expectedly, we observed some variation the results between the two methods due to the use of different diagnosis rates, particularly in the maps of AIDS diagnosis rates. AIDS represented the disease stage with the lowest diagnosis rates and therefore the highest variability in UMBME estimation, providing some explanation for the observed differences.

As part of this analysis, we excluded over half of the newly-diagnosed HIV infections to assess overall positivity rates for people diagnosed at publicly-funded testing clinics. We also excluded an additional 20% of cases whose address could not be geocoded. Therefore, the rates presented in this analysis likely underestimate the total diagnosis rates in each census tract. However, for the first time in NC, we estimated the underlying testing population at publicly-funded testing sites, providing information about utilization of health department sponsored HIV testing. Focusing our analysis to publicly-funded testing sites illustrates the effectiveness of current state and federally-funded testing programs which could inform future allocation of public resources.

In central NC, a definite core area of non-high rate diagnoses was apparent across all disease stages and testing periods. Areas of high rate diagnosis by disease stage and testing period were more spatially dynamic. Engaging recently-infected persons in care and initiating treatment could impact HIV transmission in areas with high rates of EHI diagnoses, while interventions emphasizing the importance of early diagnosis may be necessary in areas with persistent or re-emerging high rates of AIDS diagnoses. A spatial understanding of test-seeking behaviors is an effective tool in developing and targeting future HIV testing and prevention interventions.

Tables and Figures

Figure 6.1. Central North Carolina Study Area

CAPTION: 52-county study area in central North Carolina roughly corresponds to the North Carolina Division of Public Health Field Services Unit Regions 2 (Charlotte), 3 (Winston-Salem/Greensboro), 4 (Raleigh), and 5 (Fayetteville).

Table 6.1: Demographics of newly-diagnosed cases and testing population in Central North Carolina, 2005-2013

	Total Cases N=3216		Testing Population* N=664,695	
	Median	**IQR**	**Median**	**IQR**
Age	29	(23-41)	26	(21-35)
	N	**%**	**N**	**%**
Stage of Diagnosis				
AHI	156	(4.9)	156	(0.02)
RHI	904	(28.1)	904	(0.1)
CHI	1,659	(51.6)	1,659	(0.3)
AIDS	497	(15.5)	497	(0.1)
Gender				
Female	759	(23.6)	410,622	(61.8)
Male	2,457	(76.4)	250,089	(37.6)
Transgender	0	(0.0)	142	(0.0)
Race				
Black	2,265	(70.4)	293,718	(44.2)
White NH	505	(15.7)	189,293	(28.5)
Hispanic	328	(10.2)	128,886	(19.4)
Other	117	(3.6)	20,519	(3.1)
Risk Group				
MSM	1,710	(53.2)	19,166	(2.9)
IDU	71	(2.2)	7,471	(1.1)
MSM/IDU	17	(0.5)	833	(0.1)
Other	470	(14.6)	539,360	(81.1)
Region				
2: Charlotte	1,045	(32.5)	167,903	(25.3)
3: Winston-Salem	624	(19.4)	155,015	(23.3)
4: Raleigh	1,031	(32.1)	187,238	(28.2)
5: Fayetteville	516	(16.0)	97,609	(14.7)
Period of Diagnosis*				
2005-2007	1,021	(31.7)	227,236	(34.2)
2008-2010	1,390	(43.2)	343,552	(51.7)
2011-2013	805	(25.0)	299,306	(45.0)
Testing Site				
HIV Counselling and Testing Agency	2,316	(72.0)	32507	(4.9)
Sexually Transmitted Disease Clinic	217	(6.7)	254,649	(38.3)
Outpatient Facility	302	(9.4)	220,166	(33.1)
Other	342	(10.6)	123,984	(18.7)

*A person could test in each period, therefore numbers do not add up to 100%.

Note: Missing information not included in table

Table 6.2. Median, Minimum, and Maximum UMBME Diagnosis Rates (per 100,000 person-years) by Disease Stage and Testing Period

	Testing Population*	**EHI**			**CHI**			**AIDS**			***Total***		
Period	**N**	**N**	**Median**	**Range**	**N**	**Median**	**Range**	**N**	**Median**	**Range**	***N***	***Median***	***Range***
Period 1 (2005-2007)	227,236	320	120.29	(0.00-3400.70)	546	194.78	(0.00-6714.60)	155	49.25	(0.00-7512.10)	*1021*	*358.61*	*(0.00-9076.60)*
Period 2 (2008-2010)	343,552	439	81.42	(0.00-5035.40)	755	134.34	(0.00-6985.30)	196	24.32	(0.00-1903.10)	*1390*	*238.46*	*(0.00-9785.10)*
Period 3 (2011-2013)	299,306	301	85.26	(0.00-5033.00)	358	102.24	(0.00-4089.70)	146	37.92	(0.00-5020.80)	*805*	*222.19*	*(0.00-15048.00)*

*Conservative Estimate of Testing Population

Table 6.3A. Number and Percent of Overlap of High Rate Disease Stage Pixels by Testing Period: UMBME Estimation

		EHI/CHI		CHI/AIDS		EHI/AIDS		EHI/CHI/AIDS	
Testing Period	Percentile	N	%	N	%	N	%	N	%
Period 1 2005-2007	Top 10%	69	(13.48)	41	(8.01)	112	(21.88)	18	(3.52)
	Top 25%	722	(56.41)	697	(54.45)	852	(66.56)	585	(45.70)
	Top 50%	2136	(83.44)	2178	(85.08)	2169	(84.73)	1981	(77.38)
Period 2 2008-2010	Top 10%	73	(14.26)	99	(19.34)	41	(8.01)	15	(2.93)
	Top 25%	818	(63.91)	674	(52.66)	697	(54.45)	563	(43.98)
	Top 50%	2241	(87.54)	2111	(82.46)	2330	(91.02)	2004	(78.28)
Period 3 2011-2013	Top 10%	73	(14.26)	50	(9.77)	61	(11.91)	9	(1.76)
	Top 25%	575	(44.92)	552	(43.13)	782	(61.09)	447	(34.92)
	Top 50%	1960	(76.56)	2020	(78.91)	2159	(84.34)	1847	(72.15)

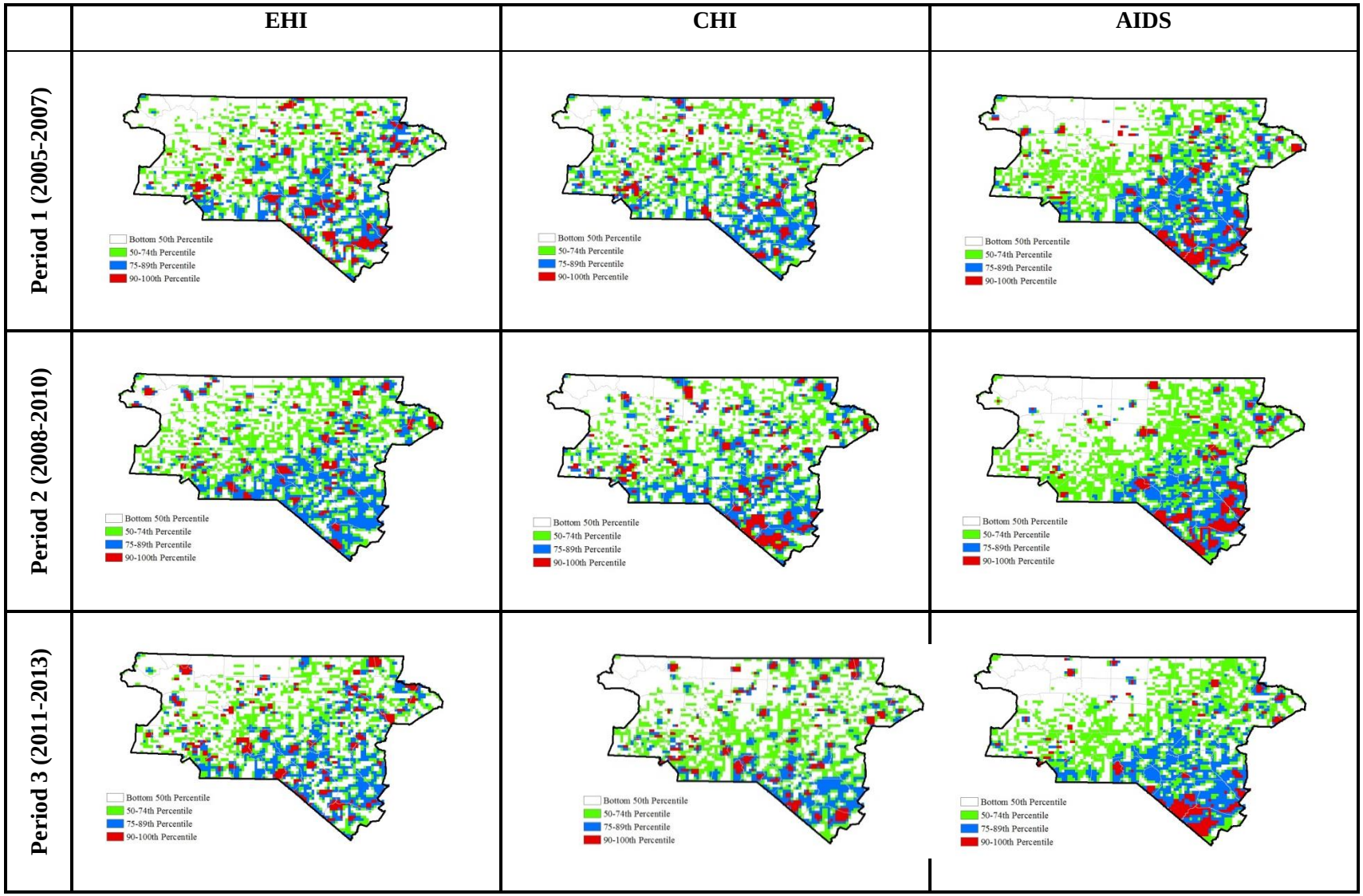
Table 6.3B. Number and Percent of Overlap of High Rate Testing Period Pixels by Disease Stage: UMBME Estimation

		Period 1 (2005-2007)/ Period 2 (2008-2010)		Period 2 (2008-2010)/ Period 3 (2011-2013)		Period 1 (2005-2007)/ Period 3 (2011-2013		Period 1 (2005-2007)/ Period 2 (2008-2010)/ Period 3 (2011-2013)	
Disease Stage	Percentile	N	%	N	%	N	%	N	%
EHI	Top 10%	71	(13.9)	72	(14.1)	106	(20.7)	37	(7.2)
	Top 25%	849	(66.3)	880	(68.8)	860	(67.2)	772	(60.3)
	Top 50%	2276	(88.9)	2275	(88.9)	2139	(83.6)	2087	(81.5)
CHI	Top 10%	130	(25.4)	95	(18.6)	62	(12.1)	44	(8.6)
	Top 25%	836	(65.3)	601	(47.0)	544	(42.5)	493	(38.5)
	Top 50%	2156	(84.2)	2011	(78.6)	1967	(76.8)	1877	(73.3)
AIDS	Top 10%	114	(22.3)	109	(21.3)	103	(20.1)	68	(13.3)
	Top 25%	783	(61.2)	806	(63.0)	951	(74.3)	733	(57.3)
	Top 50%	2398	(93.7)	2413	(94.3)	2462	(96.2)	2326	(90.9)

*Total Number of Pixels in study area=5120; 10% of Pixels=512, 25% of Pixels=1280, 50% of Pixels=2560

NOTE: Table 6A provides estimates of the percent overlap of disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS) by percentile of diagnosis rate (top 10, 25, and 50th percentile) during each testing period. Table 6B provides estimates of the percent overlap of testing period (2005-2007, 2008-2010, 2011-2013) by percentile of diagnosis rate (top 10, 25, and 50th percentile) within each disease stage (EHI, CHI, AIDS).

Figure 6.2. Percentiles of UMBME Diagnosis Rates by Stage of Disease and Testing Period



CAPTION: UMBME diagnosis rate estimates by testing period (2005-2007, 2008-2010, 2011-2013) and disease stage (early HIV infection [EHI], chronic HIV infection [CHI], and AIDS). Red indicates the top 10 percentile of testing rate, blue corresponds to the 75-89th percentiles and green corresponds to the 50-74th percentile. The remaining white areas represent the bottom 50th percentile in each testing period/disease stage map.

Table 6.4a. Overlap of High Rate Disease Stage Clusters by Testing Period detected by Kulldorff's Spatial Scan Statistic

	Census Tracts in High Rate Clusters			Overlap of Census Tracts							
	EHI	CHI	AIDS	EHI/CHI		CHI/AIDS		EHI/AIDS		EHI/CHI/AIDS	
	N	N	N	N	%	N	%	N	%	N	%
Period 1 (2005-2007)	207	172	102	134	(8.4)	10	(0.6)	14	(0.9)	5	(0.3)
Period 2 (2008-2010)	219	264	32	166	(10.4)	27	(1.7)	28	(1.8)	27	(1.7)
Period 3 (2011-2013)	184	170	149	128	(8.0)	54	(3.4)	37	(2.3)	37	(2.3)

Table 6.4b. Overlap of High Rate Testing Period Clusters by Disease Stage detected by Kulldorff's Spatial Scan Statistic

	Census Tracts in High Rate Clusters			Overlap of Census Tracts							
	Period 1 (2005-2007)	Period 2 (2008-2010)	Period 3 (2011-2013)	Period 1 (2005-2007)/ Period 2 (2008-2010)		Period 2 (2008-2010)/ Period 3 (2011-2013)		Period 1 (2005-2007)/ Period 3 (2011-2013		Period 1 (2005-2007)/ Period 2 (2008-2010)/ Period 3 (2011-2013)	
	N	N	N	N	%	N	%	N	%	N	%
EHI	207	219	184	119	(7.5)	133	(8.3)	93	(5.8)	66	(4.1)
CHI	172	264	170	122	(7.6)	145	(9.1)	107	(6.7)	95	(5.9)
AIDS	102	32	149	3	(0.2)	7	(0.4)	2	(0.1)	0	(0.0)

*1597 Census Tracts used as denominator

NOTE: Table 6.4a provides estimates of the percent overlap of EHI, CHI, and AIDS by testing period. Table 6.4b provides estimates of the percent overlap of Period 1: 2005-2007, Period 2: 2008-2010, and Period 3: 2011-2013 by disease stage.

Figure 6.3a. Overlap of Statistically Significant High Rate Disease Stage Clusters by Testing Period (Kulldorff Spatial Scan Statistic)

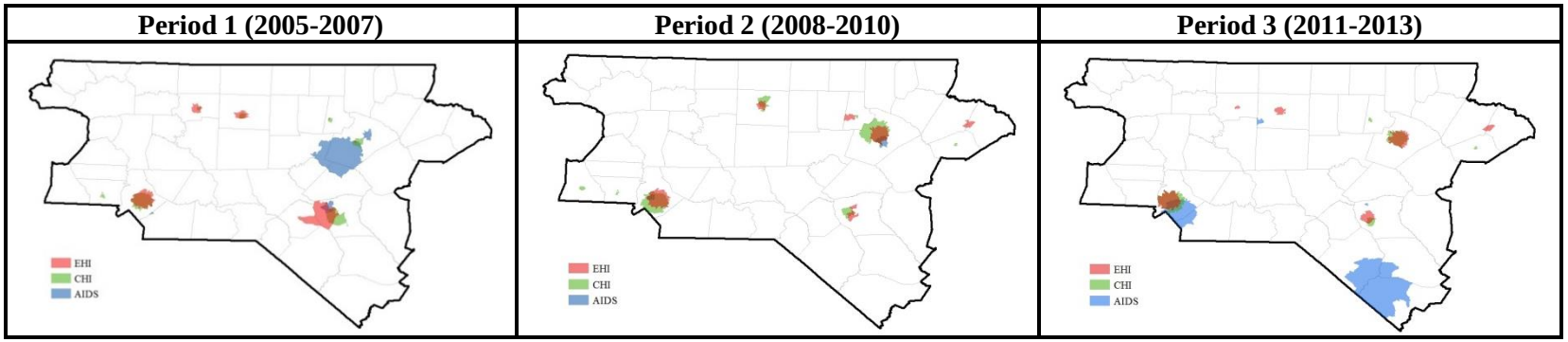
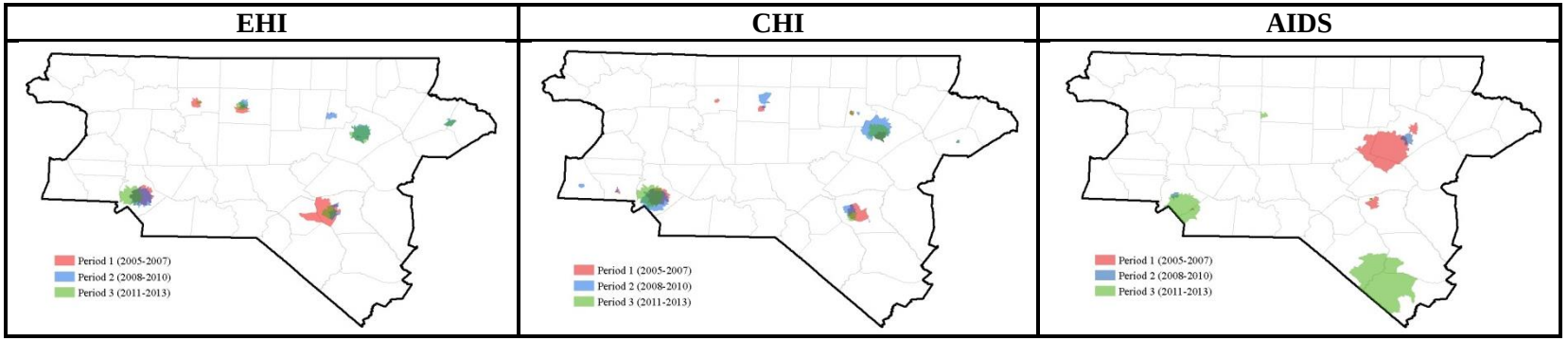


Figure 6.3b. Overlap of Statistically Significant High Rate Testing Period Clusters by Disease Stage (Kulldorff Spatial Scan Statistic)



CAPTION: Overlap of census tracts involved in high rate clusters identified by the Kulldorff Spatial Scan Statistic in SaTScan by disease stage and testing period. Figure 6.3a displays the overlap of early HIV infection [EHI] (red), chronic HIV infection [CHI] (green), and AIDS (blue) by testing period. Figure 6.3b displays the overlap of Period 1: 2005-2007 (red), Period 2: 2008-2010 (blue), and Period 3: 2011-2013 (green) by disease stage.

CHAPTER SEVEN: TRAVELLING LONGER DISTANCES THAN GEOGRAPHICALLY NECESSARY TO A TESTING SITE IS ASSOCIATED WITH DELAYS IN HIV DIAGNOSIS

Abstract:

We assessed the association between post-early-stage HIV disease at diagnosis and distance from residence to publicly-funded testing sites in central North Carolina over the period 2005-2013. Based on HIV testing results collected for surveillance purposes, we identified 1018 early-stage and 2010 post-early-stage diagnoses. Network distance between reported residence at diagnosis and publicly-funded testing sites was calculated. A slightly increased prevalence of post-early-stage diagnoses among cases diagnosed at sites that were >5 miles from their residence, but lived within 5 miles of a different publicly-funded testing site, was observed when adjusted for race/ethnicity and time period (Prevalence Ratio =1.09, 95% Confidence Interval 1.03-1.16).

Introduction:

Diagnosis and presentation to care during the early stages of HIV have substantial individual and public health benefits.[1-5] Early care and treatment initiation are linked to decreased disease-related morbidity, mortality and transmission risk.[1,7] Despite this, approximately 35-45% of HIV-infected persons in the United States are diagnosed late in the course of their disease and receive an AIDS diagnosis within one year of their HIV diagnosis.[8]

Inaccessibility of HIV services in one's community could exacerbate delays in testing.[183] A large proportion of HIV-infected persons in the southeastern United States live in rural areas,[79] and tend to test later in the course of their disease than persons living in urban areas.[12] High levels of poverty, distrust in the medical system, and perceived stigma in the community against HIV-infected persons living in the South further influences access to HIV services.[31,184] The main goal of this analysis was to describe the geographic-related characteristics of persons newly infected with HIV in North Carolina (NC) and assess the relative difference in prevalence of post-early-stage disease associated with increased distance from publicly-funded testing sites.

Methods:

The associations between later diagnosis and distance to 1) the publicly-funded testing site of diagnosis and 2) the closest publicly-funded testing site were examined with cross-sectional data reported in the NC electronic HIV/AIDS reporting system (eHARS) between July 2005 and June 2013. These data were collected for surveillance purposes and provide information about real-world testing behavior in NC. This study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Study Population:

We classified cases as any person aged 16 years or older newly diagnosed with HIV at a publicly-funded testing site in a 52-county study area in central NC. Persons diagnosed at publicly-funded clinics represent 40% of all new HIV diagnoses in the study area. Persons whose reported address at the time of diagnosis was outside of the 52-county study area or was a correctional facility were excluded from analysis.

Exposure Assessment:

Residential addresses of all new HIV cases were geocoded to an ESRI-supplied NC street basemap using ArcGIS (version 10.1, ESRI, Redlands, CA). Persons with an address that could not be geocoded or who did not provide a full address were geocoded to a population-weighted, random point in the provided zip code. Census tract at diagnosis was assigned based on the geocoded residential address.

We identified a total of 326 publicly-funded HIV testing sites in NC providing samples to the state lab of public health for processing [Figure 7.1].[16] The physical addresses of these sites were geocoded using the same method described above. The street network distance (miles) between each case's residential address and both 1) the testing site of diagnosis and 2) the closest publicly-funded testing site were calculated in ArcGIS using the Network Analyst extension.

The most appropriate form for the continuous distance variables for modeling of the association between distance and the risk for late-stage diagnosis was assessed. Because the dose-response relationship did not appear to be linear and an empirically derived cut-point was evident (data not shown), we dichotomized both distance variables ($\leq$ 5 miles versus >5 miles).

Outcome Assessment:

Using a 3-step process based on testing results reported in eHARS for all new diagnoses, we assigned a stage of disease at diagnosis: acute HIV infection (AHI), recent HIV infection (RHI), chronic HIV infection (CHI), and AIDS. The NC Screening and Tracing of Active Transmission (STAT) program has identified persons diagnosed with AHI (antibody-negative test result with reproducibly positive HIV RNA) since 2002. All STAT cases were linked to eHARS to indicate the AHI diagnosis in eHARS. Next, all cases diagnosed with AIDS in

eHARS (as defined by either 1) CD4 cell count <200 cells/mm^3, 2) CD4 count < 14 percent of all lymphocytes, or 3) a diagnosis of one or more AIDS-defining illnesses) at the time of or within 6 months of an HIV diagnosis were identified. For the remaining cases, the CDC-administered serologic testing algorithm for recent HIV seroconversion (STARHS) results were used to approximate RHI (≤6 months) from CHI (>6 months), based on a normalized optical density cut-point of <0.8 on the BED assay.[17] All non-AHI and non-AIDS cases without STARHS testing results were excluded from analysis.

In all subsequent analyses, we considered AHI and RHI diagnoses as "early stage" disease and CHI and AIDS diagnoses as "post-early stage" disease.

Statistical Analysis:

Because place frames a person's behavior, we assessed the presence of spatial autocorrelation between the geocoded addresses of early and late diagnoses with the global Moran's *I* statistic in ArcGIS. This test statistic evaluates whether diagnoses are clustered, dispersed or random in space by stage of disease.[152] The Global Moran's *I* test statistic was statistically non-significant (p=0.5), suggesting the observed spatial pattern of post-early-stage disease diagnoses is likely random and spatial autocorrelation is not present in these data. Therefore, we proceeded without accounting for spatial autocorrelation.

Log-binomial regression models using generalized estimating equations with a compound symmetry correlation matrix were fit to estimate prevalence ratios (PR) and robust 95% confidence intervals (CI) for post-early-stage diagnoses by distance (closest site and site of diagnosis). Census tracts, which served as a proxy for unobserved characteristics (e.g. education, income, and employment), were used to account for the clustering of the outcome at the

neighborhood level. Models were adjusted for race/ethnicity and period of diagnosis based on a review of the literature and construction of a directed acyclic graph.

All statistical analyses were conducted in SAS version 9.3 (Cary, NC).

Results:

Among 4023 persons diagnosed with HIV at publicly-funded testing sites in the 52-county study area between 2005 and 2013, 3242 (80.6%) had enough information in eHARS to classify stage of disease at diagnosis. Of these, 26 cases were excluded because their address could not be geocoded. Distance parameters in ArcGIS could not be calculated for an additional 188 cases, resulting in a study population of 3028 persons (1018 early-stage and 2010 post-early-stage diagnoses). Most new diagnoses were black (N=2144; 70.8%), men who have sex with men (MSM) (N=1622; 53.6%), and residing in an urban area (N=2812; 92.9%). The median age was 29 years (IQR 23-40) [Table 7.1].

Overall, 1145 (37.8%) of cases were diagnosed at a publicly-funded testing site that was ≤5 miles from their place of residence. Of the remaining 1883 cases who were diagnosed at publicly-funded testing site >5 miles from their place of residence, 1273 (67.6%) lived within 5 miles of a different publicly-funded testing site.

Compared to post-early-stage diagnoses, a larger proportion of early-stage diagnoses were black (74.5% versus 69.0%) and MSM (61.4% versus 49.6%). Early-stage diagnoses were also more common in the later time period (2011-2013) (28.3% versus 23.1%). Persons diagnosed during early stages had a lower median age (25 versus 32 years) [Table 7.1].

Some newly-diagnosed persons traveled longer distances than geographically necessary to test. All cases lived within 30 miles of a publicly-funded testing facility, with three-quarters living within 5 miles of a facility. The median distance traveled to the site of diagnosis was greater than median distance to the closest site [6.6 miles (IQR 3.6-12.3) versus 2.1 miles (IQR 1.1-4.1)]. Compared to other groups, the prevalence of persons diagnosed with post-early-stage disease at testing sites >5 miles from their place of residence but living within 5 miles of a different publicly-funded testing site was slightly elevated (69.8%) [Table 7.2].

In unadjusted analyses, the prevalence of post-early stage diagnosis was slightly greater among persons living >5 miles from their site of diagnosis (PR=1.08, 95% CI 1.02-1.14), while living >5 miles from the closest testing site had no association with no-early stage diagnosis (PR=0.97, 95% CI 0.91-1.03). There was no impact of adjustment for race/ethnicity and period of diagnosis on either of these associations [Table 7.3].

The slightly increased prevalence of post-early-stage diagnoses among cases who were diagnosed at a site that was >5 miles from their residence occurred primarily among persons who lived within 5 miles of a different publicly-funded testing site in both unadjusted (PR=1.10, 95% CI 1.05-1.17) and adjusted analyses (PR=1.09, 95% CI 1.03-1.16) [Table 7.3]. This translated to an approximately 6% increase in the absolute prevalence of post-early-stage disease in this group compared to those who tested at a site within 5 miles of their residence [unadjusted difference=6.5% (2.7-10.2%); adjusted difference=6.2% (2.4-9.9%)]. The prevalence of post-early stage diagnoses was not increased among persons that lived >5 miles of any testing site.

Discussion:

Distance to publicly-funded HIV testing facilities plays a role in test-seeking behaviors in central NC. An increase in prevalence of post-early-stage diagnoses was observed among persons diagnosed farther away from their place of residence. Most of the elevated prevalence occurred in persons who were diagnosed at testing facilities that were >5 miles from their residence yet lived within 5 miles of a different testing facility, suggesting factors other than distance may contribute to delays in testing.

A substantial proportion of HIV testing in the southeastern United States is conducted in health departments.[34] We identified 326 publicly-funded testing sites servicing the 100 NC counties. In our analysis, all identified HIV-infected persons lived within 30 miles of a testing facility and over 75% lived within 5 miles, indicating that free or low-cost HIV testing services are widely available.

The location of HIV testing appears to depend on factors beyond distance alone. Perceptions about disease-related stigma, inadequate HIV services, and lack of confidentiality may influence people living in the rural south to seek HIV testing (and possibly care) from facilities that are geographically farther away.[27,79,86,183,186] Furthermore, where a person chooses to access medical services is often a function of accumulation, whereby testing and care choices are made relative to the location of other persons (e.g. friends, family) or activities (e.g. employment, school) rather than their place of residence.[187] In this analysis, we estimated the proportion of persons for whom factors other than distance influence their choice to travel farther than geographically necessary to test for HIV. While the relative increase in observed prevalence of post-early-stage diagnosis in this group was relatively small, it is not inconsequential. The

approximately 120 post-early-stage diagnoses travelling farther than geographically necessary to test did not benefit from early care and treatment. Interventions addressing non-geographic factors related to accessibility of HIV services may be valuable to promote early identification of HIV in this setting.

While street network distance between two points is an easy-to-derive measure from data collected for surveillance purposes, it may not fully explain all dimensions of geographic accessibility to HIV services.[187] Communities differ with regard to the type and efficiency of available transportation systems.[188] This could impact both the cost and travel time required to get from one location to another that may not be evident when considering distance alone.

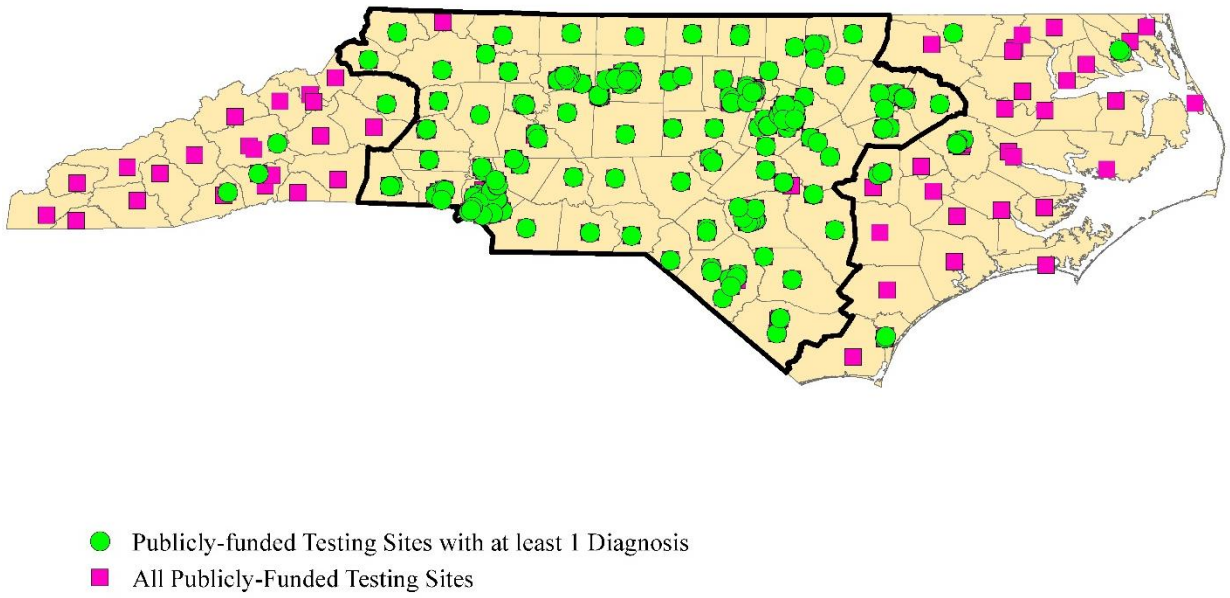
Surveillance data provides a real-world depiction of the test-seeking behaviors of HIV-infected persons that has been unmodified by study monitoring. CD4 cell counts are traditionally used to classify the disease stage of HIV-infected persons.[181] However, the novel algorithm presented in this analysis takes advantages of standard HIV testing results reported in NC surveillance databases to estimate disease stage at diagnosis. While misclassification of AIDS cases as recent infection by STARHS testing results is possible,[112] we tried to minimize this phenomenon by classifying and removing AIDS cases prior to our assessment of STARHS results.

Delays in HIV testing were apparent among persons who could in theory have tested at a nearby publicly-funded facility, but chose to travel longer distances to test. The reasons for travelling farther to test for HIV and delaying diagnosis are likely varied and may spill over to delays in linking to HIV care and initiating treatment.[34] Additional HIV testing sites may not be the most effective use of limited resources. Rather, interventions increasing the accessibility of

HIV services (e.g. providing transportation and lowering perceived stigma) for people travelling longer distances to receive a diagnosis could help in disease awareness, management, and active care engagement.

Tables and Figures

Figure 7.1 Location of All Publicly-funded HIV Testing Sites in North Carolina



CAPTION: All publicly-funded testing sites in NC were geocoded to an ESRI (Redlands, California)-supplied NC street basemap using ArcGIS (version 10.1, ESRI). The green circles represent testing sites where at least 1 case included in this analysis was diagnosed. The pink squares represent all other publicly-funded testing sites in the state. The heavy black line indicates the study area used to identify cases.

Table 7.1: HIV Diagnosis Demographics of persons newly-diagnosed with HIV in a 52 county region in Central North Carolina, 2005-2013

	Total Cases N=3028		Early Stage Cases N=1018		Post-Early Stage Cases N=2010	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age	29	(23-40)	25	(21-35)	32	(24-42)
	N	**%**	**N**	**%**	**N**	**%**
Stage of Diagnosis						
AHI	156	(4.9)	156	(4.9)	--	--
RHI	904	(28.1)	904	(28.1)	--	--
CHI	1659	(51.6)	--	--	1659	(51.6)
AIDS	497	(15.5)	--	--	497	(15.5)
Gender						
Female	717	(23.7)	238	(23.4)	479	(23.8)
Male	2311	(76.3)	780	(76.6)	1531	(76.2)
Race						
Black	2144	(70.8)	758	(74.5)	1386	(69.0)
White NH	472	(15.6)	161	(15.8)	311	(15.5)
Hispanic	302	(10.0)	65	(6.4)	237	(11.8)
Other	110	(3.6)	34	(3.3)	76	(3.8)
Risk Group						
MSM	1622	(53.6)	625	(61.4)	997	(49.6)
IDU	69	(2.3)	24	(2.4)	45	(2.2)
MSM/IDU	17	(0.6)	6	(0.6)	11	(0.5)
Other	444	(14.7)	125	(12.3)	319	(15.9)
Region						
2: Charlotte	978	(32.3)	306	(30.1)	672	(33.4)
3: Winston-Salem	589	(19.5)	224	(22.0)	365	(18.2)
4: Raleigh	980	(32.4)	325	(31.9)	655	(32.6)
5: Fayetteville	481	(15.9)	163	(16.0)	318	(15.8)
Period of Diagnosis						
2005-2007	970	(32.0)	308	(30.3)	662	(32.9)
2008-2010	1305	(43.1)	422	(41.5)	883	(43.9)
2011-2013	753	(24.9)	288	(28.3)	465	(23.1)
Testing Site						
HIV Counselling and Testing Agency	2265	(74.8)	771	(75.7)	1494	(74.3)
STD Clinic	212	(7.0)	79	(7.8)	133	(6.6)
Outpatient Facility	294	(9.7)	94	(9.2)	200	(10.0)
Other	257	(8.5)	74	(7.3)	183	(9.1)
Rural/Urban						
Urban	2812	(92.9)	949	(93.2)	1863	(92.7)
Rural	216	(7.1)	69	(6.8)	147	(7.3)

Table 7.2**:** Distance Measures of persons newly-diagnosed with HIV in a 52 county region in Central North Carolina, 2005-2013

	Early Stage Cases N=1018		Post-Early Stage Cases N=2010		
	Median	**IQR**	**Median**	**IQR**	
Distance to Testing Site of Diagnosis (Miles)	6.5	(3.4-12.7)	6.7	(3.7-12.1)	
Distance to Closest Testing Site (Miles)	2.1	(1.1-4.2)	2.2	(1.1-4.1)	
	N	**%**	**N**	**%**	**Prevalence of Post-Early Stage Diagnoses***
Distance to Testing Site of Diagnosis					
≤5 miles	419	(41.2)	726	(36.1)	63.4
>5 miles	599	(58.8)	1284	(63.9)	68.2
Distance to Closest Testing Site					
≤5 miles	803	(78.9)	1615	(80.3)	66.8
>5 miles	215	(21.1)	395	(19.7)	64.8
Distance to Testing Site of Diagnosis					
≤5 miles	419	(41.2)	726	(36.1)	63.4
>5 miles, but closest testing site within 5 miles	384	(37.7)	889	(44.2)	69.8
>5 miles and closest testing site >5 miles	215	(21.1)	395	(19.7)	64.8
Tested at Closest Testing Site					
Yes	148	(14.5)	295	(14.7)	66.3
No	870	(85.5)	1715	(85.3)	66.6

*per 100 people

Table 7.3: Prevalence Ratio (PR) and 95% Confidence Intervals (CI) Estimates of Post-Early Stage Diagnoses in a 52 county region in Central North Carolina, 2005-2013

		Crude		Adjusted*	
	N	**PR**	**95% CI**	**PR**	**95% CI**
Distance to Testing Site of Diagnosis					
≤5 miles	1145	1.00		1.00	
>5 miles	1883	1.08	(1.02-1.14)	1.07	(1.02-1.13)
Race					
Black	2144	0.98	(0.92-1.05)	0.99	(0.93-1.06)
White	472	1.00		1.00	
Hispanic	302	1.19	(1.09-1.30)	1.20	(1.10-1.31)
Other	110	1.07	(0.93-1.23)	1.08	(0.94-1.24)
Period					
2005-2007	970	1.10	(1.03-1.18)	1.11	(1.04-1.19)
2008-2010	1305	1.10	(1.02-1.17)	1.11	(1.04-1.19)
2011-2013	753	1.00		1.00	
Distance to Closest Testing Site					
≤5 miles	2418	1.00		1.00	
>5 miles	610	0.97	(0.91-1.03)	0.98	(0.92-1.04)
Race					
Black				0.98	(0.91-1.05)
White				1.00	
Hispanic				1.19	(1.09-1.30)
Other				1.07	(0.94-1.23)
Period					
2005-2007				1.11	(1.04-1.19)
2008-2010				1.11	(1.03-1.18)
2011-2013				1.00	
Distance to Testing Site of Diagnosis					
≤5 miles	1145	1.00		1.00	
>5 miles but closest TS ≤5 miles	1273	1.10	(1.05-1.17)	1.09	(1.03-1.16)
>5 miles and closest TS >5 miles	610	1.02	(0.95-1.10)	1.02	(0.95-1.10)
Race					
Black				0.98	(0.92-1.05)
White				1.00	
Hispanic				1.18	(1.09-1.29)
Other				1.08	(0.94-1.23)
Period					
2005-2007				1.11	(1.04-1.19)
2008-2010				1.11	(1.04-1.19)
2011-2013				1.00	

*Each model adjusted for Race and Testing Period

CHAPTER EIGHT: DISCUSSION

Diagnosis, presentation to care, and initiation of antiretroviral therapy (ART) during the early stages of HIV have substantial individual and public health benefits.[1-6] However, current estimates of the HIV care continuum, or care cascade, indicate that most HIV-infected persons in the US are not achieving viral suppression.[8,154] The purpose of this dissertation was to 1) characterize the cascade-related behaviors of persons participating in active transmission networks and 2) examine the geographic barriers to early diagnosis. Improved understanding of when a person is diagnosed and the subsequent cascade-related behaviors of HIV-infected persons are necessary to develop innovative interventions against HIV.

Specifically, this dissertation addressed three aims: estimation of the relative contributions of persons with AHI, previously undiagnosed established infection, and diagnosed established infection to ongoing transmission in NC (Aim 1), examination of how the spatial clustering of HIV diagnoses by stage of disease has changed as a result of the CDC's recommendations for routine, opt-out testing (Aim 2) and assessment of the effect of distance to testing sites on stage of disease at diagnosis (Aim 3).

Aim 1: HIV transmission in NC

Summary of Findings

In Aim 1, we assessed HIV status awareness and the diagnosis, care, treatment, and viral suppression status for 1) all traceable partners and 2) the most likely transmission source for

persons diagnosed with acute HIV infection (index AHI cases) in NC between 2002 and 2013 using surveillance data collected as part of the STAT program and data collected via the CHAVI-001 study. Based on prior modeling studies that used a combination of empirical data and assumptions (when empirical data was unavailable),[10,11] we hypothesized that the majority of these transmission events would be due to partners who were previously unaware of their disease status. However, the results of this analysis did not support this hypothesis.

A total of 358 index AHI cases named 932 partners, of which 218 were HIV-infected (162 (74.3%) previously-diagnosed, 11 (5.0%) new AHI, 45 (20.6%) new CHI). Among the 162 previously-diagnosed partners, 16.0% were not in care, 31.5% were in care but not on ART, and 29.6% were in care and on ART at the time of the index AHI case diagnosis. Among the 40 previously-diagnosed partners in care and with an available VL, 75.0% were unsuppressed at the time of their most recent VL prior to the index AHI case's diagnosis date. Approximately half (48.6%) of index AHI cases named at least 1 HIV-infected partner. The remaining index AHI cases only named potential transmitting partners of unknown status, did not name any partners during the 8 weeks prior to their diagnosis, or only named HIV-uninfected partners.

Most transmission events appeared attributable to previously-diagnosed partners (76.9%, 5^{th} and 95^{th} percentile 75.3-78.2%). Among previously-diagnosed partners, only 27.1% (5^{th} and 95^{th} percentiles 25.9-28.8%) were reported to be in care and on treatment near the index AHI case diagnosis date. In the subset study of 33 phylogenetically-linked cases and partners, most partners had been previously-diagnosed (60.6%, 95% CI 43.9-77.3%), although the contribution is smaller than observed in surveillance data collected as part of the STAT program.

Interpretation

Our findings highlight the fact that previously-diagnosed persons continue to engage in high-risk behaviors with persons who up until recently, were HIV-uninfected. A substantial proportion of observed transmission events appear attributable to contact with previously-diagnosed partners in North Carolina, where HIV disproportionately affects African Americans living in both urban and rural areas. Moreover, previously-diagnosed partners were uncommonly reported to be in care, on treatment and virally suppressed at the time of contact with the index AHI case, increasing the likelihood of transmission.[158,159]

Public Health Significance

This analysis provides the first empirically collected estimates of the diagnosis, care, treatment, and viral suppression status of persons involved in networks where HIV is actively being transmitted. This information is important for designing, modeling, and targeting HIV care and treatment services from both a clinical and prevention perspective.

Estimates produced as a part of this dissertation can be used on both the individual and public health level to communicate the level of risk of onward transmission among persons not in care or on effective treatment. Most observed transmission in NC appeared to be due to contact with previously-diagnosed partners, reinforcing the need for improved linkage and retention in care after diagnosis.

Additionally, these estimates can be used to update mathematical models estimating the likelihood of transmission. The contribution of newly-infected persons to onward transmission in previous mathematical models was 10-50% higher than observed in any population under analysis in this dissertation.[10,11] Because mathematical models can inform policy decisions and

resource allocation, accurate estimates of cascade-related behaviors of potential transmitting partners are necessary to maximize the public health benefits of these decisions.

Limitations

Prior modeling studies and our current empirical work approach the research question in different populations and from different angles, each with its own biases related to difficult-to-verify assumptions and missing information. In this study, approximately half of the index AHI cohort named at least one status-unknown or anonymous partner, and over one-third named only unknown/anonymous partners. Undoubtedly, some unknown/anonymous partners transmitted HIV, but could not be included in our analysis of cascade stages. Status-unknown partners have no record of a positive test in surveillance databases under the name provided by the index AHI case and either refused HIV testing or could not be located. HIV infection may be more prevalent among persons refusing HIV testing. If HIV-infected, status-unknown partners have not yet been diagnosed, were misnamed or were diagnosed outside the jurisdiction area. Anonymous partners did not have any identifiable information, and consequently, may be more likely to engage in riskier behaviors and less likely to test for HIV or enter care than identifiable partners.

Despite proximity to the date of infection, uncertainty exists in the identification of the transmitting partner. Approximately 20% of index AHI cases did not name any potential transmitting partners. Furthermore, most of the partnerships under analysis were not confirmed as known transmission pairs through phylogenetic linkages. The source of transmission cannot be verified in partnerships where phylogenetic testing was not done, even if the status of all partners was known and only one was HIV-infected. Even for pairs that have been

phylogenetically linked, a shared intermediary transmitting partner provides another possible explanation for the linkage.

Finally, partner viral suppression status at the time of transmission is difficult to assign based on information reported for surveillance purposes. Only half of the previously-diagnosed partners had an available VL in surveillance databases near the time of the index AHI case diagnosis and approximately 20% of these partners were virally suppressed. If partners are truly virally suppressed, HIV transmission is known to be unlikely.

Future Research Directions

To improve the understanding of the contribution previously-diagnosed partners make to onward HIV transmission, additional estimates of risk behaviors are required. Published mathematical models of transmission risk make assumptions about difficult-to-verify risk behaviors at the time of transmission, specifically the frequency of unprotected anal sex acts.[10,11] We are currently quantifying the risk behaviors reported by index AHI cases as part of the STAT program, including type of partnership (sexual or needle-sharing), sexual positioning, frequency of sex acts, and condom use. While we are unable to phylogenetically-confirm linkage in each potential transmitting partnership, the repeated sampling methods used in this aim can provide reasonable estimates of risk behaviors that increase the likelihood of HIV transmission.

Aim 2: Spatial assessment of early and late stage HIV diagnoses in NC

Summary of Findings

In this analysis, we examined the geographic patterns and clustering of early and late stage diagnoses in a 52-county study area in central NC both before and after the adoption of the CDC's recommendations for routine, opt-out testing. We hypothesized that persons diagnosed

with early HIV infection would be more likely to cluster in urban centers both before and after the CDC's recommendations, while late stage diagnoses would be more geographically dispersed.

Minimal overlap of high rate diagnoses (top 10 percentile) by disease stage and testing period was observed in the 52-county study area in NC between 2005 and 2013. However, at non-high rates (top 25th and 50th percentile), a disproportionate level of overlap was observed, suggestive of an underlying, "core" HIV diagnosis area in NC.

The overlap of EHI and CHI diagnoses at the highest rates (top 10 percentile) was relatively constant in terms of both quantity and location across all periods. High rate EHI and CHI diagnoses occurred predominantly in the urban centers, with a few small pockets scattered across the study area. Between Period 1 (2005-2007) and Period 2 (2008-2010), an increase in the number of overlapping high rate (top 10 percentile) areas was observed between CHI and AIDS diagnoses, possibly indicating cases that would have been diagnosed during AIDS were being found earlier and diagnosed during CHI in these areas. Most of the increase in overlap was observed in the southeastern part of the study area.

Overlap at the highest rates (top 10 percentile) of disease stage across each testing period was relatively low. Overlap of high rate EHI diagnoses across time was spatially dynamic, indicating EHI was consistently diagnosed across the study area and the location of high rate EHI diagnoses changed over time. Compared to EHI and CHI diagnoses, overlap of high rate AIDS diagnoses was highest across all 3 testing periods and was geographically prominent in the southeastern part of the study area.

Interpretation

An underlying, "core" area for HIV diagnosis was observed across each testing period and disease stage, but only at lower diagnosis rates. In these areas, stage of disease does not appear to be heavily influenced by location or the adoption of the CDC's testing recommendations. Areas with high rates of HIV diagnosis by disease stage and testing period were more spatially dynamic, with minimal observed overlap.

Spatial trends in EHI diagnosis could indicate changing trends in the underlying epidemic in central NC. Alternatively, changes could be due to shifts in testing activity, possibly due to the adoption of routine, opt-out testing. Overlap of high rate EHI diagnoses was rare, particularly outside of urban centers. Interventions other than routine, opt-out testing may be necessary to consistently identify early infection. Areas of persistent AIDS diagnoses suggest the routine, opt-out testing policies fail to find every HIV-infected person early. In this analysis, substantial overlap of high rate AIDS diagnoses across time periods was observed in the southeastern part of the state. Promoting HIV testing and possibly targeting testing to at-risk persons in this region could reduce the rates at which AID is diagnosed in this region.

Public Health Significance

Improved understanding of the geographic patterns and clustering of HIV diagnoses across North Carolina is important for informing policymakers of current trends and facilitating effective targeting of limited HIV prevention resources. One of the goals of the CDC's recommendations was to identify HIV-infected persons earlier during the course of their infection to achieve the benefits of care and ART sooner.[14] Our analysis suggests that targeted

efforts to identify EHI in areas with high rates of CHI may be an effective strategy to diagnose and link HIV-infected persons to care earlier during their infection.

A persistence of AIDS cases across all testing periods in the southeast portion of the study area suggests HIV-infected persons in this part of the state are not requesting or not being offered HIV testing early in their infection. The reasons for late stage testing are likely varied and include noncompliance with the CDC's recommendations on the part of providers as well as the patient's perceptions of risk, inaccessibility of HIV services, and stigma.[34] Targeted interventions emphasizing the importance of early diagnosis may be necessary in these parts of the state with persistent or re-emerging high rates of AIDS diagnoses.

Limitations

We present a novel method to classify stage of disease based on testing results. This algorithm is not without bias. The BED assay used for STARHS testing is a nonspecific test, whereby a proportion of persons with severe immunosuppression or with long-standing infection and on antiretroviral therapy can be misclassified as RHI.[112,113] However, we assumed this misclassification was minor since our study population included only newly-diagnosed persons who were not likely to have a history of ART use prior to STARHS testing. Furthermore, we removed all persons diagnosed with AIDS prior to the assignment of recent infection, lowering the likelihood of any potential misclassification. It is possible that the observed overlap of high rate EHI and AIDS diagnoses represents some expected misclassification.

The UMBME method used in this analysis to map diagnosis rates effectively imputes disease rates to areas where data are missing. This smoothing process can result in the addition of "noise" in the estimated rates.[144] Therefore some of the high rate areas may be an artifact of

the smoothing process used in UMBME estimation. To address this, we aggregated cases to the census tract level and to three-year testing periods. Aggregation ensures data are spatially correlated, improving the smoothing of UMBME models.[144] However, these larger units of aggregations do mask some sub-unit variation and could result in misinterpretation of true underlying spatiotemporal patterns.[182]

As part of this analysis, we excluded over half of the newly-diagnosed HIV infections to assess overall positivity rates for people diagnosed at publicly-funded testing clinics. We also excluded an additional 20% of cases whose address could not be geocoded. Therefore, the rates presented in this analysis likely underestimate the total diagnosis rates in each census tract. Furthermore, we did not have an accurate count of the testing population at publicly-funded testing sites. We deduplicated the testing events in the CTR system using a software program with over 90% sensitivity and positive predictive value when a reviewer's decision is used as the gold standard.[141] However, it is likely that this program failed to link tests that were true matches and linked tests that should have been matched. This misclassification is likely nondifferential.

Future Research Directions

In this analysis, we were able to estimate the diagnosis rates in time and space originating from publicly-funded testing sites. An obvious extension of this work would be to apply this same analysis to all persons diagnosed at both public and private testing sites. Estimation of the underlying testing population may be difficult to determine in such an analysis. However, density (e.g. number of cases per tract divided by the area of the tract) is a valid measure for estimating rates in other similar analyses[145] and could be used when the underlying testing population is difficult to estimate.

We restricted this analysis to a 52-county study area in central North Carolina where approximately 80% of all HIV diagnoses occur so that our rates would not be as influenced by the "noise" resulting from the mountain and coastal regions of the state where HIV diagnosis rates are lower. However, our study area was comprised of urban and rural areas with both high and low rates. Estimation of the true "latent" rate in these rural areas with low rates may have been overly influenced by high rate urban areas in the study area.[144] Choice of the study boundary therefore has the potential to affect the results and their interpretation for public health decision making purposes. Conducting this analysis within each region or county, where rates are likely to be similar, provides a better estimation of HIV diagnosis patterns on a local level which can translate to more effective use of resources.

Aim 3: Distance to a testing site and stage of disease at diagnosis

Summary of Findings

The purpose of the analysis in Aim 3 was to estimate the effect of distance to a publicly-funded testing site on post-early stage diagnosis in central North Carolina. The results of this analysis supported my hypothesis that persons living farther from the test site where they were diagnosed were more likely to be diagnosed with later during the course of their disease.

In unadjusted and adjusted models, the prevalence of post-early-stage diagnosis was greater among persons living >5 miles from the testing site of diagnosis (PR adjusted for race/ethnicity and time period =1.07 95% CI 1.02-1.13). However, living >5 miles from the closest testing site did not result in an increase in the prevalence of post-early-stage diagnosis (PR adjusted for race/ethnicity and time period=0.98 95% CI 0.92-1.04). Most of the increased prevalence of post-early-stage diagnoses occurred among cases who were diagnosed at a testing

diagnosed at a testing site that was >5 miles from their residence, but lived within 5 miles of a different publicly-funded testing site (PR adjusted for race/ethnicity and time period=1.09 95% CI 1.03-1.16).

Interpretation

Despite the fact that publicly-funded HIV testing sites are widely available across North Carolina, some people choose to travel farther distances than geographically necessary to test. These people may be more likely to enter care later during the course of their disease, limiting the potential effectiveness of HIV care and treatment. Proximity to the closest testing site did not appear to influence when HIV-infected persons tests, suggesting distance alone is not a major impediment to HIV testing behaviors. Perceptions about disease-related stigma, inadequate HIV services, and lack of confidentiality may influence people living in the rural south to seek HIV testing from facilities that are geographically farther away.[27,79,86,183]

Public Health Significance

To fully benefit from the ART, HIV-infected persons should not only be aware of their disease status, but also be diagnosed early. Nationwide, a substantial proportion of HIV-infected persons do not present for HIV testing until late in their course of their infection[8]; approximately half of all AIDS diagnoses in NC in 2010 were made at the same time or within six months of their HIV diagnosis.[16] Persons presenting at an advanced stage of immunosuppression are at high risk of adverse clinical events and death.[64] However, the reasons for delays in testing are varied and complex.[5,12,31,53-61,189]

In this analysis, we observed a small, yet meaningful increase in post-early stage diagnoses among persons who travelled longer distances to receive an HIV test than

geographically necessary. For these people, accessibility to HIV testing was not measured by distance alone. Other factors, possibly including perceptions about the quality of the HIV services and stigma could lead to increases in the distances traveled for a test and consequently delays in testing. Additional HIV care and testing sites may not be the most effective use of limited public health resources. Rather, interventions increasing the non-distance factors related to accessibility of HIV services (e.g. providing transportation and lowering perceived stigma) for people travelling longer distances to receive a diagnosis could help in the management of their disease status while keeping them actively engaged in care.

Limitations

While street network distance between two points is an easy-to-derive measure from data collected for surveillance purposes, it may not fully explain all dimensions of geographic accessibility to HIV services.[187] Communities differ with regard to the type and efficiency of available transportation systems.[188] This could impact both the cost and travel time required to get from one location to another that may not be evident when considering distance alone. Furthermore, perceptions related to stigma and the quality of HIV-related services were not measured. However, the use of GEE in this analysis accounts for some of these unmeasured, neighborhood-wide perceptions during statistical modeling.

The definition used in this analysis for early stage disease was heavily dependent on BED assay results used as part of STARHS testing. Because the BED assay is a nonspecific test for RHI, some persons with AIDS were likely misclassified as having RHI. We tried to minimize this phenomenon by classifying and removing AIDS cases prior to our assessment of BED assay results, however some misclassification is likely to have occurred.

Future Research Directions

Diagnoses made later during the course of the disease are generally more common among persons who are not perceived, or who do not perceive themselves to be at high risk for infection, persons not actively offered HIV testing, and marginalized groups.[44] These factors are likely intertwined with structural barriers, such as the distance a person travels to receive a diagnosis for HIV. In this analysis, we identified that persons travelling longer distances than geographically necessary are more likely to test later during the course of their disease. Focus groups among persons requesting HIV tests from a publicly-funded testing site may provide insight into the role stigma, perceived risk, quality of HIV services, and structural barriers (including distance) played in the selection a testing site.

The results from the focus groups can also be used to formulate more accurate measures of "accessibility" beyond the network distance measure used in this analysis. Improving the measurement of accessibility translates to increased accuracy in its estimated effect on late stage diagnosis. This can in turn lead to a more effective allocation of public health resources towards interventions with the highest likelihood of success.

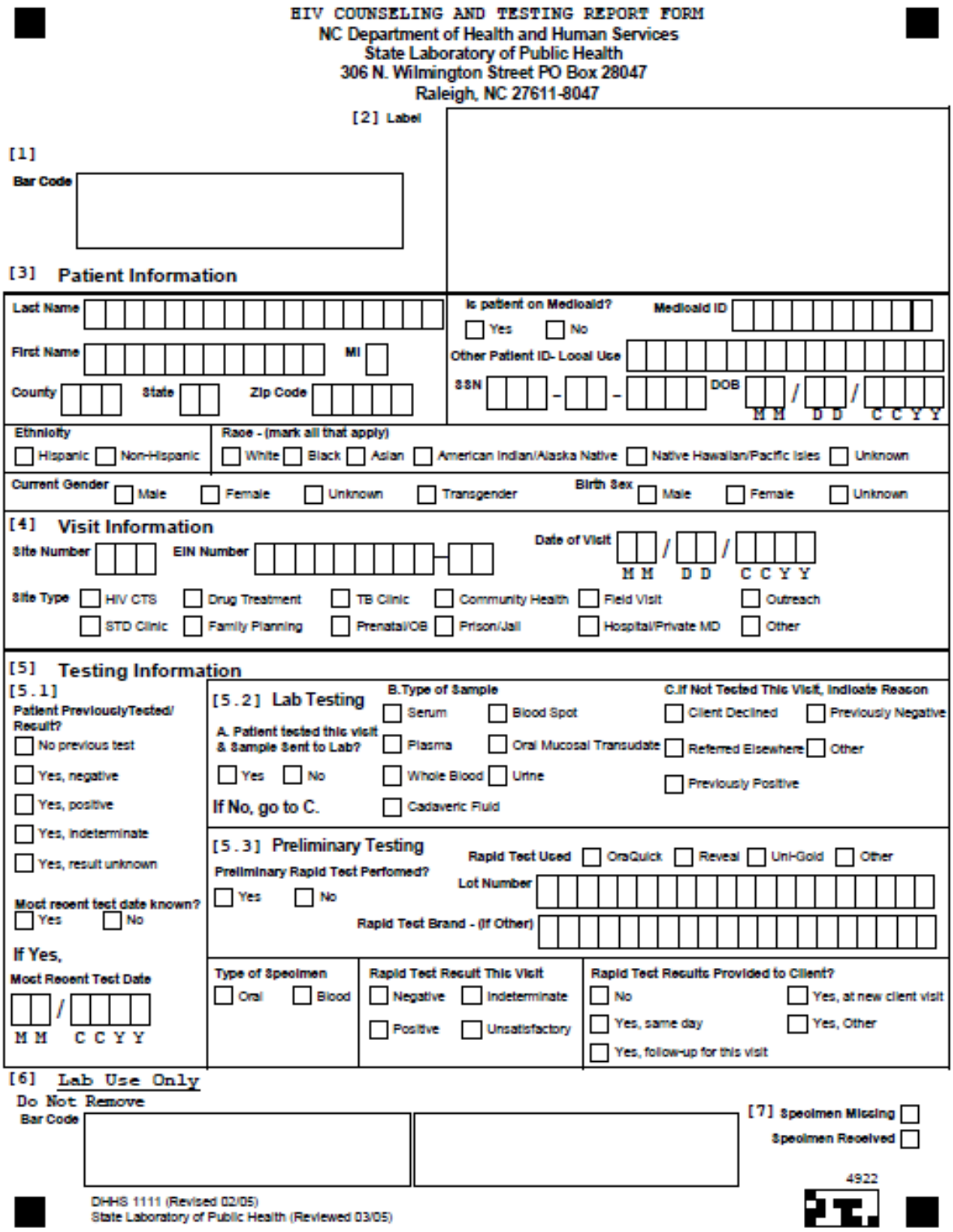
Final Remarks

HIV is spatially dispersed across central North Carolina; however diagnosis rates are highest in urban centers. The location of high rates of early infection has changed over time indicating possible shifts in the testing activity and/or the epidemic itself. The southeastern corner of the state displayed persistently high rates of AIDS diagnoses. Interventions focused on early detection of disease in these areas could impact morbidity, mortality, and transmission in this part of the state. Reasons for late stage diagnoses are likely varied. Here, we identified that

persons travelling longer distances than geographically necessary are more likely to be diagnosed with post-early stage HIV infection. Perceptions of risk, stigma, and accessibility of HIV services provide possible explanations for travelling farther than necessary for an HIV test.

Once diagnosed, it is imperative to engage HIV-infected persons in care because previously-diagnosed persons continue to engage in risk behaviors with persons who up until recently, were uninfected. Most transmission in NC appears to be a result of contact with people who are aware of their infection. Ensuring viral suppression through care and treatment of these previously-diagnosed persons could effectively prevent transmission and lower HIV incidence in this setting.

APPENDIX 1: HIV COUNSELING AND TESTING REPORT FORM



HIV COUNSELING AND TESTING REPORT FORM
NC Department of Health and Human Services
State Laboratory of Public Health
306 N. Wilmington Street PO Box 28047
Raleigh, NC 27611-8047

[2] Label

[1]
Bar Code

[3] Patient Information

Last Name
First Name
MI
County
State
Zip Code
Is patient on Medicaid? Yes No
Medicaid ID
Other Patient ID- Local Use
SSN
DOB MM / DD / CCYY

Ethnicity: Hispanic Non-Hispanic
Race - (mark all that apply): White Black Asian American Indian/Alaska Native Native Hawaiian/Pacific Isles Unknown
Current Gender: Male Female Unknown Transgender
Birth Sex: Male Female Unknown

[4] Visit Information
Site Number
EIN Number
Date of Visit MM / DD / CCYY
Site Type: HIV CTS Drug Treatment TB Clinic Community Health Field Visit Outreach STD Clinic Family Planning Prenatal/OB Prison/Jail Hospital/Private MD Other

[5] Testing Information

[5.1] Patient PreviouslyTested/ Result?
No previous test
Yes, negative
Yes, positive
Yes, indeterminate
Yes, result unknown
Most recent test date known? Yes No
If Yes,
Most Recent Test Date MM / CCYY

[5.2] Lab Testing
A. Patient tested this visit & Sample Sent to Lab? Yes No
If No, go to C.
B. Type of Sample: Serum Blood Spot Plasma Oral Mucosal Transudate Whole Blood Urine Cadaveric Fluid
C. If Not Tested This Visit, Indicate Reason: Client Declined Previously Negative Referred Elsewhere Other Previously Positive

[5.3] Preliminary Testing
Preliminary Rapid Test Performed? Yes No
Rapid Test Used: OraQuick Reveal Uni-Gold Other
Lot Number
Rapid Test Brand - (If Other)

Type of Specimen: Oral Blood
Rapid Test Result This Visit: Negative Indeterminate Positive Unsatisfactory
Rapid Test Results Provided to Client? No Yes, same day Yes, follow-up for this visit Yes, at new client visit Yes, Other

[6] Lab Use Only
Do Not Remove
Bar Code

[7] Specimen Missing
Specimen Received

4922

DHHS 1111 (Revised 02/05)
State Laboratory of Public Health (Reviewed 03/05)

HIV COUNSELING AND TESTING REPORT FORM

NC Department of Health and Human Services
State Laboratory of Public Health
306 N. Wilmington Street PO Box 28047
Raleigh, NC 27611-8047

Bar Code

[8] Pre-Test Counseling Information

Pretest Counselor	Client Counseled	If Female, Is Patient Pregnant?	If Pregnant, In Prenatal Care	Outreach Venue?
	☐ Yes ☐ No STARHS Consent ☐ Yes ☐ No	☐ Yes ☐ No ☐ Unknown	☐ Yes ☐ Refused to Answer ☐ No ☐ Not Asked	☐ Yes ☐ No

Reason for the Visit - (mark all that apply)

- ☐ Symptomatic for HIV/AIDS
- ☐ TB Related
- ☐ Client Referral
- ☐ Court Ordered
- ☐ Provider Referral
- ☐ Immigrant/Travel Req
- ☐ STD Related
- ☐ Occupational Exposure
- ☐ Drug Trmt Related
- ☐ Retest
- ☐ Family PL Related
- ☐ Requesting HIV Test
- ☐ PreNatal/OB Related
- ☐ Other

Risk Behaviors within the last 12 months - (mark all that apply)

- ☐ Sex with man
- ☐ Child of HIV infected woman
- ☐ Sex with woman
- ☐ Sex while using non-inj drugs
- ☐ Injection Drug Use
- ☐ Sex with other HIV/Aids Risk
- ☐ Sex with HIV+ person
- ☐ Hemophilia/Blood Recipient
- ☐ Sex with IDU
- ☐ Health Care Exposure
- ☐ Sex with MSM
- ☐ Victim of Sexual Assault
- ☐ Sex in exchange for drugs/money
- ☐ No acknowledged Risk
- ☐ Current STD diagnosis
- ☐ Other Risk

[9] Additional Demographic Information

Primary Language

☐ English ☐ Spanish ☐ Other

Other Primary Language

[10] Local Use Data Fields

Local Use Field 1 **Local Use Field 2** **Local Use Field 3** **Local Use Field 4**

For optimum accuracy, please print in capital letters and avoid contact with the edge of the box. Follow the sample letters and numbers as closely as possible.

A	B	C	D	E	F	G	H	I	J	K	L	M
N	O	P	Q	R	S	T	U	V	W	X	Y	Z

1	2	3	4	5	6	7	8	9	0

4922

APPENDIX 2: STAT DATA COLLECTION FORMS

STAT Log Sheet

STAT/COMM ID#: _____ **State/Event #:** _____ **County:** _____ **Zip:** _____

Sex: _____ **Age:** _____ **Race:** _____ **Student:** □ Yes □ No **Campus:** _____

Case Detection (circle): STAT Acute Comm Acute Comm Recent **Self-Identified Sex with** (circle): Men Only Women Only Men & Women

DIS Name: _____ **Date Called to DIS:** _____ **Date of Initial Interview:** _____

Test No.	Bar Code #	Testing Site and Type (e.g. STD, Prenatal, Field Visit, etc)	Date of Specimen Collection	HIV-1 EIA Ab (3rd Gen EIA)	HIV Ag/Ab Combo (4th Gen EIA)	WB	RNA/ NAAT	HIV-1 & 2 Ab Type Differen-tiating (Multi-spot)	Oral Rapid	Serum Rapid	Home Kit Rapid
1											
2											
3											
4											

Total Number of Relationships in 8 weeks before AHI Dx:

	Total	UTL	Refuse Test	Prev Pos	Tested Neg	Tested Pos	Tested Acute
Initiated							
Marginal							
Suspects							
Associates							

Alcohol Use: □ Yes □ No **Use with sex:** □ Yes □ No
Date last Used: ____/____/____
Frequency: ____ times per day /week /month /year (circle)

Drug Use: □ Yes □ No **Use with sex:** □ Yes □ No
If yes, what drugs? _____
Date last Used: ____/____/____
Frequency: ____ times per day /week /month /year (circle)

Injection Drug Use: □ Yes □ No
Injection Drugs: _____

HIV Testing History:

Other Info:

Interested in Care? □ Yes □ No
Will go to? Location: _____
Medical Provider: _____
ART started: □ Yes □ No Date Started: ___/___/____
List Meds:

Linkage to Care:	Date	Location	Confirmed Attendance (Y/N)	VL (if Available)	CD4 (if Available)
Initial HIV Visit					
Most Recent HIV Care Visit					

How does case plan to get to: (check all that apply)	Own Vehicle	Family/Friend Vehicle	Public Transport	No Transportation	DIS Transport
First HIV care visit					
Regular HIV care visits					

Last revised: Jun 2, 2014 (Version 10)

Page ___ of ___

STAT ID: _____ Date of Interview: _____ DIS: _____

STAT Contacts Information Form

Partner ID #	Initiated/Marginal/Suspect	Gender	Age	Race	County	Zip	Student (if yes, where?)

Contact with Index:	How did index meet this partner?		*If sexual* – (circle)	*If Oral or Anal, Did Index?* (circle)	*If sexual* –condom use? (circle)
□ ≤48 hrs □ 48 hrs - ≤8 wks □ ≥8 wks	□ Internet □ Bookstore □ Clubs/Bars □ Other Which ones?	□ Sexual Contact □ Needle-Sharing			
		_____ times per day/week/month/ever	Oral Y N	Insert Receive Both	Always Sometimes Never
		Start Date:	Anal Y N	Insert Receive Both	Always Sometimes Never
		Stop Date:	Vaginal Y N	NA	Always Sometimes Never

STI Hx:	Ongoing Relationship:	Drug/Alcohol Use DURING INTERVIEW PERIOD (8 wks before dx):
	□ Yes □ No	Drug Use: □ Yes □ No Use with sex: □ Yes □ No Injection Drug Use: □ Yes □ No Which Drugs: _____ Alcohol Use: □ Yes □ No Use with sex: □ Yes □ No

Counsel Status: (check all that apply)	If Refused Testing:	For HIV+ Partners (Previous or New) Only:
□ Counseled, Date _____/_____/_____ □ Partner Tested □ Unable to Locate □ Anonymous □ Located, Refused Counseling □ IPN	□ Unknown Testing □ Known Neg/ Last Test Date: ____/____/_____ □ Known Pos/ Test Date: ____/____/_____ Last VL: _____ Last VL Date: ____/____/_____ Last CD4: _____ Last CD4 Date: ____/____/_____	1. Did the Index know of this Partner's HIV+ status: □ Yes □ No 2. Did this Partner know of his/her HIV+ status prior to DIS interview: □ Yes □ No 3. Does this partner have a medical provider?: □ Yes □ No 4. Has this Partner ever used HAART?: □ Yes □ No 5. Is this partner currently on HAART? □ Yes □ No (list meds)

If Partner Tested,

Bar Code or Location if not through state lab	Test Date	HIV-1 EIA Ab (3rd Gen)	HIV Ag/Ab Combo (4th Gen)	WB	RNA/ NAAT	HIV-1 & 2 Ab Type Differentiating (Multi-spot)	Oral Rapid	Serum Rapid	Home Kit Rapid

Final Testing Result:
□ New Pos-Acute
□ New Pos-Chronic
□ Negative

Last Revised: June 2, 2014
Version 8

Bar Code #:_____ STAT ID_____ Date of Interview: _____ DIS Name:_____
Male or Female *HIV Diagnosis Date: _____*

STAT Symptoms Form

Did the patient experience the new onset of any of the following symptoms? If so, mark the corresponding box and indicate the start date and end date that the patient experienced each symptom.

Section 1: Acute Retroviral-related Symptoms
(complete at all meetings)

	Yes	Start	End
Fever		/ /	/ /
Headache		/ /	/ /
Night sweats		/ /	/ /
Weight loss			
Body aches		/ /	/ /
Joint pain		/ /	/ /
Fatigue		/ /	/ /
Rash		/ /	/ /
Sore throat		/ /	/ /
White patches in mouth		/ /	/ /
Sores or ulcers in or around mouth		/ /	/ /
Cough		/ /	/ /
Loss of appetite		/ /	/ /
Nausea or vomiting		/ /	/ /
Painful stomach		/ /	/ /
Diarrhea		/ /	/ /
Swollen lymph nodes:			
Under the arm		/ /	/ /
On the neck, under chin		/ /	/ /

Section 2: STI Diagnosis

A) Has the patient been **EVER** been diagnosed with an STI ? ☐ Yes ☐ No

B) Has the patient been diagnosed with an STI **within 8 weeks** of HIV (+) test result? ☐ Yes ☐ No

C) Complete the table below for all STI Diagnoses within 8 Weeks of HIV (+) test result:

	Yes	Dx Date	Tx Date
Gonorrhea		/ /	/ /
Chlamydia		/ /	/ /
Trichomoniasis		/ /	/ /
Genital warts (HPV)		/ /	/ /
Genital Herpes		/ /	/ /
Bacterial Vaginosis		/ /	/ /
Syphilis (Stage:____)		/ /	/ /
Additional STI Dx: STI: _____		/ /	/ /
STI: _____		/ /	/ /
STI: _____		/ /	/ /
STI: _____		/ /	/ /

Section 3: STI symptoms present at or within 8 weeks of testing date.

	Yes	Start	End
Unusual discharge from genitals		/ /	/ /
Sores/ ulcers on genital area		/ /	/ /
Bumps, growths, or warts		/ /	/ /

Section 4: Testing History and Risk Behaviors

Reason for Testing (mark all that apply)	☐ Symptomatic for HIV/AIDS ☐ Client referral ☐ Provider referral ☐ STD Related ☐ Drug Treatment Related	☐ Family Planning Related ☐ Prenatal/OB Related ☐ Partner Notification ☐ HIV Positive Exposure ☐ Court Ordered	☐ Occupational Exposure ☐ Retest ☐ Requesting HIV Test/Routine Testing ☐ Routine ☐ Other:_____
Risk Behaviors within the last 12 months (mark all that apply)	☐ Sex with man ☐ Sex with woman ☐ Injection Drug Use ☐ Sex with HIV + person ☐ Sex with IDU ☐ Sex with MSM	☐ Sex for drugs/money ☐ Current STD Diagnosis ☐ Child of HIV infected woman ☐ Sex while using non-injecting drugs ☐ Sex with other HIV/AIDS risk	☐ Hemophilia/Blood recipient ☐ Health Care Exposure ☐ Victim of sexual assault ☐ No acknowledged risk ☐ Other risk: _____
For Community Cases Only: Client previously tested?	☐ No ☐ Yes, Negative	☐ Yes, Positive ☐ Yes, Indeterminate	☐ Yes, result unknown If yes, when? _____/_____/_____

Last revised: February 7, 2014
Version 6

APPENDIX 3: AIM 1 SUPPLEMENTAL TABLES AND FIGURES

Table A3.1 Diagnosis, care, and treatment status estimates for HIV-infected partners

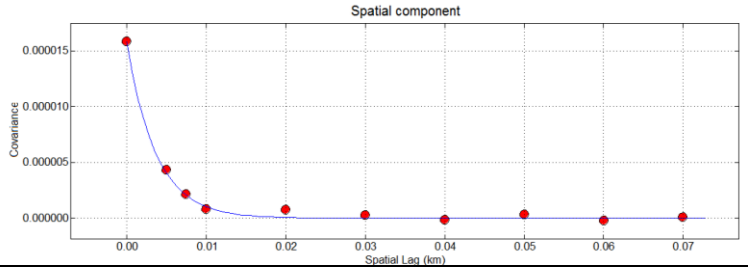
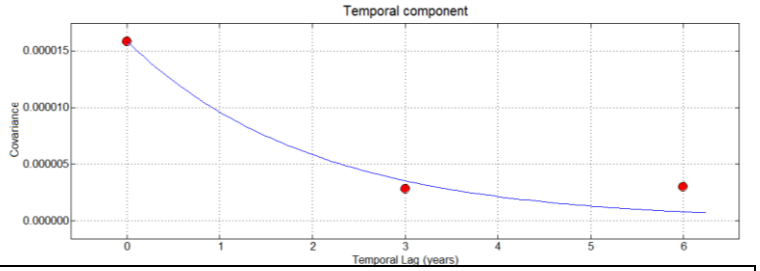
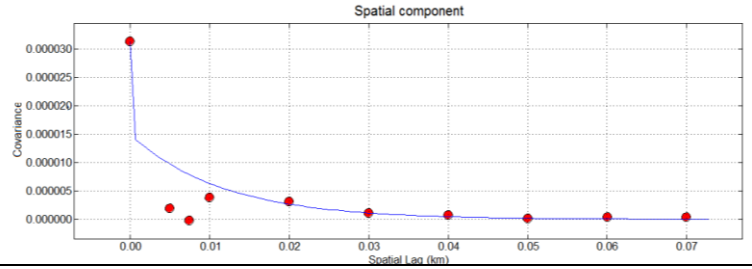
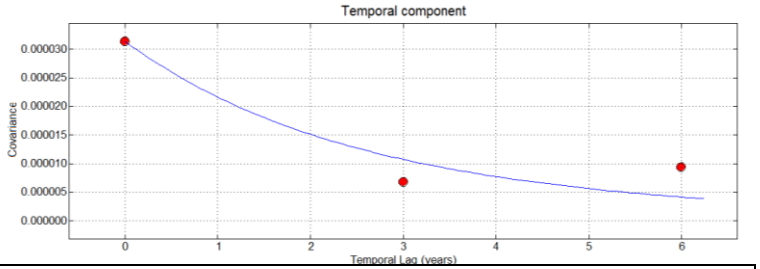
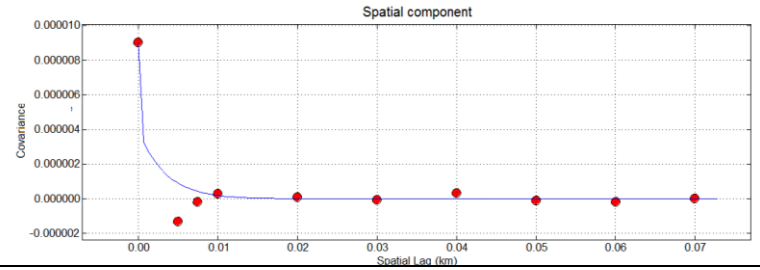
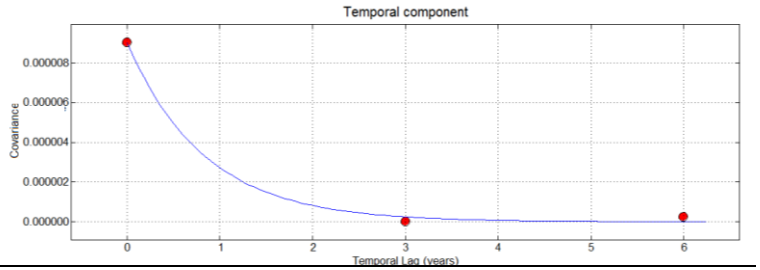
	Transmission Landscape			**Most Likely Transmission Source: Unconfirmed Linkage**									**Most Likely Transmission Source: Confirmed Linkage**		
	STAT: All Identified HIV-infected Partners			STAT Type A: 1 potential transmitting partner with all other partners testing HIV-negative			STAT Type B: >1 potential transmitting partner with at least 1 confirmed HIV-infected partner			STAT Types A+B: ≥1 potential transmitting partner with at least 1 confirmed HIV-infected partner			CHAVI-001: Phylogenetically-Linked Partner		
	HIV+ Partner N=218			Index AHI N=106 HIV+ Partner N=106			Index AHI N=68 HIV+ Partner N=112			Index AHI N=174 HIV+ Partner N=218			Index AHI N=33 HIV+ Partner N=33		
	N	$\hat{p}$	95% CI	N	$\hat{p}$	95% CI	N	$\hat{p}$	5th & 95th percentiles	N	$\hat{p}$	5th & 95th percentiles	N	$\hat{p}$	95% CI
New AHI	11	0.050	0.021-0.080	1	0.001	0.000-0.03	10	0.076	0.059-0.103	11	0.036	0.029-0.046	3	0.091	0.000-0.189
New CHI	45	0.206	0.153-0.260	23	0.217	0.139-0.295	22	0.163	0.118-0.206	45	0.196	0.178-0.213	10	0.303	0.146-0.460
Previously-diagnosed, not in care	26	0.119	0.076-0.162	19	0.179	0.106-0.252	7	0.078	0.059-0.103	26	0.140	0.132-0.149	--	--	--
Previously-diagnosed in care, not on ART	51	0.234	0.178-0.290	22	0.208	0.130-0.285	29	0.278	0.235-0.309	51	0.235	0.218-0.247	--	--	--
Previously-diagnosed, in care, on ART	48	0.220	0.165-0.275	19	0.179	0.106-0.252	29	0.244	0.206-0.279	48	0.204	0.190-0.218	--	--	--
Previously-diagnosed Unclassified Care & Treatment	*37*	*0.170*	*0.120-0.220*	*22*	*0.208*	*0.130-0.285*	*15*	*0.162*	*0.132-0.191*	*37*	*0.190*	*0.178-0.201*	*20*	*0.606*	*0.439-0.773*

NOTE: The diagnosis, care, and treatment status are presented for 1) all HIV-infected partners named by the index AHI cohort and identified by the STAT program, 2) the most likely transmission source among identified HIV-infected partners presented by the pattern of HIV-infected,

uninfected, and status-unknown partners reported to the STAT program and 3) phlyogenetically-linked partners identified via the CHAVI-001 study. For estimates of the most likely transmission source where >1 potential transmitting partner was named, repeated random sampling was used to estimate diagnosis, care, and treatment status of the partner. NOTE: Potential transmitting partner refers to any partner reported in the 8 week period prior to the index AHI diagnosis date who was not classified as HIV-uninfected (e.g. HIV-infected and status-unknown partners).

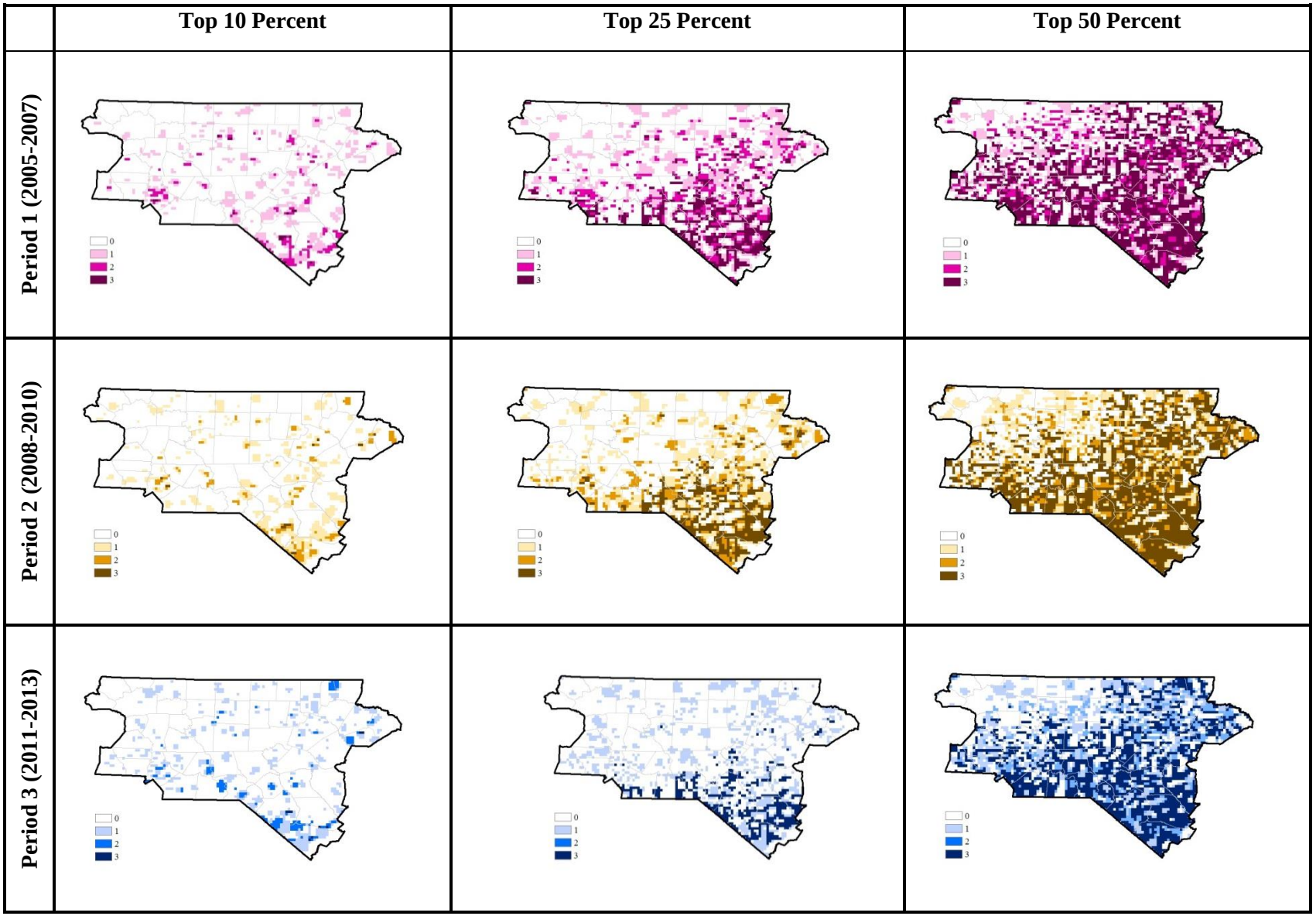
APPENDIX 4: AIM 2 SUPPLEMENTAL TABLES AND FIGURES

Figure A4.1 Spatial and Temporal Covariance Plots from UMBME Estimation

Disease Stage	Spatial	Temporal
EHI	A 	B 
CHI	C 	D 
AIDS	E 	F 

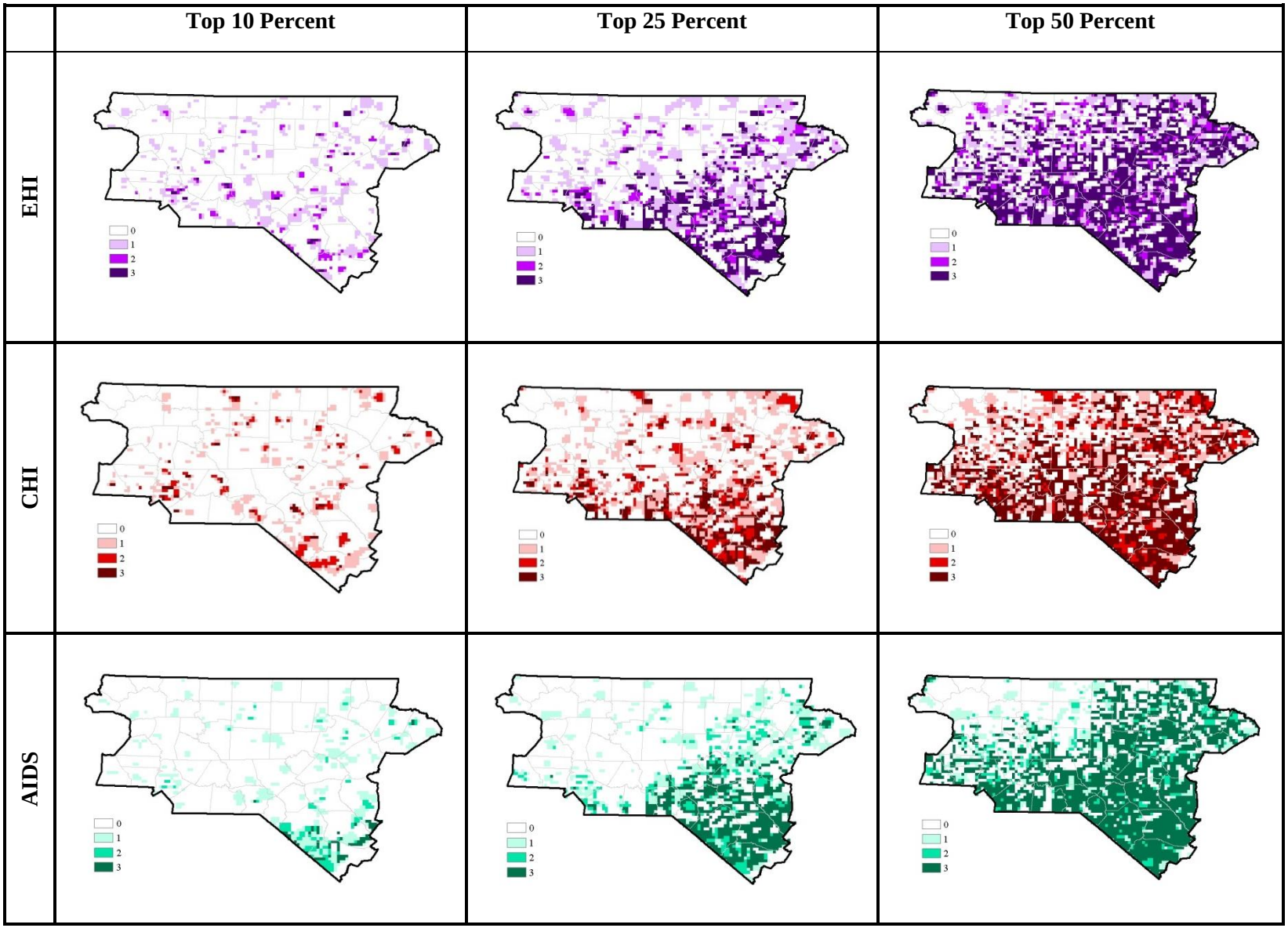
CAPTION: Spatial and temporal covariance plots estimated during UMBME modeling show the extent of spatial and temporal dependence of HIV diagnosis rates by stage of disease for the 52-county study area in central North Carolina from July 2005 to June 2013. The spatiotemporal variance is defined by the y-intercept, or sill, and is highest for CHI diagnoses. The spatial and temporal dependence is defined by the distance along the x-axis where the covariance model becomes asymptotic.

Figure A4.2. Overlap of Disease Stage by Testing Period at the top 10, 25, and 50th UMBME Diagnosis Rate Percentiles



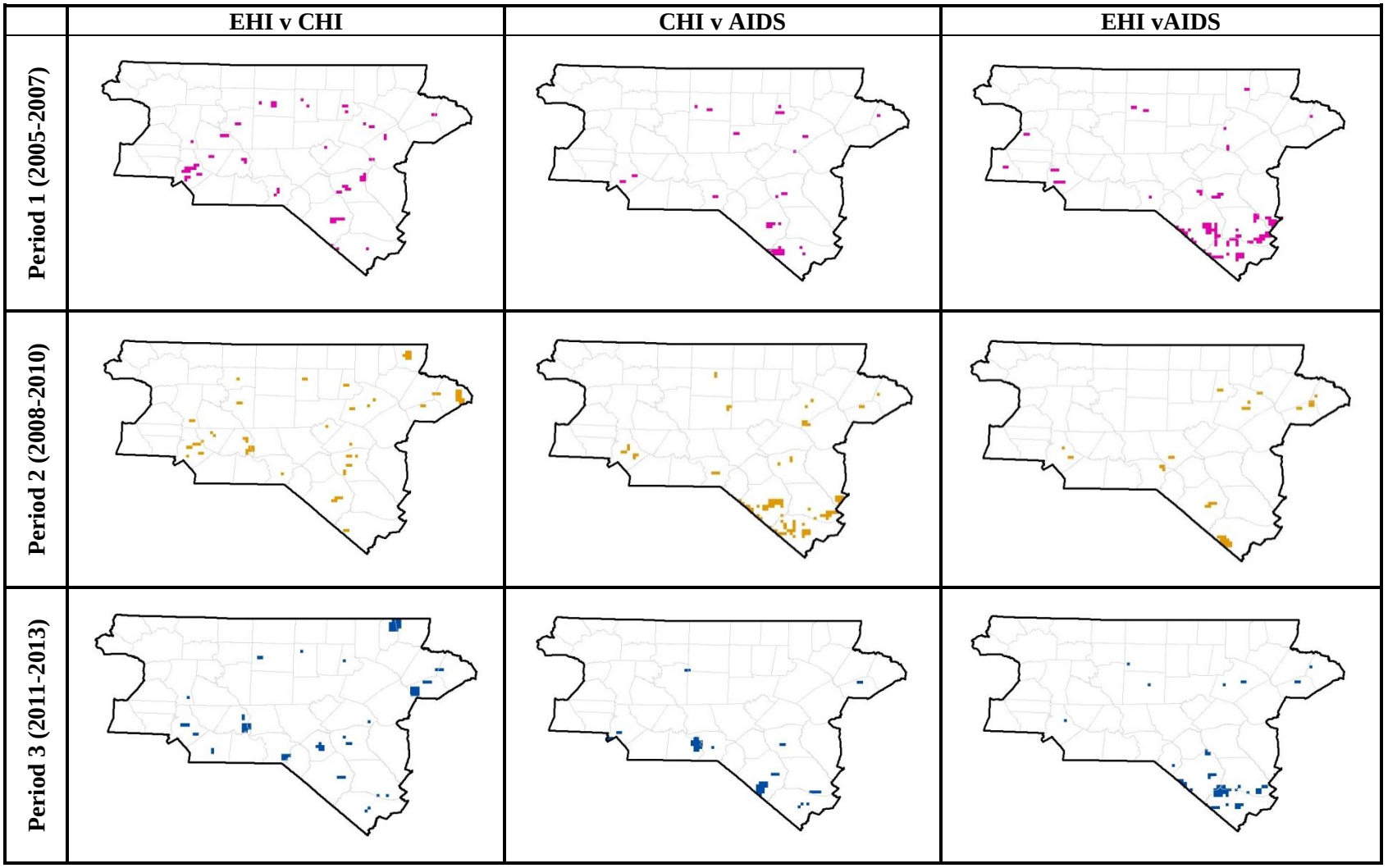
CAPTION: Overlap of disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS) by percentile of diagnosis rate (top 10, 25, and 50th percentile) during each testing period. The darkest color indicates overlap at all stages, the middle color indicates overlap of 2 stages, and the lightest color indicates no overlap. White indicates diagnoses indicate diagnosis rates at all three stages were lower than the diagnosis rate percentile presented.

Figure A4.3. Overlap of Testing Period by Disease Stage at the top 10, 25, and 50th UMBME Diagnosis Rate Percentiles



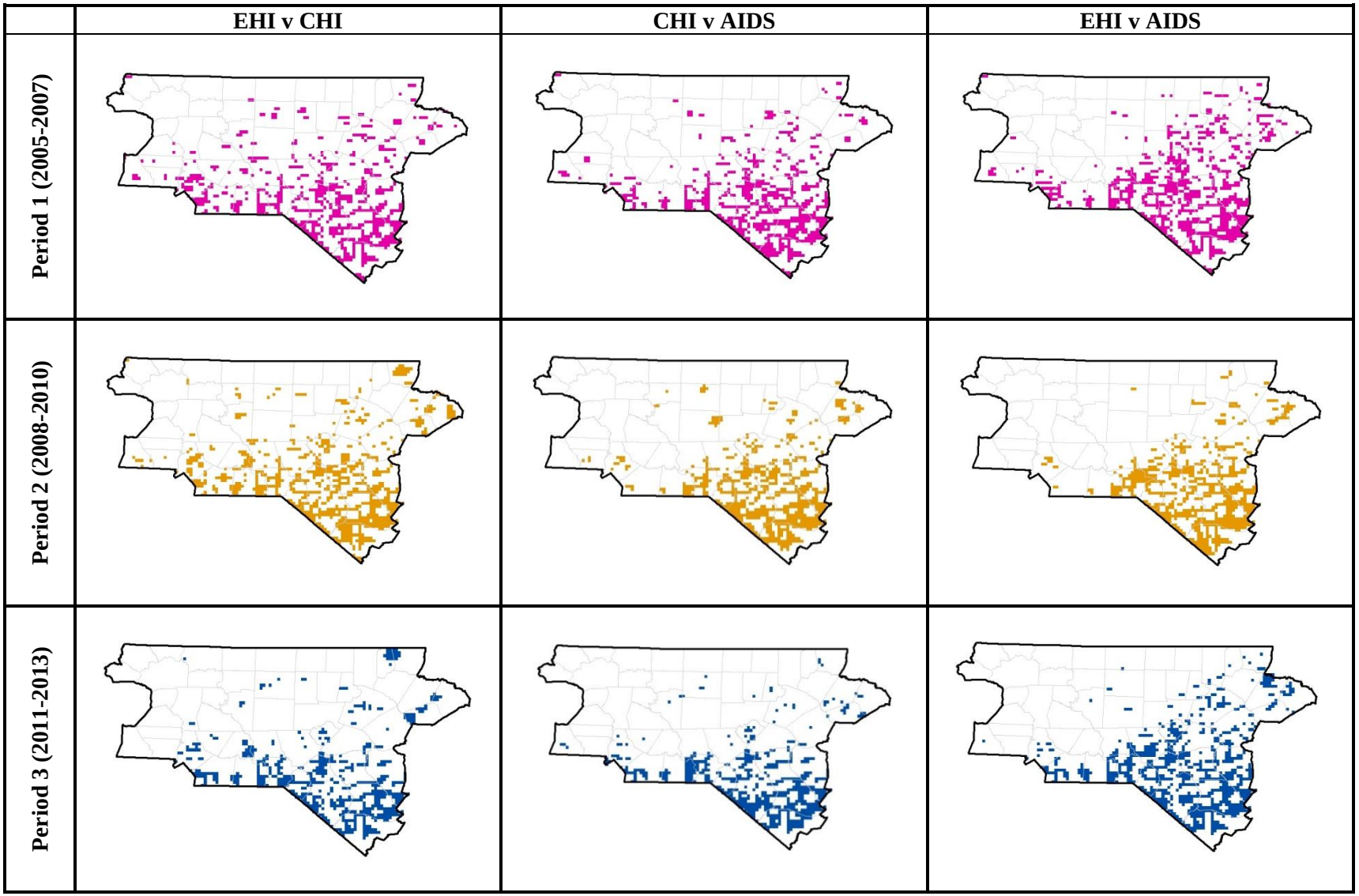
CAPTION: Overlap of testing period (2005-2007, 2008-2010, 2011-2013) by percentile of diagnosis rate (top 10, 25, and 50th percentile) within each disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS). The darkest color indicates overlap at all testing periods, the middle color indicates overlap of 2 testing periods, and the lightest color indicates no overlap. White indicates diagnoses indicate diagnosis rates during all three testing periods were lower than the diagnosis rate percentile presented.

Figure A4.4. Top 10% Testing Rate Overlap by Study Period and Stage of Disease (UMBME Results)



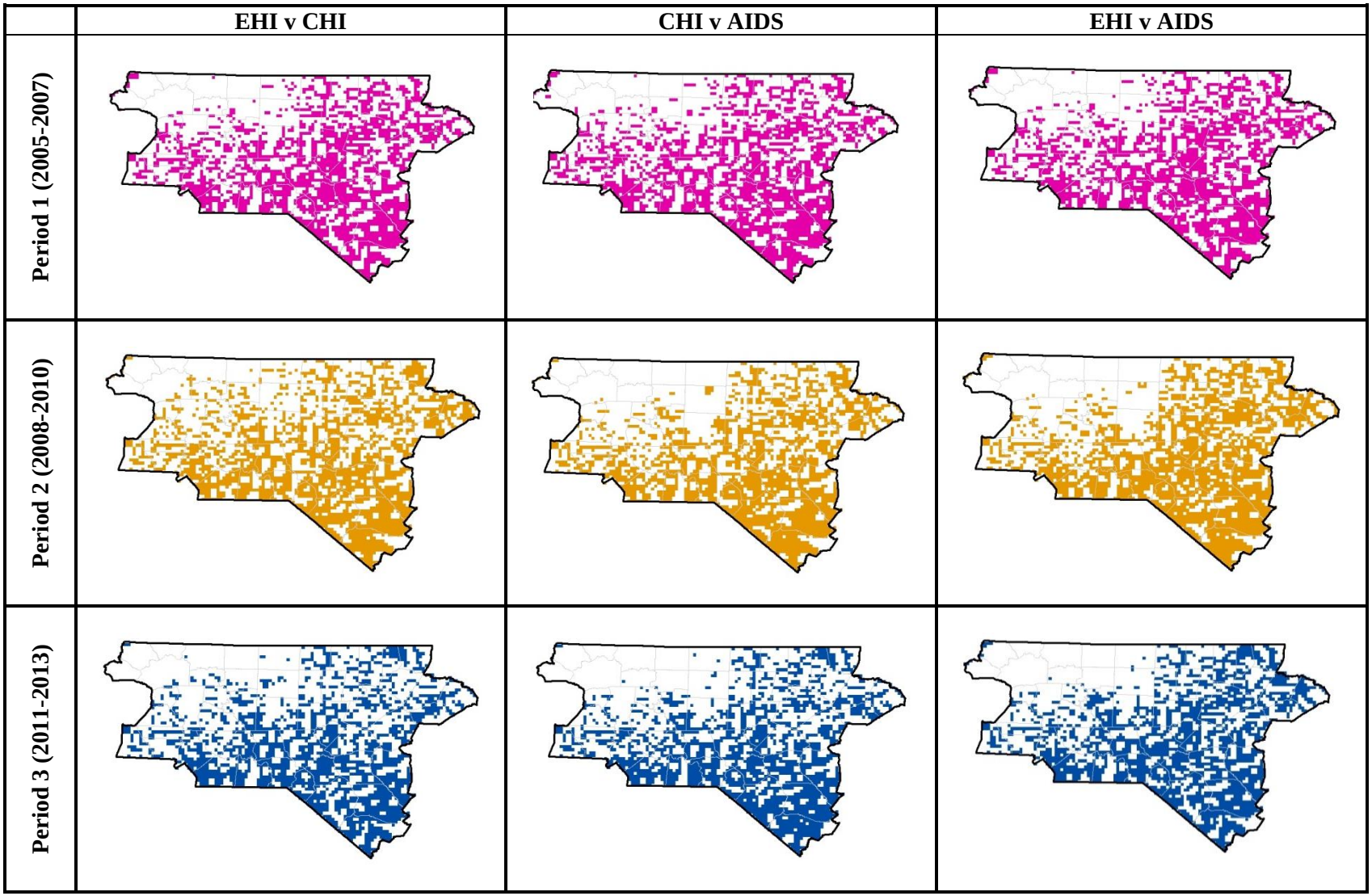
CAPTION: Overlap of top 10 percentile of disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS) diagnosis rates estimated via UMBME during each testing period. Color indicates overlap.

Figure A4.5. Top 25% Testing Rate Overlap by Study Period and Stage of Disease (UMBME Results)



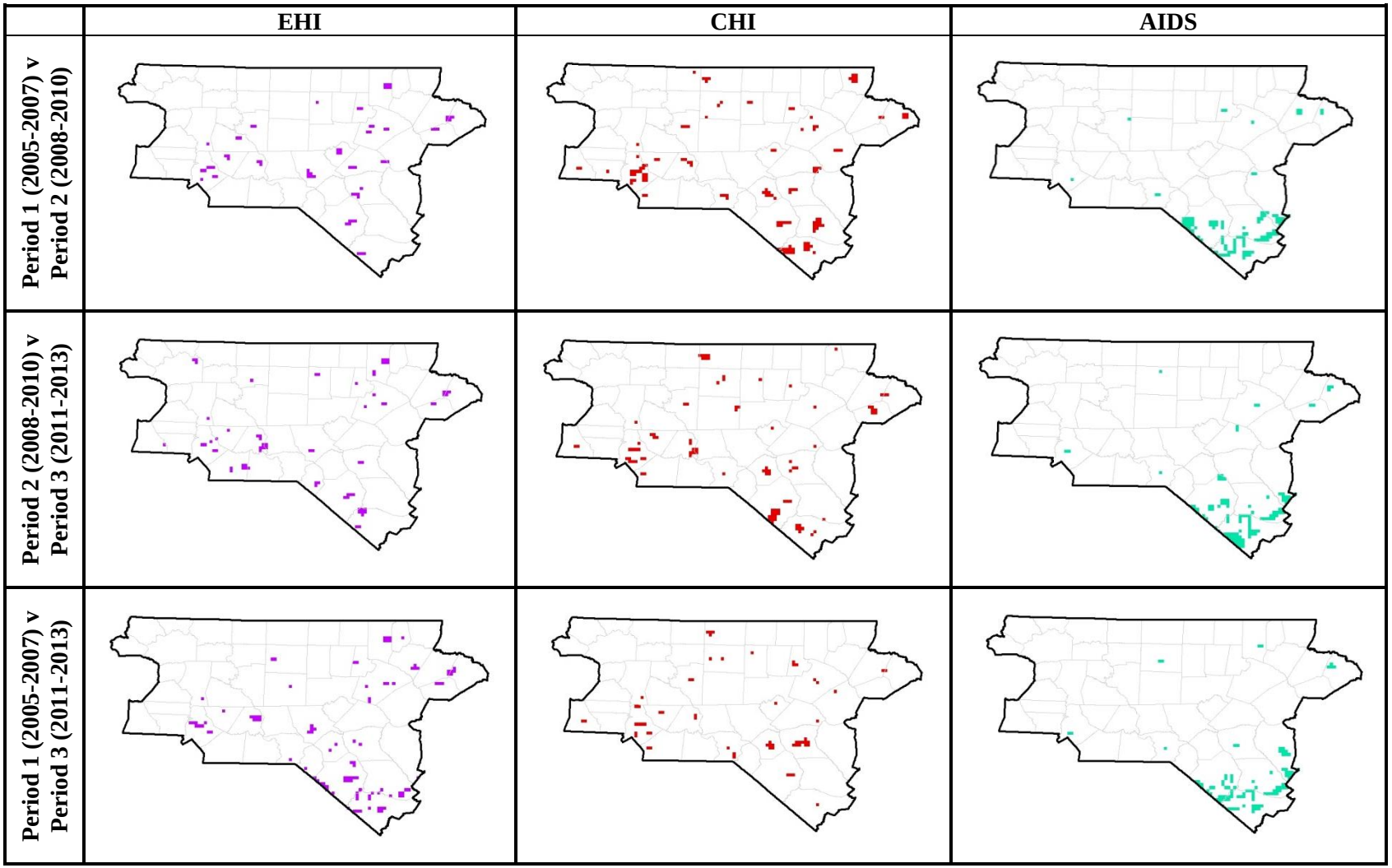
CAPTION: Overlap of top 25 percentile of disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS) diagnosis rates estimated via UMBME during each testing period. Color indicates overlap.

Figure A4.6. Top 50% Testing Rate Overlap by Study Period and Stage of Disease (UMBME Results)



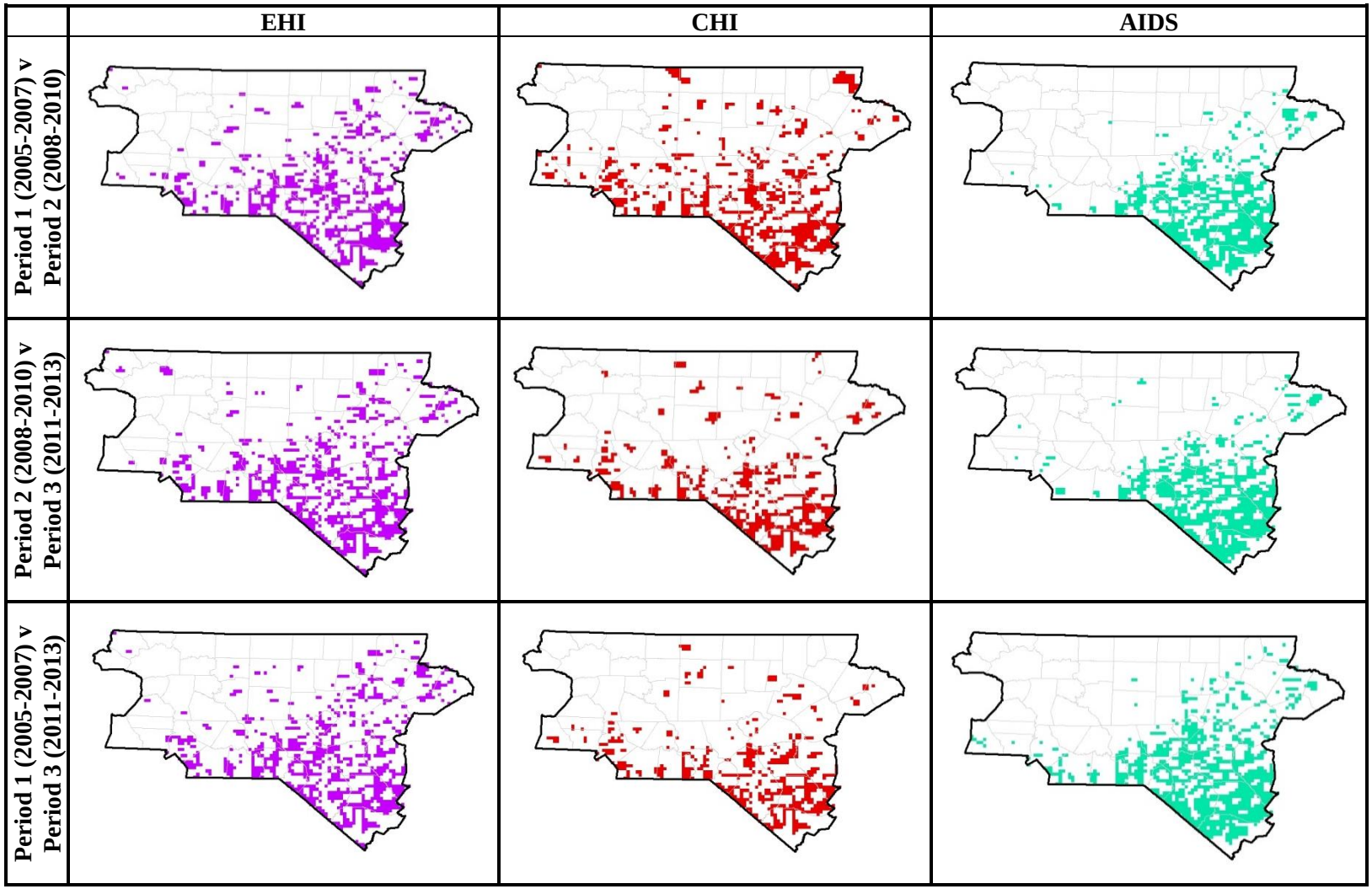
CAPTION: Overlap of top 50 percentile of disease stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS) diagnosis rates estimated via UMBME during each testing period. Color indicates overlap.

Figure A4.7. Top 10% Testing Rate Overlap by Study Period and Stage of Disease (UMBME Results)



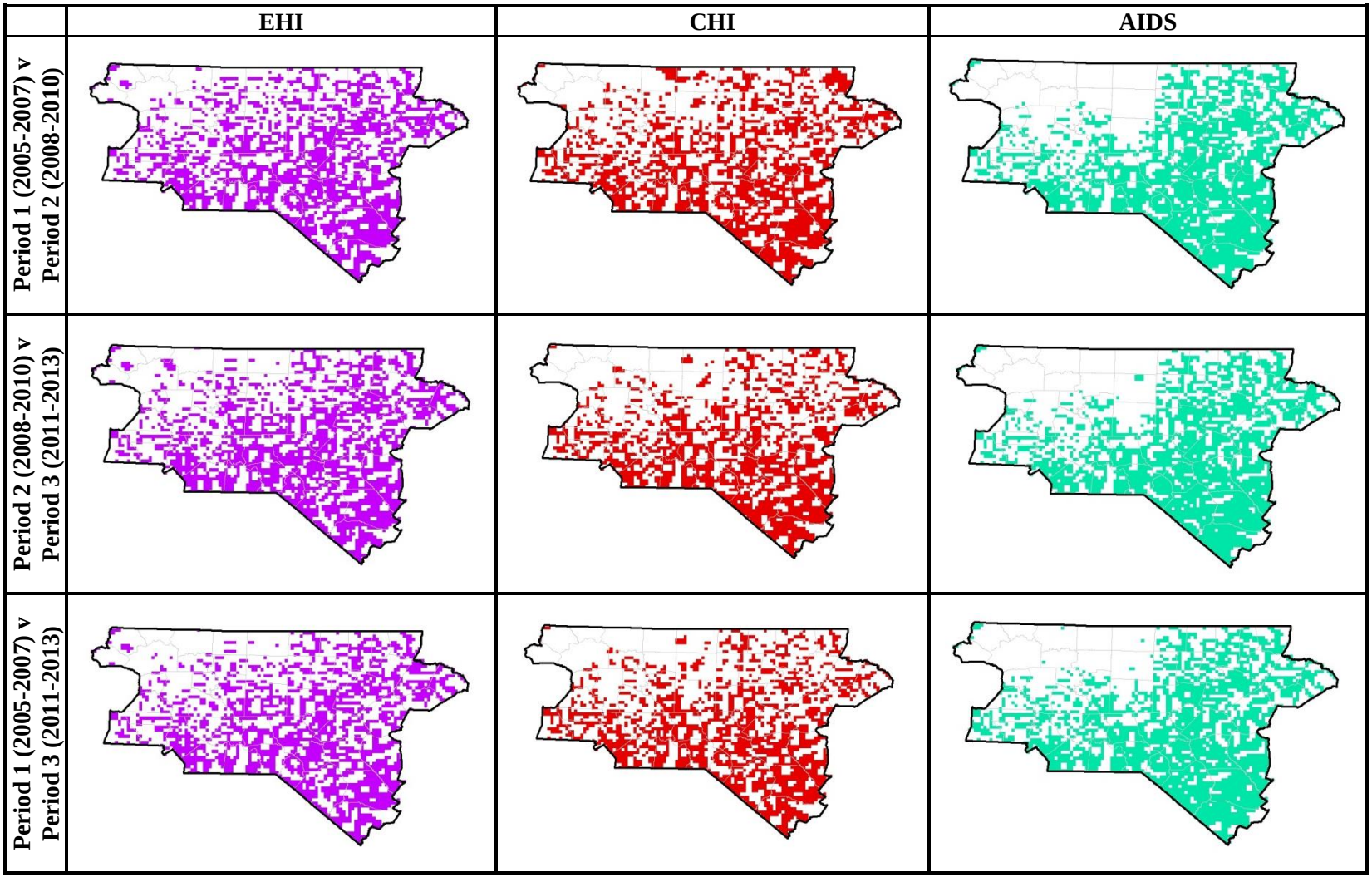
CAPTION: Overlap of top 10 percentile of testing period diagnosis rates estimated via UMBME across each diagnosis stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS). Color indicates overlap.

Figure A4.8. Top 25% Testing Rate Overlap by Study Period and Stage of Disease (UMBME Results)



CAPTION: Overlap of top 25 percentile of testing period diagnosis rates estimated via UMBME across each diagnosis stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS). Color indicates overlap.

Figure A4.9. Top 50% Testing Rate Overlap by Study Period and Stage of Disease (UMBME Results)



CAPTION: Overlap of top 50 percentile of testing period diagnosis rates estimated via UMBME across each diagnosis stage (early HIV infection [EHI], chronic HIV infection [CHI], AIDS). Color indicates overlap.

Table A4.1. Statistically-significant high rate clusters identified by the Kulldorff's Spatial Scan Statistic

	EHI				CHI				AIDS			
	Cluster	Number of Census Tracts	Relative Risk	p-value	Cluster	Number of Census Tracts	Relative Risk	p-value	Cluster	Number of Census Tracts	Relative Risk	p-value
Period 1 (2005-2007)	1	98	3.47	<0.0001	1	96	4.99	<0.0001	1	13	17.69	0.001
	2	55	3.77	<0.0001	2	23	3.9	<0.0001	2	11	6.23	0.003
	3	25	5.31	<0.0001	3	5	9.46	0.0004	3	1	371.29	0.03
	4	24	5.22	0.001	4	26	2.95	0.0004	4	77	3.85	0.03
	5	4	30.04	0.003	5	9	1.29	0.0008				
	6	1	67.2	0.04	6	9	6.75	0.003				
					7	4	7.92	0.02				
Period 2 (2008-2010)	1	101	3.86	<0.0001	1	116	4.05	<0.0001	1	19	5.87	0.0002
	2	62	3.25	<0.0001	2	95	2.4	<0.0001	2	13	7.17	0.04
	3	4	18.93	0.0002	3	3	19.7	<0.0001				
	4	4	11.22	0.002	4	3	12.36	<0.0001				
	5	15	3.58	0.02	5	3	14.73	<0.0001				
	6	21	3.52	0.04	6	19	3.74	0.0005				
	7	12	5.75	0.04	7	18	4.96	0.002				
					8	4	18.28	0.007				
					9	3	18.07	0.04				
Period 3 (2011-2013)	1	71	4.06	<0.0001	1	97	3.94	<0.0001	1	21	10.37	<0.0001
	2	61	2.99	0.001	2	56	2.88	0.003	2	120	4.65	0.0003
	3	22	5.32	0.005	3	4	29.22	0.004	3	1	184.66	0.003
	4	7	8.57	0.008	4	3	13.48	0.006	4	7	13.7	0.007
	5	23	4.23	0.008	5	10	7.82	0.02				
	6	3	14.86	0.02								

REFERENCES

1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. The New England journal of medicine 2011;365:493-505.

2. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. The New England journal of medicine 2000;342:921-9.

3. Giordano TP, Gifford AL, White AC, Jr., et al. Retention in care: a challenge to survival with HIV infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2007;44:1493-9.

4. Metsch LR, Pereyra M, Messinger S, et al. HIV transmission risk behaviors among HIV-infected persons who are successfully linked to care. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2008;47:577-84.

5. Marks G, Gardner LI, Craw J, Crepaz N. Entry and retention in medical care among HIV-diagnosed persons: a meta-analysis. AIDS 2010;24:2665-78.

6. Cohen MS, Gay C, Kashuba AD, Blower S, Paxton L. Narrative review: antiretroviral therapy to prevent the sexual transmission of HIV-1. Ann Intern Med 2007;146:591-601.

7. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372:293-9.

8. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;52:793-800.

9. Late versus early testing of HIV--16 sites, United States, 2000-2003: Centers for Disease Control and Prevention; 2003.

10. Marks G, Crepaz N, Janssen RS. Estimating sexual transmission of HIV from persons aware and unaware that they are infected with the virus in the USA. AIDS 2006;20:1447-50.

11. Hall HI, Holtgrave DR, Maulsby C. HIV transmission rates from persons living with HIV who are aware and unaware of their infection. AIDS 2012;26:893-6.

12. Ohl ME, Perencevich E. Frequency of human immunodeficiency virus (HIV) testing in urban vs. rural areas of the United States: results from a nationally-representative sample. BMC Public Health 2011;11:681.

13. Ohl M, Tate J, Duggal M, et al. Rural residence is associated with delayed care entry and increased mortality among veterans with human immunodeficiency virus infection. Med Care 2010;48:1064-70.

14. Branson B, Handsfield HH, Lampe MA, Janssen RS, Taylor AW, Lyss SB, Clark, JE. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. MMWR Surveill Summ 2006;55:1-17.

15. Pinkerton SD. HIV transmission rate modeling: a primer, review, and extension. AIDS Behav 2012;16:791-6.

16. Epidemiologic Profile for HIV/STD Prevention and Care Planning. Raleigh, NC: State of North Carolina Department of Health and Human Services; 2011.

17. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. JAMA : the journal of the American Medical Association 2008;300:520-9.

18. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006-2009. PLoS One 2011;6:3.

19. Prejean J, Tang T, Irene Hall H. HIV Diagnoses and Prevalence in the Southern Region of the United States, 2007-2010. J Community Health 2012.

20. Qian HZ, Taylor RD, Fawal HJ, Vermund SH. Increasing AIDS case reports in the South: U.S. trends from 1981-2004. AIDS Care 2006;18 Suppl 1:S6-9.

21. The Henry J. Kaiser Family Foundation: State Health Facts. (Accessed Accessed on 3/27/2013, at http://www.statehealthfacts.org/index.jsp.)

22. HIV/AIDS Surveillance Report 2010. 2010. (Accessed 3/27/2013, at http://www.cdc.gov/hiv/surveillance/resources/reports/2010report/pdf/2010_HIV_Surveillance_Report_vol_22.pdf.)

23. Fleming PL, Lansky A, Lee LM, Nakashima AK. The epidemiology of HIV/AIDS in women in the southern United States. Sexually transmitted diseases 2006;33:S32-8.

24. Lieb S, Thompson DR, Misra S, et al. Estimating populations of men who have sex with men in the southern United States. Journal of urban health : bulletin of the New York Academy of Medicine 2009;86:887-901.

25. HIV Surveillance in Men Who Have Sex with Men (MSM). (Accessed Accessed on 3/27/2013, at http://www.cdc.gov/hiv/topics/surveillance/resources/slides/msm/index.htm.)

26. Lieb S, Prejean J, Thompson DR, et al. HIV prevalence rates among men who have sex with men in the southern United States: population-based estimates by race/ethnicity. AIDS Behav 2011;15:596-606.

27. Reif S, Geonnotti KL, Whetten K. HIV Infection and AIDS in the Deep South. Am J Public Health 2006;96:970-3.

28. Adimora AA, Schoenbach VJ. Social context, sexual networks, and racial disparities in rates of sexually transmitted infections. The Journal of infectious diseases 2005;191 Suppl 1:S115-22.

29. Hanna DB, Selik RM, Tang T, Gange SJ. Disparities among US states in HIV-related mortality in persons with HIV infection, 2001-2007. AIDS 2012;26:95-103.

30. Meditz AL, MaWhinney S, Allshouse A, et al. Sex, race, and geographic region influence clinical outcomes following primary HIV-1 infection. The Journal of infectious diseases 2011;203:442-51.

31. Krawczyk CS, Funkhouser E, Kilby JM, Kaslow RA, Bey AK, Vermund SH. Factors associated with delayed initiation of HIV medical care among infected persons attending a southern HIV/AIDS clinic. South Med J 2006;99:472-81.

32. Konkle-Parker DJ, Amico KR, Henderson HM. Barriers and facilitators to engagement in HIV clinical care in the Deep South: results from semi-structured patient interviews. J Assoc Nurses AIDS Care 2011;22:90-9.

33. Konkle-Parker DJ, Erlen JA, Dubbert PM. Lessons learned from an HIV adherence pilot study in the Deep South. Patient Educ Couns 2010;78:91-6.

34. Sutton M, Anthony MN, Vila C, McLellan-Lemal E, Weidle PJ. HIV testing and HIV/AIDS treatment services in rural counties in 10 southern states: service provider perspectives. J Rural Health 2010;26:240-7.

35. Cohen T, Corbett EL. Test and treat in HIV: success could depend on rapid detection. Lancet 2011;378:204-6.

36. The White House Washington DC; 2010.

37. Ulett KB, Willig JH, Lin HY, et al. The therapeutic implications of timely linkage and early retention in HIV care. AIDS Patient Care STDS 2009;23:41-9.

38. Cheever LW. Engaging HIV-infected patients in care: their lives depend on it. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2007;44:1500-2.

39. Mugavero MJ, Amico KR, Horn T, Thompson MA. The state of engagement in HIV care in the United States: from cascade to continuum to control. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57:1164-71.

40. Campsmith ML, Rhodes PH, Hall HI, Green TA. Undiagnosed HIV prevalence among adults and adolescents in the United States at the end of 2006. J Acquir Immune Defic Syndr 2010;53:619-24.

41. Marks G, Crepaz N, Senterfitt JW, Janssen RS. Meta-analysis of high-risk sexual behavior in persons aware and unaware they are infected with HIV in the United States: implications for HIV prevention programs. J Acquir Immune Defic Syndr 2005;39:446-53.

42. Pinkerton SD, Holtgrave DR, Galletly CL. Infections prevented by increasing HIV serostatus awareness in the United States, 2001 to 2004. J Acquir Immune Defic Syndr 2008;47:354-7.

43. Volz EM, Ionides E, Romero-Severson EO, Brandt MG, Mokotoff E, Koopman JS. HIV-1 transmission during early infection in men who have sex with men: a phylodynamic analysis. PLoS Med 2013;10:e1001568; discussion e.

44. Girardi E, Sabin CA, Monforte AD. Late diagnosis of HIV infection: epidemiological features, consequences and strategies to encourage earlier testing. J Acquir Immune Defic Syndr 2007;46 Suppl 1:S3-8.

45. From the Centers for Disease Control and Prevention. Advancing HIV prevention: new strategies for a changing epidemic--United States, 2003. JAMA : the journal of the American Medical Association 2003;289:2493-5.

46. Beckwith CG, Flanigan TP, del Rio C, et al. It is time to implement routine, not risk-based, HIV testing. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005;40:1037-40.

47. Bozzette SA. Routine screening for HIV infection--timely and cost-effective. The New England journal of medicine 2005;352:620-1.

48. Frieden TR, Das-Douglas M, Kellerman SE, Henning KJ. Applying public health principles to the HIV epidemic. The New England journal of medicine 2005;353:2397-402.

49. Celada MT, Merchant RC, Waxman MJ, Sherwin AM. An ethical evaluation of the 2006 Centers for Disease Control and Prevention Recommendations for HIV testing in health care settings. Am J Bioeth 2011;11:31-40.

50. Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States--an analysis of cost-effectiveness. The New England journal of medicine 2005;352:586-95.

51. Walensky RP, Freedberg KA, Weinstein MC, Paltiel AD. Cost-effectiveness of HIV testing and treatment in the United States. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2007;45 Suppl 4:S248-54.

52. Holtgrave DR. Costs and consequences of the US Centers for Disease Control and Prevention's recommendations for opt-out HIV testing. PLoS Med 2007;4:e194.

53. Torian LV, Wiewel EW, Liu KL, Sackoff JE, Frieden TR. Risk factors for delayed initiation of medical care after diagnosis of human immunodeficiency virus. Arch Intern Med 2008;168:1181-7.

54. Gardner LI, Metsch LR, Anderson-Mahoney P, et al. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. AIDS 2005;19:423-31.

55. Conviser R, Pounds MB. The role of ancillary services in client-centred systems of care. AIDS Care 2002;14 Suppl 1:S119-31.

56. McCoy SI, Strauss RP, MacDonald PD, Leone PA, Eron JJ, Miller WC. Social support and delays seeking care after HIV diagnosis, North Carolina, 2000-2006. AIDS Care 2009;21:1148-56.

57. Reed JB, Hanson D, McNaghten AD, et al. HIV testing factors associated with delayed entry into HIV medical care among HIV-infected persons from eighteen states, United States, 2000-2004. AIDS Patient Care STDS 2009;23:765-73.

58. Mugavero MJ, Pence BW, Whetten K, et al. Predictors of AIDS-related morbidity and mortality in a southern U.S. Cohort. AIDS Patient Care STDS 2007;21:681-90.

59. Meyerson BE, Klinkenberg WD, Perkins DR, Laffoon BT. Who's in and who's out: use of primary medical care among people living with HIV. Am J Public Health 2007;97:744-9.

60. Olatosi BA, Probst JC, Stoskopf CH, Martin AB, Duffus WA. Patterns of engagement in care by HIV-infected adults: South Carolina, 2004-2006. AIDS 2009;23:725-30.

61. Mugavero MJ, Pence BW, Whetten K, et al. Childhood abuse and initial presentation for HIV care: an opportunity for early intervention. AIDS Care 2007;19:1083-7.

62. Craw JA, Gardner LI, Marks G, et al. Brief strengths-based case management promotes entry into HIV medical care: results of the antiretroviral treatment access study-II. J Acquir Immune Defic Syndr 2008;47:597-606.

63. Kuruc J, Mayo A, Sampson L, Barnhart J, Brinson M, McCoy S, Foust E, Ashby R, Pilcher C, Gay C, Leone P, Eron J. Evaluation of Six Years of Statewide Screening and Testing for Acute HIV Infection in North Carolina. In: XVIII International AIDS Conference Cape Town, South Africa; 2009.

64. Skowron G, Street JC, Obee EM. Baseline CD4(+) cell count, not viral load, correlates with virologic suppression induced by potent antiretroviral therapy. J Acquir Immune Defic Syndr 2001;28:313-9.

65. Althoff KN, Gange SJ, Klein MB, et al. Late presentation for human immunodeficiency virus care in the United States and Canada. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2010;50:1512-20.

66. Seal PS, Jackson DA, Chamot E, et al. Temporal trends in presentation for outpatient HIV medical care 2000-2010: implications for short-term mortality. J Gen Intern Med 2011;26:745-50.

67. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. In; December 1, 2009.

68. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA : the journal of the American Medical Association 2010;304:321-33.

69. Dieffenbach CW, Fauci AS. Universal voluntary testing and treatment for prevention of HIV transmission. JAMA : the journal of the American Medical Association 2009;301:2380-2.

70. Napravnik S, Eron JJ, Jr., McKaig RG, Heine AD, Menezes P, Quinlivan E. Factors associated with fewer visits for HIV primary care at a tertiary care center in the Southeastern U.S. AIDS Care 2006;18 Suppl 1:S45-50.

71. Mugavero MJ, Lin HY, Allison JJ, et al. Racial disparities in HIV virologic failure: do missed visits matter? J Acquir Immune Defic Syndr 2009;50:100-8.

72. Mugavero MJ, Lin HY, Willig JH, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2009;48:248-56.

73. Coleman SM, Rajabiun S, Cabral HJ, Bradford JB, Tobias CR. Sexual risk behavior and behavior change among persons newly diagnosed with HIV: the impact of targeted outreach interventions among hard-to-reach populations. AIDS Patient Care STDS 2009;23:639-45.

74. Berg MB, Safren SA, Mimiaga MJ, Grasso C, Boswell S, Mayer KH. Nonadherence to medical appointments is associated with increased plasma HIV RNA and decreased CD4 cell counts in a community-based HIV primary care clinic. AIDS Care 2005;17:902-7.

75. Giordano TP, White AC, Jr., Sajja P, et al. Factors associated with the use of highly active antiretroviral therapy in patients newly entering care in an urban clinic. J Acquir Immune Defic Syndr 2003;32:399-405.

76. Giordano TP. Retention in HIV Care: What the Clinician Needs to Know. Topics in Antiviral Medicine 2012;19:12-6.

77. Rajabiun S, Mallinson RK, McCoy K, et al. "Getting me back on track": the role of outreach interventions in engaging and retaining people living with HIV/AIDS in medical care. AIDS Patient Care STDS 2007;21 Suppl 1:S20-9.

78. Muessig KE, Cohen MS. Advances in HIV Prevention for Serodiscordant Couples. Current HIV/AIDS reports 2014.

79. Whetten K, Reif S. Overview: HIV/AIDS in the deep south region of the United States. AIDS Care 2006;18 Suppl 1:S1-5.

80. Reif S, Golin CE, Smith SR. Barriers to accessing HIV/AIDS care in North Carolina: rural and urban differences. AIDS Care 2005;17:558-65.

81. Kates J. Medicaid and HIV: a national analysis. Washington, DC; 2011.

82. Heberlein M BT, Alker J, Artiga S, Stephens J. Getting into gear for 2014: findings from a 50-state survey of eligibility, enrollment, renewal, and cost-sharing policies in Medicaid and CHIP, 2012–2013. Washington DC: The Henry J. Kaiser Family Foundation; 2013.

83. Adimora AA, Ramirez C, Schoenbach VJ, Cohen MS. Policies and politics that promote HIV infection in the Southern United States. AIDS 2014;28:1393-7.

84. The North Carolina AIDS Drug Assistance Program (ADAP) Communicable Disease Branch, Division of Public Health, NC DHHS. 2013. (Accessed 3/27/2013, at http://epi.publichealth.nc.gov/cd/hiv/docs/ADAPFactSheet.pdf.)

85. Weis KE, Liese AD, Hussey J, Gibson JJ, Duffus WA. Associations of rural residence with timing of HIV diagnosis and stage of disease at diagnosis, South Carolina 2001-2005. J Rural Health 2010;26:105-12.

86. Southern AIDS Coalition. 2012. (Accessed 3/27/2013, at http://www.southernaidscoalition.org/Southern+States+Manifesto-+Update+2012.pdf.)

87. Blattner WA, Oursler KA, Cleghorn F, et al. Rapid clearance of virus after acute HIV-1 infection: correlates of risk of AIDS. The Journal of infectious diseases 2004;189:1793-801.

88. Deeks SG, Kitchen CM, Liu L, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. Blood 2004;104:942-7.

89. Kelley CF, Barbour JD, Hecht FM. The relation between symptoms, viral load, and viral load set point in primary HIV infection. J Acquir Immune Defic Syndr 2007;45:445-8.

90. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. The Journal of infectious diseases 2005;191:1403-9.

91. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 Infection. The New England journal of medicine 2011;364:1943-54.

92. Cohen MS, Gay CL, Busch MP, Hecht FM. The detection of acute HIV infection. The Journal of infectious diseases 2010;202 Suppl 2:S270-7.

93. Busch MP, Dodd RY, Lackritz EM, AuBuchon JP, Birkmeyer JD, Petersen LR. Value and cost-effectiveness of screening blood donors for antibody to hepatitis B core antigen as a way of detecting window-phase human immunodeficiency virus type 1 infections. The HIV Blood Donor Study Group. Transfusion 1997;37:1003-11.

94. Murphy G, Parry JV. Assays for the detection of recent infections with human immunodeficiency virus type 1. Euro Surveill 2008;13.

95. Pilcher CD, Joaki G, Hoffman IF, et al. Amplified transmission of HIV-1: comparison of HIV-1 concentrations in semen and blood during acute and chronic infection. AIDS 2007;21:1723-30.

96. Miller WC, Rosenberg NE, Rutstein SE, Powers KA. Role of acute and early HIV infection in the sexual transmission of HIV. Curr Opin HIV AIDS 2010;5:277-82.

97. Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003;17:1871-9.

98. Daar ES, Pilcher CD, Hecht FM. Clinical presentation and diagnosis of primary HIV-1 infection. Curr Opin HIV AIDS 2008;3:10-5.

99. Powers KA, Miller WC, Pilcher CD, et al. Improved detection of acute HIV-1 infection in sub-Saharan Africa: development of a risk score algorithm. AIDS 2007;21:2237-42.

100. Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. The New England journal of medicine 2005;352:1873-83.

101. Pilcher CD, Eron JJ, Jr., Galvin S, Gay C, Cohen MS. Acute HIV revisited: new opportunities for treatment and prevention. J Clin Invest 2004;113:937-45.

102. Kuruc J, Cope AB, Sampson L, et al. Trends in Acute HIV: A 10 year Assessment (Unpublished). In: UNC; 2014.

103. Fiscus SA, Pilcher CD, Miller WC, et al. Rapid, real-time detection of acute HIV infection in patients in Africa. The Journal of infectious diseases 2007;195:416-24.

104. Patel P, Klausner JD, Bacon OM, et al. Detection of acute HIV infections in high-risk patients in California. J Acquir Immune Defic Syndr 2006;42:75-9.

105. Patel P, Mackellar D, Simmons P, et al. Detecting acute human immunodeficiency virus infection using 3 different screening immunoassays and nucleic acid amplification testing for human immunodeficiency virus RNA, 2006-2008. Arch Intern Med 2010;170:66-74.

106. Priddy FH, Pilcher CD, Moore RH, et al. Detection of acute HIV infections in an urban HIV counseling and testing population in the United States. J Acquir Immune Defic Syndr 2007;44:196-202.

107. Stekler J, Swenson PD, Wood RW, Handsfield HH, Golden MR. Targeted screening for primary HIV infection through pooled HIV-RNA testing in men who have sex with men. AIDS 2005;19:1323-5.

108. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006-2009. PLoS One 2011;6:e17502.

109. Janssen RS, Satten GA, Stramer SL, et al. New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. JAMA : the journal of the American Medical Association 1998;280:42-8.

110. Brookmeyer R, Konikoff J, Laeyendecker O, Eshleman SH. Estimation of HIV incidence using multiple biomarkers. Am J Epidemiol 2013;177:264-72.

111. Guy R, Gold J, Calleja JM, et al. Accuracy of serological assays for detection of recent infection with HIV and estimation of population incidence: a systematic review. Lancet Infect Dis 2009;9:747-59.

112. Barnighausen T, McWalter TA, Rosner Z, Newell ML, Welte A. HIV incidence estimation using the BED capture enzyme immunoassay: systematic review and sensitivity analysis. Epidemiology 2010;21:685-97.

113. Busch MP, Pilcher CD, Mastro TD, et al. Beyond detuning: 10 years of progress and new challenges in the development and application of assays for HIV incidence estimation. AIDS 2010;24:2763-71.

114. Aware™ BED™ EIA HIV-1 Incidence Test (IgG-Capture HIV-EIA) Enzyme Immunoassay for Population Estimates of HIV-1 Incidence. In. Portland, OR: Calypte Biomedical Corporation; 2004.

115. Laeyendecker O, Brookmeyer R, Cousins MM, et al. HIV incidence determination in the United States: a multiassay approach. The Journal of infectious diseases 2013;207:232-9.

116. Eshleman SH, Hughes JP, Laeyendecker O, et al. Use of a multifaceted approach to analyze HIV incidence in a cohort study of women in the United States: HIV Prevention Trials Network 064 Study. The Journal of infectious diseases 2013;207:223-31.

117. Barnhart J. Correspondence about STARHS Testing in NC. In: Cope AB, ed. Raleigh, NC; 2012.

118. Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control 2008;57:1-12.

119. Johnson AS, Heitgerd J, Koenig L, et al. Vital Signs: HIV Testing and Diagnosis Among Adults — United States, 2001–2009; 2010.

120. Donnell DJ, Hall HI, Gamble T, et al. Use of HIV case surveillance system to design and evaluate site-randomized interventions in an HIV prevention study: HPTN 065. The open AIDS journal 2012;6:122-30.

121. Buskin SE, Kent JB, Dombrowski JC, Golden MR. Migration distorts surveillance estimates of engagement in care: results of public health investigations of persons who appear to be out of HIV care. Sexually transmitted diseases 2014;41:35-40.

122. Bertolli J, Shouse RL, Beer L, et al. Using HIV surveillance data to monitor missed opportunities for linkage and engagement in HIV medical care. The open AIDS journal 2012;6:131-41.

123. Fagan JL, Bertolli J, McNaghten AD. Understanding people who have never received HIV medical care: a population-based approach. Public Health Rep 2010;125:520-7.

124. Gray KM, Kajese T, Crandell-Alden E, et al. Enhanced Collection of Laboratory Data in HIV Surveillance Among 5 States with Confidential Name-based HIV Infection Reporting, 2005-2006. The open AIDS journal 2012;6:90-7.

125. Bamford LP, Ehrenkranz PD, Eberhart MG, Shpaner M, Brady KA. Factors associated with delayed entry into primary HIV medical care after HIV diagnosis. AIDS 2010;24:928-30.

126. Zetola NM, Bernstein K, Ahrens K, et al. Using surveillance data to monitor entry into care of newly diagnosed HIV-infected persons: San Francisco, 2006-2007. BMC Public Health 2009;9:17.

127. Pilcher CD, Eron JJ, Jr., Vemazza PL, et al. Sexual transmission during the incubation period of primary HIV infection. JAMA : the journal of the American Medical Association 2001;286:1713-4.

128. McMichael AJ, Borrow P, Tomaras GD, Goonetilleke N, Haynes BF. The immune response during acute HIV-1 infection: clues for vaccine development. Nature reviews Immunology 2010;10:11-23.

129. Anderson JA, Ping LH, Dibben O, et al. HIV-1 Populations in Semen Arise through Multiple Mechanisms. PLoS Pathog 2010;6:1001053.

130. Abrahams MR, Anderson JA, Giorgi EE, et al. Quantitating the multiplicity of infection with human immunodeficiency virus type 1 subtype C reveals a non-poisson distribution of transmitted variants. J Virol 2009;83:3556-67.

131. Keele BF, Giorgi EE, Salazar-Gonzalez JF, et al. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. Proc Natl Acad Sci U S A 2008;105:7552-7.

132. Salazar-Gonzalez JF, Bailes E, Pham KT, et al. Deciphering human immunodeficiency virus type 1 transmission and early envelope diversification by single-genome amplification and sequencing. J Virol 2008;82:3952-70.

133. Edmonson PF, Mullins JI. Efficient amplification of HIV half-genomes from tissue DNA. Nucleic Acids Res 1992;20.

134. Palmer S, Kearney M, Maldarelli F, et al. Multiple, linked human immunodeficiency virus type 1 drug resistance mutations in treatment-experienced patients are missed by standard genotype analysis. J Clin Microbiol 2005;43:406-13.

135. Simmonds P, Balfe P, Ludlam CA, Bishop JO, Brown AJ. Analysis of sequence diversity in hypervariable regions of the external glycoprotein of human immunodeficiency virus type 1. J Virol 1990;64:5840-50.

136. Thompson JD, Higgins DG, Gibson TJ. CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. Nucleic Acids Res 1994;22:4673-80.

137. Tamura K, Dudley J, Nei M, Kumar S. MEGA4: Molecular Evolutionary Genetics Analysis (MEGA) software version 4.0. Mol Biol Evol 2007;24:1596-9.

138. Dennis AM, Hue S, Hurt CB, et al. Phylogenetic insights into regional HIV transmission. AIDS 2012;26:1813-22.

139. Drummond AJ, Rambaut A. BEAST: Bayesian evolutionary analysis by sampling trees. BMC Evol Biol 2007;7:214.

140. William H. Beasley JLR. Resampling Methods. The SAGE Handbook of Quantitative Methods in Psychology. SAGE Publications Ltd. London: SAGE Publications Ltd.

141. Campbell KM, Deck D, Krupski A. Record linkage software in the public domain: a comparison of Link Plus, The Link King, and a 'basic' deterministic algorithm. Health informatics journal 2008;14:5-15.

142. Armstrong MP, Rushton G, Zimmerman DL. Geographically masking health data to preserve confidentiality. Stat Med 1999;18:497-525.

143. Gesink DC, Sullivan AB, Miller WC, Bernstein KT. Sexually transmitted disease core theory: roles of person, place, and time. Am J Epidemiol 2011;174:81-9.

144. Hampton KH, Serre ML, Gesink DC, Pilcher CD, Miller WC. Adjusting for sampling variability in sparse data: geostatistical approaches to disease mapping. Int J Health Geogr 2011;10:54.

145. Gesink Law DC, Bernstein KT, Serre ML, et al. Modeling a syphilis outbreak through space and time using the Bayesian maximum entropy approach. Ann Epidemiol 2006;16:797-804.

146. Christakos G, Bogaert P, Serre ML. Temporal GIS: Advanced Functions for Field-Based Applications. New York, N.Y.: Springer-Verlag; 2002.

147. Leyland AH, Davies CA. Empirical Bayes methods for disease mapping. Stat Methods Med Res 2005;14:17-34.

148. Wakefield JC BN, Waller L. Spatial Epidemiology: Methods and Applications. Oxford: Oxford University Press; 2000.

149. Best N, Richardson S, Thomson A. A comparison of Bayesian spatial models for disease mapping. Stat Methods Med Res 2005;14:35-59.

150. Waller LA GC. Applied Spatial Statistics for Public Health Data. Hoboken, NJ: John Wiley & Sons, Inc; 2004.

151. Meliker JR RG. Introduction to opening issue on Geo-spatial Analysis and Health/Exposure Relationships. Spatial and Spatio-Temporal Epidemiology 2009;1:1-2.

152. Pfeifer D, Robinson T, Stevenson M, Stevens K, Rogers D, Clements A. Spatial Analysis in Epidemiology. New York; 2008.

153. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology 2010;21:467-74.

154. Vital signs: HIV prevention through care and treatment--United States. MMWR Morb Mortal Wkly Rep 2011;60:1618-23.

155. Miller WC, Leone PA, McCoy S, Nguyen TQ, Williams DE, Pilcher CD. Targeted testing for acute HIV infection in North Carolina. AIDS 2009;23:835-43.

156. Detection of acute HIV infection in two evaluations of a new HIV diagnostic testing algorithm - United States, 2011-2013. MMWR Morb Mortal Wkly Rep 2013;62:489-94.

157. Pilcher CD, Louie B, Facente S, et al. Performance of rapid point-of-care and laboratory tests for acute and established HIV infection in San Francisco. PLoS One 2013;8.

158. Crepaz N, Marks G, Liau A, et al. Prevalence of unprotected anal intercourse among HIV-diagnosed MSM in the United States: a meta-analysis. AIDS 2009;23:1617-29.

159. Mattson CL, Freedman M, Fagan JL, et al. Sexual risk behaviour and viral suppression among HIV-infected adults receiving medical care in the United States. AIDS 2014;28:1203-11.

160. Millett GA, Peterson JL, Flores SA, et al. Comparisons of disparities and risks of HIV infection in black and other men who have sex with men in Canada, UK, and USA: a meta-analysis. Lancet 2012;380:341-8.

161. Peters PJ, Gay C, Beagle S, Shankar A, Switzer WM, Hightow-Weidman LB. HIV infection among partners of HIV-infected black men who have sex with Men - North Carolina, 2011-2013. MMWR Morb Mortal Wkly Rep 2014;63:90-4.

162. Hurt CB, Beagle S, Leone PA, et al. Investigating a sexual network of black men who have sex with men: implications for transmission and prevention of HIV infection in the United States. J Acquir Immune Defic Syndr 2012;61:515-21.

163. Stringer JS, Sinkala M, Maclean CC, et al. Effectiveness of a city-wide program to prevent mother-to-child HIV transmission in Lusaka, Zambia. AIDS 2005;19:1309-15.

164. Rodger A BT, Cambiano V, Vernazza P, Estrada V, Van Lunzen J, Collins S, Geretti A, Phillips A, Lundgren J for the , Group PS. HIV Transmission Risk Through Condomless Sex If HIV+ Partner On Suppressive ART: PARTNER Study [CROI abstract 153LB]. In Special Issue: Abstracts From the 2014 Conference on Retroviruses and Opportunistic Infections. Topics in Antiviral Medicine 2014;22(e-1):24-5.

165. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. The New England journal of medicine 2004;350:1850-61.

166. Paredes R, Lalama CM, Ribaudo HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. The Journal of infectious diseases 2010;201:662-71.

167. Kalichman SC, Di Berto G, Eaton L. Human immunodeficiency virus viral load in blood plasma and semen: review and implications of empirical findings. Sexually transmitted diseases 2008;35:55-60.

168. White DA, Scribner AN, Martin ME, Tsai S. A Comparison of Patient Satisfaction with Emergency Department Opt-In and Opt-Out Rapid HIV Screening. AIDS research and treatment 2012;2012:904916.

169. Haukoos JS, Hopkins E, Conroy AA, et al. Routine opt-out rapid HIV screening and detection of HIV infection in emergency department patients. JAMA : the journal of the American Medical Association 2010;304:284-92.

170. Klein PW, Messer LC, Myers ER, Weber DJ, Leone PA, Miller WC. Impact of a routine, opt-out HIV testing program on HIV testing and case detection in North Carolina sexually transmitted disease clinics. Sexually transmitted diseases 2014;41:395-402.

171. Brooks L, Rietmeijer CA, McEwen D, Subiadur JA, Mettenbrink CJ. Normalizing HIV testing in a busy urban sexually transmitted infections clinic. Sexually transmitted diseases 2009;36:127-8.

172. Das-Douglas M, Zetola NM, Klausner JD, Colfax GN. Written informed consent and HIV testing rates: the San Francisco experience. Am J Public Health 2008;98:1544-5; author reply 5.

173. Nayak SU, Welch ML, Kan VL. Greater HIV testing after Veterans Health Administration policy change: the experience from a VA Medical Center in a high HIV prevalence area. J Acquir Immune Defic Syndr 2012;60:165-8.

174. Zetola NM, Grijalva CG, Gertler S, et al. Simplifying consent for HIV testing is associated with an increase in HIV testing and case detection in highest risk groups, San Francisco January 2003-June 2007. PLoS One 2008;3:e2591.

175. Results of the Expanded HIV Testing Initiative--25 jurisdictions, United States, 2007-2010. MMWR Morb Mortal Wkly Rep 2011;60:805-10.

176. Mainous AG, 3rd, Neill RA, Matheny SC. Frequency of human immunodeficiency virus testing among rural US residents and why it is done. Arch Fam Med 1995;4:41-5.

177. Pilcher CD, McPherson JT, Leone PA, et al. Real-time, universal screening for acute HIV infection in a routine HIV counseling and testing population. JAMA : the journal of the American Medical Association 2002;288:216-21.

178. U.S. Census Bureau. American FactFinder Fact sheet: North Carolina. 2010. (Accessed October 20, 2014, at http://quickfacts.census.gov/qfd/states/37000.html.)

179. U.S. Census Bureau. Percent in Poverty, 2010: Total Population. 2010. (Accessed October 20, 2014, at http://www.census.gov/did/www/saipe/data/statecounty/maps/iy2010/Tot_Pct_Poor2010.pdf.)

180. Rizza SA, MacGowan RJ, Purcell DW, Branson BM, Temesgen Z. HIV screening in the health care setting: status, barriers, and potential solutions. Mayo Clinic proceedings 2012;87:915-24.

181. Revised surveillance case definition for HIV infection--United States, 2014. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control 2014;63:1-10.

182. Wong D, Amrhein CG. Research on the MAUP: Old wine in a new bottle or real breakthrough? Geographical Systems 1996;3:73-6.

183. Leibowitz AA, Taylor SL. Distance to public test sites and HIV testing. Medical care research and review : MCRR 2007;64:568-84.

184. Konkle-Parker DJ, Erlen JA, Dubbert PM. Barriers and facilitators to medication adherence in a southern minority population with HIV disease. J Assoc Nurses AIDS Care 2008;19:98-104.

185. North Carolina Department of Health and Human Services. Communicable Disease Branch. Programs and Services: HIV/STD Testing. (Accessed July 25, 2014, at http://epi.publichealth.nc.gov/cd/stds/programs/testing.html.)

186. Krawczyk CS, Funkhouser E, Kilby JM, Vermund SH. Delayed access to HIV diagnosis and care: Special concerns for the Southern United States. AIDS Care 2006;18 Suppl 1:S35-44.

187. Eberhart MG, Share AM, Shpaner M, Brady KA. Comparison of geographic methods to assess travel patterns of persons diagnosed with HIV in Philadelphia: How close is close enough? Journal of biomedical informatics 2014.

188. Guagliardo MF. Spatial accessibility of primary care: concepts, methods and challenges. Int J Health Geogr 2004;3:3.

189. Perkins D, Meyerson BE, Klinkenberg D, Laffoon BT. Assessing HIV care and unmet need: eight data bases and a bit of perseverance. AIDS Care 2008;20:318-26.