
McKaylee Robertson

CUNY School of Public Health, mckaylee.robertson@sph.cuny.edu

Follow this and additional works at: https://academicworks.cuny.edu/sph_etds

Part of the Epidemiology Commons

Recommended Citation
https://academicworks.cuny.edu/sph_etds/35

This Dissertation is brought to you for free and open access by the CUNY Graduate School of Public Health & Health Policy at CUNY Academic Works. It has been accepted for inclusion in Dissertations and Theses by an authorized administrator of CUNY Academic Works. For more information, please contact AcademicWorks@cuny.edu.

A DISSERTATION

by

McKAYLEE M. ROBERTSON

Concentration: EPIDEMIOLOGY

Presented to the Faculty at the Graduate School of Public Health and Health Policy in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Graduate School of Public Health and Health Policy
City University of New York
New York, New York
October, 2019

Dissertation Committee:
DENIS NASH, MPH PHD
SARAH BRAUNSTEIN, MPH PHD
SHENG LI, PHD
DONALD HOOVER, PHD
ABSTRACT

Trends in the Timeliness of HIV Diagnosis and Antiretroviral Treatment (ART) Initiation before, during and after the “Treat All” Recommendation – New York City, 2006-2015: A Case Study

by

McKaylee M. Robertson

Advisor: Denis Nash, MPH PhD

BACKGROUND: Voluntary HIV testing followed by immediate antiretroviral treatment (ART) initiation (universal testing and treatment) has become an integral part of strategies to eliminate HIV and control the HIV/AIDS epidemic. Minimizing the time from HIV infection to ART initiation is essential for universal test and treatment to be optimally effective. In New York City, an epicenter of the HIV epidemic, the ‘treat all’ recommendation, immediate treatment for all people diagnosed with HIV, was made in late 2011, and efforts to ‘treat all’ were contemporaneous with large scale HIV testing initiatives in NYC. The overarching goal of this dissertation was to examine trends in the timeliness of diagnosis and ART initiation using data from the population-based New York City HIV surveillance registry before, during and after the “treat all” recommendation.

METHODS: I utilized data from the New York City population-based HIV surveillance registry to assess the timing of diagnosis and ART initiation in New York City. For aim 1, to describe and quantify trends in early diagnosis (e.g., examine median CD4 count at diagnosis and proportion of acute HIV cases among all new diagnoses) and early ART initiation (e.g., proportion with CD4 count >500 at ART initiation), I used data on NYC residents diagnosed from 2012-2015. For aim 2, to estimate the time from seroconversion to diagnosis, we applied published estimates of CD4 decline after infection from...
seroconverter cohorts to our population, NYC residents newly diagnosed with HIV. To verify the assumption that the square root of the CD4 cell count decreases linearly over time prior to antiretroviral treatment (ART) initiation, we compared estimates of diagnosis delay based on first versus second pre-ART CD4 counts, using data on NYC residents diagnosed from 2006-2015 (sub-aim 2a). Finally, using methods developed in Aim 2, we estimated the time from HIV seroconversion to diagnosis and to ART initiation among NYC residents diagnosed from 2006-2015 for aim 3.

RESULTS: In the first aim, I examined the timeliness of diagnosis and treatment initiation in the universal test and treatment era. Among 9987 NYC residents with HIV diagnosed from 2012 to 2015, diagnosis was early (a CD4 cell count ≥500/μL or diagnosed with acute HIV infection) in 35%, and 87% started ART by June 2017. The annual proportion of persons with early diagnosis did not increase appreciably (35% in 2012 vs 37% in 2015; \( P = .08 \), Cochran-Armitage test for trend). Overall, 69% of persons had started ART at 6 months after diagnosis. The time from diagnosis to ART initiation decreased from year to year. Within 6 months of diagnosis, 62%, 67%, 72% and 77% of persons with HIV diagnosed in 2012, 2013, 2014, or 2015, respectively, had started ART, with median (interquartile range) times to ART initiation of 3.34 (1.34–12.75), 2.62 (1.28–10.13), 2.16 (1.15–7.11), and 2.03 (1.11–5.61) months, respectively.

In the second aim, I adapted a CD4 decline model to estimate diagnosis delay (time from seroconversions to diagnosis). Among 12,849 NYC residents who were diagnosed with HIV from 2006 to 2015 with at least 2 pre-ART CD4 count measurements around time of diagnosis, the average diagnosis delays based on the first or second pre-ART CD4 count were similar (4.93 years (95% Confidence intervals (CI):4.84-5.03) and 4.85 years (95% CI:4.76-4.95), respectively, \( p \)-value=0.09, Wilcoxon signed-rank).

In the third aim, I used methods developed in Aim 2 to estimate the timing of seroconversion and estimated the timeliness of diagnosis and treatment initiation. Among 28,162 people diagnosed with HIV during 2006-2015, 89% initiated ART by June 2017. The median CD4 count at diagnosis increased
from 326 (Interquartile range (IQR):132-504) to 390 (IQR:216-571) cells/µL from 2006-2015. The average time from estimated seroconversion to ART initiation decreased by 33% from 8.0 years (95% confidence interval [CI]:7.8-8.2) in 2006 to 5.4 years (95%CI: 5.1-5.6) in 2015. Contributing to the reduction in time to ART initiation, the average time from estimated seroconversion to diagnosis decreased by 22%, from 6.5 years (95% CI:6.3-6.7) to 5.1 years (95% CI:4.9-5.4) from 2006-2015, and the average time from diagnosis to ART initiation reduced by 87%, from 1.5 years (95% CI:1.4-1.5) to 0.2 years (95% CI:0.2-0.3) from 2006-2015.

DISCUSSION: The time to ART initiation was reduced in tandem with expanded HIV testing and treatment efforts in New York City. We found considerable progress in rapid ART initiation: a) the proportion of persons initiating ART within 6 months of diagnosis increased from 2012 to 2015, b) the time from seroconversion to ART initiation decreased by 33% over a 10 year period, and c) the time from diagnosis to ART initiation decreased by 87%, and is now on average very short. Despite these improvements, disparities persist in the ART initiation delay so efforts should focus on subgroups for whom progress still needs to be made. Finally, substantive efforts are needed to reduce delays in diagnosis (i.e., the time from seroconversion to diagnosis). Targeted HIV testing strategies are needed to more rapidly identify people with undiagnosed HIV soon after HIV seroconversion in order to achieve further reductions in HIV incidence and mortality in key subgroups who continue to be negatively impacted by the HIV epidemic.
# TABLE OF CONTENTS

TABLE OF CONTENTS....................................................................................................................... vi
LIST OF TABLES AND FIGURES........................................................................................................... ix
ACKNOWLEDGEMENTS.......................................................................................................................... xi
DISCLOSURES ......................................................................................................................................... xii

CHAPTER 1. INTRODUCTION .................................................................................................................. 1

INTRODUCTION ...................................................................................................................................... 1
OVERVIEW OF THE DISSERTATION, AIMS AND HYPOTHESES............................................................. 2
    Aim 1: .................................................................................................................................................. 2
    Aim 2: .................................................................................................................................................. 2
    Aim 3: .................................................................................................................................................. 3
GAPS IN THE LITERATURE ...................................................................................................................... 3
PUBLIC HEALTH IMPLICATIONS ............................................................................................................ 6
OVERVIEW OF METHODOLOGICAL APPROACHES .............................................................................. 7
CONCLUSIONS ....................................................................................................................................... 8
REFERENCES .......................................................................................................................................... 8

CHAPTER 2: TIMELINESS OF HIV DIAGNOSIS AND ANTIRETROVIRAL TREATMENT INITIATION IN THE ERA OF UNIVERSAL TEST AND TREAT (AIM 1) ............................................................... 11

ABSTRACT ............................................................................................................................................. 11
INTRODUCTION ....................................................................................................................................... 12
METHODS ............................................................................................................................................ 13
RESULTS ................................................................................................................................................ 16
DISCUSSION .......................................................................................................................................... 18
REFERENCES .......................................................................................................................................... 22

TABLES AND FIGURES .......................................................................................................................... 24

Figure 1. Trends in median CD4 count at diagnosis and ART Initiation and proportion of early diagnoses and early ART Initiation – New York City, 2012-2015 .............................................................. 24
Figure 2. Time to ART Initiation overall and by year of diagnosis – New York City, 2012-2015 .......... 25
Figure 3. Time to ART Initiation by year of diagnosis, among (a) persons diagnosed with a CD4 count <200 cells/mm, (b) persons aged 18-29 years at diagnosis, (c) persons diagnosed early, (d) persons not linked to care within 3 months, (e) persons diagnosed at a screening, diagnosis and referral clinic – New York City, 2012-2015 ........................................................................................................................................ 26
Table 1. Characteristics of all Persons Diagnosed with HIV Stratified by CD4 Count at Diagnosis - New York City, 2012-2015 ................................................................................................................... 26
Table 1. Demographic Characteristics and Median Pre-treatment CD4 Values of People Diagnosed with HIV – New York City, 2006 to 2015 .......................................................... 59

Table 2. Estimated annual time from Seroconversion to ART Initiation – New York City, 2006-2015 ........................................................................................................... 61

Table 3. Estimated time from Seroconversion to ART Initiation by Subgroups – Among Persons who Initiate ART in New York City, 2006 and 2015 .................................................... 62

Supplemental Table 1. Estimated time from Seroconversion to Diagnosis by Subgroups – Among 2006 and 2015 diagnoses, New York City ........................................................................ 63

CHAPTER 5. DISCUSSION .................................................................................................................. 64

INTRODUCTION ................................................................................................................................ 64

SUMMARY OF RESULTS .................................................................................................................. 64

IMPLICATIONS FOR POLICY .............................................................................................................. 65

FURTHER RESEARCH .......................................................................................................................... 66

LIMITATIONS ..................................................................................................................................... 68

STRENGTHS AND PUBLIC HEALTH RELEVANCE ........................................................................ 69

CONCLUSIONS .................................................................................................................................... 70

REFERENCES ....................................................................................................................................... 71

APPENDIX TO CHAPTER 3: VALIDATING ESTIMATES OF DIAGNOSIS DELAY (AIM 2B) ......................... 74

OBJECTIVE ........................................................................................................................................ 74

METHODS .......................................................................................................................................... 74

RESULTS ............................................................................................................................................ 75

DISCUSSION ...................................................................................................................................... 75

REFERENCES ....................................................................................................................................... 77

TABLES AND FIGURES ......................................................................................................................... 77

Figure 1. Flow chart of overlap between CSBS dataset and the analytic cohort ......................... 77

Table 1. Comparison of Self-Report Dates of Diagnosis and Registry Dates of Diagnosis among the 73 People in the Registry but Not Matching with the Analytic Cohort .......................................................... 77

Table 2. Estimates (Years) of Diagnosis Delay (Seroconversion to Diagnosis) ............................. 78
LIST OF TABLES AND FIGURES

CHAPTER 2 – AIM 1

A. Figure 1. Trends in median CD4 count at diagnosis and ART Initiation and proportion of early diagnoses and early ART Initiation – New York City, 2012-2015

B. Figure 2. Time to ART Initiation overall and by year of diagnosis – New York City, 2012-2015

C. Figure 3. Time to ART Initiation by year of diagnosis, among (a) persons diagnosed with a CD4 count <200 cells/mm, (b) persons aged 18-29 years at diagnosis, (c) persons diagnosed early, (d) persons not linked to care within 3 months, (e) persons diagnosed at a screening, diagnosis and referral clinic – New York City, 2012-2015

D. Table 1. Characteristics of all Persons Diagnosed with HIV Stratified by CD4 Count at Diagnosis - New York City, 2012-2015

E. Table 2. The Time to and Hazards Ratios of ART Initiation1 Stratified by Year of Diagnosis and Timing of Diagnosis – New York City, 2012-2015

F. Supplemental Table 1. Clinical Characteristics of Persons Diagnosed with HIV Stratified by CD4 Count at Diagnosis - New York City, 2012-2015

G. Supplemental Table 2. The Time to and Hazards Ratios of ART Initiation1 Stratified by Demographic and Clinical Characteristics – Among 9,987 Persons Diagnosed with HIV from 2012 to 2015 and Residing in New York City

CHAPTER 3 – AIM 2A

A. Figure 1. Diagnosis delay based on first or second pre-treatment CD4 amongst entire persons diagnosed from 2006 to 2015 (A) or amongst people diagnosed from 2006 to 2015 and having a second CD4 count reported >6 months following diagnosis (B)

B. Table 1. Characteristics of people diagnosed with HIV from 2006 to 2015 and having at least two pre-treatment CD4 counts – New York City
C. Table 2. Estimates of diagnosis delay based on first or second pre-treatment CD4 amongst the entire cohort of people diagnosed with HIV from 2006 to 2015 overall (a) and restricted to people having a second CD4 count reported >6 months following diagnosis– New York City

CHAPTER 4 – AIM 3
A. Figure 1. Trends in mean or median time from seroconversion to ART initiation (S:A), seroconversion to diagnosis (S:D) and diagnosis to ART initiation (D:A) among ART initiators
B. Table 1. Demographic Characteristics and Median Pre-treatment CD4 Values of People Diagnosed with HIV – New York City, 2006 to 2015
C. Table 2. Estimated annual time from Seroconversion to ART Initiation – New York City, 2006-2015
D. Table 3. Estimated time from Seroconversion to ART Initiation by Subgroups – Among Persons who Initiate ART in New York City, 2006 and 2015
E. Supplemental Table 1. Estimated time from Seroconversion to Diagnosis by Subgroups – Among 2006 and 2015 diagnoses, New York City

APPENDIX – AIM 2B
A. Figure 1. Flow chart of overlap between CSBS dataset and the analytic cohort
B. Table 1. Comparison of Self-Report Dates of Diagnosis and Registry Dates of Diagnosis among the 73 People in the Registry but Not Matching with the Analytic Cohort.
C. Table 2. Estimates (Years) of Diagnosis Delay (Seroconversion to Diagnosis)
ACKNOWLEDGEMENTS

Many people contributed to making this dissertation possible. First, I would like to thank my committee: Denis Nash, Sarah Braunstein, Sheng Li and Donald Hoover for their guidance, time and expertise. I am most grateful to Denis Nash for his support and mentorship throughout the doctoral program and to Sarah Braunstein for allowing me to use DOHMH resources and data and for providing advice and encouragement in and outside of the office. I was fortunate to be in this program with a group of outstanding and supportive women, particularly Olga Tymejczyk, her progress always served as inspiration. Finally, I want to acknowledge my friends and family who have supported me in large and small ways throughout this process, especially my mom who encouraged me to return to school and whose support seems boundless. And I must thank my husband for listening to and for being enthusiastic about even the smallest details; words cannot describe the gratitude and luck I feel for having you in my life.
DISCLOSURES

Contributors

This dissertation is the authors’ original work. This study was strictly conducted for a doctor of philosophy degree at the City University of New York (CUNY) Graduate School of Public Health and Health Policy. The dissertation committee members contributed feedback on various drafts of each section of the dissertation.

Conflicts of Interest

None declared
CHAPTER 1. INTRODUCTION

INTRODUCTION

The Joint United Nations Programme on HIV/AIDS (UNAIDS) plan to control the global HIV/AIDS epidemic emphasizes the need to focus the public health response locally, on the cities and communities most affected by HIV.\(^1\) New York State is an epicenter of the epidemic, and in 2015, the state had the second highest number of people living with HIV infection (N=139,900; 95% Confidence intervals: 133,900-146,000) and the fourth highest number of new infections (N=3,400, 95% CI: 2,800-4,000) in the United States.\(^2\) Similar to many jurisdictions around the world, New York State is embarking on an effort to control the HIV/AIDS epidemic via reducing the annual estimated number of new HIV infections and achieving the first ever decrease in HIV prevalence in the state.\(^3\) To control the epidemic in New York and elsewhere, we must minimize the infectious period (i.e., the time a person is not on treatment) and ultimately help people living with HIV achieve sustained viral suppression, thereby decreasing HIV-related morbidity and mortality and preventing onward spread of HIV.\(^3-6\)

The achievement of timely viral suppression requires prompt testing and diagnosis following HIV seroconversion—typically an unobservable event—and timely initiation of antiretroviral treatment (ART). Timely diagnosis is necessary, as persons unaware of their HIV infection accounted for 15% of all persons living with HIV-infection in 2015 and approximately 40% of ongoing transmissions in the United States.\(^7,8\) Generally, the timeliness of diagnosis and ART initiation is assessed by examining the distribution of CD4 count at diagnosis and ART initiation, respectively, or with static measures (e.g., the proportion of people who initiate ART). In New York City (NYC), increases in CD4 counts at diagnosis and ART initiation suggest a trend toward earlier diagnosis and treatment initiation.\(^9\) Yet, in 2015 more than one in six (17%) NYC residents newly diagnosed with HIV were diagnosed late (i.e., an AIDS diagnosis within 31 days of HIV diagnosis), and one-quarter of NYC residents who were diagnosed with HIV in 2015 had not initiated ART as of 6 months post-diagnosis.\(^10,11\) At the national level, CD4 information is
rarely disseminated, beyond tracking immunologically defined AIDS (CD4 <200 cells/μL), and data on the
timeliness of ART prescriptions is not published due to small sample sizes of systematically collected ART
information on newly diagnosed people.\textsuperscript{2,12} Thus, a gap exists between guidelines, which recommend
ART initiation at diagnosis for all people living with HIV (PLWH), and the reality of when people start
treatment. And a gap exists in metrics for monitoring the care continuum, as they do not provide any
information on the amount of time that passes between infection and diagnosis and ART initiation.\textsuperscript{13,14}

In 2016, the US Centers for Disease Control and Prevention developed a new statistical method,
referred to as the “CD4 depletion model”, to generate national estimates of HIV incidence, and this
technique could be adapted to estimate the time from seroconversion to diagnosis and to ART
initiation.\textsuperscript{15} Adapting such a model to local data is critical to understanding local epidemics and shaping
local program implementation and policy designed to minimize the time elapsed since seroconversion.

\textbf{OVERVIEW OF THE DISSERTATION, AIMS AND HYPOTHESES}

Using data from the population-based NYC HIV surveillance registry, we propose to conduct a
longitudinal assessment of trends in HIV diagnosis and ART initiation and to quantify the amount of time
that elapses from seroconversion to ART initiation.

\textbf{Aim 1:} Among NYC residents diagnosed with HIV from 2012-2015 (N=9,987) describe and quantify
trends in early diagnosis (e.g., median CD4 count at diagnosis or proportion of acute HIV cases
among all new diagnoses) and early estimated ART initiation (e.g., proportion with CD4 count
>500 at ART initiation) for the city overall and by demographics (e.g., by gender and
race/ethnicity)

\textbf{H1:} Compared to 2012, more people in 2015 are being diagnosed early and initiating ART early

\textbf{H2:} Whites and men who have sex with men will have earlier diagnosis and ART initiation

\textbf{Aim 2:} Adapt a CD4 decline model to estimate the timing of HIV seroconversion among those with
newly diagnosed HIV in NYC
Sub-aim 2a: Assess the linear decline assumption using the second CD4 reported to the registry

Sub-aim 2b: Validate the adapted model using data from the Case-Surveillance-Based Sampling Project 2012-2014 (N=134) by comparing the mean distribution of estimated seroconversion dates with information on last negative and first positive HIV test dates

Aim 3: Among NYC residents diagnosed with HIV from 2006-2015 (N=28,150), estimate the time from HIV seroconversion to diagnosis, and the time from HIV seroconversion to ART initiation, changes in the metrics over-time and changes among populations of interest

H3: The time from seroconversion to ART initiation will decrease from 2006-2015

H4: Women, blacks, Latinos/Hispanics and people with a history of injection drug use will have longer delays

GAPS IN THE LITERATURE

Overview. The infectious period starts at HIV-seroconversion and ends when HIV viral load is suppressed following treatment initiation. A critical barrier to understanding the average period of infectiousness is that seroconversion is often an unobservable event. This dissertation seeks to address that barrier via the development and assessment of a local measure of seroconversion based on the first pre-treatment CD4 count reported to the surveillance registry after HIV diagnosis.

The development of a valid method to estimate the timing of seroconversion would allow for more complete characterization of local HIV epidemics. Researchers and implementers generally do not know the amount of time that passes from HIV-seroconversion to diagnosis and to treatment initiation (i.e., the HIV-infectiousness period; aim 3) at the population level in their local epidemics. Estimating the timing of seroconversion will allow for identification of groups for public health intervention (e.g., people with a long HIV-infectiousness period) and evaluating the implementation and uptake of targeted HIV testing efforts and expanded HIV treatment, which have rolled out in New York and elsewhere.
The timing of seroconversion is almost never known. And inferring a date of HIV-infection is difficult because people are rarely diagnosed during primary or acute HIV infection (AHI), the first stage of HIV-infection.20 Rather, most people are diagnosed in the later stages of HIV infection when the duration of the infection is much less certain.

Assuming no treatment has been received, the CD4 cell count at diagnosis has been proposed to estimate the time since infection at the date of first CD4 test. In seroconverter cohort studies, the trajectory of CD4 decline, on a square root scale, has typically been modeled as a linear function of the time since infection.21-23 Using model parameters (i.e., the slope and intercept estimates of CD4 decline) from the CASCADE seroconverter cohort study for subgroups of interest in the US (e.g., CD4 at seroconversion and annual decline estimates for men aged 25-29) and linear extrapolation, researchers have estimated the distribution of delay from seroconversion to diagnosis in the United States.15,16 Recently (March 2019), the Centers for Disease Control and Prevention (CDC) presented national estimates of the time from seroconversion to viral suppression as part of a conference presentation.24 To the best of our knowledge, the CD4 decline approach has not been validated or applied at the local level.15,16

The linear decline assumption of the CD4 decline approach needs to be verified. Estimated delays in diagnosis rely on the accuracy of the initial CD4 depletion model, which assumes the mean square root of CD4 count is linearly related to the time since seroconversion. Some evidence suggests the rate of—square root transformed—CD4 decline over time is nonlinear.25

Characterizing the statistical uncertainty around estimates of the time since seroconversion is critical for epidemiologists and implementers. The CD4 decline approach developed by the CDC represents a method for local HIV surveillance jurisdictions to generate estimates of diagnosis delay. However, the CDC authors have not developed an approach for incorporating variance around their national estimates of the infectious period.15
The HIV infectiousness period is rarely quantified. Randomized controlled trials have established that early effective combination ART improves the prognosis of HIV-infected people and reduces HIV morbidity and mortality, as well as reduces HIV-transmission.\textsuperscript{5,6,26,27} As a result of this and earlier observational study evidence, many local, national and global regulatory and programmatic bodies, including New York State, recommend all people diagnosed with HIV initiate treatment, regardless of CD4 count and recommend using Voluntary HIV testing followed by immediate ART initiation (universal testing and treatment) as one part of a combination of approaches to eliminate HIV and to help control the AIDS epidemic.\textsuperscript{3,28,29}

One aim of UTT is to minimize the time from HIV infection to ART initiation, and ultimately help people living with HIV achieve sustained or durable viral suppression in order to prevent onward HIV transmission and reduce morbidity and mortality.\textsuperscript{30,31} Minimizing this window requires that people are diagnosed and linked to care early in the course of HIV infection. Due to the inherent difficulty of creating a population-representative incident cohort (i.e., a cohort where HIV-seroconversion is observed) and an absence of methods for estimating seroconversion in population-representative seroprevalent cohorts, very few studies have developed population-based estimates of the time between seroconversion and diagnosis and all published estimates are for the country/national level.\textsuperscript{13,15,16,32} According to a CDC conference presentation, in the United States, people diagnosed with HIV in 2016 had been infected an estimated 39 months before diagnosis compared with an estimated 43 months among people diagnosed in 2012.\textsuperscript{24}

An HIV-infected individual’s CD4 cell count is a marker of time since infection: the lower the count, the longer (on average) the individual has been infected. In NYC, from 2006 to 2012, the median CD4 count at diagnosis increased from 325 cells/µl to 379 cells/µl.\textsuperscript{33} This data suggests that people are being diagnosed earlier in the course of infection. However, the elapsed time from seroconversion to diagnosis is unknown, making it difficult for jurisdictions to target resources accordingly to improve this
outcome. Moreover, if CD4 decline varies among population (e.g., by transmission risk group), then the average CD4 at diagnosis is not fully informative about the timeliness of diagnosis for subgroups, and estimates of time since seroconversion at the subgroup level could help suggest new or enhanced interventions to reduce diagnosis delay.

Furthermore, population-level data on how much time passes from HIV seroconversion to treatment initiation in the United States do not exist. Arguably, the primary reason these data do not exist is because the timing of seroconversion is almost never known and because population-based data on the timing of ART initiation is not collected in routine surveillance. Consequently, data on ART initiation is limited to clinical cohorts or to small numbers of newly diagnosed persons.\textsuperscript{34,35} Evidence suggests, however, that the time from seroconversion to ART initiation has decreased among certain populations. Among a cohort of injection drug users in Baltimore, no significant trend toward improvement in the CD4 count at treatment initiation was observed.\textsuperscript{36} In San Francisco from 2007-2011 and in NYC from 2006-2013, surveillance data indicated a trend toward earlier ART initiation, as demonstrated by increases in CD4 cell count at ART initiation\textsuperscript{9,37} Thus, in some populations the time from seroconversion to ART initiation is decreasing but the exact duration of time that passes (e.g., two versus three years) from seroconversion to treatment initiation is unknown. To further support TasP efforts, estimates of the time from seroconversion to ART initiation could be a priority indicator to identify gaps in time and monitor whether HIV prevention initiatives are closing such gaps.

PUBLIC HEALTH IMPLICATIONS

The dissertation addresses four knowledge gaps in the literature around quantifying the infectious period for HIV and the related treatment delay. First, the timing of HIV seroconversion has not been estimated or validated at the local population level (Aim 2). Second, the length of the HIV-infectiousness period has not been quantified (Aim 3). Third, for the CD4 decline approach developed by CDC, a method to characterize the uncertainty around estimates of diagnosis delay does not exist (Aim 2).
Fourth, the linear decline assumption of the CD4 decline approach needs to be verified (Aim 2a). If the aims of the project are achieved, this dissertation will improve understanding of the NYC HIV epidemic and will provide researchers with a novel approach for estimating seroconversion and monitoring and evaluating efforts to control the HIV epidemic. Given that all states, the District of Columbia and U.S. territories have mandatory reporting of all diagnosed cases of HIV infection, and most have comprehensive reporting of HIV-related laboratory tests, the development of such a method will have broad implications and utility in terms of monitoring the epidemic and progress toward controlling the epidemic.

OVERVIEW OF METHODOLOGICAL APPROACHES

I utilized data from the New York City population-based HIV surveillance registry to assess the timing of diagnosis and ART initiation in New York City. For aim 1, to describe and quantify trends in early diagnosis (e.g., examine median CD4 count at diagnosis and proportion of acute HIV cases among all new diagnoses) and early ART initiation (e.g., proportion with CD4 count >500 at ART initiation), I used data on NYC residents diagnosed from 2012-2015. For aim 2, to adapt a CD4 decline model to estimate the timing of HIV seroconversion among those with newly diagnosed HIV, we used data on NYC residents diagnosed from 2006-2015 and the first pre-treatment CD4 count. We applied published estimates of CD4 decline after infection from seroconverter cohorts to our population to infer timing of seroconversion. We assessed the linear decline assumption using data on NYC residents diagnosed from 2006-2015 with at least 2 CD4 counts reported before ART initiation (i.e., to examine differences in time from seroconversion to diagnosis based on first versus second CD4 count) (sub-aim 2a). Using data on NYC residents who completed an interview for the Case-Surveillance-Based Sampling Project from 2012-2014, we compared estimated diagnosis delays with self-reported diagnosis delays (sub-aim 2b). For aim 3, to estimate the time from HIV seroconversion to diagnosis and to ART initiation, we used
data on NYC residents diagnosed from 2006-2015. A detailed description of the methods is found in
subsequent chapters (for aim 1 see chapter 2, aim 2 see chapter 3, and aim 3 see chapter 4).

CONCLUSIONS

Minimizing the time from HIV infection to ART initiation is essential for universal test and treat to be
optimally effective. However, researchers have not typically focused on quantifying the HIV-
infectiousness period, partially due to the absence of data on the timing of seroconversion. In the
universal test and treat era, an estimate of the infectious period from HIV seroconversion to ART
initiation could become a priority indicator to identify gaps in time and monitor whether HIV prevention
initiatives are closing such gaps. This dissertation has laid the groundwork for a new metric for
monitoring treatment initiation and has advanced our understanding of the timeliness of diagnosis and
ART initiation. This novel method can be adopted by other researchers and surveillance jurisdictions to
monitor HIV epidemics and the impact of universal test and treat policies and programs on the HIV
epидemic.

REFERENCES

1. UNAIDS. Fast-Track: ending the AIDS epidemic by 2030. 2014;
2. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the
https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-supplemental-
2015.
6. Insight Start Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in


CHAPTER 2: TIMELINESS OF HIV DIAGNOSIS AND ANTIRETROVIRAL TREATMENT INITIATION IN THE ERA OF UNIVERSAL TEST AND TREAT (AIM 1)

ABSTRACT

Background: We describe the timing of HIV diagnosis and antiretroviral treatment (ART) initiation following implementation of universal test and treatment policies in New York City (NYC).

Methods: Using NYC population-based HIV Registry data for persons diagnosed from 2012 through 2015 and followed through June 2017, we examined trends in the proportion diagnosed early following HIV infection (i.e., with CD4 count ≥500 cells/mm3 or with acute HIV infection) and used Kaplan-Meier plots and proportional hazards regression to examine the timing of ART initiation following diagnosis.

Results: Among 9,987 NYC residents diagnosed with HIV from 2012-2015, 35% were diagnosed early and 87% initiated ART by June 2017. The annual proportion of persons diagnosed early did not increase appreciably (35% in 2012 versus 37% in 2015, p=0.08). By 6 months following diagnosis, 62%, 67%, 72% and 77% of persons diagnosed in 2012, 2013, 2014 or 2015, respectively, had initiated ART, with respective median time (months) to ART initiation of 3.34 (Interquartile range: 1.34-12.75), 2.62(1.28-10.13), 2.16(1.15-7.11), 2.03(1.11-5.61).

Conclusions: While recommendations for ART initiation upon diagnosis are increasingly being implemented, these findings suggest immediate treatment initiation is not universal. Continued efforts are needed to expand and better target HIV testing to promote earlier diagnosis.
INTRODUCTION

People with HIV (PWH) have a lower risk of developing acquired immunodeficiency syndrome (AIDS), serious illnesses, and death if they start taking antiretroviral treatment (ART) when the CD4-lymphocyte (CD4) count is above 500 cells/mm$^3$. Furthermore, early initiation of ART decreases risk of HIV transmission. Because of this and other evidence in favor of early ART for PWH, by 2012 the United States Department of Health and Human Services expanded HIV treatment guidelines from the recommendation that PWH with a CD4 count <500 cells/mm start treatment to the recommendation of ART initiation after diagnosis for all persons with HIV, regardless of CD4 count.

Voluntary HIV testing followed by immediate ART initiation (universal testing and treatment) has become an integral part of strategies to eliminate HIV and control the HIV/AIDS epidemic. Efforts aimed at ending the epidemic rely on a) high population-level ART coverage and b) early ART initiation to achieve the full potential impact of universal testing and treatment, for individual health outcomes for PWH and for HIV incidence reduction.

To attain the goals of universal test and treat and end the HIV epidemic, we must monitor the timeliness of diagnosis and ART initiation at the population-level. Yet, population-based data on ART initiation are generally not available because ART initiation and prescription are typically measured indirectly by public health departments (e.g., with viral suppression as a proxy) or with data from non-population-based sources (e.g., clinical cohorts). Data from the Medical Monitoring Project can be used to examine population-based trends in ART initiation nationally, but local data are limited. Moreover, as the HIV care cascade has become the predominant visual representation of the HIV epidemic, much of the focus has been on the proportion diagnosed and receiving ART rather than the elapsed time from infection to diagnosis and to ART initiation.

The aim of this analysis was to understand a) the timeliness of HIV diagnosis and ART initiation relative to infection by examining trends in CD4 counts, and b) the time from diagnosis to ART initiation.
and predictors of ART initiation in the era of universal testing and treatment using population-based New York City (NYC) HIV surveillance data.

METHODS

Data source and population

The Department of Health and Mental Hygiene has conducted population-based, name-based AIDS surveillance since 1981 and HIV surveillance 2000. Electronic reporting of all HIV-related laboratory tests, including positive diagnostic tests, viral load (VL), CD4 and viral nucleotide sequences, has been mandatory under NYS law since 2005. Validation work has shown that over 85% of CD4 cell counts and VL tests reported to surveillance were associated with primary (versus urgent/emergency) care, making CD4 and VL laboratory reports in the surveillance system reasonable indicators of receipt of HIV medical care in NYC. Demographic and HIV transmission risk information is obtained via review of medical charts of persons newly diagnosed with HIV. Vital status is routinely updated through matches with death records.

This analysis included NYC residents diagnosed with HIV from 2012 to 2015 and aged ≥13 years at HIV diagnosis and their laboratory information reported through June 30, 2017. We excluded persons who did not have at least one VL or CD4 reported to the Registry within 18 months of diagnosis, as these persons were most likely not receiving medical care in NYC and would not have laboratory data reported to the Registry.

This study was approved by the institutional review boards at The City University Of New York and the New York City Department of Health and Mental Hygiene. For these secondary analyses of de-identified data, we received a waiver for informed consent under 45 CFR 46.116(d)(2).

Definitions

Early Diagnosis
The CD4 count at diagnosis was defined as the first CD4 count within 6 months of the HIV diagnosis date. The CD4 count at diagnosis was categorized as CD4≥500 cells/mm³, CD4<500 cells/mm³, or CD4 not reported within 6 months of diagnosis. Persons were considered to have an early diagnosis if the CD4 count was ≥500 cells/mm³ or if they had acute HIV infection (AHI) at diagnosis. AHI was based on clinical laboratory results per the Centers for Disease Control and Prevention surveillance case definition, for example, a negative or indeterminate Western Blot and a detectable VL.

Antiretroviral Initiation

ART initiation was defined based on the earlier occurrence of either: a ≥1-log drop in detectable VL (defined as ≥200 copies/mL) over a 3-month period or a detectable VL followed by an undetectable VL (defined as <200 copies/mL). The date of probable ART initiation was defined as the mid-point between the two VLs which indicated ART initiation. We also considered ART initiation to have occurred if the first VL reported to the Registry was undetectable. In this case the estimated date of ART initiation was the mid-point between diagnosis and the undetectable VL.

The CD4 count at ART initiation was the CD4 count closest to and within the 3 months before the estimated date of ART initiation. For persons not known to have AHI at diagnosis, early ART initiation was defined as a CD4 count >500 cells/mm at ART initiation. If the CD4 count was not available at ART initiation, the timing of ART initiation was considered to be ‘unknown’. As persons diagnosed with AHI could be misclassified as having lower CD4 counts at ART initiation, we used the timing of ART initiation after diagnosis to define early ART initiation. For persons diagnosed with AHI, early ART was defined as ART initiation within 6 months after diagnosis.

Covariates

We examined the following covariates as predictors of ART initiation: sex, age at HIV diagnosis, race/ethnicity, HIV transmission risk group, year of diagnosis, CD4 count at diagnosis, linked to HIV medical care within 3 months following diagnosis, and type of diagnosing facility.
Statistical analysis

We performed descriptive analysis of demographic characteristics stratified by early diagnosis, CD4 \(<500\) units at diagnosis and unknown timing of diagnosis relative to infection (i.e., AHI or CD4 \(\geq 500\) cells/mm at diagnosis versus CD4 \(<500\) cells/mm at diagnosis versus unknown CD4 at diagnosis, respectively). To examine the timeliness of diagnoses relative to infection, we examined the annual proportion of persons diagnosed early (i.e., CD4\(\geq 500\) cells/mm or with AHI at diagnosis) using the Cochran-Armitage test for trend.

To examine the timeliness of ART initiation, we created Kaplan Meier plots and stratified by year of diagnosis overall and for all covariates. The log-rank test was used to examine the statistical significance of annual improvements in time to ART initiation for all covariates. To examine characteristics of persons who initiated ART, we used proportional hazards regression. The median time to ART initiation and the proportion who initiated ART at 6 months were generated using Kaplan-Meier product-limit estimates. For Kaplan-Meier plots and proportional hazards regression, persons contributed time in months from diagnosis to the estimated date of ART initiation, or they were censored at the earlier of death or June 30, 2017.

We also examined temporal trends in median CD4 counts at diagnosis and at ART initiation using quantile regression as an indicator for the timeliness of diagnosis and ART initiation, respectively; we modelled the median CD4 count at diagnosis and at ART initiation as a linear function of the calendar year of diagnosis. For the quantile regression we assume that lower CD4 counts indicate a longer time since HIV infection. Therefore, we ran these models with and without AHI cases, as at the time of AHI there is sometimes high viral replication which results in a drop in CD4 count.

All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, N.C.).
The analysis included 9,987 NYC residents who were diagnosed with HIV from 2012-2015 (median CD4 at diagnosis 382; interquartile range (IQR) 208-564) (Table 1). Of these, more than one-third (35%, N = 3,511) were diagnosed early following HIV infection with a CD4 ≥500 cells/mm or with AHI (median CD4 at diagnosis in this subgroup: 623; IQR 533-760). Among those diagnosed early (CD4 ≥500 cells/mm or with AHI), 29% (1,023/3,511) were diagnosed with AHI. Slightly more than half (55%, N = 5,529) of persons were diagnosed at <500 cells/mm (median CD4 at diagnosis in this subgroup: 262; 115-378) and the remaining 10% did not have a CD4 count reported within 6 months of diagnosis (Table 1).

Persons diagnosed with HIV in 2012-2015 were young (40% aged 13-29; 25% aged 30-39), male (81%), black (42%) or Latino/Hispanic (35%), and men who have sex with men (MSM) (61%) (Table 1). Most persons (91%) had any evidence of care (as indicated by a VL or CD4 report) and 75% were retained in care (as indicated by ≥2 laboratory reports ≥91 days apart) in the first year of diagnosis (Supplemental Table 1). Compared to persons with a CD4 <500 cells/mm at diagnosis, persons diagnosed earlier following HIV infection were more likely to be aged 13-29 (48% versus 33%), white (22% versus 16%), and MSM (67% versus 56%). Further details on the clinical characteristics and vital status of the cohort can be found in supplemental table 1.

Median CD4 Counts at Diagnosis and ART Initiation

From 2012 to 2015, the proportion of persons diagnosed early following HIV infection (i.e., CD4 ≥500 or with AHI) did not change appreciably (35% in 2012 vs. 37% in 2015, p=0.08 in Cochran-Armitage test for trend). Among persons diagnosed from 2012 to 2015 (i.e., including the AHI cases), the median CD4 count at diagnosis remained stable (median CD4 at diagnosis: 381; IQR: 211-568 in 2012 vs. 390; IQR: 206-553 in 2015, quantile regression coefficient = 2.50 cell increase in median CD4 count per year, 95% CI: -3.33-8.33, P = 0.40) (Figure 1). When AHI cases were excluded from the analysis of median CD4 counts at diagnosis, the median CD4 count at diagnosis remained stable (median CD4 at diagnosis: 382; IQR: 208-564 in 2012 vs. 381; IQR: 221-538 in 2015, quantile regression coefficient = 2.00 cell increase in median CD4 count per year, 95% CI: -4.13-8.13, P = 0.48).
Among persons diagnosed from 2012-2015, the median CD4 at ART initiation was 365 (IQR 200-538), and the median CD4 count at ART initiation showed a modest but statistically significant increase (median CD4 at ART initiation: 354; 195-529 in 2012 and 375; 206-553 in 2015, regression coefficient = 7.00 cell increase in median CD4 count per year, 95% CI: 1.02-12.98, P=0.02) (Figure 1). When AHI cases were excluded from the analysis, the median CD4 count at ART initiation remained stable (median CD4 at ART initiation: 344; 184-520 in 2012 and 356; 184-540 in 2015, quantile regression coefficient = 5.33 cell increase in median CD4 count per year, 95% CI: -1.65-7.14, P=0.14).

**Time from Diagnosis to ART Initiation**

The median time from HIV diagnosis to ART initiation was 2.43 months (IQR 1.21-8.66), and PWH had a median follow-up time of 3.50 years (IQR 2.5-4.5) (Table 2). Nearly 88% of individuals diagnosed from 2012 to 2015 initiated ART as of June 30, 2017. One-quarter of all persons diagnosed from 2012-2015 initiated ART early (CD4 count >500 cells/mm at ART initiation or ART initiation within 6 months of diagnosis for cases known to be an AHI) and 64% of persons diagnosed early initiated ART early.

Overall, 69% of persons had initiated ART at 6 months post-diagnosis (Table 2 and Figure 2a). The time from diagnosis to ART initiation decreased year to year (Table 2 and Figure 2b). Within 6 months of diagnosis, 62%, 67%, 72% and 76% of persons diagnosed in 2012, 2013, 2014 and 2015, respectively, had initiated ART, with respective median time (months) from diagnosis to ART initiation of 3.34 (IQR: 1.34-12.75), 2.62(1.28-10.13), 2.16(1.15-7.11), and 2.03(1.11-5.61) (Table 2). Before and after adjustment for demographic characteristics, significantly higher rates of ART initiation were observed each successive calendar year. The rate of ART initiation was 43% higher in 2015 than in 2012 (adjusted Hazards Ratio (HR): 1.43, 95% Confidence Interval: 1.34-1.52) (Table 2).
At least 90% of persons who were white or who had a CD4 count at diagnosis of 200-499 cells/mm² had initiated ART by June 30, 2017 (Supplemental Table 2). Among persons diagnosed in 2015, 77% initiated ART within 6 months of diagnosis, and this proportion increased to 87% among persons who linked to care within 3 months and represented the subgroup with the highest percentage of persons who initiated ART (Supplemental Table 2).

Year to year reductions in time from diagnosis to ART initiation were observed for all covariate subgroups except persons with a CD4 count <200 cells/mm² at diagnosis, with 77% initiating ART within 6 months of diagnosis in 2012 versus 83% initiating ART within 6 months in 2015 (Figure 3a log-rank test P=0.39). The largest year to year gains in time to ART initiation were observed among persons aged 13-29 (in 2012, 56% initiated ART within 6 months versus 75% in 2015, Figure 3b P<0.01), among persons diagnosed early (in 2012, 60% initiated ART within 6 months vs 77% in 2015, Figure 3c P<0.01), among persons not linked to care within 3 months (in 2012, 23% initiated ART within 6 months vs 43% in 2015, Figure 3d P<0.01) or among persons diagnosed at an screening, diagnostic, or referral agency (in 2012, 54% initiated ART within 6 months vs 80% in 2015, Figure 3e P<0.01).

**DISCUSSION**

We used population-based surveillance data to describe the timing of HIV diagnosis and ART initiation among persons with newly diagnosed HIV in the era of universal testing and treatment in a major epicenter of the United States HIV epidemic. We observed a slow but steady trend toward earlier ART initiation but, importantly, no trend toward earlier diagnosis among PWH diagnosed from 2012 to 2015. One-third of New Yorkers diagnosed with HIV had a CD4 count >500 cells/mm³ or an AHI at diagnosis, and this proportion remained stable from 2012 to 2015, and 77% of persons diagnosed in 2015 initiated ART within 6 months of diagnosis. These findings suggest local and national recommendations for ART initiation upon diagnosis are increasingly being implemented in NYC.26 as the
time to ART initiation decreased significantly each year. Nonetheless, ART initiation following HIV diagnosis was far from universal or immediate, even in 2015.

A hallmark of HIV infection is progressive decline of CD4 count in the absence of treatment. Therefore, if and when ART is initiated, people diagnosed with a CD4 count <500 cells will necessarily initiate ART under the 500 cell-threshold, while reductions in morbidity and mortality occur above this threshold.\textsuperscript{1,2} One-quarter of NYC PWH initiated ART with a CD4 count \( \geq 500 \) cells/mm. Individual and population benefits of early ART initiation will not be fully-realized if the majority of people with HIV are diagnosed with CD4<500 cells/mm or if some proportion of persons diagnosed \( \geq 500 \) cells/mm defer treatment initiation. HIV testing initiatives should be tailored to groups with higher frequencies of late diagnoses and/or lower testing frequencies to identify people with undiagnosed HIV sooner following their infection.\textsuperscript{30} In this analysis, persons over age 40 or with heterosexual transmission risk were more likely to diagnosed with a CD4 count <500 cells. NYC should continue to support outreach for testing among persons at high risk for HIV infection. Increasing the rate of HIV testing may be as important as a policy as universal treatment.

Immediate ART will be effective if PWH are willing and able to get HIV tested and seek care.\textsuperscript{31} The 2012 expanded treatment guidelines were viewed as more of a public health recommendation (i.e., for HIV prevention) than as a clinical recommendation (i.e., for individual health), given that trial data on the individual benefits of early ART were not available until 2015.\textsuperscript{1,2} Adoption of immediate treatment recommendations has been gradual, and we may see more rapid ART initiation in more recent years, given the focus on early ART for individual health.

We considered 90\% of diagnosed persons initiating ART as a marker of ‘high’ population-level ART coverage.\textsuperscript{6} This threshold was chosen based on the 90-90-90 treatment initiative to end the AIDS epidemic, where the goal is that 90\% of all diagnosed persons receive sustained ART.\textsuperscript{6} We observed high population-level ART coverage by the end of the study period (i.e., 90\% of those diagnosed initiated...
ART) for whites, persons with a CD4 count at diagnosis that ranged from 200-499 cells/mm, and for persons linked to care within 3 months of diagnosis. Notably, we observed lower proportions (specifically, less than 90%) initiating ART within 6 months of diagnosis for all other subgroups, even after restricting to persons diagnosed in 2015, among whom initiation rates should be high in the universal treatment era. PWH diagnosed in 2015 and linked to care within 3 months were closest to meeting the target of 90% (87% initiated ART within 6 months). Thus, a gap exists between guidelines, which recommend high population ART coverage and initiation as soon as possible after diagnosis for all PWH, and the reality of when people start treatment.

This analysis has several limitations. First, the laboratory-based measure of ART initiation we used is a proxy for clinical data on ART use. However, in a validation study, this laboratory-based measure of ART aligns with the nadir CD4 count, which is expected to fall prior to- and rise following ART initiation. Second, missing data is caused by migration out of the jurisdiction or not receiving medical care. We do not have information on migration, and substantial evidence from New York City and other jurisdictions suggests that not accounting for out-migration results in pessimistic surveillance-based care measures. Accounting for outmigration in NYC, improved retention from 63% to 91% in 2012. To minimize the potential effect of out-migration, we restricted the analysis to individuals who had at least one laboratory event reported to the NYC surveillance registry within 18 months of diagnosis, as these individuals were likely to be residing in NYC. Nearly one-quarter of the cohort was not retained in care (at least 2 laboratory events at least 90 days apart) in the first year of diagnosis. However, this restriction would exclude persons who remain in the city and do not link to care within 18 months.

Third, deaths prior to ART initiation may be viewed as a competing risk (N = 160 persons had died and not initiated ART; 1.6%). The results changed minimally when we re-ran the cumulative incidence curves with death as a competing risk (e.g., overall 68.5% initiated ART at 6 months when death prior to ART initiation was a competing risk vs. 69.1% when death was censored). Fourth, we assumed that a
lower CD4 count indicated a longer time since infection, which may not be true for certain individuals, especially persons diagnosed with AHI. To avoid having the AHI cases incorrectly represent more time since infection, we present median CD4 counts without the AHI cases and indicators of the timeliness of diagnosis and ART initiation which do not rely on CD4: a) the proportion diagnosed early (≥500 cells/mm or with AHI) and b) the time from diagnosis to ART initiation.

Fifth, New York City has a robust infrastructure for HIV care, and results may not generalize to other jurisdictions. Sixth, persons who are naturally able to control their VL without treatment (“elite controllers”) may be considered to have initiated ART since the algorithm captures those who go from detectable to undetectable. However, the population proportion of elite controllers is estimated to be small (1% of PWH maintain low to undetectable VL levels without treatment), and any effect of mischaracterizing such persons should not change our estimates substantially. Finally, 9.5% of persons diagnosed from 2012–2015 were missing a CD4 count within 6 months of diagnosis. This should not impact our estimates of ART initiation; however, our estimate of the proportion of persons diagnosed early may have been underestimated, given nearly half (49%) of individuals missing CD4 counts were aged 13-29, and younger persons were more likely to be diagnosed at higher CD4 counts. Since the demographic make-up of persons missing a CD4 count did not change from 2012 to 2015, and the proportion missing a CD4 count did not vary by year, we do not expect the trend in proportion of persons diagnosed early (i.e., >500) would be affected.

This analysis examined the timeliness of HIV diagnosis and ART initiation in the universal testing and treatment era among PWH diagnosed from 2012 to 2015 in NYC. We observed a slow trend toward earlier ART initiation but no trend toward earlier diagnosis. Characterizing the timeliness with which HIV diagnosis and ART initiation occur by geographic, demographic and other subgroups can be used to inform universal testing and treatment implementation and policy. To realize the full individual and population benefits from expanded treatment guidelines, HIV-infected persons need to be diagnosed
earlier in the course of infection, underscoring the need for continued efforts to expand and focus HIV testing in population groups with historically low testing frequency and high rates of late HIV diagnosis. Moreover, continued improvements in rates of timely ART initiation following diagnosis are necessary.

REFERENCES


TABLES AND FIGURES

**Figure 1. Trends in median CD4 count at diagnosis and ART Initiation and proportion of early diagnoses and early ART Initiation – New York City, 2012-2015**
Figure 2. Time to ART Initiation overall and by year of diagnosis – New York City, 2012-2015

*Log-rank test: p<0.0001
Figure 3. Time to ART Initiation by year of diagnosis, among (a) persons diagnosed with a CD4 count <200 cells/mm, (b) persons aged 18-29 years at diagnosis, (c) persons diagnosed early, (d) persons not linked to care within 3 months, (e) persons diagnosed at a screening, diagnosis and referral clinic – New York City, 2012-2015

Table 1. Characteristics of all Persons Diagnosed with HIV Stratified by CD4 Count at Diagnosis - New York City, 2012-2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. CD4 &lt;200</td>
<td>77.07</td>
<td>81.19</td>
<td>80.97</td>
<td>82.60</td>
</tr>
<tr>
<td>B. 13-29 years</td>
<td>56.41</td>
<td>61.97</td>
<td>67.81</td>
<td>74.58</td>
</tr>
<tr>
<td>C. CD4 ≥500 or AHI</td>
<td>59.68</td>
<td>67.19</td>
<td>73.15</td>
<td>76.87</td>
</tr>
<tr>
<td>D. Not linked to care</td>
<td>23.22</td>
<td>26.94</td>
<td>31.61</td>
<td>42.83</td>
</tr>
<tr>
<td>E. Screening, diagnosis and referral clinic</td>
<td>54.23</td>
<td>60.94</td>
<td>65.33</td>
<td>79.92</td>
</tr>
</tbody>
</table>

Log-rank test: ^p=0.39, *p<0.0001
<table>
<thead>
<tr>
<th></th>
<th>All diagnoses</th>
<th>Early: ≥500 cells/mm or an acute case at diagnosis</th>
<th>&lt;500 cells/mm at diagnosis</th>
<th>Unknown timing of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9,987 (100.00)</td>
<td>3,511 (100.00)</td>
<td>5,529 (100.00)</td>
<td>947 (100.00)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 29</td>
<td>3,989 (39.94)</td>
<td>1,693 (48.22)</td>
<td>1,826 (33.03)</td>
<td>470 (49.63)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>2,501 (25.04)</td>
<td>877 (24.98)</td>
<td>1,397 (25.27)</td>
<td>227 (23.97)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>1,889 (18.91)</td>
<td>541 (15.41)</td>
<td>1,199 (21.69)</td>
<td>149 (15.73)</td>
</tr>
<tr>
<td>50+</td>
<td>1,608 (16.10)</td>
<td>400 (11.39)</td>
<td>1,107 (20.02)</td>
<td>101 (10.67)</td>
</tr>
<tr>
<td><strong>Sex at Birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8,111 (81.22)</td>
<td>2,909 (82.85)</td>
<td>4,405 (79.67)</td>
<td>797 (84.16)</td>
</tr>
<tr>
<td>Female</td>
<td>1,876 (18.78)</td>
<td>602 (17.15)</td>
<td>1,124 (20.33)</td>
<td>150 (15.84)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4,118 (41.23)</td>
<td>1,322 (37.65)</td>
<td>2,397 (43.35)</td>
<td>399 (42.13)</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>3,468 (34.73)</td>
<td>1,220 (34.75)</td>
<td>1,922 (34.76)</td>
<td>326 (34.42)</td>
</tr>
<tr>
<td>White</td>
<td>1,834 (18.36)</td>
<td>782 (22.27)</td>
<td>877 (15.86)</td>
<td>175 (18.48)</td>
</tr>
<tr>
<td>Asian Pacific Islander</td>
<td>438 (4.39)</td>
<td>140 (3.99)</td>
<td>270 (4.88)</td>
<td>28 (2.96)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>129 (1.29)</td>
<td>47 (1.34)</td>
<td>63 (1.14)</td>
<td>19 (2.01)</td>
</tr>
<tr>
<td><strong>Transmission Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>6,064 (60.72)</td>
<td>2,366 (67.39)</td>
<td>3,114 (56.32)</td>
<td>584 (61.67)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>397 (3.98)</td>
<td>161 (4.59)</td>
<td>188 (3.40)</td>
<td>48 (5.07)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>1,916 (19.18)</td>
<td>580 (16.52)</td>
<td>1,205 (21.79)</td>
<td>131 (13.83)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1,610 (16.12)</td>
<td>404 (11.51)</td>
<td>1,022 (18.48)</td>
<td>184 (19.43)</td>
</tr>
<tr>
<td><strong>Year of Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>2,616 (26.19)</td>
<td>914 (26.03)</td>
<td>1,441 (26.06)</td>
<td>261 (27.56)</td>
</tr>
<tr>
<td>2013</td>
<td>2,577 (25.80)</td>
<td>862 (24.55)</td>
<td>1,449 (26.21)</td>
<td>266 (28.09)</td>
</tr>
<tr>
<td>2014</td>
<td>2,511 (25.14)</td>
<td>899 (25.61)</td>
<td>1,374 (24.85)</td>
<td>238 (25.13)</td>
</tr>
<tr>
<td>2015</td>
<td>2,283 (22.86)</td>
<td>836 (23.81)</td>
<td>1,265 (22.88)</td>
<td>182 (19.22)</td>
</tr>
<tr>
<td>Median CD4 at Diagnosis (IQR)</td>
<td>382 (208, 564)</td>
<td>623 (533, 760)</td>
<td>262 (115, 378)</td>
<td>NA</td>
</tr>
<tr>
<td>Median CD4 at ART (IQR)</td>
<td>365 (200, 539)</td>
<td>594 (488, 733)</td>
<td>259 (113, 376)</td>
<td>369 (232, 549)</td>
</tr>
<tr>
<td><strong>Timing of ART Initiation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500 cells/mm (early)</td>
<td>2,516 (25.19)</td>
<td>2,240 (63.80)</td>
<td>186 (3.36)</td>
<td>90 (9.50)</td>
</tr>
<tr>
<td>&lt;500 cells/mm</td>
<td>4,910 (49.16)</td>
<td>366 (10.42)</td>
<td>4,322 (78.17)</td>
<td>222 (23.44)</td>
</tr>
<tr>
<td>Missing CD4</td>
<td>1,360 (13.62)</td>
<td>538 (15.32)</td>
<td>491 (8.88)</td>
<td>331 (34.95)</td>
</tr>
<tr>
<td>No ART Initiation</td>
<td>1,201 (12.03)</td>
<td>367 (10.45)</td>
<td>530 (9.59)</td>
<td>304 (32.10)</td>
</tr>
</tbody>
</table>

NA: Not applicable; IQR: Interquartile Range. Data reported to the NYC HIV Registry as of October 31, 2017. Inclusion Criteria:

(1) These individuals did not link to care or have a CD4 count reported within 6 months

(2) ART initiation: earlier of a 1-log drop in VL or switch from detectable (>200 copies/µl) to undetectable viral load. CD4 at ART initiation is the CD4 count reported closest to and in the 91 days prior to the date of ART initiation

(3) Early ART initiation defined as ART initiation within 6 months for acute HIV infection or CD4 ≥500 cells/mm at ART initiation for persons diagnosed without acute HIV infection
Table 2. The Time to and Hazards Ratios of ART Initiation\(^1\) Stratified by Year of Diagnosis and Timing of Diagnosis – New York City, 2012-2015

| Characteristics | No. (%) of All Diagnoses who Initiated ART by 06/30/2017 | % of all 2012-2015 diagnoses initiated ART at 6 Months\(^2\) | % of all 2015 diagnoses initiated ART at 6 Months\(^2\) | Median time to ART initiation – Months (25%ile, 75%ile) Unadjusted HR Adjusted HR\(^3\) |
|-----------------|--------------------------------------------------------|----------------------------------------------------------|------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **Total**       | 8,786 (87.97)                                          | 69.07                                                    | 76.31                                            | 2.43 (1.21, 8.66)                                |                                                 |
| **Year of Diagnosis** |                                                |                                                      |                                                  |                                                 |                                                 |
| 2012            | 2,328 (88.99)                                          | 61.65                                                    | NA                                               | 3.34 (1.34, 12.75)                                | Ref                                             |
| 2013            | 2,263 (87.82)                                          | 67.19                                                    | NA                                               | 2.62 (1.28, 10.13)                                | 1.07 (1.01, 1.14)                               |
| 2014            | 2,205 (87.81)                                          | 72.15                                                    | NA                                               | 2.16 (1.15, 7.11)                                 | 1.21 (1.14, 1.28)                               |
| 2015            | 1,990 (87.17)                                          | 76.31                                                    | 76.31                                            | 2.03 (1.11, 5.61)                                 | 1.30 (1.22, 1.38)                               |
| **Timing of Diagnosis** |                                                |                                                      |                                                  |                                                 |                                                 |
| Early: >500 or AHI | 3,144 (89.55)                                          | 69.98                                                    | 76.87                                            | 2.46 (1.21, 8.79)                                | Ref                                             |
| <500            | 4,999 (90.41)                                          | 78.25                                                    | 82.72                                            | 1.97 (1.11, 4.89)                                 | 1.21 (1.16, 1.27)                               |
| Unknown CD4 at Diagnosis | 643 (67.90)                                           | 16.29                                                    | 29.03                                            | 15.87 (7.84, NA)                                 | 0.39 (0.36, 0.43)                               |

Data reported to the NYC HIV Registry as of October 31, 2017
NA: Not applicable
(1) ART initiation: earlier of a 1-log drop in VL or switch from detectable (>200 copies/µl) to undetectable viral load. Persons contributed observation time from date of diagnosis to ART initiation or were censored at the earlier of death or December 31, 2016.
(2) % of persons initiated ART and the median time to ART initiation based on Kaplan-Meier estimates of months to ART initiation.
(3) Model adjusted for age, sex, race, risk, year of diagnosis, linkage within 3 month, provider type and timing of diagnosis. CD4 at diagnosis is not adjusted for due to collinearity with timing of diagnosis.
(4) Persons were considered linked to care if a laboratory (CD4 or VL) event was reported within 8-91 days of diagnosis.
(5) CD4 at diagnosis is the first CD4 count reported within 6 months of diagnosis.

Supplemental Table 1. Clinical Characteristics of Persons Diagnosed with HIV Stratified by CD4 Count at Diagnosis - New York City, 2012-2015

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All diagnoses</th>
<th>Early: ≥500 cells/mm or an acute case at diagnosis</th>
<th>&lt;500 cells/mm at diagnosis</th>
<th>Unknown timing of diagnosis(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>9,987 (100.00)</td>
<td>3,511 (100.00)</td>
<td>5,529 (100.00)</td>
<td>947 (100.00)</td>
</tr>
<tr>
<td><strong>Linked within 3 months(^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,369 (23.72)</td>
<td>623 (17.74)</td>
<td>904 (16.35)</td>
<td>842 (88.91)</td>
</tr>
<tr>
<td>Yes</td>
<td>7,618 (76.28)</td>
<td>2,888 (82.26)</td>
<td>4,625 (83.65)</td>
<td>105 (11.09)</td>
</tr>
<tr>
<td><strong>Receipt of Care in the First Year(^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>893 (8.94)</td>
<td>163 (4.64)</td>
<td>265 (4.79)</td>
<td>465 (49.10)</td>
</tr>
<tr>
<td>Yes</td>
<td>9,094 (91.06)</td>
<td>3,348 (95.36)</td>
<td>5,264 (95.21)</td>
<td>482 (50.90)</td>
</tr>
<tr>
<td><strong>Retained in Care in the Year(^2)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2,470 (24.73)</td>
<td>655 (18.66)</td>
<td>994 (17.98)</td>
<td>821 (86.69)</td>
</tr>
<tr>
<td>Yes</td>
<td>7,517 (75.27)</td>
<td>2,856 (81.34)</td>
<td>4,535 (82.02)</td>
<td>126 (13.31)</td>
</tr>
<tr>
<td><strong>Acute HIV Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8,964 (89.76)</td>
<td>2,488 (70.86)</td>
<td>5,529 (100.00)</td>
<td>947 (100.00)</td>
</tr>
<tr>
<td>Yes</td>
<td>1,023 (10.24)</td>
<td>1,023 (29.14)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Died during follow-up</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>9,592 (96.04)</td>
<td>3,451 (98.29)</td>
<td>5,221 (94.43)</td>
<td>920 (97.15)</td>
</tr>
<tr>
<td>Yes</td>
<td>395 (3.96)</td>
<td>60 (1.71)</td>
<td>308 (5.57)</td>
<td>27 (2.85)</td>
</tr>
<tr>
<td><strong>Died prior to ART Initiation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>160 (1.60)</td>
<td>17 (0.48)</td>
<td>128 (2.31)</td>
<td>15 (1.58)</td>
</tr>
<tr>
<td>Yes</td>
<td>1,882 (18.84)</td>
<td>186 (5.30)</td>
<td>1,696 (30.67)</td>
<td>NA</td>
</tr>
</tbody>
</table>
Residing in New York City and Clinical Characteristics

Supplemental Table 2. The Time to and Hazards Ratios of ART Initiation\(^1\) Stratified by Demographic and Clinical Characteristics – Among 9,987 Persons Diagnosed with HIV from 2012 to 2015 and Residing in New York City

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%) of All Diagnoses who Initiated ART by 06/30/2017</th>
<th>% of all 2012-2015 diagnoses initiated ART at 6 Months(^2)</th>
<th>% of all 2015 diagnoses initiated ART at 6 Months(^2)</th>
<th>Median time to ART initiation – Months (25%, 75%)</th>
<th>Unadjusted HR</th>
<th>Adjusted HR(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8,786 (87.97)</td>
<td>69.07</td>
<td>76.31</td>
<td>2.43 (1.21, 8.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 29</td>
<td>3,503 (87.82)</td>
<td>64.79</td>
<td>74.58</td>
<td>3.08 (1.38, 11.18)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>30 - 39</td>
<td>2,003 (88.08)</td>
<td>70.69</td>
<td>76.70</td>
<td>2.30 (1.18, 7.93)</td>
<td>1.13 (1.07, 1.19)</td>
<td>1.09 (1.04, 1.16)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>1,673 (88.57)</td>
<td>71.27</td>
<td>76.11</td>
<td>2.10 (1.11, 7.51)</td>
<td>1.19 (1.12, 1.26)</td>
<td>1.15 (1.08, 1.22)</td>
</tr>
<tr>
<td>50+</td>
<td>1,407 (87.50)</td>
<td>74.28</td>
<td>80.01</td>
<td>2.03 (1.05, 6.03)</td>
<td>1.29 (1.21, 1.37)</td>
<td>1.19 (1.12, 1.28)</td>
</tr>
<tr>
<td>Sex at Birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7,128 (87.88)</td>
<td>68.90</td>
<td>76.28</td>
<td>2.46 (1.25, 8.66)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Female</td>
<td>1,658 (88.38)</td>
<td>69.81</td>
<td>76.47</td>
<td>2.26 (1.15, 8.75)</td>
<td>1.04 (0.99, 1.10)</td>
<td>1.06 (0.97, 1.15)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3,553 (86.28)</td>
<td>65.38</td>
<td>72.57</td>
<td>2.79 (1.25, 10.98)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>3,080 (88.81)</td>
<td>70.34</td>
<td>78.87</td>
<td>2.39 (1.25, 8.07)</td>
<td>1.10 (1.05, 1.15)</td>
<td>1.11 (1.06, 1.17)</td>
</tr>
<tr>
<td>White</td>
<td>1,657 (90.35)</td>
<td>74.61</td>
<td>80.57</td>
<td>2.00 (1.08, 6.10)</td>
<td>1.26 (1.19, 1.33)</td>
<td>1.32 (1.25, 1.41)</td>
</tr>
<tr>
<td>Asian Pacific Islander</td>
<td>388 (88.58)</td>
<td>74.14</td>
<td>78.68</td>
<td>2.10 (1.28, 6.30)</td>
<td>1.19 (1.07, 1.32)</td>
<td>1.20 (1.08, 1.34)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>108 (83.72)</td>
<td>56.59</td>
<td>60.71</td>
<td>4.46 (1.31, 20.56)</td>
<td>0.84 (0.70, 1.02)</td>
<td>0.90 (0.74, 1.08)</td>
</tr>
<tr>
<td>Transmission Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>5,436 (89.64)</td>
<td>70.73</td>
<td>79.62</td>
<td>2.39 (1.25, 7.57)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>334 (84.13)</td>
<td>61.76</td>
<td>59.76</td>
<td>3.61 (1.48, 15.77)</td>
<td>0.79 (0.71, 0.89)</td>
<td>0.76 (0.68, 0.86)</td>
</tr>
<tr>
<td>Category</td>
<td>Count (Percentage)</td>
<td>Percent (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
<td>------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterosexual</strong></td>
<td>1,704 (88.94)</td>
<td>70.45 (68.5, 72.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1,312 (81.49)</td>
<td>62.88 (61.0, 64.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Linked within 3 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,673 (70.62)</td>
<td>36.76 (35.0, 38.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7,113 (93.37)</td>
<td>80.80 (79.7, 81.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CD4 at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>702 (67.11)</td>
<td>17.67 (16.3, 19.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>1,912 (91.98)</td>
<td>80.67 (80.1, 81.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 - 350</td>
<td>1,731 (90.98)</td>
<td>75.17 (74.6, 76.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500</td>
<td>2,626 (89.87)</td>
<td>67.66 (67.2, 68.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Provider Type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Facility</td>
<td>3,564 (89.55)</td>
<td>72.42 (71.7, 73.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient Facility</td>
<td>3,122 (87.23)</td>
<td>73.18 (72.3, 73.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening, Diagnostic, Referral</td>
<td>1,209 (86.67)</td>
<td>63.27 (62.4, 64.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other/Unknown Lab</td>
<td>891 (86.25)</td>
<td>52.25 (51.4, 53.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Timing of Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early: &gt;500 or AHI</td>
<td>3,144 (89.55)</td>
<td>69.98 (69.1, 70.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤500</td>
<td>4,999 (90.41)</td>
<td>78.25 (77.4, 79.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown CD4 at Diagnosis</td>
<td>643 (67.90)</td>
<td>29.03 (28.2, 29.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data reported to the NYC HIV Registry as of October 31, 2017. Inclusion Criteria: Diagnosed Jan 1, 2012 to Dec 31, 2015, and New York City Residence at Diagnosis.

1. ART initiation: earlier of a 1-log drop in VL or switch from detectable (>200 copies/µl) to undetectable viral load. Persons contributed observation time from date of diagnosis to ART initiation or were censored at the earlier of death or December 31, 2016.
2. % of persons initiated ART and the median time to ART initiation based on Kaplan-Meier estimates of months to ART initiation.
3. Model adjusted for age, sex, race, risk, year of diagnosis, linkage within 3 month, provider type and timing of diagnosis. CD4 at diagnosis is not adjusted for due to collinearity with timing of diagnosis.
4. Persons were considered linked to care if a laboratory (CD4 or VL) event was reported within 8-91 days of diagnosis.
5. CD4 at diagnosis is the first CD4 count reported within 6 months of diagnosis.
CHAPTER 3: QUANTIFYING DIAGNOSIS DELAY FOLLOWING HIV

SEROCONVERSION: ASSESSING THE LINEARITY ASSUMPTION OF CD4 DECLINE (AIM 2A)

ABSTRACT

**Background:** One approach to estimating the timing of HIV seroconversion relative to diagnosis is to model time since seroconversion based on CD4 decline. An assumption of the CD4 decline approach is that the square root of the CD4 cell count decreases linearly over time prior to antiretroviral treatment (ART) initiation. If the assumption is true, then utilizing CD4 counts reported at any point in the pre-ART period would result in estimates of diagnosis delay that are not appreciably different.

**Methods:** Applying CD4 depletion model parameters from seroconverter cohort data to New York City residents, we compared the time from seroconversion to diagnosis (diagnosis delay) as estimated according to the square root of the first or second pre-ART CD4 count.

**Results:** Among 12,849 NYC residents who were diagnosed with HIV from 2006 to 2015 with at least 2 pre-ART CD4 count measurements around time of diagnosis, the average diagnosis delays based on the first or second pre-ART CD4 count were similar (4.93 years (95% Confidence intervals (CI):4.84-5.03) and 4.85 years (95% CI:4.76-4.95), respectively, p-value=0.09, Wilcoxon signed-rank). Among the subset of people whose second pre-ART CD4 count was measured >6 months after diagnosis (N=2,761), the average diagnosis delay based on first pre-ART CD4 count was shorter (3.52 years, 95% CI:3.35-3.68) than the second pre-ART CD4 count (3.94 years, 95% CI:3.77-4.12) but not significantly (p-value=0.115).

**Conclusions:** Our results are consistent with the linearity assumption of the CD4 depletion model. Researchers and implementers may use only one pre-ART CD4 count, including those reported more than 6 months after diagnosis, to estimate diagnosis delay at the population-level.
INTRODUCTION

In the era of universal test and treat, an estimate of the infectious period from HIV seroconversion to ART initiation could become a priority indicator to identify and monitor whether HIV testing and prevention initiatives are successfully reducing the infectious period.1-3 Yet, HIV seroconversion is almost always an unobserved event. Inferring a date of seroconversion is difficult because a minority of persons are diagnosed during primary or acute HIV infection, the first stage of HIV-infection.4 Rather, most persons are diagnosed in the later stages of HIV infection when the duration of the infection is much less certain.

One approach to estimating HIV seroconversion and the duration of infection is based on CD4 decline.5 The underlying assumption of the CD4 decline approach is that among ART-naïve people, the square root of the CD4 cell count decreases over time6, and the time since seroconversion can be inferred by applying an estimated rate of CD4 decline (from a European seroconverter cohort) to a population with pre-ART CD4 count.5,7-9 This approach has been used to estimate diagnosis delays (time from seroconversion to HIV diagnosis) locally and nationally.5,7,8,10 However, estimated delays in diagnosis rely on the accuracy of the initial CD4 depletion model, which assumes the mean square root of CD4 count is linearly related to the time since seroconversion. Some evidence suggests the rate—square root transformed—of CD4 decline over time is nonlinear.11

Using data from NYC, we compared estimated delays in diagnosis based on the first or second pre-ART CD4 count reported to HIV surveillance among people with at least two pre-ART CD4 counts. We hypothesized that estimates of diagnosis delays based on the first or the second CD4 count would not be appreciably different from one another, if the mean square root of CD4 count is linearly related to the time since infection at the population level.

METHODS

Data source and population
The NYC Department of Health and Mental Hygiene has conducted population-based, name-based AIDS surveillance since 1981 and HIV surveillance since 2000. Electronic reporting of all HIV-related laboratory tests (including viral load (VL) and CD4), has been mandatory since 2005.

This analysis included 32,556 people diagnosed with HIV in NYC from 2006 to 2015 and aged ≥13 years at HIV diagnosis, with their laboratory information reported through June 30, 2017. We excluded people who did not have at least one VL or CD4 test reported to the Registry within 18 months of diagnosis (N=4,394 excluded, leaving N=28,162 in analytic cohort), as people without a VL or CD4 for 18 months either were not receiving HIV medical care within NYC or moved out of NYC.

Approximately 20% (5,527/28,162) of all people in the 2006-2015 analytic cohort have an unknown HIV transmission risk factor in the surveillance registry. Following Centers for Disease Control and Prevention (CDC) guidance, we used sex-stratified multiple imputation procedures to assign these people a transmission risk category. Data were imputed 10 times both for males and females. We combined results from the datasets to generate an overall probability weight for transmission risk category (e.g., an individual could have a weight of 0.7 for heterosexual and 0.3 for injection drug use transmission risk, respectively).

We restricted the dataset to people who had at least two pre-ART CD4 counts reported (analytic cohort N = 12,849) and restricted the analytic cohort to people with >6 months between the two pre-ART CD4 counts (subset N= 2,761)

Definitions

ART initiation

ART initiation was defined based on the earlier occurrence of either: a ≥1-log drop in detectable VL (defined as ≥200 copies/mL) over a 3-month period or a detectable VL followed by an undetectable VL (defined as <200 copies/mL). The date of probable ART initiation was the mid-point between the two
VL occurrences. If the first VL reported to the Registry was undetectable, then the estimated date of ART initiation was the mid-point between diagnosis and the first undetectable VL.

**First or second pre-ART CD4 Count**

The first and second pre-ART CD4 counts had to be measured prior to the estimated date of ART initiation. The first pre-ART CD4 count was the first pre-ART CD4 count reported within 6 months of diagnosis. The 6-month rule was applied to help ensure we excluded post-treatment CD4 counts, given we used a proxy for treatment initiation. The second pre-ART CD4 count was the second CD4 count reported after diagnosis and following the first pre-treatment CD4 count, and no restriction on the timing of the CD4 count relative to diagnosis was applied.

**Time from seroconversion to pre-ART CD4 count**

To estimate the date of seroconversion, we applied an estimated rate of CD4 decline, which was based on previously published estimates from the CASCADE seroconverter cohort, to the NYC population, people diagnosed with HIV from 2006 to 2015 and having at least two pre-ART CD4 counts.\(^5\)

The CD4 depletion model relates the square root of the first pre-ART CD4 count (\(\sqrt{\text{CD4}}\)) to time of infection through a linear mixed model.\(^6,17\)

\[
\text{Formula 1: } \sqrt{\text{CD4}}_t = a_0 + (b_1 t) + e_{1t}
\]

Where \(t\) is the time from HIV seroconversion to the date of the first pre-ART CD4 count, \(\text{CD4}_t\) is the first pre-ART CD4 count, and the intercept \(a_0\) and the slope \(b_1\) are random variables following a normal distribution.

The duration of infection \(t\) is then estimated for an individual by Formula 2, using the previously published model parameters.

\[
\text{Formula 2: } T_i = (\sqrt{\text{CD4}} - a_0 - e_{1t}) / b_1
\]

For Formula 2, the intercept \(a\) and slope \(b\), for each person, were assumed to follow a bivariate normal distribution \(N[(a,b), (\text{standard error}_a, \text{standard error}_b), \text{correlation coefficient}(p)]\).
The mean intercept and slope, standard errors and correlation coefficient were based on published estimates for combinations of sex at birth, age group at seroconversion and risk group from the CASCADE cohort (see Song, et al 2016). Since the age group at seroconversion is unknown in our population, we used the age at diagnosis as an initial approximation of the age at seroconversion and estimated $T$ using age at diagnosis, (Formula 2). We then used $T$ to estimate age at seroconversion (Formula 3, below). 44% of the cohort was assigned an age group at seroconversion that was earlier than their age group at diagnosis, and the remaining 56% stayed in the same age group. Lastly, we re-estimated $T$ using the new estimated age at seroconversion (Formula 2).

Age at seroconversion is estimated as

$$\text{Formula 3: } \text{age at seroconversion} = \text{age at first CD4} - T_i$$

Finally, the date of seroconversion is then estimated by:

$$\text{Formula 4: Date of seroconversion} = \text{Date of first CD4} - T_i$$

In instances where seroconversion was estimated to occur after diagnosis, the date of seroconversion was set to the date of diagnosis. For people diagnosed with acute HIV infection, the date of seroconversion was assigned as the date of diagnosis.

Assuming normal distributions and with sex-, age- and risk-specific standard errors described in Song et al and above in Formulas 1 and 2, we estimated the duration ($T_i$ from seroconversion to first pre-ART CD4 count) for each person 1,000 times and took the average to infer an individual’s date of seroconversion and incorporate variance. We repeated this process using the second pre-ART CD4 count.

**Diagnosis delay**

We calculated two estimates of diagnosis delay as the difference between the date of diagnosis and the estimated date of seroconversion based on the first or the second pre-ART CD4 count.

**Statistical analysis**
We generated mean and median years since seroconversion overall and by transmission or demographic subgroups. Using the Wilcoxon signed-rank test, to compare repeated measurements on a sample, we compared the distribution of diagnosis delay based on the first pre-ART CD4 count with estimates of the diagnosis delay based on the second pre-ART CD4 count. We compared estimates of diagnosis delay based on the first or second pre-ART CD4 count among the entire population and repeated the comparison in a subset of individuals who had their second CD4 count reported >6 months after diagnosis.

We used weighted procedures to handle the imputation weights. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, N.C.).

This study was approved by the institutional review boards at The City University of New York School of Public Health and the New York City Department of Health and Mental Hygiene. For these secondary data analyses, we received a waiver for informed consent under 45 CFR 46.116(d)(2).

RESULTS

The analysis included 12,849 NYC residents who were diagnosed with HIV in NYC from 2006 to 2015 and had at least two pre-ART CD4 counts. The cohort was predominately male (77%), black or Latino/Hispanic (79%), and young (62% aged <40 years at diagnosis). The subset of people who had a second CD4 count reported >6 months after diagnosis (N = 2,761) was similar to the whole analytic cohort (N = 12,849) in terms of demographics (i.e., mostly male, black or Latino/Hispanic and young).

Among the entire cohort (N=12,849), the first pre-ART CD4 count tended to be slightly higher (median 400 cells/µL, interquartile range (IQR): 222-575) than the second pre-ART CD4 count (388 cells/µL, IQR:218-563). By design, all people had the first pre-ART CD4 within 6 months of diagnosis (median: 13 days, IQR: 136-145), and the second pre-ART CD4 was a median of 87 days (IQR:33-163) after diagnosis. The subset with a second pre-ART CD4 count >6 months after diagnosis, had higher first and second CD4 counts than the overall cohort, and the median time from diagnosis to the first or the
second pre-ART CD4 count was 28 days (IQR:8-79, with 100% in the first 6 months of diagnosis) and 300 days (IQR:224-553), respectively.

**Years from seroconversion to diagnosis**

Among the entire cohort, estimates of the average diagnosis delays based on the first and second pre-ART CD4 count were similar (4.93 years (95% Confidence intervals (CI):4.84-5.03) and 4.85 years (95% CI:4.76-4.95), respectively) (p-value for Wilcoxon test 0.09) (Table 2). We observed non-significant differences in diagnosis delay based on first or second CD4 count across all subgroups except for men (first: 4.82, 95% CI: 4.72-4.92 and second: 4.72, 95% CI: 4.62-4.82, p-value=0.040) and for men who have sex with men (first: 4.48 95% CI: 4.68-5.00 and second: 4.37, 95% CI: 4.25-4.48, p-value=0.038).

Amongst the subset of people who had their second pre-ART CD4 count measurement >6 months after diagnosis, the diagnosis delays based on first pre-ART CD4 count were shorter (3.52 years, 95% CI: 3.35-3.68) than delays based on the second pre-ART CD4 count (3.94 years, 95% CI: 3.77-4.12), although the difference was non-significant (p-value=0.115). We observed non-significant differences in diagnosis delay based on first or second CD4 count across all subgroups except for women (first: 3.56 years, 95% CI:3.16-3.95 and second: 4.31, 95% CI:3.84-4.75, p-value=0.027) and persons with heterosexual transmission risk (first: 3.82 years, 95% CI:3.50-4.15 and second: 4.65, 95% CI:4.29-5.01, p-value=0.025).

Figure 1 shows density plots for diagnosis delays based on first or second pre-ART CD4 count among the entire cohort (panel A) and the subset (panel B). Using the second pre-ART CD4 count resulted in 5,320 people (or 41% of the 12,849 cohort) with a shorter estimated delay (delay closer to value of 0) than the first pre-ART CD4 count (panel A). Among the 5,320 people with a shorter delay based on the second versus first pre-ART CD4 count, the second pre-ART CD4 count had a median value higher than the first pre-ART CD4 count (second CD4 count: 351 cells/µL versus first CD4 count: 278 cells/µL, difference of 73 cells). Among the subset of people who had a second pre-ART CD4 count reported >6 months after diagnosis, the second pre-ART CD4 count resulted in 916 people (or 33% of the 2,761
subset) with a shorter estimated delay (delay closer to value of 0) than the second pre-ART CD4 count (panel B), and the second pre-ART CD4 count had a median value higher than the first pre-ART CD4 count (385 versus 310 cells/µL, difference of 75 cells).

**DISCUSSION**

Voluntary HIV testing followed by immediate ART initiation (universal testing and treatment) has become an integral part of local and global strategies to eliminate HIV and control the HIV/AIDS epidemic.\(^{18-26}\) Minimizing the time from HIV infection to ART initiation is essential for universal test and treatment to be optimally effective. However, neither frontline implementers, nor health agencies or researchers have typically focused on quantifying the HIV-infectiousness period, partially due to the absence of population-based data on the timing of seroconversion.\(^3\) We used a CD4 decline model to estimate years since seroconversion among NYC residents with at least two pre-ART CD4 counts.\(^5\) An assumption of the CD4 decline model is that the square root of the CD4 cell count decreases linearly over time. If the assumption is valid, then we should estimate similar lengths of diagnosis delay utilizing CD4 counts reported at any point in the pre-ART period. We found that average diagnosis delay did not vary meaningfully between estimates based on the first or second pre-ART CD4 count in the overall cohort (4.93 years versus 4.85 years, respectively) or in the subset, people with a second CD4 count reported >6 months after diagnosis (3.52 years versus 3.94 years, respectively). Our results are consistent with the linearity assumption of the square root CD4 depletion model. Researchers and implementers may use only one pre-ART CD4 count, including those reported more than 6 months after diagnosis, to estimate diagnosis delay at the population-level.

We estimated diagnosis delay among the subset of people with a second CD4 count reported >6 months after diagnosis, as estimates were based on a second pre-ART CD4 count that was lower and more remote (relative to date of diagnosis and seroconversion) than the first pre-ART CD4 count. The later and generally lower second pretreatment CD4 counts contributed to longer estimates of diagnosis
delay, as estimates of delay based on the second pre-ART CD4 count were slightly longer, albeit non-significantly, than estimates based on the first pre-ART CD4 count. The Centers for Disease Control and Prevention recommends HIV surveillance jurisdictions use the first CD4 count reported within 3 months of diagnosis for inferring time since seroconversion, as this restriction ensure that post-treatment CD4 counts are excluded. Our analysis suggest that researchers could validly use CD4 counts reported much later than 3 months following diagnosis, assuming they have an actual or proxy date of initial treatment following diagnosis to restrict to the pre-ART CD4 counts.

As expected, given progressive decline of CD4 count in the absence of treatment, the first pre-ART CD4 count had a median value higher than the second pre-ART CD4 count in the overall cohort (first CD4 count: 400 versus second CD4 count: 388, difference of 12 cells). While estimated delays based on first or second pre-ART CD4 count were not materially different, the estimates based on the first pre-ART count were longer than the second pre-ART CD4 count in the overall analytic cohort but not in the subset with a second CD4 count reported >6 months after diagnosis. The shorter estimated values based on second pre-ART CD4 count were due to a large proportion of people (41% of the cohort) with a higher second versus first pre-ART CD4 counts and likely occurred for two reasons. First, our proxy metric of ART initiation may have incorrectly attributed some post-treatment CD4 measures to the pre-ART period. Second, CD4 measurements at the individual level have been shown to be highly variable due to factors such as smoking, menstruation, physical exercise, measurement error and comorbidities.

The following limitations apply. First, we have shown that CD4 counts at different points in the pre-ART period result in similar estimates of diagnosis delay, but the accuracy of these estimates in a given population depends on the accuracy of the CD4 depletion model parameters. The CD4 decline parameters assume no changes in virulence of HIV strains over time, which, if present in NYC, could alter the average rates of CD4 decline in the population. Future research should attempt to validate
estimated diagnosis delay based on CD4 counts, perhaps among people with HIV intertest intervals documented in medical records or in more recent seroconverter cohorts. Second, we tested for differences in diagnosis delay based on the first or second pre-ART CD4 count. Findings consistent with the null hypothesis could mean either that there was no significant difference in estimated delay based on first or second pre-ART CD4 counts or that the analysis was underpowered to observe a difference. In the smaller subset (N =2,761), we may have been underpowered to observe a difference, particularly in subgroups. Finally, our approach provides evidence that the decline between the first and second pre-ART CD4 counts in this cohort was likely linear but does not give evidence about the period prior to the first pre-treatment CD4 count. However, excluding the acute phase of infection, we do not have reason to expect the shape of decline prior to the first pre-ART CD4 count would be different than the shape of decline between the first and second pre-ART CD4 counts.

Estimating diagnosis delays is important for monitoring and tracking progress of universal test and treat strategies and efforts aimed at ending the HIV/AIDS epidemic. We used a CD4 decline model to estimate years since seroconversion among NYC residents with at least two pre-ART CD4 counts. This approach assumes the mean square root of CD4 count is linearly related to the time since infection. We found that average diagnosis delay did not vary between estimates based on the first or second pre-ART CD4 count, and average diagnosis delay did not vary when the first and second pre-ART CD4 values were separated even by an average of 15 months. These results suggest that parameter estimates based on the linear assumption may be valid for population-level estimation of diagnosis delay and that pre-ART CD4 counts reported more than 6 months after diagnosis may be used to infer time since seroconversion.

REFERENCES


10. Robertson M, Braunstein S, D N. Methodology application for estimating the time from HIV seroconversion to ART initiation using HIV surveillance data International Workshop on HIV and Hepatitis Observational Database; March 28-30, 2019; Athens, Greece.


TABLES AND FIGURES

Figure 1. Diagnosis delay based on first or second pre-treatment CD4 amongst entire persons diagnosed from 2006 to 2015 (A) or amongst people diagnosed from 2006 to 2015 and having a second CD4 count reported >6 months following diagnosis (B)
### Table 1. Characteristics of people diagnosed with HIV from 2006 to 2015 and having at least two pre-treatment CD4 counts – New York City

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>People with ≥2 Pre-Treatment CD4 Counts</th>
<th>People with Second CD4 &gt;6 Months After Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>First CD4 Median (IQR)</td>
</tr>
<tr>
<td>Total</td>
<td>12,849 (100.0)</td>
<td>400 (222, 575)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>9,914 (77.16)</td>
<td>2,935 (22.84)</td>
</tr>
<tr>
<td>Black</td>
<td>402 (232, 570)</td>
<td>388 (187, 593)</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>392 (225, 561)</td>
<td>371 (181, 571)</td>
</tr>
<tr>
<td>White</td>
<td>2,122 (76.86)</td>
<td>639 (23.14)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>401 (3.12)</td>
<td>1,428 (51.72)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>402 (235, 562)</td>
<td>378 (201, 548)</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 29</td>
<td>4,670 (36.35)</td>
<td>446 (308, 602)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>3,288 (25.59)</td>
<td>399 (226, 568)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>2,944 (22.91)</td>
<td>351 (142, 553)</td>
</tr>
<tr>
<td>50+</td>
<td>1,947 (15.15)</td>
<td>283 (86, 483)</td>
</tr>
<tr>
<td>Transmission Risk (Imputed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sexual contact (MSM)</td>
<td>7,998 (62.24)</td>
<td>411 (260, 576)</td>
</tr>
<tr>
<td>Injection drug use (IDU)</td>
<td>720 (5.61)</td>
<td>312 (112, 518)</td>
</tr>
<tr>
<td>MSM &amp; IDU</td>
<td>287 (2.23)</td>
<td>417 (261, 576)</td>
</tr>
<tr>
<td>Heterosexual contact</td>
<td>3,845 (29.92)</td>
<td>337 (143, 536)</td>
</tr>
</tbody>
</table>
Table 2. Estimates of diagnosis delay based on first or second pre-treatment CD4 amongst the entire cohort of people diagnosed with HIV from 2006 to 2015 overall (a) and restricted to people having a second CD4 count reported >6 months following diagnosis—New York City

<table>
<thead>
<tr>
<th>People with ≥2 Pre-Treatment CD4 Counts (N = 12,849)</th>
<th>People with Second CD4 &gt;6 Months After Diagnosis (N = 2,761)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First CD4</td>
</tr>
<tr>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Total</td>
<td>2.81</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.83</td>
</tr>
<tr>
<td>Female</td>
<td>2.73</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>3.35</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>2.77</td>
</tr>
<tr>
<td>White</td>
<td>1.61</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>3.74</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>2.43</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>13 - 29</td>
<td>2.23</td>
</tr>
<tr>
<td>30 - 39</td>
<td>2.59</td>
</tr>
<tr>
<td>40 - 49</td>
<td>3.26</td>
</tr>
<tr>
<td>50+</td>
<td>4.35</td>
</tr>
<tr>
<td>Transmission Risk (Imputed)</td>
<td></td>
</tr>
<tr>
<td>Male sexual contact (MSM)</td>
<td>2.61</td>
</tr>
<tr>
<td>Injection drug use (IDU)</td>
<td>3.46</td>
</tr>
<tr>
<td>MSM &amp; IDU</td>
<td>1.88</td>
</tr>
<tr>
<td>Heterosexual contact</td>
<td>3.45</td>
</tr>
</tbody>
</table>
CHAPTER 4: ESTIMATES OF THE DURATION OF HIV INFECTIOUSNESS AMONG PEOPLE NEWLY DIAGNOSED WITH HIV FROM 2006 TO 2015, NEW YORK CITY (AIM 3)

ABSTRACT

Background: We estimated the time from HIV seroconversion to ART initiation in a population-based sample of people diagnosed with HIV during an era of expanding HIV testing and treatment efforts.

Methods: Applying CD4 depletion model parameters from seroconverter cohort data to our population-based sample, we related the square root of the first pre-treatment CD4 count to time of seroconversion though a linear mixed model and estimated the time from seroconversion to diagnosis and ART initiation.

Results: Among 28,162 people diagnosed with HIV during 2006-2015, 89% initiated ART by June 2017. The median CD4 count at diagnosis increased from 326 (Interquartile range (IQR):132-504) to 390 (IQR:216-571) cells/µL from 2006-2015. The average time from estimated seroconversion to ART initiation decreased by 33% from 8.0 years (95% confidence interval [CI]:7.8-8.2) in 2006 to 5.4 years (95%CI: 5.1-5.6) in 2015. Contributing to the reduction in time to ART initiation, the average time from estimated seroconversion to diagnosis decreased by 22%, from 6.5 years (95% CI:6.3-6.7) to 5.1 years (95% CI:4.9-5.4) from 2006-2015, and the average time from diagnosis to ART initiation reduced by 87%, from 1.5 years (95% CI:1.4-1.5) to 0.2 years (95% CI:0.2-0.3) from 2006-2015.

Conclusions: The estimated time from seroconversion to ART initiation was reduced in tandem with expanded HIV testing and treatment efforts. While the time from diagnosis to ART initiation decreased from 1.5 to 0.2 years, the time from seroconversion to diagnosis was 5.0 years among people diagnosed in 2015, highlighting the need for more effective strategies for earlier HIV diagnosis.
INTRODUCTION

To end HIV/AIDS as a public health threat, we must minimize the time from infection to treatment (i.e., the infectious period) and support the achievement of early and sustained viral suppression, thereby decreasing HIV-related morbidity and mortality and preventing onward spread of HIV.\textsuperscript{1-4} The achievement of timely viral suppression requires prompt testing and diagnosis following HIV seroconversion—typically an unobservable event—and timely initiation of antiretroviral treatment (ART). It is critical, therefore, to better understand and monitor treatment and diagnosis delays following seroconversion.\textsuperscript{5}

Generally, researchers assess the timeliness of HIV diagnosis and ART initiation by examining the distribution of CD4 counts at diagnosis and ART initiation, respectively, or with static measures (e.g., the proportion of people who initiate ART).\textsuperscript{6,7} In New York City (NYC), an epicenter of the HIV epidemic, increases in CD4 counts at diagnosis and ART initiation suggest a trend toward earlier diagnosis and treatment initiation.\textsuperscript{5,7} Yet, in 2015 more than one in six (17\%) NYC residents newly diagnosed with HIV were diagnosed late (i.e., AIDS diagnosis within 30 days of HIV diagnosis), and one-quarter of NYC residents who were diagnosed with HIV in 2015 had not initiated ART as of 6 months post-diagnosis.\textsuperscript{6,8}

In New York City, the ‘treat all’ recommendation, immediate treatment for all people diagnosed with HIV, has existed since late 2011, and efforts to ‘treat all’ were contemporaneous with large scale HIV testing initiatives in NYC.\textsuperscript{9-11} Yet, commonly used metrics (e.g., the HIV care cascade or median CD4 counts) provide an incomplete picture of subsequent progress towards ‘treat all’, as they do not give information on the amount of time that passes between infection and diagnosis and ART initiation.\textsuperscript{5,12} We estimated the elapsed time from seroconversion to diagnosis and to ART initiation to quantify the infectious period of HIV at the population level in NYC before and after the ‘treat all’ recommendation.

METHODS

Data source and population
The NYC Department of Health and Mental Hygiene has conducted population-based, name-based AIDS surveillance since 1981 and HIV surveillance since 2000. Electronic reporting of all HIV-related laboratory tests (including viral load (VL) and CD4), has been mandatory since 2005. CD4 counts and VL reported to surveillance are considered reliable indicators of HIV medical care receipt.

This analysis included people diagnosed with HIV from 2006 to 2015 and aged ≥13 years at HIV diagnosis with their laboratory information reported through June 30, 2017 (N=32,556). We excluded people who did not have at least one VL or CD4 test reported to the Registry within 18 months of diagnosis (N=4,394 excluded, leaving N=28,162 in analytic cohort), as people without a VL or CD4 for 18 months either moved out of NYC or were not receiving HIV medical care within NYC.

Approximately 20% (5,527/28,162) of all people diagnosed from 2006 to 2015 were reported as having an unknown transmission risk factor. Following Centers for Disease Control and Prevention guidance, we used sex-stratified multiple imputation procedures to assign these people a transmission risk category and assigned an individual a weight based on imputed transmission risk categories.

Data were imputed 10 times both for males and females. We combined results from the datasets to generate an overall probability weight for transmission risk category. For example, if 7 models imputed heterosexual transmission risk and 3 imputed injection drug use for an individual with an unknown transmission risk category, that individual was assigned two weights of 0.7 for heterosexual and 0.3 for injection drug use transmission risk factors, respectively.

To account for people without a pre-treatment CD4 count result (16% of the sample: 4,624/28,162), we assigned a weight to people with a pre-treatment CD4 count. The weight was the reciprocal of the proportion of cases with a CD4 test in each stratum, where strata were a combination of sex, transmission risk category (known or imputed), age at diagnosis, year of diagnosis, race/ethnicity or clinical status (AIDS diagnosis) as of June 30, 2017. The final weight was the product of the transmission risk category weight and the CD4 weight.
Definitions

ART initiation

ART initiation was defined based on the earlier occurrence of either: a ≥1-log drop in detectable VL (defined as ≥200 copies/mL) over a 3-month period or a detectable VL followed by an undetectable VL (defined as <200 copies/mL).7,18 The estimated date of ART initiation was the mid-point between the two VLs occurrences. If the first VL reported to the Registry was undetectable, then the estimated date of ART initiation was the mid-point between diagnosis and the undetectable VL.

Viral suppression

Viral suppression was defined as the last VL in the 12 months post-ART initiation being <200 copies/mL.

Pre-treatment CD4 Count

The pre-treatment CD4 count was defined as an individual’s first CD4 count within 6 months of diagnosis, when the first CD4 count was reported prior to the estimated date of ART initiation.

Date of seroconversion

To estimate the date of seroconversion in newly diagnosed people, we applied an estimated rate of CD4 decline, which was based on previously published estimates from the CASCADE seroconverter cohort, to the NYC population, PLWH diagnosed from 2006 to 2015.17 An underlying assumption of the CD4 decline model is that among ART-naïve people, the square root of the CD4 cell count decreases linearly over time19, and the time since seroconversion can be estimated by applying an estimated rate of CD4 decline (from CASCADE cohort) to a population with at least one pre-treatment CD4 count (NYC newly diagnosed PLWH).17,20-22

The CD4 depletion model relates the square root of the first pre-treatment CD4 count (CD4_{i}) to time of infection through a linear mixed model.19,23

Formula 1: \( \sqrt{CD4_{t}} = a_{0} + (b_{1}t) + e_{1t} \)
Where \( t \) is the time from HIV seroconversion to the date of the first pre-treatment CD4 count, \( CD_4_t \) is the first pre-treatment CD4 count, and the intercept \( a_0 \) and the slope \( b_1 \) are random variables following a normal distribution.

The duration of infection \( (t) \) is then estimated for an individual by Formula 2, using the previously published model parameters.

\[
Formula 2: T_i = (\sqrt{CD_4} - a_0)/ b_1
\]

For Formula 2, to incorporate the error term, the intercept \( a \) and slope \( b \), for each person, were assumed to follow a bivariate normal distribution \( \mathcal{N}[(a,b), (\text{standard error}_a, \text{standard error}_b), \text{correlation coefficient}(p)] \). The mean intercept and slope, standard errors and correlation coefficient were based on published estimates for combinations of sex, age group at seroconversion and risk group from the CASCADE cohort (see Song, et al 2016\(^7\)).

Since the age group at seroconversion is a necessary parameter, but unknown in our population, we used the age at diagnosis as an initial approximation of the age at seroconversion and estimated \( T \) using age at diagnosis (Formula 2). We then used \( T \) to estimate age at seroconversion (Formula 3, below). 44% of the cohort was assigned an age group at seroconversion that was earlier than the age group at diagnosis, and the remaining 56% stayed in the same age group. Lastly, we re-estimated \( T \) using the new age at seroconversion (Formula 2).

Age at seroconversion was estimated as

\[
Formula 3: \text{age at seroconversion} = \text{age at first CD4} - T_i
\]

Finally, the date of seroconversion was then estimated by:

\[
Formula 4: \text{Date of seroconversion} = \text{Date of first CD4} - T_i
\]

In instances where seroconversion was estimated to occur after diagnosis, the date of seroconversion was set to the date of diagnosis. For people diagnosed with acute HIV infection, the date of seroconversion was assigned as the date of diagnosis.
Assuming normal distributions and with sex-, age- and risk-specific standard errors described in Song et al\textsuperscript{17} and above in Formulas 1 and 2, we estimated the duration ($T_i$ from seroconversion to first pre-treatment CD4 count) by sampling for each person 1,000 times and took the average to infer an individual’s date of seroconversion and incorporate variance.

**Elapsed time to diagnosis and ART initiation**

We examined 3 metrics: time from seroconversion to ART initiation, time from seroconversion to diagnosis and time from diagnosis to ART initiation. For each metric, we calculated the difference between the respective dates and expressed elapsed time as number of years.

**Statistical analysis**

We generated the mean and median number of years since seroconversion overall and by subgroup in 2006 and 2015. We used weighted procedures to handle the sample weights. All analyses were conducted in SAS version 9.4 (SAS Institute, Cary, N.C.).

This study was approved by the institutional review boards at The City University of New York School of Public Health and the New York City Department of Health and Mental Hygiene. For these secondary analyses, we received a waiver for informed consent under 45 CFR 46.116(d)(2).

**RESULTS**

The analysis included 28,162 NYC residents who were diagnosed with HIV from 2006 to 2015. New diagnoses were mostly men (78%), black or Latino/Hispanic (78%), younger (36% aged 13-29, 26% aged 30-39 years), and men who have sex with men (63%) (Table 1). The median pre-ART CD4 count was 362 cells/$\mu$L (interquartile range, 188-542), with 27% having a pre-ART CD4 count <200 and 30% having a pre-ART CD4 count of $\geq$500. By July 2017, 89% had initiated ART and 69% were virally suppressed one year after ART initiation. The annual number of new diagnoses decreased from 2006 ($N = 3,227$) to 2015 ($N = 2,283$). The median pre-ART CD4 count increased from 326 cells/$\mu$L (IQR: 132-504) in 2006 to 390 cells/$\mu$L (IQR: 216-571) in 2015 (Table 2).
Estimated time from seroconversion to ART initiation from 2006 to 2015

Among people who initiated ART, the mean time from seroconversion to ART initiation decreased from 8.0 years (95% CI 7.8-8.2) in 2006 to an average of 5.3 years (5.1-5.6) in 2015, representing a 33% decline over a decade (Table 2). The median time from seroconversion to ART initiation was 6.4 years and 3.7 years among those diagnosed in 2006 and 2015, respectively. Among people who initiate ART, the mean time from seroconversion to diagnosis was reduced by 22%, from 6.5 years (6.3-6.7) in 2006 to 5.1 years (4.9-5.4) in 2015. Estimates of diagnosis delay (seroconversion to diagnosis) did not vary when the denominator was all people diagnosed. The mean time from diagnosis to ART initiation was reduced by 87%, from 1.5 years (1.4-1.5) in 2006 to 0.2 years (0.2-0.3) in 2015 (Table 2 and Figure 1).

Estimated time from seroconversion to ART initiation by Subgroups – 2006 versus 2015

Among people who were diagnosed with HIV in 2015 and initiated ART, the estimated time from seroconversion to ART initiation was shortest among people who were white (4.3 years, 95% CI:3.7-4.8), young (age 13-19 at diagnosis, 4.2 years, 95% CI:3.8-4.5), had both IDU and MSM transmission risk (3.2 years, 95% CI:2.4-4.1), or were diagnosed at a screening, diagnosis or referral facility (3.3 years, 95% CI:2.7-3.8). The estimated time from seroconversion to ART initiation was longest among women (5.9 years, 95% CI:5.1-6.5), people who were black (6.0 years, 95% CI:5.6-6.4), older (age 50+ at diagnosis, 6.3 years, 95% CI:5.8-6.9), had heterosexual transmission risk (6.5 years, 95% CI:5.9-7.1), or were diagnosed at an inpatient facility (7.0 years, 95% CI:6.6-7.5). From 2006 to 2015 the percentage decrease in diagnosis delay (seroconversion to diagnosis) ranged from 38% among MSM and IDU (largest decrease) to 11% among people aged 30-39 at diagnosis (smallest decrease). The percentage decrease in ART delay (diagnosis to ART initiation) over the period ranged from 94% among white people to 77% among both women and people aged 50+ at diagnosis. Estimates of diagnosis delay among all people diagnosed were similar to the estimates of diagnosis delay among ART initiators (Supplemental Table 1).
DISCUSSION

Voluntary HIV testing followed by immediate ART initiation (universal testing and treatment) has become an integral part of strategies to eliminate HIV and control the HIV/AIDS epidemic. Minimizing the time from HIV infection to ART initiation is essential for universal test and treatment to be optimally effective. However, neither frontline implementers, nor health agencies or researchers have typically focused on quantifying the HIV-infectiousness period, partially due to the absence of population-based data on the timing of seroconversion. During 2006-2015, before and after the 2011 recommendation to ‘treat all’ people with diagnosed HIV regardless of CD4 count, we estimated the time from HIV seroconversion to ART initiation in New York City, a major epicenter of the HIV epidemic in the US, using population-based surveillance data in which seroconversion events are not observed. Over a period of 10 years, the mean time from seroconversion to ART initiation decreased by one-third or 2.7 years, from 8.0 years (7.8-8.2) in 2006 to 5.3 years (5.1-5.6) in 2015.

We represented the time from seroconversion to ART initiation as having two phases: 1) from seroconversion to diagnosis, and 2) from diagnosis to ART initiation. The time from seroconversion to diagnosis declined by 22% or 1.4 years. The time from diagnosis to ART initiation reduced by 87% or 1.3 years. The time from diagnosis to ART initiation decreased more substantially than the time from seroconversion to diagnosis. A little more than half (56% or 1.5/2.7 years) of the overall reduction in the time from seroconversion to ART initiation was due to decreases in the time between diagnosis and ART initiation, suggesting more emphasis on rapid treatment initiation following diagnosis than on testing for earlier identification of people with undiagnosed HIV. While ‘treat all’ policies are increasingly implemented, greater efforts and more effective strategies for earlier HIV diagnosis and linkage are needed to reduce the much larger time interval between seroconversion and diagnosis, which could result in the substantial declines in incidence and mortality needed to ‘end the HIV epidemic’ as a public health threat.
In the era of universal test and treat, an estimate of the infectious period from HIV seroconversion to ART initiation could become a priority indicator to identify gaps in time and monitor whether HIV testing and prevention initiatives are closing such gaps.\textsuperscript{12,17,20,31} The analytic period (2006 to 2015) overlaps with many national and citywide testing and treatment initiatives. These included a) large scale testing initiatives (Bronx Knows, Brooklyn Knows and New York Knows) which aimed to make all respective residents aware of their HIV status and assist with linkage to HIV care;\textsuperscript{32,33} b) introduction of a new state law which required all health care professionals to offer a voluntary HIV test;\textsuperscript{33} and c) changing state ART guidelines.\textsuperscript{25,34} New York City’s robust infrastructure to support HIV testing, care and treatment likely contributed to reductions in the time from seroconversion to ART initiation.\textsuperscript{11}

This study found that people who were born female, were older, black or heterosexual had the longest delays in the time from seroconversion to ART initiation in 2015, and the bulk of this delay was in the time from seroconversion to diagnosis. Despite long-term and largely successful efforts to improve HIV testing in NYC, some individuals and groups are still not being reached. Our findings could be used to inform the development of HIV testing initiatives for groups with the longest diagnosis delay.\textsuperscript{11} To achieve the goal of ‘ending the epidemic’ in New York, earlier identification of people with undiagnosed HIV infection is necessary so they can be engaged in care and treatment sooner.

The following limitations apply. First, the seroconversion estimate is based on previously published model parameters, which depend on initial model assumptions (e.g., linearity) and generalizing CD4 decline from a European seroconverter cohort to NYC residents.\textsuperscript{17,19,35} The estimates we used from the CASCADE cohort were restricted to the HIV subtypes most common in the US (predominately subtype B) and should be applicable from that perspective.\textsuperscript{17} Further, the CD4 decline parameters assume no changes in virulence of HIV strains over time, which, if present in NYC, could alter the average rates of CD4 decline in the population. If the predominant HIV strains became more or less virulent in NYC, our analysis would over or underestimate the time, respectively. Second, we used age at diagnosis to
approximate age at infection. Given age at infection should be the same or less than age at diagnosis, people may incorrectly remain in an older age group, which may underestimate elapsed time, as rates of decline are faster for older groups.

Third, people who migrate out of NYC after diagnosis will not have longitudinal laboratory information reported to the NYC surveillance system. Therefore, missing pre-treatment data can be caused by a lack of engagement in care or migration out of the jurisdiction. The analysis was weighted for people missing a CD4 count at diagnosis; however, we would be unable to observe ART initiation among people who migrate from NYC prior to initiating ART. To minimize the issue of outmigration, we excluded people considered to have left the city because they did not have any HIV-related laboratory test information reported the registry within 18 months of diagnosis. Our estimates of time from diagnosis to ART should therefore generalize to the population that is diagnosed and initiates ART in the city following their HIV diagnosis.

Our analysis shows considerable progress in rapid ART initiation following an HIV diagnosis in the era of ‘treat all’ recommendations in New York City. This has contributed substantially to declines in the infectious period for HIV at the population level over a 10-year period of about 33% overall. Specifically, the time from diagnosis to ART initiation decreased by 87%, and is now on average very short. Despite these improvements, disparities persist in the ART initiation delay so efforts should focus on subgroups for whom progress still needs to be made. Substantive efforts are needed to reduce the time from seroconversion to diagnosis. Targeted HIV testing strategies are needed to more rapidly identify people with undiagnosed HIV soon after HIV seroconversion in order to achieve further reductions in HIV incidence and mortality in key subgroups who continue to be negatively impacted by the HIV epidemic.

REFERENCES


Figure 1. Trends in mean or median time from seroconversion to ART initiation (S:A), seroconversion to diagnosis (S:D) and diagnosis to ART initiation (D:A) among ART initiators

<table>
<thead>
<tr>
<th>Year</th>
<th>Median S:A</th>
<th>Mean S:A</th>
<th>Median S:D</th>
<th>Mean S:D</th>
<th>Median D:A</th>
<th>Mean D:A</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>6.4</td>
<td>8.0</td>
<td>4.7</td>
<td>6.5</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>2007</td>
<td>6.2</td>
<td>7.6</td>
<td>4.6</td>
<td>6.3</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>2008</td>
<td>5.7</td>
<td>7.2</td>
<td>4.3</td>
<td>5.9</td>
<td>0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>2009</td>
<td>5.1</td>
<td>6.7</td>
<td>3.8</td>
<td>5.9</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>2010</td>
<td>4.8</td>
<td>6.3</td>
<td>3.9</td>
<td>5.2</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>2011</td>
<td>4.3</td>
<td>5.9</td>
<td>3.5</td>
<td>5.0</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>2012</td>
<td>4.1</td>
<td>5.6</td>
<td>3.3</td>
<td>5.0</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>2013</td>
<td>4</td>
<td>5.6</td>
<td>3.1</td>
<td>4.9</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>2014</td>
<td>3.5</td>
<td>5.4</td>
<td>3.0</td>
<td>5.0</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>2015</td>
<td>3.7</td>
<td>5.3</td>
<td>2.9</td>
<td>5.0</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Table 1. Demographic Characteristics and Median Pre-treatment CD4 Values of People Diagnosed with HIV – New York City, 2006 to 2015

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>All Diagnoses 2006-2015(^1)</th>
<th>2006 Diagnoses(^1)</th>
<th>2015 Diagnoses(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weighted N (%)</td>
<td>Median CD4 (IQR)</td>
<td>Weighted N (%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>28,162 (100.0)</td>
<td>362 (188, 542)</td>
<td>3,227 (100.0)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21,918 (77.8)</td>
<td>367 (195, 541)</td>
<td>2,360 (73.1)</td>
</tr>
<tr>
<td>Female</td>
<td>6,244 (22.2)</td>
<td>344 (164, 547)</td>
<td>867 (26.9)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>12,550 (44.6)</td>
<td>363 (193, 538)</td>
<td>1,535 (47.6)</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>9,312 (33.1)</td>
<td>381 (190, 564)</td>
<td>1,063 (32.9)</td>
</tr>
<tr>
<td>White</td>
<td>5,110 (18.1)</td>
<td>328 (185, 499)</td>
<td>540 (16.7)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>987 (3.5)</td>
<td>342 (164, 522)</td>
<td>70 (2.2)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>203 (0.7)</td>
<td>417 (240, 594)</td>
<td>19 (0.6)</td>
</tr>
<tr>
<td><strong>Age at Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 - 29</td>
<td>10,023 (35.6)</td>
<td>422 (285, 581)</td>
<td>919 (28.5)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>7,224 (25.7)</td>
<td>368 (190, 542)</td>
<td>937 (29.0)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>6,318 (22.4)</td>
<td>312 (113, 517)</td>
<td>827 (25.6)</td>
</tr>
<tr>
<td>50+</td>
<td>4,597 (16.3)</td>
<td>240 (78, 440)</td>
<td>544 (16.9)</td>
</tr>
<tr>
<td><strong>Transmission Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men (MSM)</td>
<td>17,779 (63.1)</td>
<td>387 (227, 555)</td>
<td>1,698 (52.6)</td>
</tr>
<tr>
<td>Injection drug use (IDU)</td>
<td>1,450 (5.1)</td>
<td>281 (94, 502)</td>
<td>279 (8.6)</td>
</tr>
<tr>
<td>MSM &amp; IDU</td>
<td>623 (2.2)</td>
<td>398 (222, 594)</td>
<td>77 (2.4)</td>
</tr>
<tr>
<td>Heterosexual contact</td>
<td>8,310 (29.5)</td>
<td>308 (125, 508)</td>
<td>1,173 (36.3)</td>
</tr>
<tr>
<td><strong>Facility of Diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>11,230 (39.9)</td>
<td>399 (244, 573)</td>
<td>1,247 (38.6)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>11,132 (39.5)</td>
<td>283 (89, 475)</td>
<td>1,359 (42.1)</td>
</tr>
<tr>
<td>Screening, Diagnosis or Referral</td>
<td>3,388 (12.0)</td>
<td>432 (296, 592)</td>
<td>243 (7.5)</td>
</tr>
<tr>
<td>Other</td>
<td>2,412 (8.6)</td>
<td>380 (198, 568)</td>
<td>378 (11.7)</td>
</tr>
<tr>
<td><strong>Pre-treatment CD4 Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>7,442 (26.4)</td>
<td>NA</td>
<td>1,058 (32.8)</td>
</tr>
<tr>
<td>200-349</td>
<td>6,073 (21.6)</td>
<td>NA</td>
<td>677 (21.0)</td>
</tr>
<tr>
<td>350-499</td>
<td>6,204 (22.0)</td>
<td>NA</td>
<td>668 (20.7)</td>
</tr>
<tr>
<td>500+</td>
<td>8,443 (30.0)</td>
<td>NA</td>
<td>824 (25.5)</td>
</tr>
<tr>
<td><strong>Initiated ART by July 2017</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25,021 (88.8)</td>
<td>359 (190, 537)</td>
<td>2,841 (88.0)</td>
</tr>
<tr>
<td>No</td>
<td>3,141 (11.2)</td>
<td>390 (161, 576)</td>
<td>386 (12.0)</td>
</tr>
<tr>
<td><strong>Viral Suppression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19,541 (69.4)</td>
<td>351 (190, 524)</td>
<td>1,850 (57.3)</td>
</tr>
<tr>
<td>No</td>
<td>8,621 (30.6)</td>
<td>397 (195, 591)</td>
<td>1,377 (42.7)</td>
</tr>
</tbody>
</table>

1 Dataset weighted for imputed transmission risk and persons missing a CD4 at diagnosis.
Table 2. Estimated annual time from Seroconversion to ART Initiation – New York City, 2006-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Weighted N (%)</th>
<th>Median CD4 (IQR)</th>
<th>Median</th>
<th>Mean (95% CI)</th>
<th>Diagnosis Delay, Years²⁻³ Among All Diagnosed Persons</th>
<th>Median</th>
<th>Mean (95% CI)</th>
<th>ART Delay, Years¹⁻² Among ART Initiators</th>
<th>Median</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>3,227 (11.5)</td>
<td>326 (132, 504)</td>
<td>6.4</td>
<td>8.0 (7.8, 8.2)</td>
<td>4.6</td>
<td>6.5</td>
<td>6.3 (6.3, 6.7)</td>
<td>0.5</td>
<td>1.5</td>
<td>1.4 (1.4, 1.5)</td>
</tr>
<tr>
<td>2007</td>
<td>3,225 (11.5)</td>
<td>335 (144, 513)</td>
<td>6.2</td>
<td>7.6 (7.4, 7.8)</td>
<td>4.4</td>
<td>6.3</td>
<td>6.1 (6.1, 6.5)</td>
<td>0.5</td>
<td>1.3</td>
<td>1.2 (1.1, 1.4)</td>
</tr>
<tr>
<td>2008</td>
<td>3,186 (11.3)</td>
<td>341 (166, 531)</td>
<td>5.7</td>
<td>7.2 (7.0, 7.4)</td>
<td>4.1</td>
<td>6.0</td>
<td>5.8 (5.8, 6.2)</td>
<td>0.4</td>
<td>1.2</td>
<td>1.1 (1.1, 1.3)</td>
</tr>
<tr>
<td>2009</td>
<td>2,995 (10.6)</td>
<td>366 (187, 535)</td>
<td>5.1</td>
<td>6.7 (6.4, 6.9)</td>
<td>3.7</td>
<td>5.6</td>
<td>5.4 (5.4, 5.9)</td>
<td>0.4</td>
<td>1.1</td>
<td>1.0 (1.0, 1.1)</td>
</tr>
<tr>
<td>2010</td>
<td>2,787 (9.9)</td>
<td>359 (200, 542)</td>
<td>4.8</td>
<td>6.3 (6.1, 6.6)</td>
<td>3.8</td>
<td>5.5</td>
<td>5.3 (5.3, 5.7)</td>
<td>0.3</td>
<td>0.9</td>
<td>0.8 (0.8, 0.9)</td>
</tr>
<tr>
<td>2011</td>
<td>2,755 (9.8)</td>
<td>379 (211, 559)</td>
<td>4.3</td>
<td>5.9 (5.7, 6.1)</td>
<td>3.4</td>
<td>5.2</td>
<td>5.0 (5.0, 5.4)</td>
<td>0.3</td>
<td>0.7</td>
<td>0.7 (0.7, 0.8)</td>
</tr>
<tr>
<td>2012</td>
<td>2,616 (9.3)</td>
<td>381 (216, 563)</td>
<td>4.1</td>
<td>5.6 (5.4, 5.9)</td>
<td>3.2</td>
<td>5.1</td>
<td>4.9 (4.9, 5.3)</td>
<td>0.2</td>
<td>0.5</td>
<td>0.5 (0.5, 0.6)</td>
</tr>
<tr>
<td>2013</td>
<td>2,577 (9.2)</td>
<td>376 (213, 550)</td>
<td>4.0</td>
<td>5.6 (5.4, 5.8)</td>
<td>3.5</td>
<td>5.2</td>
<td>5.0 (5.0, 5.4)</td>
<td>0.2</td>
<td>0.4</td>
<td>0.4 (0.4, 0.4)</td>
</tr>
<tr>
<td>2014</td>
<td>2,511 (8.9)</td>
<td>382 (212, 558)</td>
<td>3.5</td>
<td>5.4 (5.2, 5.7)</td>
<td>3.2</td>
<td>5.2</td>
<td>4.9 (4.9, 5.4)</td>
<td>0.2</td>
<td>0.3</td>
<td>0.3 (0.3, 0.3)</td>
</tr>
<tr>
<td>2015</td>
<td>2,283 (8.1)</td>
<td>390 (216, 571)</td>
<td>3.7</td>
<td>5.3 (5.1, 5.6)</td>
<td>3.3</td>
<td>5.1</td>
<td>4.9 (4.9, 5.4)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2 (0.2, 0.3)</td>
</tr>
</tbody>
</table>

1. Dataset weighted for imputed transmission risk and persons missing a CD4 at diagnosis
2. Estimated among all persons who started ART
3. Estimated among all diagnosed persons
Table 3. Estimated time from Seroconversion to ART Initiation by Subgroups – Among Persons who Initiate ART in New York City, 2006 and 2015

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>2006 Diagnoses</th>
<th>2015 Diagnoses</th>
<th>% change from 2006 to 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated time from seroconversion to ART initiation</td>
<td>Diagnosis delay – Among ART initiators</td>
<td>ART delay – Among ART initiators</td>
</tr>
<tr>
<td></td>
<td>(Medi an, Mean [95% CI])</td>
<td>(Medi an, Mean [95% CI])</td>
<td>(Medi an, Mean [95% CI])</td>
</tr>
<tr>
<td>Total</td>
<td>6.4 (8.0 [7.8, 8.2])</td>
<td>4.7 (6.5 [6.3, 6.7])</td>
<td>0.5 (1.5 [1.4, 1.5])</td>
</tr>
<tr>
<td>Sex</td>
<td>6.5 (8.0 [7.7, 8.2])</td>
<td>4.6 (6.5 [6.2, 6.7])</td>
<td>0.6 (1.5 [1.5, 1.6])</td>
</tr>
<tr>
<td>Female</td>
<td>6.2 (7.9 [7.4, 8.4])</td>
<td>4.8 (6.6 [6.1, 7.1])</td>
<td>0.4 (1.3 [1.2, 1.4])</td>
</tr>
<tr>
<td>Age at Diagnosis</td>
<td>5.9 (6.9 [6.5, 7.3])</td>
<td>3.5 (5.0 [4.6, 5.4])</td>
<td>1.0 (1.9 [1.7, 2.1])</td>
</tr>
<tr>
<td>30 – 39</td>
<td>6.1 (8.1 [7.6, 8.5])</td>
<td>4.0 (6.6 [6.2, 7.1])</td>
<td>0.5 (1.5 [1.3, 1.6])</td>
</tr>
<tr>
<td>40 – 49</td>
<td>7.0 (8.8 [8.3, 9.2])</td>
<td>5.5 (7.4 [7.0, 7.9])</td>
<td>0.4 (1.3 [1.2, 1.5])</td>
</tr>
<tr>
<td>50+</td>
<td>7.5 (8.4 [7.9, 8.8])</td>
<td>5.9 (7.4 [7.0, 7.9])</td>
<td>0.3 (0.9 [0.8, 1.1])</td>
</tr>
<tr>
<td>Transmission Risk</td>
<td>6.1 (7.7 [7.3, 8.0])</td>
<td>4.2 (6.0 [5.7, 6.3])</td>
<td>0.7 (1.6 [1.5, 1.8])</td>
</tr>
<tr>
<td>MSM</td>
<td>6.8 (7.3 [6.9, 7.8])</td>
<td>5.2 (6.1 [5.6, 6.6])</td>
<td>0.5 (1.2 [1.1, 1.4])</td>
</tr>
<tr>
<td>IDU</td>
<td>6.4 (6.8 [6.1, 7.5])</td>
<td>2.7 (4.7 [3.8, 5.5])</td>
<td>0.9 (2.1 [1.7, 2.5])</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>6.0 (8.6 [8.2, 9.0])</td>
<td>5.5 (7.4 [6.9, 7.8])</td>
<td>0.4 (1.2 [1.1, 1.3])</td>
</tr>
<tr>
<td>Facility of Diagnosis</td>
<td>5.6 (6.7 [6.4, 7.0])</td>
<td>3.3 (5.1 [4.8, 5.4])</td>
<td>0.6 (1.6 [1.5, 1.7])</td>
</tr>
<tr>
<td>Inpatient</td>
<td>8.1 (9.4 [9.0, 9.7])</td>
<td>6.7 (8.2 [7.8, 8.6])</td>
<td>0.3 (1.2 [1.1, 1.3])</td>
</tr>
<tr>
<td>SDR</td>
<td>5.4 (6.3 [5.7, 7.0])</td>
<td>2.9 (4.4 [3.7, 5.2])</td>
<td>0.9 (1.9 [1.6, 2.2])</td>
</tr>
<tr>
<td>Other</td>
<td>7.0 (8.3 [7.6, 9.0])</td>
<td>5.2 (6.6 [6.0, 7.3])</td>
<td>0.7 (1.7 [1.5, 1.9])</td>
</tr>
</tbody>
</table>

API: Asian/Pacific Islander, ART: Antiretroviral treatment, IDU: Injection drug use history, MSM: men who have sex with men, SDR: screening, diagnosis or referral agency
1 Estimated time from seroconversion to ART is estimated among all persons who initiated ART and may not be the sum of the diagnosis and ART delay as not all diagnosed persons initiated ART
2 Diagnosis delay refers to the time (years) from the estimated date of seroconversion to diagnosis and is estimated among all persons diagnosed
3 ART delay refers to the time (years) from diagnosis to ART initiation and is estimated among all persons who initiate ART
### Supplemental Table 1. Estimated time from Seroconversion to Diagnosis by Subgroups – Among 2006 and 2015 diagnoses, New York City

<table>
<thead>
<tr>
<th></th>
<th>2006 Diagnosis delay&lt;sup&gt;2&lt;/sup&gt; – Among all diagnosed persons</th>
<th>2015 Diagnosis delay&lt;sup&gt;2&lt;/sup&gt; – Among all diagnosed persons</th>
<th>% Decrease in Diagnosis Delay from 2006 to 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean (IQR)</td>
<td>Median</td>
</tr>
</tbody>
</table>

| **Total**            | 4.6    | 6.5 (6.3, 6.7) | 3.3    | 5.1 (4.9, 5.4) | 21.5 |
| **Sex**              |        |                |        |                |      |
| Male                 | 4.5    | 6.5 (6.2, 6.7) | 3.3    | 5.0 (4.7, 5.3) | 23.1 |
| Female               | 4.7    | 6.5 (6.0, 6.9) | 3.9    | 5.8 (5.1, 6.5) | 10.8 |
| **Race/Ethnicity**   |        |                |        |                |      |
| Black                | 4.8    | 6.8 (6.5, 7.1) | 3.9    | 5.8 (5.4, 6.1) | 14.7 |
| Latino/Hispanic      | 4.7    | 6.7 (6.3, 7.1) | 3.1    | 4.9 (4.5, 5.3) | 26.9 |
| White                | 3.2    | 5.1 (4.6, 5.6) | 1.8    | 4.0 (3.5, 4.5) | 21.6 |
| API                  | 5.8    | 6.9 (5.4, 8.4) | 4.6    | 5.8 (4.6, 6.9) | 15.9 |
| Other/Unknown        | 8.0    | 9.1 (6.0, 12.2) | 2.9    | 5.7 (3.0, 8.3) | 37.4 |
| **Age at Diagnosis** |        |                |        |                |      |
| 13 – 29              | 3.2    | 4.9 (4.6, 5.3) | 2.4    | 3.8 (3.5, 4.2) | 22.4 |
| 30 – 39              | 4.0    | 6.7 (6.2, 7.1) | 3.4    | 6.0 (5.4, 6.6) | 10.4 |
| 40 – 49              | 5.5    | 7.4 (6.9, 7.8) | 4.1    | 6.2 (5.6, 6.9) | 16.2 |
| 50+                  | 6.8    | 7.4 (7.0, 7.8) | 4.4    | 5.9 (5.4, 6.4) | 20.3 |
| **Transmission Risk**|        |                |        |                |      |
| MSM                  | 4.1    | 6.0 (5.7, 6.3) | 3.1    | 4.9 (4.6, 5.1) | 18.3 |
| IDU                  | 5.5    | 6.3 (5.9, 6.8) | 2.3    | 3.9 (3.1, 4.8) | 38.0 |
| MSM & IDU            | 2.7    | 4.5 (3.8, 5.3) | 1.7    | 2.7 (2.0, 3.4) | 40.0 |
| Heterosexual         | 5.2    | 7.2 (6.8, 7.6) | 4.7    | 6.3 (5.8, 6.9) | 12.5 |
| **Facility of Diagnosis** |        |                |        |                |      |
| Outpatient           | 3.1    | 5.0 (4.7, 5.3) | 2.6    | 4.3 (4.0, 4.6) | 14.0 |
| Inpatient            | 6.9    | 8.2 (7.9, 8.6) | 5.2    | 6.9 (6.4, 7.3) | 15.9 |
| SDR                  | 2.8    | 4.3 (3.7, 5.0) | 1.3    | 3.0 (2.5, 3.5) | 30.2 |
| Other                | 4.8    | 6.4 (5.8, 7.0) | 3.8    | 5.6 (4.7, 6.6) | 12.5 |

API: Asian/Pacific Islander, ART: Antiretroviral treatment, IDU: Injection drug use history, MSM: men who have sex with men, SDR: screening, diagnosis or referral agency

<sup>1</sup> Estimated time from seroconversion to ART is estimated among all persons who initiated ART and may not be the sum of the diagnosis and ART delay as not all diagnosed persons initiated ART

<sup>2</sup> Diagnosis delay refers to the time (years) from the estimated date of seroconversion to diagnosis and is estimated among all persons diagnosed

<sup>3</sup> ART delay refers to the time (years) from diagnosis to ART initiation and is estimated among all persons who initiate ART
CHAPTER 5. DISCUSSION

INTRODUCTION

Voluntary HIV testing followed by immediate ART initiation (universal testing and treatment) has become an integral part of strategies to control the HIV/AIDS epidemic.\(^1\)\(^-\)\(^8\) Minimizing the time from HIV infection to ART initiation is essential for universal test and treatment to be optimally effective. In New York City, the ‘treat all’ recommendation, immediate treatment for all people diagnosed with HIV, was made in late 2011, and efforts to ‘treat all’ were contemporaneous with roll out of large-scale HIV testing initiatives in NYC.\(^9\)\(^-\)\(^11\) The overarching goal of this dissertation was to examine trends in the timeliness of HIV diagnosis and ART initiation using data from the population-based New York City HIV surveillance registry before, during and after the “treat all” recommendation, including methodologic work related to metrics for timeliness.

SUMMARY OF RESULTS

In the first aim, I examined the timeliness of diagnosis and treatment initiation in the universal test and treatment era. Among 9987 NYC residents with HIV diagnosed from 2012 to 2015, diagnosis was early (i.e., with CD4>500 cells/μL or with AHI) in 35%, and 87% started ART by June 2017. The annual proportion of persons with early diagnosis did not increase appreciably (35% in 2012 vs 37% in 2015; \(P = .08\), Cochran-Armitage test for trend). Overall, 69% of persons had started ART at 6 months after diagnosis. The time from diagnosis to ART initiation decreased from year to year. Within 6 months of diagnosis, 62%, 67%, 72% and 77% of persons with HIV diagnosed in 2012, 2013, 2014, or 2015, respectively, had started ART, with median (interquartile range) times to ART initiation of 3.34 (1.34–12.75), 2.62 (1.28–10.13), 2.16 (1.15–7.11), and 2.03 (1.11–5.61) months, respectively.

In the second and third aims, I adapted a CD4 decline model to estimate the timing of seroconversion in a large cohort of newly diagnosed people and estimated the timeliness of diagnosis and treatment initiation overall and among sex, age and HIV transmission risk sub-groups. Among
28,162 people diagnosed with HIV during 2006-2015, 89% initiated ART by June 2017. The median CD4 count at diagnosis increased modestly over a 10-year period from 326 (Interquartile range (IQR):132-504) to 390 (IQR:216-571) cells/µL from 2006-2015. The estimated average time from seroconversion to ART initiation decreased by 33% from 8.0 years (95% confidence interval [CI]:7.8-8.2) in 2006 to 5.4 years (95%CI: 5.1-5.6) in 2015. Contributing to the reduction in time to ART initiation, the estimated average time from seroconversion to diagnosis decreased by 22%, from 6.5 years (95% CI:6.3-6.7) to 5.1 years (95% CI:4.9-5.4) from 2006-2015, and the average time from diagnosis to ART initiation decreased by 87%, from 1.5 years (95% CI:1.4-1.5) to 0.2 years (95% CI:0.2-0.3) from 2006-2015. People who were born female, were older, black or had heterosexual transmission risk had the longest delays in the time from seroconversion to ART initiation in 2015, and the bulk of these delays was in the time from seroconversion to diagnosis.

IMPLICATIONS FOR POLICY

We represented the time from seroconversion to ART initiation as having two phases: 1) from seroconversion to diagnosis, and 2) from diagnosis to ART initiation. The time from seroconversion to diagnosis declined by 22% or 1.4 years during the 10-year period from 2006-15. The time from diagnosis to ART initiation reduced by 87% or 1.3 years. Relative to the time from seroconversion to diagnosis, the time from diagnosis to ART initiation decreased more substantially. A little more than half (56% or 1.5/2.7 years) of the overall reduction in the time from seroconversion to ART initiation was due to decreases in the time between diagnosis and ART initiation, suggesting more emphasis on or effectiveness of rapid treatment initiation following diagnosis than on testing for earlier identification of people with undiagnosed HIV. While ‘treat all’ policies are increasingly implemented, greater efforts and more effective strategies for earlier HIV diagnosis and linkage are needed to reduce the much larger time interval between seroconversion and diagnosis, which could result in the substantial declines in incidence and mortality needed to ‘end the HIV epidemic’ as a public health threat.
In the era of universal test and treat, an estimate of the infectious period from HIV seroconversion to ART initiation should become a priority indicator to identify gaps in time and monitor whether HIV testing and prevention initiatives are closing such gaps.\textsuperscript{12-15} The aim 3 analytic period (2006 to 2015) overlaps with many national and citywide testing and treatment initiatives. These included a) large scale testing initiatives (Bronx Knows, Brooklyn Knows and New York Knows) which aimed to make all respective residents aware of their HIV status and assist with linkage to HIV care;\textsuperscript{16,17} b) introduction of a new New York state law which required all health care professionals to offer a voluntary HIV test;\textsuperscript{17} and c) expanding local ART guidelines.\textsuperscript{3,18} New York City’s robust infrastructure to support HIV testing, care and treatment likely contributed to reductions in the time from seroconversion to ART initiation.\textsuperscript{11}

Despite long-term and largely successful efforts to improve HIV testing in NYC, some individuals and groups are still not being reached (e.g., female, older, black or heterosexual people). This points to the importance of targeted versus universal approaches of testing to reach undiagnosed persons. Our findings could be used to inform the development of HIV testing initiatives targeting groups with the longest diagnosis delay.\textsuperscript{11} To achieve the goal of ‘ending the epidemic’ in New York, earlier identification of individuals with undiagnosed HIV infection is necessary so they can be engaged in care and treatment sooner.

**FURTHER RESEARCH**

**Validate ART proxy.** We used a laboratory-based proxy to estimate the date of ART initiation based on the earlier of 1) a 1-log decline in viral load within 2 months or 2) a switch from undetectable to detectable viral load. Our proxy metric of ART initiation may have incorrectly attributed some post-treatment CD4 measures to the pre-treatment period. In our (Braunstein, Nash and Robertson) previous validation study, the nadir of the CD4 trajectory, with CD4 falling until ART initiation and rebounding after ART initiation, corresponded with the estimated date of ART initiation for 67% of the population. Future work should validate the ART proxy with gold standard clinical data on ART initiation.
Validate estimates of the timing of seroconversion. We estimated seroconversion based on previously published model parameters, which depend on initial model assumptions (e.g., linearity) and generalizing CD4 decline from a European seroconverter cohort to NYC residents.\textsuperscript{12,19,20} Further, the CD4 decline parameters assume no changes in virulence of HIV strains over time, which, if present in NYC, could alter the average rates of CD4 decline in the population. Future research should attempt to validate the estimates of time from seroconversion to diagnosis, perhaps among people with HIV intertest intervals documented in medical records or in more recent seroconverter cohorts. In our validation (aim 2b), we were limited by inaccuracies in self-reported interest intervals and small sample sizes.

Explore additional methods for incorporating variance around estimates of timing of seroconversion. We estimated the duration ($T_t$ from seroconversion to first pre-treatment CD4 count) by sampling for each person 1,000 times and took the average to infer an individual’s date of seroconversion and incorporate variance. However, other methods should be explored for incorporating variance, including re-weighting the data to incorporate all 1,000 samples per individual or developing prediction intervals.\textsuperscript{21,22}

Evaluate the impact of universal test and treatment efforts on population incidence. Four large-scale, community-based randomized controlled intervention trials (ANRS, Ya Tse, SEARCH and PopART) aimed to assess the impact of universal test and treat strategies with community HIV incidence as a primary outcome. All four trials were set in sub-Saharan Africa. Preliminary evidence from these trials relating to the impact of universal test and treat on population HIV incidence is mixed, with two of the four showing universal test and treat reduces population incidence.\textsuperscript{23-26}

The CD4 decline approach allowed us to estimate when people seroconverted and is being used to estimate incidence. Given the inconsistent results from trials, more studies on the impact of UTT are needed. Potentially, we could design an ecologic study using incidence estimates from the CD4 decline
model as the outcome and, for example, population-based viral load suppression from HIV surveillance and population-based HIV testing from the Community Health Survey could serve as model inputs.

**Understand HIV testing coverage.** To achieve the goal of ‘ending the epidemic’ in New York, earlier identification of individuals with undiagnosed HIV infection is necessary so they can be engaged in care and treatment sooner. This requires understanding coverage of HIV Testing in New York City and if testing efforts are reaching the right people and at the right frequency. Such information could be used in triangulation with data on delays in seroconversion to further inform targeted testing approaches.

**LIMITATIONS**

The dissertation has the following limitations, which have also been outlined in individual chapters. First, the seroconversion estimate is based on previously published model parameters, which depend on initial model assumptions (e.g., linearity) and generalizing CD4 decline from a European seroconverter cohort to NYC residents (Aims 2-3). The estimates we used from the CASCADE cohort were restricted to the HIV subtypes most common in the US (predominately subtype B) and should be applicable from that perspective. Further, the CD4 decline parameters assume no changes in virulence of HIV strains over time, which, if present in NYC, could alter the average rates of CD4 decline in the population. If the predominant HIV strains became more or less virulent in NYC, our analysis would over or underestimate the time, respectively. When seroconversion was estimated to occur after diagnosis, the date of seroconversion was set to the date of diagnosis. The model and estimation may not perform as well for persons with high diagnostic CD4 counts (>500 cells).

Second, we used age at diagnosis to approximate age at seroconversion (Aims 2-3). Older age groups have faster rates of CD4 decline than younger age groups. A CD4 decline of 200 cells (from 500 to 300) in a person age 65 versus 35 at infection may translate to a 2 versus 5 year delay in diagnosis, respectively. The age at seroconversion is by definition the same or less than the age at diagnosis, and people may have been incorrectly classified as being in the wrong (older) age group at seroconversion
based on their age at diagnosis. Consequently, diagnosis delay may be underestimated elapsed time (as 2 years and not 5 years in prior example) for persons incorrectly assigned to an older age group. Third, our proxy metric of ART initiation may have incorrectly attributed some post-treatment CD4 measures to the pre-treatment period (Aims 1-3). Fourth, CD4 measurements have been shown to be highly variable due to factors such as smoking, menstruation, physical exercise, comorbidities, and laboratory measurement error (Aims 1-3). The CD4 decline approach should be used at the population-level and should not be used to present estimates of the timing of seroconversion for individuals.

Finally, missing data in the NYC surveillance system is caused by migration out of the jurisdiction or people not receiving medical care in NYC (Aims 1-3). We do not have information on migration, and substantial evidence from New York City and other jurisdictions suggests that not accounting for out-migration results in surveillance-based care measures that are lower than the truth. For example, accounting for outmigration in NYC, increased retention estimates from 63% to 91% in 2012. To minimize the potential biasing effect of out-migration or loss to the surveillance system, we restricted the analysis to individuals who had at least one laboratory event reported to the NYC surveillance registry within 18 months of diagnosis, as these individuals were likely to be receiving medical care in NYC. Thus, this restriction would exclude persons who remain in the city and do not link to care within 18 months. Our estimates of time from diagnosis to ART should therefore generalize to the population that is linked to NYC HIV medical care within 18 months following their HIV diagnosis. Estimates of median time should not be biased, as >50% of people initiated ART by 18 months.

**STRENGTHS AND PUBLIC HEALTH RELEVANCE**

Characterizing the timeliness with which HIV diagnosis and ART initiation occur by geographic, demographic and other subgroups can be used to inform universal testing and treatment implementation and policy. To realize the full individual and population benefits from expanded treatment guidelines, HIV-infected persons need to be diagnosed earlier in the course of infection,
underscoring the need for continued efforts to expand and focus HIV testing efforts to achieve earlier
diagnosis of HIV in population groups with historically low testing frequency and high rates of late HIV
diagnosis.

To the best of my knowledge, this dissertation is the first to present population-based estimates of
the amount of time between seroconversion and ART initiation in the United States. Arguably, the
primary reason these data do not exist is because the timing of seroconversion is almost never known
and because population-based data on the timing of ART initiation are limited to clinical cohorts, which
are not population-representative, or to small numbers of newly diagnosed persons. Given that all
states, the District of Columbia and U.S. territories have mandatory reporting of all diagnosed cases of
HIV infection and most have comprehensive laboratory reporting, the development of this method and
metric using local data has broad implications and utility in terms of monitoring the epidemic and
progress toward controlling the epidemic. Local estimates are paramount, given that ending the
epidemic initiatives emphasize the need to focus the public health response on the cities and
communities most affected by HIV.

CONCLUSIONS

In the last decade, the time to ART initiation was reduced in tandem with expanded HIV testing and
treatment policies in New York City, a major epicenter for HIV in the U.S. We found considerable
progress in rapid ART initiation: a) the proportion of persons initiating ART within 6 months of diagnosis
increased from 2012 to 2015, b) the time from seroconversion to ART initiation decreased by 33% over a
10 year period, and c) the time from diagnosis to ART initiation decreased by 87%. Despite these
improvements, disparities persist in ART initiation delay so efforts should focus on subgroups for whom
progress still needs to be made. Finally, substantive efforts are needed to reduce delays in HIV diagnosis
(i.e., the time from seroconversion to diagnosis). Targeted (versus universal) HIV testing strategies are
needed to more rapidly identify individuals with undiagnosed HIV soon after HIV seroconversion in
order to achieve further reductions in HIV incidence and mortality in key subgroups who continue to be negatively impacted by the HIV epidemic.

REFERENCES


APPENDIX TO CHAPTER 3: VALIDATING ESTIMATES OF DIAGNOSIS

DELAY (AIM 2B)

OBJECTIVE

To validate dates of seroconversion estimated via the CD4 decline approach, we compared the mean values of (1) estimated seroconversion dates based on the CD4 decline approach with (2) estimated seroconversion dates based on an HIV intertest interval from people who were a) sampled and interviewed for the case-surveillance-based sampling (CSBS) project and b) diagnosed with HIV from 2006 to 2015.

METHODS

Population. The analysis required merging two data sources. The first data source was the HIV Surveillance Registry. We included people who were diagnosed from 2006 to 2015, aged ≥13 years at HIV diagnosis with their laboratory information reported through June 30, 2017 (N=32,556). We excluded people who did not have at least one VL or CD4 test reported to the Registry within 18 months of diagnosis (N=4,394 excluded, leaving N=28,162 in analytic cohort), as people without a VL or CD4 for 18 months either moved out of NYC or were not receiving HIV medical care within NYC.

The second data source was interview data from the case-surveillance-based sampling (CSBS) project. The CSBS project provides information about clinical outcomes and behaviors of people living with HIV with respect to care seeking and care utilization. People are randomly sampled from the HIV surveillance registry and recruited for a CSBS interview. ¹ We included people who were interviewed for CSBS from 2012 to 2014 and reported a diagnosis date within the 5 years before the CSBS interview and reported a last negative HIV test date (N = 134).

Metrics. We calculated 3 estimates of diagnosis delay (time in years from seroconversion to HIV diagnosis). The first estimate of diagnosis delay relied on CSBS data, and diagnosis delay was calculated
as the midpoint between the reported last negative HIV test and the reported date of diagnosis. The second estimate of diagnosis delay relied on CSBS and Registry data, and diagnosis delay was calculated as the midpoint between the CSBS reported last negative HIV test and the Registry date of diagnosis. The third estimate of diagnosis delay was based on the CD4 decline approach (as previously described in Chapter 4).

RESULTS

134 people reported that they were diagnosed within the 5 years before the CSBS interview and reported a last negative HIV test date (Figure 1). We merged the CSBS sample with our analytic cohort (N = 23,538 people who were diagnosed from 2006 to 2015 and had at least one laboratory value (CD4 or viral load) and had a pre-treatment CD4 count). Among the 134 people who reported a last negative HIV test date, N = 79 (59%) did not overlap with the analytic cohort and N = 55 (41%) people overlapped with the analytic cohort.

Among the 79 people who were not in the analytic cohort, N = 6 did not match with the HIV Surveillance Registry. N = 73 people were in the HIV surveillance registry but not the analytic cohort because they were missing the diagnosis date variable used to create the cohort (i.e., HIVDXDTAFTER). The 73 people in the Registry but not the analytic cohort reported dates of diagnosis that were much later than their registry date of diagnosis (73% (N=53/73) reported a diagnosis date from 2006 to 2012 versus 18% (N=13/73) with a Registry date of diagnosed from 2006 to 2012) (Table 1).

Among the 73 people, 59 (81%) had at least 1 laboratory test reported as of June 30, 2017. Among the 59 with any laboratory events, 3 people had only 1 event reported, and mean number of laboratory events reported per person was N = 44 (median = 41). The length of time from diagnosis to first report date was quite long (mean of 47 months), this was due to diagnoses happening prior to mandatory laboratory reporting (60/73 or 82%) were diagnosed before 2006.
Among the 55 people who were in the CSBS and in the analytic dataset, 17 (30%) were excluded due to missing a pre-treatment CD4 count or due to a last negative HIV test date being reported after the date of diagnosis (thus, we were unable to calculate a self-reported date of seroconversion). We were left with N=38 people in the CSBS and in the analytic cohort (Figure 1).

Reported dates resulted in shorter estimates of diagnosis delay. The average diagnosis delay was a) 1.6 years based on reported date of diagnosis and reported negative HIV test date, b) 4.8 years based on Registry date of diagnosis and reported negative HIV test date, and c) 6.3 years based on CD4 decline approach (Table 2).

DISCUSSION

In a small sample of people (N=34) with an estimated diagnosis delay based on self-reported intertest intervals and the CD4 decline approach, the CD4 decline approach resulted in longer estimates of delay than the self-reported HIV intertest interval. The difference between the two estimates based on an HIV intertest interval was changing from self-report to Registry dates of diagnosis. The finding that diagnosis delays were shorter when using a reported versus Registry date of diagnosis (mean of 1.6 versus 4.8 years, respectively) implies that people report a date of diagnosis that is more recent than the date documented in the Registry. A similar observation can be drawn from the 73 people who were in the Registry but not the analytic cohort; reported dates of diagnosis were more recent than Registry dates of diagnosis (73% and 18% diagnosed from 2006 to 2012, respectively), and the group appeared to be aware of the HIV diagnosis (81% (59/73) ever received HIV care, as indicated by laboratory reporting).

Thus, self-reported dates of diagnosis are not accurate. This is notable because a diagnosis date is arguably a more salient event than a negative test date. If people do not accurately remember diagnosis dates, then they are unlikely to remember the last negative test date. Self-reported HIV test dates appear to have low validity. Therefore, our measures of diagnosis delay based on reported HIV
interest interval date would be expected to have low validity and reported intertest intervals are not a good metric to use for validating the diagnosis delay based on the CD4 decline approach. We suggest this analysis be completed among a population with intertest intervals that do not rely on patient recall, perhaps from a medical clinic or sexually transmitted disease clinic.

REFERENCES


TABLES AND FIGURES

Figure 1. Flow chart of overlap between CSBS dataset and the analytic cohort

Table 1. Comparison of Self-Report Dates of Diagnosis and Registry Dates of Diagnosis among the 73 People in the Registry but Not Matching with the Analytic Cohort.

<table>
<thead>
<tr>
<th>HIVDXDT (Registry)</th>
<th>N = 73</th>
<th>Self-Report Diagnosis Date</th>
<th>N = 73</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006-2012</td>
<td>13</td>
<td>2006-2012</td>
<td>53</td>
</tr>
<tr>
<td>Prior to 2006</td>
<td>60</td>
<td>Prior to 2006</td>
<td>20</td>
</tr>
</tbody>
</table>
Table 2. Estimates (Years) of Diagnosis Delay (Seroconversion to Diagnosis) Among the 38 People with an Intertest Interval

<table>
<thead>
<tr>
<th>Metric</th>
<th>Wtd N</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Median</th>
<th>25th Pctl</th>
<th>75th Pctl</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 decline estimate</td>
<td>38</td>
<td>6.34</td>
<td>4.95</td>
<td>5.42</td>
<td>0.73</td>
<td>9.39</td>
<td>0</td>
<td>18.54</td>
</tr>
<tr>
<td>Using Registry diagnosis date and self-report last negative test date</td>
<td>38</td>
<td>4.77</td>
<td>3.7</td>
<td>3.97</td>
<td>0.73</td>
<td>8.55</td>
<td>0</td>
<td>13.77</td>
</tr>
<tr>
<td>Using self-reported diagnosis date and self-reported last negative test date</td>
<td>38</td>
<td>1.61</td>
<td>2.34</td>
<td>0.5</td>
<td>0.25</td>
<td>1.62</td>
<td>0.12</td>
<td>12.07</td>
</tr>
</tbody>
</table>