AN EVALUATION OF AN EXPANDED HIV TESTING PROGRAM IN NORTH CAROLINA SEXUALLY-TRANSMITTED DISEASE CLINICS

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ABSTRACT

PAMELA WHITNEY KLEIN: An Evaluation of an Expanded HIV Testing Program in North Carolina Sexually-Transmitted Disease Clinics
(Under the direction of Dr. William C. Miller and Dr. Peter A. Leone)

Over 20% of the 1.1 million persons infected with HIV in the United States are unaware of their HIV infection; these persons contribute to approximately 50% of new transmission events each year. To address this problem, the Centers for Disease Control and Prevention released recommendations supporting routine, opt-out HIV testing in clinical settings. We conducted a before-after intervention analysis of a routine, opt-out HIV testing program implemented in North Carolina sexually transmitted disease (STD) clinics.

The study population included all adult North Carolina residents who were tested for HIV in any of the 102 North Carolina STD clinics from July 1, 2005 through June 30, 2011. Exposure was dichotomized at the date of intervention implementation on November 1, 2007. Three primary outcomes were considered: (1) HIV testing, as absolute counts and rate per 100,000 population; (2) detection of new HIV-infected persons, as absolute counts and HIV-positivity per 1000 tests; and (3) progression to AIDS within 12 months of HIV diagnosis. Interrupted time series analyses were used to examine trends in HIV testing and case detection over the study period; Poisson regression and multilevel regression models with county-specific random intercept terms were used to evaluate the overall impact of the intervention.

Pre-intervention, 426 new HIV-infected cases were identified from 128,029 tests (0.33%), whereas 816 new HIV-infected cases were found from 274,745 tests post-intervention (0.30%). Pre-intervention, HIV testing increased by 55 tests per month (95%

confidence interval [CI]: 41, 72), but only increased by 34 tests per month (95% CI: 26, 42) post-intervention. A slight pre-intervention decline in the monthly rate of case detection was mitigated by the intervention (mean difference in HIV-positivity=0.01; 95% CI: -0.02, 0.05). Overall, no association was observed between the introduction of the intervention and risk of progression to AIDS within 12 months of initial HIV diagnosis (risk ratio=1.05, 95% CI: 0.77, 1.43).

The impact of a routine, opt-out HIV testing program in North Carolina STD clinics was minimal. Persons not traditionally targeted for HIV testing, particularly women, experienced the greatest benefit. HIV prevention interventions should be continually evaluated for program efficacy.

To my parents, Roberta and Arthur Klein,
for always supporting and believing in me

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Completing a dissertation is far from an individual endeavor. From the initial development of the project, to the many hours spent analyzing the data, to the final write-up, this dissertation has been a truly collaborative product.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

95% CI	95% confidence interval
AIDS	Acquired immunodeficiency syndrome
ARIMA	Autoregressive moving average
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
ED	Emergency department
eHARS	Electronic HIV/AIDS Reporting System
EIA	Enzyme immunoassay
HIV	Human immunodeficiency virus
MD	Mean difference
MeSA	Metropolitan statistical area
MiSA	Micropolitan statistical area
MSM	Men who have sex with men
OR	Odds ratio
QALY	Quality-adjusted life year
RD	Risk difference
RNA	Ribonucleic acid
RR	Risk ratio
SLPH	State Laboratory of Public Health
STD	Sexually-transmitted disease
UC	Urgent care
VA	Veteran’s Administration

CHAPTER 1: SPECIFIC AIMS

In 2006, the Centers for Disease Control and Prevention (CDC) recommended routine, opt-out human immunodeficiency virus (HIV) testing in clinical settings and launched a funding initiative to support the implementation of expanded HIV testing programs that focus on routine screening.[1,2] Approximately 20% of persons infected with HIV are unaware of their HIV-infected status; disease transmission from these individuals accounts for 50% of new HIV infections in the United States.[3-5] From 2007 through 2010, the CDC initiative funded 2.8 million HIV tests and identified over 18,000 new HIV-infected cases.[2] However, these newly-diagnosed persons represent only a fraction of the approximately 150,000 new transmission events that occurred in the United States during the same time period.[6]

Although, routine, opt-out HIV testing programs have increased HIV testing, the evidence is inconclusive regarding the impact of these programs on HIV case detection and HIV-related clinical outcomes (Table A1.2).[7-13] To date, presentation of data on these programs are predominated by descriptive analyses that fail to compare the intervention to any control group (Table A1.1). Evaluations that used control groups have focused on clinical facilities in major metropolitan centers, limiting generalizability the Southeastern United States, which bears a disproportionate burden of HIV infection.[14] Due to small numbers and inadequate statistical methods, the public health importance of existing evaluations is questionable.

Using a before-after study design, we assessed the impact of a routine, opt-out expanded HIV testing program implemented in North Carolina sexually-transmitted disease

(STD) clinics on: HIV testing, the new diagnosis HIV-infected cases, and risk of progression to acquired immunodeficiency syndrome (AIDS) shortly after HIV diagnosis.

Aim 1: Estimate the impact of a routine, opt-out expanded HIV testing program on HIV testing patterns and the detection of new HIV-infected cases in North Carolina STD clinics

Hypothesis: Both the number and rate of HIV testing and new HIV-infected cases were higher post-intervention (post-intervention period: November 1, 2007 – June 30, 2011) than pre-intervention (pre-intervention period; July 1, 2005 – October 31, 2007).

Overview: To address the inconclusive data available regarding the detection of HIV-infected persons with an expanded HIV testing program, we used a before-after intervention analysis of persons tested for HIV in North Carolina STD clinics. Interrupted time series analyses were used to assess the change in outcome trends over time, while accounting for underlying temporal correlation. Multilevel regression models were used to evaluate the overall impact of the intervention and account for patient clustering within STD clinics.

Aim 2: Estimate the impact of a routine, opt-out expanded HIV testing program on the risk of progression to AIDS within 12 months of initial HIV diagnosis among newly-identified HIV-infected cases detected in North Carolina STD clinics

Hypothesis: New HIV-infected cases identified post-intervention (post-intervention period: November 1, 2007 – June 30, 2011) had a lower risk of progression to AIDS within 12 months of initial HIV diagnosis new HIV-infected cases identified pre-intervention (pre-intervention period: July 1, 2005 – October 31, 2007).

Overview: A large proportion of new HIV-infected cases present as “late diagnoses”, cases with advanced HIV disease that are diagnosed with AIDS within one year of their HIV diagnosis.[15,16] If routine, opt-out HIV testing programs successfully identify individuals earlier

in their disease progression, fewer patients would present at late stages of infection. We used a before-after intervention analysis to compare the risk of progression to AIDS among new HIV-infected cases diagnosed in North Carolina STD clinics before and after the implementation of a routine, opt-out HIV testing intervention. Multilevel regression models were used to evaluate the overall impact of the intervention and account for patient clustering within STD clinics.

Efficient HIV testing strategies are essential to engage HIV-infected persons in HIV-specific medical care, which subsequently prevents HIV-related morbidity and mortality, as well as the further disease transmission.[3,17-23] Although routine HIV testing is feasible and acceptable, its impact on HIV case detection and risk of progression to AIDS is unclear (Table A1.1, Table A1.2). This study used a before-after intervention analysis study design in STD clinics to examine the statewide impact of a routine, opt-out expanded HIV testing program. Routine, opt-out HIV testing programs must be rigorously evaluated to ascertain the extent to which the intervention attains programmatic goals.

CHAPTER 2: INTRODUCTION

In 2006, in an effort to increase population awareness of HIV status and, eventually reduce HIV transmission in the United States, the CDC released recommendations for routine, opt-out HIV screening in clinical settings.[1] Expanded HIV testing programs showed the acceptability and feasibility of routine HIV screening in clinical settings (Table A1.1).[7,9,10] However, the ability of expanded HIV testing programs to adequately address the specific goals of the CDC's recommendations remained unclear.

Importance of HIV Testing

HIV testing is the gateway to accessing the continuum of HIV care, which includes linkage, engagement, and retention in HIV-specific medical care (Figure 2.1).[3] HIV care, especially treatment with antiretroviral therapy, is important from both the personal and public health perspectives. Once engaged in HIV care, patients can be treated with antiretroviral medication to achieve viral load suppression.[17-19] Patients with suppressed viral loads are less likely to experience negative health outcomes, such as opportunistic infections, and are more likely to have increased life expectancy and improved quality of life.

Of the 1.1 million persons believed to be living with HIV in the United States, 21% are not aware of their HIV-infected status.[3] These HIV-infected persons who are unaware of their status contribute to approximately 50% of all new HIV transmission events in the United States.[4,5] Increased HIV transmission from persons who are unaware of their HIV-infected status can be attributed a lack of safe sex practices and, as HIV therapy reduces

the likelihood of HIV transmission, failure to engage in HIV care.[20-25] Without case detection and engagement HIV care, suppression is not possible.

History and Rationale for CDC Recommendations

The importance of HIV testing to both the treatment of HIV-infected persons and preventing disease transmission has been well-recognized.[1] However, shortcomings mire current HIV testing strategies. Before the CDC recommendations, most HIV testing protocols called for diagnostic or risk-based HIV testing (Table 2.1).

Diagnostic testing screens patients because of clinical signs and/or symptoms commensurate with advanced HIV infection (Figure 2.2).[26] HIV is largely asymptomatic before progression to AIDS; the asymptomatic phase of infection lasts approximately 10 years.[27,28] Therefore, diagnostic testing based on symptoms of opportunistic infections detects people late in the course of their infection. In addition to poor health outcomes for the HIV-infected individual, if the person has been unaware of his/her infection for many years, there is an increased likelihood that this person contributed to further disease transmission.[4]

Since many years can pass between seroconversion and the development of clinical symptoms, a person presenting late for HIV testing may have had multiple prior contacts with medical providers without an HIV testing encounter. Among patients diagnosed with AIDS within 1 year of their initial HIV diagnosis in South Carolina, 73% made at least one visit to a health-care facility before their diagnosing HIV test.[29] Late diagnoses and these missed opportunities for HIV testing highlight the limitations of diagnostic HIV testing strategies. Although highly specific for case detection, diagnostic testing is an inadequate public health intervention.

Targeted HIV tested based on risk factors, or “risk-based HIV testing”, identifies patients based on risk factors associated with HIV transmission.[26] Usually, a formal risk

assessment is conducted by an HIV counselor. HIV counselors inquire about a patient's sexual history and practices, past drug use, trading sex for drugs or money, incarceration, or history of other sexually transmitted diseases. The goal of risk-based HIV testing is to identify HIV-infected persons before they present with AIDS-related symptoms, while concentrating resources on patients who are at high risk for HIV acquisition.[30]

Testing only patients with prescribed risk factors further stigmatizes the disease and the at-risk patient population.[31-33] Risk assessments often misrepresent a person's true risk profile; persons may be hesitant to report risky behaviors, such as multiple sexual partners, same-gender sexual interactions (especially men who have sex with men), or drug use.[30,34-39] Additionally, many persons with HIV do not belong to traditional high-risk groups, limiting the utility of risk assessments to identify HIV-infected persons.[30,40] Misrepresentation of a person's true risk profile limits the utility of the risk assessment and can lead to decreased HIV testing of truly high-risk persons.

The shortcomings of both diagnostic and risk-based HIV testing led to the investigation of alternative HIV testing strategies through mathematical simulations and cost-effectiveness models. A "test and treat" HIV prevention protocol, in which all persons in a population are regularly tested for HIV and all HIV-infected persons are provided with antiretroviral therapy, was explored in a mathematical model. [41] This model demonstrated the potential for the "test and treat" paradigm to significantly halt the HIV epidemic in South Africa.

To examine the economic feasibility of a universal HIV testing strategy in the United States, incremental cost-effectiveness analyses were used to compare routine HIV screening with diagnostic testing. These economic analyses found routine HIV screening to be cost-effective, costing approximately $40,000 per quality-adjusted life year (QALY), compared with diagnostic testing.[42-44] The generally accepted threshold for a cost-effective of medical screening procedures is below $50,000/QALY.[45] Because of improved quality of

life and reduced medical bills from opportunistic infections, as well as prevention of secondary disease transmission, routine HIV screening results in a low cost per QALY.[46]

CDC Recommendations for Routine HIV Screening

The CDC released recommendations for routine HIV screening in clinical settings to reach the population of HIV-infected persons who present late for HIV testing.[1] These recommendations were further supported by the limitations of diagnostic and risk-based testing, the potential of the "test and treat" paradigm to impede the HIV epidemic, and the estimated cost-effectiveness of routine HIV screening. The recommendations urged routine, opt-out HIV screening in clinical settings where the prevalence of infection was at least 0.1%.[1] The primary goals of the CDC recommendations were to (a) increase HIV testing, (b) detect previously unaware HIV-infected persons, and (c) identify HIV-infected persons earlier in the course of their HIV infection, compared with diagnostic or risk-based HIV testing protocols.

The CDC disbursed funding to city and state health departments with high HIV/AIDS burdens to implement expanded HIV testing programs in clinical settings. Since the introduction of this funding initiative in 2007, clinical setting personnel have performed 2.8 million HIV tests and identified 18,000 new HIV-infected cases (0.7% positivity).[2] However, these new diagnoses only represent a fraction of the estimated 150,000 new HIV transmission events during the same period.[6]

Existing Literature Neglects Program Goals and Lacks Generalizability

Since the release of the CDC recommendations in 2006, over 50 peer-reviewed publications have described expanded HIV testing programs in clinical settings (Table A1.1). The majority of publications are solely descriptive, demonstrating the feasibility and acceptability of expanded HIV testing programs. While feasibility and acceptability are

crucial to the success of expanded HIV testing programs, they do not directly address the goals of the CDC's recommendations. Clinical measures, such as concurrent AIDS diagnosis, CD4 counts, or viral load measurements, are only included in a small fraction of publications.[7-9,11-13,47-56] Comparison between publications is challenging because the programs described vary in their scope and HIV testing protocols (Table A1.1).

Over half (22/55) of the publications detail HIV testing programs in emergency departments. This focus on emergency departments limits the generalizability of these studies to similar acute care settings (Table A1.1). Emergency departments act as access points for many uninsured persons who are at increased risk for HIV acquisition, but they represent a selected subset of the overall US health-care seeking population.[57,58] Other expanded HIV testing programs have been described in community health centers (3), prisons/jails (6), dental clinics (1), STD clinics (5), primary care settings (2), hospital inpatient settings (5), and health care systems (4).

Contradictory Evidence from Comparison Studies

In contrast with the plethora of descriptive analyses, only 19 of these program evaluations included a comparison group (Table A1.2). The majority of evaluations with comparison groups showed an increased number of HIV tests performed with the introduction of the expanded HIV testing program. However, the magnitude of this increase varied based on the clinical setting. In most clinical settings, very little HIV testing was done prior to the intervention, so the number of HIV tests conducted could increase greatly.[11,49,56,59-62] In other clinical settings with high-risk patient populations, like STD clinics, the baseline rate of HIV testing was so high that the maximum benefit from an HIV testing program was minimal.[63]

Data indicating the ability of expanded HIV testing programs to detect more HIV-infected persons, one of the CDC's primary goals, are contradictory. Expanded HIV testing

programs were associated with an increase in HIV case detection in many clinical settings (Table A1.2). However, some sites showed a decrease or no change in the proportion of patients testing positive for HIV.[7,8,11,12,49,56,62,64,65] The investigator's choice of outcome used to assess program yield, either the number of newly identified HIV-infected persons or the positivity proportion, can change the interpretation of a programs' ability to identify new HIV-infected persons. For example, an Veteran's Administration health system in Washington, DC observed that the number of HIV- infected persons identified increased from 47 to 69 with the introduction of routine HIV screening, yet the positivity proportion decreased from 1.5% to 1.1%.[62] This discrepancy can be attributed to the large increase in HIV testing that was needed to detect additional HIV cases.

These analyses with comparison groups are often restricted to a single clinical facility, which limits the size of the population under study. Because HIV is a rare infection in the general population (1% HIV prevalence is considered very high), very few new HIV-infected cases were identified in these single-facility HIV testing programs (Table A1.2). The public health significance of findings based on such small numbers is questionable. Additionally, the focus on single clinical facilities limits the generalizability of the findings to similar settings – most commonly, urban emergency departments with limited pre-intervention HIV testing. One must question the applicability of these findings to other clinical settings or more rural areas of the United States.

Few program evaluations consider the immunologic state of newly-diagnosed persons at diagnosis or the timing of progression to AIDS.[7,8,11,13] Ecologic data from New York City and Rhode Island suggested an improvement in the immunologic status of newly-diagnosed HIV-infected persons with the introduction of programs or policies that facilitated routine, opt-out HIV testing.[66,67] However, these studies did not examine the individual-level impact of interventions, but rather the association between a system-wide change (New York City: "Bronx Knows" HIV testing campaign; Rhode Island: a legislative amendment

allowing routine, opt-out HIV testing) and the immunologic status of a sample of persons in the catchment area of the system-wide change (New York City: Bronx HIV surveillance records; Rhode Island: clinical data on persons attending an HIV clinic).

Other program evaluations were based in emergency departments in major metropolitan centers. In a study from Oakland, California, the proportion of persons diagnosed with AIDS at the time of their HIV diagnosis (CD4 ≤ 200) was 48% during an experimental opt-out HIV testing program, compared with 25% in the opt-in protocol comparison group.[13] However, when the same emergency department changed from a diagnostic-based testing program to routine screening, the average CD4 cell count at diagnosis increased from 99 cells/uL to 356 cells/uL.[11] In an emergency departments in Denver, Colorado, and Chicago, Illinois, CD4 cell counts increased with a change from diagnostic-based HIV testing to routine, opt-out screening.[7,8]

Although these programs examined clinical outcomes, they could only assess immunologic status at diagnosis and not progression to an immune-compromised state over time. Medical records were restricted to the single facility that performed the diagnosing HIV test; data were not linked to surveillance records and HIV- infected persons could not be tracked for engagement in HIV care in other clinical settings. As discussed previously, HIV is a rare outcome and the sample sizes of these evaluations are inadequate to confidently describe any potential public health impact. In combination, these studies only examined 90 HIV-infected persons pre-intervention and 134 HIV-infected persons post-intervention.[7,8,11,13]

Gaps in the Comparison Study Literature

Further research is needed to critically evaluate expanded HIV testing programs using a valid comparison group to identify if expanded HIV testing programs are indeed meeting CDC goals. The number and proportion of HIV- infected patients must be measured, as well as a clinical marker of disease state at diagnosis. In addition, the current

focus on clinical settings with limited HIV testing pre-intervention, such as emergency departments, sets unrealistic expectations. The maximum potential of an intervention in a clinical setting is dictated by the clinic's size and capacity. The potential increase in HIV testing in clinical settings with low pre-intervention levels of HIV testing is much greater than could possibly be observed in clinical settings with high pre-intervention levels of testing. As clinical settings with a high proportion of at-risk patients would, presumably, already have some HIV testing capacity, a greater emphasis should be placed on the incremental impact of HIV testing programs in these settings.

Although useful to indicate the ability of routine HIV testing programs to perform a greater number of HIV tests, the current literature does not provide consistent evidence that these programs have led to more HIV- infected persons are being identified, or identified any earlier in the course of infection.

Southeastern United States is an Area of High HIV Burden

The geographical and social context of an HIV epidemic is crucial to consider when planning HIV prevention efforts. Following the "test and treat" simulation model based in South Africa, the gross differences between the South African and American HIV epidemics necessitated inquiry as to the translation of the model's results to the American context.[68-71] United States-based simulation models identified the potential for "test and treat" interventions to reduce transmission, although the extent of that reduction varied. However, the US epidemic also experiences regional variation, which is often ignored in nationally-aggregated HIV prevention data, including official reports of the CDC's expanded HIV testing funding initiative.[2]

In particular, the bulk of the expanded HIV testing literature focuses on major metropolitan centers or highly urbanized regions of the northern part of the United States. A program that is efficient in New York City or San Francisco may not be as successful in

other, more rural areas of the country. Only 6 publications cite expanded HIV testing programs in the Southeastern United States.[54,61,72-75]

The Southeastern US experiences some of the country's highest rates of HIV infection (Figure 2.3).[14] In the early 2000s, the number of new AIDS cases in the Deep South increased 35.6%, compared with an increase of only 5.6% in other states.[76] Given issues with late diagnosis and potential transmission of HIV infection when the disease is left untreated, the disproportionate burden of HIV infection born by the Southeastern United States is not surprising.

In North Carolina, an estimated 35,000 persons are living with HIV/AIDS, including 7,000 who may be unaware of their infection.[40] Approximately 1,500 new HIV cases are detected annually. North Carolina has the 8th highest rate of new HIV diagnoses at 23.8 cases per 100,000 (US rate 21.1 per 100,000) and the 13th highest rate of adults and adolescents living with HIV infection at 294.0 per 100,000 (US rate = 337.5 per 100,000). North Carolina also has the 11th highest rate of AIDS diagnoses at 11.6 per 100,000 (US rate = 11.2 per 100,000).

The prevalence of many poor health indicators is higher in the Southeastern United States than other regions of the country; many of these poor health indicators can facilitate, directly or indirectly, HIV transmission. These poor health indicators include: high levels of poverty, inconsistent availability and quality of health care services, and a high prevalence of STDs and other comorbid conditions.[76]

Racial/ethnic disparities in the HIV-infected population are more pronounced in the Southeast than in other regions of the country.[14] In North Carolina non-Hispanic blacks account for 22% of the state's population, but represent over 66% of the state's HIV case burden.[40] In 2010, the rate of HIV diagnoses was 94 cases/100,000 among non-Hispanic black men, compared with 11.6 cases/100,000 among non-Hispanic white men. Similar disparities are observed in women. These disparities can be attributed, in part, to high rates

of incarceration among non-Hispanic black men, which disrupts the normal gender ratios of communities, and concurrent sexual relationships.[77-80]

Acute infection is a major concern in areas like North Carolina, where transmission is not solely driven by persons with established infection, but by newly infected individuals. In the early 2000s, an outbreak of acute HIV infection among young, black men who have sex with men was identified in the college student population in North Carolina.[81] Since 2003, 176 acute cases of HIV have been identified. Eighty percent of these cases were male and 69% were black; he median age of infection was 25 years.[40] Acute HIV infection is indicative of a more recent, evolving epidemic, rather than an epidemic of more established, chronic infection seen in many metropolitan centers.

The rural nature of much of the Southeastern United States also complicates HIV prevention efforts. Persons living in rural areas are more likely to experience stigma related to HIV infection, which could adversely impact the success of HIV testing efforts and disclosure of HIV status to sexual partners.[82-85] Persons living in rural areas are more likely to present with late diagnosis of HIV and experience barriers in accessing HIV care.[82,86-90] These barriers could be related to social stigma or structural barriers, such as a lack of transportation to HIV care specialists.

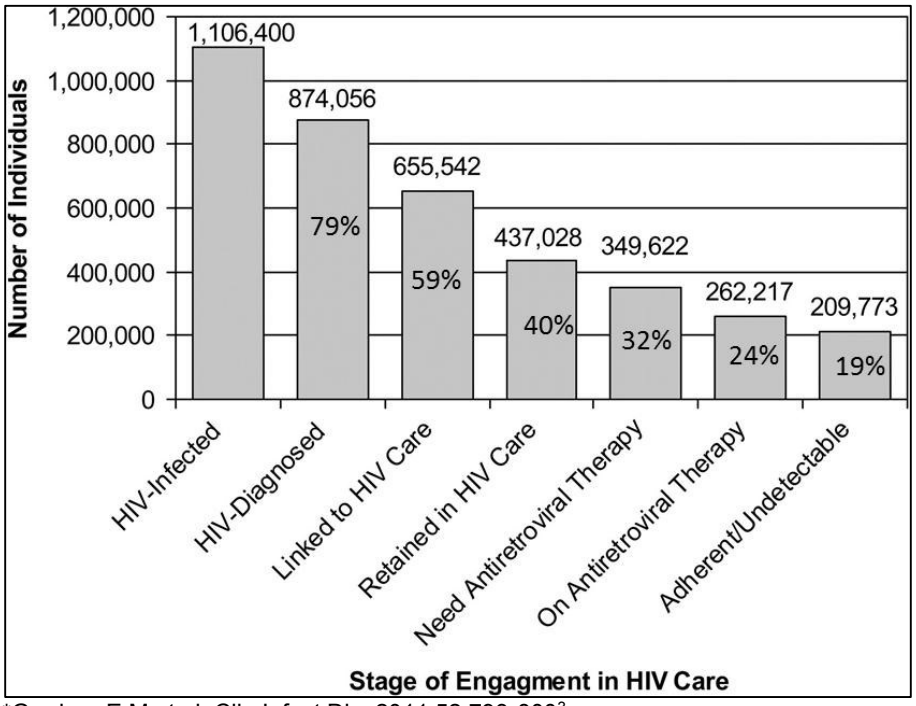
The Role of HIV Testing in Current HIV Treatment Paradigms

With the advancement of new HIV care paradigms like “treatment as prevention” after the successful HIV Prevention Trials Network Study 052, HIV testing’s role as the access point to the HIV treatment cascade is of even greater importance.[24] Yet, the ability of routine HIV screening to increase detection of HIV-infected persons and identify HIV-infected persons early in the course of their infection is unclear. While proof of concept has been shown in experimental environments, the effectiveness of routine HIV screening in all

geographic regions of the US has not yet been demonstrated.[7] Through this study, we aim to address the impact of routine, opt-out HIV testing in a real-world environment.

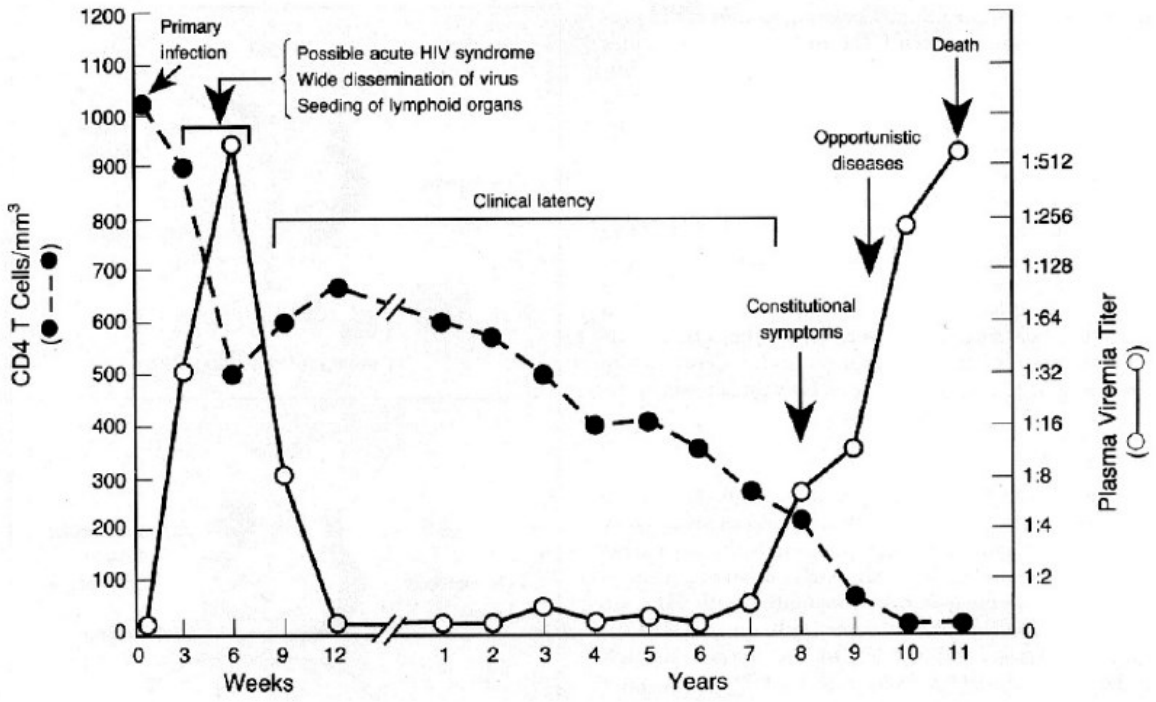
Tables and Figures

Figure 2.1: The Spectrum of Engagement in HIV Care in the United States



*Gardner E M et al. Clin Infect Dis. 2011;52:793-800[3]

Figure 2.2: Progression of HIV Infection, by CD4 Count and HIV RNA Viral Load



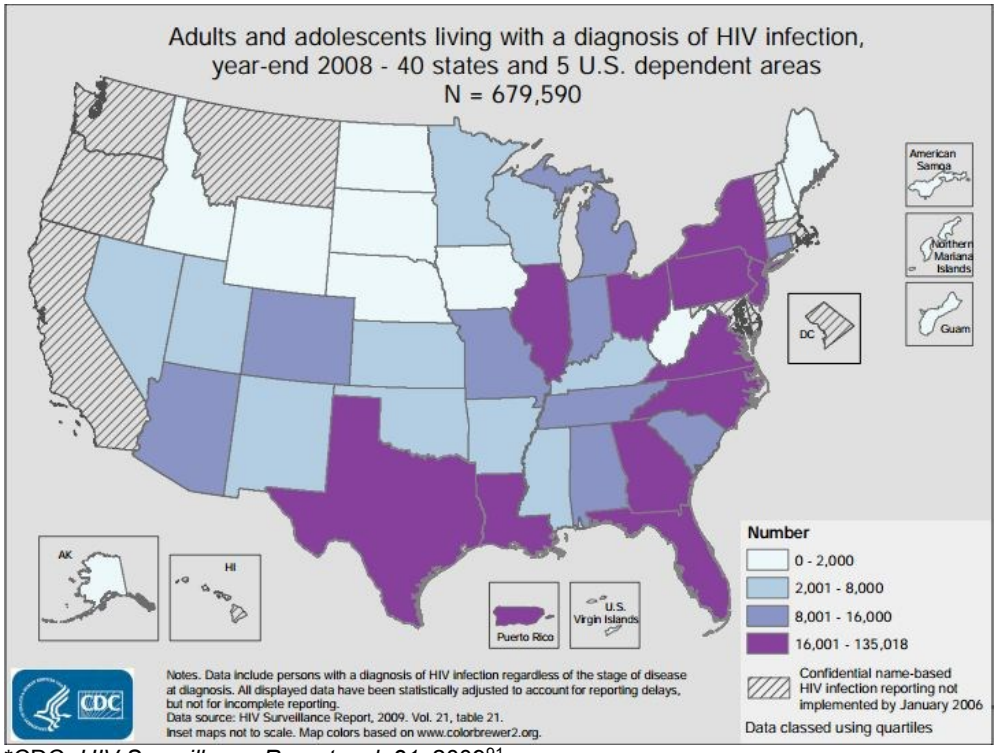
*Pantaleo, NEJM, 1993.[28]

Table 2.1: Comparison of HIV Testing Strategies

Testing Strategies	Description
Diagnostic Testing	Selection or intended selection of patients because of clinical signs and symptoms suspected to be due to HIV infection
Targeted Screening	Selection or intended selection of all patients from among a defined *subpopulation* that are thought to have an increased likelihood of infection when compared with the base population
Nontargeted Screening	Selection or intended selection of *any* patient within the available population without respect to risk, but not intended to comprehensively include every available patient
Universal Screening	Selection or intended selection of *all* patients in the available population on a nontargeted basis; intended to comprehensively include every available patient

*Adapted from Lyons, et al. *Acad Emerg Med.* 2009 [26]

Figure 2.3: Adults and Adolescents Living with a Diagnosis of HIV Infection, Year-End 2008, 40 States and 5 US Dependent Areas



*CDC, *HIV Surveillance Report, vol. 21.* 2009[91]

CHAPTER 3: RESEARCH DESIGN AND METHODS

Study Design: A Before-After Intervention Analysis

This study used a before-after intervention analysis design to assess a) HIV testing, b) the detection of new HIV-infected persons, and c) the risk of progression to AIDS among newly-diagnosed persons, before and after the implementation of a routine, opt-out HIV testing program in North Carolina STD clinics. The impact of the intervention was determined by comparing the outcome frequencies before and after the implementation of the program (before: July 1, 2005 – October 31, 2007; after: November 1, 2007 – June 30, 2011). Data from 28 months prior to the implementation of the intervention was used as a comparison group.

To examine the success of this routine, opt-out HIV testing program, we compared post-implementation data from STD clinics with pre-implementation data from the same STD clinics. A cluster randomized trial would be the ideal study design to isolate the effects of the intervention. However, the intervention was not randomized to clinical sites at the start of program implementation. Randomization cannot occur after the introduction of the intervention, so an observational retrospective study design must be used.

All North Carolina STD clinics participated in this routine, opt-out HIV testing intervention. A before-after design with an internal comparison group represented the best approximation of a counterfactual. By comparing HIV testing and diagnoses before and after the implementation of the intervention within the same facilities, we hoped to isolate the effect of the intervention without many other pre- and post-intervention differences. However, not all STD clinics were identical to one another. To account for underlying

differences between STD clinics, we used multilevel regression models with county-specific random intercept terms.

Our before-after design was further strengthened by the large number of HIV tests performed in the STD clinics (over 400,000) and the large number of STD clinics in the state (102). This large sample size allowed us to stratify our results by patient and clinic covariates to evaluate if the impact of the intervention was uniform across all population subgroups. HIV testing protocols and technologies did not change over the study period; the only change to testing practices was the introduction of the intervention in November 2007. North Carolina is a geographically and demographically-diverse state, which will make our results generalizable to STD clinic patients in the Southeastern region.

This before-after study design avoided issues of confounding that would have biased our results if STD clinics were compared to other types of facilities, such as private physician offices. However, by restricting our analysis to STD clinics, we limited the generalizability of our results to the STD clinic patient population.

Study Setting: North Carolina STD Clinics

The Southeastern United States bears a disproportionate burden of HIV infection, accounting for nearly 50% of the new AIDS cases in the United States in 2009 and 2010.[14,40] The rate of new HIV infections (23.8 per 100,000) and new AIDS diagnoses (11.6 per 100,000) in North Carolina is higher than the national average (HIV: 21.1 per 100,000; AIDS: 11.2 per 100,000).[40] Due to demonstrated need for HIV prevention activities in North Carolina, the state was chosen as a grantee for the CDC's expanded HIV testing initiative in 2007.[2]

In North Carolina, the expanded HIV testing program focused on initiating or expanding HIV testing in the following venues: STD clinics, county jails, prisons, emergency departments, and community health centers.[40] In late 2007, North Carolina modified its

administrative code to allow clinical facilities to remove the requirement for a separate written consent form for HIV and to incorporate routine, opt-out HIV testing.[92] This policy change led to the establishment of many new HIV testing programs with routine, opt-out testing protocols.

With this intervention, a conventional, non-rapid, blood-based HIV test was offered to every STD clinic patient. Blood samples were tested at the State Laboratory for Public Health (SLPH), with automatic pooling for detection of acute HIV infection by ribonucleic acid (RNA) testing. Before the implementation of the intervention, HIV testing was performed selectively based on risk and presumptive syphilis status using an opt-in protocol with separate written consent. A standardized protocol for routine, opt-out HIV testing was used by all STD clinics that participated in the intervention (n=102).

Data Sources

Subject inclusion in this analysis was conditional on the successful completion of an HIV test. Therefore, HIV testing data was used as the primary data source. Multiple data sources provided a comprehensive picture of HIV testing in North Carolina STD clinics (Table 3.1).

STD Clinic Data and Laboratory Data

Data on demographic information and HIV testing results were abstracted from the SLPH electronic laboratory database. A paper form containing patient demographic and clinical information was filled out by STD clinic staff upon HIV testing, and accompanied each blood sample sent to and processed at the SLPH.

Once the blood sample arrived at the SLPH, the demographic and clinical information from this form was entered into the SLPH electronic database. Laboratory test results were added to the patient's SLPH record. The SLPH electronic database is regularly

maintained by staff members of the North Carolina Division of Public Health based in Raleigh, NC.

Data for HIV-Infected Persons

All persons who tested positive for HIV on both a 3rd generation EIA laboratory test and a confirmatory Western Blot laboratory test were considered confirmed HIV-infected cases by North Carolina (Figure 3.1).[40] Persons who tested negative on the 3rd generation EIA laboratory test but tested RNA-positive for HIV viral RNA were designated as acute HIV infections, and were also considered confirmed HIV-infected cases.

All HIV-positive test results from the SLPH database were linked to or entered into the electronic HIV/AIDS Reporting System (eHARS). eHARS is the surveillance system used by the North Carolina Division of Public Health to collect and organize information on all HIV-infected cases in North Carolina. eHARS data are collected from state-mandated HIV case report forms and laboratory data, and updated by reports from HIV clinical providers. Other clinical data, such as the date of AIDS diagnosis, are also included in eHARS.

If the HIV-positive test in the study period was the case's first HIV-positive test result in North Carolina, a new eHARS record was created for that patient and the patient was considered a new HIV diagnosis for surveillance purposes. If, however, the same patient was previously entered in eHARS, their positive test result during the study was documented in the patient's pre-existing eHARS record and the patient was considered a previous HIV diagnosis for surveillance purposes. Protocol dictates that disease intervention specialists interview new HIV-infected cases, perform tracing of sexual contacts, and help bridge new HIV-infected cases to HIV-specific medical care.

Clinic-Level Covariates

Clinic-level covariate data was obtained from publically-available datasets, including data from the US Census Bureau (metro/micropolitan statistical area categorizations, county population density, percentage living below poverty line), clinic-specific information (presence of an in-house HIV clinic), and published North Carolina HIV/AIDS surveillance reports (reported HIV case rate for the STD clinic county).

Aim 1: HIV Testing and Case Detection

Estimate the impact a routine, opt-out expanded HIV testing intervention on HIV testing patterns and the detection of new HIV-infected cases in North Carolina STD clinics

Study Population

The study population included all patients tested for HIV in North Carolina STD clinics in the 28 months prior to the implementation of the intervention through June 30, 2011 (pre-intervention period: July 1, 2005 – October 31, 2007; post-intervention period: November 1, 2007 – June 30, 2011). Included patients were aged 18-64 and maintained a permanent residence in North Carolina.

STD clinic resources and programs were not restricted to residents of North Carolina. However, any out-of-state patients who tested HIV-positive were not included in the North Carolina surveillance database. For these out-of-state cases, the confirmation of their HIV-infected status, designation as a new or previously known infected case, and clinical measures (e.g. CD4 counts, viral loads, concurrent AIDS diagnoses) would not be available. Therefore, out-of-state individuals were excluded from analysis.

Outcome

Outcome 1: HIV Testing

The first outcome for Aim 1 was HIV testing performed in the STD clinics, evaluated both as the absolute number of HIV tests per month and as the HIV testing rate per 100,000 population. All persons included in the study population were tested for HIV and contributed to this outcome. The absolute number of HIV tests was evaluated over time with serial monthly cross-sections evaluated using interrupted time series analysis. The HIV testing rate per 100,000 population was evaluated in both interrupted time series analysis and multilevel regression modeling.

Annual intercensal population estimates were used as the denominator for the HIV testing rate (Table A2.7). Due to limitations of the available datasets, we could not create a denominator-based on the actual number of patient visits in the STD clinics. Intercensal population estimates are annually-updated population estimates using data from the most recent national census to capture population changes between 10-year census surveys, stratified by county and by demographic subgroups.

Outcome 2: Newly-Diagnosed HIV-Infected Persons

The second outcome for Aim 1 was the identification of newly-diagnosed HIV-infected persons in North Carolina STD clinics. This outcome was evaluated both as the absolute number of newly-diagnosed HIV-infected persons and as the HIV positivity per 1,000 HIV tests. An HIV-infected diagnosis was defined as a person who tested HIV positive on a 3rd generation blood-based enzyme immunoassay (EIA) diagnostic test and was confirmed positive via Western Blot, or a person who tested HIV negative on a 3rd generation blood-based EIA diagnostic test, but positive on HIV RNA testing (Figure 3.1).[93]

All HIV-infected cases reported to the North Carolina Division of Public Health were categorized as new or previously-known, based on surveillance records. Previously-known

patients had either already been reported to North Carolina Division of Public Health, or were known to be a confirmed case of HIV in another state. All preliminary HIV test results (rapid tests, EIAs, etc.) were confirmed by Western Blot analysis, in accordance with North Carolina testing protocols.

For this study, a new HIV-infected case met the above diagnostic criteria for a confirmed HIV-infected case, but had never before been reported as a case of HIV. A new HIV-infected case was defined as a person with a positive HIV test result in the same calendar month as the patient's HIV diagnosis date as documented in eHARS. This window period allowed for potential reporting delays and uncertainty regarding some persons who lacked a specific date of HIV diagnosis; these persons were assigned to the 15th day of their diagnosis month. This approximation recoded 69 HIV-infected cases as newly-diagnosed, when they otherwise would have been considered a previous diagnosis (3.3% of patients with a positive test result, 0.009% of the total study population).

All results were stratified by patient and clinic characteristics to identify trends in population subgroups and assist with public health decision making. These stratified results will help to direct limited public health resources to areas of greatest impact, as well as identify areas of continued need.

Exposure

The exposure variable in this analysis was time, which was used to denote the presence or absence of the intervention in the STD clinic. The intervention was introduced to STD clinics in November 2007. Exposure was coded dichotomously for descriptive analyses; persons tested for HIV on or after November 1, 2007 were considered "exposed" and those tested prior to that date were considered "unexposed". A monthly time scale was used to examine temporal trends.

Base case regression models included a lag period of 3 months. The inclusion of a lag period allowed for the exclusion of a short period of unusual variability post-intervention that may not be attributable to the intervention under study. Lag periods capture the real-world challenges of implementing an intervention in a clinical setting, while allowing staff and clinicians to fully adjust to and operationalize the intervention as dictated in standard operating procedures. Previous studies of HIV testing programs in North Carolina community health centers indicate that some HIV testing outcomes may be inflated during this lag period, before the outcomes stabilizes.[94] Therefore, in base case regression analyses, persons tested prior to November 1, 2007 were considered "unexposed" and those tested after February 1, 2008 were considered "exposed"; HIV testing and case detection patterns for persons in the lag period were modeled separately. In sensitivity analyses, the length of the lag period was varied from 0 months (no lag) to 6 months.

Patient and Clinic Covariates

As our analysis used a quasi-experimental before-after study design within a closed set of STD clinics, the primary difference between pre- and post-intervention periods should only have been the introduction of the intervention. This approach is complementary to a randomized controlled trial, in which the investigators aim to create two identical groups that only differ by the assignment of exposure. Covariates that may have been associated with the outcome were determined *a priori,* and included in statistical modeling. Since the exposure variable was time and the intervention was a direct result of an external public health initiative, we did not expect a confounding relationship between covariates and the exposure. Models were adjusted for sets patient covariates (gender, race/ethnicity, age), clinic covariates (metropolitan status, population density, percentage of county living below the poverty line, presence of an in-house HIV clinic, baseline HIV case rate), or all covariates. Adjusted effect estimates were compared with crude, unadjusted effect

estimates. Due to our quasi-experimental study design, we anticipated that the crude, unadjusted effect estimates would be valid.

Patient date of birth was used to calculate age at time of HIV testing and was coded categorically (age 18-24, 25-34, 35-44, 45-64). Sex was assessed as male/female. Patient race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, or other (Asian, Hawaiian/Pacific Islander, Native American, multi-race).

Urban/rural categorizations of counties were described by the US Census Bureau's metropolitan/micropolitan statistical area groups (MeSA, MiSA, neither) and by the county population density (<199, 200-399, 400-599, ≥600 persons per square mile).[95,96] The percentage of the county's population living below the poverty line was used as a marker of the economic status of each county (<15%, 15-19.9%, 20-24.9%, ≥25%).[97] The average baseline county-level estimated HIV case rate per 100,000 from 2005 to 2007 was included as a categorical variable categorized for analysis as (0-4.9, 5-9.9, 10-14.9, ≥15).[40] A dichotomous variable identified the presence or absence of an in-house HIV clinic; STD clinics with an in-house HIV clinic were Durham, Mecklenberg, and Wake Counties.

Data Analysis

Preliminary Descriptive, Univariate, and Bivariate Analyses

The temporal trends of HIV testing and case detection were first assessed descriptively. The frequency and distributions of all variables (exposure, outcomes, and covariates) were assessed using tabular and graphical representations. Bivariate associations of potential covariates by exposure level (pre/post intervention) were also presented descriptively using counts and frequency distributions. Chi-square statistics were calculated to describe differences in covariate distributions by exposure level.

Assessing Missing Data

The amount of missing exposure or outcome data in this analysis was unknown. SLPH and eHARS surveillance databases may have had incomplete records. We assumed that only a small amount of the exposure or outcome data were missing. Unfortunately, this assumption could not be verified.

The covariates were evaluated for patterns of missingness in frequency tables, both overall, and in strata of the exposure (pre- and post-intervention). Given the small proportion of study subjects missing individual-level covariate information (age, sex, race/ethnicity; n=9,961, 2.4% of patients with a valid HIV test result), a complete case analysis was conducted. The final analysis cohort included 402,774 unique HIV tests performed over 72 monthly time points.

Multivariate Analyses

Multivariate analyses were conducted using two distinct, but complementary methods: interrupted time-series analysis and multilevel modeling. Both methods incorporate time, however, under different functional assumptions. Interrupted time-series analysis uses monthly cross-sections as the unit of analysis and controls for underlying temporal trends to examine changes in the outcome over time. Multilevel models evaluate the overall impact of the intervention while controlling for clinic-level correlation.

Time Series (ARIMA) Models: Rationale

Interrupted time series analyses evaluate non-randomized interventions by assessing a repeated series of observations on the same study population.[98,99] These analyses evaluate the modeled exposure-outcome associations over time, in the context of underlying temporal trends. The unit of analysis for interrupted time series analyses is the cross-sectional time period (months, in this analysis).

Interrupted time series analysis is considered the most rigorous evaluation method for non-randomized observation studies.[100] Although initially designed for use in economics, interrupted time series analyses are now used regularly in evaluations of community interventions, new clinical policies, and medication use.[98,101,102]

Time Series (ARIMA) Model: Design

Interrupted time series analyses were used to determine if the change in HIV testing or case detection after implementation of the intervention was greater or less than would be expected in the absence of the intervention, while accounting for time-based correlation in the data.[98,99] Segmented regression lines characterized the temporal trends in the outcome by the 'level' at which the segment starts (intercept) and the trend (slope). The analysis examined how the level (intercept) and trend (slope) of the segment changed after the introduction of the intervention. A lag period, or transitional period, of 3 months was specified to account for a period of program ramp-up to ideal levels. In sensitivity analysis, the lag period was varied from 0 months (no lag) to 6 months.

The specific interrupted time series technique used in this analysis was autoregressive integrative moving average (ARIMA) models. ARIMA models are used when error terms are potentially associated with one another and not independent.[98,99,103] Since this analysis used repeated sampling of the same STD clinics over time, we expected that error terms would be correlated with one another. Based on autocorrelation and partial autocorrelation plots, we observed an autocorrelation of 1 (AR=1) for all outcomes except HIV positivity. Autocorrelation of 1 means that the outcome at time 2 is correlated with the outcome at time 1, the outcome at time 3 is correlated with the outcome at time 2, etc.[99]

The ARIMA model was fit to a binomial distribution with an identity link to calculate mean differences (MDs) and corresponding 95% confidence intervals. Potential covariates were considered for inclusion in the model according to the *a priori* criteria described above.

Base ARIMA Model:[98]

$$Y_t = \beta_0 + \beta_1 * time_t + \beta_2 * intervention_t + \beta_3 * time\ after\ intervention_t + e_t$$

Y_t: mean outcome in month *t*

Time: time in months at time *t* from the start of the study period

Intervention: indicator for time *t* occurring before (intervention = 0) or after (intervention = 1) the implementation of the intervention

Time after intervention: continuous variable counting number of months after intervention at time *t*, coded 0 before the intervention

β_0: pre-intervention intercept

β_1: pre-intervention slope, change in the outcome per month before the intervention

β_2: post-intervention intercept, immediate change after introduction of intervention

β_3: post-intervention slope attributable to the intervention, incremental difference in slope compared with the pre-intervention slope

e_t: error term, random variability not explained by the model

Time Series (ARIMA): Outcome

The primary outcome of interest in the ARIMA model was the change in outcome (HIV testing or case detection) attributable to the intervention (β_3). The overall post-intervention slope was described as the sum of the pre-intervention slope (β_1) and the change in outcome attributable to the intervention (β_3).

In addition to identifying the overall impact of the intervention, the ARIMA models were stratified by patient- and clinic-level covariates. Due to the ecologic structure of the ARIMA model, a separate dataset of each population subgroup was created and then analyzed using ARIMA regression models.

Multilevel Models: Rationale

We used multilevel, or hierarchical, regression models to account for correlation between STD clinics. Persons who visited a specific STD clinic may be similar to one another, yet different from patients at other STD clinics. This clustering of similar patients within STD clinics violates the independence assumption of traditional linear models.[104,105] Advanced modeling techniques that account for the correlation between STD clinics were necessary to calculate valid estimates.

Multilevel models included both individual-level and group-level covariates. In this analysis, patients were nested within STD clinics, and the exposure-outcome association may have been influenced by both patient-level and clinic-level covariates. Multilevel models provide an intermediate approach between analyzing all patients as an aggregate population (ignoring clinic-level covariates) and creating a separate regression line for each clinic, which may overestimate the differences between clinics.[104,105]

Multilevel Models: Design

Multilevel models are “mixed” models that can include both random and fixed effects. Random components can be introduced for either the intercept term, slope term, or both terms. For our base case model, we fit a fixed-slope random intercept model with a separate intercept term for each county. The random intercept term allowed for each STD clinic to have its own intercept, but assumed that the intervention had the same effect in all STD clinics. The degree of correlation within and between STD clinics was quantified using the intraclass correlation coefficient (ICC).

Fixed-Slope Random intercept model:[104,105]

$$y_{ij} = (\beta_1 + \zeta_{1j}) + \beta_2 x_{ij} + \cdots + \beta_p x_{pij} + \epsilon_{ij}$$

i: patient-specific indicator

j: facility-specific indicator

β_1: patient-specific fixed intercept

ζ_{1j}: facility-specific random intercept, deviation of facility *j*'s intercept from the mean intercept

β_1; weighted average of the within-facility and between group-facility intercept estimates; normally distributed with mean=0 and variance=ψ [~N(0,ψ)]

β_2: patient-specific fixed slope

β_p: coefficient for additional covariates

ϵ_{ij}: patient-specific error; random deviation of y_{ij} from facility *j*'s mean

In sensitivity analyses, this random intercept model was compared with a model without random components (fixed effects model). Fixed effects models assume that no parameters vary by group (or clinic, in this case) – including both intercept and slope parameters. These models essentially examine the study population as one aggregate group, ignoring possible correlation between clinics.

Multilevel Models: Intervention/Time

Time, the exposure variable, was coded as a 3-level categorical variable in the base case scenario to allow for the 3-month lag period. A knot was placed at the start of the lag period (November 1, 2007) and another at the start of the intervention analysis period used in analysis (February 1, 2008).

Sensitivity analyses considered two alternative lag periods of 0 months (no lag) and 6 months. In the sensitivity analysis that did not include a lag period, time was coded dichotomously with the only knot on November 1, 2007. The 6-month lag period was modeled similarly to the 3-month lag, but with the second knot occurring at May 1, 2008.

To account for additional underlying temporal trends, models were adjusted for the year of HIV testing using an indicator term. All models were calculated with and without this calendar year indicator variable.

Multilevel Models: Outcomes

The HIV testing rate per 100,000 population was modeled using a Poisson distribution and a log link. Poisson regression, which can either examine counts or rates, needs an offset term when the outcome is in the form of a rate. The offset for this analysis was calculated as the log of the intercensal population denominator. These Poisson models yielded rate ratios (RR) and corresponding 95% confidence intervals. Because we lacked individual-level denominator data, we only considered an unadjusted, fixed effects regression model.

HIV positivity is a rare outcome; the overall HIV positivity from the CDC-funded HIV testing initiative in North Carolina in 2010 was 0.25% (includes all emergency departments, community health centers, STD clinics, and county jails).[40] This analysis examined serial cross-sections and could not evaluate risk of HIV acquisition over time. A model with a binomial distribution and logit link function was used to calculate odds ratios (ORs), which approximated prevalence ratios, and corresponding 95% confidence intervals.

Multilevel models result in an overall estimate of association, not clinic-specific estimates. The overall beta coefficient for the exposure represented the expected change in the log HIV positivity with the implementation of the intervention in all STD clinics in North

Carolina. The width of the confidence intervals was influenced by degree of variability observed at the facility level.

Multilevel Models: Covariates

As discussed above, our results should not be biased by confounders because we used the STD clinics as internal controls. However, as our comparator group is not a perfect counterfactual, covariates determined *a priori* to influence the outcome were evaluated as potential confounders. Models were adjusted for sets of covariates: patient-level covariates (gender, race/ethnicity, age), clinic-level covariates (metropolitan status, population density, percentage of the county below the poverty line, presence of an in-house HIV clinic, and baseline HIV case rate), and patient + clinic level covariates. Nested models were compared to one another using likelihood ratio tests at an a priori significance level of 0.10.

All statistical analyses will be conducted with SAS version 9.2 (SAS Institute, Cary, NC).[106]

Aim 2: Progression to AIDS

Estimate the impact of a routine, opt-out expanded HIV testing program on the risk of progression to AIDS within 12 months of initial HIV diagnosis among newly-identified HIV-infected cases detected in North Carolina STD clinics

Study Population

The study population consisted of all patients newly diagnosed as HIV-infected in North Carolina STD clinics from 28 months prior to intervention implementation (July 1, 2005) through June 30, 2011. The inclusion criteria were identical to the outcome definition for a new HIV-infected case in Aim 1.

Outcome

Outcome: Risk of Progression to AIDS

The outcome for Aim 2 was the risk of progression to AIDS after a new diagnosis of HIV, defined as the proportion of newly diagnosed HIV-infected patients who progress to AIDS (and were reported as such) within 1 year of their initial HIV diagnosis. AIDS cases were based on the North Carolina Division of Public Health definition of a person who meets certain immunologic criteria (CD4 count <200 or <14%) or who becomes ill with one of 26 AIDS-defining conditions.[40]

Sensitivity analyses varied the window period for progression to AIDS from 1 month to 18 months. Specific alternative outcome time frames considered were 1 month, 6 months, and 18 months post-diagnosis. Although the CDC uses a 12 month window period to define "late HIV diagnosis", the North Carolina Division of Public Health uses a 6 month time frame.[15,40] Other definitions of "late HIV diagnosis" from the literature include AIDS at diagnosis, based on the CD4 count measured within 1 or 3 months post-diagnosis.[107-109] To allow for potential reporting delays or imprecise dates of HIV or AIDS diagnosis, an additional 15 days were added to each outcome time period (1 month + 15 days, 6 months + 15 days, etc.).

Exposure

As in Aim 1, the exposure for this analysis was time, which was used to denote the presence or absence of the intervention in the STD clinic. Patients diagnosed post-intervention (after November 2007) were categorized as "exposed"; those diagnosed pre-intervention were categorized as "unexposed".

In Aim 1, we included a lag period of 3 months, to allow for greater variability immediately post-intervention. Evidence does not suggest a similar short-term increase in variability in the outcome of Aim 2. Therefore, no lag period was included in this aim. This

assumption was evaluated in sensitivity analysis with the inclusion of 3 and 6 month lag periods.

Patient and Clinic Covariates

As described in Aim 1, covariates were considered for adjustment if they were determined, *a priori,* to be associated with the outcome of interest. In addition to the covariates examined in Aim 1, we also considered the patient's self-reported previous HIV testing history (yes/no) and self-reported risk profile. A combination variable that included gender and self-reported sexual risk factors was created, yielding the following categories: female, male heterosexual, and man who had sex with other men (MSM). These risk groups were selected for this variable based on the key risk groups in North Carolina.[40] We expected the unadjusted, crude effect estimate to be the most valid, but tested sets of covariates for model inclusion (patient covariates [gender, race/ethnicity, age, previous HIV test, risk behaviors], clinic covariates [metropolitan status, population density, percentage of the county living below the poverty line, presence of an in-house HIV clinic, baseline HIV case rate], patient and clinic covariates) using likelihood ratio tests in nested models with an a priori significance level of 0.10.

Data Analysis

Preliminary Descriptive, Univariate, and Bivariate Analyses

Descriptive and graphical analyses of progression to AIDS within 1, 6, 12, and 18 months provided an overview of all HIV-infected cases. As described in Aim 1, the frequency and distributions of all variables (exposure, outcome, and covariates) were assessed using tabular and graphical representations. Bivariate associations of potential covariates by exposure level (pre- or post-intervention) were also presented descriptively

using counts and frequency distributions. Chi-square statistics were calculated to describe differences in covariate distributions by exposure level.

Assessing Missing Data

As noted in Aim 1, missing data may be present in set of covariates. Given the small proportion of study subjects missing individual-level covariate information (age, sex, race/ethnicity, previous HIV test, risk group; n=39, 3.1% of patients with a new HIV diagnosis), a complete case analysis was conducted. The final analysis cohort included 1203 persons newly diagnosed with HIV during the study period.

Multilevel Models: Rationale and Design

As described in the analysis plan for Aim 1, the patients in this dataset were naturally clustered within STD clinics, which introduces a correlation structure that violates the independence assumption of traditional generalized linear models.[104,105] The correlation that exists within and between STD clinics was accounted for with multilevel modeling. The structure of the multilevel models used in this aim mirrored those described in the Aim 1 analysis plan with a county-specific random-intercept model as a base case model structure. Fixed effects models that lacked random effects components were explored in sensitivity analyses.

Multilevel Models: Outcomes

Based on national and local surveillance data, we estimated the proportion of persons who would progress to AIDS within 12 months of their initial HIV diagnosis be approximately 10-30%. As such, a binomial regression model was used to calculate risk ratios (RR). The overall beta coefficient for the model represented the expected change in the log risk of progression to AIDS within a specific time period with the implementation of

the intervention in all STD clinics in North Carolina. Facility-specific beta coefficients were not evaluated.

All results were stratified by patient and clinic characteristics to identify trends in specific population subgroups. Stratified estimates were obtained with interaction terms. The interaction terms were tested for significance using likelihood ratio tests at an a priori significance level of 0.10.

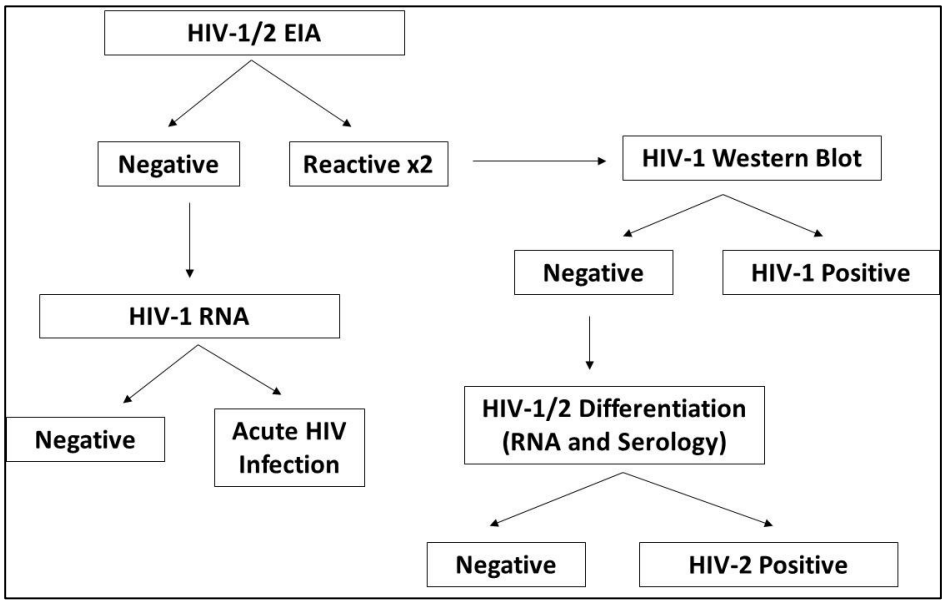
All statistical analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).[106]

Tables and Figures

Table 3.1: Data Sources

Data Source	Variables
NC State Laboratory of Public Health	HIV test results Patient demographics (age, gender, race, risk factors for HIV acquisition, previous HIV testing history)
Electronic HIV/AIDS Reporting System (eHARS)	Distinguish new or previously-known positives Date of AIDS diagnosis
US Census Bureau	Metropolitan/Micropolitan Statistical Areas County population density Percentage of county living below poverty line
North Carolina HIV/AIDS Surveillance Reports	Estimated HIV/AIDS incidence in clinic region
Facility-Specific Data	Joint HIV/STD clinic

Figure 3.1: North Carolina State Lab of Public Health HIV Testing Algorithm



CHAPTER 4: IMPACT OF A ROUTINE, OPT-OUT HIV TESTING PROGRAM ON HIV TESTING AND CASE DETECTION IN NORTH CAROLINA SEXUALLY-TRANSMITTED DISEASE CLINICS

Introduction

In the United States, approximately 20% of people infected with HIV are unaware of their HIV-infected status; disease transmission from these individuals accounts for 50% of new HIV infections.[3,5] Effective HIV testing programs are essential to identify HIV-infected persons and enroll them in medical care, thereby slowing disease progression and reducing further HIV transmission.[18,22] In 2006, the Centers for Disease Control and Prevention (CDC) recommended routine, opt-out HIV testing in clinical settings.[1] From 2007 through 2010, testing programs funded by the CDC's expanded HIV testing initiative performed 2.8 million HIV tests and identified over 18,000 new HIV-infected cases.[2] However, these cases represent only a small fraction of the approximately 150,000 new HIV infections acquired over the same period.[6]

Routine, opt-out HIV testing can be feasible to implement and acceptable to both patients and providers.[7,9,10] Although the number of HIV tests performed increases with the introduction of an expanded HIV testing program, the impact on the identification of new HIV-infected cases has been inconclusive. While some expanded HIV testing programs showed an increase in case detection, others showed a decrease or no change.[7,9,13,62,63,65,110-112] These programs have been limited by small numbers and a focus on clinical settings with minimal HIV testing prior to implementation.

We conducted a statewide, before-after analysis of a routine, opt-out expanded HIV testing program in all 102 North Carolina sexually transmitted disease (STD) clinics. North

Carolina, like many southeastern states, bears a large burden of HIV infection and STDs.[14] The program's impact was measured by the number of HIV tests performed and new detection of HIV-infected cases. We aimed to determine the incremental impact of an expanded HIV testing program in a clinical setting with a high baseline level of HIV testing.

Methods

Study Population & Setting

This study included all patients aged 18-64 years who were tested for HIV in North Carolina's 102 county-level STD clinics from July 1, 2005 through June 30, 2011. Non-North Carolina residents and patients lacking an HIV test result were excluded from analysis (n=1,149 of 414,015 HIV tests).

Patients who agreed to HIV testing had blood samples drawn and, along with a form with patient demographic information, processed at the North Carolina State Laboratory for Public Health (SLPH). At the SLPH, the samples were tested for HIV antibodies using a 3rd generation enzyme immunoassay (EIA); all reactive samples were confirmed via Western Blot. EIA-negative samples were pooled for acute HIV testing by polymerase chain reaction for viral RNA. Test results and demographic information were entered into the SLPH HIV testing database; results were provided to the patient in a follow-up STD clinic visit. All patients with a positive HIV test were checked for a previous entry in the state HIV surveillance database, the electronic HIV/AIDS reporting system (eHARS). If no prior record existed, the patient was entered into eHARS as a new HIV-infected case. Patient-level data for this analysis were collected by linking the SLPH and eHARS electronic surveillance databases by a unique HIV testing identifier.

Intervention: Expanded HIV Testing Program

The North Carolina Expanded HIV Testing Program was introduced in November 2007, with a focus on routine, opt-out HIV testing in clinical settings. Because of the high-risk patient population, HIV testing was already quite common in STD clinics.[113] Therefore, unlike lower risk clinical populations, the expanded HIV testing program in STD clinics focused on providing routine screening to *all* STD clinic patients.

Exposure Definition

The intervention was implemented on November 1, 2007. We assumed a lag period of 3 months from the start date of the intervention to full implementation. Therefore, in regression analyses, persons tested for HIV prior to November 1, 2007 were considered "unexposed" to the expanded HIV testing program; persons tested for HIV after February 1, 2008 were considered "exposed". This lag period was varied from 0 to 6 months in sensitivity analyses (Table A2.6, Table A2.9).

Outcome Assessment

Two primary outcomes were evaluated: HIV testing and the new detection of HIV-infected cases. HIV testing was measured as the number of HIV tests performed, as well as the HIV testing rate per 100,000 persons, based on annual intercensal population estimates (Table A2.7).[114] Case detection was measured as both the number of new HIV-infected cases and HIV-positivity per 1000 HIV tests.

A new case of HIV infection was defined as a patient with a positive HIV test in the same calendar month as the person's diagnosis date in eHARS. This window period accounted for possible reporting delays and uncertainty regarding patients who lacked an exact date of HIV diagnosis; these patients were assigned to the 15th day of their diagnosis month. This approximation recoded 69 HIV-infected cases as newly-diagnosed, when they

otherwise would have been considered a previous diagnosis (3.3% of patients with a positive test result, 0.009% of the total study population).

Patient demographics at the time of HIV testing were abstracted from the SLPH database and included gender (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), and age. STD clinics were categorized by population density (<199, 200-399, 400-599, ≥600 persons per square mile), metropolitan/micropolitan statistical areas (MeSA, MiSA, neither), and proportion of the county living below the poverty line (<15%, 15-19.9%, 20-24.9%, ≥25%).[95-97] A baseline HIV rate was calculated as he average number of reported HIV cases per 100,000 from 2005 through 2007 (categorized for analysis as 0-4.9, 5-9.9, 10-14.9, ≥15).[115] A dichotomous variable identified the presence or absence of an in-house HIV clinic; STD clinics with an in-house HIV clinic were Durham, Mecklenberg, and Wake Counties.

Statistical Analysis

Descriptive analyses were used to examine trends in HIV testing and case detection before and after the introduction of the intervention. Multivariate regression analyses were conducted with two distinct approaches: interrupted time series analyses and multilevel modeling. Given the small proportion of study subjects missing individual-level covariate information (age, sex, race/ethnicity; n=9961, 2.4% of patients with a valid HIV test result), a complete case analysis was conducted. The final analysis cohort included 402,774 unique HIV tests performed over 72 monthly time points.

Interrupted time series methods, specifically autoregressive integrated moving average (ARIMA) models, were applied to serial monthly cross-sections of HIV testing data. Because HIV testing in one month is dependent on testing in the prior month and influences testing in subsequent months, we used ARIMA models to account for underlying temporal correlation between parameter estimates and their residual errors. This method describes

the trend (slope) of an outcome over time, and how this trend changes with the introduction of an intervention. We identified parameters representing the (a) pre-intervention intercept, (b) pre-intervention slope, (c) overall post-intervention slope, and (d) change in slope attributable to the intervention. Mean differences (MDs) and corresponding 95% confidence intervals (95% CIs) were calculated for all patients and stratified by patient- and clinic-level characteristics.

To evaluate the overall association between the intervention and the rate of HIV testing per 100,000 population, we used Poisson regression to calculate rate ratios and 95% CIs. The rate denominator was created from annual intercensal population estimates. To broadly adjust for time trends, models were also adjusted for calendar year.

Fixed slope random intercept multilevel regression models were used to evaluate the intervention's impact on HIV case detection, while accounting for clustering by STD clinic. Intercepts were allowed to vary to accommodate different county-level HIV risk levels. In sensitivity analyses, we compared the random-intercept models to models without county - level clustering (Table A2.8). Since HIV-positivity is a rare outcome, we used logistic regression to calculate odds ratios (ORs), corresponding 95% CIs, and confidence limit ratios.

With an externally-determined time point as the demarcation between the exposed and unexposed periods, measured covariates were not associated with the "exposure" (intervention) and could not be confounders. To address potential differences in the covariate distributions over time, the multilevel model was adjusted for patient- and clinic-level characteristics (Table 4.1). An indicator for calendar year was added to broadly account for underlying time trends.

All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).[106] This study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill.

Results

Patient Demographics

Pre-intervention, 128,029 HIV tests were performed, of which 426 (0.33%) were new HIV-infected cases. In the post-intervention period, 274,745 HIV tests were performed, detecting 816 (0.30%) new HIV-infected cases (Table 4.1).

Just over half of the tested patients were female, although more female patients were tested in the post-intervention phase (51.8% vs. 54.9%). The proportion of non-Hispanic black patients increased from 53.18% to 58.40%, while the proportion of non-Hispanic white, Hispanic, and other race/ethnicity decreased. The age distribution of patients receiving an HIV test did not change over the study period. Few changes in clinic-level characteristics were observed between the pre- and post-intervention periods.

Number of HIV Tests Performed

In July 2005, the baseline number of HIV tests performed per month was 3832. Prior to the intervention, the number of HIV tests performed per month increased at a rate of 55 tests per month (95% CI: 41, 72), or an increase of 0.81 tests per 100,000 persons per month (Figure 4.1; Table A2.2, Table A2.3). Post-intervention, the monthly increase in the number of tests slowed to 34 tests per month (95% CI: 26, 42), or an increase of 0.46 tests per 100,000 persons per month. Compared with the monthly rate of HIV testing predicted in the absence of the intervention, the monthly rate of HIV testing attributable to the intervention decreased by 20 tests per month (95% CI: -37, -5) or -0.35 tests per 100,000 persons per month.

This overall trend in HIV testing was driven by specific demographic subpopulations (Table 4.2; Table A2.2, Table A2.3). Decreases in the rate of HIV testing per 100,000 population per month attributable to the intervention were observed among males (MD=-

0.45, 95% CI: -0.70, -0.21), non-Hispanic blacks (MD=-1.57, 95% CI: -2.34, -0.80), Hispanics (MD=-1.55, 95% CI: -2.19, -0.92), and patients in the youngest age categories (18-24 years; MD=-1.34, 95% CI: -2.07, -0.61; 25-34 years: MD=-0.54, 95% CI: -1.03, -0.05). Decreases in the rate of HIV testing per month attributable to the intervention were also pronounced in clinics located in counties of high population density (MD=-0.63, 95% CI: -1.0, -0.25) and high baseline HIV case rates (MD=-0.74, 95% CI: -1.1, -0.40).

Unadjusted Poisson models identified an increase in the rate of HIV testing associated with the intervention (rate ratio=1.33; 95% CI: 1.32, 1.34). However, after adjustment for calendar year, the association was inverted (rate ratio=0.88; 95% CI: 0.85, 0.91) and in agreement with the interrupted time series results, which showed a slight negative association.

New HIV-Infected Cases

The baseline number of new HIV-infected cases detected was 13.82 per month (95% CI: 10.82, 16.82), or 3.59 cases per 1,000 HIV tests per month (95% CI: 3.05, 4.12; Figure 4.1, Table A2.4, Table A2.5). Little temporal trend in HIV-positivity per 1000 tests per month was observed in either the pre- or post-intervention time periods (pre-intervention MD=-0.02; 95% CI: -0.05, 0.02; post-intervention MD=0.00, 95% CI: -0.02, 0.02).

Despite the lack of a significant trend in HIV-positivity, the expanded HIV testing program did slightly mitigate the negative slope observed prior to the intervention (MD=0.01, 95% CI: -0.02, 0.05; Table 4.3, Table A2.4, Table A2.5). This mitigation was driven by increases in monthly case detection rates attributable to the intervention among females (MD=0.03, 95% CI: 0.01, 0.07) and non-Hispanic black patients (MD=0.05, 95% CI: 0.00, 0.10). Slight increases in the rate of case detection per month attributable to the intervention were also observed in clinics without an in-house HIV clinic (MD=0.03, 95% CI: -0.02, 0.07), and in counties with moderate levels of poverty and high baseline rates of HIV.

Based on the unadjusted multilevel regression model, the introduction of the expanded HIV testing program was associated with a 0.11% reduction in HIV-positivity (OR=0.89, 95% CI: 0.79, 1.00; Table 4.4). The inclusion of patient-level covariates slightly attenuated this association, but did not alter precision (OR=0.93, 95% CI: 0.82, 1.05). Adjustment of the multilevel model for calendar year attenuated the observed association completely to the null (OR=1.02, 95% CI: 0.69, 1.52) and adversely effected precision.

Discussion

Despite the CDC's recommendation for routine, opt-out HIV testing in clinical settings, the impact of expanded HIV testing programs is unclear.[1,7,9,13,62,63,65,110-112] We evaluated HIV testing and case detection of a routine, opt-out HIV testing program in North Carolina STD clinics using a before-after intervention analysis. Due to a consistent increase in HIV testing prior to the intervention, the incremental impact of the expanded HIV testing program was minimal.

In the post-intervention phase, the monthly rate of HIV testing increased, but at a slower rate than before the intervention. This attenuation was driven primarily by a slower increase in the rate of HIV testing among patients regularly targeted for testing (males, non-Hispanic blacks, Hispanics, younger patients) and increased testing rate attributable to the intervention in populations not traditionally considered at high-risk for HIV (females, non-Hispanic whites).[6,116]

Although the change in HIV testing rates attributable to the intervention among traditionally high-risk patients decreased, the overall rate of HIV testing per month continued to increase. HIV testing is an outcome bounded by the size and capacity of the STD clinic and cannot increase infinitely. By expanding HIV testing services, we believe that the intervention will eventually allow for a higher maximum level of HIV testing to be reached than would have been observed without the intervention.

Among Hispanics, the overall post-intervention rate of HIV testing decreased. This result is concerning: in the Hispanic community, HIV prevalence is high and many barriers complicate HIV prevention.[40,117] However, underlying changes in the migrant Hispanic population due to poor employment in the economic downturn in 2008, which coincided with the post-intervention period, could explain this result. If the overall population of migrant Latino workers decreased, they would be removed disproportionately from the numerator of STD clinic clients but not from the intercensal population-based denominator, which could artificially decrease HIV testing rates.

Since the greatest increase in HIV testing was among persons at lower risk for HIV acquisition, the incremental increases in case detection were minimal. This minimal impact indicates that providers were already successfully identifying HIV-infected persons without the intervention. Increases in case detection rates attributable to the intervention were observed in populations with increased HIV testing (females) and populations that reflect HIV epidemic trends in North Carolina (non-Hispanic blacks).

The small magnitude of the increase in HIV testing is consistent with evaluations of HIV testing programs in other settings with high baseline levels of HIV testing. In a single Denver STD clinic, HIV testing only increased 1.2% because 79% of patients tested for syphilis were already being tested for HIV before the intervention.[63] Expectations of an HIV testing intervention's magnitude should be tempered by the limits of the setting, which can be dictated by pre-existing HIV testing and case detection levels.

The impact of expanded HIV testing programs on case detection is inconclusive. Interventions have led to both increases and decreases in case detection.[7,9,13,62,63,65,110-112] By examining the trajectory of case detection for over 2 years prior to the intervention, we were able to detect a declining trend prior to the intervention. This decline was followed by a steady rate of case detection during the post-intervention phase, driven by increased diagnoses in certain population groups.

Nearly all extant evaluations of HIV testing programs reduced the pre-intervention level of HIV testing and case detection to a cross-sectional measure. A program in San Francisco was evaluated with a dynamic pre-intervention comparison, but was implemented in an urban setting with a low level of pre-intervention HIV testing and lacked generalizability.[112] A static measure of baseline HIV testing would not adequately capture pre-existing trends in HIV testing or case detection. In our evaluation, using a cross-sectional or aggregate measure of HIV testing without adjusting for calendar year overestimated the impact of an HIV testing intervention. An aggregate measure of case detection underestimated the impact of the intervention, even showing a spurious negative association.

Interrupted time series and multilevel regression analyses answer complementary research questions. Interrupted time series analysis addresses the change in the rate of an outcome over time and is an ecologic method; the unit of analysis is the cross-sectional calendar month. Although we urge caution in the over-interpretation of ecologic analyses, the agreement between the interrupted time series and multilevel regression models including calendar year strengthens our confidence in the interrupted time series results. We could not directly account for unmeasured covariates, such as changing perceptions of HIV, HIV-related stigma, and shifting disease dynamics. However, our study's "quasi-experimental" design should account for many unmeasured covariates.

The use of routinely-collected public health surveillance data allowed us to evaluate this intervention throughout North Carolina, without redirecting resources from public health activities. This rich data source led to a larger study population than would have been feasible in a standard research environment or if analyses were restricted to a single clinical facility. However, surveillance data are not collected for research purposes and the completeness and accuracy of records and data elements cannot be verified.

Despite the disproportionately high burden of HIV in the southeastern United States, this study is the first to evaluate an expanded HIV testing program in the region using a comparison group.[54,72-75] HIV prevention interventions in the South face unique challenges due to the high rates of comorbid conditions, socioeconomic disparities, and a stark contrast between urban and rural areas, which contribute to HIV-related stigma and difficulty accessing HIV medical care.[76]

In North Carolina STD clinics, the introduction of a routine, opt-out expanded HIV testing program did not significantly alter the trajectory of HIV testing or case detection. Given the bounded nature of these outcomes, these results are not surprising. We believe that, due to the increased population eligible for HIV testing, this intervention allowed for the HIV testing saturation point to settle at higher level than would be observed without the intervention. We also identified slight increases in case detection that mitigated a pre-intervention decline in identification of new HIV-infected cases. As HIV testing of the highest-risk populations was already very successful in the STD clinics, the incremental impact of expanding testing to lower-prevalence populations was marginal.

Tables and Figures

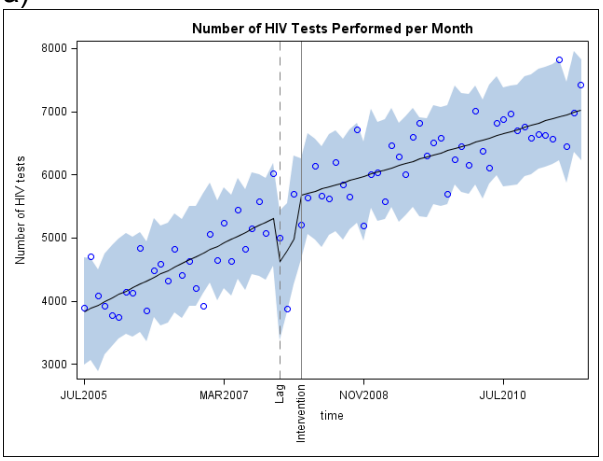
Table 4.1: Demographic and Clinic-Level Characteristics of Persons Tested for HIV in North Carolina STD Clinics, July 2005 through June 2011

	Total N=402,774		Pre-Intervention (7/2005-10/2007) N=128,029		Post-Intervention (11/2007-6/2011) N=274,745	
	n	(%)	n	(%)	n	(%)
Result						
New Positive	1,242	(0.31)	426	(0.33)	816	(0.30)
Not New Positive	401,532	(99.69)	127,603	(99.67)	273,929	(99.70)
Patient Covariates						
Gender						
Male	185,714	(46.11)	61,743	(48.23)	123,971	(45.12)
Female	217,060	(53.89)	66,286	(51.77)	150,774	(54.88)
Race/Ethnicity						
White Non-Hispanic	116,230	(28.86)	39,342	(30.73)	76,888	(27.99)
Black Non-Hispanic	228,538	(56.74)	68,081	(53.18)	160,457	(58.40)
Hispanic	35,126	(8.72)	11,113	(8.68)	24,013	(8.74)
Other	22,880	(5.68)	9,493	(7.41)	13,387	(4.87)
Age (years)						
18-24	179,780	(44.64)	56,961	(44.49)	122,819	(44.70)
25-34	129,717	(32.21)	40,803	(31.87)	88,914	(32.36)
35-44	57,295	(14.23)	18,908	(14.77)	38,387	(13.97)
45-64	35,982	(8.93)	11,357	(8.87)	24,625	(8.96)
Clinic Covariates						
Metropolitan Status*						
Metropolitan	300,266	(74.55)	96,327	(75.24)	203,939	(74.23)
Micropolitan	81,054	(20.12)	25,427	(19.86)	55,627	(20.25)
Neither	21,454	(5.33)	6,275	(4.9)	15,179	(5.52)
Population Density#						
<199	135,938	(33.75)	42,106	(32.89)	93,832	(34.15)
200-399	81,262	(20.18)	26,025	(20.33)	55,237	(20.1)
400-599	31,048	(7.71)	10,602	(8.28)	20,446	(7.44)
≥600	154,526	(38.37)	49,296	(38.5)	105,230	(38.3)
% Below Poverty Line						
<15%	70,298	(17.45)	23,275	(18.18)	47,023	(17.12)
15-19.9%	250,865	(62.28)	79,907	(62.41)	170,958	(62.22)
20-24.9%	59,706	(14.82)	17,772	(13.88)	41,934	(15.26)
≥25%	21,905	(5.44)	7,075	(5.53)	14,830	(5.4)
In-House HIV Clinic						
Yes	83,850	(20.82)	27,603	(21.56)	56,247	(20.47)
No	318,924	(79.18)	100,426	(78.44)	218,498	(79.53)
Baseline HIV Rate (2005-2007)^						
0-4.9	18,353	(4.56)	5,912	(4.62)	12,441	(4.53)
5-9.9	62,317	(15.47)	19,975	(15.6)	42,342	(15.41)
10-14.9	78,829	(19.57)	25,595	(19.99)	53,234	(19.38)
≥15	243,275	(60.40)	76,547	(59.79)	166,728	(60.68)

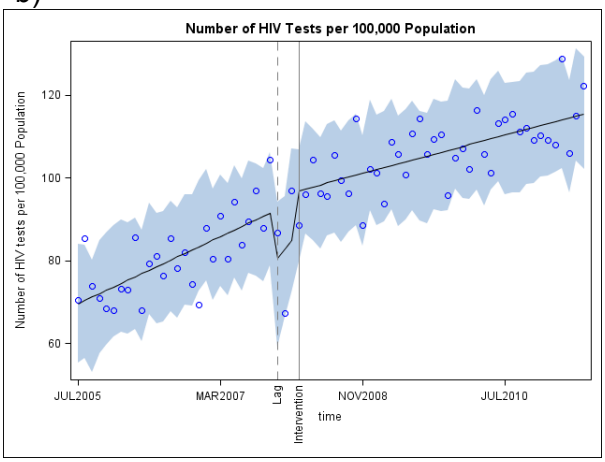
*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas
^Calculated as the average reported HIV case rate per 100,000 population 2005-2007
#per square mile

Figure 4.1: Interrupted Time Series Analysis of Overall Monthly Trends in (a) the Number of HIV Tests, (b) the Number of HIV Tests per 100,000 Population, (c) the Number of New HIV-Infected Cases, and (d) the New HIV-Positivity per 1,000 HIV Tests in North Carolina STD Clinics, July 2005 through June 2011

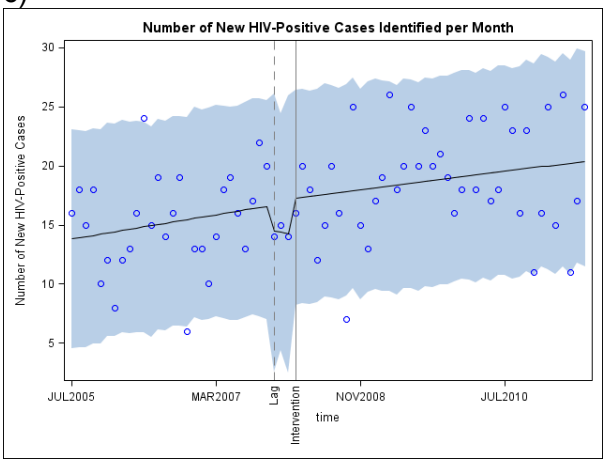
a)



b)



c)



d)

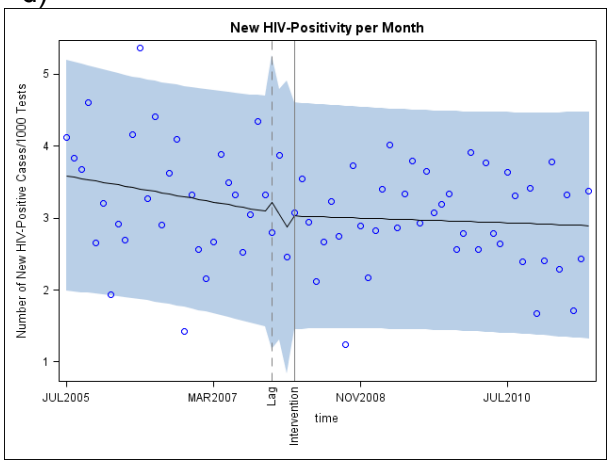
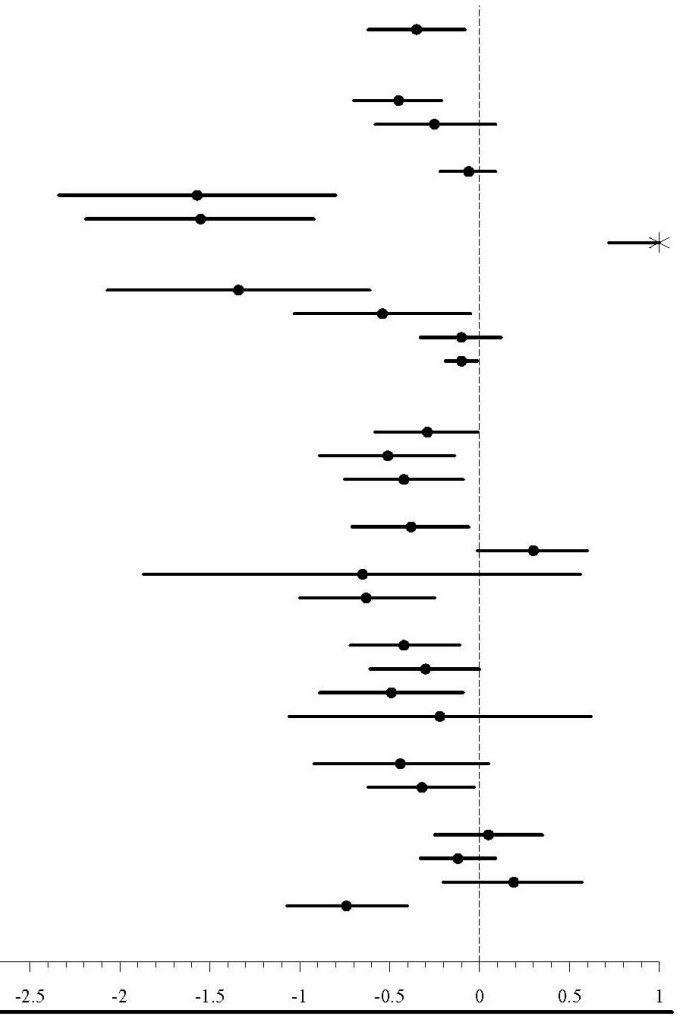


Table 4.2: Monthly Change in the Rate of HIV Tests per 100,000 Population in North Carolina STD Clinics Attributable to the North Carolina Expanded HIV Testing Program, July 2005-June 2011

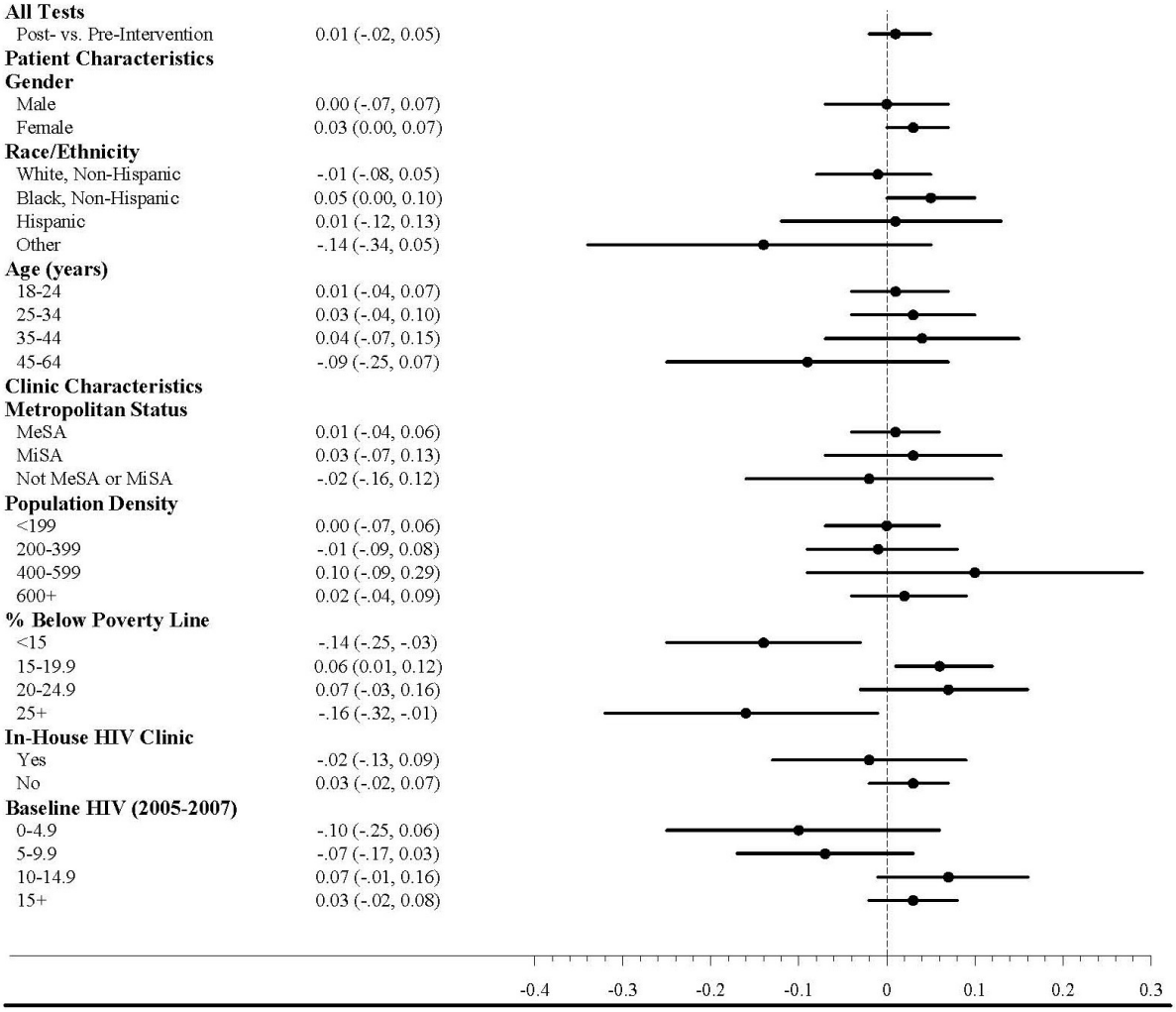
Characteristic	MD (95% CI)
All Tests	
Post- vs. Pre-Intervention	-.35 (-.62, -.08)
Patient Characteristics	
Gender	
Male	-.45 (-.70, -.21)
Female	-.25 (-.58, 0.09)
Race/Ethnicity	
White, Non-Hispanic	-.06 (-.22, 0.09)
Black, Non-Hispanic	-1.6 (-2.3, -.80)
Hispanic	-1.6 (-2.2, -.92)
Other	2.65 (0.72, 4.58)
Age (years)	
18-24	-1.3 (-2.1, -.61)
25-34	-.54 (-1.0, -.05)
35-44	-.10 (-.33, 0.12)
45-64	-.10 (-.19, -.01)
Clinic Characteristics	
Metropolitan Status	
MeSA	-.29 (-.58, -.01)
MiSA	-.51 (-.89, -.14)
Not MeSA or MiSA	-.42 (-.75, -.09)
Population Density	
<199	-.38 (-.71, -.06)
200-399	0.30 (-.01, 0.60)
400-599	-.65 (-1.9, 0.56)
600+	-.63 (-1.0, -.25)
% Below Poverty Line	
<15	-.42 (-.72, -.11)
15-19.9	-.30 (-.61, 0.00)
20-24.9	-.49 (-.89, -.09)
25+	-.22 (-1.1, 0.62)
In-House HIV Clinic	
Yes	-.44 (-.92, 0.05)
No	-.32 (-.62, -.03)
Baseline HIV (2005-2007)	
0-4.9	0.05 (-.25, 0.35)
5-9.9	-.12 (-.33, 0.09)
10-14.9	0.19 (-.20, 0.57)
15+	-.74 (-1.1, -.40)



*MD: Mean Difference, 95% CI: 95% confidence intervals
MeSA/MiSA: defined by the US Census Bureau's metropolitan and micropolitan statistical areas
Baseline HIV (2005-2007): calculated as the average reported HIV case rate per 100,000 population 2005-2007
Population density: per square mile

Table 4.3: Monthly Change in the Rate of New HIV-Positivity per 1,000 HIV Tests Performed in North Carolina STD Clinics Attributable to the North Carolina Expanded HIV Testing Program, July 2005-June 2011

Characteristic	MD (95% CI)
All Tests	
Post- vs. Pre-Intervention	0.01 (-.02, 0.05)
Patient Characteristics	
Gender	
Male	0.00 (-.07, 0.07)
Female	0.03 (0.00, 0.07)
Race/Ethnicity	
White, Non-Hispanic	-.01 (-.08, 0.05)
Black, Non-Hispanic	0.05 (0.00, 0.10)
Hispanic	0.01 (-.12, 0.13)
Other	-.14 (-.34, 0.05)
Age (years)	
18-24	0.01 (-.04, 0.07)
25-34	0.03 (-.04, 0.10)
35-44	0.04 (-.07, 0.15)
45-64	-.09 (-.25, 0.07)
Clinic Characteristics	
Metropolitan Status	
MeSA	0.01 (-.04, 0.06)
MiSA	0.03 (-.07, 0.13)
Not MeSA or MiSA	-.02 (-.16, 0.12)
Population Density	
<199	0.00 (-.07, 0.06)
200-399	-.01 (-.09, 0.08)
400-599	0.10 (-.09, 0.29)
600+	0.02 (-.04, 0.09)
% Below Poverty Line	
<15	-.14 (-.25, -.03)
15-19.9	0.06 (0.01, 0.12)
20-24.9	0.07 (-.03, 0.16)
25+	-.16 (-.32, -.01)
In-House HIV Clinic	
Yes	-.02 (-.13, 0.09)
No	0.03 (-.02, 0.07)
Baseline HIV (2005-2007)	
0-4.9	-.10 (-.25, 0.06)
5-9.9	-.07 (-.17, 0.03)
10-14.9	0.07 (-.01, 0.16)
15+	0.03 (-.02, 0.08)



*MD: Mean Difference, 95% CI: 95% confidence intervals
MeSA/MiSA: defined by the US Census Bureau's metropolitan and micropolitan statistical areas
Baseline HIV (2005-2007): calculated as the average reported HIV case rate per 100,000 population 2005-2007
Population density: per square mile

Table 4.4: Overall Impact of North Carolina Expanded HIV Testing Program on HIV-Positivity using County-Specific Random Intercept Multilevel Regression, North Carolina STD Clinics, July 1, 2005 through June 30, 2011

	County Random Intercept	
	Post-Intervention OR (95% CI)	3-month Lag Period OR (95% CI)
Unadjusted		
Post-Intervention	0.90 (0.80, 1.01)	0.88 (0.64, 1.21)
Pre-Intervention	1.00	1.00
Patient Covariates^		
Post-Intervention	0.92 (0.82, 1.04)	0.89 (0.65, 1.23)
Pre-Intervention	1.00	1.00
Clinic Covariates#		
Post-Intervention	0.90 (0.80, 1.01)	0.88 (0.64, 1.21)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates		
Post-Intervention	0.92 (0.82, 1.04)	0.89 (0.65, 1.23)
Pre-Intervention	1.00	1.00
Year		
Post-Intervention	1.13 (0.57, 2.23)	1.02 (0.69, 1.52)
Pre-Intervention	1.00	1.00
Patient Covariates + Year		
Post-Intervention	1.16 (0.59, 2.28)	1.04 (0.70, 1.55)
Pre-Intervention	1.00	1.00
Clinic Covariates + Year		
Post-Intervention	1.12 (0.57, 2.21)	1.02 (0.68, 1.51)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates + Year		
Post-Intervention	0.92 (0.82, 1.04)	0.89 (0.65, 1.23)
Pre-Intervention	1.00	1.00

OR: odds ratio; 95% CI: 95% confidence interval

^Patient covariates include gender, race/ethnicity, and age

#Clinic covariates include metropolitan status, population density, % below poverty line, affiliated HIV clinic, and baseline HIV rate

CHAPTER 5: RISK OF PROGRESSION TO AIDS AMONG NEWLY-DIAGNOSED HIV-INFECTED PERSONS BEFORE AND AFTER THE INTRODUCTION OF A ROUTINE, OPT-OUT HIV TESTING PROGRAM IN NORTH CAROLINA SEXUALLY-TRANSMITTED DISEASE CLINICS

Introduction

Persons who do not perceive themselves to be at risk for acquiring HIV infection may not seek HIV testing, leading to delays in HIV diagnosis.[118] Delays in HIV diagnosis, and subsequent delays in treatment, can lead to poor health and decreased quality of life, as well as a greater chance of transmission to others.[18,22] Approximately 50% of new HIV infections in the United States each year are attributable to the 20% of persons living with HIV who are unaware of their infection.[3,5]

In 2006, the Centers for Disease Control and Prevention (CDC) recommended routine, opt-out HIV testing in clinical settings to provide HIV testing services to all persons, regardless of self- or provider-perceived risk.[1] By reducing "missed opportunities" for HIV testing in clinical settings, the goal of these recommendations was to increase status awareness and identify HIV-infected persons earlier in the course of infection.[1,16]

Despite these recommendations, many persons continue to be diagnosed with HIV infection late in the course of disease. Nationally, 32.5% of persons diagnosed with HIV develop AIDS within 1 year of their HIV diagnosis.[15] In the absence of HIV therapy, most HIV-infected persons progress to clinical AIDS within 10 years of HIV seroconversion.[27] Therefore, persons who progress to AIDS within 1 year of their HIV diagnosis could have been infected with HIV but unaware of their infection for approximately 9 years. Late HIV diagnosis is most common among males, persons of older ages, racial/ethnic minorities and those infected via heterosexual transmission.[119-121] These subgroups may experience

barriers in accessing healthcare, HIV-related stigma, and low perceived risk of HIV acquisition.

The impact of routine, opt-out HIV testing programs regarding program impact on immunologic status at diagnosis are inconclusive.[7,8,11,13,66,67] However, these evaluations were limited in their scope to HIV testing programs in single facilities, were not linked with surveillance data, and could not describe disease progression following diagnosis.

We conducted a statewide evaluation of the impact of a routine HIV testing program on the risk of progression to AIDS of newly-identified HIV-infected persons in North Carolina sexually transmitted disease (STD) clinics. We aimed to determine if this routine, opt-out HIV testing program successfully reached the population of persons who do not perceive themselves to be at risk for HIV acquisition and would otherwise not seek HIV testing.

Methods

Study Population and Setting

This study included all North Carolina residents aged 18-64 who were identified as new HIV-infected cases in North Carolina STD clinics from July 1, 2005 through June 30, 2011.

A new HIV-infected case was defined as a person with a positive HIV test result in the same calendar month as the person's surveillance-recorded HIV diagnosis date. HIV test and HIV/AIDS diagnosis dates were abstracted from the electronic HIV/AIDS reporting system (eHARS), the surveillance database of all HIV-infected persons in North Carolina.

The HIV testing protocol in the North Carolina STD clinics has been described in detail elsewhere (Chapter 3). Briefly, blood samples and demographic information were collected for patients who agreed to HIV testing and processed in the North Carolina State Laboratory for Public Health (SLPH). All test results and demographic information were entered into the SLPH database and results were provided to patients. If a person tested

positive and no previous record existed in eHARS, the patient was entered into the surveillance system as a new case of HIV. Patient-level data were collected by linking the SLPH and eHARS electronic surveillance systems in December 2012, allowing for at least 18 months of follow-up data on all HIV-infected persons.

Intervention: Expanded HIV Testing Program

In November 2007, the North Carolina expanded HIV testing program was introduced, in conjunction with a modification of the state's administrative code to allow for routine, opt-out HIV testing. This HIV testing program included guidelines for routine HIV screening in North Carolina STD clinics. Since the patient population in STD clinics is at a high risk for HIV acquisition, HIV testing was already performed frequently.[113] This analysis focuses on the incremental impact of offering routine HIV screening to all STD clinic patients.

Exposure Definition

The intervention was implemented on November 1, 2007. All new HIV-infected cases identified before this date were considered "unexposed" to the intervention, those tested after were "exposed". In sensitivity analyses, we explored the inclusion of 3- or 6-month lag periods to allow for full implementation of the intervention (Table A3.5).

Outcome Assessment

"Late HIV diagnosis" is a broad term that describes persons who were diagnosed in, or quickly progressed to, an immune-compromised HIV-related state. Using the dates of HIV and AIDS diagnosis from eHARS, we constructed 4 definitions that capture progression to AIDS. AIDS diagnosis was dependent on clinical presentation with an opportunistic infection or a measured CD4 count <200 (or 14%).[40]

The primary outcome definition was chosen, in agreement with CDC definitions, to be an AIDS diagnosis within 12 months of HIV diagnosis.[15] Three additional definitions were also considered: AIDS within 1 month, 6 months, and 18 months. To account for possible reporting delays and for persons lacking an exact date of HIV diagnosis, a 15 day period was added to each outcome definition (1 month + 15 days, 6 months + 15 days, etc.).

Covariate Assessment

Patient-level covariates were abstracted from the SLPH databases at the date of HIV testing and included gender (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), age and previous HIV testing (yes, no). A covariate that combined information on both the patient's gender and self-reported sexual risk factors was created (female, heterosexual male, men who have sex with men [MSM]). Sexual risk factors, particularly identifying MSM, were selected for inclusion because the majority of HIV transmission in North Carolina is driven by heterosexual and MSM transmission.[40]

Clinic-level covariates were abstracted from publically-available datasets and included population density (<199, 200-399, 400-599, ≥600 persons per square mile), metropolitan/micropolitan statistical areas (MeSA, MiSA, neither), and proportion of the county living below the poverty line (<15%, 15-19.9%, 20-24.9%, ≥25%).[95-97] To account for underlying burden of HIV in each county, the number of reported HIV cases per 100,000 persons were averaged from 2005 through 2007 to determine a baseline HIV rate (categorized for analysis as <10, 10-14.9, ≥15).[115] A covariate that identified STD clinics that housed a clinic dedicated to HIV care (Durham, Mecklenberg, and Wake Counties) was also created.

Statistical Analyses

Descriptive analyses were used to examine overall trends in late HIV diagnosis before and after the introduction of the expanded HIV testing program. The association between the introduction of the intervention and risk of progression to AIDS was examined with multilevel regression models to account for STD clinic clustering using a random-intercept term unique to each STD clinic. In sensitivity analyses, these fixed-slope random intercept models were compared with models that do not allow for clustering between clinics (Table A3.4). We used binomial regression models calculate risk differences (RDs) and risk ratios (RRs), with corresponding 95% confidence intervals (95% CIs) for progression to AIDS.

Based on national surveillance data showing that the overall risk of late HIV diagnosis has not changed drastically over time, we assumed that we would not observe a time trend in our outcomes beyond the impact of our dichotomized intervention.[15,122,123] However, in sensitivity analyses, we also tested models that broadly account for temporal trends in over the study period using both indicator variables and a linear term for study year (Table A3.2).

As the intervention (exposure) was determined externally and implemented uniformly across North Carolina, the intervention should be independent of all patient- and clinic-level covariates. Over the study period, there were no significant changes in HIV-related definitions, clinical practice, or policies. This quasi-experimental design should negate traditional confounders. Nonetheless, we examined the impact of accounting for patient- and clinic-level covariates in multivariate regression.

In addition to the overall effect of the intervention on late diagnosis, we examined the impact of the intervention in strata of patient (gender, gender/risk, race/ethnicity, age, previous HIV test), and clinic (metropolitan status, population density quartiles, percent below poverty line quartiles, affiliated HIV clinic, baseline HIV case rate tertiles) subgroups.

Stratified estimates were compared using confidence limit ratios and interaction terms were evaluated using likelihood ratio tests at an *a priori* alpha level of 0.10.

All statistical analyses were performed in SAS version 9.2.[106] The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Results

From July 1, 2005 through June 30, 2011, 1203 persons were identified as new HIV-infected cases in North Carolina STD clinics. Of these persons, 12% and 13% were diagnosed with AIDS within 12 months of their initial HIV diagnosis in the pre- and post-intervention periods, respectively (Tables 5.1). Approximately 5% of persons were diagnosed with AIDS within 1 month of their HIV diagnosis and over 14% of persons were diagnosed with AIDS within 18 months of their HIV diagnosis (Table 5.2).

Nearly 80% of newly-diagnosed persons were male, including approximately 45% MSM (Table 5.1). Over 65% of HIV-infected persons were non-Hispanic black and 35% were under 25 years of age at the time of their HIV diagnosis. Over 70% of newly-diagnosed HIV-infected persons reported an HIV testing experience prior to their diagnosis.

The proportion of male HIV-infected cases increased over the study period, from 75% in the pre-intervention period to 82% in the post-intervention period. The proportion of non-Hispanic black persons increased from 61% to 70%, with a decline in the proportion of persons of other racial and ethnic backgrounds. A larger proportion of HIV-infected persons were diagnosed in low population density counties (<199 per square mile) in the post-intervention period, compared with the pre-intervention period (pre-intervention: 18%, post-intervention: 28%).

Overall, we did not observe evidence of an association between the introduction of the expanded HIV testing program and the risk of progression to AIDS within 12 months of HIV diagnosis (Table 5.3). Compared with the pre-intervention period, the risk of

progression to AIDS within 12 months of HIV diagnosis was 0.006 higher (RD = 0.006, 95% CI: -0.033, 0.044), or 1.04 times greater (RR = 1.04, 95% CI: 0.77, 1.43), in the post-intervention period. Since adjustment for patient- and clinic-level characteristics did not alter the results, we found little evidence for confounding by measured covariates. Adjustment for calendar year of HIV testing also did not change the estimates, but was accompanied by a loss of precision (Table A3.2). Point estimates of the risk ratios differed slightly with each definition of "late HIV diagnosis", the overall substantive interpretation of the results did not change. However, the intervention was associated with a slight increase in risk of progression to AIDS within 1 month of HIV diagnosis (RR = 1.23, 95% CI: 0.75, 2.01).

Although we did not observe an overall association between the intervention and the risk of late diagnosis in the entire study population, stratification by patient-level characteristics suggested differences by subgroups (Table 5.4). Among women, the introduction of the intervention was associated with an increased risk of progression to AIDS (RR=2.32, 95% CI: 1.06, 4.83). Further analysis revealed that the risk progression to AIDS among women was relatively low in the pre-intervention period, peaked in 2008 and 2009, then slightly decreased in 2010 and 2011(Table A3.7). Among men, the introduction of the intervention was associated with a slight decrease in risk of progression to AIDS (RR=0.86, 95% CI: 0.61, 1.22).

Persons who, according to self-report, had previously been tested for HIV were different from those who had not previously been tested. The intervention was associated with an increase in late HIV diagnosis among persons who had previously been tested for HIV (RR=1.42, 95% CI: 0.92, 2.19), but a decrease among persons who had not been previously tested for HIV (RR=0.67, 95% CI: 0.43, 1.06).

As the definition of late HIV diagnosis was broadened to AIDS within 6 months of HIV diagnosis and beyond, these stratum-specific differences were attenuated towards the null. Stratification by other patient- and clinic-level covariates did not identify other

population subgroups with unique associations between the intervention and late HIV diagnosis (Table A3.6).

Discussion

The CDC's recommendations for routine, opt-out HIV testing were driven by a desire to increase status awareness and diagnose persons earlier in the course of infection by reducing missed HIV testing opportunities in clinical settings.[1,16] Following these recommendations and the introduction of many expanded HIV testing programs, the impact of HIV testing interventions on the timing of HIV diagnosis is unclear.[7,8,11,13,66,67] In North Carolina STD clinics, the introduction of a routine, opt-out expanded HIV testing program did not change the risk of progression to AIDS.

Although no overall association was detected between the intervention and progression to AIDS, stratification by gender and previous HIV testing status revealed important associations. Among women, the intervention was associated with an increased risk of progression to AIDS. Women are not traditionally seen as particularly high-risk for HIV acquisition; in the absence of HIV testing interventions, men are more often diagnosed in poorer immunological states than women .[16,86,107,108,119,120,123-126]

This intervention may have succeeded in identifying women with advanced HIV disease who would otherwise have not been identified in STD clinics, but would have been identified in urgent care or emergency settings. After an initial post-intervention surge in late diagnoses, we would expect this effect to dissipate. Our results support this hypothesis – we observed an increase in the risk of late diagnosis among women in 2008 and 2009, immediately after the intervention. In 2010 and 2011, the risk of late diagnosis decreased, but still settled above pre-intervention levels.

In general, persons testing for HIV in the STD clinic were not naïve to HIV testing; over 70% self-reported a previous HIV test. Although this high level of exposure to HIV

testing may seem promising, among persons self-reporting a previous HIV test, this HIV testing intervention was associated with an increased risk of progression to AIDS. Persons who tested negative on a previous HIV test may feel immune to HIV and continue to engage in risky sexual behavior, while delaying further HIV testing.[25,127-129] This delay in HIV testing could result in an arti-factual increase in late diagnoses in the period immediately following the introduction of the intervention.

Among persons who did not report a previous HIV test, the intervention was associated with a decrease in the risk of progression to AIDS. These persons may not have perceived themselves to be at risk for HIV acquisition, failed to seek out HIV testing, or may not have been identified in risk-based HIV testing.[30,130] This result supports the CDC's hypothesis: if persons are offered HIV testing routinely, they will be detected earlier in the course of infection.

Previous HIV testing status was based on self-report, which may not accurately capture previous HIV testing history.[128,131] Despite this potential for misclassification, self-reported HIV testing history would be more closely linked with self-perceived HIV risk than with actual HIV testing history. If a patient previously visited a clinical facility and had blood drawn but was not informed of an HIV test result, the patient may incorrectly assume that he/she tested negative for HIV .[132] Alternatively, a patient may forget that he/she received an HIV test in a previous medical encounter.[128]

Routine HIV testing programs in emergency departments have been evaluated for impact on immunologic status at diagnosis, but yield inconclusive results. In Oakland, California, the proportion of persons concurrently diagnosed with AIDS increased with the introduction of opt-out HIV testing; in Denver Colorado, the proportion of persons diagnosed with a CD4 count < 350 decreased with a routine HIV testing intervention.[7,13] However, these evaluations were limited by very small numbers of HIV-infected persons and reliance only on laboratory data immediately following HIV diagnosis. Our study expands upon these

previous evaluations with a statewide analysis using surveillance data to capture progression to AIDS in any clinical facility in North Carolina.

The use of surveillance data allowed us to evaluate this research question statewide, without redirecting limited public health resources. Surveillance data are collected for public health, not research, purposes and we cannot verify the accuracy or completeness of the data. The date of AIDS diagnosis was used to determine whether the patient had progressed to AIDS within a specific time period. This measure depended upon the patient seeking contact with a medical provider to receive an AIDS diagnosis, and the subsequent reporting of this diagnosis. Although many HIV-infected persons do not seek routine HIV medical care, the symptoms associated with progression to AIDS should prompt most persons to seek medical attention, which would lead to inclusion in our dataset.[3]

Nationally, 32.5% of persons are diagnosed with AIDS within 12 months of their initial HIV diagnosis; in North Carolina, 26.1% progress to AIDS within 6 months.[15,40] Consistent with national data of late diagnosis and data from other states, we observed a low proportion of STD clinic patients presenting as late diagnoses, with 10.8% progressing to AIDS within 6 months of HIV diagnosis.[15,66,108,133,134] This low prevalence of late HIV diagnosis may be attributable to the generally high-risk status of the patients attending STD clinics, patients with frequent HIV testing during follow-up STD clinic visits, and increased provider awareness of the importance of HIV testing.[113,127]

The success of the CDC recommendations and resultant routine HIV screening programs hinge on the assumption that persons often diagnosed late in the course of their HIV infect have prior clinical visits, or “missed opportunities” for HIV testing.[1] Each missed opportunity is a potential intervention point for HIV testing to reduce the proportion of late diagnoses. Routine HIV testing aims to eliminate those missed opportunities and, using a structural intervention, ensure that persons with low self-perceived HIV risk have access to HIV testing services.

In this study, the overall proportion of persons progressing to AIDS over time did not change with the introduction of a routine, opt-out HIV testing program. This result indicates that the intervention was not successful in identifying the subset of persons who often present late for HIV testing. Contrary to the intentions of routine, opt-out HIV testing, we observed an increase in the risk of progression to AIDS among women and persons with a previous HIV test. Although persons who quickly progressed to AIDS comprised a small proportion of all new HIV diagnoses from the STD clinic, the lack of change in this proportion with this routine HIV testing intervention highlights that these persons do not regularly access the STD clinic healthcare system. Persons who do not seek interactions with the health care system cannot benefit from routine HIV testing programs in clinical settings.

Tables and Figures

Table 5.1: Demographic and Clinic-Level Characteristics of Newly-Identified HIV-Infected Persons in North Carolina STD Clinics, July 2005 through June 2011

	Total N=1203		Pre-Intervention (7/2005-10/2007) N=422		Post-Intervention (11/2007-6/2011) N=781	
	n	(%)	n	(%)	n	(%)
Progression to AIDS within 1 year						
Yes	154	(12.8)	52	(12.3)	102	(13.0)
No	1049	(87.2)	374	(88.7)	679	(86.9)
Clinic Characteristics						
Metropolitan Status*						
Metropolitan	958	(79.6)	350	(82.9)	608	(77.8)
Micropolitan	198	(16.5)	64	(15.2)	134	(17.2)
Neither	47	(3.9)	8	(1.9)	39	(5.0)
Population Density per square mile						
<199	297	(24.7)	78	(18.5)	219	(28.0)
200-399	191	(15.9)	71	(16.8)	120	(15.4)
400-599	163	(13.5)	65	(15.4)	98	(12.6)
≥600	522	(45.9)	208	(49.3)	344	(44.0)
% Below Poverty Line						
<15%	234	(19.4)	96	(22.8)	138	(17.7)
15-19.9%	755	(62.8)	272	(64.4)	483	(61.8)
20-24.9%	158	(13.1)	40	(9.5)	118	(15.1)
≥25%	56	(4.7)	14	(3.3)	42	(5.4)
Affiliated HIV Clinic						
Yes	340	(28.3)	127	(30.1)	213	(27.3)
No	863	(71.7)	295	(69.9)	568	(72.7)
Baseline HIV Rate (2005-2007)^						
<10	145	(12.0)	48	(11.4)	97	(12.4)
10-14.9	173	(14.4)	56	(13.3)	117	(15.0)
≥15	885	(73.6)	318	(75.3)	567	(72.6)

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas
^Calculated as the average reported HIV case rate per 100,000 population 2005-2007

Table 5.2: Progression to AIDS After Initial HIV Diagnosis, Base and Alternative Definitions, among Newly-Identified HIV-Infected Persons in North Carolina STD Clinics, July 1, 2005 through June 30, 2011

	Total n=1203		Pre-Intervention (7/2005-10/2007) n=422		Post-Intervention (11/2007-6/2011) n=781	
	n	(%)	n	(%)	n	(%)
Base Definition						
AIDS within 12 months						
Yes	154	(12.80)	21	(4.98)	49	(6.27)
No	1049	(87.20)	401	(95.02)	732	(93.73)
Alternative Definitions						
AIDS within 1 months						
Yes	70	(5.82)	47	(11.14)	83	(10.63)
No	1133	(94.18)	375	(88.86)	698	(89.37)
AIDS within 6 months						
Yes	130	(10.81)	52	(12.32)	102	(13.06)
No	1073	(89.19)	370	(87.68)	679	(86.94)
AIDS within 18 months						
Yes	171	(14.21)	61	(14.45)	110	(14.08)
No	1032	(85.79)	361	(85.55)	671	(85.92)

Table 5.3: Unadjusted and Adjusted Associations between the Expanded HIV Testing Program and Risk of Progression to AIDS using County-Specific Random Intercept Regression Models

	Base Definition	Alternative Definitions		
	AIDS within 12 months	AIDS within 1 month	AIDS within 6 months	AIDS within 18 months
Adjustment Set	RR (95% CI)*	RR (95% CI)*	RR (95% CI)*	RR (95% CI)*
Unadjusted				
Post-Intervention	1.05 (0.77, 1.43)	1.23 (0.75, 2.01)	0.95 (0.67, 1.33)	0.97 (0.72, 1.29)
Pre-Intervention	1.00	1.00	1.00	1.00
Patient Covariates				
Post-Intervention	0.99 (0.72, 1.36)	1.19 (0.72, 1.95)	0.91 (0.65, 1.29)	0.91 (0.68, 1.21)
Pre-Intervention	1.00	1.00	1.00	1.00
Clinic Covariates				
Post-Intervention	1.01 (0.74, 1.39)	1.22 (0.74, 2.01)	0.91 (0.65, 1.28)	0.93 (0.69, 1.24)
Pre-Intervention	1.00	1.00	1.00	1.00
Patient + Clinic Covariates				
Post-Intervention	0.96 (0.70, 1.32)	1.17 (0.70, 1.94)	0.89 (0.63, 1.25)	0.87 (0.65, 1.17)
Pre-Intervention	1.00	1.00	1.00	1.00

*RR = risk ratio for progression to AIDS within specified time period for persons diagnosed after the introduction of a routine HIV testing intervention (exposed) vs. before (unexposed)
^Patient covariates include gender, race/ethnicity, age, and self-reported previous HIV test
#Clinic covariates include metropolitan status, population density, % below poverty line, affiliated HIV clinic, and baseline HIV rate

Table 5.4: Association between the Expanded HIV Testing Program and Risk of Progression to AIDS, Stratified by Patient-Level Characteristics

	Base Definition	Alternative Definitions		
	AIDS within 12 months RR* (95% CI)	AIDS within 1 month RR* (95% CI)	AIDS within 6 months RR* (95% CI)	AIDS within 18 months RR* (95% CI)
Overall	1.05 (0.77, 1.43)	1.23 (0.75, 2.01)	0.95 (0.67, 1.33)	0.97 (0.72, 1.29)
Stratified Estimates				
Gender				
Male	**0.86 (0.61, 1.22)**	**0.98 (0.57, 1.69)**	**0.77 (0.53, 1.11)**	**0.84 (0.61, 1.16)**
Female	**2.26 (1.06, 4.83)**	**3.00 (0.88, 10.27)**	**2.17 (0.95, 4.93)**	**1.66 (0.86, 3.24)**
Risk Group w/ Gender				
Female	2.26 (1.06, 4.83)	3.01 (0.88, 10.31)	2.17 (0.96, 4.94)	1.66 (0.85, 3.24)
Male Heterosexual	0.78 (0.48, 1.26)	0.89 (0.41, 1.95)	0.75 (0.44, 1.27)	0.77 (0.48, 1.22)
MSM	0.93 (0.57, 1.53)	1.07 (0.49, 2.31)	0.77 (0.46, 1.31)	0.89 (0.57, 1.40)
Race/Ethnicity				
White Non-Hispanic	0.76 (0.35, 1.64)	0.92 (0.29, 2.92)	0.71 (0.32, 1.56)	0.69 (0.32, 1.46)
Black Non-Hispanic	1.23 (0.82, 1.83)	1.70 (0.86, 3.35)	1.09 (0.70, 1.70)	1.10 (0.77, 1.58)
Hispanic	0.56 (0.21, 1.52)	0.22 (0.05, 1.00)	0.56 (0.21, 1.51)	0.49 (0.19, 1.28)
Other	1.08 (0.37, 3.20)	*NE	1.36 (0.42, 4.36)	1.08 (0.37, 3.20)
Age (years)				
18-24	1.24 (0.68, 2.24)	1.78 (0.67, 4.72)	1.13 (0.60, 2.12)	1.21 (0.70, 2.10)
25-34	1.01 (0.58, 1.78)	1.02 (0.45, 2.30)	0.94 (0.51, 1.74)	0.91 (0.54, 1.54)
35-44	1.12 (0.54, 2.34)	4.15 (0.52, 33.22)	1.11 (0.51, 2.43)	0.86 (0.44, 1.70)
45-64	0.80 (0.42, 1.51)	0.65 (0.26, 1.62)	0.61 (0.30, 1.26)	0.81 (0.44, 1.48)
Previous HIV Test				
Yes	**1.42 (0.92, 2.19)**	**1.96 (0.95, 4.03)**	**1.38 (0.86, 2.22)**	**1.19 (0.81, 1.76)**
No	**0.67 (0.43, 1.06)**	**0.69 (0.34, 1.40)**	**0.57 (0.35, 0.93)**	**0.69 (0.45, 1.07)**

*RR = risk ratio for progression to AIDS within specified time period for persons diagnosed after the introduction of a routine HIV testing intervention (exposed) vs. before (unexposed), not adjusted for patient- or clinic-level covariates

Bold = statistically significant interaction term by likelihood ratio test at an a prior alpha level of 0.10

NE = not-estimable due to small numbers

CHAPTER 6: CONCLUSION

Approximately 20% of the 1.1 million persons infected with HIV in the United States are unaware of their HIV infection; these persons contribute to nearly 50% of new HIV transmission events each year.[3-5] To increase awareness of HIV status and identify HIV-infected persons earlier in infection, the CDC released revised recommendations for routine, opt-out HIV testing in clinical settings.[1] From 2007 through 2010, over 1.8 million HIV tests were conducted under the CDC's expanded HIV testing initiative, yielding 18,000 new HIV diagnoses (0.7% positivity).[2] However, these new diagnoses only represent a fraction of the approximately 150,000 new transmission events during the same period.[6]

Despite widespread implementation of these recommendations in clinical settings, the impact of these interventions is inconclusive.[7,8,11-13] Extant program evaluations are limited by descriptive analyses, small numbers, and a focus on emergency departments and clinical settings in major metropolitan centers. These evaluations are not generalizable, especially not to the southeastern United States, which bears a disproportionate burden of HIV infection.[14]

We evaluated the impact of a routine, opt-out HIV testing program in North Carolina STD clinics with a high pre-intervention baseline level of HIV testing for (a) HIV testing, (b) case detection, and (c) progression to AIDS among newly diagnosed persons. Using a before-after intervention analysis, we examined the impact of this intervention in the context of underlying temporal trends. We used statewide HIV surveillance data, resulting in an extremely large study population that was generalizable to STD clinic patients in the entire southeastern region of the United States. Overall, due to high levels of HIV testing success

prior to the intervention, the incremental benefit of this expanded HIV testing program was minimal.

Summary of Findings

HIV Testing

Although the rate of HIV testing increased post-intervention, the increase was less than what was observed prior to the intervention. Prior to the intervention, the number of HIV tests performed per month increased at a rate of 55 tests per month (95% CI: 41, 72), or an increase of 0.81 tests per 100,000 persons per month. Post-intervention, the monthly increase in the number of tests slowed to 34 tests per month (95% CI: 26, 42), or an increase of 0.46 tests per 100,000 persons per month.

Using aggregate measures of HIV testing pre- and post-intervention did not adequately capture the underlying trends in HIV testing over time, identifying a spurious increase in HIV testing with the intervention. However, after roughly accounting for time by adjusting for calendar year, the association was inverted and in agreement with our interrupted time series results described above.

A decrease in the monthly rate of HIV testing attributable to the intervention was observed in most patient- and clinic-level strata. However, the monthly rate of HIV testing did not differ among two traditionally low-risk groups: females and non-Hispanic white patients. This lack of change in the monthly rate of HIV testing suggests continued HIV testing at a high level.

Case Detection

We observed little pre- or post-intervention temporal trend in the detection of new HIV-infected persons; the rate of HIV case detection was approximately 0.3% for the total study period. However, we did note a slight decrease in the rate of case detection prior to

the intervention, which was mitigated post-intervention. In the post-intervention period, the rate of case detection remained steady and did not increase or decrease. This mitigation was predominately driven by increases in the monthly rate of case detection attributable to the intervention among females and non-Hispanic black patients. These populations reflect epidemic trends in North Carolina (non-Hispanic blacks) and groups in which we saw continued increases in HIV testing rates (females).[40]

Despite these subtle changes in the rates of case detection over time, aggregate pre- and post-intervention measures of HIV positivity showed a decrease in case detection with the introduction of the intervention (OR=0.89, 95% CI: 0.79, 1.00). After adjusting for calendar year of HIV testing, this association attenuated toward the null (OR=1.02, 95% CI: 0.69, 1.52), indicating that the majority of the unadjusted association was due to underlying temporal trends.

Progression to AIDS

Overall, we did not observe any association between the introduction of a routine, opt-out HIV testing program in North Carolina STD clinics and the risk of progression to AIDS within 12 months of HIV diagnosis. This result was consistent across all definitions of "late HIV diagnosis", from 6 month to 18 months. However, we did observe a slight positive association between the intervention and risk of progression to AIDS within 1 month of HIV diagnosis (RR = 1.23, 95 % CI: 0.75, 2.01).

The intervention was associated with an increased risk of progression to AIDS among persons who had previously been tested for HIV, but a decrease among persons who had not been previously tested. Persons who had already been tested for HIV may feel immune to HIV infection, while continuing to engage in risky behavior.[30,130] Among women, the introduction of the intervention was associated with an increased risk of progression to AIDS.

Interpretation of Results

Due to the high pre-intervention rates of HIV testing and case detection in the North Carolina STD clinics, the overall impact of the intervention was marginal. HIV testing and case detection are bounded quantities; HIV testing is limited by the capacity and size of the clinical setting and case detection is limited by the clinic's underlying HIV prevalence. Therefore, in a clinical setting with a high baseline level of HIV testing and case detection like an STD clinic, the maximum room for improvement is quite small.

However, the greatest potential impact can be reached by sub-populations that were not adequately offered HIV testing prior to the intervention. In this analysis, the persons traditionally considered low-risk for HIV testing, particularly women, reaped the greatest benefit. Pre-intervention, HIV testing was focused on persons at highest risk for HIV acquisition based on risk behavior and potential for syphilis infection, groups mostly comprised of men. Women were not regularly targeted for HIV testing unless they presented with significant risk factors. Therefore, with the introduction of routine, opt-out HIV testing, the monthly rate of HIV testing among women in the STD clinics continued to increase rapidly and case detection rates attributable to the intervention also increased.

The increased risk of progression to AIDS among women immediately following the introduction of the intervention suggests the identification of late-stage infected women who would otherwise have been identified in urgent care or emergency settings. This increase in late diagnoses is to be expected immediately after the introduction of an HIV testing intervention, when the "low hanging fruit" in the newly tested population is identified. With sustained routine HIV testing of this population over a longer period of time, we would expect attenuation of this association.

Therefore, although the overall impact of this intervention was minimal, the introduction of this program partially accomplished the CDC's goals of expanding HIV

testing services to all persons, regardless of risk. Risk-based testing often fails accurately identify high-risk persons and is especially troubling in a high-risk clinical setting, like an STD clinic.[30] Because the greater increase in HIV testing was observed in low-risk persons with little undiagnosed HIV infection, we did not observe a corresponding increase in case detection.

The risk of progression to AIDS did not change with the introduction of the intervention, except for a slightly elevated risk of progression to AIDS within 1 month of HIV diagnosis. Consistent with national data of late diagnosis and data from other states, we observed a low proportion of STD clinic patients presenting as late diagnoses with 10.8% progressing to AIDS within 6 months of HIV diagnosis. Nationally, persons diagnosed with HIV at STD clinics tend to have better immunological profiles than persons diagnosed in other clinical settings.[15,66,108,133,134] This relatively low proportion of late diagnoses was most likely due to the high baseline levels of HIV testing in STD clinics and frequent HIV testing.

By offering HIV testing at all clinical visits through routine HIV screening, the CDC hoped there would be fewer missed opportunities for HIV testing and persons would be identified earlier in infection. However, this noble goal of reducing missed opportunities hinges on the assumption that persons who are diagnosed late have interactions with the medical community before they develop clinical AIDS. The near constant level of late diagnoses in this study suggests that routine HIV screening in STD clinics is not a viable method to reach these individuals. Persons who visit STD clinics for care are not representative of the general healthcare seeking population. However, regardless of the clinical setting, undiagnosed HIV-infected individuals must seek out healthcare services in order to gain access to HIV testing interventions that are housed in clinical facilities.

Public Health Significance

In this analysis, we evaluated an HIV prevention program that was created with a very specific purpose in mind: increase HIV testing and HIV case detection in clinical settings. Contrary to expectations, we did not observe the intended or expected effects. Although HIV testing continued to increase post-intervention, this increase was dwarfed by significant levels of pre-intervention HIV testing. Overall, no significant changes in case detection or risk of progression to AIDS were observed post-intervention. These unexpected results highlight the importance of comprehensively evaluating public health interventions, rather than blindly assuming the intervention was successful. No matter how convincing the one may find the theoretical basis for an intervention, mathematical simulation models, or randomized controlled trials, real-world evaluations of public health interventions are irreplaceable.

We focused on evaluating routine, opt-out HIV testing in the specific population of persons seeking clinical care at public STD clinics in North Carolina. Therefore, we cannot comment on the impact of this intervention in other clinical settings or geographic regions. A universal policy recommended by a national body, like the CDC's recommendation for routine HIV testing, may not perform as expected in all types of clinical settings. This study makes an important contribution to the literature by examining the impact of a universal policy recommendation in a very specific medical setting.

STD clinics are unique locations for delivery of HIV prevention services because they inherently cater to persons at high risk for HIV acquisition. Pre-intervention, the North Carolina STD clinics were very successful at providing HIV testing services to their patient population. However, we did observe post-intervention improvements in HIV testing, particularly among persons at lower risk for HIV acquisition.

The high baseline rates of HIV testing in this clinical setting raise important substantive and methodological considerations. Due to limitations in our data, we were

unable to describe the population of STD clinic patients who were not tested for HIV during the study period. Therefore, we do not know if the observed increase in the rate of HIV testing among lower-risk persons under the intervention was at the expense of offering HIV testing services to higher-risk persons. By promoting routine HIV testing for all persons, regardless of risk profile, this intervention may have had the unintended consequence of sacrificing HIV testing among higher-risk persons, simply to adhere to the prescribed HIV testing protocol.

Methodologically, the high pre-intervention rates of HIV testing emphasize the importance of considering the trajectory of HIV testing in both the pre- and post-intervention periods. These trajectories can help public health decision makers to place the intervention in context of underlying trends and comprehend the maximum potential benefit of an intervention. When we used an aggregate pre-intervention comparison group, our results were in agreement with prior studies, identifying an increase in the HIV testing rate and the absolute number of HIV cases identified, but a decrease in HIV positivity.[7,11,12,49,62] However, after adjusting for calendar year, the intervention was associated with a decrease in the rate of HIV testing and no change in the rate of case detection. Ignoring underlying temporal trajectories oversimplified the impact of the intervention, yielding spurious results.

Our analytic methods, interrupted time series analysis and multilevel regression models, were complementary approaches to addressing correlated observations in our complex dataset. Interrupted time series analyses accurately captured underlying temporal trends and correlated observations over time, but relied on ecologic monthly cross-sections of the study population. Multilevel regression models accounted for correlation between and within STD clinics, but could only include crude measures of calendar time. While neither method offered a complete picture of HIV testing or case detection, their concurrent use in this study shows the potential application of sophisticated epidemiologic methods in the evaluation of HIV prevention programs.

Just as universal policy recommendations may not have the same effects in different clinical settings, their effects may also differ by geographic region. Despite the successes of routine, opt-out HIV testing programs in major metropolitan centers like New York City and San Francisco, this study is the first to evaluate the translation of these interventions to more rural areas of the country. The Southeastern United States bears a disproportionate burden of HIV infection and high rates of the many comorbid conditions that facilitate, either directly or indirectly, HIV transmission, including: STD infections, socioeconomic and racial disparities, stigma, and inadequate access to healthcare services.[14,76] HIV infection and these comorbid conditions create a complex web of barriers that can complicate the delivery of HIV prevention services. This study fills an important gap by evaluation routine, opt-out HIV testing in this difficult and oft-ignored region of the United States.

Future Research Directions

In this study, we identified the importance of considering an HIV prevention intervention as a dynamic process, with interplay between the intervention, the undiagnosed HIV-infected population the intervention seeks to identify, and STD clinic capacity. We suggest the continued evaluation of this intervention for sustainability over a longer post-intervention period. Such an evaluation would aid in the identification of the maximum potential testing levels of an STD clinic. Also, we hypothesize that any slight increases in the risk of progression to AIDS observed in the post-intervention period of this study may be mitigated when examining a time period further from the initial date of implementation. Theoretically, after identifying prevalent HIV cases who may be further along in their disease progression, a routine, opt-out HIV testing program would predominantly identify incident cases of HIV. We also encourage investigators in other states to replicate our study design in different geographies and clinical settings, especially including long pre-intervention comparison periods.

Data that currently available for analysis did not include information on the larger population of patients seeking care in the STD clinics. We would like to examine the impact of this intervention in a few select STD clinics in which we could gather denominator data on all clinic attendees. These data could be used to track HIV test refusal over time and calculate more accurate HIV testing rates based on the denominator of patients attending the STD clinic. Data on repeat testers could be used to calculate inter-test intervals, which could also be examined as an outcome of this intervention.

In this study, we categorized late HIV diagnosis by three commonly-used definitions based on the time to AIDS. Further research could investigate the impact of this intervention on the absolute time to AIDS using proportional hazards regression models. Time to event analysis could be completed among persons diagnosed in STD clinics, as well as in a larger sample of all persons diagnosed from other clinical sites in North Carolina that implemented routine, opt-out HIV testing programs.

Health departments not only rely on the results of epidemiologic studies to make decisions about public health prevention programs, but also on economic analyses. We suggest incremental cost-effectiveness and budget impact analyses of this intervention, compared with the previous targeted HIV testing strategy. These economic analysis methods could then be applied to other clinical settings with HIV testing programs to determine the optimal HIV testing strategy for a clinical facility, based on the facility's patient population.

Final Remarks

Overall, the introduction of routine, opt-out HIV testing in North Carolina STD clinics had minimal impact on HIV testing, case detection, and risk of progression to AIDS. However, the lack of a significant impact of this intervention does not imply that the intervention should be discontinued. Rather, persons who are not traditionally at risk for HIV

infection, but are still at some increased risk by virtue of visiting an STD clinic, reaped the greatest benefit from this intervention. The outcomes under study in this analysis were bounded quantities and could not increase indefinitely. By expanding HIV testing services, we believe that the intervention will eventually allow for a higher set-point of HIV testing to be reached than would have been observed without the intervention. Due to the high levels of sexual exposure to HIV, we also believe that sustaining this intervention will eventually shift from the detection of prevalent HIV cases to identifying incident HIV infection. We strongly urge the continued evaluation of this routine, opt-out HIV testing program and other HIV prevention programs to assess prolonged population-level impact.

Appendix 1: Literature Review of Routine HIV Testing Studies

Table A1.1: Overview of Published Studies Describing HIV Testing Interventions in the United States

Source	Setting	Location	Intervention-Affiliated HIV Tests	New HIV-Infected n (%)	Clinical Outcomes	Comparison Group
Anaya, 2013[59]	Primary Care	Veteran's Adm. (MA, TX)	4886	14 (0.3%)	No	Yes
Beckwith, 2007[135]	Jail	RI	95	0 (0%)	No	No
Beckwith, 2011[136]	Jail	RI	1343	1 (0.07%)	No	No
Beckwith, 2012[137]	Jail	Baltimore, MD	2066	7 (0.34%)	No	No
	Jail	Philadelphia, PA	27000	75 (0.28%)	No	No
	Jail	Washington, DC	12546	60 (0.48%)	No	No
Blackstock, 2010[47]	Dental Clinic	New York, NY	3865	19 (0.53%)	Yes	No
Brooks, 2009[63]	STD Clinic	Denver, CO	30405	0.5%-0.8%	No	Yes
Brown, 2007[138]	ED	Washington, DC	2486	9 (0.36%)	No	No
Brown, 2010[48]	ED	Washington, DC	--	55	Yes	No
	ED	Oakland, CA	--	114	Yes	Yes
Calderon, 2009[139]	ED	Bronx, NY	6214	57 (0.92%)	Yes	No
Campos-Outcalt, 2006[140]	STD Clinic	Phoenix, AZ	12176	68 (0.56%)	No	No
CDC, 2007[141]	ED	Los Angeles, CA	1709	13 (0.8%)	No	No
	ED	New York, NY	1288	19 (1.5%)	No	No
	ED	Oakland, CA	6368	65 (1.0%)	No	No
CDC, 2011[49]	Prison	WA	5899	6 (0.1%)	Yes	Yes
Chen, 2011[142]	ED (VA)	Los Angeles, CA	121	0 (0%)	No	No
Christopoulos, 2010[50]	ED	New York, NY	2569	21 (0.9%)	Yes	No
Christopoulos, 2011[51]	Hospital	San Francisco, CA	5340	65 (1.1%)	Yes	Yes
Christopoulos, 2013[143]	ED	San Francisco, CA	9938	46 (0.58%)	Yes	No
Conners, 2012[144]	Substance Use	Veteran's Adm.	414	--	No	Yes
Copeland, 2012[74]	ED	Atlanta, GA	5610	140 (2.5%)	No	No
Cunningham, 2009[145]	Comm. Health.	New York, NY	105	0 (0%)	No	No
Donnell-Fink, 2012[146]	ED	Boston, MA	1111	2 (0.2%)	No	No
Freeman, 2009[72]	ED	Augusta, GA	5080	24 (0.47%)	No	No
Goetz, 2008[65]	Health System	Veteran's Adm.	11%	0.45%	No	Yes
Goetz, 2009[147]	Health System	Veteran's Adm.	11.60%	0.45%	No	No
Hack, 2013[64]	Pediatric ED	Newark, NJ	213	0 (0.0%)	No	Yes

Table A1.1 (continued): Overview of Published Studies Describing HIV Testing Interventions in the United States

Source	Setting	Location	Intervention-Affiliated HIV Tests	New HIV-Infected n (%)	Clinical Outcomes	Comparison Group
Halloran, 2012[148]	Health System	Veteran's Admn.	483759	3972 (0.8%)	No	No
Haukoos, 2010[7]	ED	Denver, CO	6702	10 (0.15%)	Yes	Yes
Hoxhaj, 2011[52]	ED	Houston, TX	14093	80 (0.57%)	Yes	No
Hsieh, 2011[149]	ED	Baltimore, MD	2958	44 (1.5%)	No	No
Keller, 2011[150]	STD Clinic	Baltimore, MD	5101	34 (0.67%)	No	No
Kendrick, 2005[151]	STD Clinic	Chicago, IL	1372	37 (2.7%)	No	No
Liang, 2005[152]	STD Clinic	Baltimore, MD	439	18 (4.1%)	No	No
Liddicoat, 2006[153]	Prison	Boston, MA	734	2 (0.3%)	No	Yes
Lubelchek, 2011[53]	ED	Chicago, IL	4755	30 (0.6%)	Yes	No
Lyss, 2007[8]	ED	Chicago, IL	2824	34 (1.2%)	Yes	Yes
MacGowan, 2009[75]	Jail	FL, LA, NY, WI	33211	269 (0.8%)	No	No
Maxwell, 2010[154]	ED	Washington, DC	7528	65 (0.9%)	No	No
Mehta, 2008[155]	Hospital	Boston, MA	16750	1.37%	No	No
Merchant, 2008[156]	ED	Providence, RI	825	0 (0.0%)	No	No
Mullins, 2010[157]	ED	Cincinnati, OH	1460	--	No	Yes
Myers, 2009[61]	CHC	NC, SC, MI	10769	17 (0.16%)	No	Yes
Nayak, 2012[62]	Hospital (VA)	Washington, DC	6429	69 (1.1%)	No	Yes
Scott, 2009[158]	Hospital	Washington, DC	5637	38 (0.67%)	No	No
Sattin, 2011[54]	ED	Augusta, GA	8504	35 (0.41%)	Yes	No
Schrantz, 2011[55]	ED	Chicago, IL	1258	28 (2.2%)	Yes	No
Siegel, 2010[56]	Inpatient (VA)	Washington, DC	824	7 (0.85%)	Yes	Yes
Silva, 2007[159]	ED	Chicago, IL	1428	10 (0.6%)	No	No
Valenti, 2012[160]	Primary Care	Detroit, MI	367	1 (0.27%)	No	No
Walensky, 2005[161]	Urgent Care	Boston, MA	2444	48 (2%)	No	Yes
Walensky, 2011[9]	ED	Boston, MA	1371	0 (0.0%)	Yes	No
Weis, 2009[73]	Comm. Health.	Aiken, SC	574	0 (0%)	No	No
White, 2009[11]	ED	Oakland, CA	7923	55 (0.7%)	Yes	Yes
White, 2010[12]	ED	Oakland, CA	5009	43 (0.9%)	Yes	Yes
	Urgent Care	Oakland, CA	2914	12 (0.4%)	Yes	Yes
White, 2011[13]	ED	Oakland, CA	4679	21 (0.4%)	Yes	Yes
White, 2011[162]	ED	Oakland, CA	599	10 (1.7%)	No	No
Zetola, 2008[112]	Health System	San Francisco, CA	4.38/1000 per month	8.9/mo - 14.9/mo	No	Yes

Table A1.2: Published Evaluations of Routine HIV Testing Programs with Comparison Groups

Source	Setting	Location	Testing Model	HIV Tests n (% of visits)	New Positive n (% of tests)
Anaya, 2013[59]	Primary Care	Veteran's Adm. (MA, TX)	**Intervention:** routine, opt-out testing	4886 (13.6%)	14 (0.3%)
			Comparison: diagnostic/targeted testing	111 (0.3%)	--
Brooks, 2009[63]	STD Clinic	Denver, CO	**Intervention:** opt-out testing	96% of RPRs	0.7%
			Comparison 1: discontinuation of ELISA	92% of RPRs	0.6%
			Comparison 2: streamlined consent	86% of RPRs	0.8%
			Comparison 3: optional rapid testing	79% of RPRs	0.5%
CDC, 2011[49]	Prison	WA	**Intervention:** opt-out HIV testing	5899 (90%)	6 (0.1%)
			Comparison 1: opt-in HIV testing	4780 (72%)	13 (0.3%)
			Comparison 2: request or clinical indication	360 (3.0%)	3 (0.8%)
Christopoulos, 2011[51]	Hospital	San Francisco, CA	**Intervention:** targeted testing	273/month	4/month
			Comparison: diagnostic testing	114/month	1.5/month
Conners, 2012[144]	Substance Use	Veteran's Adm.	**Intervention:** routine, opt-out HIV testing	414 (36.1%)	--
			Comparison 1: continuation of intervention	246 (28.2%)	--
			Comparison 2: diagnostic/targeted testing	293 (22.7%)	--
Goetz, 2008[65]	Health System	Veteran's Adm.	**Intervention:** targeted testing for "at-risk" patients	Site A: 10.8% Site B: 12.8%	30 (0.5%)
			Comparison: diagnostic testing	Site A: 4.8% Site B: 5.5%	15 (0.5%)
Hack, 2013[64]	Pediatric ED	Newark, NJ	**Intervention:** routine, opt-in testing	213 (8.1%)	0 (0.0%)
			Comparison: targeted/diagnostic testing	39 (?%)	0 (0.0%)
Haukoos, 2010[7]	ED	Denver, CO	**Intervention:** routine testing	6702 (23.9%)	10 (0.2%)
			Comparison: diagnostic testing	243 (0.8%)	4 (1.7%)
Liddicoat, 2006[153]	Prison	0	**Intervention:** routine testing	734 (73.1%)	2 (0.3%)
			Comparison: opt-in testing	318 (18.5%)	--
Lyss, 2007[8]	ED	Chicago, IL	**Intervention:** routine, opt-out testing	2824 (58.2%)	34 (1.2%)
			Comparison: provider-referred testing	414 (95.0%)	48 (11.6%)
Mullins, 2010[157]	ED	Cincinnati, OH	**Intervention:** routine testing of adolescents	1460 (44.6%)	--
			Comparison 1: post-CDC recommendations, but pre-intervention	889 (27.7%)	--
			Comparison 2: pre-CDC recommendations	378 (12.6%)	--
Myers, 2009[61]	CHC	NC, SC, MI	**Intervention:** routine testing	10769 (18.4%)	17 (0.2%)
			Comparison: targeted/diagnostic testing	3078 (3.0%)	--
Nayak, 2012[62]	Health System (VA)	Washington, DC	**Intervention:** routine opt-out testing	6429 (10.3%)	69 (1.1%)
			Comparison: targeted testing	3222 (5.5%)	47 (1.5%)
Siegel, 2010[56]	Inpatient (VA)	Washington, DC	**Intervention:** routine testing	824 (31.2%)	7 (0.9%)
			Comparison: targeted testing	256 (2.6%)	8 (3.1%)

Table A1.2 (continued): Published Evaluations of Routine HIV Testing Programs with Comparison Groups

Source	Setting	Location	Testing Model	HIV Tests n (% of visits)	New Positive n (% of tests)
Walensky, 2005[161]	Urgent Care	Boston, MA	**Intervention: r**outine HIV testing	2444	48 (2%)
			Comparison: self-referral clinics	13890	262 (1.9%)
White, 2009[11]	ED	Oakland, CA	**Intervention:** routine, opt-in testing	7923 (17.5%)	55 (0.7%)
			Comparison: diagnostic testing	1543 (1.6%)	44 (2.9%)
White, 2010[12]	ED/Urgent Care (UC)	Oakland, CA	**Intervention:** routine testing	ED: 5009 (6.7%) UC: 2914 (7.8%)	ED: 43 (0.9%) UC: 12 (0.4%)
			Comparison: diagnostic testing	ED: 1187 (1.6%) UC: 342 (0.9%)	ED: 37 (3.1%) UC: 9 (2.6%)
White, 2011[13]	ED	Oakland, CA	**Intervention;** opt-out testing	4679 (20.1%)	21 (0.4%)
			Comparison: opt-in testing	4053 (15.2%)	8 (0.2%)
Zetola, 2008[112]	Health System	San Francisco, CA	**Intervention:** no requirement for written consent	17.9/1000 visits	14.9/month
			Comparison: separate written consent	13.5/1000 visits	8.9/month

Table A1.2 (continued): Published Evaluations of Routine HIV Testing Programs with Comparison Groups Examining Clinical Outcomes

Source	Setting	Location	Testing Model	CD4	VL
CDC, 2011[49]	Prison	WA	**Intervention:** opt-out HIV testing	422 (range: 71-898)	--
			Comparison 1: opt-in HIV testing	--	--
			Comparison 2: request or clinical indication	--	--
Christopoulos, 2011[51]	Hospital	San Francisco, CA	**Intervention:** targeted testing	268	--
			Comparison: diagnostic testing	--	--
Haukoos, 2010[7]	ED	Denver, CO	**Intervention:** routine testing	69 (IQR: 17-430)	108,790 (IQR: 56,000-153,562)
			Comparison: diagnostic testing	13 (IQR: 11-15)	146,000 (IQR: 50,700-470,000)
Lyss, 2007[8]	ED	Chicago, IL	**Intervention:** routine, opt-out testing	CD4 <200: 45.2%	--
			Comparison: provider-referred testing	CD4 <200: 82.2%	--
Siegel, 2010[56]	Inpatient (VA)	Washington, DC	**Intervention:** routine testing	171 (range: 95-679)	48,013 (range: 1763->500,000)
			Comparison: targeted testing	--	--
White, 2009[11]	ED	Oakland, CA	**Intervention:** routine, opt-in testing	356 (range: 4-1020)	--
			Comparison: diagnostic testing	99 (range: 9-1224)	--
White, 2010[12]	ED/Urgent Care (UC)	Oakland, CA	**Intervention:** routine testing	ED: 195 UC: 381	--
			Comparison: diagnostic testing	--	--
White, 2011[13]	ED	Oakland, CA	**Intervention;** opt-out testing	CD4 <200: 48%	--
			Comparison: opt-in testing	CD4 <200: 25%	--

Table A1.3: Survey-Based and Ecologic Evaluations of Routine HIV Testing Programs with Comparison Groups

Source	Setting	Location	Testing Model	HIV Tests n (% of visits)	CD4
Leeper, 2013[66]	HIV clinic	Providence, RI	**Intervention:** legislative change for routine, opt-out HIV testing without separate consent (2005)	--	349.8 (IQR: 102-550)
			a	--	454.4 (IQR: 190-671)
Myers, 2012[67]	BRFSS	Bronx, NY	**Intervention:** Bronx Knows HIV campaign (2009)	69.30%	Concurrent AIDS: 23.6%
			Comparison: pre-intervention (2005)	79.10%	Concurrent AIDS: 30.1%
West-Ojo, 2010[111]	BRFSS	Washington, DC	**Intervention:** DC DOH testing campaign (2007)	14.90%	--
			Comparison: pre-intervention (2005)	18.70%	--
Wing, 2009[163]	BRFSS	New York	**Intervention:** legislative change for routine, opt-out HIV testing without separate consent (2006)	31.4% increase	--
			Comparison: pre-legislative change (2004)	--	--

Appendix 2: Aim 1 Supplemental Tables and Figures

Table A2.1: Demographic and Clinic Characteristics of Persons Tested for HIV in North Carolina STD Clinics by HIV Test Results, July 2005 through June 2011

	All Patients Tested		New HIV-Infected		Not New HIV-Infected	
	n	(%)	n	(%)	n	(%)
Intervention						
Pre-Intervention	128029	(31.79)	426	(34.30)	127603	(31.78)
Post-Intervention	274745	(68.21)	816	(65.70)	273929	(68.22)
All Tests						
Patient Covariates						
Gender	185714	(46.11)	984	(79.23)	184730	(46.01)
Male	217060	(53.89)	258	(20.77)	216802	(53.99)
Female						
Race/Ethnicity	116227	(28.86)	222	(17.87)	116008	(28.89)
White, NH	228538	(56.74)	830	(66.83)	227708	(56.71)
Black, NH	35126	(8.72)	81	(6.52)	35045	(8.73)
Hispanic	22880	(5.68)	109	(8.78)	22771	(5.67)
Other						
Age (years)	179780	(44.64)	441	(35.51)	179339	(44.66)
18-24	129717	(32.21)	400	(32.21)	129317	(32.21)
25-34	57295	(14.23)	232	(18.68)	57063	(14.21)
35-44	35982	(8.93)	169	(13.61)	35813	(8.92)
45-64						
Clinic Covariates	300266	(74.55)	992	(79.87)	299274	(74.53)
Metropolitan Status*	81054	(20.12)	202	(16.26)	80852	(20.14)
Metropolitan	21454	(5.33)	48	(3.86)	21406	(5.33)
Micropolitan						
Neither						
Population Density#	135938	(33.75)	300	(24.15)	135638	(33.78)
<199	81262	(20.18)	197	(15.86)	81065	(20.19)
200-399	31048	(7.71)	168	(13.53)	30880	(7.67)
400-599	154526	(38.37)	577	(46.46)	153949	(38.34)
600+						
% Below Poverty	70298	(17.45)	244	(19.65)	70054	(17.45)
<15%	250865	(62.28)	783	(63.04)	250082	(62.28)
15-<20%	59706	(14.82)	159	(12.80)	59547	(14.83)
20-<25%	21905	(5.44)	56	(4.51)	21849	(5.44)
25+%						
Affiliated HIV Clinic	83850	(20.82)	354	(28.50)	83496	(20.79)
Yes	318924	(79.18)	888	(71.50)	318036	(79.21)
No						
Baseline HIV rate^	18353	(4.56)	26	(2.09)	18327	(4.56)
0-5	62317	(15.47)	123	(9.90)	62194	(15.49)
5-10	78829	(19.57)	175	(14.09)	78654	(19.59)
10-15	243275	(60.40)	918	(73.91)	242357	(60.36)

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas
^Calculated as the average reported HIV case rate per 100,000 population 2005-2007
#per square mile

Table A2.2: Interrupted Time Series Analysis of the Number of HIV Tests Performed per Month in North Carolina STD Clinics, July 2005 through June 2011

	Pre-Intervention Intercept # Tests (95% CI)	Pre-Intervention Slope MD (95% CI)	Overall Post-Intervention Slope MD (95% CI)	Slope Attributable to Intervention MD (95% CI)
All Tests	3832 (3613, 4050)	54.69 (40.72, 68.66)	33.75 (25.93, 41.57)	-20.94 (-36.95, -4.94)
Patient Covariates				
Gender				
Male	1893 (1795, 1992)	23.07 (16.78, 29.35)	9.64 (6.12, 13.16)	-13.42 (-20.63, -6.22)
Female	1938 (1802, 2074)	31.67 (22.98, 40.36)	24.23 (19.36, 29.10)	-7.44 (-17.39, 2.52)
Race/Ethnicity				
White, NH	1250 (1167, 1334)	11.44 (6.11, 16.77)	8.10 (5.11, 11.09)	-3.34 (-9.45, 2.77)
Black, NH	1875 (1743, 2008)	41.02 (32.58, 49.46)	23.19 (18.46, 27.91)	-17.83 (-27.50, -8.17)
Hispanic	301 (265, 338)	7.09 (4.78, 9.39)	0.92 (-0.39, 2.22)	-6.17 (-8.82, -3.52)
Other	390 (321, 458)	-3.79 (-8.09, 0.51)	1.97 (-0.49, 4.43)	5.76 (0.80, 10.72)
Age (years)				
18-24	1706 (1614, 1798)	24.29 (18.41, 30.16)	13.42 (10.13, 16.71)	-10.87 (-17.59, -4.14)
25-34	1208 (1127, 1290)	18.33 (13.14, 23.52)	13.39 (10.48, 16.30)	-4.94 (-10.89, 1.01)
35-44	586 (545, 628)	6.57 (3.95, 9.20)	3.83 (2.36, 5.30)	-2.74 (-5.76, 0.27)
45-64	330 (301, 359)	5.57 (3.72, 7.41)	3.21 (2.17, 4.25)	-2.35 (-4.47, -0.23)
Clinic Covariates				
Metropolitan Status*				
Metropolitan	2914 (2753, 3076)	38.80 (28.50, 49.11)	26.46 (20.69, 32.23)	-12.34 (-24.15, -0.53)
Micropolitan	744 (679, 809)	12.16 (8.04, 16.28)	5.71 (3.40, 8.02)	-6.45 (-11.18, -1.73)
Neither	173 (152, 193)	3.81 (2.49, 5.13)	1.82 (1.08, 2.57)	-1.99 (-3.50, -0.47)
Population Density#				
<199	1240 (1134, 1347)	19.49 (12.71, 26.27)	10.04 (6.23, 13.85)	-9.45 (-17.23, -1.67)
200-399	817 (769, 865)	8.35 (5.27, 11.44)	11.60 (9.87, 13.33)	3.24 (-0.29, 6.78)
400-599	309 (255, 364)	5.17 (1.73, 8.61)	3.25 (1.29, 5.21)	-1.92 (-5.88, 2.04)
600+	1464 (1362, 1566)	21.88 (15.40, 28.37)	9.47 (5.83, 13.10)	-12.42 (-19.85, -4.98)
% Below Poverty				
<15%	664 (615, 713)	12.40 (9.27, 15.53)	7.03 (5.28, 8.79)	-5.37 (-8.96, -1.78)
15-<20%	2447 (2294, 2600)	29.99 (20.25, 39.73)	19.23 (13.77, 24.69)	-10.76 (-21.93, 0.40)
20-<25%	484 (442, 526)	11.18 (8.52, 13.84)	7.25 (5.76, 8.74)	-3.93 (-6.98, -0.88)
25+%	235 (202, 268)	1.36 (-0.74, 3.46)	0.70 (-0.50, 1.90)	-0.66 (-3.08, 1.75)
Affiliated HIV Clinic				
Yes	818 (729, 908)	12.42 (6.76, 18.07)	6.47 (3.27, 9.67)	-5.95 (-12.44, 0.55)
No	3010 (2825, 3196)	42.59 (30.76, 54.42)	27.74 (21.11, 34.37)	-14.85 (-28.41, -1.30)
Baseline HIV rate^				
0-5	184 (165, 204)	1.99 (0.74, 3.24)	2.16 (1.46, 2.86)	0.17 (-1.26, 1.60)
5-10	592 (553, 631)	9.01 (6.51, 11.50)	7.01 (5.61, 8.40)	-2.00 (-4.86, 0.86)
10-15	830 (772, 888)	6.23 (2.53, 9.93)	8.13 (6.06, 10.21)	1.90 (-2.34, 6.14)
15+	2225 (2089, 2361)	37.53 (28.85, 46.21)	16.60 (11.74, 21.46)	-20.93 (-30.87, -10.98)

MD: mean difference, 95% CI: 95% confidence interval

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas

^Calculated as the average reported HIV case rate per 100,000 population 2005-2007

#per square mile

Table A2.3: Interrupted Time Series Analysis of the Rate of HIV Testing per 100,000 Population per Month in North Carolina STD Clinics, July 2005 through June 2011

	Pre-Intervention Intercept Test Rate (95% CI)	Pre-Intervention Slope MD (95% CI)	Overall Post-Intervention Slope MD (95% CI)	Slope Attributable to Intervention MD (95% CI)
All Tests	69.59 (65.87, 73.30)	0.81 (0.58, 1.05)	0.46 (0.33, 0.60)	-0.35 (-0.62, -0.08)
Patient Covariates				
Gender				
Male	69.56 (66.20, 72.92)	0.69 (0.48, 0.91)	0.24 (0.12, 0.36)	-0.45 (-0.70, -0.21)
Female	69.61 (65.01, 74.21)	0.93 (0.64, 1.22)	0.68 (0.52, 0.85)	-0.25 (-0.58, 0.09)
Race/Ethnicity				
White	33.09 (30.95, 35.23)	0.25 (0.12, 0.39)	0.19 (0.11, 0.26)	-0.06 (-0.22, 0.09)
Black	162.02 (151.50, 172.55)	2.99 (2.32, 3.66)	1.42 (1.04, 1.79)	-1.57 (-2.34, -0.80)
Hispanic	92.20 (83.48, 100.92)	1.36 (0.80, 0.00)	-0.20 (-0.51, 0.12)	-1.55 (-2.19, -0.92)
Other	174.09 (147.58, 200.60)	-2.26 (-3.93, -0.58)	0.39 (-0.56, 1.35)	2.65 (0.72, 4.58)
Age (years)				
18-24	200.14 (190.16, 210.11)	2.45 (1.81, 3.08)	1.10 (0.75, 1.46)	-1.34 (-2.07, -0.61)
25-34	102.03 (95.34, 108.72)	1.47 (1.04, 1.89)	0.92 (0.69, 1.16)	-0.54 (-1.03, -0.05)
35-44	44.92 (41.81, 48.04)	0.44 (0.24, 0.63)	0.33 (0.22, 0.44)	-0.10 (-0.33, 0.12)
45-64	15.27 (14.03, 16.51)	0.19 (0.11, 0.27)	0.09 (0.05, 0.13)	-0.10 (-0.19, -0.01)
Clinic Covariates				
Metropolitan Status*				
Metropolitan	75.57 (71.66, 79.49)	0.78 (0.53, 1.03)	0.49 (0.35, 0.63)	-0.29 (-0.58, -0.01)
Micropolitan	61.57 (56.44, 66.69)	0.91 (0.58, 1.24)	0.40 (0.22, 0.58)	-0.51 (-0.89, -0.14)
Neither	38.87 (34.37, 43.36)	0.80 (0.51, 1.08)	0.38 (0.22, 0.54)	-0.42 (-0.75, -0.09)
Population Density#				
<199	53.73 (49.32, 58.14)	0.74 (0.46, 1.02)	0.36 (0.20, 0.52)	-0.38 (-0.71, -0.06)
200-399	74.65 (70.52, 78.77)	0.60 (0.33, 0.86)	0.89 (0.75, 1.04)	0.30 (-0.01, 0.60)
400-599	97.77 (81.06, 114.48)	1.52 (0.47, 2.58)	0.87 (0.27, 1.47)	-0.65 (-1.87, 0.56)
600+	81.81 (76.70, 86.91)	0.90 (0.58, 1.23)	0.28 (0.09, 0.46)	-0.63 (-1.00, -0.25)
% Below Poverty				
<15%	61.52 (57.35, 65.68)	0.87 (0.60, 1.13)	0.45 (0.30, 0.60)	-0.42 (-0.72, -0.11)
15-<20%	71.54 (67.32, 75.75)	0.71 (0.44, 0.98)	0.40 (0.25, 0.56)	-0.30 (-0.61, 0.00)
20-<25%	66.34 (60.86, 71.83)	1.43 (1.08, 1.78)	0.94 (0.74, 1.13)	-0.49 (-0.89, -0.09)
25+%	84.32 (72.71, 95.93)	0.43 (-0.30, 1.16)	0.21 (-0.21, 0.63)	-0.22 (-1.06, 0.62)
Affiliated HIV Clinic				
Yes	69.55 (62.88, 76.22)	0.73 (0.31, 1.16)	0.29 (0.05, 0.53)	-0.44 (-0.92, 0.05)
No	69.50 (65.45, 73.56)	0.84 (0.58, 1.10)	0.52 (0.38, 0.67)	-0.32 (-0.62, -0.03)
Baseline HIV rate^				
0-5	39.68 (35.57, 43.79)	0.40 (0.13, 0.66)	0.45 (0.30, 0.59)	0.05 (-0.25, 0.35)
5-10	46.07 (43.21, 48.94)	0.58 (0.40, 0.76)	0.46 (0.36, 0.56)	-0.12 (-0.33, 0.09)
10-15	80.45 (75.14, 85.76)	0.46 (0.12, 0.80)	0.65 (0.46, 0.84)	0.19 (-0.20, 0.57)
15+	81.57 (76.99, 86.16)	1.11 (0.82, 1.41)	0.38 (0.21, 0.54)	-0.74 (-1.07, -0.40)

MD: mean difference, 95% CI: 95% confidence interval

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas

^Calculated as the average reported HIV case rate per 100,000 population 2005-2007

#per square mile

Table A2.4: Interrupted Time Series Analysis of the Number of New HIV-Infected Diagnoses per Month in North Carolina STD Clinics, July 2005 through June 2011

	Pre-Intervention Intercept # Infected (95% CI)	Pre-Intervention Slope MD (95% CI)	Overall Post-Intervention Slope MD (95% CI)	Slope Attributable to Intervention MD (95% CI)
All Tests	13.82 (10.81, 16.82)	0.10 (-0.09, 0.29)	0.08 (-0.03, 0.19)	-0.03 (-0.24, 0.19)
Patient Covariates				
Gender				
Male	9.34 (7.13, 12)	0.15 (0.01, 0.29)	0.09 (0.01, 0.17)	-0.06 (-0.23, 0.10)
Female	4.48 (3.36, 5.60)	-0.05 (-0.12, 0.02)	-0.01 (-0.05, 0.03)	0.04 (-0.04, 0.12)
Race/Ethnicity				
White, NH	2.62 (1.45, 3.80)	0.04 (-0.04, 0.11)	0.01 (-0.03, 0.05)	-0.03 (-0.11, 0.06)
Black, NH	8.83 (6.45, 11.21)	0.04 (-0.12, 0.19)	0.07 (-0.01, 0.16)	0.04 (-0.14, 0.21)
Hispanic	1.12 (0.26, 1.97)	0.00 (-0.06, 0.05)	-0.01 (-0.05, 0.02)	-0.01 (-0.08, 0.05)
Other	1.34 (0.48, 2.19)	0.03 (-0.03, 0.08)	0.01 (-0.02, 0.04)	-0.01 (-0.08, 0.05)
Age (years)				
18-24	4.32 (2.68, 5.96)	0.07 (-0.03, 0.17)	0.08 (0.03, 0.14)	0.01 (-0.11, 0.13)
25-34	5.00 (3.72, 6.27)	-0.02 (-0.10, 0.06)	0.00 (-0.05, 0.04)	0.02 (-0.08, 0.11)
35-44	3.00 (1.61, 4.40)	0.02 (-0.07, 0.11)	0.03 (-0.02, 0.08)	0.01 (-0.09, 0.11)
45-64	1.60 (0.49, 2.72)	0.03 (-0.04, 0.10)	-0.03 (-0.07, 0.01)	-0.06 (-0.14, 0.02)
Clinic Covariates				
Metropolitan Status*				
Metropolitan	11.45 (8.82, 14.08)	0.09 (-0.08, 0.25)	0.06 (-0.03, 0.16)	-0.02 (-0.21, 0.17)
Micropolitan	2.10 (0.98, 3.22)	0.01 (-0.06, 0.09)	0.02 (-0.02, 0.06)	0.01 (-0.08, 0.09)
Neither	0.19 (-0.43, 0.82)	0.01 (-0.03, 0.05)	-0.01 (-0.03, 0.02)	-0.01 (-0.06, 0.03)
Population Density#				
<199	2.62 (1.31, 3.92)	0.01 (-0.07, 0.10)	-0.03 (-0.08, 0.01)	-0.05 (-0.14, 0.05)
200-399	1.75 (0.54, 2.96)	0.06 (-0.02, 0.13)	0.07 (0.03, 0.12)	0.01 (-0.07, 0.10)
400-599	2.51 (1.36, 3.67)	-0.01 (-0.09, 0.06)	0.01 (-0.03, 0.05)	0.03 (-0.06, 0.11)
600+	6.81 (4.53, 9.09)	0.05 (-0.09, 0.20)	0.03 (-0.05, 0.11)	-0.03 (-0.19, 0.14)
% Below Poverty				
<15%	1.10 (-0.63, 2.84)	0.18 (0.07, 0.28)	0.01 (-0.05, 0.07)	-0.16 (-0.29, -0.04)
15-<20%	11.19 (8.64, 13.74)	-0.10 (-0.26, 0.06)	0.05 (-0.04, 0.14)	0.15 (-0.04, 0.34)
20-<25%	1.34 (0.48, 2.21)	0.01 (-0.05, 0.06)	0.04 (0.01, 0.07)	0.03 (-0.03, 0.10)
25+%	0.12 (-0.63, 0.87)	0.03 (-0.02, 0.08)	-0.02 (-0.05, 0.01)	-0.05 (-0.10, 0.01)
Affiliated HIV Clinic				
Yes	3.52 (1.66, 5.39)	0.08 (-0.04, 0.20)	0.00 (-0.06, 0.07)	-0.08 (-0.21, 0.06)
No	10.30 (7.60, 13.00)	0.03 (-0.15, 0.20)	0.08 (-0.02, 0.17)	0.05 (-0.15, 0.25)
Baseline HIV rate^				
0-5	-0.05 (-0.57, 0.48)	0.02 (-0.01, 0.06)	0.00 (-0.01, 0.02)	-0.02 (-0.06, 0.02)
5-10	0.63 (-0.42, 1.68)	0.06 (-0.01, 0.13)	0.01 (-0.02, 0.05)	-0.05 (-0.13, 0.03)
10-15	2.89 (1.47, 4.31)	-0.07 (-0.16, 0.02)	0.00 (-0.05, 0.06)	0.07 (-0.03, 0.17)
15+	10.38 (7.45, 13.31)	0.08 (-0.10, 0.27)	0.06 (-0.05, 0.16)	-0.03 (-0.24, 0.19)

MD: mean difference, 95% CI: 95% confidence interval

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas

^Calculated as the average reported HIV case rate per 100,000 population 2005-2007

#per square mile

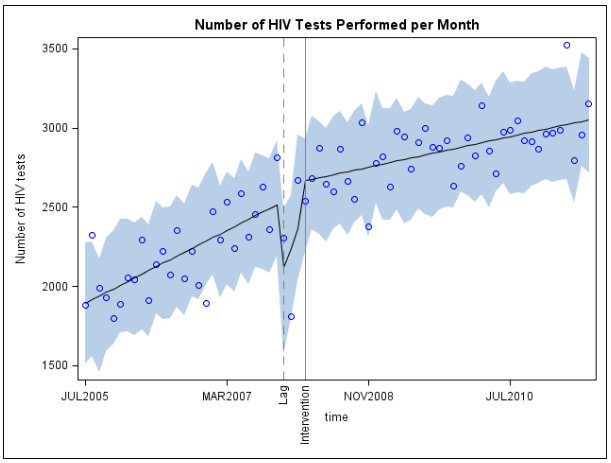
Table A2.5: Interrupted Time Series Analysis of the Rate of New HIV-Infected Diagnosis per 1,000 HIV Tests per Month in North Carolina STD Clinics, July 2005 through June 2011

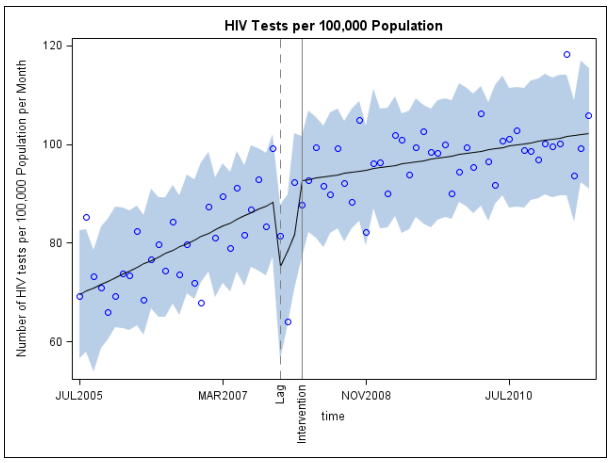
	Pre-Intervention Intercept Positivity Rate (95%CI)	Pre-Intervention Slope MD (95% CI)	Overall Post-Intervention Slope MD (95% CI)	Slope Attributable to Intervention MD (95% CI)
All Tests	3.59 (3.04, 4.13)	-0.02 (-0.05, 0.02)	0.00 (-0.02, 0.02)	0.01 (-0.02, 0.05)
Patient Covariates				
Gender				
Male	5.02 (4.07, 6)	0.01 (-0.05, 0.07)	0.01 (-0.02, 0.05)	0.00 (-0.07, 0.07)
Female	2.20 (1.73, 2.68)	-0.04 (-0.07, -0.01)	-0.01 (-0.03, 0.01)	0.03 (0.00, 0.07)
Race/Ethnicity				
White, NH	2.09 (1.21, 2.97)	0.01 (-0.05, 0.07)	0.00 (-0.03, 0.03)	-0.01 (-0.08, 0.05)
Black, NH	4.58 (3.87, 5.30)	-0.05 (-0.10, -0.01)	0.00 (-0.03, 0.02)	0.05 (0.00, 0.10)
Hispanic	3.44 (1.72, 5.15)	-0.04 (-0.15, 0.07)	-0.03 (-0.09, 0.03)	0.01 (-0.12, 0.13)
Other	2.98 (0.31, 5.65)	0.16 (-0.01, 0.33)	0.01 (-0.08, 0.11)	-0.14 (-0.34, 0.05)
Age (years)				
18-24	2.54 (1.74, 3.33)	0.00 (-0.05, 0.05)	0.02 (-0.01, 0.05)	0.01 (-0.04, 0.07)
25-34	3.97 (3.05, 4.89)	-0.05 (-0.11, 0.01)	-0.02 (-0.05, 0.01)	0.03 (-0.04, 0.10)
35-44	5.20 (3.64, 6.76)	-0.03 (-0.13, 0.07)	0.01 (-0.04, 0.07)	0.04 (-0.07, 0.15)
45-64	4.74 (2.59, 6.90)	0.00 (-0.13, 0.14)	-0.08 (-0.16, -0.01)	-0.09 (-0.25, 0.07)
Clinic Covariates				
Metropolitan Status*				
Metropolitan	3.88 (3.22, 4.54)	-0.02 (-0.06, 0.03)	0.00 (-0.03, 0.02)	0.01 (-0.04, 0.06)
Micropolitan	3.02 (1.68, 4.36)	-0.03 (-0.12, 0.05)	0.00 (-0.05, 0.05)	0.03 (-0.07, 0.13)
Neither	1.29 (-0.62, 3.20)	0.00 (-0.12, 0.12)	-0.02 (-0.09, 0.05)	-0.02 (-0.16, 0.12)
Population Density#				
<199	2.21 (1.31, 3.12)	-0.02 (-0.08, 0.04)	-0.03 (-0.06, 0.01)	0.00 (-0.07, 0.06)
200-399	2.12 (1.01, 3.24)	0.04 (-0.03, 0.11)	0.04 (0.00, 0.08)	-0.01 (-0.09, 0.08)
400-599	7.58 (4.96, 10.20)	-0.11 (-0.28, 0.05)	-0.01 (-0.10, 0.08)	0.10 (-0.09, 0.29)
600+	4.65 (3.73, 5.56)	-0.03 (-0.08, 0.03)	0.00 (-0.04, 0.03)	0.02 (-0.04, 0.09)
% Below Poverty				
<15%	2.32 (0.85, 3.79)	0.12 (0.03, 0.22)	-0.01 (-0.07, 0.04)	-0.14 (-0.24, -0.03)
15-<20%	4.38 (3.66, 5.10)	-0.07 (-0.11, -0.02)	0.00 (-0.03, 0.02)	0.06 (0.01, 0.12)
20-<25%	3.01 (1.67, 4.36)	-0.04 (-0.13, 0.04)	0.02 (-0.03, 0.07)	0.07 (-0.03, 0.16)
25+%	0.65 (-1.49, 2.78)	0.10 (-0.04, 0.23)	-0.06 (-0.14, 0.01)	-0.16 (-0.32, -0.01)
Affiliated HIV Clinic				
Yes	4.52 (3.05, 5.99)	0.01 (-0.09, 0.10)	-0.02 (-0.07, 0.04)	-0.02 (-0.13, 0.09)
No	3.33 (2.74, 3.92)	-0.03 (-0.06, 0.01)	0.00 (-0.02, 0.02)	0.03 (-0.02, 0.07)
Baseline HIV rate^				
0-5	0.01 (-2.10, 2.11)	0.10 (-0.04, 0.23)	0.00 (-0.07, 0.08)	-0.10 (-0.25, 0.06)
5-10	1.05 (-0.29, 2.38)	0.07 (-0.02, 0.15)	0.00 (-0.05, 0.05)	-0.07 (-0.17, 0.03)
10-15	3.35 (2.16, 4.53)	-0.08 (-0.16, -0.01)	-0.01 (-0.05, 0.03)	0.07 (-0.01, 0.16)
15+	4.64 (3.91, 5.38)	-0.03 (-0.08, 0.02)	0.00 (-0.03, 0.03)	0.03 (-0.02, 0.08)

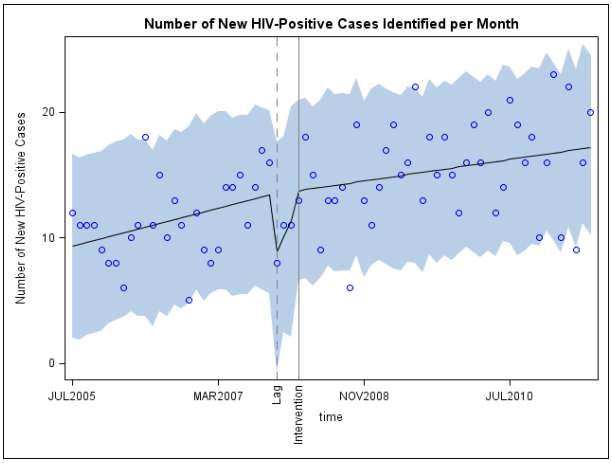
MD: mean difference, 95 CI: 95% confidence intervanl
*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas
^Calculated as the average reported HIV case rate per 100,000 population 2005-2007
#per square mile

Figure A2.1(a-aa): Results of Interrupted Time Series Analysis in North Carolina STD Clinics, July 1, 2005 through June 30, 2011, Stratified by Patient and Clinic Characteristics

Figure A2.1(a): Men







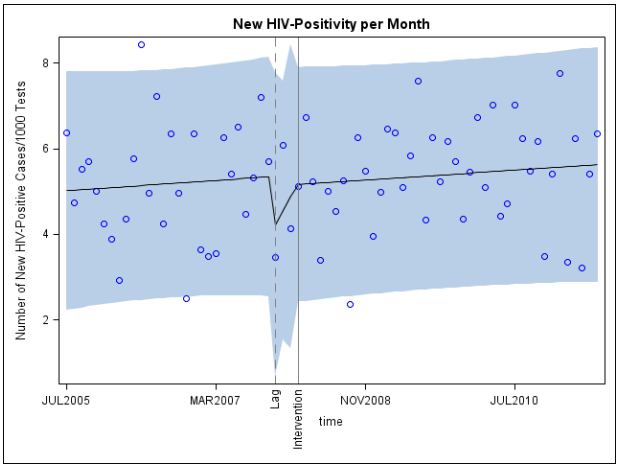
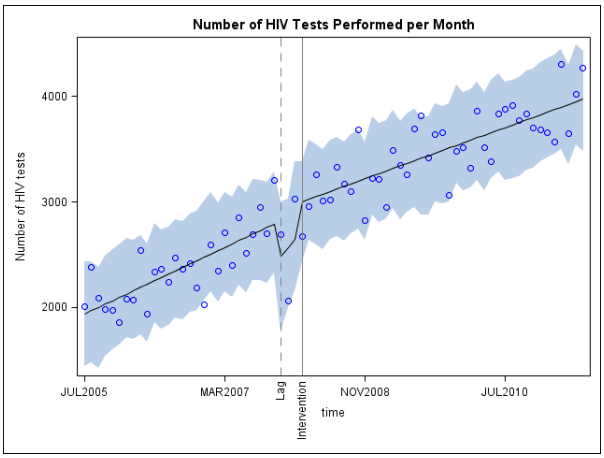
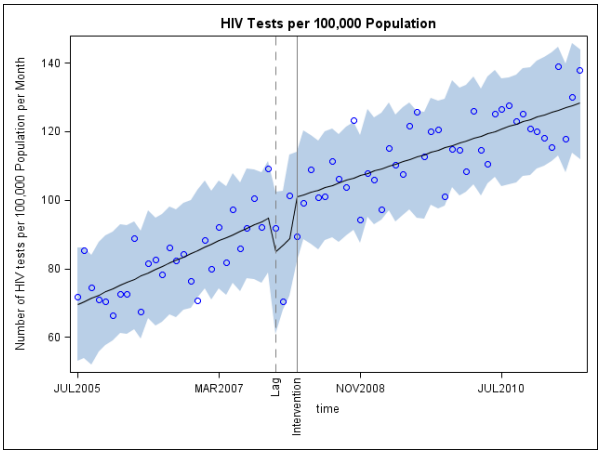
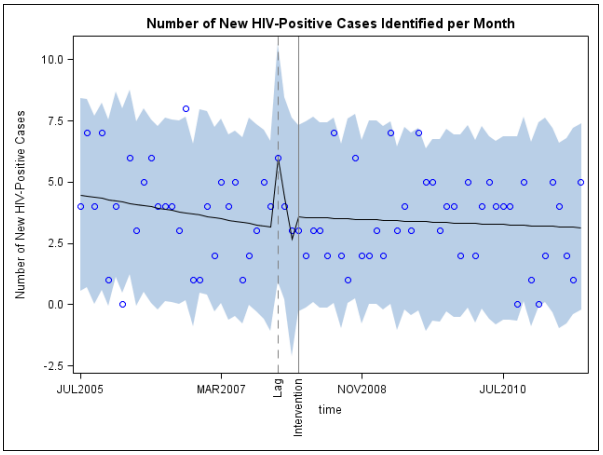


Figure A2.1(b): Women







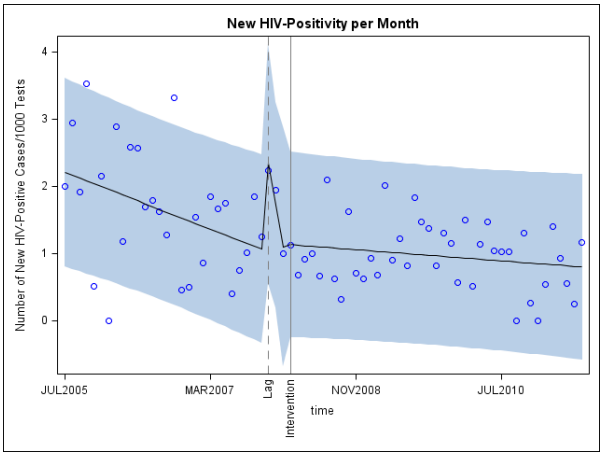
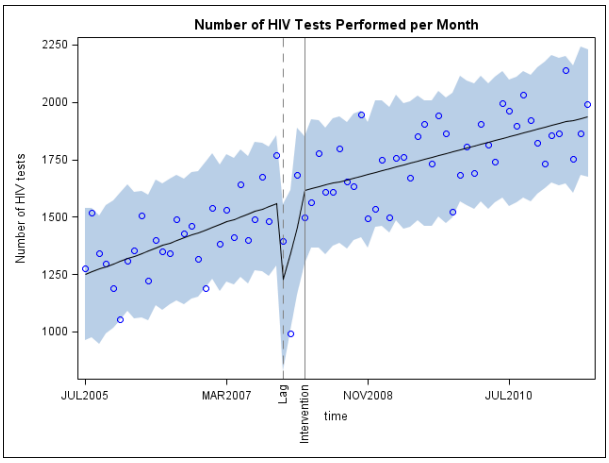
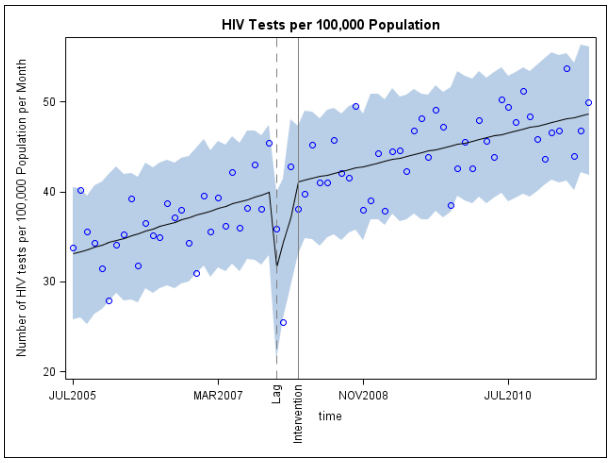
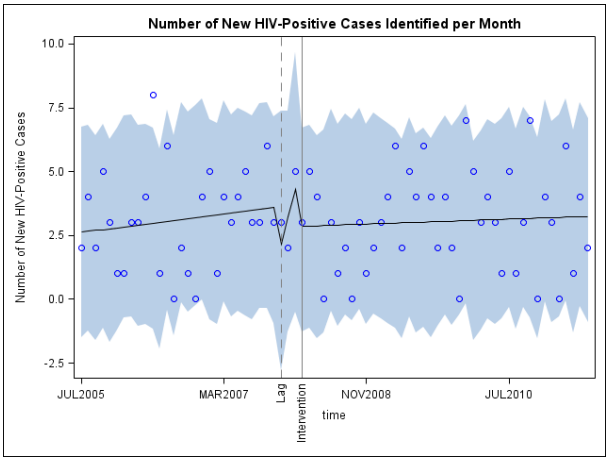


Figure A2.1(c): Non-Hispanic Whites







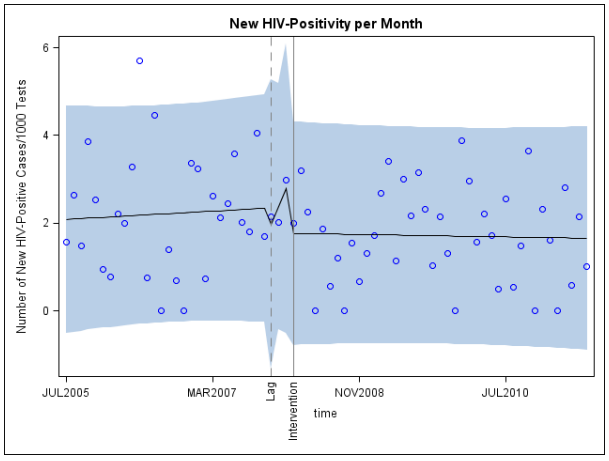


Figure A2.1(d): Non-Hispanic Blacks

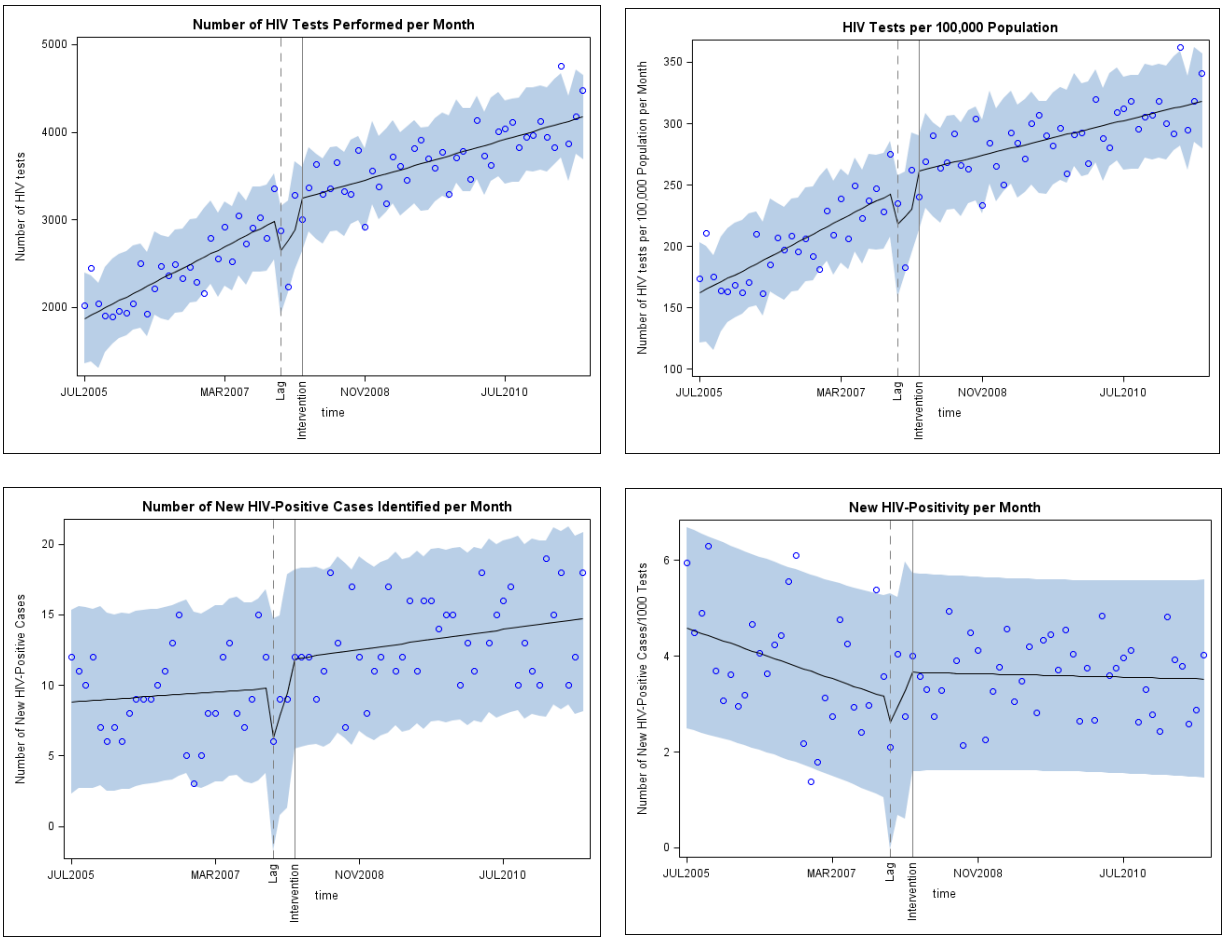
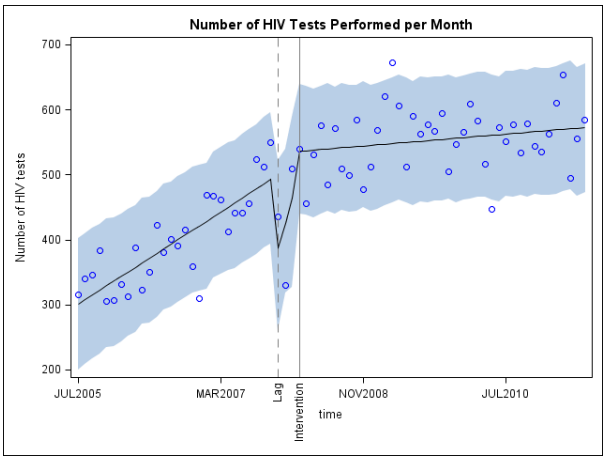
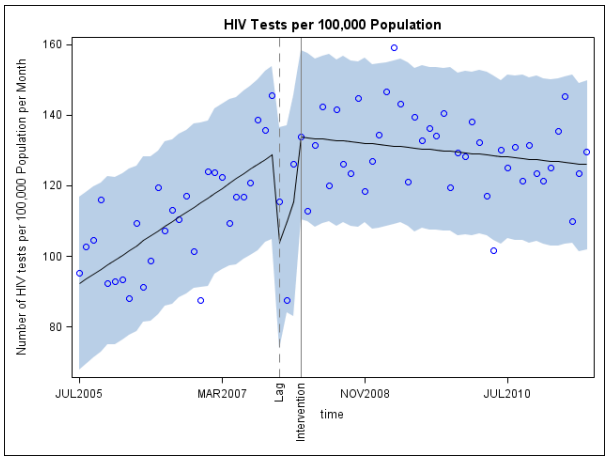
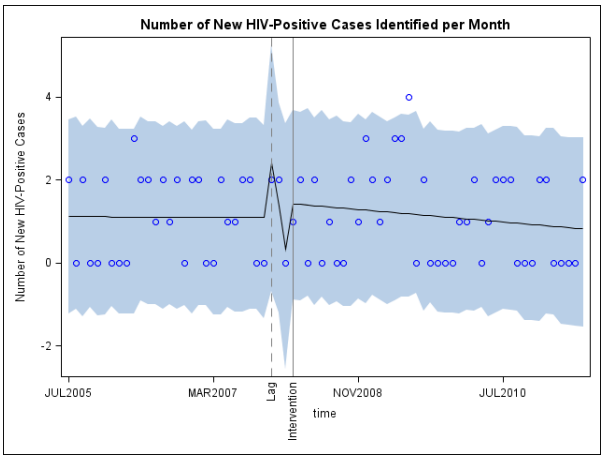


Figure A2.1(e): Hispanics







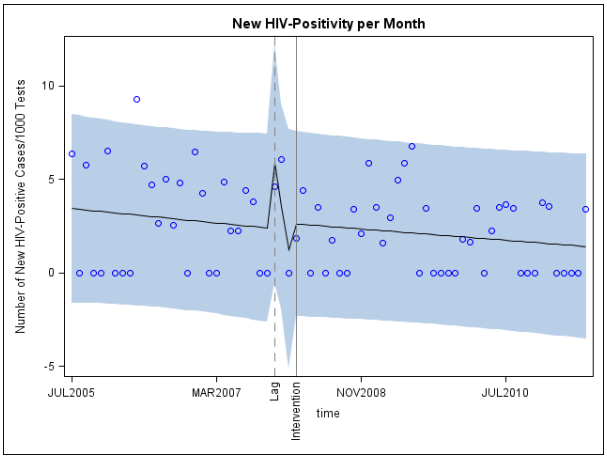
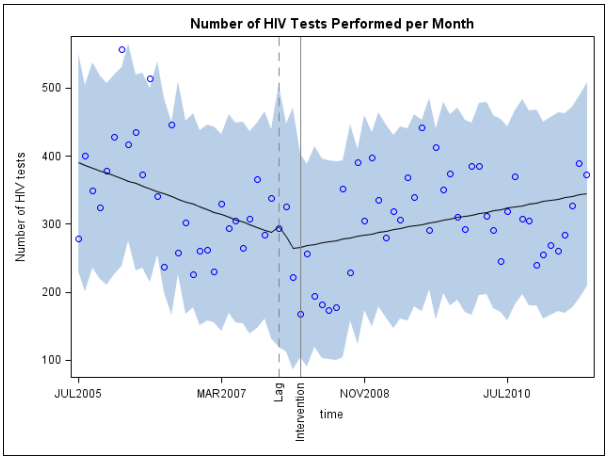
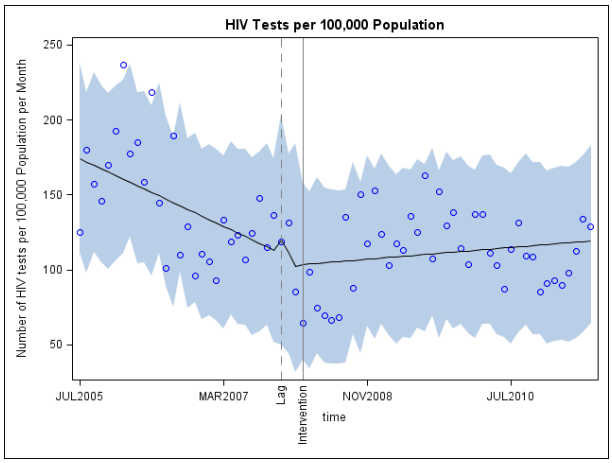
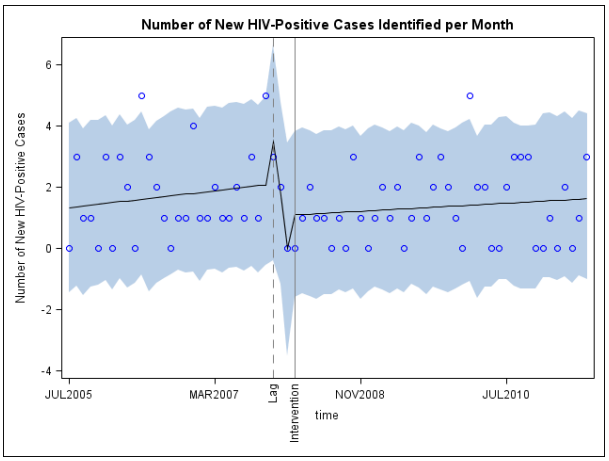


Figure A2.1(f): Other Race/Ethnicities







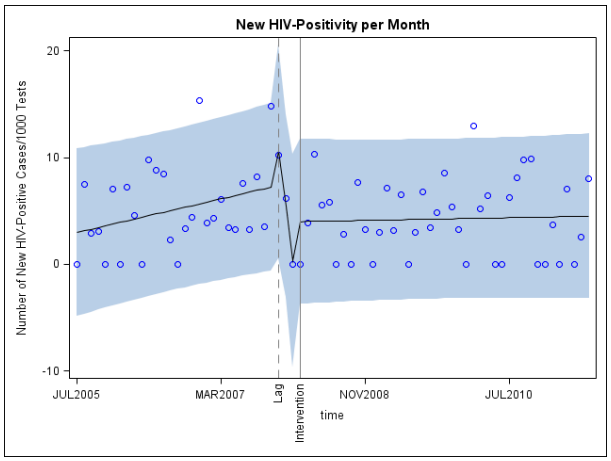
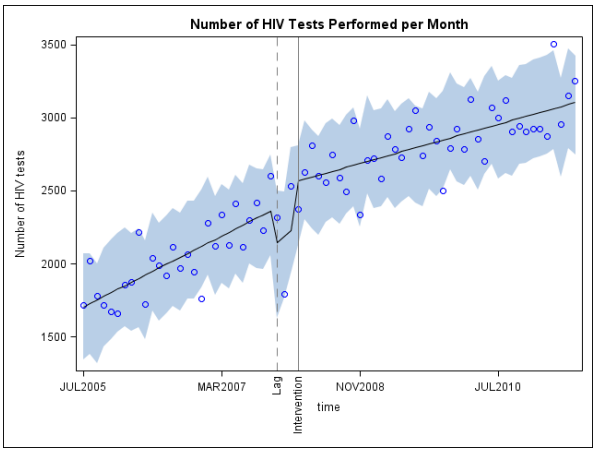
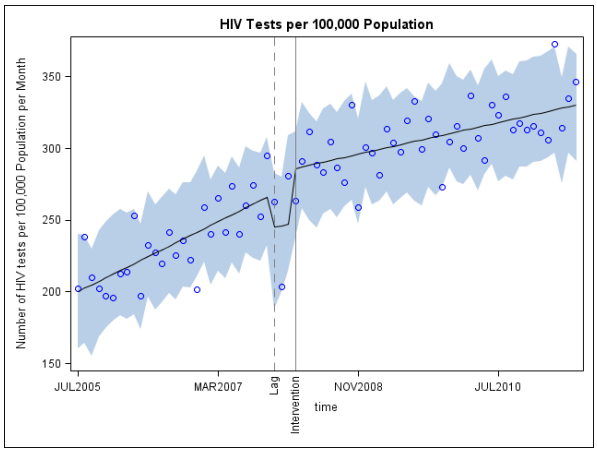
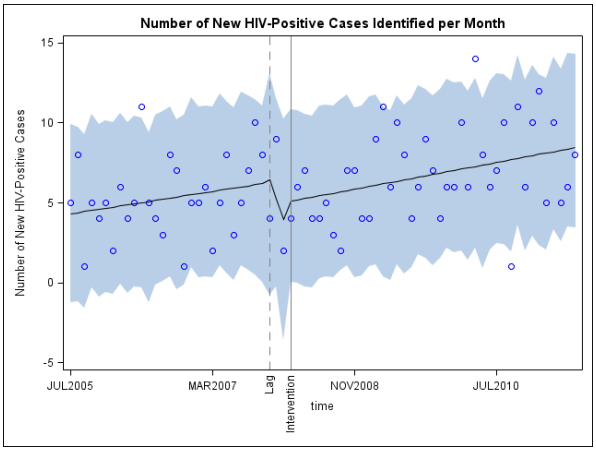


Figure A2.1(g): Aged 18-24







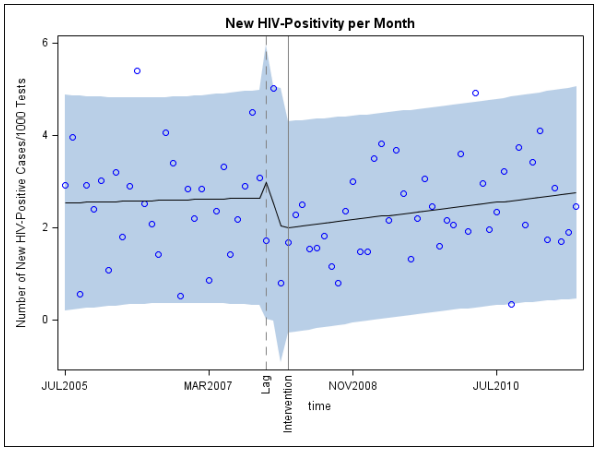
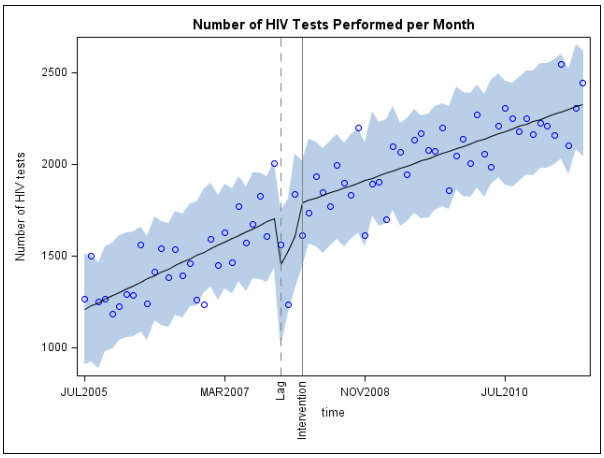
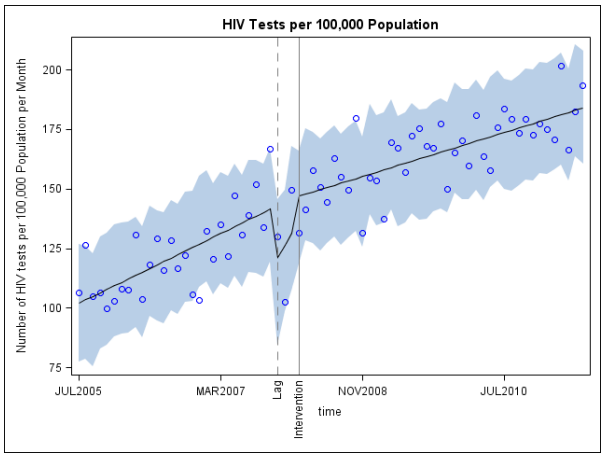
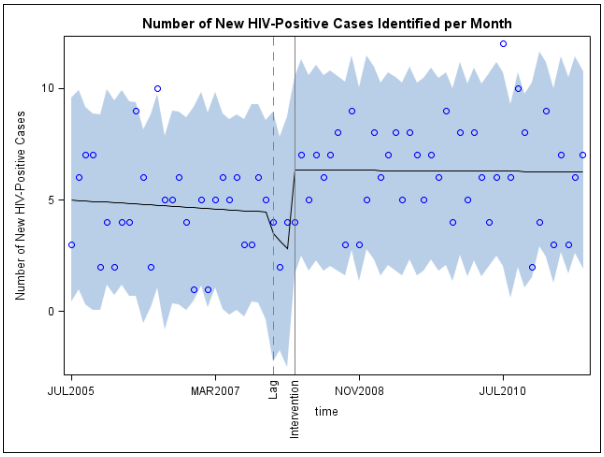


Figure A2.1(h): Aged 25-34







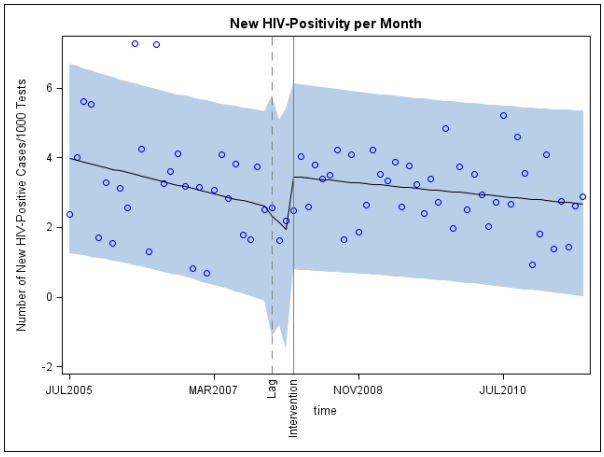
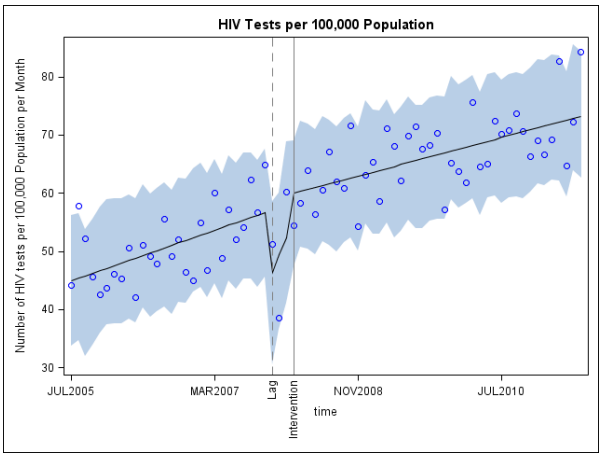
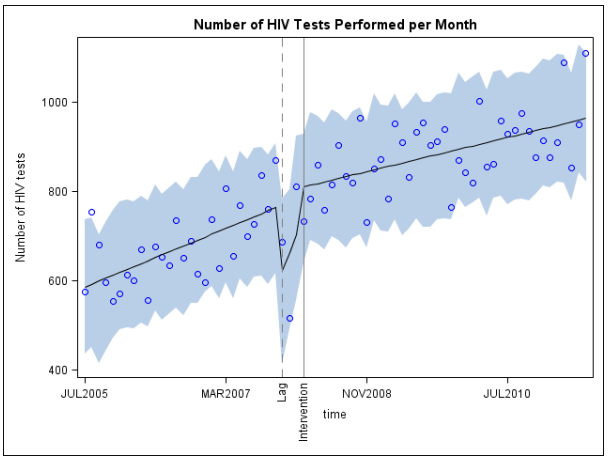
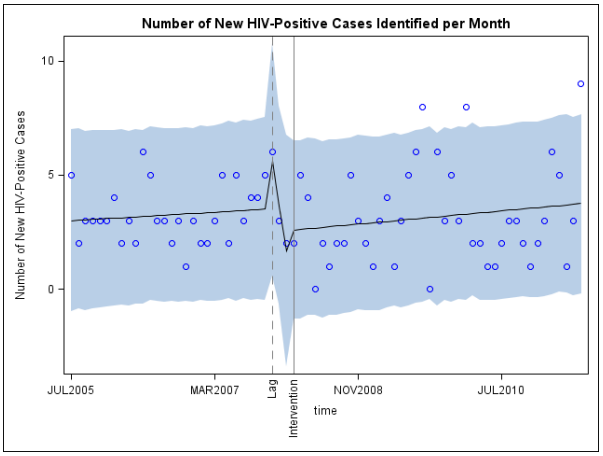


Figure A2.1(i): Aged 35-44







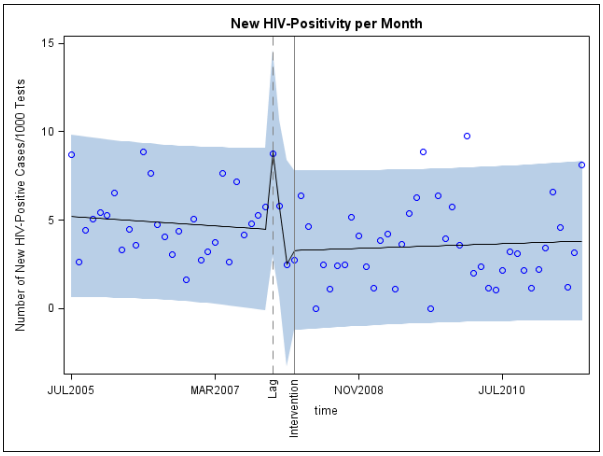
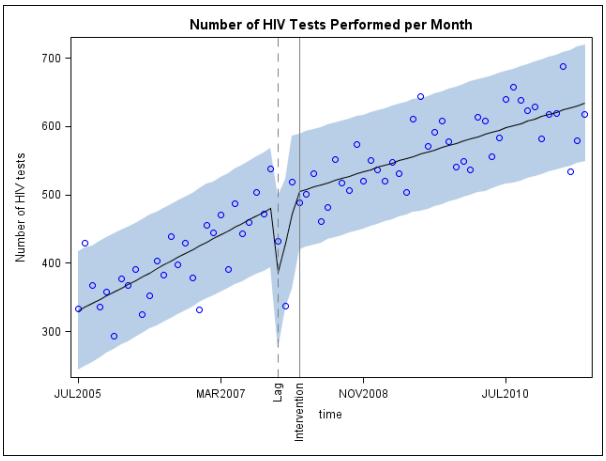
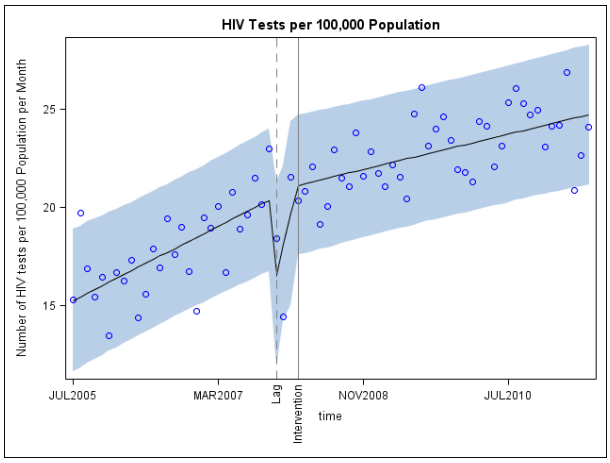
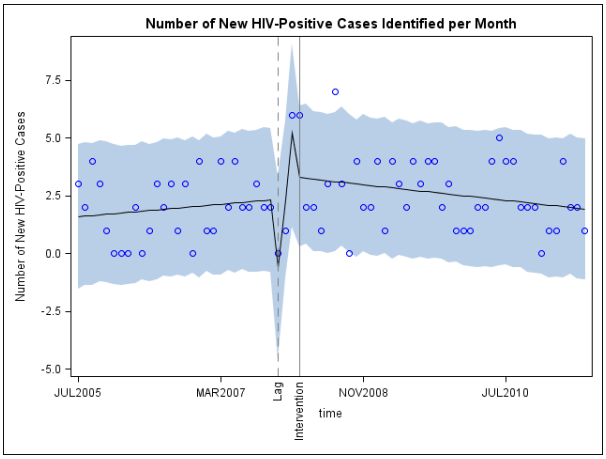


Figure A2.1(j): Aged 45-64







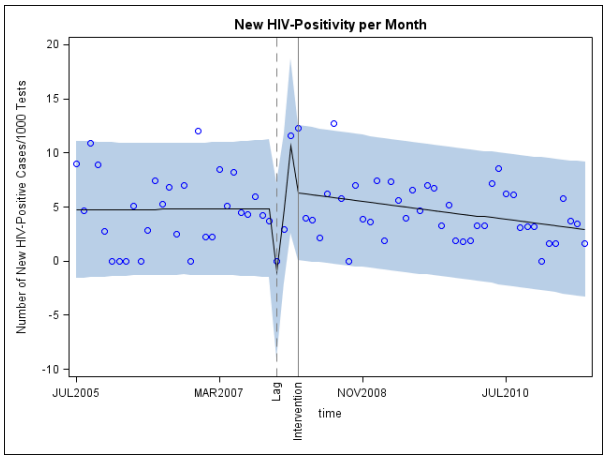
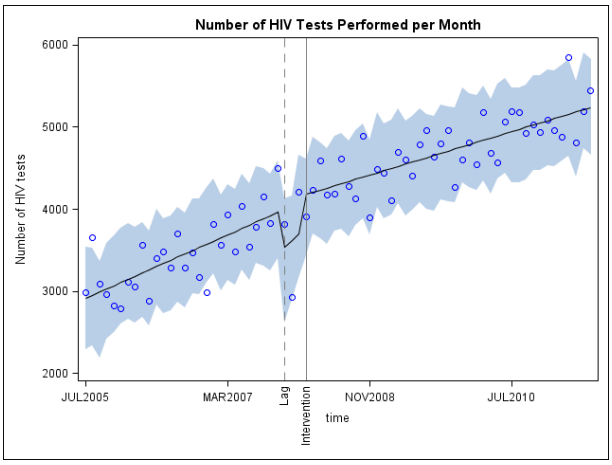
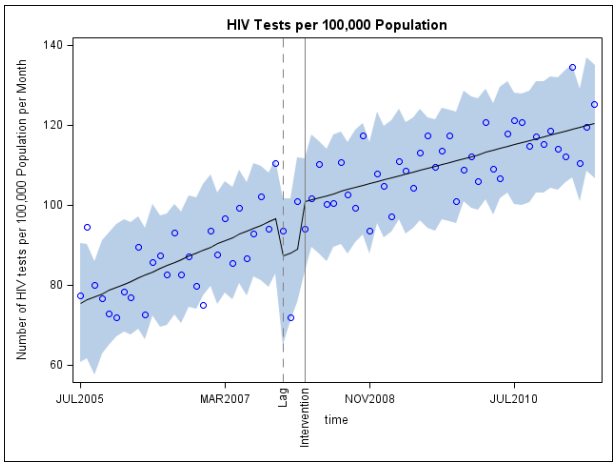
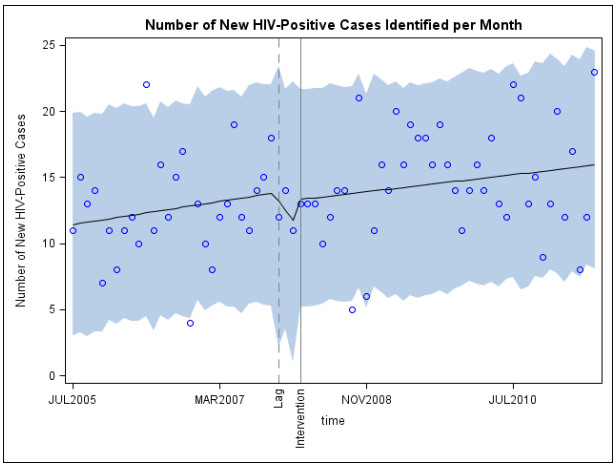


Figure A2.1(k): Clinics in Metropolitan Statistical Areas







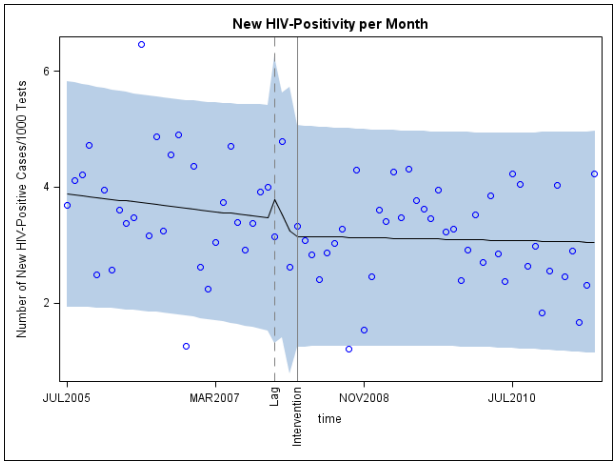


Figure A2.1(l): Clinics in Micropolitan Statistical Areas

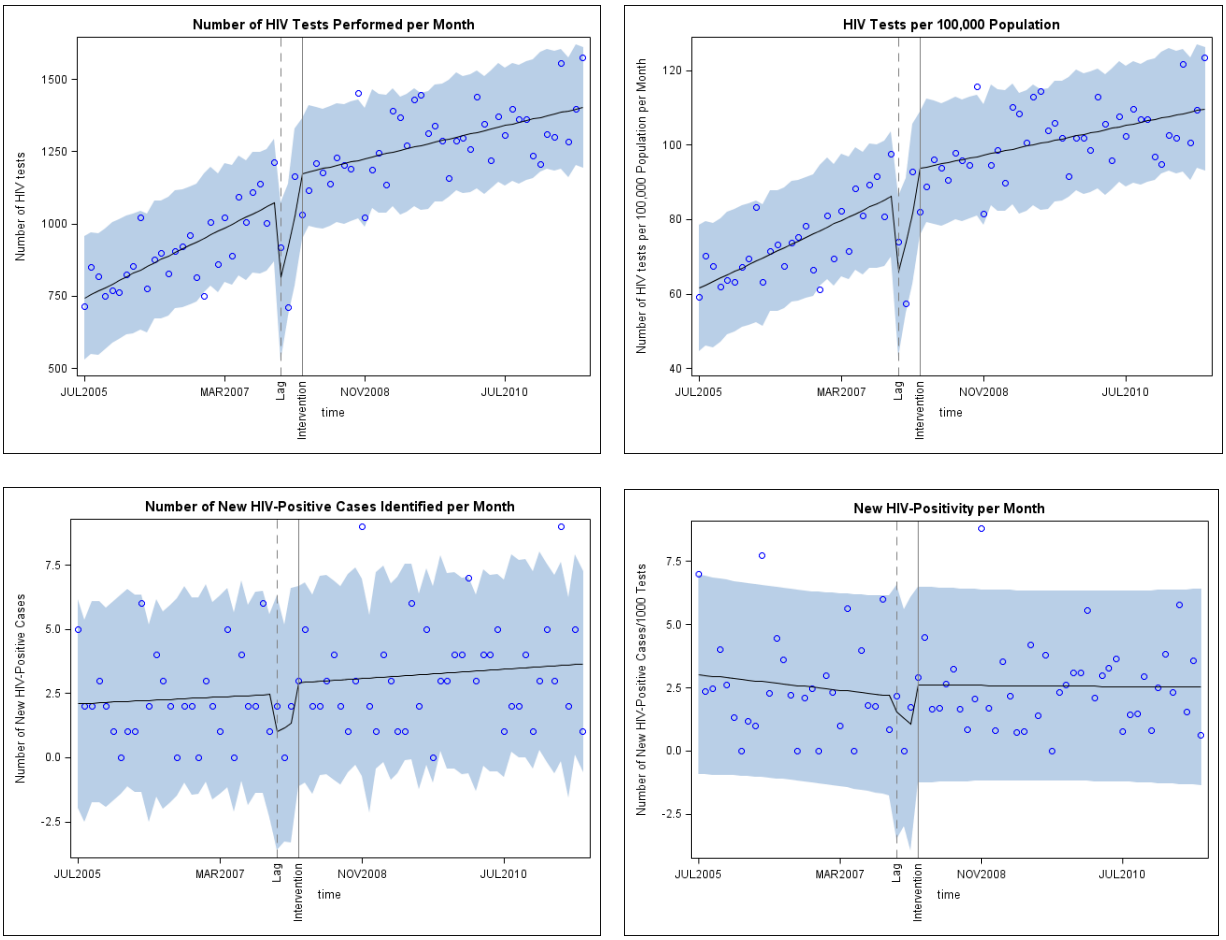
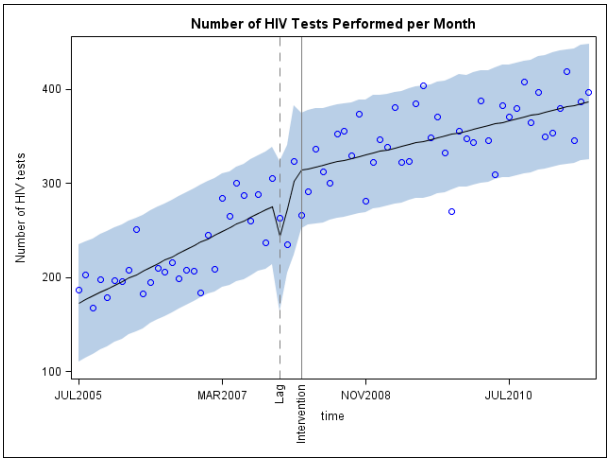
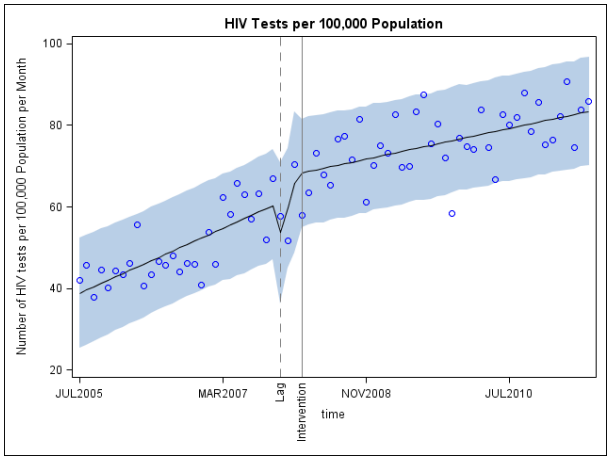
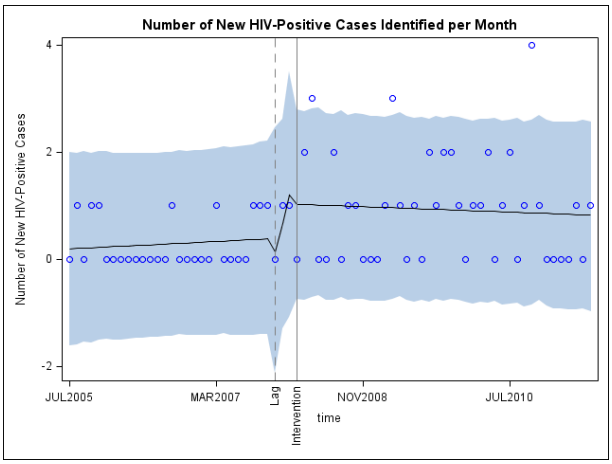


Figure A2.1(m): Clinics in Neither Metropolitan nor Micropolitan Statistical Areas







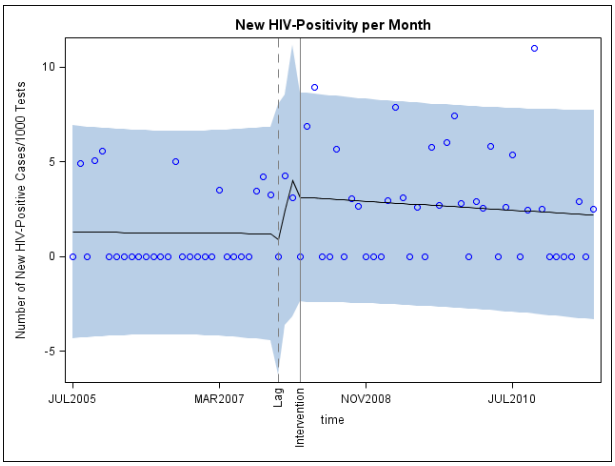
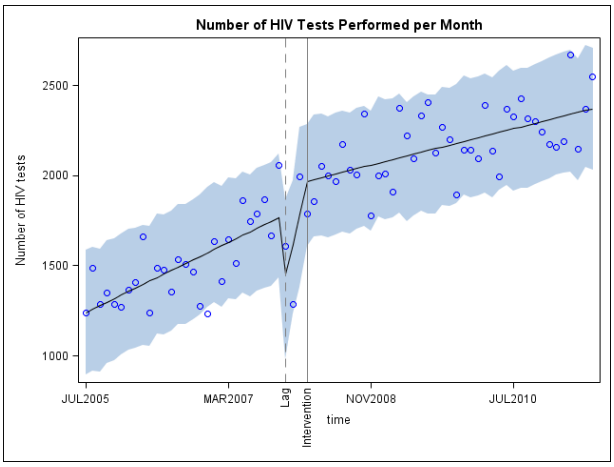
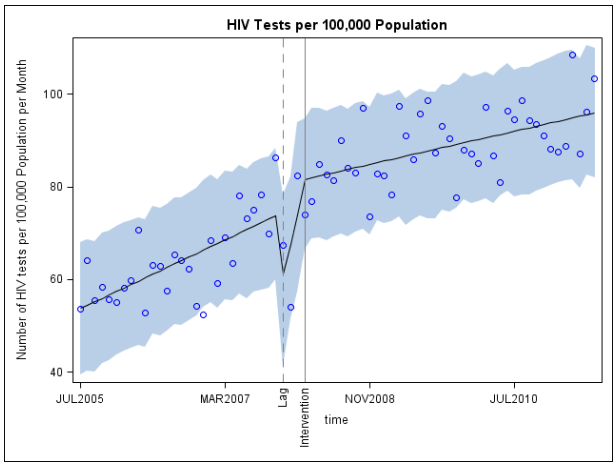
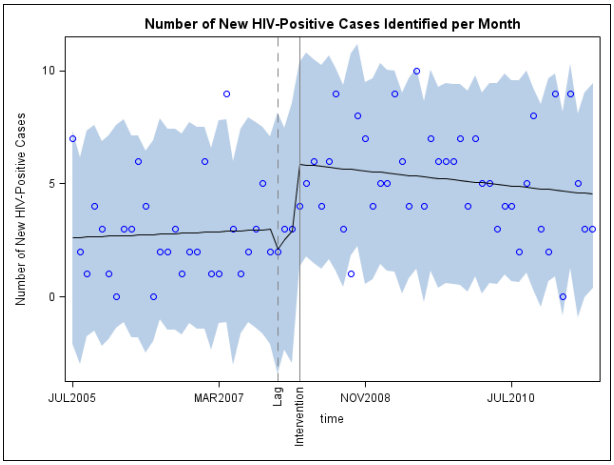


Figure A2.1(n): Clinics in Counties of Population Density <199 Persons per Square Mile







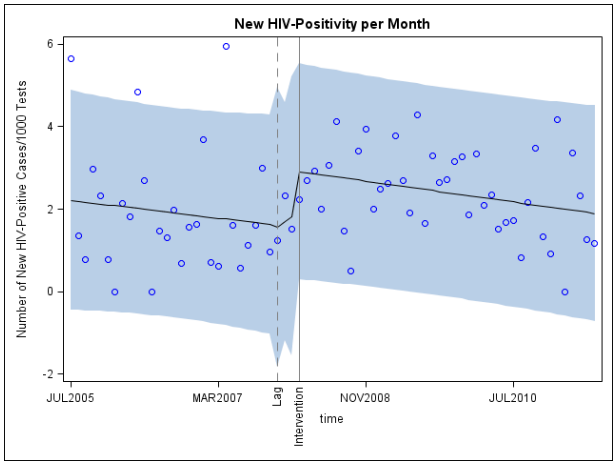
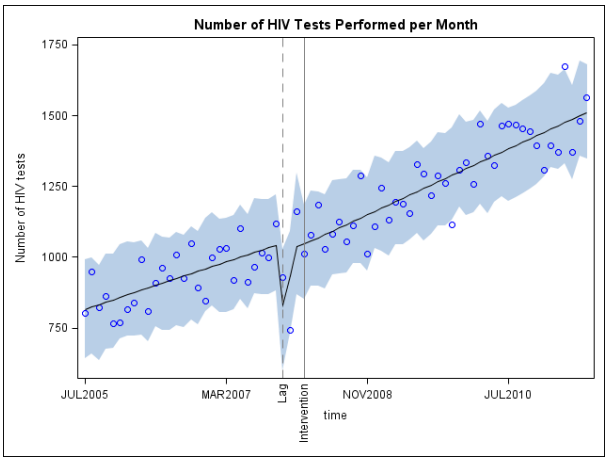
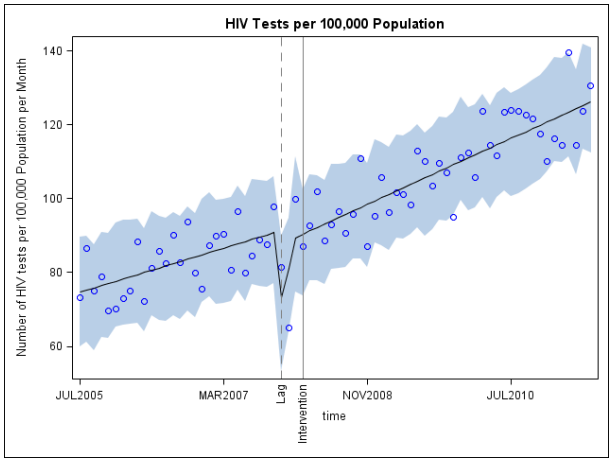
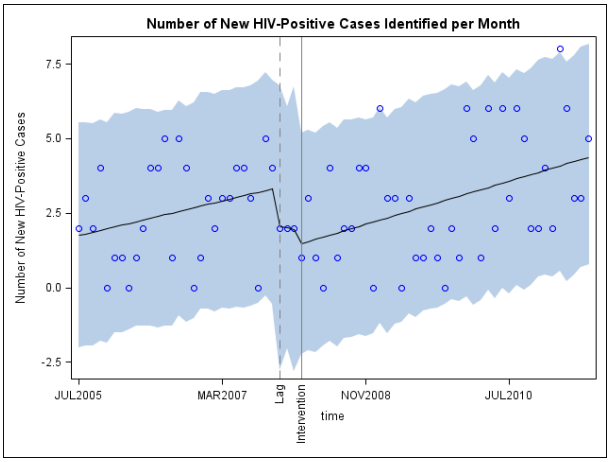


Figure A2.1(o): Clinics in Counties of Population Density 200-399 Persons per Square Mile







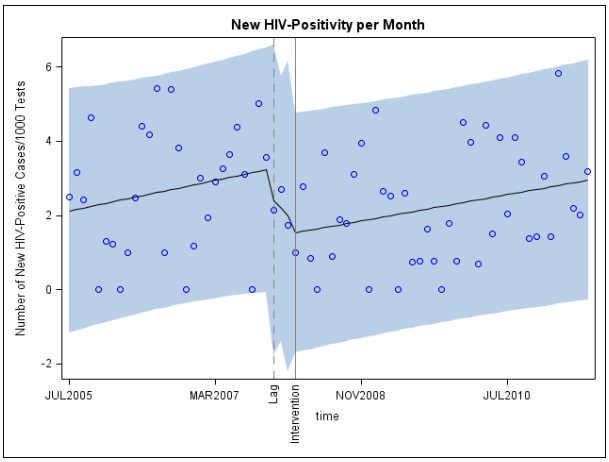
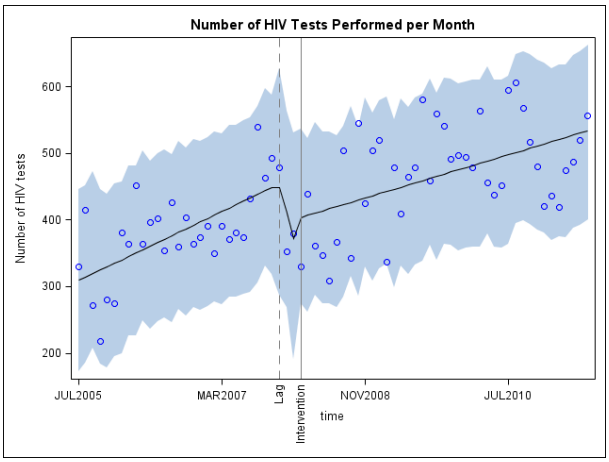
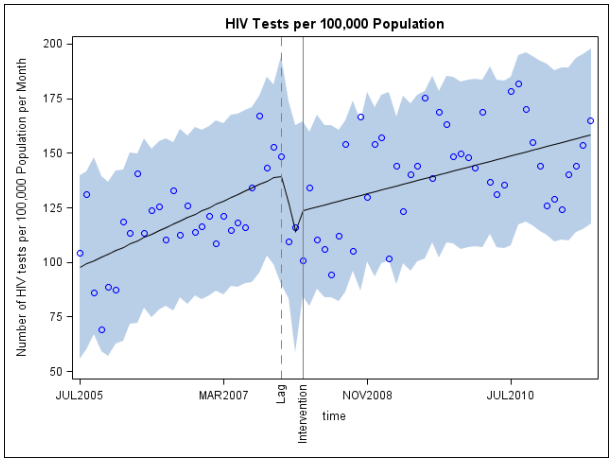
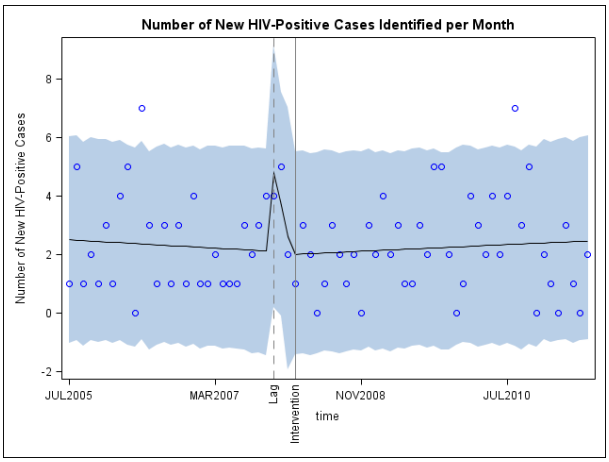


Figure A2.1(p): Clinics in Counties of Population Density 400-500 Persons per Square Mile







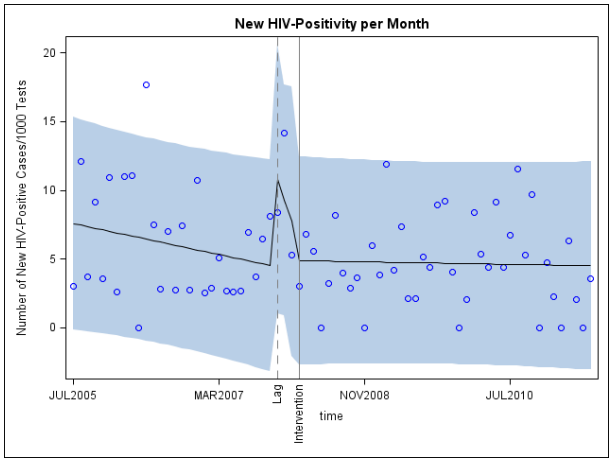


Figure A2.1(q): Clinics in Counties of Population Density ≥600 Persons per Square Mile

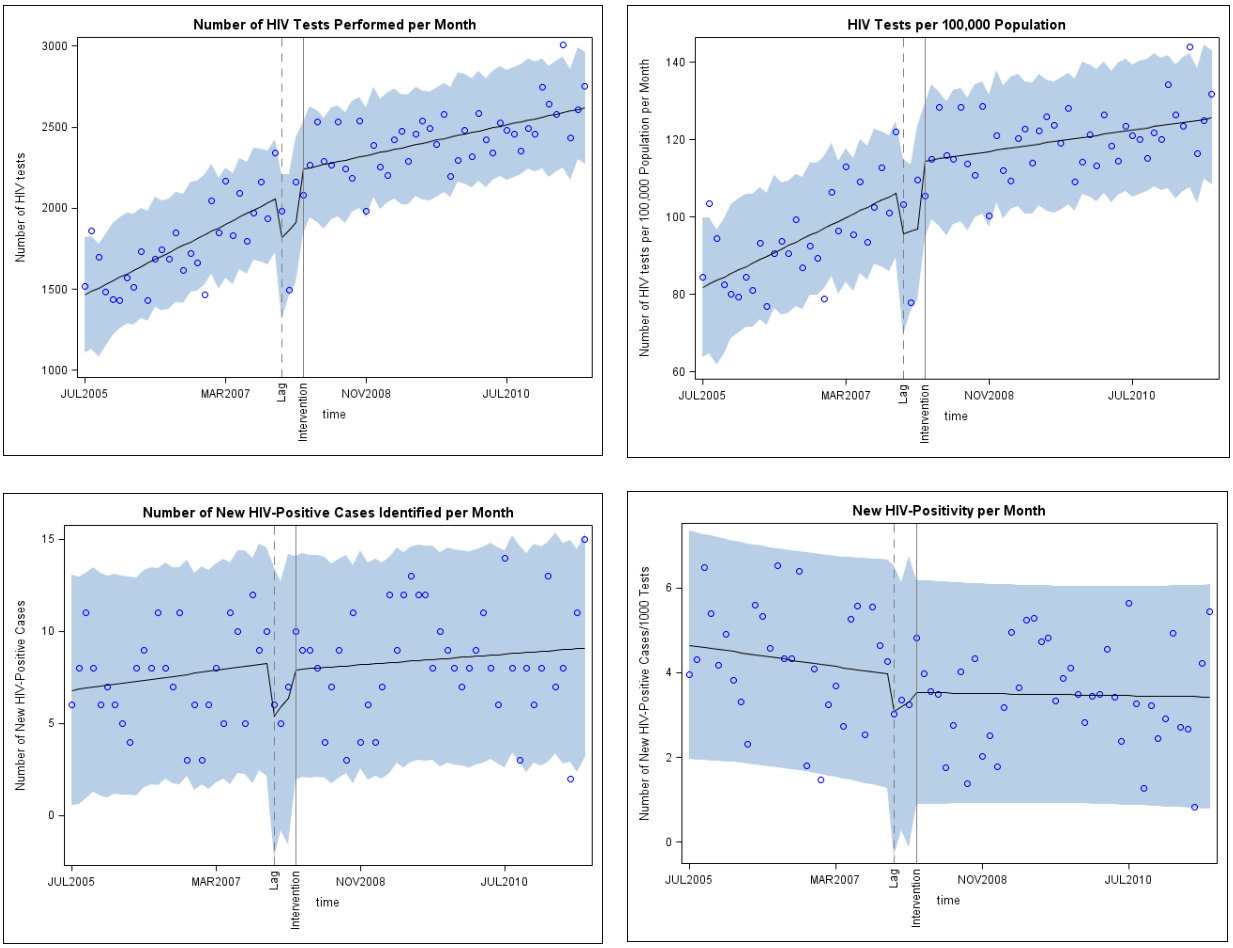
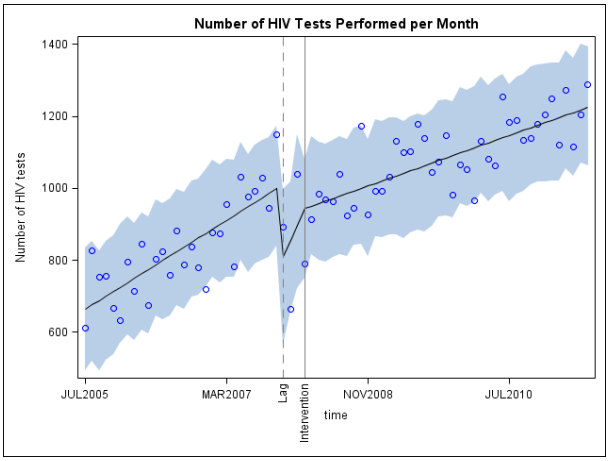
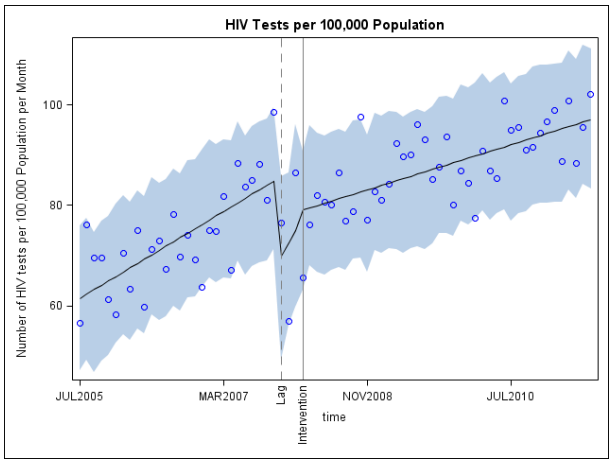
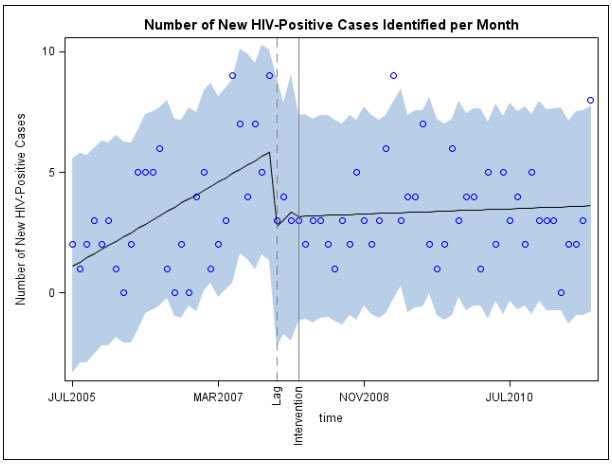


Figure A2.1(r): Clinics in Counties with <15% of the Population Below the Poverty Line







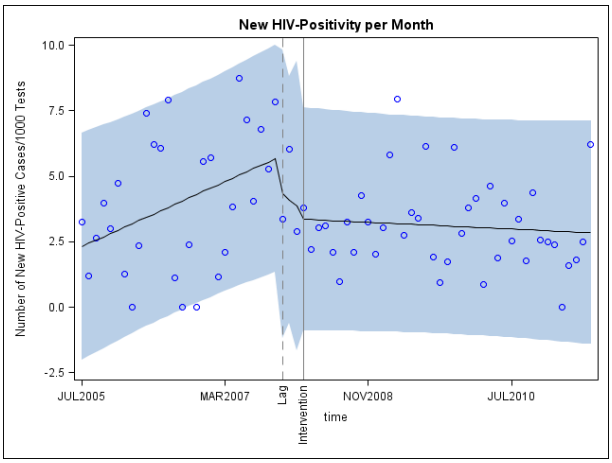
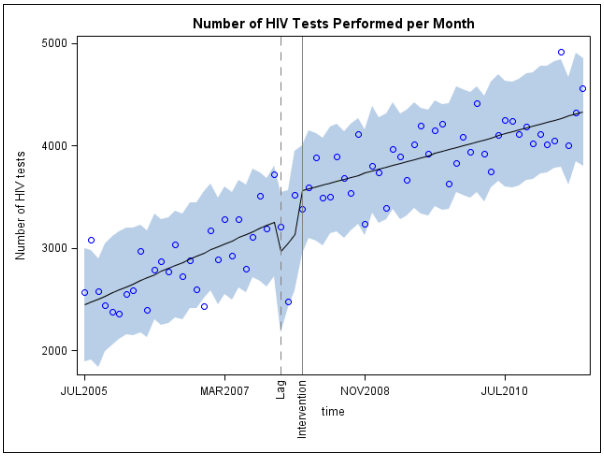
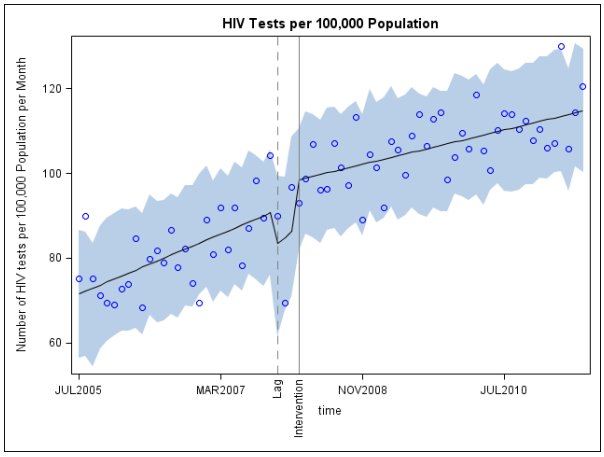
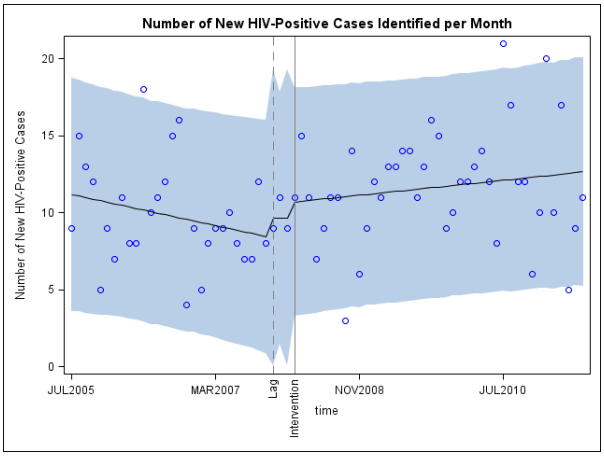


Figure A2.1(s): Clinics in Counties with 15-19.9% of the Population Below the Poverty Line







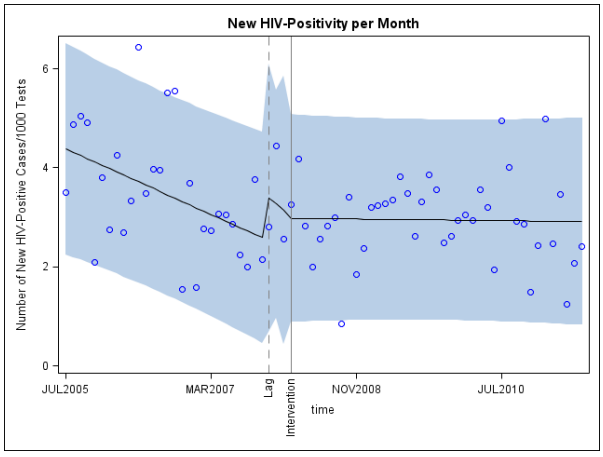


Figure A2.1(t): Clinics in Counties with 20-24.9% of the Population Below the Poverty Line

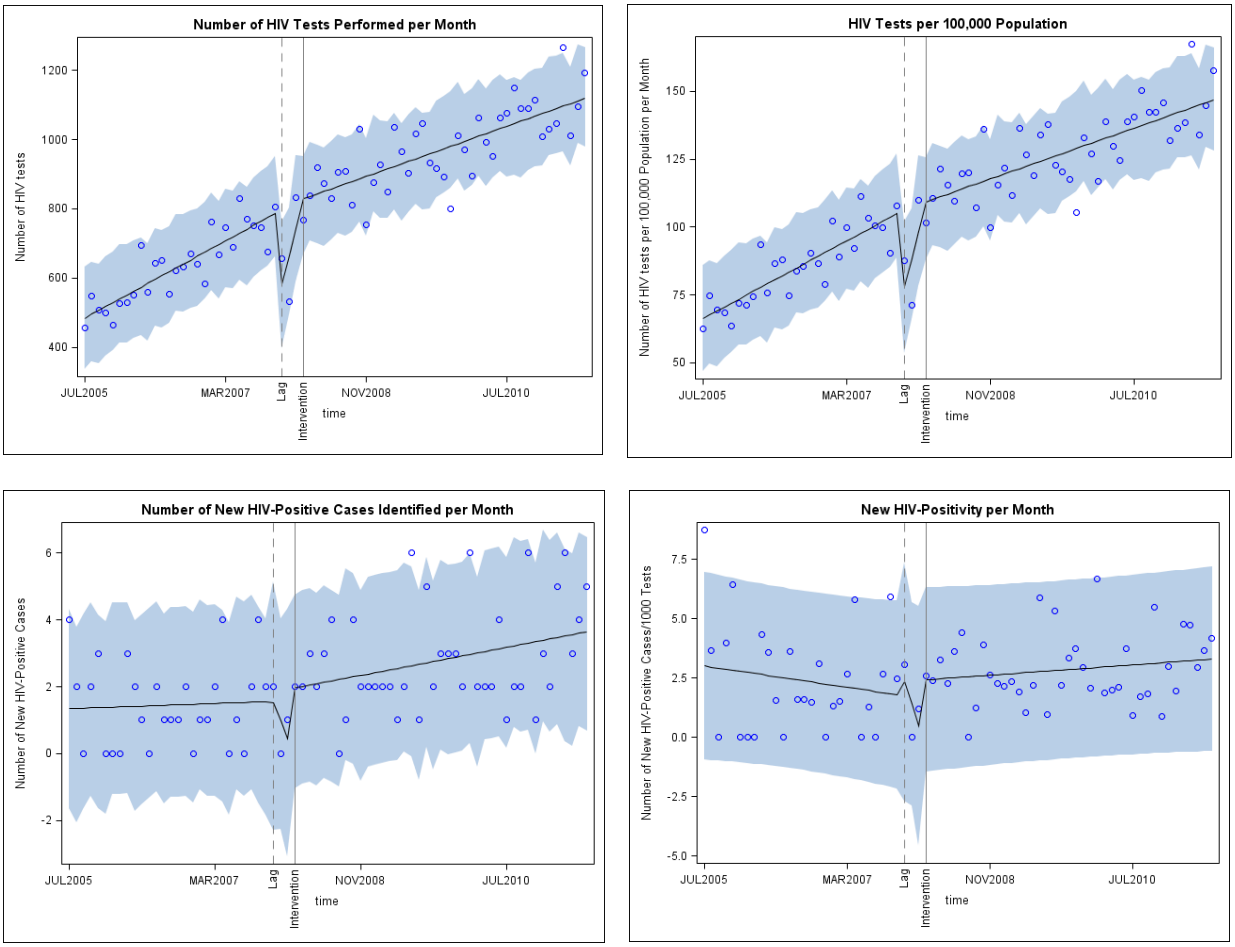
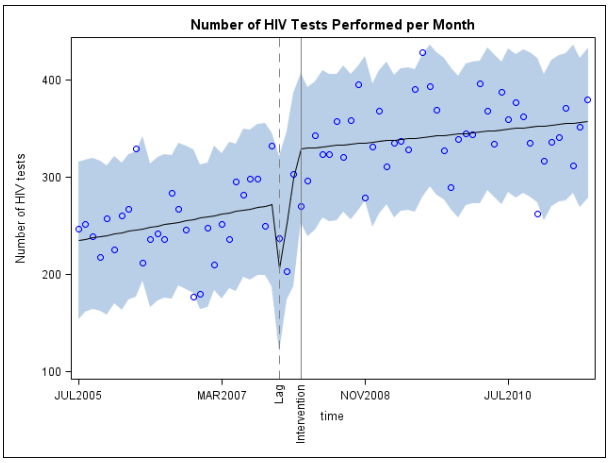
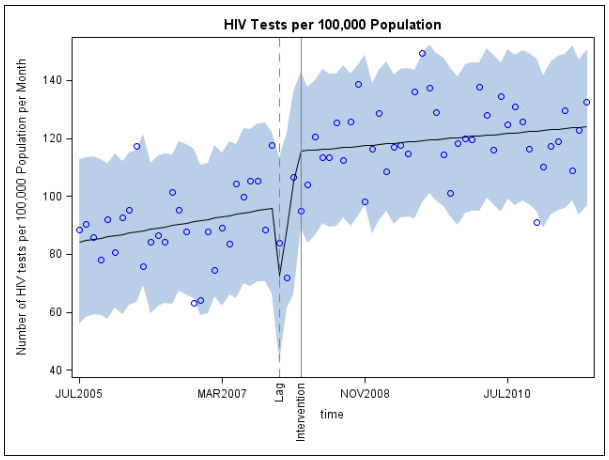
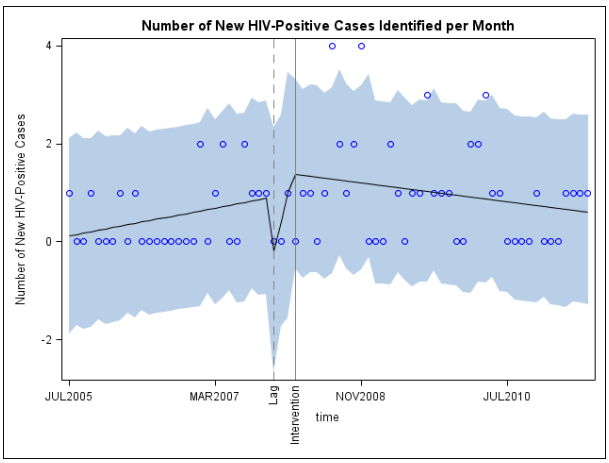


Figure A2.1(u): Clinics in Counties with ≥25% of the Population Below the Poverty Line







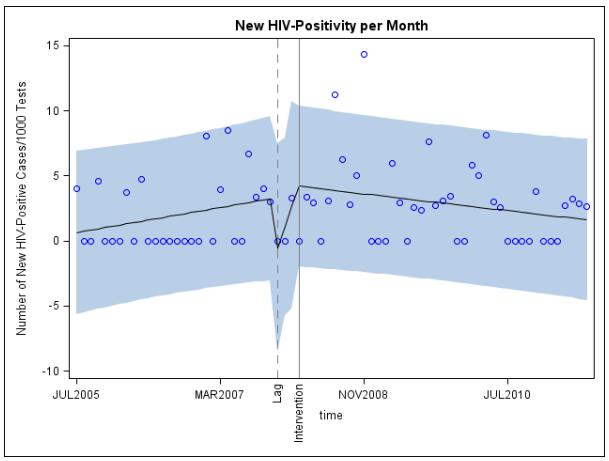
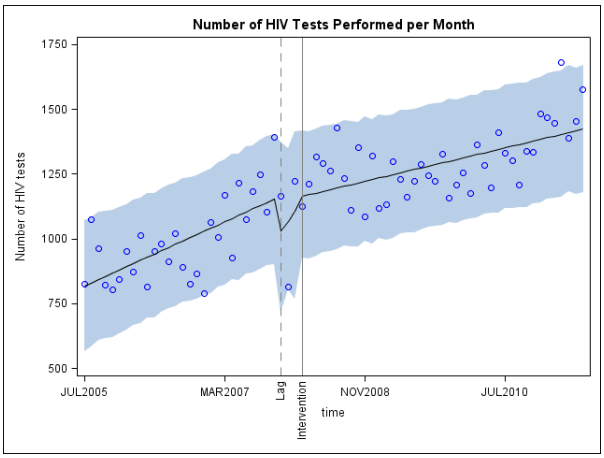
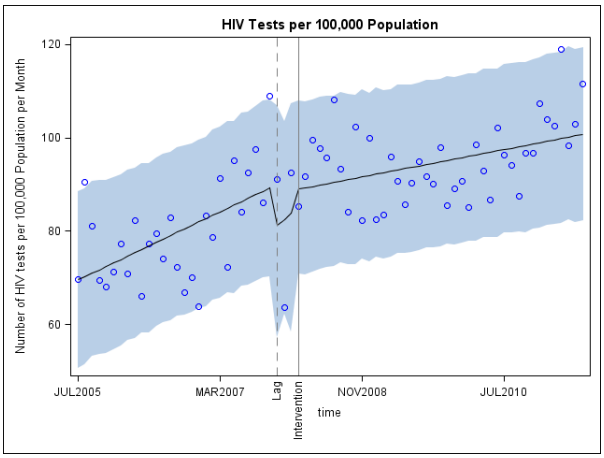
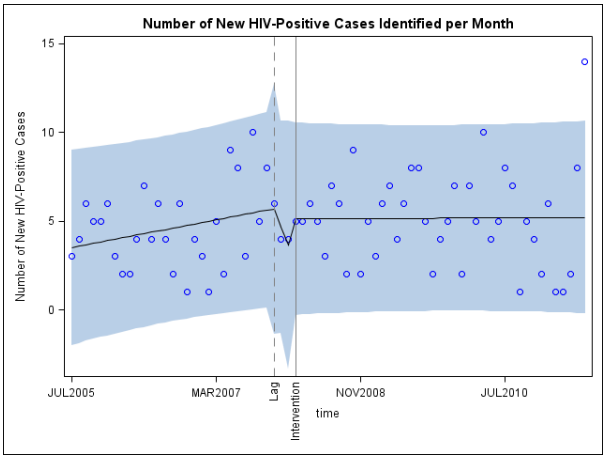


Figure A2.1(v): Clinics with an In-House HIV Clinic







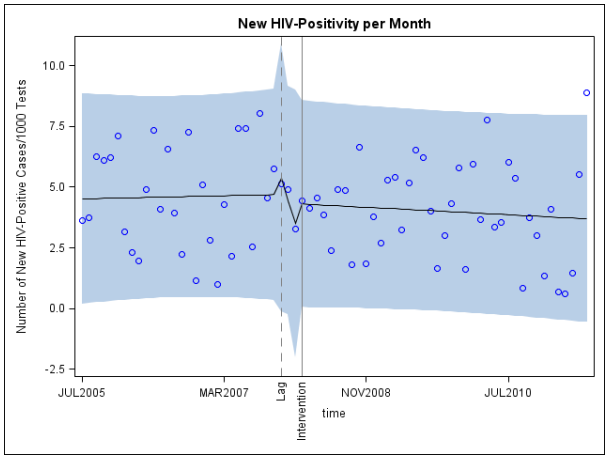
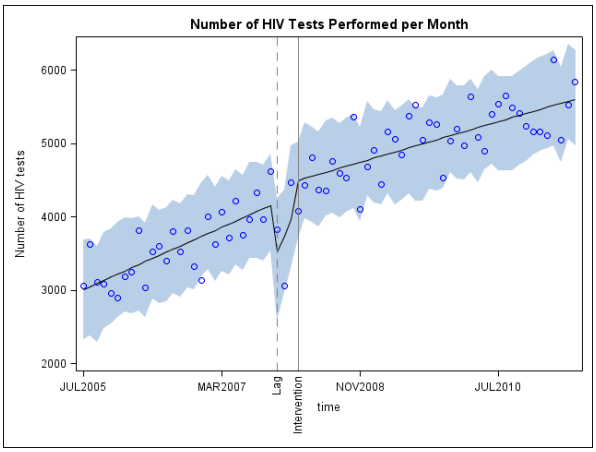
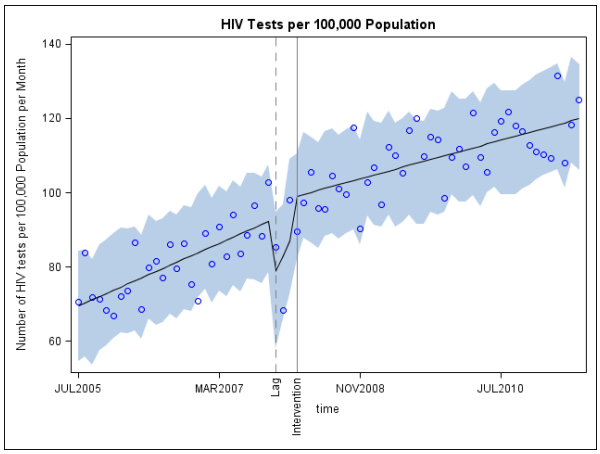
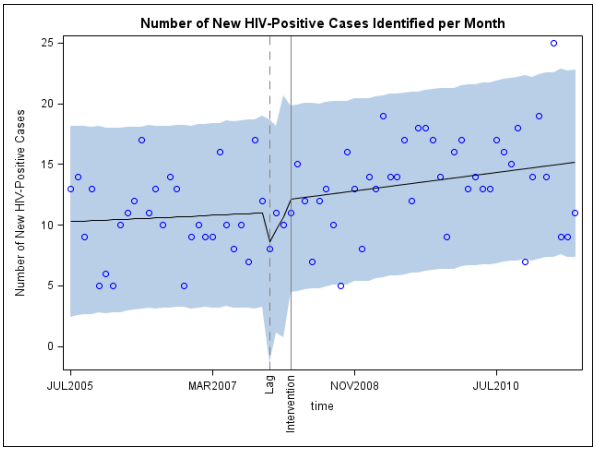


Figure A2.1(w): Clinics without an In-House HIV Clinic







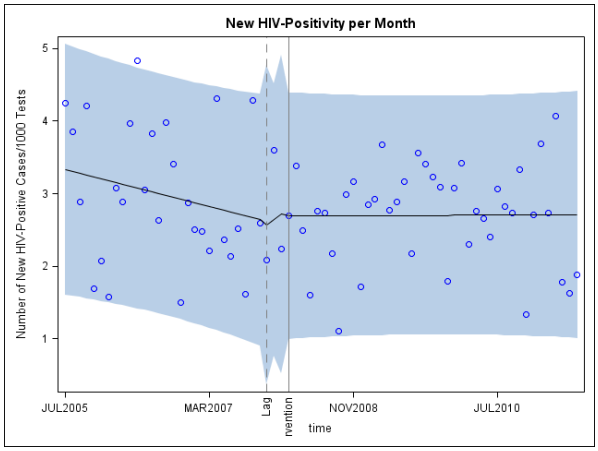
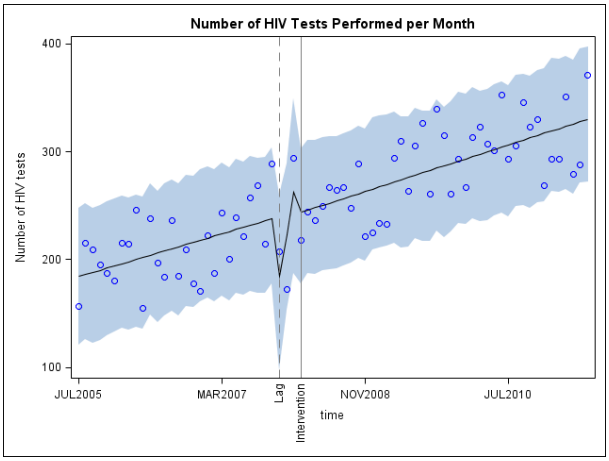
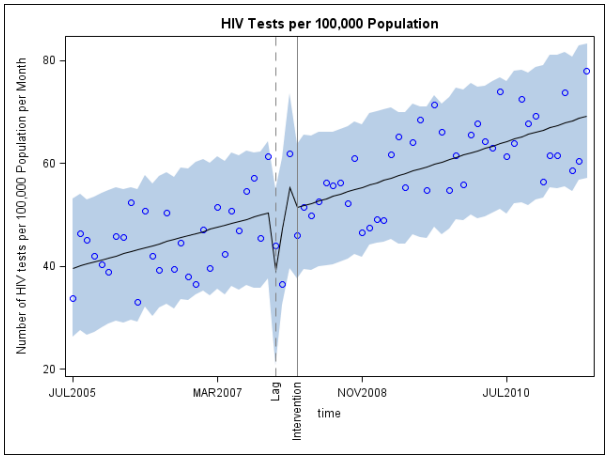
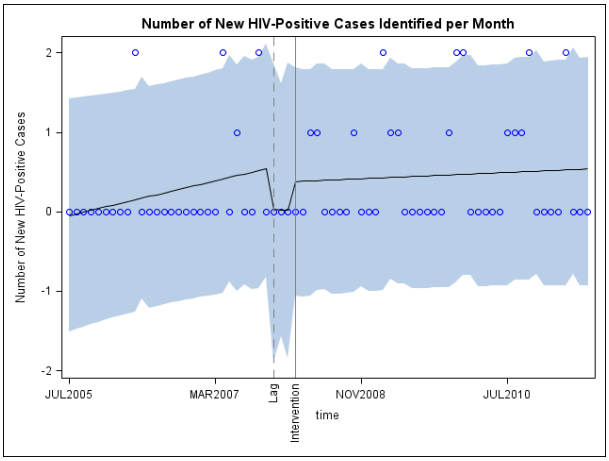


Figure A2.1(x): Clinics in Counties with Baseline HIV Case Rate of 0-4.9 per 100,000 Population







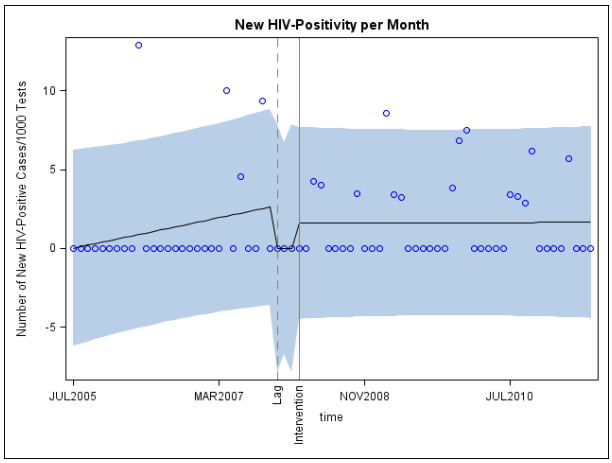
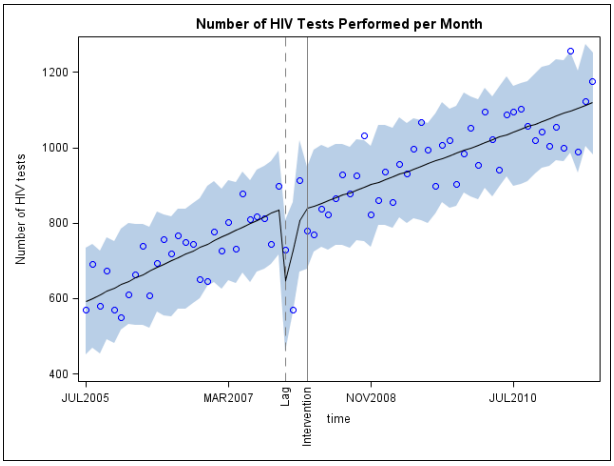
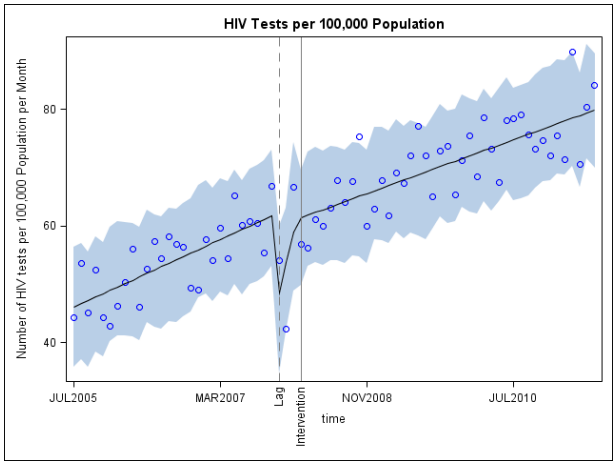
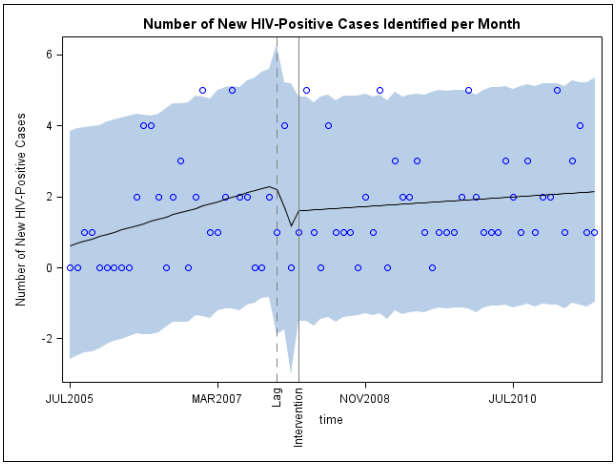


Figure A2.1(y): Clinics in Counties with Baseline HIV Case Rate of 5-9.9 per 100,000 Population







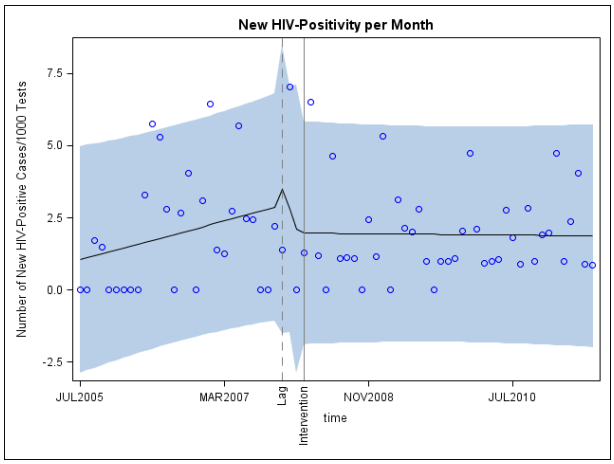
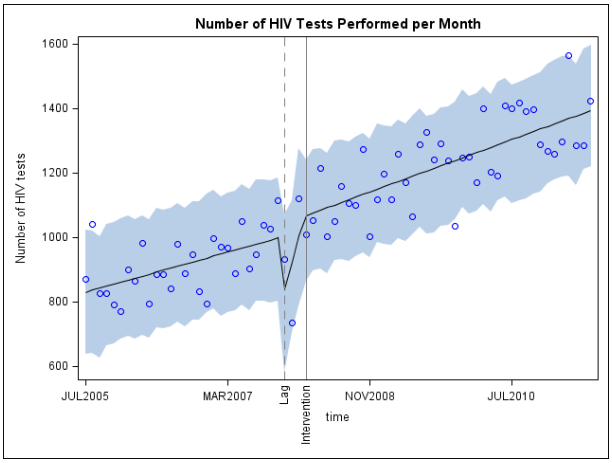
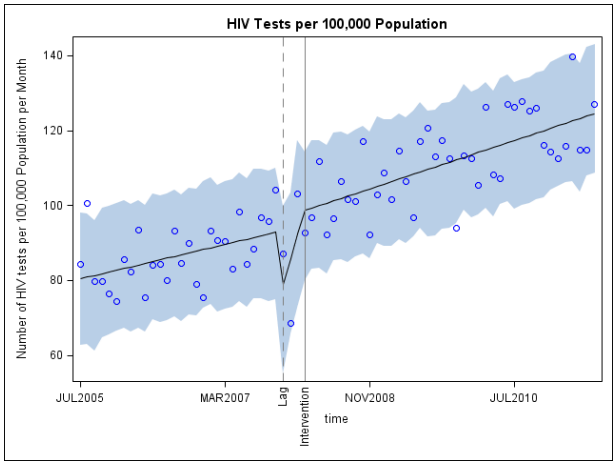
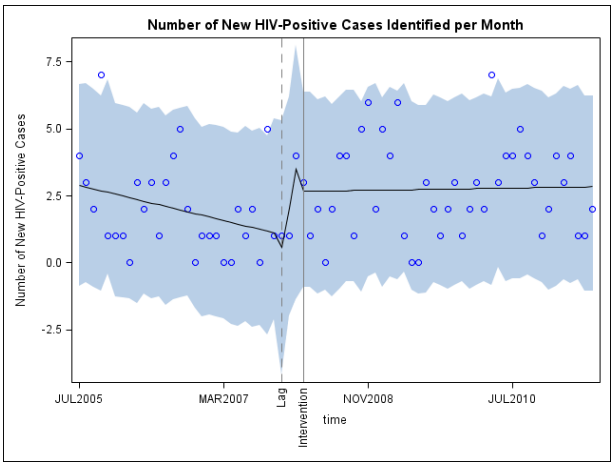


Figure A2.1(z): Clinics in Counties with Baseline HIV Case Rate of 10-14.9 per 100,000 Population







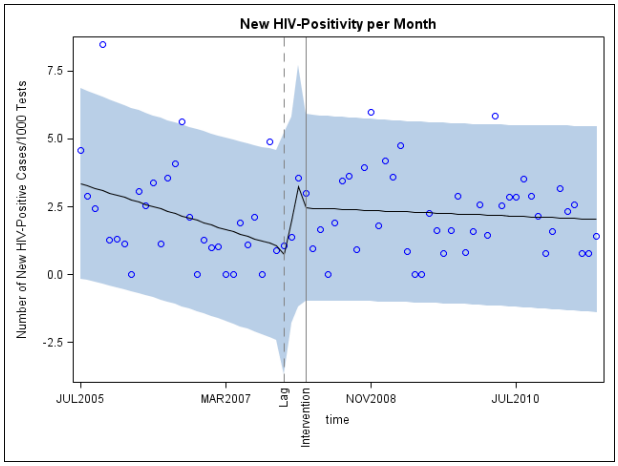


Figure A2.1(aa): Clinics in Counties with Baseline HIV Case Rate of ≥15 per 100,000 Population

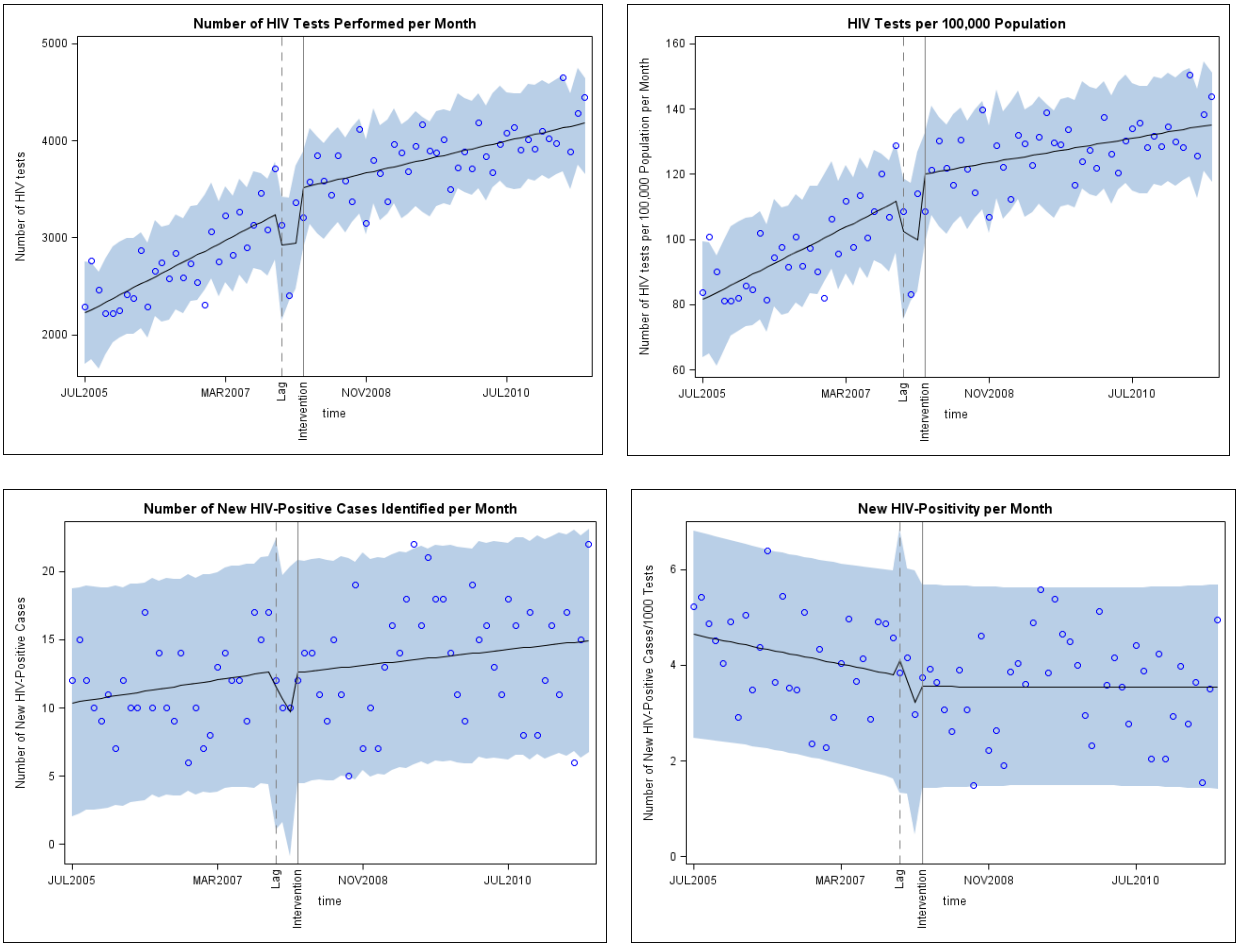


Table A2.6: Sensitivity Analysis: Comparison of Lag Periods (0 months, 3 months, 6 months) on Interrupted Time Series Results for HIV Testing and Case Detection Outcomes

	Pre-Intervention MD (95% CI)*	Overall Post-Intervention MD (95% CI)*	Attributable to Intervention MD (95% CI)*
Number of HIV Tests			
No Lag	54.11 (37.36, 70.86)	40.66 (32.20, 49.11)	-13.45 (-32.13, 5.24)
3 Month Lag	**54.69 (40.72, 68.66)**	**33.75 (25.93, 41.57)**	**-20.94 (-36.95, -4.94)**
6 Month Lag	54.83 (40.81, 68.84)	33.76 (24.96, 42.57)	-21.06 (-37.61, -4.52)
Rate of HIV Testing per 100,000 Population			
No Lag	0.84 (0.56, 1.12)	0.57 (0.42, 0.71)	-0.27 (-0.59, 0.05)
3 Month Lag	**0.81 (0.58, 1.05)**	**0.46 (0.33, 0.60)**	**-0.35 (-0.62, -0.08)**
6 Month Lag	0.82 (0.58, 1.05)	0.46 (0.31, 0.61)	-0.36 (-0.64, -0.07)
Number of HIV-Infections			
No Lag	0.10 (-0.09, 0.29)	0.10 (0.00, 0.20)	0.00 (-0.21, 0.21)
3 Month Lag	**0.10 (-0.09, 0.29)**	**0.08 (-0.03, 0.19)**	**-0.03 (-0.24, 0.19)**
6 Month Lag	0.10 (-0.09, 0.30)	0.09 (-0.04, 0.21)	-0.02 (-0.25, 0.21)
Rate of HIV-Positivity per 1,000 Tests			
No Lag	-0.02 (-0.05, 0.02)	0.00 (-0.02, 0.01)	0.01 (0.00, 0.05)
3 Month Lag	**-0.02 (-0.05, 0.02)**	**0.00 (-0.02, 0.02)**	**0.01 (-0.02, 0.05)**
6 Month Lag	-0.02 (-0.05, 0.02)	0.00 (-0.02, 0.02)	0.02 (-0.02, 0.06)

*MD: mean difference, 95% CI: 95% confidence interval
Bold: base case scenario

Table A2.7: Intercensal Population Estimates, 2005-2011

	Intercensal Population Estimates						
	2005	2006	2007	2008	2009	2010	2011
Overall	5,519,921	5,651,861	5,767,073	5,877,799	5,955,804	6,025,081	6,076,089
Gender							
Male	2,721,668	2,788,186	2,832,321	2,888,829	2,922,520	2,957,715	2,980,145
Female	2,798,253	2,863,675	2,934,752	2,988,970	3,033,284	3,067,366	3,095,944
Race/Ethnicity							
White	3,779,507	3,842,024	3,890,934	3,931,518	3,953,351	3,971,835	3,983,752
Black	1,163,462	1,194,311	1,222,168	1,250,609	1,273,130	1,293,847	1,311,611
Hisp	331,213	354,463	377,358	403,755	423,092	440,503	450,392
Other	222,491	235,055	247,397	259,988	271,112	281,528	290,296
Age (years)							
18-24	847,897	874,719	881,226	901,791	916,011	927,628	939,829
25-34	1,187,065	1,192,318	1,201,650	1,223,875	1,237,192	1,254,196	1,262,635
35-44	1,307,014	1,326,333	1,342,822	1,347,032	1,336,480	1,324,496	1,316,460
45-64	2,177,945	2,258,491	2,341,375	2,405,101	2,466,121	2,518,761	2,557,165
Metropolitan Status*							
Metropolitan	3,866,718	3,976,406	4,072,924	4,164,999	4,232,414	4,290,295	4,350,692
Micropolitan	1,209,927	1,226,883	1,240,785	1,255,810	1,264,050	1,273,688	1,277,319
Neither	445,344	450,654	455,515	459,136	461,502	463,223	462,011
Population Density#							
<199	2,312,142	2,352,558	2,385,196	2,417,870	2,437,836	2,461,135	2,464,184
200-399	1,096,360	1,119,612	1,142,663	1,163,101	1,175,948	1,186,362	1,198,801
400-599	315,463	320,475	322,295	326,929	331,296	333,399	337,642
600+	1,798,024	1,861,298	1,919,069	1,972,044	2,012,885	2,046,311	2,089,395
% Below Poverty Line							
<15%	1,085,677	1,127,720	1,167,253	1,201,416	1,224,891	1,245,853	1,261,929
15-<20%	3,426,561	3,505,672	3,571,876	3,637,433	3,686,387	3,728,244	3,786,094
20-<25%	730,682	740,230	747,374	756,502	760,277	765,204	755,491
25+%	279,069	280,320	282,720	284,594	286,409	287,905	286,508
Affiliated HIV Clinic							
Yes	1,184,289	1,232,826	1,278,948	1,321,812	1,355,406	1,381,556	1,412,691
No	4,337,700	4,421,117	4,490,276	4,558,133	4,602,559	4,645,650	4,677,331
Baseline HIV Rate^							
0-5	464,178	468,982	471,482	474,363	476,057	477,178	476,010
5-10	1,286,784	1,319,251	1,345,695	1,370,263	1,381,777	1,394,504	1,398,344
10-15	1,033,586	1,050,743	1,069,678	1,087,349	1,099,117	1,109,906	1,119,654
15+	2,737,441	2,814,968	2,882,369	2,947,970	3,001,013	3,045,619	3,096,014

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas
^Calculated as the average reported HIV case rate per 100,000 population 2005-2007
#per square mile

Table A2.8: Sensitivity Analysis: Comparison of Fixed Effects Models and County-Specific Random Intercept Multilevel Models on HIV Positivity, Adjusted for Patient and Clinic Covariate Sets and Calendar Year of Testing

	County-Specific Random Intercept OR (95% CI)*	Fixed Effects Only OR (95% CI)*
Unadjusted		
Post-Intervention	0.90 (0.80, 1.01)	0.89 (0.79, 1.00)
Pre-Intervention	1.00	1.00
Patient Covariates^		
Post-Intervention	0.92 (0.82, 1.04)	0.93 (0.82, 1.05)
Pre-Intervention	1.00	1.00
Clinic Covariates#		
Post-Intervention	0.90 (0.80, 1.01)	0.90 (0.80, 1.02)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates		
Post-Intervention	0.92 (0.82, 1.04)	0.93 (0.82, 1.05)
Pre-Intervention	1.00	1.00
Year		
Post-Intervention	1.13 (0.57, 2.23)	1.18 (0.60, 2.31)
Pre-Intervention	1.00	1.00
Patient Covariates + Year		
Post-Intervention	1.16 (0.59, 2.28)	1.18 (0.60, 2.32)
Pre-Intervention	1.00	1.00
Clinic Covariates + Year		
Post-Intervention	1.12 (0.57, 2.21)	1.13 (0.58, 2.22)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates + Year		
Post-Intervention	0.92 (0.82, 1.04)	1.16 (0.59, 2.28)
Pre-Intervention	1.00	1.00

*OR: odds ratio, 95% CI: 95% confidence interval

^Patient covariates include gender, race/ethnicity, and age

#Clinic covariates include metropolitan status, population density, % below poverty line, affiliated HIV clinic, and baseline HIV rate

Table A2.9: Sensitivity Analysis: Comparison of Lag Periods (0 months, 3 months, 6 months) on Multilevel Model Results on HIV Positivity, Adjusted for Patient and Clinic Covariate Sets and Calendar Year of Testing

	Base Case	Alternative Lags	
	3-Month Lag OR (95% CI)*	No Lag OR (95% CI)*	6-Month Lag OR (95% CI)*
Unadjusted			
Post-Intervention	0.90 (0.80, 1.01)	0.90 (0.80, 1.01)	0.89 (0.79, 1.01)
Pre-Intervention	1.00	1.00	1.00
Patient Covariates^			
Post-Intervention	0.92 (0.82, 1.04)	0.92 (0.82, 1.04)	0.92 (0.81, 1.04)
Pre-Intervention	1.00	1.00	1.00
Clinic Covariates#			
Post-Intervention	0.90 (0.80, 1.01)	0.90 (0.80, 1.01)	0.90 (0.79, 1.01)
Pre-Intervention	1.00	1.00	1.00
Patient + Clinic Covariates			
Post-Intervention	0.92 (0.82, 1.04)	0.92 (0.82, 1.04)	0.92 (0.82, 1.04)
Pre-Intervention	1.00	1.00	1.00
Year			
Post-Intervention	1.13 (0.57, 2.23)	1.02 (0.69, 1.52)	0.89 (0.54, 1.46)
Pre-Intervention	1.00	1.00	1.00
Patient Covariates + Year			
Post-Intervention	1.16 (0.59, 2.28)	1.04 (0.70, 1.54)	0.92 (0.56, 1.51)
Pre-Intervention	1.00	1.00	1.00
Clinic Covariates + Year			
Post-Intervention	1.12 (0.57, 2.21)	1.02 (0.68, 1.51)	0.88 (0.54, 1.45)
Pre-Intervention	1.00	1.00	1.00
Patient + Clinic Covariates + Year			
Post-Intervention	0.92 (0.82, 1.04)	1.03 (0.69, 1.53)	0.91 (0.55, 1.50)
Pre-Intervention	1.00	1.00	1.00

*OR: odds ratio, 95% CI: 95% confidence interval

^Patient covariates include gender, race/ethnicity, and age

#Clinic covariates include metropolitan status, population density, % below poverty line, affiliated HIV clinic, and baseline HIV rate

Appendix 3: Aim 2 Supplemental Tables and Figures

Table A3.1: Demographic and Clinic Characteristics of Persons Tested for HIV in North Carolina STD Clinics by Risk of Progression to AIDS within 12 Months of Initial HIV Diagnosis, July 2005 through June 2011

	All New Infections		AIDS within 12 months		No AIDS within 12 months	
	n	(%)	n	(%)	n	(%)
Intervention						
Pre-Intervention	422	(35.08)	52	(33.77)	370	(35.27)
Post-Intervention	781	(64.92)	102	(66.23)	679	(64.73)
Patient Characteristics						
Gender						
Male	952	(79.14)	121	(78.57)	831	(79.22)
Female	251	(20.86)	33	(21.43)	218	(20.78)
Race/Ethnicity						
White	214	(17.79)	23	(14.94)	191	(18.21)
Black	803	(66.75)	106	(68.83)	697	(66.44)
Hisp	78	(6.48)	13	(8.44)	65	(6.20)
Other	108	(8.98)	12	(7.79)	96	(9.15)
Age (years)						
18-24	429	(35.66)	47	(30.52)	382	(36.42)
25-34	386	(32.09)	48	(31.17)	338	(32.22)
35-44	225	(18.70)	27	(17.53)	198	(18.88)
45-64	163	(13.55)	32	(20.78)	131	(12.49)
Previous Test						
Yes	347	(28.84)	61	(39.61)	286	(27.26)
No	856	(71.16)	93	(60.39)	763	(72.74)
Gender/Risk						
Female	251	(20.86)	33	(21.43)	218	(20.78)
Male Heterosexual	417	(34.66)	60	(38.96)	357	(34.03)
MSM	535	(44.47)	61	(39.61)	474	(45.19)
Clinic Characteristics						
Metropolitan Status*						
Metropolitan	958	(79.63)	114	(74.03)	844	(80.46)
Micropolitan	198	(16.46)	30	(19.48)	168	(16.02)
Neither	47	(3.91)	10	(6.49)	37	(3.53)
Population Density#						
<199	297	(24.69)	51	(33.12)	246	(23.45)
200-399	191	(15.88)	21	(13.64)	170	(16.21)
400-599	163	(13.55)	18	(11.69)	145	(13.82)
600+	552	(45.89)	64	(41.56)	488	(46.52)
% Below Poverty Line						
<15%	234	(19.45)	34	(22.08)	200	(19.07)
15-<20%	755	(62.76)	84	(54.55)	671	(63.97)
20-<25%	158	(13.13)	23	(14.94)	135	(12.87)
25+%	56	(4.66)	13	(8.44)	43	(4.10)
Affiliated HIV Clinic						
Yes	863	(71.74)	113	(73.38)	750	(71.50)
No	340	(28.26)	41	(26.62)	299	(28.50)
Baseline HIV Rate^						
0-10	145	(12.05)	16	(10.39)	129	(12.30)
10-15	173	(14.38)	26	(16.88)	147	(14.01)
15+	885	(73.57)	112	(72.73)	773	(73.69)

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas
^Calculated as the average reported HIV case rate per 100,000 population 2005-2007
#per square mile

Table A3.2: Sensitivity Analysis: Impact of Adjusting for Calendar Year of HIV Testing on Associations between the Expanded HIV Testing Program and Risk of Progression to AIDS using County-Specific Random Intercept Regression Models

	Base Definition	Alternate Definitions		
	AIDS within 12 months RR (95% CI)*	AIDS within 1 month RR (95% CI)*	AIDS within 6 months RR (95% CI)*	AIDS within 18 months RR (95% CI)*
Unadjusted				
Post-Intervention	1.05 (0.77, 1.43)	1.23 (0.75, 2.01)	0.95 (0.67, 1.33)	0.97 (0.72, 1.29)
Pre-Intervention	1.00	1.00	1.00	1.00
Patient Covariates^				
Post-Intervention	0.99 (0.72, 1.36)	1.19 (0.72, 1.95)	0.91 (0.65, 1.29)	0.91 (0.68, 1.21)
Pre-Intervention	1.00	1.00	1.00	1.00
Clinic Covariates[#]				
Post-Intervention	1.01 (0.74, 1.39)	1.22 (0.74, 2.01)	0.91 (0.65, 1.28)	0.93 (0.69, 1.24)
Pre-Intervention	1.00	1.00	1.00	1.00
Patient + Clinic Covariates				
Post-Intervention	0.96 (0.70, 1.32)	1.17 (0.70, 1.94)	0.89 (0.63, 1.25)	0.87 (0.65, 1.17)
Pre-Intervention	1.00	1.00	1.00	1.00
Year				
Post-Intervention	0.39 (0.05, 2.86)	1.04 (0.13, 8.15)	0.43 (0.06, 3.11)	0.69 (0.17, 2.82)
Pre-Intervention	1.00	1.00	1.00	1.00
Patient Covariates + Year				
Post-Intervention	0.40 (0.06, 2.91)	1.01 (0.13, 7.90)	0.41 (0.06, 3.00)	0.72 (0.18, 2.93)
Pre-Intervention	1.00	1.00	1.00	1.00
Clinic Covariates + Year				
Post-Intervention	0.41 (0.06, 3.00)	1.20 (0.15, 9.38)	0.46 (0.06, 3.37)	0.72 (0.18, 2.94)
Pre-Intervention	1.00	1.00	1.00	1.00
Patient + Clinic Covariates + Year				
Post-Intervention	0.45 (0.06, 3.43)	1.24 (0.15, 10.36)	0.48 (0.06, 3.69)	0.79 (0.18, 3.48)
Pre-Intervention	1.00	1.00	1.00	1.00

*RR = risk ratio for progression to AIDS within specified time period for persons diagnosed after the introduction of a routine HIV testing intervention (exposed) vs. before (unexposed)

^Patient covariates include gender, race/ethnicity, age, and self-reported previous HIV test

[#]Clinic covariates include metropolitan status, population density, % below poverty line, affiliated HIV clinic, and baseline HIV rate

Table A3.4: Sensitivity Analysis: Comparison of Fixed and County-Specific Random Intercept Regression Models on Associations between the Expanded HIV Testing Program and Risk of Progression to AIDS

	Random Intercept RR (95% CI)*	Fixed Effects RR (95% CI)*
Base Definition		
12 months		
Unadjusted		
Post-Intervention	1.05 (0.77, 1.43)	1.06 (0.78, 1.45)
Pre-Intervention	1.00	1.00
Patient Covariates^		
Post-Intervention	0.99 (0.72, 1.36)	1.00 (0.73, 1.37)
Pre-Intervention	1.00	1.00
Clinic Covariates#		
Post-Intervention	1.01 (0.74, 1.39)	1.01 (0.74, 1.39)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates		
Post-Intervention	0.96 (0.70, 1.32)	0.96 (0.70, 1.32)
Pre-Intervention	1.00	1.00
Alternative Definitions		
1 month		
Unadjusted		
Post-Intervention	1.23 (0.75, 2.01)	1.26 (0.77, 2.07)
Pre-Intervention	1.00	1.00
Patient Covariates		
Post-Intervention	1.19 (0.72, 1.95)	1.17 (0.71, 1.93)
Pre-Intervention	1.00	1.00
Clinic Covariates		
Post-Intervention	1.22 (0.74, 2.01)	1.23 (0.75, 2.02)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates		
Post-Intervention	1.17 (0.70, 1.94)	1.17 (0.70, 1.95)
Pre-Intervention	1.00	1.00
6 months		
Unadjusted		
Post-Intervention	0.95 (0.67, 1.33)	0.95 (0.68, 1.34)
Pre-Intervention	1.00	1.00
Patient Covariates		
Post-Intervention	0.91 (0.65, 1.29)	0.92 (0.65, 1.29)
Pre-Intervention	1.00	1.00
Clinic Covariates		
Post-Intervention	0.91 (0.65, 1.28)	0.91 (0.65, 1.28)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates		
Post-Intervention	0.89 (0.63, 1.25)	0.89 (0.63, 1.25)
Pre-Intervention	1.00	1.00
18 months		
Unadjusted		
Post-Intervention	0.97 (0.72, 1.29)	0.97 (0.73, 1.30)
Pre-Intervention	1.00	1.00
Patient Covariates		
Post-Intervention	0.91 (0.68, 1.21)	0.91 (0.68, 1.22)
Pre-Intervention	1.00	1.00
Clinic Covariates		
Post-Intervention	0.93 (0.69, 1.24)	0.93 (0.69, 1.24)
Pre-Intervention	1.00	1.00
Patient + Clinic Covariates		
Post-Intervention	0.87 (0.65, 1.17)	0.87 (0.65, 1.17)
Pre-Intervention	1.00	1.00

*RR = risk ratio for progression to AIDS within 12 months for persons diagnosed after the introduction of a routine HIV testing intervention (exposed) vs. before (unexposed)
^Patient covariates include gender, race/ethnicity, age, and self-reported previous HIV test
#Clinic covariates include metropolitan status, population density, % below poverty line, affiliated HIV clinic, and baseline HIV rate

Table A3.5: Sensitivity Analysis: Comparison of Lag Periods (0 months, 3 months, and 6 months) on Associations between the Expanded HIV Testing Program and Risk of Progression to AIDS

	Base Case Lag	Alternative Lags	
	No Lag RR (95% CI)*	3-Month Lag RR (95% CI)*	6-Month Lag RR (95% CI)*
Base Definition			
12 months			
Post-Intervention	1.05 (0.77, 1.43)	1.03 (0.75, 1.42)	1.06 (0.77, 1.47)
Pre-Intervention	1.00	1.00	1.00
Alternative Definitions			
1 month			
Post-Intervention	1.23 (0.75, 2.01)	1.23 (0.74, 2.05)	1.25 (0.75, 2.09)
Pre-Intervention	1.00	1.00	1.00
6 months			
Post-Intervention	0.91 (0.65, 1.28)	0.95 (0.67, 1.34)	0.97 (0.68, 1.37)
Pre-Intervention	1.00	1.00	1.00
18 months			
Post-Intervention	0.97 (0.72, 1.29)	0.93 (0.69, 1.26)	0.94 (0.70, 1.27)
Pre-Intervention	1.00	1.00	1.00

*RR = risk ratio for progression to AIDS within specified time period for persons diagnosed after the introduction of a routine HIV testing intervention (exposed) vs. before (unexposed)

Table A3.6: Association between the Expanded HIV Testing Program and Risk of Progression to AIDS, Stratified by Clinic-Level Characteristics

	Base Definition	Alternative Definitions		
	AIDS within 12 months RR (95% CI)	AIDS within 1 month RR (95% CI)	AIDS within 6 months RR (95% CI)	AIDS within 18 months RR (95% CI)
Unadjusted				
Post-Intervention	1.05 (0.77, 1.43)	1.23 (0.75, 2.01)	0.95 (0.67, 1.33)	0.97 (0.72, 1.29)
Pre-Intervention	1.00	1.00	1.00	1.00
Clinic Characteristics				
Metropolitan Status*				
Metropolitan	1.06 (0.74, 1.52)	1.17 (0.67, 2.04)	0.94 (0.64, 1.40)	0.98 (0.70, 1.37)
Micropolitan	1.11 (0.54, 2.28)	2.34 (0.53, 10.43)	1.07 (0.49, 2.32)	0.95 (0.49, 1.84)
Neither	0.48 (0.16, 1.49)	0.43 (0.09, 1.95)	0.41 (0.13, 1.33)	0.55 (0.18, 1.63)
Population Density#				
<199	0.94 (0.54, 1.64)	1.74 (0.61, 4.94)	0.98 (0.53, 1.80)	0.97 (0.57, 1.66)
200-399	0.95 (0.41, 2.19)	0.47 (0.13, 1.69)	0.67 (0.25, 1.78)	0.82 (0.39, 1.76)
400-599	0.82 (0.34, 1.98)	*NE	0.67 (0.25, 1.83)	0.74 (0.32, 1.71)
≥600	1.16 (0.71, 1.88)	1.16 (0.60, 2.28)	1.01 (0.60, 1.69)	1.01 (0.65, 1.57)
% Below Poverty Line				
<15%	1.27 (0.66, 2.45)	1.59 (0.57, 4.43)	1.19 (0.57, 2.48)	1.02 (0.56, 1.86)
15-19.9%	0.96 (0.63, 1.46)	1.12 (0.59, 2.12)	0.87 (0.56, 1.35)	0.93 (0.63, 1.38)
20-24.9%	1.61 (0.58, 4.45)	1.56 (0.36, 6.85)	1.18 (0.41, 3.37)	1.19 (0.52, 2.73)
≥25%	0.54 (0.21, 1.38)	0.32 (0.02, 4.95)	0.58 (0.20, 1.72)	0.60 (0.24, 1.49)
Affiliated HIV Clinic				
Yes	1.30 (0.70, 2.42)	2.31 (0.66, 8.09)	1.11 (0.57, 2.16)	1.10 (0.63, 1.90)
No	0.96 (0.67, 1.38)	1.05 (0.61, 1.81)	0.89 (0.60, 1.32)	0.92 (0.65, 1.29)
Baseline HIV Rate^				
<10	0.64 (0.25, 1.61)	0.50 (0.15, 1.67)	0.71 (0.24, 2.12)	0.62 (0.26, 1.47)
10-14.9	1.05 (0.49, 2.28)	1.15 (0.23, 5.75)	0.77 (0.34, 1.74)	1.12 (0.52, 2.41)
≥15	1.13 (0.78, 1.63)	1.50 (0.83, 2.71)	1.03 (0.69, 1.53)	1.00 (0.71, 1.41)

RR = risk ratio for progression to AIDS within specified time period for persons diagnosed after the introduction of a routine HIV testing intervention (exposed) vs. before (unexposed), not adjusted for patient- or clinic-level covariates

*Defined by the US Census Bureau's metropolitan and micropolitan statistical areas

^Calculated as the average reported HIV case rate per 100,000 population 2005-2007

#per square mile

Table A3.7: Absolute Risks of HIV (per 1000 Tests) and Progression to AIDS within 12 months for Women over the Study Period (July 1, 2005 through June 30, 2011)

	Risk of HIV per 1000 Tests (95% CI)	Risk of Progression to AIDS within 12 months (95% CI)
2005	2.20 (1.37, 3.02)	14.81 (1.23, 28.40)
2006	1.67 (1.18, 2.15)	4.44 (-1.62, 10.51)
2007	1.42 (1.01, 1.83)	4.55 (-1.65, 10.75)
2008	0.97 (0.65, 1.28)	29.41 (13.99, 44.83)
2009	1.22 (0.81, 1.56)	18.37 (7.47, 29.27)
2010	1.36 (0.55, 1.08)	8.82 (-0.76, 18.41)
2011	0.81 (0.45, 1.17)	16.67 (-0.74, 34.06)

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