Title

On the road to zero in San Francisco: understanding population dynamics, HIV transmission and internalized HIV stigma in order to get to zero HIV transmission, zero HIV-related deaths and zero HIV stigma

Author

Hughes, Alison J.

Publication Date

2016

Peer reviewed|Thesis/dissertation

On the road to zero in San Francisco: understanding population dynamics, HIV transmission and internalized HIV stigma in order to get to zero HIV transmission, zero HIV-related deaths and zero HIV stigma

by

Alison J. Hughes

A dissertation submitted in partial satisfaction
of the requirements for the degree of
Doctor of Philosophy
in
Epidemiology
in the
Graduate Division
of the
University of California, Berkeley

Committee in charge:

Professor Arthur Reingold, Chair
Dr. Susan Scheer
Professor Maya Petersen
Professor Fenyong Liu

Fall 2016

On the road to zero in San Francisco: understanding population dynamics, HIV transmission and internalized HIV stigma in order to get to zero HIV transmission, zero HIV-related deaths and zero HIV stigma

By Alison J. Hughes

ABSTRACT

On the road to zero in San Francisco: understanding population dynamics, HIV transmission and internalized HIV stigma in order to get to zero HIV transmission, zero HIV-related deaths and zero HIV stigma

by
Alison J. Hughes
Doctor of Philosophy in Epidemiology
University of California, Berkeley
Professor Arthur Reingold, Chair

As of December 31, 2015, there were 15,995 diagnosed and reported persons living with human immunodeficiency virus (HIV) who were residents of San Francisco, California at time of diagnosis. Approximately one quarter of men who have sex with men (MSM) in San Francisco are HIV-positive. Despite a high HIV burden, a higher proportion of HIV-positive San Franciscans are virally suppressed (72% in 2014 in San Francisco) than nationally (55% nationally in 2013), and 81% of all cases in San Francisco had at least one HIV viral load or CD4 test in 2014 (versus 71% nationally in 2013). Recently, new strategies have emerged to prevent HIV transmission, including post-exposure prophylaxis, treatment as prevention and pre-exposure prophylaxis (PrEP). With these new tools, the end of the HIV epidemic is within reach. New HIV diagnoses in San Francisco are now half of what they were a decade ago, down from 528 new HIV diagnoses in 2006 to 255 in 2015. The Getting to Zero (GTZ) consortium, formed in San Francisco after World AIDS Day in 2013, which is comprised of representatives from the San Francisco Department of Public Health, the University of California San Francisco, public and private medical providers, community based organizations, other San Francisco government agencies and people living with HIV (PLWH), aims to get to zero new HIV transmissions, zero HIV deaths and zero HIV stigma in San Francisco. My dissertation is aligned with the mission of the GTZ consortium.

My dissertation seeks to address how the population dynamics of MSM (through migration and HIV serostatus) could affect the prevalence and incidence of HIV in San Francisco and may help explain why there is ongoing HIV transmission in the era of PrEP and treatment as prevention. The ability to migrate has increased for PLWH as survival markedly improved following introduction of combination antiretroviral therapy in 1996. Although there is a high frequency of migration among the general U.S. population and among PLWH in San Francisco, migration patterns of MSM in San Francisco have, to my knowledge, never been described. Output from the novel migration model outlined in Chapter 2 can be used to understand the dynamics of the MSM population in San Francisco and macro-level forces that could affect the prevalence and incidence of HIV in the population. Estimating the number of MSM by HIV status also allows researchers to have a denominator of this hidden population for use in estimating prevalence, incidence, service needs and funding allocations. Further, estimating the number of HIV-negative in-migrants relative to the overall MSM population is important

because research has shown that recent MSM migrants to metropolitan areas are at increased risk of HIV acquisition because of higher risk behaviors. My results suggest that the overall MSM population and all the MSM subpopulations studied decreased in size from 2006 to 2014. Further, there were differences in migration patterns by race and by HIV serostatus.

Next, given the goal of eliminating all transmission of HIV, I assessed the association between knowledge of an HIV-negative partner's PrEP use and reported condomless anal sex (CAS) among sexually active MSM in San Francisco. In 2010, the iPrEx trial showed that a daily dose of tenofovir disoproxil fumerate (TDF) and emtricitabine (FTC) for HIV-negative persons in HIV serodiscordant relationships could reduce HIV transmission by 42%. In 2012, the FDA approved daily FTC/TDF for HIV prophylaxis. Although no increase in CAS was observed in the iPrEx trial, there is concern that expansion of PrEP could result in reduced condom use. The study population for iPrEx, individuals who consented to participate in a randomized-controlled trial, likely did not represent the general population of MSM. Furthermore, participants knew that they could have been randomized to receive a placebo and, therefore, it is not surprising that in this setting, no increase in CAS was observed. Recent research has focused on PrEP use and CAS reported by HIV-negative individuals on PrEP; no research to my knowledge has focused on PLWH's reported condom use during sex if they know that their HIV-negative partner is on PrEP. I found that there was a higher prevalence of reported CAS and insertive condomless anal sex (ICAS) in partnerships that were either seroconcordant or serodiscordant with PrEP, compared to partnerships that were serodiscordant without PrEP. There was evidence that men in this sample were adapting their condom use based on their sexual partner's HIV status and PrEP use, and their own viral suppression status. Discordant partnerships with PrEP had an increased adjusted prevalence of reported CAS and ICAS.

I used causal inference methods to determine the effect of internalized HIV stigma (IHS) on viral suppression. Past research on IHS has focused on ART adherence as an outcome, and depression has been determined to be a mediator along this path. To my knowledge, no research has looked at the effect of IHS on viral suppression as an outcome. Research focusing on IHS in San Francisco has been limited to subgroups of HIV-positive individuals, such as homeless and marginally housed HIV-positive adults. Causal inference methods were used to estimate the counterfactual proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did not experience IHS compared to the proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did experience IHS, by following the causal roadmap. Three estimators were used to estimate the average treatment effect: simple substitution, inverse probability of treatment weighting, and targeted maximum likelihood estimation (TMLE). The results from each estimator were similar, and a statistically significant causal effect was observed for all. Using TMLE, the counterfactual proportion of adults virally suppressed would decrease by roughly 4.5% if all adults did not experience internalized HIV stigma as opposed to if all adults experience internalized HIV stigma.

For my parents, Robert and Kristine Hughes

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

First and foremost, the work in this dissertation would not have been possible if it weren't for the generosity of those who participated in the Medical Monitoring Project. Thank you for sharing your experience.

I would like to also thank my academic advisor at the University of California, Berkeley and Dissertation Chair, Professor Arthur Reingold. I am very grateful for his support and guidance over the past three years and for his valuable input into my research and this dissertation. I am also grateful for my other committee members, Professor Maya Petersen and Professor Fenyong Liu for their helpful feedback on my research. I am indebted to Professor Petersen for teaching me causal inference methods and for generating my excitement to ask causal questions.

I am deeply appreciative of the support I have received from my mentor, Dr. Susan Scheer. A few years ago when others asked me where I wanted to go in my career, I would say, "I'm going to be the next Susan Scheer." I stopped telling others that, not because it is untrue, but because I have realized that if this is what I strive for, I am going to have bigger shoes to fill than I originally anticipated. Susan is brilliant, dedicated, sincere, and kind. I am very grateful for Susan's encouragement and enthusiasm for me to pursue a PhD in Epidemiology and for the guidance she provided in pursuing the work that is presented in this dissertation.

My family has been incredibly supportive throughout this process. My parents, Kristine and Robert Hughes have always been my greatest champions. They have truly led by example and they showed me from an early age what hard work and dedication look like. They also emphasize the importance of living a balanced life and encourage me to live each day to the fullest. I'm grateful to my brother Matt and my sister-in-law Sharon for offering their home as a dissertation-writing retreat. Percy, Matt and Sharon's cat, kept me company during two weeks of solitude and literally sat by my side as I wrote this dissertation. I am thankful that my cousins, Aunt Jan and Uncle Gary have also offered their support in my academic endeavors. My cousin and close friend Laura has been particularly encouraging and supportive during my PhD studies. I am fortunate to have gone through parallel milestones in life with Laura, being doctoral students at the same time is just one of many experiences we have been able to share. I also wish to recognize and thank my four loving grandparents, Arthur and Johanna Meyer, and Lawrence and Edith Hughes, who are no longer alive but were instrumental in my success. Most of all, James has kept me grounded and encouraged me to write this dissertation, one sentence at a time.

I am fortunate to have many wonderful friends (too many to list!) who have supported me during my graduate studies. I wish to thank you all for listening to me babble about my epidemiology hero Janet Lane Claypon too many times. Most importantly, you all have provided welcome distraction from the sometimes-stressful events of my education, and never ending support throughout this process. I'm also grateful for my colleagues at SFDPH, particularly Maree Kay Parisi, Anne Hirozawa and Yea-Hung Chen for your

support (always) but especially during my time at UC Berkeley. I could not imagine my time at Berkeley without having such distinguished and friendly classmates to share my experience with and to learn from. Thank you to Jenn Ames, Emily Yette, Monika Izano, Amelia Wallace, Deysia Levin, Ryan Gamba and Kunchok Dorjee for your support and friendship.

I foresee the day when transmission of HIV, HIV stigma, and HIV-related deaths have been eliminated- not just in San Francisco, but worldwide. Although I personally have made only a small impact on this endeavor, I am extremely proud to have traveled on this path, and am continually inspired by the countless HIV survivors, researchers, community members, clinicians, politicians, mentors, friends, co-workers and classmates who have all joined me on the "Road to Zero".

Chapter 1

Introduction

Early HIV History in San Francisco

In the early 1980s, many healthy young men suddenly fell ill with two previously rare diseases- Kaposi's Sarcoma, a type of skin cancer, and Pneumocystis carinii pneumonia, a pneumonia that at the time was considered to occur only in immunocompromised individuals (e.g. organ transplant recipients). San Francisco reported its first case of acquired immune deficiency syndrome (AIDS) in 1980 [1]. Since then, approximately 50,000 HIV/AIDS cases have been reported in San Francisco [1]. Early in the epidemic there was no understanding of the etiology of AIDS and no diagnostic test or treatment was available. Survival following a diagnosis of AIDS was very short and many cases were ascertained only at the time of death. The median survival after a diagnosis of AIDS was 11 months for cases diagnosed between 1980-1984 and 18 months for cases diagnosed in 1980-1989 [1-3]. In 1982, the San Francisco Department of Public Health (SFDPH) responded to the AIDS crisis by creating the comprehensive "San Francisco Model of Care", which included not only medical services at San Francisco General Hospital (SFGH), but also support services such as health education, hospice, counseling, and housing and food assistance in collaboration with community-based organizations [4-6]. In addition, the San Francisco Board of Supervisors approved funding to support the response to the AIDS epidemic [4-6]. In 1984, human immunodeficiency virus (HIV) was identified as the etiologic agent responsible for AIDS [7], and in 1985 the U.S. Food and Drug Administration (FDA) approved the first diagnostic test for HIV, an enzyme linked immunosorbant assay test. The first antiretroviral drug, azidothymidine (AZT), was approved by the FDA in March 1987, and survival with AIDS began to increase after its introduction, with a median survival of 38 months for cases diagnosed in 1990-1995 [1,8]. However, it wasn't until the introduction of combination antiretroviral treatment in 1996 that survival with Stage 3 HIV (AIDS) drastically improved- 79% of cases diagnosed in 1996-2000 survived at least 60 months and 87% of cases diagnosed in 2006-2013 survived at least 60 months [1].

Current Epidemiologic Features of HIV/AIDS in San Francisco

As of December 31, 2015, there were 15,995 diagnosed and reported persons living with human immunodeficiency virus (HIV) who were residing in San Francisco at the time of diagnosis, 1.8% of the total population [1]. The majority of those living with HIV are male (92%), white (60%) and ≥ 50 years of age (60%) [1]. Most (74%) are men who have sex with men (MSM) or MSM who inject drugs (15%) [1].

There is a high burden of HIV in the MSM community in San Francisco. Approximately one quarter of MSM in San Francisco are HIV-positive and this proportion has remained stable from 2004 to 2011 [9-12]. Data suggest there has been at most a modest (not statistically significant) decline in HIV incidence in MSM and overall in San Francisco over time [1,9,12]. For example, the National HIV Behavioral Surveillance (NHBS) estimated an HIV incidence of 2.6% per year in 2004 (95% CI: 0.8% to 4.3%) and of 1.0% per year in 2011 (95% CI: 0.02% to 1.9%), which would suggest a decline in HIV incidence; however, this decline was not statistically significant [9]. In addition, it is estimated that 39.5% of trans females, persons assigned male at birth who identify their gender as female, in San Francisco are HIV-positive [13], reflecting a heavy burden of HIV in this population. However, compared to MSM, trans females represent a much smaller population (in San Francisco, 378 trans females were living with HIV compared to 14,227 MSM in 2015 [1]).

HIV surveillance and reporting laws

California law requires that all laboratory tests indicative of HIV infection, including HIV diagnostic tests and HIV viral load tests, be reported to the local county health department by both the diagnosing provider and the laboratory performing the test [14]. CD4+ lymphocyte test results became reportable to the county health department by state law in 2008 [14]. Through a combination of active and passive surveillance activities, the San Francisco Department of Public Health collects diagnostic, demographic, and mode of HIV acquisition information for all reported cases of HIV [1,15-17]. This information is stored in the Enhanced HIV/AIDS Reporting System (eHARS) case registry.

Medical Monitoring Project

San Francisco data from the Medical Monitoring Project (MMP) will be used for Aims 2 and 3. MMP is a national, CDC-funded, supplemental HIV surveillance project. MMP utilized a three-stage sampling approach in 2007 to 2014 to obtain an annual cross-sectional, locally representative, population-based sample to monitor clinical and behavioral outcomes among adults receiving outpatient HIV care in San Francisco. The three sampling stages are: 1) U.S. states and territories, 2) outpatient facilities providing HIV care, and 3) HIV-positive adults aged ≥18 years who had at least one medical care visit to a participating facility between January 1st and April 30th of each cycle. Beginning in 2015, a two-stage sampling process was implemented. Once San Francisco was selected as an MMP site, adults living with HIV were sampled directly from the national

case-based HIV registry. Persons were eligible for sampling in the 2015 MMP if they were ≥18 years of age, not known to have died, and their most recent residential address recorded in the National HIV Surveillance System was in San Francisco as of December 31, 2014. Four hundred patients are selected for MMP each cycle in San Francisco. San Francisco, one of 23 project areas funded to conduct MMP, has conducted MMP since 2007. Data from the 2014 and 2015 cycles of MMP in San Francisco were used for Aim 2 and data from the 2012-2014 cycles of MMP were used for Aim 3. Table 1.1 summarizes the facility response rates (for 2012-2014 cycles) and patient interview and MRA response rates for all MMP cycles that were used in this dissertation.

MMP data collection consists of a structured interview and a medical record abstraction. Trained interviewers conduct a face-to-face or telephone, computer-assisted structured interview in either English or Spanish with the sampled individuals. Interviews take approximately 45 minutes to complete. The standard interview collects information on demographic information; access to and use of health care; met and unmet needs for supportive services; sexual behavior; depression; gynecologic and reproductive history (for women); drug and alcohol use; and use of HIV prevention services. Trained MMP staff review and abstract medical records after the interview is conducted. Information collected in the medical record abstraction (MRA) includes: demographic data, date of HIV diagnosis, history of opportunistic infections, co-morbid conditions, prescription of antiretroviral and other medications, HIV laboratory test results, and health care visits in the 12 months before the interview. Data are weighted for the probability of selection, based on known probabilities of selection at each sampling stage. In addition, data are weighted to adjust for nonresponse using predictors of patient level response, including facility size, race/ethnicity, time since HIV diagnosis, and age group.

Engagement in HIV Care

The HIV care continuum is a powerful model for assessing engagement in various stages of HIV care [18-20]. Without a cure, the goal of HIV care is to suppress the virus to an undetectable level, which can markedly reduce both HIV transmission and morbidity and mortality [21-28]. In order for an HIV-positive individual to become virally suppressed, she/he must first be diagnosed as having HIV; receive HIV care; be prescribed antiretroviral treatment (ART); and adhere to ART.

HIV surveillance data can be used to assess how well the HIV-positive population in San Francisco is engaged along the care continuum. Among individuals with a new HIV diagnosis in 2014, 91% were linked to HIV care within three months of diagnosis; 73% of those linked to care were in care 3-9 months after linkage; and 75% of those with a new diagnosis were virally suppressed within 12 months of diagnosis [1]. Among all individuals living with HIV in San Francisco in 2014, 81% had at least one reported viral load or CD4 test and 72% of all PLWH had a suppressed most recent HIV viral load test in 2014 (those without an HIV viral load test were included in the denominator and were classified as not being virally suppressed) [1].

Clinical care and outcomes among patients in HIV care in San Francisco are overall very good. Among patients in HIV care in San Francisco in 2011 and 2012, 53% had a CD4 cell count ≥500 cells/mm^3 and 85% were virally suppressed [29]. Fifty-eight percent of patients in care had ≥3 CD4 count or HIV viral load tests during the previous 12 months [29] and an ART prescription was documented in the medical chart of 93% of patients [29]. Self-reported ART adherence to dose, schedule, and instructions during the prior three days was 90%, 78%, and 72%, respectively [29].

New prevention strategies

Recently, new strategies have emerged to prevent transmission of HIV, including post-exposure prophylaxis (PEP), treatment as prevention and pre-exposure prophylaxis (PrEP). Post exposure prophylaxis is a 28-day course of antiretroviral treatment given within 72 hours of exposure (occupational or non-occupational, such as injection drug use or condomless intercourse) to HIV. In 2005, CDC issued recommendations for use of PEP in non-occupational settings [30].

Treatment as prevention is now seen as one of the most effective and promising new HIV prevention strategies. In 2011, results from the HPTN052 study demonstrated that early ART (i.e. initiation of ART early after diagnosis or without waiting for a decline in CD4 count to <350 cells/mm^3) could reduce HIV transmission events in serodiscordant couples by 96% compared to delayed ART initiation [31]. In 2012, the National Institutes of Health began recommending universal ART to all HIV-positive adults, regardless of CD4 count, due to the evidence of both individual and population level benefits of early ART [32]. Recently, data were released from the START trial, which demonstrated that early ART (at CD4 count >350 cells/mm^3) significantly reduced AIDS-related, non-AIDS related and all death events [33]. Data from San Francisco, where universal ART was recommended to all people living with HIV (PLWH) regardless of CD4 count starting in 2010, demonstrate a trend towards early initiation of ART between 2007 and 2010 and an increase in the proportion of those with viral suppression among those seen in a public clinic with a CD4 cell count >500 cells/mm^3 between 2001 to 2011 [34-35].

Another emerging HIV prevention tool is PrEP. In 2010, the iPrEx trial showed that a daily dose of tenofovir disoproxil fumerate (TDF) and emtricitabine (FTC) given to HIV-negative persons in HIV serodiscordant relationships could decrease transmission of HIV by 42% [36]. In 2012, the FDA approved daily FTC/TDF to prevent transmission of HIV. Data suggest that there are approximately 5,000 HIV-negative MSM PrEP users in San Francisco, but that approximately 16,000 MSM are eligible to use PrEP, based on behavioral survey data [37]. Additionally, a modeling analysis demonstrated that if 14,000 HIV-negative MSM were to take PrEP, new HIV transmissions could be reduced by 70% [37].

Getting to Zero

With these new prevention tools, the end of the HIV epidemic is within reach. San Francisco has experienced a drop in the estimated number of new HIV diagnoses, from

528 in 2006 to 255 in 2015 [1, Figure 1.1]. There was also a marked decline in HIV-related deaths, from 327 in 2006 to 197 in 2015 [1, Figure 1.1]. PrEP (approved by the FDA in 2012) and universal ART (i.e. irrespective of CD4 count), which has been shown to lengthen survival and decrease transmission of HIV [26-28, 38-39], have likely contributed to the decreases in new HIV diagnoses and HIV-related deaths observed in San Francisco.

The Getting to Zero (GTZ) consortium, formed in San Francisco after World AIDS Day in 2013, is made up of representatives from the San Francisco Department of Public Health, the University of California San Francisco, public and private medical providers, community based organizations, other San Francisco government agencies and people living with HIV (PLWH); it aims to reach zero new HIV transmissions, zero HIV deaths and zero HIV stigma in San Francisco [40-42]. In an effort to contribute to the mission of the GTZ Consortium, I planned my dissertation to align with its goals. Although there have recently been great strides in reducing new HIV transmissions and HIV-related deaths, there are still ~250 new HIV diagnoses annually in San Francisco, and 28% of those with HIV are not virally suppressed. My dissertation seeks to address how the population dynamics of MSM (through migration and HIV serostatus) may affect the prevalence and incidence of HIV in San Francisco and may help to explain why we continue to see sustained transmission of HIV in the era of PrEP and treatment as prevention. With the goal of eliminating all HIV transmission events, I assessed the association between knowledge of an HIV-negative partner's PrEP use and reported condomless anal sex among MSM in San Francisco. Last, in an effort to address HIV stigma, I used causal inference methods to determine the effect of internalized HIV stigma on viral suppression.

RESEARCH QUESTIONS

How does migration of MSM of varying HIV status contribute to the prevalence and incidence of HIV in San Francisco? As a first step, I estimated in and out migration of MSM in San Francisco; future steps will include building a compartmental HIV transmission model that accounts for these migration estimates. Does knowledge of an HIV-negative partner's PrEP use increase the likelihood of condomless anal sex by HIV-positive MSM? Does experiencing internalized HIV stigma affect the likelihood of viral suppression?

Specific Aims

1. Estimate in and out migration patterns of MSM in San Francisco, by HIV serostatus and by race.
2. Determine if there is an association between knowledge of an HIV-negative partner's PrEP use and reported condomless anal intercourse among MSM in San Francisco.
3. Quantify the effect of internalized HIV stigma on HIV viral suppression among adults in HIV care in San Francisco.

TABLE

Table 1.1: San Francisco Medical Monitoring Project Response Rates, 2012-2015.

Year	Facility Response Rate	Patient Interview and MRA Response Rate	Overall[b] Response Rate
2012	88.9%	62.1%	55.2%
2013	88.0%	58.6%	51.6%
2014	88.0%	58.5%	51.5%
2015[a]	------	45.5%	45.5%

[a]No sampling through facilities occurred in 2015 so there is no reported facility response rate.
[b]Overall response rate= facility response rate x patient response rate

FIGURE

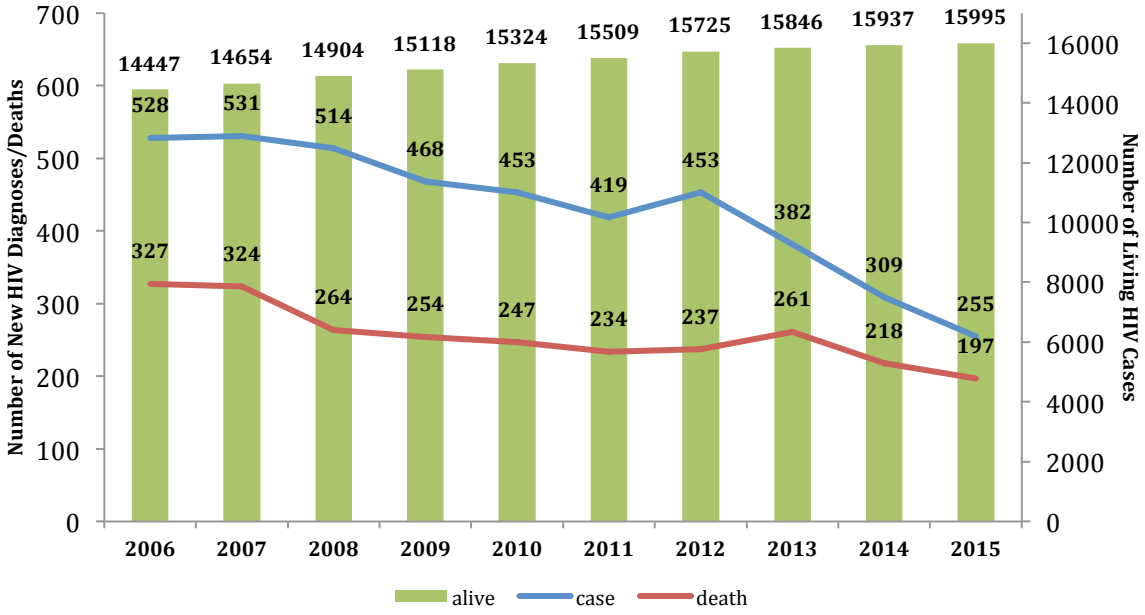

Figure 1.1: Number of persons living with HIV, new HIV diagnoses and HIV deaths reported to San Francisco Department of Public Health, San Francisco, 2006-2015 [1].

REFERENCES

1. HIV Epidemiology Section, San Francisco Department of Public Health. HIV Epidemiology Annual Report 2015. San Francisco: San Francisco Department of Public Health September 2016; pp. 1-91.

2. Bacchetti P, Osmond D, Chaisson RE, et al. Survival patterns of the first 500 patients with AIDS in San Francisco. *J Infect Dis.* 1988;157:1044-1047.

3. Lemp GF, Payne SF, Neal D, et al. Survival trends for patients with AIDS. *JAMA.* 1990;263: 402-406.

4. Arno PS. The nonprofit sector's response to the AIDS epidemic: community-based services in San Francisco. *Am J Public Health.* 1986;76:1325-1330.

5. Arno PS, Hughes RG. Local policy responses to the AIDS epidemic: New York and San Francisco. *N Y State J Med.* 1987;87:264-72.

6. Benjamin AR, Lee PR, Solkowitz SN. Case management of persons with acquired immunodeficiency syndrome in San Francisco. *Health Care Financ Rev.* 1988; Suppl:69-74.

7. Barré-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). *Science.* 1983;220:868-871.

8. Osmond D, Charlebois E, Lang W, et al. Changes in AIDS survival time in two San Francisco cohorts of homosexual men, 1983 to 1993. *JAMA*. 1994; 271:1083-1087.

9. Raymond HF, Chen YH, Ick T, et al. A new trend in the HIV epidemic among men who have sex with men, San Francisco, 2004–2011. *J Acquir Immune Defic Syndr*. 2013;62: 584-589.

10. Raymond HF, Bereknyei S, Berglas N, et al. Estimating population size, HIV prevalence and HIV incidence among men who have sex with men: a case example of synthesising multiple empirical data sources and methods in San Francisco. *Sex Transm Infect*. 2013;89:383-387.

11. Schwarcz S, Scheer S, McFarland W, et al. Prevalence of HIV infection and predictors of high-transmission sexual risk behaviors among men who have sex with men. *Am J Public Health.* 2007;97: 1067-1075.

12. Scheer S, Kellogg T, Klausner JD, et al. HIV is hyperendemic among men who have sex with men in San Francisco: 10-year trends in HIV incidence, HIV prevalence, sexually transmitted infections and sexual risk behaviour. *Sex Transm Infect*. 2008;84: 493-498.

13. Rapues J, Wilson EC, Packer T, et al. Correlates of HIV infection among transfemales, San Francisco, 2010: results from a respondent-driven sampling study. *Am J Public Health.* 2013;103:1485-1492.

14. State of California, Department of Public Health. Requirements for HIV case and CD4 test result reporting. California Health and Safety Code, Sections 121022-121023. Available from: http://www.leginfo.ca.gov/cgi-bin/displaycode?section=hsc&group=120001-121000&file=120975-121023. Accessed December 18, 2014.

15. Nakashima AK, Fleming PL. HIV/AIDS surveillance in the United States,1981–2001. *J Acquir Immune Defic Syndr.* 2003; 32(Suppl 1):S68–85.

16. Hsu LC, Chen M, Kali J, et al. Assessing receipt of medical care and disparity among persons with HIV/AIDS in San Francisco, 2006–2007. *AIDS Care*. 2011;23:383–392.

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

18. Gardner EM, McLees MP, Steiner JF, et al. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis.* 2011;52:793-800.

19. Hall HI, Frazier E, Rhodes P, et al. Differences in human immunodeficiency virus care and treatment among subpopulations in the United States. *JAMA Intern Med.* 2013;173:1337-1344.

20. Centers for Disease Control and Prevention. Vital signs: HIV prevention through care and treatment--United States. *MMWR Morb Mortal Wkly Rep.* 2011; 60: 1618-1623.

21. Ray M, Logan R, Sterne JA, et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. *AIDS*. 2010; 24:123–137.

22. Lee LM, Karon JM, Selik R, et al. Survival after AIDS diagnosis in adolescents and adults during the treatment era, United States, 1984- 1997. *JAMA*. 2001;285:1308–1315.

23. Li TS, Tubiana R, Katlama C, et al. Long-lasting recovery in CD4 T-cell function and viral-load reduction after highly active antiretroviral therapy in advanced HIV-1 disease. *Lancet*. 1998;351:1682–1686.

24. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998; 338: 853–860.

25. Detels R, Tarwater P, Phair JP, et al. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis. *AIDS*. 2001;15:347–355.

26. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. 2010;375:2092–2098.

27. Del Romero J, Castilla J, Hernando V, et al. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ*. 2010;340:c2205.

28. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011;25:473–477.

29. San Francisco Department of Public Health. Behavioral and Clinical Characteristics of Persons Receiving HIV Medical Care - Medical Monitoring Project, San Francisco 2011- 2012. San Francisco: San Francisco Department of Public Health. May 11, 2016; 1-43.

30. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the US Department of Health and Human Services. *MMWR Recomm Rep*. 2005;54: 1-20.

31. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.

32. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services, March 27 2012. Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

33. INSIGHT START Study Group. Initiation of Antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med.* 2015: Epub ahead of print.

34. Geng EH, Hare CB, Kahn JO, et al. The effect of a "universal antiretroviral therapy" recommendation on HIV RNA levels among HIV-infected patients entering care with a CD4 count greater than 500/ml in a public health setting. *Clin Infect Dis*. 2012;55:1690-7.

35. Hsu LC, Truong HH, Vittinghoff E, et al. Trends in Early Initiation of Antiretroviral Therapy and Characteristics of Persons With HIV Initiating Therapy in San Francisco, 2007-2011. *J Infect Dis.* 2014;209:1310-4.

36. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587-2599.

37. Grant RM, Liu A, Hecht J, et al. Scale-up of preexposure prophylaxis in San Francisco to impact HIV incidence. CROI 2015. February 23-26, 2015. Seattle, Washington. Abstract 25.

38. Grinsztejn, B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis.* 2014;14:281-290.

39. Montaner JS, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the "HIV Treatment as Prevention" experience in a Canadian setting. *PLoS One*. 2014; 12: e87872.

40. Mehroz B. How San Francisco is Getting to Zero On HIV. Huffington Post, 12/10/14. Available at: http://www.huffingtonpost.com/mehroz-baig/how-san-francisco-is-getting-to-zero-on-hiv_b_6290636.html

41. PBS Newshour. "How San Francisco Plans to 'get to zero' new infections of HIV" April 11, 2015. Available at: http://www.pbs.org/newshour/bb/san-francisco-plans-get-zero-new-infections-hiv/

42. Park A. The End of AIDS. *Time Magazine*. Nov 2014;44-52.

Chapter 2

A novel modeling approach for estimating patterns of migration in and out of San Francisco by HIV status and race among men who have sex with men

ABSTRACT

In the early 1980s, men who have sex with men (MSM) in San Francisco were one of the first populations to be affected by the human immunodeficiency virus (HIV) epidemic and they continue to bear a heavy HIV/AIDS burden. Once a rapidly fatal disease, survival with AIDS improved drastically following the introduction of combination antiretroviral therapy in 1996. As a result, the ability of HIV-positive persons to move into and out of San Francisco has increased due to lengthened survival. Although there is a high level of migration among the general U.S. population and among HIV-positive persons in San Francisco, in- and out-migration patterns of MSM in San Francisco have, to my knowledge, never been described. Understanding migration patterns by HIV serostatus is crucial in determining how migration could influence both HIV transmission dynamics and estimates of the prevalence and incidence of HIV infection. In this chapter, I describe methods, results and implications of a novel approach for estimating in- and out-migration patterns, and consequently population size, of MSM by HIV serostatus and race in San Francisco. The results suggest that the overall MSM population and all the MSM subpopulations studied decreased in size from 2006 to 2014. Further, there were differences in migration patterns by race and by HIV serostatus.

BACKGROUND

History of the Castro District and the AIDS Epidemic

San Francisco, particularly the Castro District, is considered by many to be a "gay Mecca." Political, social and economic forces shaped the Castro neighborhood's identity during the second-half of the 20th century [1]. San Francisco has a long history of having transient populations, due to its geographical location on the San Francisco Bay, including the presence of a large military population during and after World War II; prostitution, which emerged during the Gold Rush era; and an open, tolerant view towards sexuality [2]. For gay men or men who have sex with men (MSM), the rise of the Castro District in the 1960s helped create a sense of belonging to a community, a pocket of acceptability in an otherwise hostile country, and a space for gay sexual expression. As a result, large numbers of MSM migrated to San Francisco during the 1960s and 1970s, and by 1980 an estimated 17% of the city's population was gay [3-4]. The first AIDS case in San Francisco was reported in 1980 and the Castro District, home to most MSM in the city, was heavily affected by the AIDS epidemic in the 1980s. By the time the etiologic agent of AIDS (human immunodeficiency virus or HIV) was discovered and the first diagnostic test for HIV was approved in 1985, approximately 50% of MSM in San Francisco were HIV-positive [5]. Initially, in the absence of any available specific treatment, survival with AIDS was poor. The median survival after diagnosis of AIDS was 11 months for persons diagnosed between 1980 and 1984 [6]. The first antiretroviral drug, azidothymidine (AZT), was approved by the FDA in March 1987, and survival with AIDS began to increase. Between 1990 and 1995, the median survival of individuals with AIDS had increased to 38 months [6].

MSM in San Francisco continue to be disproportionately affected by HIV, accounting for 89% of persons living with HIV in the county [6]. Approximately one quarter of MSM in San Francisco are currently living with HIV and the prevalence of HIV in MSM remained stable from 2004 to 2011 [7]. Data suggest a level or only slight (but not statistically significant) decline in the number of new HIV transmissions in San Francisco from 2007 to 2013 [6,8]. The incidence of HIV infection among MSM in San Francisco, based on data from the National HIV Behavioral Surveillance (NHBS), was 2.6% per year in 2004 (95% CI: 0.8% to 4.3%) and 1.0% per year in 2011 (95% CI: 0.02% to 1.9%) [7].

San Francisco demographic characteristics and migration

The City and County of San Francisco comprises a small geographic area of 47 square miles situated on the edge of the San Francisco Bay. The estimated population size was 852,469 in July 2014, a 5.9% increase from April 2010 [9]. Currently, white non-Latinos account for 41.2% of the population, 34.9% are Asian, 15.3% are Hispanic or Latino, and 5.8% are black or African American. On average, San Francisco residents tend to be of higher socioeconomic status than Californians overall. The median household income in 2014 for San Francisco residents was $78,378, and 52.9% of persons over the age of 25 had at least a bachelor's degree [9]. Recently, San Francisco has undergone significant

economic shifts that are resulting in demographic changes. The proportion of the population earning between $50,000 and $75,000 fell from 15% in 2009 to 13.1% in 2014 and the proportion of households earning $200,000 or more increased 3.7% during the same time period to 15% in 2014 [10]. A housing crisis has resulted in a net out-migration of middle class San Franciscans. At the same time, San Francisco has experienced population growth. The American Community Survey (ACS) from 2013 estimates that there were 66,829 in-migrants (or 8.1% of the population) to San Francisco, and 64,763 out-migrants (7.8% of the population) from San Francisco in the prior 12 months.

Data from the NHBS survey in 2014 on MSM in San Francisco show some demographic similarities and differences between MSM and the overall population of San Francisco. MSM were mostly white (55.7%); 25.8% were Latino, 6.1% were black, 5.6% were Asian and 6.8% were another race/ethnicity or mixed. The median age of MSM was 36 years and the median annual income was $50,000-$60,000. The majority (53.2%) of San Francisco MSM had a bachelor's degree or higher. In-migration to San Francisco was more common among MSM than among the overall population, with 15.8% of the 411 MSM surveyed in the 2014 NHBS reporting having moved to San Francisco within the previous 12 months.

Migration in the context of HIV

HIV infection, and the resultant AIDS, was once a rapidly fatal disease; however, survival drastically improved following introduction of combination antiretroviral therapy in 1996. The ability of HIV-positive individuals to migrate has increased as a result of lengthened survival. Recent data from the San Francisco Department of Public Health (SFDPH) indicate that HIV-positive individuals are migrating into and out of San Francisco. Approximately 29% of HIV-positive individuals receiving HIV care in San Francisco in 2014 were living elsewhere at the time of their HIV diagnosis, indicating substantial in-migration from other areas to San Francisco [6]. Between November 2012 and May 2015, SFDPH conducted a pilot project, "Case-Surveillance-Based Sampling", in which HIV-positive adults with a most recent address of San Francisco were sampled from the HIV registry and recruited for participation in a survey. In this study, approximately 25% of the persons sampled and located persons no longer resided in San Francisco at the time of recruitment, indicating significant out-migration among persons living with HIV. HIV serostatus may influence migration because of the desire to migrate to an area perceived as having less HIV stigma, a higher level of community acceptance of HIV, better quality of or better access to medical care or other HIV-related services, more affordable health care or a lower cost of living for those who may be on permanent disability due to HIV-associated disease.

Challenges in estimating migration among MSM

Studying migration among MSM is challenging for several reasons. First, the population size (or underlying "denominator") of all MSM is not readily available. The U.S. Census does not collect data on sexual orientation and it is, therefore, very difficult to obtain an

estimate of the size of the MSM population in San Francisco, as well as the sizes of each racial/ethnic subgroup of MSM. In addition, there are currently no reliable data sources or research studies that are tracking out-migration by MSM, including HIV-positive and negative MSM, from San Francisco. There are limited existing self-reported survey data on in-migration for MSM into San Francisco from the National HIV Behavioral Surveillance (NHBS) survey, and there is limited information on out-migration by HIV-positive MSM in San Francisco from HIV surveillance data. While a case record in the HIV surveillance database may be updated as part of routine HIV case surveillance activities if the individual has migrated out of San Francisco, the data from this source are not reliable for estimating out-migration by HIV-positive individuals for a number of reasons. For example, the time at which out-migration occurred is often difficult or impossible to ascertain through HIV surveillance data, and there are substantial discrepancies between HIV surveillance data and self-reported information on address of current residence that limit the reliability of surveillance data as a source of information on out-migration. There are, essentially, no data on out-migration for HIV-negative MSM in San Francisco.

Study objectives

Although there is a high level of mobility among the general U.S. population and among people living with HIV in San Francisco, migration patterns of MSM in San Francisco have, to my knowledge, never been described. Understanding migration patterns is crucial in determining how migration by HIV infected and uninfected individuals could influence transmission of HIV. Due to the difficulty of directly estimating the population size of MSM and out-migration of MSM, a modeling approach was relied on to estimate in- and out-migration of MSM by HIV serostatus and by race, as those in different racial groups are disproportionately affected by HIV and also may have different migration patterns. The analysis was limited to white MSM, black MSM and all MSM combined, due to the small numbers of MSM of other races (e.g. Asian) and ethnicities in San Francisco. Here, I describe methods, results and implications for a novel approach to estimating in- and out-migration patterns of MSM, and consequently population size, by HIV serostatus and race in San Francisco.

METHODS

Model overview

A mathematical model was built according to a simple population growth model. For example, Equation 1 can be used to calculate the population size of MSM in San Francisco on January 1, 2008 (MSM_{t+1}) as equal to the population size that existed on January 1, 2007 (MSM_t), plus the MSM who entered the population during 2007 ($in_{\Delta t}$), minus the MSM who exited the population during 2007 ($out_{\Delta t}$). This model was stratified by HIV serostatus (Equations 1a, 1b and 2) and subsequently by white and black race (equations not shown). Below I describe the methods used to calculate the model for the entire MSM population (all race/ethnicities); however, I applied the same

modeling approach to create separate models for white MSM (WMSM) and black MSM (BMSM). All modeling analyses were conducted using R version 3.2.2 and U.S. Census data were analyzed using SAS version 9.3.

Equation 1:
$$MSM_{t+1} = MSM_t + in_{\Delta t} - out_{\Delta t}$$

Equation 1a:
$$MSM_{t+1}^{HIV+} = MSM_t^{HIV+} + in_{\Delta t}^{HIV+} - out_{\Delta t}^{HIV+}$$

Equation 1b:
$$MSM_{t+1}^{HIV-} = MSM_t^{HIV-} + in_{\Delta t}^{HIV-} - out_{\Delta t}^{HIV-}$$

Equation 2:
$$\left(MSM_{t+1}^{HIV+} + MSM_{t+1}^{HIV-}\right) = \left(MSM_t^{HIV+} + MSM_t^{HIV-}\right) + \left(in_{\Delta t}^{HIV+} + in_{\Delta t}^{HIV-}\right) - \left(out_{\Delta t}^{HIV+} + out_{\Delta t}^{HIV-}\right)$$

Equation 3:
$$in_{\Delta t}^{HIV+} = i_{\Delta t}^{HIV+} + s_{\Delta t}$$

Equation 4:
$$in_{\Delta t}^{HIV-} = i_{\Delta t}^{HIV-}$$

Equation 5:
$$i_{\Delta t} = i_{\Delta t}^{HIV+} + i_{\Delta t}^{HIV-}$$

Equation 6:
$$out_{\Delta t}^{HIV+} = o_{\Delta t}^{HIV+} + d_{\Delta t}^{HIV+}$$

Equation 7:
$$out_{\Delta t}^{HIV-} = o_{\Delta t}^{HIV-} + d_{\Delta t}^{HIV-} + s_{\Delta t}$$

Equation 8:
$$o_{\Delta t} = o_{\Delta t}^{HIV+} + o_{\Delta t}^{HIV-}$$

Equation 9:
$$MSM_t^{HIV+} = u_t^{HIV+} + k_t^{HIV+}$$

Equation 10:
$$MSM_{t+1} = \left(u_t^{HIV+} + k_t^{HIV+} + MSM_t^{HIV-}\right) + \left(i_{\Delta t}^{HIV+} + s_{\Delta t} + i_{\Delta t}^{HIV-}\right) - \left(o_{\Delta t}^{HIV+} + d_{\Delta t}^{HIV+} + o_{\Delta t}^{HIV-} + d_{\Delta t}^{HIV-} + s_{\Delta t}\right)$$

In my model, I accounted for MSM who entered the population during a specific timeframe of one year ($in_{\Delta t}$). Equation 3 shows that those entering the HIV-positive population (${in_{\Delta t}}^{HIV+}$) equaled the sum of HIV-positive in-migrants (${i_{\Delta t}}^{HIV+}$) and those who newly acquired HIV (or "seroconverters") during the timeframe ($s_{\Delta t}$). HIV-negative in-migrants (${i_{\Delta t}}^{HIV-}$) accounted for all who entered the HIV-negative population (${in_{\Delta t}}^{HIV-}$) in the model (Equation 4). The total in-migrants ($i_{\Delta t}$) are the sum of the HIV-negative in-migrants (${i_{\Delta t}}^{HIV-}$) and HIV-positive in-migrants (${i_{\Delta t}}^{HIV+}$) (Equation 5).

I also accounted for exiting from the San Francisco MSM population ($out_{\Delta t}$). Individuals could exit the HIV-positive population (${out_{\Delta t}}^{HIV+}$) either through out-migration (${o_{\Delta t}}^{HIV+}$) or by death (${d_{\Delta t}}^{HIV+}$), including death from HIV or any other cause, which is shown by Equation 6. Exiting the HIV-negative population (${out_{\Delta t}}^{HIV-}$) occurred by out-migration (${o_{\Delta t}}^{HIV-}$), death from any cause among HIV-negative MSM (${d_{\Delta t}}^{HIV-}$), and HIV seroconversion, when previously HIV-negative persons moved into the HIV-positive population ($s_{\Delta t}$) as in Equation 7. The total out-migrants ($o_{\Delta t}$) are the sum of the HIV-negative out-migrants (${o_{\Delta t}}^{HIV-}$) and HIV-positive out-migrants (${o_{\Delta t}}^{HIV+}$) (Equation 8). Additionally, because not all MSM who are HIV-positive are aware of their HIV status, the model further differentiates the starting HIV-positive population size (${MSM_t}^{HIV+}$) between unknown HIV (${u_t}^{HIV+}$) and known HIV (${k_t}^{HIV+}$), as described in Equation 9. Substituting Equations 3, 4, 6, 7, and 9 into Equation 2 yields Equation 10, which describes each individual parameter that was used in my migration model.

Data sources and estimated parameters

National HIV Behavioral Surveillance

Various data sources were used to estimate the parameters in this model. Data from the National HIV Behavioral Surveillance (NHBS) project in San Francisco were used to estimate the number of MSM with unrecognized HIV (${u_t}^{HIV+}$) and the proportion of MSM who moved to San Francisco within the prior 12 months who were HIV-positive ($n_{\Delta t}$). NHBS is a CDC-funded, national HIV behavioral surveillance project that used time-location sampling methods to collect data on MSM in San Francisco through standardized behavioral surveys, including HIV-antibody and incidence testing. NHBS did not sample MSM every year, so data from 2004, 2008, 2011 and 2014 were used for estimating parameters in the model. Data for missing years (i.e. 2005, 2006, 2007, 2009, 2010, 2012, and 2013) were imputed by taking the known data points and drawing a straight line between them.

MSM Population Estimates

I used previously published data on estimated MSM population size for all race/ethnicities combined in 2006 (n=63,577) as the estimated starting population size for the model (MSM_t), where t equals 2006 [11]. To calculate the MSM population size in 2006 for white MSM and black MSM, the means of the proportions for each race were calculated from NHBS 2004 and 2008 (because 2006 was the halfway point between these time points) and multiplied by the total estimated MSM population size in 2006 [7].

My assumption concerning the proportion of the male population that is MSM in San Francisco (p_{MSM}) was derived using the above estimated MSM population sizes (all, white and black sub-groups) in 2006 and then dividing by the corresponding total San Francisco adult male population sizes in 2006 reported by the U.S. Census Bureau. This yielded an estimate that 19% of all adult males in San Francisco were MSM, whereas 23% of all black adult males were MSM and 21% of all white adult males were MSM.

U.S. Census Bureau American Community Survey

The U.S. Census Bureau American Community Survey (ACS) collects information on demographic information, migration status, employment, and housing characteristics for a sub-sample of persons and households in the U.S. Census. Data are given weights accounting for the probability of selection and non-response, and these weights were used to calculate population estimates. Data from the ACS single year estimates for the years 2006-2014 were used to estimate the total number of adult male in-migrants and out-migrants for San Francisco. The estimated proportion of all adult men who are MSM (p_{MSM}) was then applied to obtain the total number of MSM in-migrants ($i_{\Delta t}$) and out-migrants ($o_{\Delta t}$).

HIV Surveillance data

California law requires that all laboratory tests indicative of HIV infection, including HIV diagnostic tests and HIV viral load tests, be reported to the local county health department by both the diagnosing provider and the laboratory performing the test [12]. Through a combination of active and passive surveillance activities, the San Francisco Department of Public Health collects diagnostic, demographic, mode of HIV acquisition, and vital status information for all reported persons diagnosed with HIV [13-14]. This information is stored in the Enhanced HIV/AIDS Reporting System (eHARS) case registry. HIV surveillance data were used to estimate a number of model parameters, including the current number of MSM living in San Francisco with known HIV diagnosis (${k_t}^{HIV+}$), new HIV diagnoses each year or "seroconversions" ($s_{\Delta t}$), and deaths due to any cause in HIV-positive MSM (${d_{\Delta t}}^{HIV+}$). Additionally, the number of deaths in adult male San Francisco residents each year from 2006-2013, from the San Francisco Department of Public Health Vital Records, was multiplied by the proportion of all adult men who are MSM (p_{MSM}) to yield the estimated number of deaths in MSM each year ($d_{\Delta t}$). To calculate the number of deaths among HIV-negative MSM (${d_{\Delta t}}^{HIV-}$), the deaths among HIV-positive MSM (${d_{\Delta t}}^{HIV+}$) were subtracted from all MSM deaths ($d_{\Delta t}$), as explained in Table 2.1.

Derivation of other model components

The remaining model components were derived after all the estimated parameters were calculated from the data sources as described above. The numbers of MSM with known (${k_t}^{HIV+}$) and unrecognized (${u_t}^{HIV+}$) HIV were estimated using information from eHARS and NHBS, and the sum of these yielded the total number of HIV-positive MSM for a given time period (${MSM_t}^{HIV+}$). Subtracting the total number of HIV-positive MSM from

the total population of MSM (MSM_t) yielded the estimated number of HIV-negative MSM for each time period (${MSM_t}^{HIV-}$).

Equation 11:
$${i_{\Delta t}}^{HIV+} = \ n_{\Delta t} * i_{\Delta t}$$

Equation 12:
$${i_{\Delta t}}^{HIV-} = \ (1 - n_{\Delta t}) * i_{\Delta t}$$

After using ACS data to calculate the total number of MSM in-migrants ($i_{\Delta t}$), I used the proportion of in-migrants in the past 12 months who were HIV-positive ($n_{\Delta t}$) from NHBS data to obtain the number of in-migrants who were HIV-positive and HIV-negative, as in Equations 11 and 12. Once the number of in-migrants was estimated, I used the number of seroconversions ($s_{\Delta t}$) to estimate the total in HIV-positive (${in_{\Delta t}}^{HIV+}$), total in HIV-negative (${in_{\Delta t}}^{HIV-}$) and total in ($in_{\Delta t}$).

Deriving the number of out-migrants by HIV serostatus was the main objective for this model, as there are no available data sources that can be used to estimate these values. To generate this estimate, I first used Equation 1a and then re-arranged it to solve for total out HIV-positive (${out_{\Delta t}}^{HIV+}$).

$${out_{\Delta t}}^{HIV+} = {MSM_t}^{HIV+} + {in_{\Delta t}}^{HIV+} - \ {MSM_{t+1}}^{HIV+}$$

Likewise, I re-arranged Equation 1b to derive the total number of HIV-negative men who "exited" the population (${out_{\Delta t}}^{HIV-}$).

$${out_{\Delta t}}^{HIV-} = {MSM_t}^{HIV-} + {in_{\Delta t}}^{HIV-} - {MSM_{t+1}}^{HIV-}$$

The total number of MSM leaving the population ($out_{\Delta t}$) is the sum of the total out of HIV-positive MSM (${out_{\Delta t}}^{HIV+}$) and HIV-negative MSM (${out_{\Delta t}}^{HIV-}$).

After all other parameters were derived, I solved for the information that the model was created to estimate: the numbers of HIV-positive out-migrants (${o_{\Delta t}}^{HIV+}$) and HIV-negative out-migrants (${o_{\Delta t}}^{HIV-}$), by re-arranging Equations 6 and 7. In order to obtain the number of HIV-positive out-migrants (${o_{\Delta t}}^{HIV+}$), I took the total that exited the HIV-positive population from time t_0 to t_1 (${out_{\Delta t}}^{HIV+}$) and subtracted the HIV-positive deaths (${d_{\Delta t}}^{HIV+}$).

$${o_{\Delta t}}^{HIV+} = \ {out_{\Delta t}}^{HIV+} - {d_{\Delta t}}^{HIV+}$$

Finally, to calculate the number of HIV-negative out-migrants (${o_{\Delta t}}^{HIV-}$), I took the total number of MSM who exited the HIV-negative population from time t_0 to t_1 (${out_{\Delta t}}^{HIV-}$) and subtracted the HIV-negative deaths (${d_{\Delta t}}^{HIV-}$) and the seroconverters ($s_{\Delta t}$).

$${o_{\Delta t}}^{HIV-} = \ {out_{\Delta t}}^{HIV-} - \ {d_{\Delta t}}^{HIV-} - s_{\Delta t}$$

Output from the model determined my estimates of the numbers of in-migrants, out-migrants and MSM population size from 2006-2013 and a final population size in 2014. These outputs were further stratified by HIV status and by black and white race.

Model fit and calibration

I used external estimates of the prevalence of HIV for all San Francisco MSM, white MSM and black MSM to calibrate the models. I specified that if the confidence intervals for the model generated prevalence of HIV and the confidence intervals for the NHBS prevalence of HIV overlapped for each of the three data points (years 2007, 2011 and 2014), the criterion for proper model fit was met. The model fit for the BMSM model was poor, so I adjusted the p_{MSM} parameter, due to the fact that it had the most uncertainty, to optimize the fit. I changed p_{MSM} incrementally from 23% until I met the above outlined criterion for the BMSM model. For out migration, the proportion of all adult men who were MSM (p_{MSM}) was changed from 23% to 11.5%, for in-migration p_{MSM} was 25% and for deaths p_{MSM} remained at 23%. Making these changes for the BMSM resulted in a better fitting model when comparing the published estimate of the prevalence of HIV to the estimate of the prevalence of HIV from the model and met my model fit criterion outlined above.

Uncertainty analysis

Due to potential uncertainty in parameter estimation, I performed an uncertainty analysis to assess how sensitive the model results were to changes in estimated model parameters and to obtain plausible bounds on the model output. The parameters that were varied in the sensitivity analysis are highlighted in Table 2.1. One of the assumptions I varied in the sensitivity analysis was the proportion of the adult male population in San Francisco who are MSM, where I assumed that for all races/ethnicities the proportion was 19% for in-migrants, out-migrants and deaths. For whites, the proportion of the adult male population who were MSM was 21% for in-migrants, out-migrants and deaths. For blacks, it was 11.5% for out-migrants, 25% for in-migrants and 23% for deaths. I sampled from a normal distribution centered on these assumed values, with a standard deviation of 10%, and allowed the proportion to vary by year and by which parameter I used (total number of MSM in-migrants, total number of MSM out-migrants and MSM HIV-negative deaths). Another estimated parameter I varied for the uncertainty analyses was the number of MSM with unrecognized HIV, where I sampled from a normal curve centered on the NHBS estimate with a 2.5% standard deviation (5% standard deviation for the BMSM model). Likewise, I varied the estimate from NHBS of the proportion of in-migrants who were HIV-positive, by sampling randomly from a normal distribution centered at the empirical estimate with a standard deviation of 2.5% (5% for BMSM). Last, because the starting population size was also uncertain, I sampled from a normal distribution centered at the starting population estimate (for all race/ethnicities, white and black) with a standard deviation of 5% of the population (10% for BMSM). All of the above parameters were varied in parallel and then the model was run to obtain a new model output; models were run 100,000 times in order to obtain a good spread of high

and low parameter variations for everything that was sampled and varied. The 100,000 model runs yielded 100,000 model output copies, and the 2.5 and 97.5 percentiles of the distribution of each output variable were used to create a plausible 95% confidence interval.

Ethical Considerations

The data used for this chapter did not require the University of California, Berkeley Committee for Protection of Human Subjects review because it did not fall within the regulatory definition of research involving human subjects. Data used to estimate model parameters were publicly available, gathered from publications, or were obtained from reports published by the San Francisco Department of Public Health.

RESULTS

Migration estimates

I first ran a model and uncertainty analysis for MSM of all races/ethnicities in San Francisco. Migration patterns differed for HIV-positive and HIV-negative MSM in San Francisco (Table 2.2). For HIV-negative MSM, there was a higher proportion of both in- and out-migration than for HIV-positive MSM. For HIV-positive MSM, there was net out-migration in all years, with the highest net out-migration occurring during 2008-2010 (approximately -4.0% per year). There was net out-migration of HIV-negative MSM in 2006-2007 and net in-migration in 2008-2013, with the highest in-migration (4.5%) in 2011.

Next, I ran a migration model for white MSM (WMSM) only. There were different migration patterns for HIV-positive and HIV-negative WMSM (Table 2.3). For HIV-negative WMSM, there was a higher proportion of both in- and out-migration than for HIV-positive WMSM. For HIV-positive WMSM, there was a slight net out-migration in all years, ranging from -0.7% to -1.6% net-migration per year. For HIV-negative WMSM, net-migration differed by year. There was net out-migration for HIV-negative WMSM in 2006, 2007 and 2010, and net in-migration in each year in 2008-2013, with the highest net in-migration (4.8%) during 2011.

Finally, I ran the model on black MSM (BMSM) only. The proportion of the HIV-positive and HIV-negative BMSM who were in-migrants was roughly similar each year, but there was higher out-migration among HIV-positive BMSM compared to HIV-negative BMSM (Table 2.4). Among HIV-positive BMSM, there was net out-migration in all years, with the highest out-migration in 2006 and in 2007 (-9.9% and -9.4%, respectively). Among HIV-negative BMSM, there was net in-migration in all years except 2013, when the net-migration was -2.0%.

Population size estimates

The model output showed that the population size of all MSM subgroups decreased from 2006 to 2014 (Table 2.5). The all race/ethnicity MSM model showed that the overall population of MSM decreased 7.8%, from 63,577 in 2006 to 58,605 in 2014. Figure 2.1 shows that the HIV-positive MSM population decreased 5.4%, from 15,269 in 2006 to 14,452 in 2014, and the HIV-negative MSM population decreased 8.6%, from 48,308 in 2006 to 44,154 in 2014. The model for WMSM showed that the population of WMSM decreased from 34,904 to 32,705 between 2006 and 2014 (6.3%). There was a modest decrease (2.1%) in the HIV-positive WMSM population, from 9,264 in 2006 to 9,066 in 2014, and there was a 7.8% decrease in HIV-negative WMSM, from 25,640 in 2006 to 23,639 in 2014 (Figure 2.2). The model showed the largest relative population size decreases for BMSM. There was an 11.9% decrease in all BMSM. The HIV-positive BMSM population decreased 27.8%, from 1,968 in 2006 to 1,421 in 2014, while the HIV-negative BMSM population remained steady, at 2,705 in 2006 and 2,697 in 2014 (Figure 2.3). Although the models showed decreases in every subpopulation between 2006 and 2014, after running the uncertainty analysis, the plausible ranges calculated show that there could have been population decreases or increases in each subpopulation (see population ranges in Table 2.5 and Figures 2.1-2.3). The only exception was that the uncertainty analysis yielded a true decrease in the number of HIV-positive BMSM, from 1,968 (range 1,674-2,382) in 2006 to 1,421 (1,275-1,605) in 2014.

Prevalence of HIV

I compared the prevalence of HIV estimated from the model to estimates of the prevalence of HIV from the NHBS study to validate the model (Table 2.6). The estimates of the prevalence of HIV for all races/ethnicities of MSM in San Francisco were very similar between the model (steady prevalence) and NHBS (slightly increasing), suggesting a prevalence of HIV around 21-25% during 2007 to 2014. Similarly, the prevalence of HIV was steady in my model for white MSM in San Francisco, 27% in 2007, 29% in 2011 and 28% in 2014, while NHBS estimated a slightly increasing prevalence, from 21% in 2007 to 26% in 2014. I observed a decreasing prevalence of HIV over time for black MSM in San Francisco. My model showed a decrease in the prevalence of HIV from 39% in 2007 to 35% in 2014. Similarly, NHBS data showed that for black MSM, the prevalence of HIV decreased slightly from 30% in 2007 to 28% in 2014.

DISCUSSION

I found that all of the nine MSM populations I studied (all MSM, BMSM, WMSM and each of these populations stratified by HIV status) decreased in population size from 2006 to 2014. There are several reasons why there may be decreasing MSM populations in San Francisco. Given recent cultural shifts, the Castro neighborhood may no longer be seen as a ‘gay Mecca.’ As U.S. culture has evolved and the LGBT communities have found more acceptance, and stigma has decreased, it may be less important for MSM to

live in areas defined as 'gay friendly' or a 'gay Mecca.' Using General Social Survey data, Baunach, et al. found that acceptance of same sex marriage increased greatly in the United States from 1988 to 2010 [15]. Their analysis also found that the shifts in attitudes towards same-sex marriage were due primarily to general societal changes in attitudes and not to demographic shifts in the US. Likewise, Keleher and Smith found that acceptance of gays and lesbians in the United States increased in almost every demographic subgroup between 1991 and 2010, and they showed that generational replacement and period effects were in part responsible for the increased public acceptance of homosexuality [16]. The potential for these cultural shifts to change migration patterns of MSM moving into and away from San Francisco is likely coupled with the economic changes and cost of living increases that San Francisco experienced during the time period I modeled. San Francisco MSM have similar levels of educational attainment as the entire San Francisco population (53% of both groups had a college education or higher in 2014), although the median income of MSM was lower than the median income of all San Franciscans in 2014. This suggests that it may be difficult for MSM to continue to stay in or to migrate to San Francisco, a city where the average price for new one-bedroom apartment rentals was $3,500 in November 2015, and the lower median income for MSM may be another reason why I observed a decline in the size of the MSM population in San Francisco [17].

I also found some differences in migration by race and HIV status. For all racial groups, the HIV-positives had net out-migration every year, although BMSM had the highest proportion of net out-migration for all years. Living with HIV could affect one's ability to work full time and could increase expenses for health care, which could also make it difficult to continue to live in San Francisco, where the cost of living has continued to rise. Racial differences in socio-economic status may explain the higher proportion of out-migration for BMSM estimated in the model. In contrast, one might expect that San Francisco would attract people living with HIV because of the variety of HIV care services that are available and often free or at a low cost, but the model output found that there was net out-migration of HIV-positive MSM for all years from 2006 to 2014.

For the HIV-negative populations, there tended to be net in-migration, but after accounting for HIV seroconversions, deaths and migration, the populations of both HIV-negative racial groups declined from 2006 to 2014. Of note, a substantially higher proportion of HIV-negative MSM in-migrated versus the proportion of HIV-positive MSM that in-migrated for all races combined and for WMSM. One reason I may have observed a general pattern of more out-migration for HIV-positive individuals and net in-migration of HIV-negatives is an effect of age structure. The prevalence of HIV increases with age, and in San Francisco the majority (58%) of persons living with HIV are over 50 years old [6]. Therefore, the older age structure of HIV-positive out-migrants may be the result of persons of older or retirement age no longer working or wanting or needing to live in San Francisco and therefore migrating out of San Francisco to lower cost areas that are appealing to retirees. Similarly, HIV-negative MSM likely are on average younger, and younger MSM may be more likely to move to San Francisco due to employment opportunities, or because of the "gay Mecca" aspects of San Francisco that attract gay men. Black et al. argued that due to extra resource availability (due to lower

frequency of having children and lower demand for larger housing units suitable for families), gay men live in San Francisco for the access to "urban amenities" such as art, entertainment, and fine dining; HIV-negative MSM may have more economic resources than MSM living with HIV, which could explain why there is more in-migration by HIV-negative MSM [18].

The models presented here are subject to several limitations. Because it was not possible to quantify migration patterns of San Francisco MSM by race and HIV status from empirical data, I had to rely on modeling. I made a number of assumptions in creating the models and was limited by the variables I was able to include in the model. For example, I did not look at migration patterns by age or income or for races/ethnicities other than white and black. The largest uncertainty in the model was for the estimation of the proportion of the total adult male population (p_{MSM}) who are MSM. However, I accounted for the uncertainty of p_{MSM}, and uncertainty in the estimation of other parameters, such as the starting MSM population sizes, by performing an uncertainty analysis and including ranges of plausible values for the model outputs.

In this chapter, I outline a novel approach to using data from multiple sources to estimate in- and out-migration of MSM. My models for estimating migration patterns for MSM use a straightforward method that other researchers can apply in their respective geographical locations, using data that should be readily available. Output from these models may be useful in understanding how migration affects the prevalence and incidence of HIV over time. The size of the denominator of HIV-negative and HIV-positive men has a significant effect on the estimates of prevalence and incidence of HIV. My models showed that migration was a key driver in the observed decline in prevalence of HIV in NHBS data for the San Francisco BMSM population. Researchers in King County, Washington recently showed that failure to account for migration resulted in an overestimation of the number of persons living with HIV and the number of persons who were out of HIV care in that jurisdiction [19]. Similarly, another recent finding demonstrated that the number of people living with HIV in the U.S. may be overestimated by as much as 25% when using HIV case reporting data [20]. The authors noted that this overestimation is, in part, due to migration of people living with HIV across public health jurisdictions and that failure to de-duplicate these cases results in an HIV case being counted more than once in the national HIV registry [20]. Outputs from the model presented here can be applied as a migration "adjustment factor" to improve the accuracy of data on persons living with HIV, such as routinely collected HIV surveillance data, that have not been adjusted for migration in jurisdictions that are unable to allocate resources to update the current addresses of HIV cases in their HIV surveillance registry. This migration "adjustment factor" would allow for more precise estimation of the burden of HIV in a given jurisdiction based on current residence, instead of residence at the time of diagnosis of HIV. Additionally, as more health departments use HIV surveillance data to identify persons out of HIV care and re-engage them in care, migration can make efforts to track people presumed to be living in that jurisdiction more difficult [21-22]. For example, a surveillance project in San Francisco attempted to contact persons living with HIV who had a most recent high or "detectable" HIV viral load test result nine months earlier, in order to re-engage them in HIV care and

to assess barriers to accessing care. However, 17% of these persons presumed to be living in San Francisco had migrated out of the Greater Bay Area [21].

Migration estimates from these models can also be used as inputs in HIV transmission models to determine how migration by HIV serostatus can influence HIV transmission patterns. Modeling HIV transmission in South Africa under different migration pattern scenarios has shown that if migration is coupled with higher sexual risk behaviors, it can increase transmission ten-fold [23]. Migration could affect HIV transmission not only if it is related to higher risk behaviors, like engaging in condomless sex, but also if HIV-positive migrants experience a disruption in their HIV care and their HIV viral load levels increase enough to transmit HIV. Prior research in Africa has shown that migration is a risk factor for acquiring HIV that may be related to riskier sexual behaviors, having more sexual partners or expanded sexual networks. However, this research was focused on heterosexual men and women [24-26]. Another analysis found that foreign-born MSM and US-born MSM in San Francisco did not have a significantly different odds of having HIV after controlling for other factors [27]. More research is needed, however, to characterize age, employment status and income of MSM who are migrating, their reasons for migrating, and how these factors relate to their risk of acquiring or transmitting HIV.

One concern is that the most vulnerable people living with HIV are being displaced in San Francisco, due to rising cost of living, and they may be re-locating to areas where funding and infrastructure to provide the services they need to manage HIV do not exist. Disruption in HIV care can lead to an increase in HIV viral load, which can negatively affect a person's health and increase the risk of HIV transmission. Homelessness among persons living with HIV in San Francisco has been associated with failure to have a suppressed HIV viral load, putting homeless HIV-positive individuals at increased risk of poor health outcomes and of transmitting HIV to others [28]. Stable housing has been shown to improve health outcomes, such as adherence to ART medication, and to increase utilization of health and social services [29]. The "displacement" theory of a shrinking MSM population in San Francisco aligns well with my model results and with the recent economic changes in San Francisco, but further research needs to be conducted to determine if displacement or homelessness has contributed to a decline in the number of MSM in San Francisco.

Using a novel approach to estimate in- and out-migration patterns of MSM, I found that all MSM population sizes I studied declined from 2006 to 2014. I also found that migration patterns differed by race and by HIV serostatus. The modeling methods outlined in this chapter can be applied by other researchers interested in how migration patterns may contribute to the prevalence of HIV. I aim to use output from these models in a transmission model to better understand how migration can impact HIV transmission among MSM in San Francisco.

TABLES:

Table 2.1: Migration model parameters and description as to how the parameter was either estimated from external data or derived from other model parameters.

Description	Notation	Estimated	Derived	Varied in Uncertainty Analysis	Notes
Total MSM	MSM_t	✔	✔	✔	Published population estimate used for 2006. Each subsequent year derived by taking prior year population, adding total in (during Δt) and subtracting total out (during Δt) as described in Equation 1.
Total HIV+ MSM	${MSM_t}^{HIV+}$		✔		Derived from Equation 9.
Known HIV+	${k_t}^{HIV+}$	✔			Estimated using eHARS data.
Unknown HIV+	${u_t}^{HIV+}$	✔		✔	Estimated using NHBS data.
Total HIV- MSM	${MSM_t}^{HIV-}$		✔		${MSM_t}^{HIV-} = MSM_t - {MSM_t}^{HIV+}$
Total In	$in_{\Delta t}$		✔		$in_{\Delta t} = {in_{\Delta t}}^{HIV+} + {in_{\Delta t}}^{HIV-}$
Total In HIV+	${in_{\Delta t}}^{HIV+}$		✔		Derived from Equation 3.
Total In HIV-	${in_{\Delta t}}^{HIV-}$		✔		Equal to Total In-Migrants HIV-.
Newly Diagnosed HIV+	$s_{\Delta t}$	✔			Estimated using eHARS data.
Total MSM In-Migrants	$i_{\Delta t}$	✔		✔	Number of adult male in-migrants from time t_0 to t_1 was estimated using ACS Census data. I then multiplied this by the proportion of all adult males that were MSM (p_{MSM}) to get Total MSM In-Migrants.
New arrival HIV+ proportion	$n_{\Delta t}$	✔		✔	Proportion of MSM that in-migrated from time t_0 to t_1 that are HIV+ was estimated from NHBS data.
In-Migrants HIV+	${i_{\Delta t}}^{HIV+}$		✔		Derived from Equation 11.
In-Migrants HIV-	${i_{\Delta t}}^{HIV-}$		✔		Derived from Equation 12.
Total Out MSM	$out_{\Delta t}$		✔		$out_{\Delta t} = {out_{\Delta t}}^{HIV+} + {out_{\Delta t}}^{HIV-}$
Total Out HIV+	${out_{\Delta t}}^{HIV+}$		✔		Solve for by re-arranging Equation 1a.
Total Out HIV-	${out_{\Delta t}}^{HIV-}$		✔		Solve for by re-arranging Equation 1b.
Total MSM Out-Migrants	$o_{\Delta t}$	✔		✔	Number of adult male out-migrants during time t_0 to t_1 was estimated using ACS Census data. I then multiplied this by the proportion of all adult males that were MSM (p_{MSM}) to get Total MSM Out-Migrants.
Out-Migrants HIV+	${o_{\Delta t}}^{HIV+}$		✔		Solve for by re-arranging Equation 6.
Out-Migrants HIV-	${o_{\Delta t}}^{HIV-}$		✔		Solve for by re-arranging Equation 7.
Total Deaths	$d_{\Delta t}$		✔		$d_{\Delta t} = {d_{\Delta t}}^{HIV+} + {d_{\Delta t}}^{HIV-}$
HIV+ Deaths	${d_{\Delta t}}^{HIV+}$	✔			All-cause deaths were estimated by using eHARS data.
HIV- Deaths	${d_{\Delta t}}^{HIV-}$	✔		✔	Vital Statistics data were used to obtain total number of adult male San Francisco resident deaths from time t_0 to t_1. I multiplied the total number of adult male deaths by the proportion of all adult males that were MSM (p_{MSM}) to get all MSM Deaths and then subtracted the number of HIV+ MSM deaths (${d_{\Delta t}}^{HIV+}$) to get MSM HIV- Deaths.
MSM proportion	p_{MSM}	✔		✔	Assumptions were made based on empirical data about the proportion of all adult males that are MSM.

Abbreviations: MSM, men who have sex with men; eHARS, Enhanced HIV/AIDS Reporting System; ACS, American Community Survey; NHBS, National HIV Behavioral Surveillance

Table 2.2: In-, out- and net-migration estimates for all MSM in San Francisco by HIV serostatus, 2006-2013.

	In-Migrants		Out-Migrants		Net-Migrants		Total[b]
	n	%[a]	n	%[a]	n	%[a]	n
HIV-positive							
2006	407	2.7%	446	2.9%	-39	-0.3%	15,269
2007	367	2.4%	413	2.7%	-46	-0.3%	15,474
2008	415	2.7%	1,099	7.0%	-684	-4.4%	15,643
2009	447	2.9%	1,099	7.2%	-652	-4.3%	15,214
2010	548	3.7%	1,164	7.9%	-616	-4.2%	14,771
2011	706	4.9%	848	5.9%	-142	-1.0%	14,331
2012	802	5.6%	941	6.6%	-139	-1.0%	14,355
2013	951	6.6%	1,096	7.6%	-145	-1.0%	14,447
HIV-negative							
2006	4,684	9.7%	5,254	10.9%	-570	-1.2%	48,308
2007	4,081	8.7%	5,593	12.0%	-1,512	-3.2%	46,660
2008	4,463	10.1%	3,503	7.9%	960	2.2%	44,109
2009	4,412	10.0%	4,332	9.8%	80	0.2%	44,051
2010	4,987	11.6%	4,404	10.2%	583	1.4%	43,167
2011	5,958	13.9%	4,034	9.4%	1,924	4.5%	42,843
2012	5,264	12.0%	3,900	8.9%	1,364	3.1%	43,849
2013	5,054	11.4%	4,233	9.6%	821	1.9%	44,244

Abbreviation: MSM, men who have sex with men

[a] percentage is out of total HIV-positive or HIV-negative respectively

[b] Total HIV-positive and HIV-negative population size estimate accounts for migration, HIV seroconversion, death during past year and unrecognized HIV

Table 2.3: In-, out- and net-migration estimates for white MSM in San Francisco by HIV serostatus, 2006-2013.

	In-Migrants		Out-Migrants		Net-Migrants		Total[b]
	n	%[a]	n	%[a]	n	%[a]	n
HIV-positive							
2006	177	1.9%	318	3.4%	-141	-1.5%	9,264
2007	148	1.6%	300	3.2%	-152	-1.6%	9,242
2008	133	1.4%	194	2.1%	-61	-0.7%	9,187
2009	149	1.6%	214	2.3%	-65	-0.7%	9,235
2010	168	1.8%	233	2.5%	-65	-0.7%	9,243
2011	276	3.0%	406	4.4%	-130	-1.4%	9,240
2012	354	3.9%	484	5.3%	-130	-1.4%	9,199
2013	469	5.1%	597	6.5%	-128	-1.4%	9,159
HIV-negative							
2006	2,771	10.8%	2,887	11.3%	-116	-0.5%	25,640
2007	2,704	10.8%	3,213	12.9%	-509	-2.0%	24,922
2008	2,957	12.4%	2,313	9.7%	644	2.7%	23,831
2009	2,779	11.6%	2,745	11.5%	34	0.1%	23,923
2010	2,684	11.4%	2,697	11.5%	-13	-0.1%	23,448
2011	3,841	16.7%	2,731	11.9%	1,110	4.8%	22,946
2012	3,260	13.8%	2,599	11.0%	661	2.8%	23,548
2013	3,137	13.2%	2,713	11.4%	424	1.8%	23,710

Abbreviation: MSM, men who have sex with men

[a] percentage is out of total HIV-positive or HIV-negative respectively

[b] Total HIV-positive and HIV-negative population size estimate accounts for migration, HIV seroconversion, death during past year and unrecognized HIV

Table 2.4: In-, out- and net-migration estimates for black MSM in San Francisco by HIV serostatus, 2006-2013.

	In-Migrants		Out-Migrants		Net-Migrants		Total[b]
	n	%[a]	n	%[a]	n	%[a]	n
HIV-positive							
2006	85	4.3%	279	14.2%	-194	-9.9%	1,968
2007	125	7.0%	294	16.4%	-169	-9.4%	1,794
2008	117	7.2%	192	11.8%	-75	-4.6%	1,632
2009	85	5.4%	153	9.8%	-68	-4.3%	1,572
2010	158	10.4%	223	14.6%	-65	-4.3%	1,525
2011	98	6.6%	129	8.8%	-31	-2.1%	1,471
2012	142	9.8%	173	11.9%	-31	-2.1%	1,452
2013	115	8.0%	145	10.1%	-30	-2.1%	1,436
HIV-negative							
2006	340	12.6%	67	2.5%	273	10.1%	2,705
2007	292	10.3%	0	0.0%	292	10.3%	2,822
2008	176	5.8%	124	4.1%	52	1.7%	3,003
2009	140	4.8%	135	4.6%	5	0.2%	2,926
2010	286	10.2%	86	3.1%	200	7.2%	2,797
2011	196	6.8%	157	5.4%	39	1.4%	2,884
2012	178	6.3%	0	0.0%	178	6.3%	2,804
2013	92	3.2%	151	5.3%	-59	-2.0%	2,879

Abbreviation: MSM, men who have sex with men

[a] percentage is out of total HIV-positive or HIV-negative respectively

[b] Total HIV-positive and HIV-negative population size estimate accounts for migration, HIV seroconversion, death during past year and unrecognized HIV

Table 2.5: Total population size estimates for all MSM, white MSM and black MSM stratified by HIV serostatus in San Francisco, 2006-2014.

	All MSM n (range[a])	WMSM n (range[a])	BMSM n (range[a])
All			
2006	63,577 (57,338-69804)	34,904 (31,494-38,338)	4,673 (3,761-5,589)
2007	62,134 (52,229-72,024)	34,164 (28,904-39,410)	4,615 (3,482-5,697)
2008	59,752 (47,303-72,129)	33,018 (26,331-39,680)	4,635 (3,369-5,816)
2009	59,264 (45,141-73,307)	33,158 (25,538-40,784)	4,497 (3,105-5,762)
2010	57,938 (42,009-73,867)	32,691 (24,158-41,232)	4,322 (2,825-5,659)
2011	57,174 (39,229-74,960)	32,186 (22,841-41,508)	4,355 (2,712-5,787)
2012	58,204 (38,414-77,856)	32,747 (22,225-43,200)	4,256 (2,520-5,748)
2013	58,691 (37,391-79,716)	32,869 (21,487-44,200)	4,315 (2,527-5,837)
2014	58,605 (35,923-81,148)	32,705 (20,508-44,914)	4,119 (2,246-5,694)
HIV-positive			
2006	15,269 (14,395-16,250)	9,264 (8,787-9,796)	1,968 (1,674-2,382)
2007	15,474 (14,596-16,464)	9,242 (8,775-9,758)	1,794 (1,551-2,126)
2008	15,643 (14,759-16,637)	9,187 (8,728-9,697)	1,632 (1,428-1,903)
2009	15,214 (14,396-16,136)	9,235 (8,782-9,739)	1,572 (1,386-1,817)
2010	14,771 (14,009-15,622)	9,243 (8,790-9,742)	1,525 (1,352-1,748)
2011	14,331 (13,623-15,122)	9,240 (8,852-9,736)	1,471 (1,311-1,676)
2012	14,355 (13,648-15,131)	9,199 (8,941-9,687)	1,452 (1,297-1,651)
2013	14,447 (13,869-15,225)	9,159 (9,031-9,639)	1,436 (1,285-1,625)
2014	14,452 (14,018-15,219)	9,066 (9,066-9,535)	1,421 (1,275-1,605)
HIV-negative			
2006	48,308 (41,968-54,601)	25,640 (22,187-29,105)	2,705 (1,704-3,671)
2007	46,660 (36,721-56,562)	24,922 (19,649-30,189)	2,822 (1,638-3,925)
2008	44,109 (31,635-56,495)	23,831 (17,126-30,513)	3,003 (1,704-4,193)
2009	44,051 (29,858-58,125)	23,923 (16,292-31,565)	2,926 (1,505-4,201)
2010	43,167 (27,205-59,099)	23,448 (14,899-32,001)	2,797 (1,274-4,142)
2011	42,843 (24,880-60,619)	22,946 (13,580-32,270)	2,884 (1,224-4,322)
2012	43,849 (24,058-63,491)	23,548 (12,981-33,982)	2,804 (1,053-4,299)
2013	44,244 (22,885-65,282)	23,710 (12,268-35,005)	2,879 (1,078-4,405)
2014	44,154 (21,434-66,698)	23,639 (11,342-35,774)	2,697 (813-4,275)

Abbreviations: MSM, men who have sex with men; WMSM, white men who have sex with men; BMSM, black men who have sex with men

[a]Range calculated from 2.5% and 97.5% of the uncertainty analysis distributions

Table 2.6: HIV prevalence comparisons between external NHBS source and model output.

	2007	2011	2014
MSM NHBS	20.8% (17.4%-24.3%)	22.4% (18.8%-26.1%)	24.3% (20.2%-28.5%)
MSM model	24.9% (21.2%-29.9%)	25.1% (19.0%-36.7%)	24.7% (17.8%-40.4%)
WMSM NHBS	21.1% (16.4%-25.7%)	24.7% (19.9%-29.6%)	26.2% (20.5%-31.9%)
WMSM model	27.1% (23.2%-32.2%)	28.7% (22.2%-40.6%)	27.7% (20.4%-44.7%)
BMSM NHBS	29.5% (15.8%-43.3%)	25.8% (10.4%-41.2%)	28.0% (10.4%-45.6%)
BMSM model	38.9% (30.0%-53.9%)	33.8% (24.8%-55.1%)	34.5% (24.5%-64.0%)

Abbreviations: MSM, men who have sex with men; WMSM, white men who have sex with men; BMSM, black men who have sex with men; NHBS, National HIV Behavioral Surveillance

FIGURES:

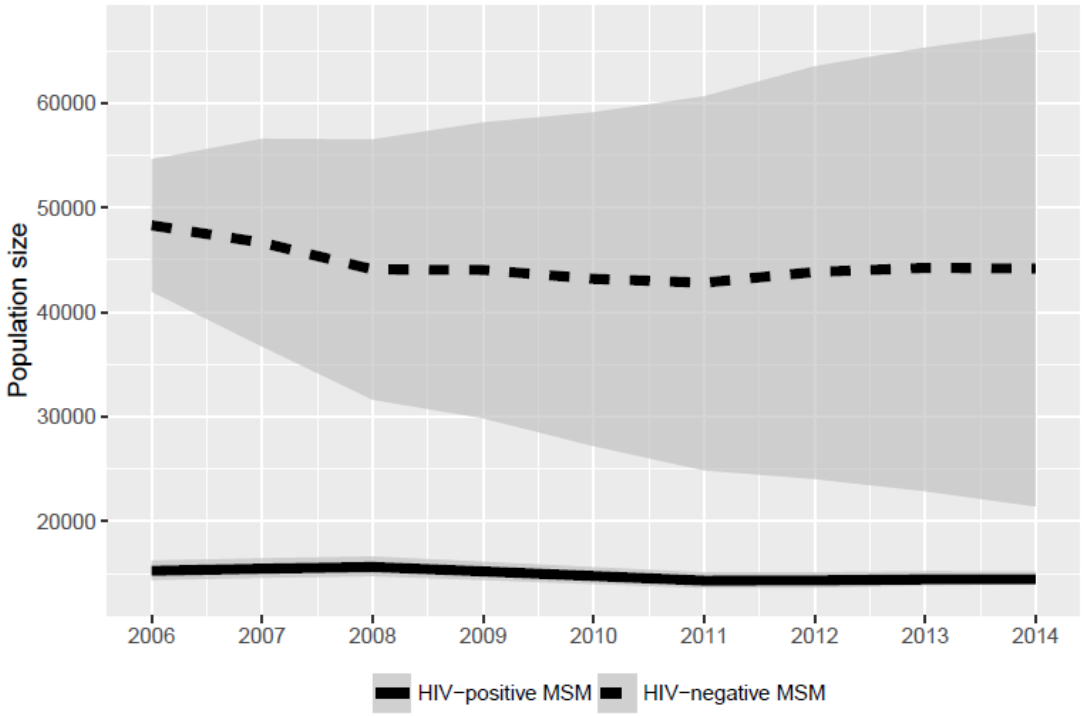

Figure 2.1: HIV-positive and HIV-negative MSM population size, San Francisco, 2006-2014.

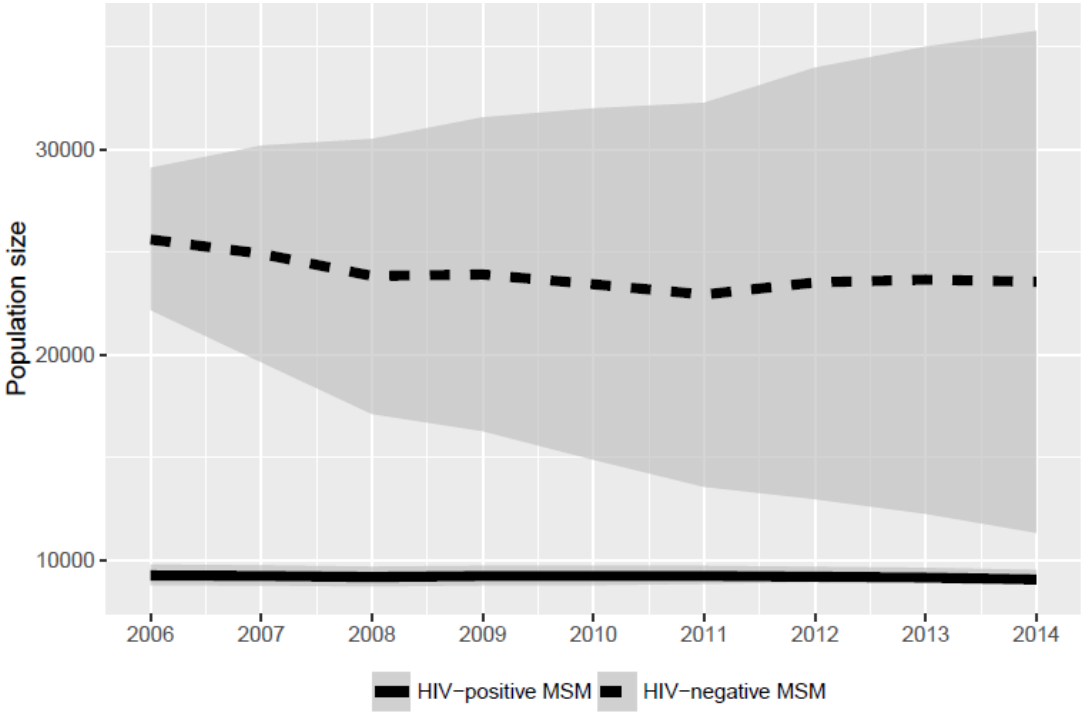

Figure 2.2: HIV-positive and HIV-negative white MSM population size, San Francisco, 2006-2014.

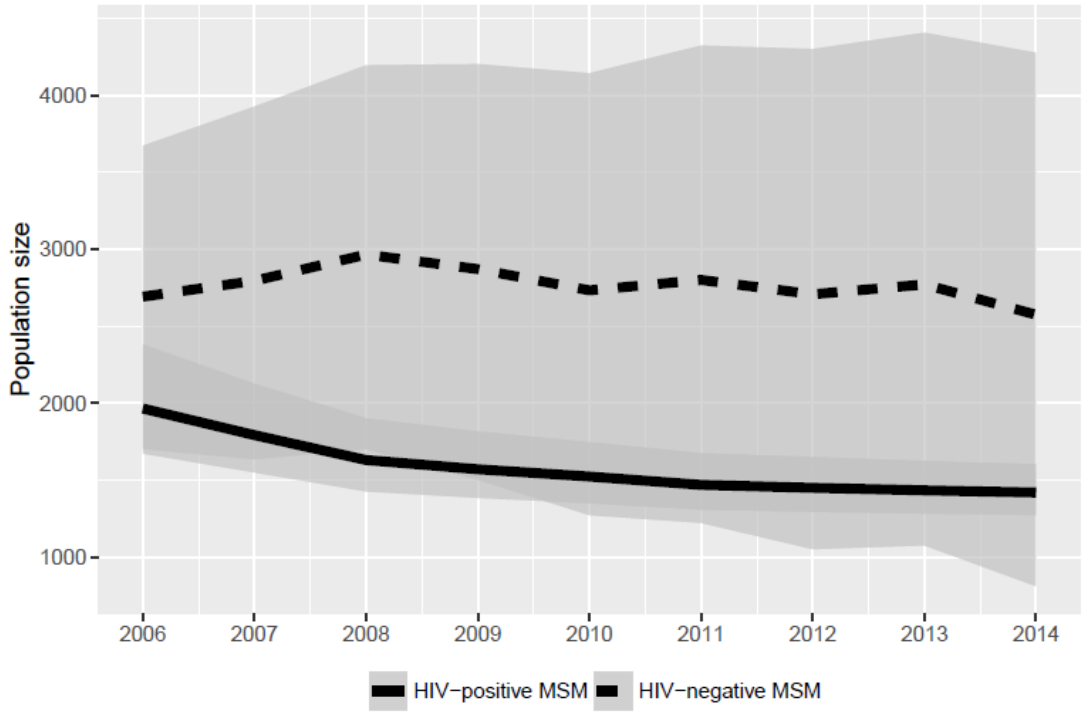

Figure 2.3: HIV-positive and HIV-negative black MSM population size, San Francisco, 2006-2014.

REFERENCES:

1. Kitchin R. Sexing the city: The sexual production of non-heterosexual space in Belfast, Manchester and San Francisco. *City*. 2002;6:205-18.

2. Howe AC. Queer pilgrimage: The San Francisco homeland and identity tourism. *Cultural Anthropology*. 2001;16:35-61.

3. Weston K. Get thee to a big city: Sexual imaginary and the great gay migration. *GLQ: A Journal of Lesbian and Gay Studies*. 1995;2:253-77.

4. Hindle, P. Gay communities and gay space in the city. *The Margins of the City: Gay Men's Urban Lives.*1994:7-25.

5. Winkelstein W, Lyman DM, Padian N, et al. Sexual practices and risk of infection by the human immunodeficiency virus: the San Francisco Men's Health Study. *JAMA*. 1987;257:321-5.

6. HIV Epidemiology Section, San Francisco Department of Public Health. HIV Epidemiology Annual Report 2014. San Francisco: San Francisco Department of Public Health August 2015; pp. 1-80.

7. Raymond HF, Chen YH, Ick T, et al. A new trend in the HIV epidemic among men who have sex with men, San Francisco, 2004–2011. *J Acquir Immune Defic Syndr*. 2013;62: 584-589.

8. Raymond HF, Chen YH, McFarland W. Estimating incidence of HIV infection among men who have sex with men, San Francisco, 2004–2014. *AIDS Behav*. 2016;20:17-21.

9. US Census Bureau. "QuickFacts, San Francisco County, California*"* 2015. Available at: https://www.census.gov/quickfacts/table/PST045215/06075,00

10. Palamino, J. "How the fade of S.F.'s middle class affects a slice of the city" December 7 2015. *SF Chronicle.* Available at: http://www.sfchronicle.com/bayarea/article/S-F-s-vanishing-middle-class-Dramatic-growth-6679627.php

11. HIV Epidemiology Section, San Francisco Department of Public Health. HIV Epidemiology Annual Report 2004. San Francisco: San Francisco Department of Public Health August 2005; pp. 1-67.

12. State of California, Department of Public Health. Requirements for HIV case and CD4 test result reporting. California Health and Safety Code, Sections 121022-121023. Available at: http://www.leginfo.ca.gov/cgibin/displaycode?section=hsc&group=120001-121000&file=120975-121023.

13. Nakashima AK, Fleming PL. HIV/AIDS surveillance in the United States,1981–2001. *J Acquir Immune Defic Syndr.* 2003; 32(Suppl 1):S68–85.

14. Hsu LC, Chen M, Kali J, et al. Assessing receipt of medical care and disparity among persons with HIV/AIDS in San Francisco, 2006–2007. *AIDS Care*. 2011;23:383–392.

15. Baunach DM. Changing same-sex marriage attitudes in America from 1988 through 2010. *Public Opin Q*. 2012;76:364-78.

16. Keleher A, Smith ER. Growing support for gay and lesbian equality since 1990. *J Homosex*. 2012;59:1307-26.

17. Anderson, T. "Cost of average San Francisco rent actually fell (a little) last month" Decemeber 11, 2015. *SF Chronicle*. Available at: http://www.sfchronicle.com/bayarea/article/San-Francisco-rent-cost-drop-rental-6690357.php

18. Black D, Gates G, Sanders S, Taylor L. Why do gay men live in San Francisco?. *J Urban Econ.* 2002;51:54-76.

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

20. Xia Q, Braunstein SL, Wiewel EW, et al. Persons Living with HIV in the United States: Fewer Than We Thought. *J Acquir Immune Defic Syndr*. 2016;72: 552-557.

21. Buchacz K, Chen MJ, Parisi MK, et al. Using HIV surveillance registry data to re-link persons to care: the RSVP Project in San Francisco. *PloS One*. 2015;10:1-14.

22. Udeagu CC, Webster TR, Bocour A, et al. Lost or just not following up: public health effort to re-engage HIV-infected persons lost to follow-up into HIV medical care. *AIDS*. 2013;27:2271-9.

23. Coffee M, Lurie MN, Garnett GP. Modelling the impact of migration on the HIV epidemic in South Africa. *AIDS*. 2007;21:343-50.

24. Brockerhoff M, Biddlecom AE. Migration, sexual behavior and the risk of HIV in Kenya. *Int Migr Rev.*1999;33:833-56.

25. Zuma K, Gouws E, Williams B, Lurie M. Risk factors for HIV infection among women in Carletonville, South Africa: migration, demography and sexually transmitted diseases. *Int J STD AIDS.* 2003;14:814-7.

26. Welz T, Hosegood V, Jaffar S, et al. Continued very high prevalence of HIV infection in rural KwaZulu-Natal, South Africa: a population-based longitudinal study. *AIDS*. 2007;21:1467-72.

27. Lama TT, Sudhinaraset M, McFarland W, Raymond HF. Migration and HIV Risk Among Men Who Have Sex With Men, San Francisco, 2011. *AIDS Educ Prev.* 2015;27:538-46.

28. Muthulingam D, Chin J, Hsu L, et al. Disparities in engagement in care and viral suppression among persons with HIV. *J Acquir Immune Defic Syndr*. 2013;63:112-9.

29. Leaver CA, Bargh G, Dunn JR, Hwang SW. The effects of housing status on health-related outcomes in people living with HIV: a systematic review of the literature. *AIDS Behav*. 2007;11:85-100.

Chapter 3

Knowledge of partner's HIV serostatus and pre-exposure prophylaxis use and condomless anal sex among HIV-positive San Francisco men who have sex with men

ABSTRACT

The objective of this chapter is to determine if partnership type, defined by partner's HIV serostatus and pre-exposure prophylaxis (PrEP) use, is associated with condomless anal sex (CAS) and insertive condomless anal sex (ICAS) among men who have sex with men (MSM) living with HIV in San Francisco. Data from the Medical Monitoring Project (MMP), an annual cross-sectional sample of adults living with HIV in San Francisco, were used. HIV positive participants reported the HIV status and PrEP use of their partners. Data from up to five anal sex partners were collected. A four-level partnership type exposure variable was created: seroconcordant, potentially discordant, discordant with no PrEP, and discordant with PrEP. The two outcomes of interest were CAS and ICAS during the past 12 months. To account for correlation of multiple observations per participant, generalized estimating equations (GEE) were used to calculate adjusted prevalence ratios and 95% confidence intervals of CAS and ICAS. GEE models were stratified by HIV viral suppression. Condom use during any anal sex and insertive anal sex varied based on partnership type and viral suppression of the MMP participant. There was a higher prevalence of CAS and ICAS in partnerships that were either seroconcordant or serodiscordant with PrEP compared to partnerships that were serodiscordant without PrEP. There was evidence that men in this sample were adapting their condom use based on their sexual partner's HIV status and PrEP use, and their own viral suppression status. Discordant partnerships with PrEP had an increased adjusted prevalence of CAS and ICAS.

BACKGROUND

New HIV prevention tools have recently emerged, including treatment as prevention and pre-exposure prophylaxis (PrEP). In 2011, HPTN 052 results showed that early antiretroviral treatment (ART) reduced HIV transmission by 96% in a study of serodiscordant heterosexual couples [1]. In 2012, national treatment guidelines in the U.S. were changed, recommending ART for all adults living with HIV, regardless of immune status, due to the individual-level benefits of ART (i.e. increased survival, decreased morbidity and fewer opportunistic infections) and population-level benefits (i.e. reduced likelihood of sexual transmission) [2]. In 2010, the iPrEx trial showed that a daily dose of tenofovir disoproxil fumerate (TDF) and emtricitabine (FTC) for HIV-negative persons in HIV serodiscordant relationships could decrease the risk of HIV transmission by 44% [3]. In 2012, the FDA approved pre-exposure prophylaxis (PrEP) with FTC/TDF for preventing HIV acquisition [4].

There is concern that uptake of PrEP and treatment as prevention could result in risk compensation, specifically decreased use of condoms [5]. A qualitative study among men who have sex with men (MSM) about perceptions of PrEP suggested that MSM would reduce their condom use while taking PrEP [6-7]. No increase in condomless anal sex was observed among MSM in randomized trials of pre-exposure prophylaxis or the iPrEx open label extension [8-10]. In contrast, among a subset of MSM who initiated PrEP at Kaiser Permanente Medical Center in San Francisco from 2012 to 2015, 41% reported decreased condom use six months after initiating PrEP [11], and in an open label randomized trial among MSM in England, the immediate PrEP group had a significantly higher odds of receptive condomless anal sex with ten or more partners compared to the deferred PrEP group [12]. In addition, having an undetectable HIV viral load has been associated with increased condomless anal sex in MSM [13-15].

Much of the previous research on PrEP and condom use has come from randomized controlled trials. However, individuals who participate in experimental studies are generally not representative of the sexually active MSM population. Additionally, in the iPrEx trial, participants knew that they might have been randomized to receive a placebo; as a result, it is not surprising that no increase in condomless sex was observed. Observational data are needed to describe which prevention strategies MSM are utilizing and how the prevention strategy employed may be related to condom use. Many studies focusing on prevention strategies or seroadaptive behaviors, especially PrEP, have been comprised of HIV-negative individuals. In this chapter, I examine whether partnership type (i.e. partner's HIV serostatus and PrEP use) is associated with condomless anal sex (CAS) and insertive condomless anal sex (ICAS) in men who have sex with men living with HIV.

METHODS

Study Population

The Medical Monitoring Project (MMP) is an annual survey that assesses health care utilization, clinical outcomes and HIV-related risk behaviors among persons living with HIV in 23 sites in the United States, including 16 states, six cities and one U.S. territory. San Francisco is one MMP site and data from MMP cycles in San Francisco were used for this analysis. Due to the fact that information about pre-exposure prophylaxis and HIV status at the sexual partnership level was not collected prior to 2014, and because of small sample sizes, data from the 2014 and 2015 cycles of MMP in San Francisco were combined. The 2014 MMP sample was drawn using three-stage sampling; details of the sampling approach have previously been described [16-18]. Briefly, after San Francisco was selected as one of 23 national MMP sites, a sample of HIV care facilities in San Francisco was selected and 400 adults who received HIV care at the sampled facilities between January 1-April 30, 2014 were randomly selected for the 2014 MMP cycle. In 2015, a two-stage sampling process was implemented. After San Francisco was selected as a MMP site, adults living with HIV were sampled directly from the national case-based HIV registry. Persons were eligible for sampling in 2015 MMP if they were 18 years or older, not known to have died, and had a most recent residential address recorded in the National HIV Surveillance System in San Francisco as of December 31, 2014. Four hundred adults living with HIV and presumed to be living in San Francisco were randomly selected for the 2015 MMP cycle in San Francisco.

Data Collection

Face-to-face or telephone interviews were conducted from August 2014 through April 2016. Men who reported anal sex with at least one male partner (MSM) in the 12 months prior to interview were included in this analysis; each participant could report up to five most recent sexual partners in the past 12 months. Only male-male anal sex partnerships were included in this analysis. In addition, a medical record abstraction was conducted at the sampled HIV care provider (in 2014 MMP) or the self-reported primary place of HIV care (in 2015 MMP) for each participant interviewed. Trained staff gathered information from the medical record on demographic variables, HIV diagnosis date, prescription of antiretroviral therapy, and HIV laboratory test results. Interview data for each participant were linked to the medical record abstraction (MRA) data.

Measures

Participants reported the HIV status of their five most recent partners (unknown, HIV-negative or HIV-positive) and PrEP use at last sex for all HIV-negative partners. These variables were used to create a four-level exposure for partnership type: seroconcordant (both the participant and the partner were HIV-positive), potentially discordant (the participant did not know the HIV status of the partner), discordant and no PrEP (the participant reported the partner was HIV-negative and was not known to be taking PrEP the last time they had anal sex), and discordant with PrEP (the participant reported the partner was HIV-negative and

was taking PrEP the last time they had anal sex). PrEP use was only collected for HIV-negative partners. The two outcomes of interest were any reported condomless anal sex (CAS) and any insertive (from the perspective of the MMP participant) condomless anal sex (ICAS) during the past 12 months. If the participant indicated during the interview that a condom was not used "every time" he engaged in anal/insertive anal sex with a male partner, then he was coded as engaging in CAS/ICAS with that partner.

Covariates included MMP participant factors, such as age, race/ethnicity, education, homelessness, foreign born status, current ART use, drug or alcohol use before/during sex, total number of sexual partners in the prior 12 months, and sustained viral suppression, which was defined as having all HIV viral load test results undetectable or <200 copies/ml during the prior 12 months. Other covariates included partnership factors, such as disclosure of HIV status of the participant to his partner, participant's commitment level to his partner and number of anal sex acts during past year with that partner. The anal sex partner's age and race/ethnicity were also included as covariates. All variables were self-reported during interview, except sustained viral suppression, which was derived from the medical record abstraction data.

Data Analysis

Missing interview data on MMP participant's race/ethnicity and date of HIV diagnosis were substituted using data from the medical record abstraction (MRA) and the HIV surveillance registry. There were no missing data for exposure or for either the CAS or ICAS outcome, but there were missing data for disclosure of HIV status to partner, partner commitment level, partner's race and age, and number of sex acts in the partnership over the past 12 months. For these variables, an additional category was created for "missing", so all observations could be used in models.

Demographic characteristics of participants in the two MMP cycles were compared by chi-square tests. To account for correlation of multiple observations per participant, generalized estimating equations (GEE) with robust standard errors were used to calculate unadjusted and adjusted prevalence ratios (PR) and 95% confidence intervals (CIs) of CAS and ICAS. For GEE models, a Poisson with log-link distribution and exchangeable working correlation structure was specified. All covariates described above were included in the adjusted models, having been shown to be risk factors for CAS and ICAS in prior studies; MMP cycle year was also included in the models. Viral suppression was determined a priori to be a potential effect modifier of the association between partnership type and CAS/ICAS, so GEE models were stratified by this variable. Because the outcome of ICAS could reflect a preference in sexual positioning, an additional GEE analysis restricted to partnerships that involved insertive (from the perspective of the MMP participant) anal sex was performed.

Ethical Considerations

This research was reviewed and approved by the Committee for Protection of Human Subjects at University of California, Berkeley (Protocol Number 2015-09-7927).

RESULTS

There were 218 sexually active MSM, reporting 683 male-male sexual partnerships included in the analysis. The median age of participants was 50 years (range: 24-74). The majority of participants were white (62%), diagnosed with HIV ten or more years before interview (68%), had an education beyond high school (87%), reported being on antiretroviral treatment (97%) and were durably virally suppressed (76%) (Table 3.1). The median reported number of male sexual partners during the prior 12 months was four (range: 1-960). Of the 218 MSM, 185 (85%) had CAS with at least one partner in the prior 12 months and 147 (67%) had ICAS with at least one partner in the prior 12 months. There were some differences between MSM in the two cycles of MMP. MSM in the 2015 cycle of MMP were more likely to be 30-39 years of age, homeless, and to use alcohol before sex and were less likely to have beyond high school education than were MSM in the 2014 MMP cycle.

Of the 683 partnerships, 357 (52%) were seroconcordant, 157 (23%) potentially discordant, 112 (16%) discordant with no PrEP and 57 (8%) discordant with PrEP. In the majority of partnerships (88%), the MMP participant had disclosed his HIV status, was not at all committed to the partner (67%), the partner was white (56%), and there was CAS (76%); the mean number of sex acts in each partnership during the past 12 months was 13 (Table 3.2). Of all the partnerships, 49% had ICAS during the previous 12 months, and in partnerships involving insertive anal sex (n=427), 79% had ICAS. Partnership characteristics differed by partnership type. Disclosure of HIV status was much less frequent in potentially discordant partnerships, and the partner was more likely to be younger in the discordant with PrEP partnerships. CAS was reported most frequently (94%) in the seroconcordant partnerships, but was also reported in most discordant with PrEP partnerships (86%). Likewise, ICAS was reported most frequently in seroconcordant partnerships (63%) and in partnerships that were discordant with PrEP (61%).

Table 3.3 describes the outcomes of interest (CAS and ICAS), stratified by partnership type and viral suppression of the MMP participant. Outcomes varied by both partnership type and by sustained viral suppression. There was a general pattern of the highest level of CAS and ICAS among seroconcordant partnerships, followed by partnerships that were serodiscordant with PrEP for both durably virally suppressed and not durably virally suppressed participants. However, among those participants who were not virally suppressed, CAS and ICAS were reported more often in partnerships involving a discordant partner not on PrEP than for potentially discordant partnerships. For participants who were virally suppressed, CAS and ICAS were reported more often in potentially discordant partnerships compared to discordant and no PrEP partnerships (Table 3). Of note, there were 33 partnerships (5% of all partnerships) that used no apparent HIV prevention strategy, including 17 potentially discordant partnerships and 16 discordant without PrEP partnerships in which there was condomless anal sex and the MMP participant was not virally suppressed. Of the 218 MSM, there were 17 (8%) who reported not using any apparent HIV prevention strategy.

There were 501 partnerships involving a participant who was virally suppressed. After adjustment for covariates, the PR for CAS comparing a seroconcordant partnership to a discordant not on PrEP partnership (reference) was 1.81 (95% CI: 1.47-2.23), (Table 3.4). The adjusted PR for CAS comparing a serodiscordant with PrEP partnership versus a discordant not on PrEP partnership (reference) was 1.50 (95% CI: 1.19-1.89), and no statistically significant difference in CAS was found when comparing potentially discordant partnerships to discordant no PrEP partnerships.

Among the partnerships involving a participant who was virally suppressed, the adjusted PR for ICAS comparing a seroconcordant partnership to a discordant not on PrEP partnership (reference) was 3.25 (95% CI: 2.18-4.87), (Table 3.4). The adjusted PR for ICAS comparing a serodiscordant with PrEP partnership to a discordant not on PrEP partnership (reference) was 2.87 (95% CI: 1.91-4.32). The adjusted PR for ICAS comparing potentially discordant partnerships to discordant no PrEP partnerships was 2.29 (95% CI: 1.32-3.97).

There were 182 partnerships that involved a participant who was not virally suppressed. After adjustment for covariates, the adjusted PR for CAS comparing a seroconcordant partnership to a discordant not on PrEP partnership (reference) was 1.85 (95% CI: 1.20-2.85), (Table 3.4). The adjusted PR for CAS comparing a serodiscordant with PrEP partnership to a discordant not on PrEP partnership (reference) was 1.85 (95% CI: 1.19-2.87), and no difference in CAS was found comparing potentially discordant partnerships to discordant no PrEP partnerships.

Among the partnerships that involved a participant who was not virally suppressed, the adjusted PR for ICAS comparing a seroconcordant partnership to a discordant not on PrEP partnership (reference) was 2.78 (95% CI: 1.23-6.30), (Table 3.4). The adjusted PR for ICAS comparing a serodiscordant with PrEP partnership to a discordant not on PrEP partnership (reference) was 3.50 (95% CI: 1.62-7.57), and no difference in ICAS was found comparing potentially discordant partnerships to discordant no PrEP partnerships.

Last, in order to determine if partnership type was associated with ICAS while accounting for sexual position preference, GEE analysis was restricted to ICAS among only those partnerships that involved insertive anal sex during the past 12 months (Table 3.5). Among the 309 partnerships involving insertive anal sex with a participant who was virally suppressed, the adjusted PR for ICAS comparing a seroconcordant partnership to a discordant not on PrEP partnership (reference) was 2.49 (95% CI: 1.76-3.54), (Table 3.5). The adjusted PR for ICAS comparing a discordant with PrEP partnership to a discordant not on PrEP partnership (reference) was 2.11 (95% CI: 1.46-3.07). No difference was detected in the frequency of ICAS when comparing potentially discordant partnerships to discordant no PrEP partnerships. Among the 118 partnerships that involved a participant who was not virally suppressed and insertive anal sex in the past 12 months, no differences were detected in ICAS comparing all the partnerships types to discordant not on PrEP partnerships.

Perceived HIV viral load was collected only in the 2014 MMP interview. As a result, HIV viral load test results from the MRA were used because they were available in both cycles. To determine the possible effect of this limitation, an additional GEE analysis using only

perceived HIV viral load data from the 2014 MMP dataset was conducted; the results of this analysis were similar to those reported above, but with wider confidence intervals due to the smaller sample size (Table A.1).

DISCUSSION

In this sample of MSM living with HIV in San Francisco, there was evidence that condom use varied not only with the partner's HIV status and PrEP use, but also by the participant's own viral suppression status. I found that, overall, there was a higher prevalence of condomless anal sex and insertive condomless anal sex in partnerships that were either seroconcordant or serodiscordant with PrEP, compared to serodiscordant partnerships without PrEP. I also found that viral suppression modified the association between partnership type and CAS/ICAS. For instance, among all partnerships involving a virally suppressed MMP participant, the prevalence of ICAS was roughly 2.3 times higher in potentially discordant partnerships compared to serodiscordant partnerships without PrEP. In partnerships involving an MMP participant who was not virally suppressed, there was no statistically significant difference in the prevalence of ICAS (aPR: 1.2).

Other research has pointed to similar findings. Otis et al. found that many HIV-negative MSM tailored their condom use decisions based on their partner's HIV status, such that they were more likely to use condoms with HIV-positive or unknown HIV status partners [19]. Other strategies for deciding a HIV prevention strategy were reported as well, such as serosorting (i.e. having sex only with other presumed HIV-negative men); seropositioning (i.e. having insertive anal sex only if their partner was HIV-positive); and consideration of HIV-positive partner's viral suppression to determine condom use [19]. Newcomb et al. found that MSM using mobile geosocial dating applications frequently had encountered men who had disclosed use of biomedical prevention strategies on their profile (e.g. PrEP in HIV-negative men and undetectable HIV viral load in HIV-positive men), and when the men in the survey met up with these potential sex partners, the majority reported engaging in condomless anal sex [20].

Although I found that serodiscordant partnerships with PrEP had a high prevalence of condomless anal sex, current recommendations call for individuals on PrEP to use condoms during sex [21]. I was not able to assess temporality between PrEP use and condomless anal sex because the data were cross-sectional. It is possible that the HIV-negative partners using PrEP in this dataset were engaging in condomless anal sex before they initiated PrEP. Another possibility is that condom use decreased after PrEP initiation among the HIV-negative partners using PrEP, or some combination of both scenarios.

In addition to the findings that condom use varied based on sex partner's PrEP use and viral suppression of the MMP participant, I found that serosorting was a risk reduction strategy being used by MSM with HIV in San Francisco. Given that the prevalence of HIV in MSM in San Francisco is approximately 25% [22], if sexual partners were chosen at random with respect to HIV status, one would expect 25% of partnerships to be seroconcordant; in fact, nearly twice as many partnerships were seroconcordant (52%). This finding suggests that

MSM living with HIV in San Francisco are likely adopting serosorting as a prevention strategy. Serosorting as a strategy to reduce transmission of HIV among MSM in San Francisco has been previously documented [23-25].

This analysis is subject to several limitations. Because both the exposure and outcome were self-reported, information bias is a concern. Specifically, with reported sexual behaviors, there is the concern that social-desirability bias may have lead to under-reporting of condomless anal sex. Reporting of either outcome differentially with respect to exposure could occur if participants tended to accurately report condomless anal sex with HIV-positive partners but under reported condomless sex with HIV-negative partners. This could result in bias either towards or away from the null because the outcome misclassification would be differential with respect to the exposure. However, the MMP protocol includes measures to mitigate social-desirability bias, such as using a standardized questionnaire, training interviewers to conduct the interview in a sensitive and cultural manner, and use of quality assurance approaches to ensure interviews are conducted exactly per protocol.

Another possible limitation was that data collected during the interview on most recent sexual partners in the prior 12 months included only up to five partners, while 37% of MSM in the sample reported more than five male partners in the previous 12 months. Additionally, even though perceived HIV viral load is thought to have more of an effect on sexual behaviors than actual HIV viral load, perceived HIV viral load was collected only in the 2014 MMP interview, whereas both cycles of MMP collected HIV viral load test results in the MRA. However, I ran an additional GEE analysis using only perceived HIV viral load data from the 2014 MMP dataset to determine the possible effect of this limitation and found similar results as the GEE models using both cycles of data and HIV viral load from the MRA. It has also been previously reported that there is good agreement between self-reported HIV viral load and the HIV viral load test results in the MRA [26] so it is unlikely that this limitation had much impact on the results. Last, this analysis was cross-sectional in nature, so temporality between the exposure (partnership type) and the outcomes (CAS and ICAS) cannot be assessed.

Despite these limitations, this analysis provides valuable information on seroadaptive strategies being employed among a sample of MSM living with HIV during a period of rapid uptake of PrEP in San Francisco. Much of the previous research on PrEP and sexual behaviors has come from randomized trials involving HIV-negative PrEP users or open-label extensions of such trials; this is one of the first analyses using observational data to describe the association between sexual partner's PrEP use and condom use among HIV-positive individuals. Individuals who participate in randomized controlled trials are likely not representative of the population of HIV-negative MSM who are using PrEP and having sex with HIV-positive men; one major strength of this analysis is that observational data were used to understand condom use behaviors of the HIV-positive MSM community.

Although the number of new HIV infections in San Francisco has decreased substantially since 2012, transmission still occurs, with 209 new HIV diagnoses among MSM documented in 2015 [27]. If MSM are using seroadaptive strategies to reduce HIV transmission,

suboptimal adherence to ART or PrEP, together with inconsistent condom use, could provide a false sense of security. Although I found that only 5% of the partnerships reported no apparent HIV transmission prevention strategy, it is possible that even this low level of unsafe behavior, could be enough to sustain transmission of HIV in the San Francisco MSM community. Further, the prevention strategies reported in the remaining 95% of partnerships may have been misclassified due to social desirability bias (i.e. the participant reported 100% condom use while condoms were actually used inconsistently), and the prevention strategies employed by partnerships may not have been 100% effective (i.e. condom failure due to breakage or slippage). Less than perfect protection against transmission of HIV in partnerships that did report employing seroadaptive strategies can also contribute to sustained transmission of HIV.

Prevention messages and education need to be targeted all individuals, including individuals in serodiscordant partnerships using no apparent HIV prevention strategy (i.e. not using condoms consistently, not on PrEP and the HIV-positive partner is not virally suppressed) in order to achieve San Francisco's goal of zero HIV transmission by 2030 [28]. More research is needed to monitor condom use and use of seroadaptive HIV prevention strategies, particularly uptake of PrEP, as more MSM adopt new HIV prevention strategies. Research has shown racial disparities in PrEP uptake [29-30] and in acquisition of HIV [27, 31]. In order to achieve the goal of zero HIV transmission, these disparities must be addressed and public health programs need to ensure these persons at greatest risk of HIV acquisition are targeted for and have access to new prevention interventions and strategies.

Diagnoses of other sexually transmitted infections (STIs) have increased among MSM nationally and in San Francisco, and this increase has been particularly dramatic in San Francisco [32]. A recently published meta-analysis has determined that the incidence of STIs among MSM using PrEP is much higher than among MSM not using PrEP [33]. The meta-analysis reported incidence rate ratios of 45 for *Treponema pallidum* infection, 25 for *Neisseria gonorrhoeae* infection and 11 for *Chlamydia trachomatis* infection, comparing MSM on PrEP to MSM not taking PrEP [33]. It is not known whether PrEP is less effective in preventing HIV in persons co-infected with another STI, but such co-infections have been shown to increase transmission of HIV [34]. Concerns have been raised that the uptake of new biomedical HIV prevention strategies may not offset transmission of HIV at a population level because of decreases in condom use [12, 35]. To date, HIV seroconversion has not been documented among current PrEP users in San Francisco, but more information is needed on PrEP adherence because it has been shown that persons who seroconverted to HIV-positive in clinical PrEP trials had suboptimal adherence [3]. In this sample of sexually active HIV-positive MSM, those in discordant partnerships and using PrEP had an increased adjusted prevalence of CAS and ICAS. Whether or not decreased condom use or STIs could offset the protection of PrEP for transmission of HIV warrants further investigation.

TABLES

Table 3.1: Demographic and other characteristics of sexually active MSM, Medical Monitoring Project San Francisco, 2014-2015.

	Total	2014	2015	
	n (%)	n (%)	n (%)	p-value
Total	**218 (100%)**	**118 (100**	**100 (100%)**	
Age (years)				0.02
18-29	7 (3.2%)	5 (4.2%)	2 (2.0%)	
30-39	39 (17.9%)	13 (11.0%)	26 (26.0%)	
40-49	63 (28.9%)	33 (28.0%)	30 (30.0%)	
50+	109 (50.5%)	67 (56.8%)	42 (42.0%)	
Race/Ethnicity				0.88
White	134 (61.5%)	73 (61.9%)	61 (61.0%)	
African American	16 (7.3%)	10 (8.5%)	6 (6.0%)	
Latino	56 (25.7%)	29 (24.6%)	27 (27.0%)	
Other/Multiracial	12 (5.5%)	6 (5.1%)	6 (6.0%)	
Time diagnosed with HIV				0.33
<5 years	28 (12.8%)	15 (12.7%)	13 (13.0%)	
5-9 years	41 18.8%)	18 (15.3%)	23 (23.0%)	
≥10 years	149 (68.4%)	85 (72.0%)	64 (64.0%)	
Homeless	30 (13.8%)	11 (9.3%)	19 (19.0%)	0.04
Foreign born	44 (20.2%)	22 (18.6%)	22 (22.0%)	0.54
Education				0.10
Less than high school	5 (2.3%)	2 (1.7%)	3 (3.0%)	
High school or equivalent	23 (10.6%)	8 (6.8%)	15 (15.0%)	
Some college or higher	190 (87.2%)	108 (91.5%)	82 (82.0%)	
On ART[a]	211 (96.8%)	116 (98.3%)	95 (95.0%)	0.25
Sustained HIV viral suppression, past 12 months[b]	166 (76.2%)	95 (80.5%)	71 (71.0%)	0.10
Substance use before sex, past 12 months				
Alcohol	102 (46.8%)	44 (37.3%)	58 (58.0%)	<0.01
Non-injection drugs	98 (45.0%)	51 (43.2%)	47 (47.0%)	0.58
Injection drugs	32 (14.7%)	16 (13.6%)	16 (16.0%)	0.61
Number of male sex partners in past 12 months				0.90
1	68 (31.2%)	36 (30.5%)	32 (32.0%)	
2-5	69 (31.7%)	37 (31.4%)	32 (32.0%)	
6-10	26 (11.9%)	13 (11.0%)	13 (13.0%)	
>10	55 (25.2%)	32 (27.1%)	23 (23.0%)	

Abbreviations: MSM, men who have sex with men; ART, antiretroviral treatment
[a] self-reported
[b] from MRA

Table 3.2: Characteristics of the 683 male-male partnerships involving anal sex reported by 218 MSM, stratified by partnership type.

	Total	Sero-concordant	Potentially discordant	Discordant, no PrEP	Discordant, with PrEP
	n (%)	n (%)	n (%)	n (%)	n (%)
Total	**683 (100%)**	**357 (100%)**	**157 (100%)**	**112 (100%)**	**57 (100%)**
Disclosed HIV status to partner	590 (87.9%)	356 (99.7%)	68 (46.6%)	109 (98.2%)	57 (100%)
Commitment level					
Not at all committed	451 (66.6%)	219 (61.7%)	141 (92.2%)	48 (42.9%)	43 (75.4%)
Somewhat committed	115 (17.0%)	73 (20.6%)	8 (5.2%)	27 (24.1%)	7 (12.3%)
Very committed	56 (8.3%)	33 (9.3%)	2 (1.3%)	17 (15.2%)	4 (7.0%)
Committed to above and beyond anyone else	55 (8.1%)	30 (8.5%)	2 (1.3%)	20 (17.9%)	3 (5.3%)
Partner's Age (years)					
18-29	123 (18.4%)	41 (11.5%)	44 (30.3%)	24 (21.4%)	14 (24.6%)
30-39	217 (32.4%)	103 (28.9%)	53 (36.6%)	37 (33.0%)	24 (42.1%)
40-49	191 (28.5%)	128 (36.0%)	29 (20.0%)	23 (20.5%)	11 (19.3%)
50+	139 (20.8%)	84 (23.6%)	19 (13.1%)	28 (25.0%)	8 (14.0%)
Partner's Race/Ethnicity					
White	349 (55.9%)	201 (61.3%)	55 (38.5%)	61 (59.2%)	32 (64.0%)
African American	57 (9.1%)	22 (6.7%)	26 (18.2%)	6 (5.8%)	3 (6.0%)
Latino	167 (26.8%)	80 (24.4%)	53 (37.1%)	26 (25.2%)	8 (16.0%)
Other/Multiracial	51 (8.2%)	25 (7.6%)	9 (6.3%)	10 (9.7%)	7 (14.0%)
Any condomless anal sex during past 12 months	522 (76.4%)	335 (93.8%)	83 (52.9%)	55 (49.1%)	49 (86.0%)
Any insertive[a] anal sex during past 12 months	427 (62.5%)	234 (65.6%)	96 (61.2%)	59 (52.7%)	38 (66.7%)
Any insertive[a] condomless anal sex during past 12 months	336 (49.2%)	225 (63.0%)	52 (33.1%)	24 (21.4%)	35 (61.4%)
Any receptive[a] anal sex during past 12 months	451 (66.0%)	235 (65.8%)	83 (52.9%)	92 (82.1%)	41 (71.9%)
Any receptive[a] condomless anal sex during past 12 months	353 (51.7%)	226 (63.3%)	46 (29.3%)	45 (40.2%)	36 (63.2%)
Number of anal sex acts in partnership during past 12 months					
mean	13.0	13.2	8.1	18.6	13.6
median	3.0	3.0	2.0	4.0	2.0
range	1-360	1-360	1-360	1-360	1-360

Abbreviation: MSM, men who have sex with men; PrEP, pre-exposure prophylaxis

[a] from the perspective of participant

Table 3.3: Percentage of partnerships with any condomless anal sex or any insertive condomless anal sex during previous 12 months, stratified by partnership type and viral suppression of participant.

	CAS	ICAS	
	n (%)	n (%)	(%)[a]
Total (n=683)	**522 (76.4%)**	**336 (49.1%)**	**(78.7%)**
Durably Virally Suppressed (n=501)	390 (77.8%)	247 (49.3%)	(79.9%)
Discordant, no PrEP (n=82)	39 (47.6%)	15 (18.3%)	(34.9%)
Potentially discordant (n=116)	66 (56.9%)	42 (36.2%)	(59.2%)
Discordant, with PrEP (n=46)	38 (82.6%)	27 (58.7%)	(90.0%)
Seroconcordant (n=257)	247 (96.1%)	163 (63.4%)	(98.8%)
Not Durably Virally Suppressed (n=182)	132 (72.5%)	89 (48.9%)	(75.4%)
Discordant, no PrEP (n=30)	16 (53.3%)	9 (30.0%)	(56.3%)
Potentially discordant (n=41)	17 (41.5%)	10 (24.4%)	(40.0%)
Discordant, with PrEP (n=11)	11 (100%)	8 (72.7%)	(100.0%)
Seroconcordant (n=100)	88 (88.0%)	62 (62.0%)	(89.9%)

Abbreviations: CAS, condomless anal sex; ICAS, insertive condomless anal sex; PrEP, pre-exposure propyhlaxis

[a] among partnerships involving insertive (from the perspective of the participant) anal sex (n=427)

Table 3.4: Generalized estimating equation models stratified by sustained HIV viral load predicting condomless anal sex and insertive condomless anal sex during the past 12 months in partnership.

	CAS				ICAS			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	PR (95% CI)	p-value	aPR (95% CI)	p-value	PR (95% CI)	p-value	aPR (95% CI)	p-value
Virally Suppressed (n=501)								
Discordant, no PrEP	ref		ref		ref		ref	
Potentially discordant	1.09 (0.82-1.45)	0.57	1.17 (0.88-1.56)	0.28	1.67 (1.01-2.76)	0.04	2.29 (1.32-3.97)	<0.01
Discordant, with PrEP	1.59 (1.25-2.03)	<0.01	1.50 (1.19-1.89)	<0.01	2.75 (1.81-4.16)	<.0001	2.87 (1.91-4.32)	<.0001
Seroconcordant	1.84 (1.48-2.30)	<.0001	1.81 (1.47-2.23)	<.0001	3.10 (2.06-4.65)	<.0001	3.25 (2.18-4.87)	<.0001
Not Virally Suppressed (n=182)								
Discordant, no PrEP	ref		ref		ref		ref	
Potentially discordant	1.16 (0.54-2.48)	0.71	1.59 (0.82-3.06)	0.17	1.48 (0.58-3.75)	0.41	1.19 (0.40-3.57)	0.76
Discordant, with PrEP	1.90 (1.06-3.41)	0.03	1.85 (1.19-2.87)	0.01	3.39 (1.48-7.73)	<0.01	3.50 (1.62-7.57)	<0.01
Seroconcordant	1.90 (1.09-3.30)	0.02	1.85 (1.20-2.85)	0.01	2.87 (1.23-6.73)	0.02	2.78 (1.23-6.30)	0.01

Abbreviations: CAS, condomless anal sex; ICAS, insertive condomless anal sex; CI, confidence interval; PR, prevalence ratio; aPR, adjusted prevalence ratio; PrEP, pre-exposure prophylaxis

Table 3.5: Generalized estimating equation models stratified by sustained HIV viral load predicting insertive condomless anal sex among partnerships that involved insertive anal sex during past 12 months, (n=427).

	Unadjusted		Adjusted	
	PR (95% CI)	**p-value**	**aPR (95% CI)**	**p-value**
Virally Suppressed (n=309)				
Discordant, no PrEP	ref		ref	
Potentially discordant	1.49 (0.95-2.35)	0.08	1.51 (0.97-2.35)	0.07
Discordant, with PrEP	2.21 (1.50-3.25)	<.0001	2.11 (1.46-3.07)	<.0001
Seroconcordant	2.57 (1.78-3.72)	<.0001	2.49 (1.76-3.54)	<.0001
Not Virally Suppressed (n=118)				
Discordant, no PrEP	ref		ref	
Potentially discordant	1.60 (0.60-4.29)	0.35	1.52 (0.62-3.73)	0.36
Discordant, with PrEP	2.22 (0.91-5.42)	0.08	1.84 (0.93-3.65)	0.08
Seroconcordant	2.00 (0.81-4.91)	0.13	1.70 (0.83-3.46)	0.15

Abbreviations: CI, confidence interval; PR, prevalence ratio; aPR, adjusted prevalence ratio; PrEP, pre-exposure prophylaxis

REFERENCES

1. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.

2. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. Department of Health and Human Services; 2012. Available at: http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/ adultandadolescentgl.pdf.

3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemo-prophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587–99.

4. Holmes D. FDA paves the way for pre-exposure HIV prophylaxis. *Lancet*. 2012;380:325.

5. Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention. *BMJ*. 2006;332:605-7.

6. Golub SA, Kowalczyk W, Weinberger CL, Parsons JT. Preexposure prophylaxis and predicted condom use among high-risk men who have sex with men. *J Acquir Immune Defic Syndr.* 2010;54:548.

7. Brooks RA, Landovitz RJ, Kaplan RL, et al. Sexual risk behaviors and acceptability of HIV pre-exposure prophylaxis among HIV-negative gay and bisexual men in serodiscordant relationships: a mixed methods study. *AIDS Patient Care STDS.* 2012; 26:87-94.

8. Marcus JL, Glidden DV, Mayer KH, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. *PloS One*. 2013;8:e81997.

9. Liu AY, Vittinghoff E, Chillag K, et al. Sexual risk behavior among HIV-uninfected men who have sex with men (MSM) participating in a tenofovir pre-exposure prophylaxis (PrEP) randomized trial in the United States. *J Acquir Immune Defic Syndr*. 2013;64:87.

10. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014;14:820-9.

11. Volk JE, Marcus JL, Phengrasamy T, et al. No new HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. *Clin Infect Dis.* 2015;61:1601-3.

12. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet*. 2016; 387:53-60.

13. Van de Ven P, Mao L, Fogarty A, et al. Undetectable viral load is associated with sexual risk taking in HIV serodiscordant gay couples in Sydney. *AIDS*. 2005;19:179-84.

14. Prestage G, Mao L, Kippax S, et al. Use of viral load to negotiate condom use among gay men in Sydney, Australia. *AIDS and Behav*. 2009;13:645-51.

15. Stolte IG, De Wit JB, Van Eeden A, et al. Perceived viral load, but not actual HIV-1-RNA load, is associated with sexual risk behaviour among HIV-infected homosexual men. *AIDS*. 2004 Sep 24;18(14):1943-9.

16. McNaghten AD, Wolfe MI, Onorato I, et al. Improving the representativeness of behavioral and clinical surveillance for persons with HIV in the United States: the rationale for developing a population-based approach. *PLoS One*. 2007;2:e550.

17. Frankel MR, McNaghten AD, Shapiro MF, et al. A probability sample for monitoring the HIV-infected population in care in the U.S. and in selected states. *Open AIDS J.* 2012; 6: 67–76.

18. Centers for Disease Control and Prevention. Behavioral and Clinical Characteristics of Persons Receiving Medical Care for HIV Infection—Medical Monitoring Project, United States, 2013 Cycle (June 2013–May 2014). HIV Surveillance Special Report 16; January 2016. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/#panel2.

19. Otis J, McFadyen A, Haig T, et al. Beyond Condoms: Risk Reduction Strategies Among Gay, Bisexual, and Other Men Who Have Sex With Men Receiving Rapid HIV Testing in Montreal, Canada. *AIDS Behav*. 2016:1-5.

20. Newcomb ME, Mongrella MC, Weis B, et al. Partner disclosure of PrEP use and undetectable viral load on geosocial networking apps: Frequency of disclosure and decisions about condomless sex. *J Acquir Immune Defic Syndr*. 2016;71:200-6.

21. US Public Health Service (PHS) and Centers for Disease Control and Prevention (CDC), Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2014 Clinical Practice Guideline; 2014. Available at: http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf.

22. Raymond HF, Chen YH, Ick T, et al. A new trend in the HIV epidemic among men who have sex with men, San Francisco, 2004–2011. *J Acquir Immune Defic Syndr*. 2013;62:584–9.

23. McFarland W, Chen YH, Nguyen B, et al. Behavior, intention or chance? A longitudinal study of HIV seroadaptive behaviors, abstinence and condom use. *AIDS Behav*. 2012;16:121-31.

24. Parsons JT, Schrimshaw EW, Wolitski RJ, et al. Sexual harm reduction practices of HIV-seropositive gay and bisexual men: serosorting, strategic positioning, and withdrawal before ejaculation. *AIDS*. 2005;19:S13-25.

25. Snowden JM, Raymond HF, McFarland W. Seroadaptive behaviours among men who have sex with men in San Francisco: the situation in 2008. *Sex Trans Infect*. 2011;87:162-4.

26. Hughes A, Scheer S. Congruence between self-report and medical record CD4 lymphocyte and HIV viral load test results among HIV-infected patients in care. 2012 Council for State and Territorial Epidemiologists Conference, Omaha, Nebraska, June 2012.

27. HIV Epidemiology Section, San Francisco Department of Public Health. HIV Epidemiology Annual Report 2015. San Francisco: San Francisco Department of Public Health September 2016; pp. 1-91.

28. Mehroz B. How San Francisco is Getting to Zero On HIV. Huffington Post, 12/10/14. Available at: http://www.huffingtonpost.com/mehroz-baig/how-san-francisco-is-getting-to-zero-on-hiv_b_6290636.html

29. Bush S, Magnuson D, Rawlings M, et al. Racial Characteristics of FTC/TDF for Pre-Exposure Prophylaxis Users in the US. ICAAC 2016. June 16-20, 2016. Boston, MA. Abstract 2651.

30. Marcus JL, Hurley LB, Hare CB, et al. Disparities in Uptake of HIV Preexposure Prophylaxis in a Large Integrated Health Care System. *Am J Public Health.* 2016;106: e2-e3.

31. Centers for Disease Control and Prevention. HIV Surveillance Report, 2014. vol. 26; November 2015. Available at: http://www.cdc.gov/hiv/library/reports/surveillance/

32. San Francisco Department of Public Health. San Francisco Sexually Transmitted Disease Annual Summary, 2014. San Francisco Department of Public Health, San Francisco, California. December 2015; pp. 1-130.

33. Kojima N, Davey DJ, Klausner JD. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. *AIDS*. 2016; 30:2251-2252.

34. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Trans Infect*. 1999;75:3-17.

35. Chen YH, Snowden JM, McFarland W, Raymond HF. Pre-exposure Prophylaxis (PrEP) Use, Seroadaptation, and Sexual Behavior Among Men Who Have Sex with Men, San Francisco, 2004–2014. *AIDS and Behav*. 2016:1-7.

Chapter 4

The causal effect of internalized HIV stigma on viral suppression among San Francisco adults in HIV care

ABSTRACT

One of the goals of the Getting to Zero committee in San Francisco is to eliminate HIV stigma. The causal effect of HIV stigma on viral suppression was estimated in this analysis using data from 2012-2014 cycles of the Medical Monitoring Project collected from June 2012 through May 2015. Self-reported internalized HIV stigma (IHS) was measured through patient interview using the AIDS Stigma Scale. Information concerning sustained HIV viral suppression, defined as all reported HIV viral loads within 12 months after interview being suppressed (≤200 copies/mL or "undetectable" result), was obtained through the HIV surveillance registry. Descriptive analyses were performed and weighted modified Rao–Scott chi-squares were used to examine differences in characteristics of the patients. Following the causal roadmap, causal inference methods were used to estimate the counterfactual proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did not experience IHS compared to the proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did experience IHS. Three estimators were used to estimate the average treatment effect: simple substitution, inverse probability of treatment weighting, and targeted maximum likelihood estimation (TMLE). The results from each estimator were similar, and a statistically significant causal effect was observed for all. Using TMLE, the counterfactual proportion of adults virally suppressed would decrease by roughly 4.5% if all adults did not experience internalized HIV stigma as opposed to all adults experiencing internalized HIV stigma.

BACKGROUND

The Vision for the National HIV/AIDS Strategy, which states "The United States will become a place where new HIV infections are rare and when they do occur, every person, regardless of age, gender, race/ethnicity, sexual orientation, gender identity or socio-economic circumstance, will have unfettered access to high quality, life-extending care, *free from stigma* and discrimination", has provided motivation for my third dissertation aim [1]. There is also substantial interest in understanding and eliminating HIV stigma in San Francisco. The Medical Monitoring Project (MMP) is the only measure of internalized HIV stigma (IHS) I am aware of among a representative sample of HIV-positive adults in San Francisco. Past research on internalized HIV stigma has focused on how stigma can affect antiretroviral treatment (ART) adherence [2-7]. Depression has been determined to be a mediator along this path [8-10]. To my knowledge, no research has focused on the effect of internalized stigma on sustained HIV viral suppression. Research on internalized stigma in San Francisco has been limited to studies of selected subgroups of HIV-positive individuals, such as homeless and marginally housed HIV-positive adults [8]. Additionally, to my knowledge, causal inference methods have not been used to assess the effect of internalized HIV stigma on an HIV-related outcome. By using causal inference methods, I estimated the counterfactual proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did not experience IHS compared to the proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did experience IHS.

METHODS

Study population

Data from 2012-2014 cycles of the Medical Monitoring Project (MMP) were used for this analysis. MMP is an annual, cross-sectional HIV surveillance project that assesses health care utilization, clinical outcomes and HIV-related risk behaviors among HIV-positive persons receiving care. Three-stage probability-proportional-to-size sampling was used to sample 400 HIV-positive adults per cycle at health care facilities in San Francisco. Data collection on participating patients consisted of a face-to-face or telephone interview and medical chart abstraction (MRA), and the resulting data were weighted to account for known probabilities of selection and patient non-response. Data were collected from June 2012 through May 2015.

Measures

Exposure

Self-reported internalized HIV stigma (IHS) was the exposure of interest; it was measured through patient interview using the AIDS Stigma Scale, which is a validated measure of internalized HIV stigma [11]. Table 4.3 provides the statements used in the scale; the patient responded either "agree" or "disagree" to each item. I determined internal consistency for this measure using 2011 MMP data and found a Cronbach's alpha of 0.76, which is considered

good. With the goal being to eliminate all stigma, the exposure was made into a dichotomous variable: experiencing any internalized HIV stigma (A=0) and not experiencing any internalized HIV stigma (A=1).

Outcome

Sustained HIV viral suppression was the outcome of interest. Data from MMP were linked to data from the HIV surveillance registry to obtain HIV viral load test results (which are reportable by law to the health department). All HIV viral load measurements during the 12 months after the interview were matched for each individual and included in the analysis. HIV viral load test results were used to create the specific binary outcome of "sustained viral suppression", which is defined as all reported HIV viral loads during the 12 months after the interview being suppressed (≤200 copies/mL or "undetectable" result). Missing outcome data were imputed using sustained viral suppression from the MMP MRA data; if MMP MRA data were missing, this value was imputed using the most recent HIV viral load from the HIV surveillance registry.

Covariates

Potential confounders, that were all self-reported during the interview, included: time since HIV diagnosis (using self-reported date of HIV diagnosis to create three categories: <5 years, 5-9 years and ≥10 years), age (calculated from patient's reported date of birth), gender identity (male, female or transgender), race/ethnicity (white/Caucasian, black/African American, Hispanic/Latino, or Multiracial/Other), education (less than high school, high school diploma or equivalent, some college or more), sexual orientation (homosexual/gay/lesbian, heterosexual/straight, or bisexual), foreign born status (yes or no), private health insurance status (yes or no), social support (patient reported satisfaction or dissatisfaction from support received by family and friends), homelessness (yes or no), binge drinking in prior 30 days (yes or no), using non-injection drugs in the previous 12 months (yes or no), injection drugs in previous 12 months (yes or no), incarceration more than 24 hours in the past 12 months (yes or no), discrimination by health care workers since testing HIV-positive (yes or no), current depression, provider distrust (being completely comfortable discussing health concerns with primary HIV provider or not), ART use (yes or no) and ART adherence (100% adherent or not during previous 72 hours to schedule, dose and special instruction). Current depression was diagnosed by administering the Patient Health Questionnaire (PHQ-8) during the patient interview, and a PHQ-8 score ≥10 was defined as current depression [12]. Another potential confounder was prior depression, which was obtained from the medical record abstraction component of MMP. Prior depression was defined as a doctor's diagnosis of depression noted in the medical chart during the 12 months prior to patient interview date. Last, all CD4 cell counts were obtained from the HIV surveillance registry for the 12 months after the patient interview; all CD4 cell count results were used to create one covariate variable, geometric mean CD4 cell count, which is the mean of all CD4 cell count test results for each individual during the 12 months after interview.

Data Analysis

Descriptive Data Analysis

First, univariate and bivariate analyses were performed to describe the data. Weighted univariate frequencies were calculated to estimate the prevalence and 95% confidence intervals of sociodemographic variables, stigma and discrimination experiences, health characteristics, antiretroviral treatment use, ART adherence, depression, and viral suppression. Next, weighted modified Rao–Scott chi-squares were calculated to examine differences in characteristics among patients who experienced any internalized HIV stigma versus those who did not experience any internalized HIV stigma. Again, weighted modified Rao–Scott chi-squares were used to compare patients who had sustained viral suppression to those who did not have sustained viral suppression. Descriptive analyses were conducted using SAS version 9.3 survey procedures to utilize the complex survey design variables, including strata, cluster and person weights.

Causal Data Analysis

Causal inference methods were utilized to estimate the counterfactual proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did not experience IHS compared to the proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did experience IHS, following the causal roadmap [13]. Figure 4.1 depicts the directed acyclic graph (DAG) involved in this analysis. This DAG represents my knowledge of the relationships between the exposure (IHS), the outcome (viral suppression) and the covariates, which are described in detail in Table 4.1. Both endogenous and exogenous (unmeasured) nodes are depicted and there were no independence assumptions made for the exogenous factors. Causal analyses were conducted in R version 3.2.2.

Structural Causal Model (SCM) $\boldsymbol{\mathcal{M}^{\mathcal{F}}}$

The endogenous variables are specified as X = (W1, W2, A, Z, Y). The exogenous nodes U are specified as $U=(U_{W1}, U_{W2}, U_A, U_Z, U_Y) \sim P_{U,}$ where U includes unobserved factors (e.g. genetics) that determine the values of the endogenous variables X. Based on the causal diagram depicted in Figure 4.1, the structural equations ($\mathcal{F}$) are specified as follows:

$$W1 = f_{W1}(U_{W1})$$
$$W2 = f_{W2}(W1, U_{W2})$$
$$A = f_A(W1, W2, U_A)$$
$$Z = f_z(W1, W2, A, U_z)$$
$$Y = f_Y(W1, W2, A, Z, U_Y)$$

The causal model makes no assumptions about the functional form and there were no exclusion restrictions made based on my knowledge of the data generating process. Although the interview data from MMP are cross-sectional in nature, some time ordering was possible. For instance, variables collected in the set W2 were measured as present at the time of interview (for ART adherence it was for the 72 hours before the interview). I assumed that the

set of covariates W1 was either fixed or came before the current time at interview. Sociodemographic factors, such as age, race, gender identity, time since HIV diagnosis, education, and foreign born, were assumed to have occurred before the interview. Other factors in W1 were collected from the interview and had a recall period of the 12 months prior to the interview: incarceration, homelessness, private insurance status, and substance use. The recall period for discrimination was any time since testing positive for HIV and was assumed to occur before W2 covariates, which were measured at the time of the interview. Prior depression was measured from the MRA as any physician's diagnosis of depression noted in the medical chart in the 12 months before the interview and was also assumed to have occurred before W2 confounders. The exposure A (IHS) was measured at the same time point as confounder set W2, making the ordering of these variables difficult to establish. Leaving W2 unadjusted could leave some backdoor paths from the exposure (IHS) to the outcome (viral suppression); therefore, it was assumed that W2 affects A in order to avoid uncontrolled confounding. There was temporal ordering established for both Z (immune status for the 12 months after the interview) and Y (sustained viral suppression for the 12 months after interview) because this information was extracted from the HIV surveillance registry for the time period after which W1, W2 and A were measured.

Target Causal Parameter

My target causal parameter was the average treatment effect (ATE), which is the difference in the counterfactual expected proportion of HIV-positive adults who are virally suppressed if all adults in HIV care in San Francisco did not experience IHS compared to the expected proportion of HIV-positive adults who are virally suppressed if all adults in HIV care in San Francisco did experience IHS. The ATE is given by the difference in the counterfactual distributions when A=1 (no IHS) and A=0 (any IHS).

Target causal parameter: $\Psi^{\mathrm{F}}(P_{\mathrm{u,x}}) = E_{\mathrm{u,x}}[Y_1 - Y_0]$
where,
$E[\mathrm{Y}_1]$= expected proportion of HIV-positive adults who are virally suppressed if all adults in HIV care in San Francisco did not experience IHS

$E[\mathrm{Y}_0]$= expected proportion of HIV-positive adults who are virally suppressed if all adults in HIV care in San Francisco did experience IHS

Estimation

I assumed the observed data O = {W1, W2, A, Z, Y}~ $\mathrm{P_O}$ were generated by sampling n independent times (n i.i.d. observations) from a data generating system compatible with the structural causal model $\mathcal{M}^{\mathcal{F}}$. There were open backdoor paths from exposure A (IHS) to outcome Y (viral suppression) in the structural causal model $\mathcal{M}^{\mathcal{F}}$, so the target causal parameter was not identifiable without making further assumptions and adjusting for confounders to block backdoor pathways. I assumed that all of the exogenous (U) factors were independent of each other, which is sufficient but not minimal. Using the DAG (Figure 4.1), I determined that the set of confounders (W) that needed to be adjusted for in the

analysis to block the backdoor pathways was W=(W1, W2). Additionally, I needed to make a positivity assumption, where:

$P_o[A = a|W = w] > 0$ for all w such that $P_o[W = w] > 0$ and $a \in \{0,1\}$

In words, in every group defined by combinations of adjustment covariates, there must be a non-zero probability of an individual experiencing and not experiencing internalized HIV stigma in P_o. Based on my understanding of the causal relationships depicted in Figure 4.1, I did not believe that there are any positivity violations but examined the distribution of propensity scores and corresponding weights to assess if there were any positivity violations.

Given identifiability, I was able to define the statistical target parameter of the observed data $\psi(P_0)$ as equivalent to the causal parameter $\Psi^F(P_{u,x})$. The statistical target parameter can be expressed by the G-computation formula for no IHS compared to any IHS:

$$\psi(P_0) = \sum_w [\, E_0(Y|A = 1, W = w) - E_0(Y|A = 0, W = w)]P_0(W = w)$$

The statistical estimand $\psi(P_O)$, the target causal parameter of the observed data distribution, is the difference in the strata-specific conditional probability of being virally suppressed among individuals who do not experience IHS and those who do experience IHS, averaged with respect to the distribution of covariate set W. For analysis, I used three estimators to estimate the ATE: simple substitution, inverse probability of treatment weighting (IPTW), and targeted maximum likelihood estimation (TMLE) [14-15]. Because I had no a priori knowledge of the functional form of my observed data, I used the SuperLearner package in R to determine which combinations of algorithms best predicted viral suppression based on internalized HIV stigma and covariates (which was used in all three estimators) and also used SuperLearner to predict the treatment mechanism, which is the probability of experiencing no IHS given covariates [13-16].

SuperLearner was used in the simple substitution estimator to select a convex combination of algorithms that predicted the probability of viral suppression, based on IHS and covariates. Next, that algorithm was used to predict the probability of each individual's viral suppression under two different scenarios – if she/he experienced any IHS and if she/he didn't experience IHS. The ATE was estimated as the mean difference in participants' probability of viral suppression comparing not experiencing IHS to experiencing IHS. The stabilized Hortvitz-Thompson IPTW estimator was chosen to address concerns of a finite sample and practical positivity violations [17]. The stabilized IPTW estimator used SuperLearner to select a convex combination of algorithms to predict the probability of treatment (no IHS) based on covariates and then used the inverse of each participant's probability of treatment (experiencing IHS or not experiencing IHS) to weight the individual's outcome (viral suppression). The ATE was estimated by taking the difference of the mean weighted outcomes divided by the sum of the weights for each treatment (experiencing or not experiencing IHS) comparing those who didn't experience IHS and those who did. TMLE used both the algorithms that predict the probability of viral suppression based on IHS and

covariates, and the algorithms that predict the probability of receiving treatment (not experiencing IHS) given covariates. TMLE "targeted" the estimate of the causal parameter by calculating a "clever covariate" for each individual, and a corresponding coefficient. This value is represented as $\bar{Q}^*_n$ which is the "updated" prediction of probability of viral suppression given IHS, covariates, and "clever covariate." The ATE was estimated as the mean difference in participants' probability of viral suppression comparing not experiencing IHS to experiencing IHS by using $\bar{Q}^*_n$. Assuming normality, non-parametric bootstrap with 500 repetitions was used to obtain 95% confidence intervals for each estimator.

Ethical Considerations

The research presented in this chapter was reviewed and approved by the Committee for Protection of Human Subjects at University of California, Berkeley (Protocol Number 2015-09-7927).

RESULTS

There were 711 adults in HIV care in the sample. Nineteen persons were excluded from analysis, one interview was terminated shortly after it began and 18 persons died within 12 months of interview, leaving 692 persons in HIV care for analysis. Of the remaining 692, 35 persons were missing HIV viral load tests in the HIV surveillance registry in the 12 months after interview, 31 were imputed by using sustained viral suppression from the MRA (for the 12 months prior to interview) and four were imputed using most recent HIV viral load test result from the HIV surveillance registry. The median number of viral load test results in the HIV surveillance registry was two (range: 0-12, IQR:2-3).

The majority of adults in HIV care in San Francisco were male (92.4%), identified as homosexual, gay or lesbian (79.6%), white (61.6%), attained more than a high school education (81.6%), were born in the United States (83.5%), were diagnosed with HIV >10 years prior to interview (75.7%), and had health insurance coverage (99.4%), (Table 4.2). About half of adults in HIV care had private health insurance, 11.8% were homeless and 1.8% had been incarcerated in the past 12 months (Table 4.2).

Table 4.3 displays the internalized HIV stigma and discrimination experiences of adults receiving HIV care in San Francisco. The most commonly reported stigma constructs included being difficult to tell others about having HIV (52.5%), hiding HIV status from others (47.4%), and feeling guilty about being HIV positive (24.2%). The majority of patients (67.9%) experienced some type of internalized HIV stigma. Since testing HIV positive, 26.0% reported someone in the health care system exhibiting hostility or a lack of respect, 15.9% reported receiving less attention than other patients and 11.2% reported being refused service; 30.6% reported experiencing at least one kind of discrimination since testing HIV positive. Of those who experienced discrimination from someone in the health care system, the most frequently reported reasons for discrimination were being HIV-positive (79.1%) and sexual orientation or practices (53.8%).

The majority of adults in HIV care had a geometric mean CD4 cell count ≥500 cells/mm^3 (62.7%) and 87.7% had sustained viral suppression (Table 4.4). Almost all (95.2%) reported current use of ART at the time of interview. Of those currently taking ART, 88.2% reported 100% dose adherence, 73.7% reported 100% schedule adherence and 75.5% reported 100% special instruction adherence. The majority of patients were satisfied with the support they received from family and friends (88.9%) and reported being completely comfortable discussing their health with medical providers (85.4%). A diagnosis of depression during the 12 months prior to interview was noted in the MRA of 35.1% of patients, and 20.1% met criteria for a diagnosis of depression at the time of interview (PHQ-8 score ≥10). Binge drinking in the 30 days prior to interview was reported by 21.3% patients, any non-injection drug use in the prior 12 months by 45.3% of patients, and injecting drugs in the prior 12 months by 8.7% of patients.

Table 4.5 shows characteristics of those who experienced internalized HIV stigma (n=471) versus those who did not (n=221). Non-Latino whites were more likely to report not having experienced IHS, whereas Black or African American, Latino and Multiracial persons were more likely to report having experienced IHS ($p<0.01$). Persons ≥50 years of age were less likely to report having experienced IHS ($p=0.01$). Foreign-born adults in HIV care were more likely to report having experienced IHS ($p<0.01$), as were persons diagnosed with HIV <10 years prior to interview ($p<0.01$), persons who had private health insurance ($p=0.01$), patients reporting dissatisfaction with the support received from family and friends ($p<0.01$), and those not completely comfortable discussing their health with their medical provider ($p<0.01$). Current depression and binge drinking during the prior 30 days were each associated with experiencing IHS ($p=0.01$ and $p<0.01$, respectively).

Next, differences in characteristics of patients who had sustained viral suppression versus those who were not virally suppressed for the 12 months after interview were determined (Table 4.6). Female and transgender patients each were less likely to be virally suppressed ($p<0.01$). Those who identified as heterosexual or straight were less likely to be virally suppressed, compared to homosexual, gay, lesbian and bisexual persons ($p=0.05$). Persons ≥50 years of age were more likely to be virally suppressed ($p=0.03$), while those who were homeless or incarcerated were less likely to be virally suppressed ($p<0.01$ for each). Persons with private health insurance were more likely to be virally suppressed compared to those without private health insurance ($p<0.01$). Having a geometric mean CD4 cell count ≥500 cells/mm^3 for the 12 months after the interview and self-reported ART use were each associated with being virally suppressed ($p<0.01$ for each). Those reporting 100% dose and schedule ART adherence were more likely to be virally suppressed ($p<0.01$ for each), while those reporting taking an ART drug holiday during the prior 12 months were less likely to be virally suppressed ($p<0.01$). Those who were dissatisfied with the support they had received from family and friends and those who were not completely comfortable discussing their health with their medical provider were more likely to not be virally suppressed ($p<0.01$ for each). Those with current depression (PHQ-8 ≥10) were less likely to be virally suppressed ($p<0.01$). Substance use was associated with not being virally suppressed; those who reported using non-injection and injection drugs in the prior 12 months were less likely to be virally

suppressed (p=0.04 and p<0.01, respectively), while those who reported being discriminated against by someone in the health care system since testing HIV positive were less likely to be virally suppressed (p=0.02). Of note, there was no difference in likelihood of being virally suppressed between those who did and did not experience IHS (p=0.49).

Table 4.7 summarizes the three ATE estimates with corresponding 95% confidence limits using the three different estimators. The results from each estimator were similar, and a statistically significant causal effect was observed for all three. Using the simple substitution estimator, the difference in the counterfactual proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did not experience IHS compared to the proportion of HIV-positive adults virally suppressed if all adults in HIV care in San Francisco did experience IHS was -1.75% (95% CL: -2.31%, -1.20%). Using the Horvitz-Thompson stabilized IPTW estimator, this causal risk difference was -2.57% (95% CL: -3.17%, -1.96%). Using TMLE, the difference in the counterfactual proportion of viral suppression if all adults did not experience internalized HIV stigma as opposed to all adults experiencing internalized HIV stigma was -3.12% (95% CL: -3.63%, -2.61%).

DISCUSSION

In this analysis, I found that the counterfactual proportion of adults virally suppressed would decrease by roughly two to three percent if all adults in HIV care in San Francisco did not experience IHS compared to if all adults did experience IHS. This result was unexpected because prior research, although not using causal methods, has shown that internalized HIV stigma is associated with lower antiretroviral treatment adherence [2-7]. One interpretation of this result is that there truly is a causal effect of internalized HIV stigma on increased viral suppression in the population of adults who accessed HIV care in San Francisco from 2012-2014.

Other results from prior research align with the results of this analysis. Vanable et al. found that internalized HIV stigma was associated with a greater likelihood of disclosure of HIV status to family, friends, co-workers and social contacts [7]. If persons living with HIV who experience IHS are more likely to disclose their HIV status to others, then those with IHS may be more likely to disclose their HIV status to health professionals and be more engaged in HIV care, and thus more likely to be virally suppressed. Also, if more of an individual's social contacts are aware of one's HIV status, the individual may receive more support in terms of remembering to attend HIV care visits to adhere to ART treatment and in turn, more likely to be virally suppressed. Lee et al. found that those experiencing internalized HIV stigma were more likely to worry about transmitting HIV to others [18]. Although the variable "worrying about infecting others" was not collected in the MMP, if it is true that one effect of IHS is concern about transmitting HIV to others, this could be one possible explanation of the observed effect of IHS on viral suppression. It is possible that there is an underlying mechanism whereby IHS would lead someone to worry about transmitting HIV and in turn motivate that individual to stay in HIV care, adhere to ART and maintain viral suppression.

The results of this analysis warrant further investigation into how internalized HIV stigma could influence an individual's motivation to adhere to HIV care and treatment.

This analysis had several limitations. The outcome (sustained viral suppression for the 12 months after interview) is subject to measurement error. Sustained viral suppression relies on complete reporting of HIV viral load test results to the health department and data could be missing for several reasons. For example, the patient could have died or left HIV care and had no HIV viral load measurements, or moved to another state or country where the HIV viral load information is not reported back to SFDPH or the California Department of Public Health. In addition, there could be a delay in reporting or some other problem that prevented the HIV viral load test results from being imported into the HIV case surveillance database (eHARS). However, SFDPH regularly evaluates the completeness and timeliness of HIV laboratory reporting and has found that the median time from HIV viral load sample date to the date when the information is imported into the eHARS database is 42 days, while validation studies of completeness have revealed that the public health laboratory has 99.5% completeness. Therefore, it is likely that persons with missing outcome information have moved away from San Francisco or decided to move their care outside of San Francisco, or potentially dropped out of care. There were 35 individuals who were missing HIV viral load data in eHARS and the missing values were imputed by taking sustained viral suppression for 31 persons in the 12 months prior to the interview, while for four individuals the HIV viral load was imputed by using most recent HIV viral load in eHARS. Although not perfect, I argue that imputation improved the missing outcome data better than the approach of coding everyone that was missing HIV viral loads as not being virally suppressed. This is because among the subset that had sustained HIV viral load data in both the MRA of MMP (for 12 months prior to interview) and in eHARS (for the 12 months after interview), 88% had the same sustained HIV viral load value in both measures. Additionally, 80% of persons in the subset with both measures were virally suppressed in both measures, so coding each person who was missing HIV viral load as not being virally suppressed would misclassify many of the 35 missing outcome values.

These results from this analysis are likely not generalizable outside of a population in HIV care because HIV-positive adults who are out of care or who have never accessed HIV care were not included in the sampling frame of the Medical Monitoring Project (MMP) during these years. People who are out of care are likely to be virally unsuppressed, and their experiences of IHS may be different from the IHS experiences of the MMP sample. Internalized HIV stigma may have an effect on accessing HIV care, by causing people to be either more or less likely to seek HIV care. Therefore, these results can only be applied to adults in HIV care.

I framed my research question to align with Getting to Zero targets and was interested in what would happen if the prevalence of internalized HIV stigma was zero (compared to if everyone experienced IHS). For that reason, I defined my exposure as dichotomous - no IHS or any IHS. It is possible that specific questions from the AIDS Stigma Scale have different effects on sustained viral suppression, and I plan to conduct future work exploring the specific

measures of the AIDS Stigma Scale as well as a potential cumulative effect of experiencing multiple internalized HIV stigma measures from the AIDS Stigma Scale.

In order to identify my target parameter, I needed to assume that there were no unmeasured confounders and no positivity violations. In theory, persons in the population of all combinations of confounders should have a positive probability of receiving treatment (not experiencing IHS), but given the sample size of 692 persons and the fact that there were 20 confounders with 2-5 levels in my adjustment set, there were concerns of practical positivity violations. I checked the propensity score weights, however, and the median weight was 1.6 (range: 1.1-8.2). Given that there were no extreme weights, there were not any practical positivity violations. Additionally, in choosing my estimators, I decided to use the Horvitz-Thompson stabilized IPTW estimator instead of IPTW without stabilized weights so that it would address poor performance of IPTW with practical positivity violations. I also had to assume that there was no unmeasured confounding. It is possible that there are factors that influence both internalized HIV stigma and viral suppression. Although there could have been unmeasured confounding, a major strength of MMP and this analysis is the large adjustment set that was available, and many of the known confounders like gender identity and time since HIV diagnosis were adjusted for in this analysis.

In this chapter, the total effect of IHS on viral suppression was estimated in a representative sample of adults in HIV care in San Francisco. I found that the counterfactual proportion of adults virally suppressed would decrease if all adults did not experience IHS, compared to if all adults did experience IHS. Given that this sample did not include those out of HIV care, and internalized HIV stigma could affect an individual's decision to access and be retained in HIV care, further research in a population containing all HIV-positive adults is needed. Recent changes in the Medical Monitoring Project sampling will facilitate this future analysis. In 2015, MMP changed from sampling patients in HIV care through their HIV medical providers to sampling directly out of the National HIV Surveillance System which has resulted in a sample of adults who are both in and out of HIV care. At the time of this analysis, 2015 MMP data collection had just ended (in June 2016) and there was not enough follow-up time to measure sustained viral suppression for 12 months after the interviews. However, MMP data including people both in and out of HIV care will be valuable in the future in order to fill in gaps on how IHS affects persons out of HIV care. In addition, in 2015 MMP, new stigma questions were added to the MMP interview, which now includes four domains of stigma, including personalized stigma, public attitudes towards persons living with HIV, disclosure concerns, and negative self-image, which can all be incorporated into a causal model to determine which domains may affect viral suppression.

I hypothesized that not experiencing internalized HIV stigma compared to experiencing IHS would increase viral suppression, yet I found the opposite unexpected finding. This warrants further research to understand if stigma is related to an unknown behavioral mechanism that could motivate individuals to stay in HIV care, adhere to antiretroviral treatment, and maintain viral suppression. The data and causal model used in this chapter can be applied to study if any other nodes have an effect on viral suppression. One future analysis I plan to perform will quantify the total effect of various "exposures" in this causal model, especially

nodes that can be intervened upon in the real world. One such node of interest is current depression, which may be feasible to intervene on by screening patients in care for HIV for depression at each medical visit and then treating depression with mental health care and/or medication. Other nodes that could also be considered in the future are incarceration, substance use and homelessness. Causal inference methods can be used to determine which real world interventions (either by intervening on one determinant of viral suppression or multiple determinants at the same time) will have the greatest effect on sustained viral suppression, which in turn will enable San Francisco to implement the highest impact interventions and "Get to Zero".

TABLES

Table 4.1: List of endogenous and exogenous nodes in causal diagram.	
Notation in DAG	**Description**
A	Exposure; internalized HIV stigma
Y	Outcome; sustained viral suppression 12 months after the interview
W1	Set of confounders that capture experiences prior to interview: time since HIV diagnosis, age, gender, race, education, sexual orientation, foreign born status, private insurance status, homelessness, substance use, incarceration, prior depression, past discrimination
W2	Confounders at time of interview: Social support, current depression, ART use, provider distrust, ART adherence
Z	CD4 cell count during 12 months after interview
U	Unmeasured confounders

Table 4.2: Demographic characteristics of adults receiving HIV care, Medical Monitoring Project, San Francisco, 2012-2014.

	n[a]	%[b]	(95% CI)[c]
Gender			
Male	639	92.4%	(90.3%- 94.5%)
Female	38	5.6%	(3.8%- 7.4%)
Transgender[d]	15	2.0%	(0.9%- 3.1%)
Sexual orientation			
Homosexual, gay, or lesbian	539	79.6%	(75.8%- 83.5%)
Heterosexual or straight	98	13.7%	(10.3%- 17.1%)
Bisexual	47	6.7%	(4.9%- 8.5%)
Race/Ethnicity			
White	418	61.6%	(57.6%- 65.5%)
Black or African American	86	11.6%	(8.6%- 14.6%)
Hispanic or Latino[e]	140	20.2%	(17.4%- 23.1%)
Multiracial/Other	48	6.6%	(4.7%- 8.4%)
Age at time of interview (years)			
18-29 years	15	2.4%	(1.1%- 3.7%)
30-39 years	66	10.1%	(7.5%- 12.6%)
40-49 years	190	26.4%	(23.3%- 29.5%)
≥50 years	421	61.1%	(57.4%- 64.8%)
Education			
<High School	38	5.2%	(3.6%- 6.7%)
High School diploma or equivalent	96	13.2%	(10.4%- 16.0%)
Some college or more	558	81.6%	(78.4%- 84.9%)
College degree or higher	276	41.1%	(37.2%- 45.0%)
Country or territory of birth			
United States	577	83.5%	(80.8%- 86.2%)
Other	115	16.5%	(13.8%- 19.2%)
Time since HIV diagnosis			
<5 years	70	10.3%	(7.9%- 12.8%)
5-9 years	95	14.0%	(11.3%- 16.7%)
≥10 years	527	75.7%	(72.5%- 78.9%)
Homeless[f] at any time in the past 12 months	89	11.8%	(9.4%- 14.1%)
Incarcerated for longer than 24 hours in the past 12 months	14	1.8%	(0.8%- 2.9%)
Had health insurance coverage, past 12 months	688	99.4%	(98.8%- 100.0%)
Had private health insurance	325	50.0%	(45.8%- 54.1%)
Total	**692**		

Abbreviations: CI, confidence interval

[a] Numbers are unweighted

[b] Percentages are weighted percentages

[c] CIs incorporate weighted percentages

[d] Patients were classified as transgender if sex at birth and gender reported by the patient were different, or if the patient chose transgender in response to the question about self-identified gender

[e] Hispanics or Latinos might be of any race. Patients are classified in only one race/ethnicity category.

[f] Living on the street, in a shelter, in a single-room–occupancy hotel, or in a car

Table 4.3: Stigma and discrimination experiences of adults receiving HIV care, Medical Monitoring Project, San Francisco, 2012-2014.

	n[a]	%[b]	(95% CI)[c]
Agreed to the following:			
It is difficult to tell people about my HIV infection.	355	52.5%	(48.5%- 56.4%)
Being HIV positive makes me feel dirty.	126	18.2%	(15.3%- 21.1%)
I am guilty that I am HIV positive.	169	24.2%	(21.0%- 27.3%)
I am ashamed that I am HIV positive.	135	19.6%	(16.6%- 22.6%)
I sometimes feel worthless because I am HIV positive.	123	17.4%	(14.6%- 20.3%)
I hide my HIV status from others.	319	47.4%	(43.6%- 51.3%)
Experienced any internalized HIV stigma	471	67.9%	(64.5%- 71.3%)
Discrimination by anyone in the health care system since testing positive for HIV			
Exhibited hostility or a lack of respect toward you	181	26.0%	(22.5%- 29.4%)
Given you less attention than other patients	110	15.9%	(13.1%- 18.7%)
Refused you service	77	11.2%	(8.7%- 13.7%)
Experienced any discrimination since testing positive for HIV	213	30.6%	(27.0%- 34.2%)
Discrimination occured because of:[d]			
HIV infection	158	79.1%	(73.6%- 84.6%)
Gender	15	7.1%	(3.3%- 10.8%)
Sexual orientation or practices	105	53.8%	(47.0%- 60.5%)
Race or ethnicity	29	13.6%	(8.6%- 18.5%)
Drug injecting habit	26	11.7%	(7.5%- 15.8%)
Total	**692**		

Abbreviations: CI, confidence interval

[a] Numbers are unweighted

[b] Percentages are weighted percentages

[c] CIs incorporate weighted percentages

[d] Among those who ever experienced discrimination

Table 4.4: Health characteristics, antiretroviral treatment use, adherence, depression and viral suppression, Medical Monitoring Project, San Francisco, 2012-2014.

	n[a]	%[b]	(95% CI)[c]
Geometric mean CD4 count			
0-199 cells/mm^3	42	6.0%	(4.3%- 7.8%)
200-349 cells/mm^3	93	13.0%	(10.6%- 15.4%)
350-499 cells/mm^3	131	18.3%	(15.6%- 21.1%)
≥500 cells/mm^3	426	62.7%	(59.1%- 66.3%)
Viral suppression			
Undetectable or <200 copies/mL	604	87.7%	(85.3%- 90.1%)
Any HIV viral load measurement in 12 months after interview ≥200 copies/mL	88	12.3%	(9.9%- 14.7%)
Self-reported ART use	659	95.2%	(93.6%- 96.8%)
100% ART medication adherence (during preceding 72 hours)[d]			
By dose	567	88.2%	(85.6%- 90.7%)
By schedule	487	73.7%	(70.3%- 77.2%)
By special instructions	257	75.5%	(71.1%- 80.0%)
Took drug holiday[e]	60	8.5%	(6.4%- 10.6%)
Friend and family support satisfaction[d]			
Dissatisfied	74	11.1%	(8.7%- 13.6%)
Satisfied	564	88.9%	(86.4%- 91.3%)
Completely comfortable discussing health with medical providers	581	85.4%	(82.9%- 88.0%)
Depression diagnosis in MRA 12 months before interview	247	35.1%	(31.5%- 38.6%)
Current depresssion	142	20.1%	(17.3%- 23.0%)
Binge drinking past 30 days	144	21.3%	(18.2%- 24.4%)
Used non-injection drugs past 12 months	314	45.3%	(41.6%- 49.0%)
Used injection drugs past 12 months	64	8.7%	(6.5%-10.9%)
Total	**692**		

Abbreviations: CI, confidence interval; ART, antiretroviral treatment; MRA, medical record abstraction

[a] Numbers are unweighted

[b] Percentages are weighted percentages

[c] CIs incorporate weighted percentages

[d] Among those currently taking ART

[e] Among those who have ever taken ART

Table 4.5: Characteristics stratified by stigma experiences, Medical Monitoring Project, San Francisco, 2012-2014.

	Experienced stigma			Did not experience stigma			
	n[a]	%[b]	(95% CI)[c]	n[a]	%[b]	(95% CI)[c]	p-value
Gender							0.1557
Male	429	91.1%	(88.1%- 94.1%)	210	95.1%	(92.3%- 98.0%)	
Female	29	6.3%	(3.8%- 8.8%)	9	4.1%	(1.4%- 6.7%)	
Transgender[d]	13	2.6%	(0.9%- 4.2%)	2	0.8%	(0.0%- 1.9%)	
Sexual orientation							0.0966
Homosexual, gay, or lesbian	357	77.5%	(73.1%- 82.0%)	182	84.1%	(78.5%- 89.6%)	
Heterosexual or straight	76	15.6%	(11.7%- 19.5%)	22	9.6%	(4.9%- 14.3%)	
Bisexual	33	6.8%	(4.6%- 9.1%)	14	6.4%	(3.2%- 9.5%)	
Race/Ethnicity							<.0001
White	256	55.6%	(51.0%- 60.1%)	162	74.2%	(67.9%- 80.6%)	
Black or African American	65	12.9%	(9.5%- 16.2%)	21	9.0%	(4.6%- 13.4%)	
Hispanic or Latino[e]	108	23.0%	(19.3%- 26.7%)	32	14.4%	(9.8%- 19.0%)	
Multiracial/Other	42	8.6%	(5.9%- 11.2%)	6	2.4%	(0.5%- 4.3%)	
Age at time of interview (years)							0.0093
18-29 years	12	3.0%	(1.2%- 4.7%)	3	1.3%	(0.0%- 2.7%)	
30-39 years	46	10.4%	(7.2%- 13.6%)	20	9.4%	(5.4%- 13.3%)	
40-49 years	145	29.6%	(25.7%- 33.5%)	45	19.7%	(14.6%- 24.7%)	
≥50 years	268	57.0%	(52.6%- 61.5%)	153	69.7%	(63.7%- 75.7%)	
Education							0.4334
<High School	29	5.8%	(3.8%- 7.9%)	9	3.7%	(1.3%- 6.1%)	
High School diploma or equivalent	66	13.4%	(10.2%- 16.6%)	30	12.8%	(8.2%- 17.3%)	
Some college or more	376	80.7%	(76.9%- 84.6%)	182	83.5%	(78.6%- 88.4%)	
Country or territory of birth							<.0001
United States	372	78.9%	(75.3%- 82.5%)	205	93.2%	(89.9%- 96.5%)	
Other	99	21.1%	(17.5%- 24.7%)	16	6.8%	(3.5%- 10.1%)	
Time since HIV diagnosis							0.0007
<5 years	57	12.3%	(9.2%- 15.4%)	13	6.1%	(2.7%- 9.5%)	
5-9 years	74	16.3%	(12.6%- 20.1%)	21	9.0%	(5.6%- 12.5%)	
≥10 years	340	71.4%	(67.1%- 75.7%)	187	84.9%	(80.3%- 89.4%)	
Homeless[f] at any time in the past 12 months	63	12.3%	(9.2%- 15.4%)	26	10.7%	(6.8%- 14.5%)	0.5282
Incarcerated for longer than 24 hours in the past 12 months	9	1.7%	(0.6%- 2.8%)	5	2.1%	(0.0%- 4.3%)	0.7109
Experienced discrimination since testing HIV positive	151	31.4%	(27.0%- 35.9%)	62	28.8%	(22.9%- 34.7%)	0.4788
Had private health insurance	234	53.3%	(48.7%- 58.0%)	91	42.8%	(36.0%- 49.6%)	0.0078
Geometric mean CD4 count							0.7336
0-199	27	5.7%	(3.8%- 7.6%)	15	6.8%	(3.4%- 10.2%)	
200-349	63	12.8%	(10.0%- 15.7%)	30	13.2%	(8.6%- 17.8%)	
350-499	86	17.5%	(14.2%- 20.7%)	45	20.1%	(14.6%- 25.7%)	
≥500	295	64.0%	(59.7%- 68.4%)	131	59.9%	(53.2%- 66.5%)	

Table 4.5 continued

Viral suppression							0.4924
Undetectable or <200 copies/mL	413	88.3%	(85.6%- 91.1%)	191	86.4%	(81.7%- 91.2%)	
Any HIV viral load measurement in 12 months after interview ≥200 copies/mL	58	11.7%	(8.9%- 14.4%)	30	13.6%	(8.8%- 18.4%)	
Self-reported ART use	447	95.1%	(93.2%- 97.0%)	212	95.5%	(92.5%- 98.5%)	0.8184
100% ART medication adherence (during preceding 72 hours)[g]							
By dose	387	88.5%	(85.5%- 91.5%)	180	87.5%	(82.8%- 92.2%)	0.7220
By schedule	325	72.7%	(68.5%- 76.9%)	162	76.0%	(70.0%- 82.0%)	0.3753
By special instructions	181	75.2%	(69.9%- 80.5%)	76	76.3%	(67.4%- 85.1%)	0.8485
Took drug holiday[h]	47	9.8%	(7.0%- 12.6%)	13	6.0%	(2.8%- 9.2%)	0.1127
Friend and family support satisfaction[g]							0.0026
Dissatisfied	61	13.7%	(10.5%- 16.8%)	13	6.1%	(2.9%- 9.2%)	
Satisfied	367	86.3%	(83.2%- 89.5%)	197	93.9%	(90.8%- 97.1%)	
Comfort discussing health with provider							0.0001
Not completely	87	18.0%	(14.6%- 21.5%)	17	7.3%	(4.0%- 10.6%)	
Completely	380	82.0%	(78.5%- 85.4%)	201	92.7%	(89.4%- 96.0%)	
Depression diagnosis in MRA 12 months before interview	167	34.8%	(30.1%- 39.5%)	80	35.7%	(28.8%- 42.6%)	0.8446
Current depression	111	22.6%	(18.8%- 26.4%)	31	13.9%	(9.6%- 18.1%)	0.0057
Binge drinking past 30 days	118	25.5%	(21.5%- 29.5%)	26	12.0%	(7.4%- 16.6%)	0.0002
Used non-injection drugs past 12 months	210	44.1%	(39.9%- 48.4%)	104	47.4%	(40.2%- 54.6%)	0.4422
Used injection drugs past 12 months	38	7.5%	(5.2%- 9.8%)	26	11.3%	(7.2%- 15.5)	0.0750
Total	**471**	100%		**221**	100%		

Abbreviations: CI, confidence interval; ART, antiretroviral treatment; MRA, medical record abstraction

[a] Numbers are unweighted

[b] Percentages are weighted percentages

[c] CIs incorporate weighted percentages

[d] Patients were classified as transgender if sex at birth and gender reported by the patient were different, or if the patient chose transgender in response to the question about self-identified gender

[e] Hispanics or Latinos might be of any race. Patients are classified in only one race/ethnicity category

[f] Living on the street, in a shelter, in a single-room–occupancy hotel, or in a car

[g] Among those currently taking ART

[h] Among those who have ever taken ART

Table 4.6: Characteristics stratified by viral suppression, Medical Monitoring Project, San Francisco, 2012-2014.

	Virally suppressed			Not virally suppressed			
Characteristic	**n[a]**	**%[b]**	**(95% CI)[c]**	**n[a]**	**%[b]**	**(95% CI)[c]**	**p-value**
Gender							0.0003
Male	564	93.4%	(91.3%- 95.5%)	75	85.4%	(77.7%- 93.2%)	
Female	32	5.4%	(3.5%- 7.3%)	6	6.9%	(1.4%- 12.4%)	
Transgender[d]	8	1.2%	(0.3%-2.1%)	7	7.6%	(1.4%- 13.9%)	
Sexual orientation							0.0489
Homosexual, gay, or lesbian	479	80.8%	(76.8%- 84.7%)	60	71.4%	(61.5%- 81.3%)	
Heterosexual or straight	78	12.5%	(9.1%- 16.0%)	20	22.1%	(13.0%- 31.2%)	
Bisexual	41	6.7%	(4.8%- 8.7%)	6	6.4%	(1.4%- 11.4%)	
Race/Ethnicity							0.4194
White	368	62.2%	(58.0%- 66.3%)	50	57.2%	(46.9%- 67.6%)	
Black or African American	70	10.9%	(7.6%- 14.2%)	16	17.1%	(9.5%- 24.7%)	
Hispanic or Latino[e]	124	20.4%	(17.4%- 23.4%)	16	19.4%	(10.5%- 28.3%)	
Multiracial/Other	42	6.6%	(4.7%- 8.5%)	6	6.3%	(1.3%- 11.4%)	
Age at time of interview (years)							0.0283
18-29 years	11	2.1%	(0.8%- 3.5%)	4	4.4%	(0.2%- 8.7%)	
30-39 years	54	9.5%	(6.8%- 12.2%)	12	14.0%	(6.2%- 21.7%)	
40-49 years	158	25.1%	(21.9%- 28.4%)	32	35.4%	(25.2%- 45.6%)	
≥50 years	381	63.2%	(59.3%- 67.1%)	40	46.2%	(35.2%- 57.2%)	
Education							0.0559
<High School	30	4.6%	(3.1%- 6.2%)	8	8.9%	(2.8%- 15.1%)	
High School diploma or equivalent	79	12.5%	(9.6%- 15.5%)	17	18.3%	(10.3%- 26.3%)	
Some college or more	495	82.9%	(79.6%- 86.2%)	63	72.7%	(63.3%- 82.2%)	
Country or territory of birth							0.8803
United States	503	83.4%	(80.4%- 86.4%)	74	84.1%	(76.3%- 91.9%)	
Other	101	16.6%	(13.6%- 19.6%)	14	15.9%	(8.1%- 23.7%)	
Time since HIV diagnosis							0.0526
<5 years	55	9.3%	(6.9%- 11.8%)	15	17.4%	(9.1%- 25.7%)	
5-9 years	80	13.7%	(10.6%- 16.7%)	15	16.3%	(8.6%- 24.0%)	
≥10 years	469	77.0%	(73.5%- 80.5%)	58	66.3%	(56.1%- 76.6%)	
Homeless[f] at any time in the past 12 months	63	9.6%	(7.3%- 11.9%)	26	27.3%	(17.8%- 36.8%)	<.0001
Incarcerated for longer than 24 hours in the past 12 months	6	0.9%	(0.1%- 1.8%)	8	8.5%	(2.8%- 14.2%)	<.0001
Had private health insurance	302	53.0%	(48.6%- 57.4%)	23	28.0%	(18.2%- 37.8%)	<.0001
Geometric mean CD4 count							<.0001
0-199	25	4.3%	(2.6%- 6.0%)	17	18.7%	(10.6%- 26.8%)	
200-349	77	12.2%	(9.6%- 14.7%)	16	18.6%	(10.4%- 26.9%)	
350-499	106	17.1%	(14.2%- 19.9%)	25	27.4%	(18.0%- 36.8%)	
≥500	396	66.5%	(62.7%- 70.3%)	30	35.3%	(25.3%- 45.3%)	
Self-reported ART use	592	98.2%	(97.2%- 99.2%)	67	74.2%	(64.5%- 83.9%)	<.0001

Table 4.6 continued

100% ART medication adherence (during preceding 72 hours)[g]							
By dose	519	89.8%	(87.3%- 92.4%)	48	72.4%	(61.4%- 83.5%)	<.0001
By schedule	455	76.5%	(72.9%- 80.1%)	32	47.6%	(35.9%- 59.4%)	<.0001
By special instructions	236	76.5%	(71.9%- 81.2%)	21	65.1%	(47.9%- 82.4%)	0.1744
Took drug holiday[h]	39	6.2%	(4.2%- 8.2%)	21	27.7%	(17.7%- 37.7%)	<.0001
Friend and family support satisfaction[g]							<.0001
Dissatisfied	57	9.5%	(7.1%- 11.9%)	17	27.1%	(16.0%- 38.2%)	
Satisfied	519	90.5%	(88.1%- 92.9%)	45	72.9%	(61.8%- 84.0%)	
Comfort discussing health with provider							0.0025
Not completely	81	13.0%	(10.4%- 15.6%)	23	25.5%	(16.1%- 34.9%)	
Completely	516	87.0%	(84.4%- 89.6%)	65	74.5%	(65.1%- 83.9%)	
Depression diagnosis in MRA 12 months before interview	207	33.8%	(30.1%- 37.5%)	40	44.2%	(33.7%- 54.7%)	0.0513
Current depression	114	18.3%	(15.3%- 21.2%)	28	30.9%	(21.6%- 40.3%)	0.0040
Binge drinking past 30 days	130	21.8%	(18.5%- 25.0%)	14	17.0%	(8.6%- 25.5%)	0.3417
Used non-injection drugs past 12 months	265	43.8%	(40.0%- 47.6%)	49	55.3%	(44.7%- 65.9%)	0.0396
Used injection drugs past 12 months	45	6.9%	(4.9%- 8.9%)	19	21.5%	(12.8%- 30.3%)	<.0001
Experienced stigma	413	68.4%	(64.7%- 72.0%)	58	64.6%	(54.3%- 74.8%)	0.4924
Experienced discrimination since testing HIV positive	176	29.1%	(25.3%- 32.8%)	37	41.4%	(30.7%- 52.2%)	0.0209
Total	**604**	100%		**88**	100%		

Abbreviations: CI, confidence interval; ART, antiretroviral treatment; MRA, medical record abstraction

[a] Numbers are unweighted

[b] Percentages are weighted percentages

[c] CIs incorporate weighted percentages

[d] Patients were classified as transgender if sex at birth and gender reported by the patient were different, or if the patient chose transgender in response to the question about self-identified gender

[e] Hispanics or Latinos might be of any race. Patients are classified in only one race/ethnicity category

[f] Living on the street, in a shelter, in a single-room–occupancy hotel, or in a car

[g] Among those currently taking ART

[h] Among those who have ever taken ART

Table 4.7: Average treatment effect of internalized HIV stigma on sustained viral suppression using three estimators.

	Estimate	(95% CL)[a]
Simple substitution	-1.75%	(-2.31%, -1.20%)
Stabilized IPTW	-2.57%	(-3.17%, -1.96%)
TMLE	-3.12%	(-3.63%, -2.61%)

Abbreviations: CL, confidence limits; IPTW, inverse probability of treatment weighting; TMLE, targeted minimum loss estimation

[a] 95% CL obtained by non-parametric bootstrap with 500 repetitions

FIGURE

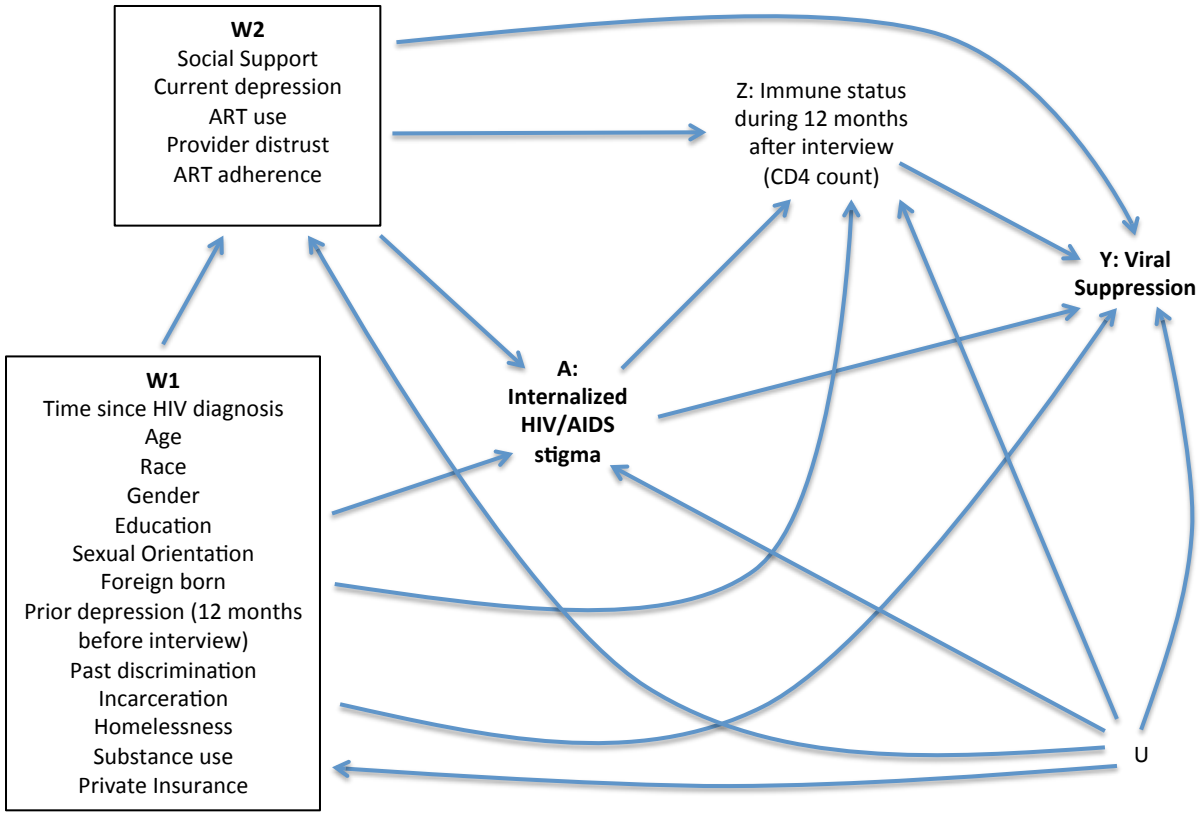

Figure 4.1: Directed acyclic graph (DAG) depicting endogenous variables involved in estimation of causal effect of internalized HIV stigma on sustained HIV viral suppression.

REFERENCES

1. The White House. National HIV/AIDS Strategy for the United States: Updated to 2020. July 2015. Available at: https://www.aids.gov/federal-resources/national-hiv-aids-strategy/nhas-update.pdf

2. Martinez J, Harper G, Carleton RA, et al. The impact of stigma on medication adherence among HIV-positive adolescent and young adult females and the moderating effects of coping and satisfaction with health care. *AIDS Patient Care STDS.* 2012;26: 108-115.

3. Rao D, Kekwaletswe TC, Hosek S, et al. Stigma and social barriers to medication adherence with urban youth living with HIV. *AIDS Care*. 2007; 19: 28-33.

4. Ware NC, Wyatt MA, Tugenberg T. Social relationships, stigma and adherence to antiretroviral therapy for HIV/AIDS. *AIDS Care.* 2006;18: 904-910.

5. Rintamaki LS, Davis TC, Skripkauskas S, et al. Social stigma concerns and HIV medication adherence. *AIDS Patient Care STDS.* 2006;20: 359-368.

6. Sayles JN, Wong MD, Kinsler JJ, et al. The association of stigma with self-reported access to medical care and antiretroviral therapy adherence in persons living with HIV/AIDS. *J Gen Intern Med*. 2009;24:1101-1108.

7. Vanable PA, Carey MP, Blair DC, Littlewood RA. Impact of HIV-related stigma on health behaviors and psychological adjustment among HIV-positive men and women. *AIDS Behav*. 2006;10:473-82.

8. Tsai AC, Weiser SD, Petersen ML, et al. A marginal structural model to estimate the causal effect of antidepressant medication treatment on viral suppression among homeless and marginally housed persons with HIV. *Arch Gen Psychiatry*. 2010;67: 1282-1290.

9. Rao D, Feldman BJ, Fredericksen RJ, et al. A structural equation model of HIV-related stigma, depressive symptoms, and medication adherence. *AIDS Behav.* 2012;16: 711-716.

10. Li L, Lee SJ, Thammawijaya P, et al. Stigma, social support, and depression among people living with HIV in Thailand. *AIDS Care.* 2009;21: 1007-1013.

11. Kalichman SC, Simbayi LC, Cloete A, et al. Measuring AIDS stigmas in people living with HIV/AIDS: the Internalized AIDS-Related Stigma Scale. *AIDS Care*. 2009;21:87-93.

12. Kroenke K, Strine TW, Spitzer RL, et al. The PHQ-8 as a measure of current depression in the general population. *J Affect Disord*. 2009;114:163-73.

13. Petersen ML, Van der Laan MJ. Causal models and learning from data: integrating causal modeling and statistical estimation. *Epidemiology.* 2014; 25: 418-426.

14. Van der Laan MJ, Gruber S. Targeted minimum loss based estimation of causal effects of multiple time point interventions. *Int J Biostat*. 2012; 8: 1.

15. Van der Laan MJ, Rose S. Targeted learning: causal inference for observational and experimental data. *Springer Science & Business Media*; 2011 Jun 17.

16. Van der Laan MJ, Polley EC, Hubbard AE. Super learner. *Stat Appl Genet Mol Biol*. 2007;6:1.

17. Berger YG. Rate of convergence for asymptotic variance of the Horvitz–Thompson estimator. *J Stat Plan Inference*. 1998;74:149-68.

18. Lee RS, Kochman A, Sikkema KJ. Internalized stigma among people living with HIV-AIDS. *AIDS Behav*. 2002;6:309-19.

Chapter 5

Conclusion

In the early 1980s, many healthy young men suddenly fell ill with two rare diseases- Kaposi's Sarcoma, a rare type of skin cancer, and Pneumocystis carinii pneumonia, a form of pneumonia that at the time was found in immunocompromised individuals, such as organ transplant recipients. San Francisco reported its first case of acquired immune deficiency syndrome (AIDS) in 1980. Since then, approximately 21,000 San Franciscans with HIV/AIDS have died [1].

Although San Francisco has been heavily affected by the HIV epidemic, there is hope and reason to believe that even without a vaccine or a cure, we can reach the goal of zero new HIV transmissions, zero HIV-related deaths and zero HIV stigma. Recently, new strategies have emerged to prevent transmission of HIV, including post-exposure prophylaxis (PEP), treatment as prevention, and pre-exposure prophylaxis (PrEP). During the time period that these new tools emerged, San Francisco experienced a marked decline in new HIV diagnoses, from 528 in 2006 to 255 in 2015, and in HIV-related deaths, from 327 deaths in 2006 to 197 deaths in 2015 [1]. PrEP, which was approved by the FDA in 2012, and universal ART irrespective of CD4 count, which has been shown to lengthen survival and decrease HIV transmission [2-6], have likely contributed to the decrease in new HIV diagnoses and the decrease in HIV-related deaths observed in San Francisco.

Still, there are disparities in the uptake of biomedical prevention strategies, in new HIV diagnoses, and among those living with HIV. Recent findings show racial disparities in PrEP uptake, where African American, Latino and younger persons are disproportionately less likely to be using PrEP [7-8]. The incidence of new HIV diagnoses in San Francisco in 2015 was 140 per 100,000 in African American men, and 83 per 100,000 in Latino men, compared with only 52 per 100,000 in white men [1]. Similarly for women, the incidence of new HIV diagnoses was highest in African American women in 2015 and was approximately three times higher than that of any other racial/ethnic group [1]. Unfortunately, linkage to care, retention in HIV care and HIV viral suppression for persons with a new diagnosis of HIV follow a similar pattern. African American, Latino, PWID (people who inject drugs) and younger persons have

the lowest proportions of linkage, retention and viral suppression [1]. The proportion of African Americans diagnosed in 2006-2013 that survived at least five years after HIV diagnosis was 79%, compared to 88% for whites [1]. These disparities must be addressed in order to get to zero new HIV transmissions, zero HIV stigma and zero HIV-related deaths.

My dissertation seeks to fill gaps in knowledge and help San Francisco get to zero new HIV transmissions, zero HIV-related deaths and zero HIV stigma. In Chapter 2, I described methods, results and implications of a novel approach for estimating in- and out-migration patterns, and consequently population size, of MSM by HIV infection status and race in San Francisco. I found that the overall MSM population and all the MSM subpopulations I studied decreased in size between 2006 and 2014. Further, there were differences in migration patterns by race and by HIV serostatus. Black MSM had the highest net out-migration in all years studied. More research is needed to determine if displacement in San Francisco due to rising costs is leading to disruption in HIV care, and subsequently a detectable HIV viral load. Differences observed in the migration patterns of MSM by race may contribute to disparities in HIV transmission and viral suppression among those living with HIV, but more work is needed to understand and address these racial disparities.

In Chapter 3, cross-sectional data from the Medical Monitoring Project (MMP) were used to determine if partnership type was associated with condomless anal sex (CAS) and insertive condomless anal sex (ICAS) among men who have sex with men living with HIV in San Francisco. There was a higher prevalence of CAS and ICAS in partnerships that were either seroconcordant or serodiscordant with PrEP, compared to partnerships that were serodiscordant without PrEP. There was evidence that men in this sample were adapting their condom use based on their sexual partner's HIV status and PrEP use and their own viral suppression status. A prior meta-analysis estimated that the incidence of syphilis was 45 times higher in MSM using PrEP compared to MSM who were not using PrEP [9]. Future work should determine whether decreased condom use and the high incidence of sexually transmitted infections in PrEP users could be offset by the protection offered by PrEP for HIV transmission.

One of the goals of the Getting to Zero consortium in San Francisco is elimination of HIV stigma. In Chapter 4, the causal effect of internalized HIV stigma on HIV viral suppression was estimated using data from the 2012-2014 cycles of MMP. Using TMLE, the counterfactual proportion of adults virally suppressed would decrease by roughly 3% if all adults did not experience internalized HIV stigma, as opposed to all adults experiencing internalized HIV stigma. Although experiencing internalized stigma was unexpectedly found to increase viral suppression, I argue that living in a stigma and discrimination free world is a fundamental human right for PLWH and warrants a high priority for "getting to zero" in San Francisco. Additional research should focus on understanding how stigma affects persons out of HIV care, especially with respect to accessing and not retaining in HIV care. Other factors influencing viral suppression must be identified in order to target interventions to the most vulnerable persons living with HIV in San Francisco.

REFERENCES

1. HIV Epidemiology Section, San Francisco Department of Public Health. HIV Epidemiology Annual Report 2015. San Francisco: San Francisco Department of Public Health September 2016; pp. 1-91.

2. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. 2010;375:2092–2098.

3. Del Romero J, Castilla J, Hernando V, et al. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. *BMJ*. 2010;340:c2205.

4. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011;25:473–477.

5. Grinsztejn, B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. *Lancet Infect Dis.* 2014;14:281-290.

6. Montaner JS, Lima VD, Harrigan PR, et al. Expansion of HAART coverage is associated with sustained decreases in HIV/AIDS morbidity, mortality and HIV transmission: the "HIV Treatment as Prevention" experience in a Canadian setting. *PLoS One*. 2014; 12: e87872.

7. Bush S, Magnuson D, Rawlings M, et al. Racial Characteristics of FTC/TDF for Pre-Exposure Prophylaxis Users in the US. ICAAC 2016. June 16-20, 2016. Boston, MA. Abstract 2651.

8. Marcus JL, Hurley LB, Hare CB, et al. Disparities in Uptake of HIV Preexposure Prophylaxis in a Large Integrated Health Care System. *Am J Public Health.* 2016;106: e2-e3.

9. Kojima N, Davey DJ, Klausner JD. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. *AIDS*. 2016; 30:2251-2252.

Appendix

Table A.1: Generalized estimating equation models stratified by self-reported HIV viral load predicting condomless anal sex and insertive condomless anal sex during the past 12 months in partnership, Medical Monitoring Project, San Francisco, 2014.

	CAS				ICAS			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	PR (95% CI)	p-value	aPR (95% CI)	p-value	PR (95% CI)	p-value	aPR (95% CI)	p-value
Virally Suppressed (n=311)								
Discordant, no PrEP	ref		ref		ref		ref	
Potentially discordant	0.84 (0.55-1.28)	0.42	0.89 (0.56-1.40)	0.61	1.56 (0.74-3.28)	0.24	2.23 (1.02-4.87)	0.05
Discordant, with PrEP	1.74 (1.25-2.40)	<.01	1.66 (1.27-2.18)	<.01	3.16 (1.69-5.89)	<.01	3.87 (2.24-6.68)	<.01
Seroconcordant	1.73 (1.28-2.35)	<.01	1.74 (1.34-2.27)	<.01	3.18 (1.716-5.92)	<.01	3.57 (2.04-6.26)	<.01
Not Virally Suppressed (n=69)[a]								
Discordant, no PrEP	ref		ref					
Potentially discordant	2.63 (0.67-10.38)	0.17	6.10 (1.15-32.33)	0.03	ref		ref	
Discordant, with PrEP	2.11 (0.82-5.45)	0.12	3.62 (0.70-18.72)	0.13	1.39 (0.21-9.28)	0.73	1.57 (0.29-8.57)	0.60
Seroconcordant	4.00 (1.13-14.21)	0.03	8.39 (1.41-49.83)	0.02	3.96 (0.81-19.38)	0.09	4.48 (0.59-33.93)	0.15

Abbreviations: CAS, condomless anal sex; ICAS, insertive condomless anal sex; CI, confidence interval; PR, prevalence ratio; aPR, adjusted prevalence ratio; PrEP, pre-exposure prophylaxis

[a] Reference group was changed to "potentially discordant" for this model due to zero observations in the "discordant no PrEP" group with the outcome of interest (ICAS)