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Receipt, Predictors and Effectiveness of Smoking Cessation Medications among
People Living with HIV (PLWH) in the National Veterans Health Administration

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Abstract

Receipt, Predictors and Effectiveness of Smoking Cessation Medications among People Living with HIV (PLWH) in the National Veterans Health Administration

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Cigarette smoking is the leading cause of morbidity and mortality worldwide, and is highly prevalent among people living with HIV (PLWH). Prescription pharmacotherapies—nicotine replacement therapy (NRT), varenicline, and bupropion—have been shown to be comparably effective in promoting smoking cessation for PLWH and HIV-uninfected persons, and are recommended by the Veterans Health Administration (VHA) to treat tobacco use disorder. We used data from the Veterans Aging Cohort Study (VACS), which is the largest epidemiologic study of PLWH receiving health care in the United States, to specifically test: (1) whether PLWH are less likely to receive smoking cessation medications compared with HIV-uninfected individuals, and which patient-level factors are associated with receipt; (2) whether rates of medication receipt among PLWH and uninfected controls have changed over time; and

(3) whether and which medications are most effective for smoking cessation among PLWH in routine care.

Our findings were: (1) PLWH in a cross-sectional analysis were less likely to receive NRT, but not other medications; contemplating cessation and recent diagnoses for pulmonary disease and psychiatric illness were associated with receipt of smoking cessation medication among PLWH, but sociodemographic characteristics, alcohol use, substance use, or recent CVD diagnosis were not; (2) the rate of change in receiving any medication per year improved for both populations, largely due to greater receipt of NRT; PLWH experienced a slightly greater increase in rate of receiving medications; and (3) bupropion and varenicline were associated with increased likelihood of smoking cessation, but were underutilized as treatments for tobacco use disorder in the VHA; single NRT was not associated with smoking cessation and combination NRT was associated with continuing to smoke.

In summary, smoking cessation may be promoted and health improved among PLWH by providing this population greater access to the most effective treatments for tobacco use disorder. The results of this innovative research could be used to better inform HIV service providers and policies within the VHA to fill gaps in care and deliver effective and tailored smoking interventions to their patients.

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I thank my sisters (Shakira and Shazana), my brother (Shafiq), and my parents (Fuziah, Pat, and Shahrir) who have nurtured a strong foundation in education throughout my life. As I write this, I think of my Baba whose own doctoral pursuits led my family to leave Malaysia and immigrate to the United States. I also think of my Mom who left a career in Journalism to raise four children in a foreign country and support a doctoral student.

Finally, I am forever grateful to my husband, Justin, for his enduring love and faith in me. To my son, Ian, you are my biggest inspiration.

DEDICATION

To Justin and Ian

1 Chapter 1. INTRODUCTION

1.1 SIGNIFICANCE

Tobacco use remains the leading cause of preventable death and disease in the United States (U.S.) and is extremely harmful for people living with HIV (PLWH) [1]. Although HIV infection was previously considered to be fatal, it has increasingly become a manageable chronic disease due to advancements in HIV treatment [2, 3]. As PLWH live longer as a result of antiretroviral therapy (ART), they now experience substantial comorbid, non-AIDS-related illness [4-9]. These include cardiovascular disease (CVD) [2, 3], chronic obstructive pulmonary disease (COPD) [4, 5], and cancers of the head, neck, and lung [6, 7]—all diseases for which smoking is a major risk factor. Smoking is also associated with increased respiratory infections [8-10], respiratory symptoms [4, 11], decreased quality of life [12, 13], and two-fold greater mortality among PLWH [14]. Furthermore, several studies have suggested that PLWH who smoke may have poorer viral and immunologic responses to ART and higher risk of developing AIDS [15].

Cigarette smoking is highly prevalent among PLWH. Greater than 40% of PLWH currently smoke, with rates in some subpopulations reaching as high as 74% [1, 16-18], in contrast to 14% among the general U.S. population [19]. In other words, despite the independent and compounding risks associated with tobacco use and HIV infection, smoking is three to five times more prevalent among PLWH compared with populations without HIV. Given the aging of PLWH due to decreased mortality from AIDS-defining illnesses and increased prevalence of tobacco use, smoking-related comorbidities are becoming increasingly common. Thus, smoking cessation has emerged as a critical, modifiable component to improve the health of PLWH.

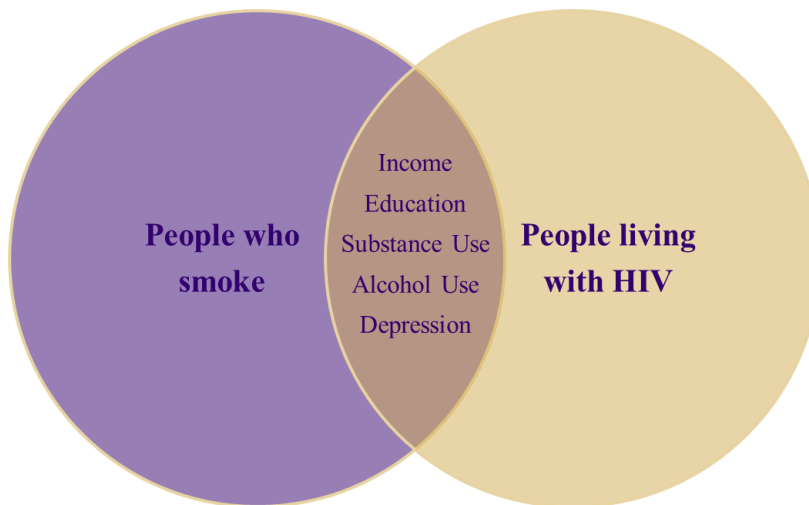
Smoking cessation medications can significantly increase rates of long-term cessation and PLWH would greatly benefit from receiving these effective and evidence-based treatments. Nicotine replacement therapy (NRT), varenicline, and bupropion, have been shown to greatly improve quit rates 1.5-2 fold over placebo in samples of people recruited to clinical trials without HIV infection [20, 21]. Observational and clinical trial data indicate that NRT, varenicline, and bupropion are similarly effective in PLWH compared with HIV-uninfected groups [22-27]. Additionally, several studies indicate that the majority of PLWH who smoke (63%-75%) want to quit and have attempted to quit previously [28-30]. Given that the prevalence of current smoking remains significantly higher among PLWH relative to the general population, these data suggest that patient-level interest is not a major barrier to smoking cessation and perhaps we should examine whether existing treatments, including pharmacotherapies, are being differentially administered.

Smoking cessation medications represent a crucial strategy in reducing the prevalence of smoking and maintaining the health of PLWH, though some subgroups of PLWH may be more vulnerable to under-receipt. Several studies have found cigarette smoking and HIV to be associated with low income and low education levels [31, 32]. Lower levels of education and income are also associated with smoking behaviors such as higher smoking prevalence, higher nicotine-dependence rates, greater use of non-filter, high-tar cigarettes, and a lower quit rate [33]. Additionally, PLWH experience high rates of depression, concurrent alcohol use disorder, and other substance use disorders [29, 34, 35]. In particular, depression [18] and substance use disorders [36, 37] are separately and independently associated with tobacco use among PLWH and may represent major barriers to smoking cessation. For example, depression is associated with lower self-efficacy to quit smoking among PLWH [38]. Furthermore, the majority of

PLWH in two studies reported that smoking helped them to control their anger, anxiety, and depression [18, 39]. A large proportion of respondents in interview also believed that smoking helped them increase social contact and be accepted by other smokers [39].

In a study conducted in the VACS survey cohort, unhealthy alcohol use in PLWH was negatively associated with contemplating cessation and having made a quit attempt in the last year compared with PLWH without unhealthy alcohol use [28]. Injection drug use has also been shown to be associated with a lack of motivation to quit smoking among PLWH [34, 40]. However, other investigations provide evidence that smoking cessation is possible with at least moderate efficacy in populations with serious comorbidities, specifically in individuals with alcohol use disorders [41], psychiatric disorders [42], and depression [42] with little evidence of exacerbation of these conditions.

Figure 1.1: Overlapping Vulnerabilities Facing PLWH and People who Smoke



PLWH may have limited access to smoking cessation medications due to their comorbid complex care needs and disproportionate exposure to social determinants of adverse health. In managing HIV clinical characteristics, concomitant substance abuse, mental health, and other comorbidities in their patient population, HIV care clinicians may not have enough time and be

less prepared to address smoking. Over a third of HIV practitioners report having inadequate time to address smoking cessation with their patients during clinic visits [43]. A lack of training and a lack of confidence to influence smoking cessation among infectious disease providers [29, 44] suggest that receipt of effective smoking cessation medications may be potentially disparate among PLWH and the HIV-uninfected population. For example, in a study conducted among HIV and non-HIV providers in the VHA, infectious diseases specialists proved almost three times more likely to fail to identify current smoking patients in their care compared with general practitioners [44]. In a nationwide survey, fewer than half of HIV clinicians reported frequently prescribing NRT, bupropion, or varenicline [43].

Still, several system-level initiatives may have influenced provision of smoking cessation medications over time among PLWH receiving routine care. As pharmacotherapy has become standard care in treating tobacco use disorders, understanding how rates of receipt of key smoking cessation medications are changing, or not changing, among PLWH compared with HIV-uninfected controls will indicate whether this population is given the opportunity to receive effective treatment at similar rates. While general use of smoking cessation medications has increased, patterns of use over time among PLWH have not been described. Clinical Practice Guidelines put forth by the U.S. Health and Human Services (HHS) and VHA directives recommend addressing smoking cessation at each visit, administering two smoking cessation medications in combination with counseling, and re-prescribing smoking cessation medications after relapse because every attempt to quit improves the probability of eventual success [45]. In response to these guidelines, the VHA created several resources to providers, one of which was specifically designed to help HIV care providers address tobacco use among their patient

population [46]. As general U.S. and VHA culture around pharmacotherapy to quit smoking improves, the receipt of smoking cessation medications is likely to increase over time.

It is unknown whether PLWH receiving these medications in routine care benefit from them, and medications may be differentially effective. Of medications approved by the U.S. Food and Drug Administration (FDA) to treat tobacco use disorder, varenicline has been shown to be superior in promoting cessation over other pharmacotherapies [47-49]. However, it is considered a second-line treatment and has been strictly controlled within the VHA due to several cases specifically involving veterans in which it exacerbated underlying mental illness [50]. For example, patients who are prescribed varenicline are required not to have active mental health disorder and are known to have been previously unsuccessful at quitting on NRT and combination therapies. This practice has implications in the ability to prescribe what has been demonstrated as the most effective medication for treating tobacco use disorder. Nevertheless, whether and what smoking cessation pharmacotherapies impact cessation among PLWH receiving routine care has not been previously studied in the VHA and may better inform future prescription practices.

In this dissertation, we describe receipt of smoking cessation medications among PLWH, overall and relative to those without HIV, and examine the patient-level factors associated with receipt of principal pharmacotherapies by HIV status. We also explore changing patterns in receiving these medications over time, and examine the effectiveness of specific medications among PLWH in routine care settings. By elucidating these gaps in the literature, we may provide a road map for increasing access to effective tobacco cessation in this population for whom smoking is particularly harmful. Further, they could be used to better inform HIV care providers in delivering effective and tailored smoking cessation interventions, especially those

most vulnerable to under-receipt. Therefore, we propose to address these gaps in the literature using data from the Veterans Aging Cohort Study (VACS)—the largest epidemiologic study of PLWH receiving health care in the U.S.

1.2 THE VETERANS AGING COHORT STUDY AND OTHER DATA SOURCES

VACS consists of two ongoing cohorts. The first, assembled from national VHA data alone beginning in 1997, is a Virtual Cohort (VACS VC) of >50,000 PLWH receiving care in the VHA matched 1:2 to (>100,000) HIV-uninfected participants by five-year blocks of age, race/ethnicity, sex, and site of care [51]. At the end of each fiscal year, this cohort is updated to include veterans with new diagnoses of HIV infection and matched controls receiving care in the same fiscal year. The second is a prospectively-consented, substudy cohort of veterans with and without HIV currently in care at nine VHA medical centers around the country (VACS 9). These VHA facilities are Atlanta, Baltimore, the Bronx, Dallas, Houston, Los Angeles, Manhattan/Brooklyn, Pittsburgh, and Washington D.C.

The VHA is the largest system of health care in the nation and is the single largest health care provider to PLWH nationally [46]. At least 25% of veterans living with HIV in care are current smokers based on administrative data [52]; by self-report 51% of this population enrolled in VACS are current smokers [52], allowing for a large evaluation of the dissertation aims.

The VHA Corporate Data Warehouse (CDW) is a national data repository that incorporates data from all patients seen in the VHA from clinical and administrative systems into one standard database structure. The CDW is the source of the VACS VC and is also used to supplement survey data with pharmacy, clinical, and diagnostic data for VACS 9. This repository provides all smoking-related “Health Factors” data that is conducted by VHA health care providers and documented in the VHA’s electronic health record (EHR). HF data is the

basis for classifying smoking status within VACS, if not identified via survey response. These data are collected nationally through automated annual clinical reminders that are embedded in the EHR, prompting VHA providers to ask patients about their tobacco use. Based on kappa statistic, these data had substantial agreement with smoking status collected from survey response [53].

In addition, the CDW provides all filled outpatient prescriptions for smoking cessation pharmacotherapy, specifically NRT, varenicline, and bupropion. It also provides lab results on our subject population as well as incident disease diagnoses. Data collected from VACS survey (also called COMpAAAS survey based on the National Institute on Alcohol Abuse and Alcoholism-funded consortium title to which VACS belongs) provides detailed information on alcohol use, drug use, pain, depression, and physical and mental health scores.

1.3 DISSERTATION AIMS

In the following chapters, we examine the receipt of smoking cessation medication to quit smoking among PLWH and uninfected controls in both the VACS 9 survey cohort (Aim 1) and the larger VACS VC (Aims 2 and 3).

Aim 1: Test the cross-sectional association between HIV and smoking cessation pharmacotherapy receipt, and compare patient-level factors associated with receipt of these medications among PLWH compared with uninfected controls. The purpose of Aim 1 is to, first, assess whether smoking cessation medications received in the year following survey is statistically disparate by HIV status and, second, identify patient-level factors associated with outpatient prescription fill among PLWH and HIV-uninfected populations. We apply marginal multivariable log-linear regression with a Poisson working model to estimate the relative risk and 95% confidence interval of pharmacotherapy receipt. We hypothesized that PLWH who

smoke would be less likely to have received pharmacotherapies to quit smoking compared with HIV-uninfected controls. PLWH who had co-occurring alcohol or other substance use disorders, and who had mental health comorbidity would have decreased likelihood of receipt compared with uninfected controls.

Aim 2: Test whether rates of pharmacotherapy receipt among PLWH have changed over time and whether these changes are different compared with an uninfected control group from January 1, 2006 to December 31, 2018. The purpose of Aim 2 is to evaluate whether the rate of change in receipt of pharmacotherapy is different by HIV status. We use multivariable log-linear regression with a modified Poisson working model in order to estimate the relative risk of receipt and 95% confidence interval. In this longitudinal dataset, we apply generalized estimated equations (GEE), for a population-level interpretation. We hypothesized that HIV-uninfected participants would have greater receipt of smoking cessation medications compared with PLWH though there will be a trend over time towards greater equity in receipt of pharmacotherapy.

Aim 3: Test which smoking cessation medications are associated with changes in smoking status from current smoker to former smoker among PLWH from January 1, 2013 to December 31, 2018. The purpose of Aim 3 is to evaluate which pharmacotherapies are associated with becoming a former smoker among PLWH who smoke. We apply marginal multivariable log-linear regression with a modified Poisson working model to estimate the relative risk of “cessation”, i.e. changing from current to former smoker status, and 95% confidence interval. We also apply inverse probability treatment weighting (IPTW) to estimate average treatment effects and account for bias by indication. We hypothesized that varenicline

would be most greatly associated with former smoking status among PLWH, though the least prescribed.

This research makes several contributions to advance the science of smoking cessation among PLWH. First, this work examines demographic, behavioral, and psychosocial factors associated with receipt of smoking cessation pharmacotherapy in PLWH compared with a demographically similar uninfected group. Second, it evaluates changes in receipt of these medications over time, as prescription practices and VHA culture has changed towards greater provision in general and specifically among PLWH. Lastly, it assesses the effectiveness of the principal smoking cessation medications in impacting the potential for cessation among PLWH. When taken together, the results from these aims hope to inform the population health priorities, practice, and strategies HIV providers can adopt when assisting their patients to quit smoking.

1.4 CONCEPTUAL FRAMEWORK

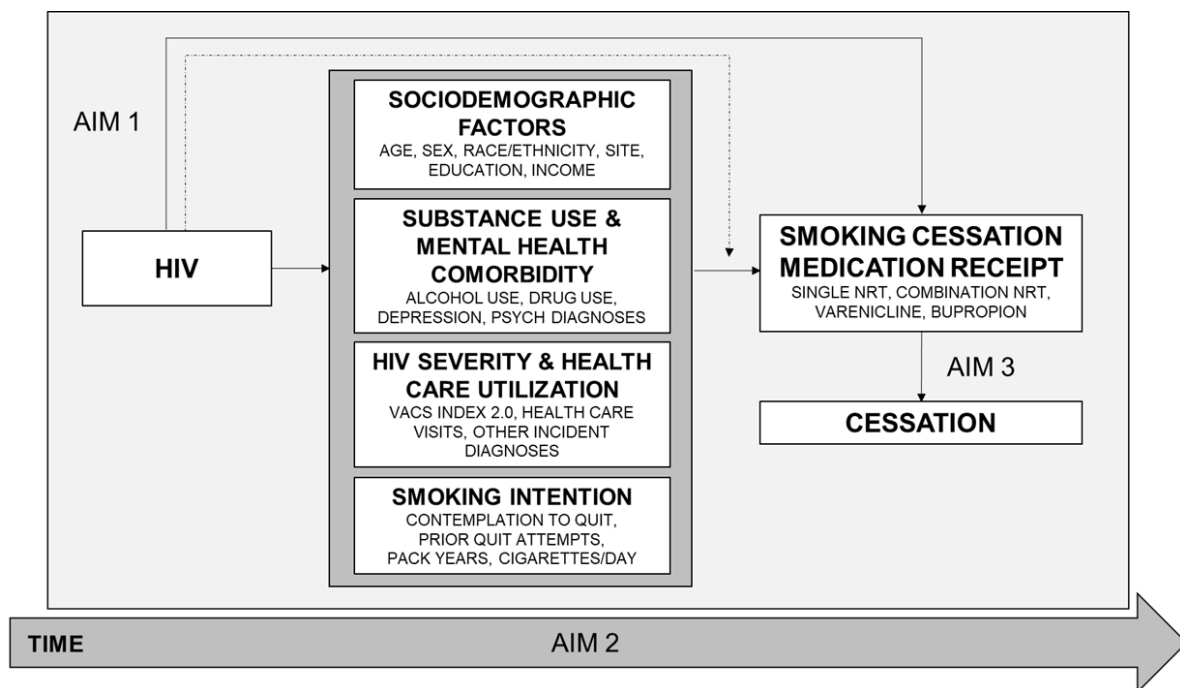
The conceptual model for this project represents our three aims, the three pathways, in which we believe HIV influences receipt of smoking cessation pharmacotherapy. We believe HIV directly and indirectly impacts the likelihood of receiving pharmacotherapy to quit smoking through associated sociodemographic factors, substance use and mental health comorbidity, HIV severity and health care utilization, and smoking intention. Specific covariates of interest described in the literature include education, income, alcohol use, drug use, and depression. Furthermore, HIV itself may effect receipt of smoking cessation medications.

Changes in culture and practice in the prescription of NRT, varenicline, and bupropion over time, within the VHA and in general, may improve the potential receipt of smoking cessation pharmacotherapy among PLWH. After Clinical Practice Guidelines were issued by the HHS, the VHA promoted similar material to reflect the growing need and priority to address

tobacco use in their patient population living with HIV. We hypothesized that while disparity persists in the receipt of these medications by HIV, there will be a trend over time towards greater equity.

Finally, regardless of HIV, but specifically within this subsample of patients, we believe that receipt of smoking cessation medication leads to smoking cessation. Among veterans with HIV, we posited that those who have received pharmacotherapy are more likely have a change in smoking status from current to former smoker. Additionally, the conceptual model guides our rationale to adjust for differences in the sociodemographic, substance use and mental health factors, and other characteristics that disproportionately affect patients with HIV who receive smoking cessation medications from those who do not.

Figure 1.2: Conceptual Model for HIV, Medication Receipt, and Smoking Cessation



Our conceptual model specifically characterizes aspects of the problem regarding HIV and smoking that we defined in earlier sections with the ability to ascertain key influential

factors of this relationship from our data sources. Receipt of smoking cessation medication is only one piece of this issue, and individual characteristics constitute only one level. Of course, there are many more radiating levels of influence (societal, community, interpersonal, etc.) of which this dissertation represents a very small part. Further research is imperative and recommendations for this work can be found in Chapter 5.

1.5 ROAD MAP

The rest of this dissertation is organized as follows: Chapters 2 through 4 present the study design, analytic methods, and results from Aims 1, 2, and 3, respectively. Finally, Chapter 5 summarizes the findings, policy implications, and future directions from this dissertation.

2 Chapter 2. RECEIPT AND PREDICTORS OF SMOKING CESSATION MEDICATIONS AMONG PEOPLE LIVING WITH HIV AND HIV-UNINFECTED VETERANS

2.1 INTRODUCTION

As HIV increasingly becomes a manageable chronic disease due to effective antiretroviral therapy (ART) [1, 54], people living with HIV (PLWH) are surviving albeit with an increased burden of non-infectious, non-AIDS-related illnesses, such as cardiovascular disease (CVD) [2, 3]. Smoking and HIV are independent risk factors for CVD, and the health consequences of CVD are compounded for PLWH who smoke [3, 55]. Consequently, smoking cessation has emerged as a critical, modifiable component to improve the health of PLWH. Effective pharmacologic treatments for tobacco use disorder exist for PLWH, namely nicotine replacement therapy (NRT), bupropion, and varenicline. These medications are approved by the U.S. Food and Drug Administration (FDA) and have been shown to be comparably effective in improving quit rates in populations with and without HIV [22-27].

PLWH and HIV-uninfected persons may have differing access to smoking cessation pharmacotherapies as a result of factors across multiple domains (e.g., factors related to comorbid conditions, smoking-related behaviors and attitudes, issues specific to the experience of living with HIV, and receiving regular care for HIV). For example, PLWH may have limited access to smoking cessation pharmacotherapy relative to uninfected populations due to their comorbid, complex care needs. Comorbid substance use and mental health disorders (e.g., unhealthy alcohol use and depression) are separately and independently associated with tobacco use among PLWH and may represent major barriers to smoking cessation [18, 36, 37]. Management of these conditions in combination with HIV clinical characteristics, may present

logistical (e.g, time) or training (e.g., content expertise) barriers to addressing smoking in HIV care settings [29, 43, 44]. On the other hand, PLWH may have greater health care utilization than HIV-uninfected persons as a result of receiving regular HIV care consistent with clinical guidelines to ensure immune competence and appropriate viral suppression [56]. As a result, PLWH may be in more frequent contact with a medical provider and have greater opportunity to receive smoking cessation medications.

Despite the importance of promoting smoking cessation among PLWH, it is unclear at what rates PLWH who smoke are receiving pharmacotherapies. Therefore, in a national sample of patients receiving care in the Veterans Health Administration (VHA) recruited to the Veterans Aging Cohort Study (VACS), we describe receipt of smoking cessation medications among PLWH, overall and compared with a matched sample of HIV-uninfected patients, and describe patient-level factors associated with receipt of pharmacotherapy among PLWH and uninfected patients separately.

2.2 METHODS

Study Data Sources and Sample

VACS is a multi-site, longitudinal, prospective cohort study of PLWH and uninfected controls receiving care in nine Veterans Health Administration (VHA) Infectious Disease (ID) and General Medicine Clinics, respectively [52]. Specifically, HIV-uninfected participants are matched by five-year blocks of age, race/ethnicity, sex, and site of care to veterans with HIV from VHA facilities in Atlanta, Baltimore, the Bronx, Dallas, Houston, Los Angeles, Manhattan/Brooklyn, Pittsburgh, and Washington D.C. For the present study, we included 1722

patients (814 PLWH and 908 HIV-uninfected) who were surveyed between 2012 and 2017 and reported current smoking.

VACS survey data for the sample were linked to electronic health record (EHR) data extracted from the VHA Corporate Data Warehouse (CDW), which includes clinical, administrative, pharmacy, and utilization data for all users of VHA care [57].

Primary independent measure

HIV status was defined as having two outpatient or one inpatient diagnostic codes from the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) for either AIDS (042) or HIV (V08), consistent with prior research conducted in VACS [51].

Outcomes

The primary outcome of interest was a dichotomous measure identifying receipt of any smoking cessation pharmacotherapy (NRT, bupropion, and varencline), based on outpatient prescription fill data from VHA pharmacy data in the CDW, 0-365 days following the date of completed survey. Secondary outcomes were derived to measure receipt of each specific medication 0-365 days following the date of completed survey.

Covariates

Covariate selection was guided by a conceptual model that includes factors hypothesized to impact the likelihood of receiving smoking cessation pharmacotherapy. These include socio-demographic factors, substance use and mental health comorbidity, smoking-related comorbid conditions, HIV severity, health care utilization, and smoking-related attitudes and behaviors.

Sociodemographic factors such as age at time of survey (continuous), sex (male versus female), and race/ethnicity (black, Hispanic, white, other) were asked on survey and verified in

administrative data sources. “Other” race included American Indian or Alaska Native, Asian, and Native Hawaiian or Pacific Islander. Education (less than high school, high school graduate or GED, some college or technical school, college graduate or graduate school), and annual income (earning less than \$1200, \$12000-24999, \$25000 or greater) were assessed in individual survey items.

Substance use and mental health comorbidity were ascertained through both survey items and the EHR system. In the survey, alcohol use was evaluated using the three-item Alcohol Use Disorders Identification Test Consumption (AUDIT-C) questionnaire, which is a brief alcohol screen validated to identify patients with unhealthy alcohol use [58]. Men who scored 4 or greater and women who scored 3 or greater were identified as having unhealthy alcohol use [59]. Surveyed participants were also asked to identify the frequency with which they had used cocaine or crack, amphetamines, and/or heroin in the last 12 months. We coded a dichotomous “any substance use in the last year” measure as those participants who reported “less than once per month” or more frequent use of any of these drugs compared with those reporting “no use in the last year” or “have never tried” for all drugs. Depression was assessed via survey using the Patient Health Questionnaire (PHQ-9), a 9-item screen for which a value greater than nine has an 88% sensitivity and 88% specificity for diagnosing moderate to severe depression [60]. ICD-9 codes pertaining to other psychiatric conditions (bipolar disorder, major/minor depression, post-traumatic stress disorder, schizophrenia, and other psychosis) were grouped together [61], and were defined as having a recent psychiatric diagnosis if a code occurred 0-365 days prior to completing survey.

Smoking-related comorbid conditions were ascertained using diagnostic coding in the EHR, and included CVD (ICD-9 CM codes for acute myocardial infarction, coronary artery

disease, congestive heart failure, hypertension, stroke, other CVD); chronic pulmonary disease (ICD-9 CM codes for COPD, obstructive lung disease, pulmonary hypertension, other pulmonary disorder); and non-AIDS malignancies (e.g., Hodgkin lymphoma and cancers of the mouth, throat, liver, lung, and anus) [28] documented in the 0-365 days prior to survey date.

HIV severity was measured using the VACS Index 2.0, a composite measure of HIV severity that predicts all-cause mortality, cause-specific mortality, frailty, and other clinical outcomes in people with HIV [62] as well as in persons without HIV infection [63, 64]. VACS Index 2.0 includes CD4 cell count and HIV-1 RNA in combination with other disease markers [65-67], and is generated using a combination of administrative, clinical, and laboratory data. Individual components of VACS 2.0 documented in the CDW closest to date of survey was used to calculate the continuous summary score.

Table 2.1. VACS Index 2.0 Components
Age
Race
Sex
CD4 cell count
HIV-1 RNA
Hemoglobin
Platelet count
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Fibrosis-4 score
Creatinine
Estimated glomerular filtration rate (eGFR)
Hepatitis C virus (HCV) coinfection
Albumin
White Blood Cell count
Body Mass Index

Health care utilization included outpatient and inpatient visits captured using visit and stop codes documented in the CDW in the 0-365 days prior to survey date. The number of outpatient visits was limited to primary care encounters. These were summed and then categorized into 1-2, 3-5, and 6 visits or greater based on 1-106 visits distribution [68]. Inpatient visits were summed and categorized into 0, 1, and 2 visits or greater based on a 0-16 visits distribution.

Smoking-related attitudes and behaviors were ascertained via survey questions. One survey item asked whether respondents were currently thinking about quitting. We coded a dichotomous “contemplating to quit” measure as those thinking about quitting, while grouping

those who selected that they were “not sure” or “not thinking about quitting” or “not ready to quit” as not contemplating cessation. Respondents who reported at least one quit attempt were coded as having a past quit attempt. Average number of cigarettes smoked per day was also assessed on the survey and measured in our study as less than 10, 10-20, and greater than 20 cigarettes.

Analysis

We described the demographic and clinical characteristics of the sample, overall and across HIV status using chi-square tests of independence, Student’s t-test, and Wilcoxon Rank-Sum test as appropriate. We also described the rate of primary and secondary pharmacotherapy outcomes in the overall sample.

To assess receipt of pharmacotherapy among PLWH overall and relative to HIV-uninfected persons, we first conducted bivariate comparisons of the prevalence of primary and secondary outcomes (across HIV status using chi-square tests). Subsequently, we fit marginal multivariable log-linear regression models with a Poisson distribution to estimate the adjusted relative risk (ARR) and 95% confidence interval (CI) of pharmacotherapy receipt for PLWH compared with uninfected participants. Models were adjusted for all measured covariates in the domains described above. Poisson, rather than logistic regression, was used because the outcome was expected to be fairly common, in which case odds ratios may overestimate the associations [69, 70]. In order to account for the multi-level nature of the data, we clustered by site of care and specified an exchangeable correlation structure. Further, we used a robust sandwich estimator to calculate standard errors and obtain a valid inference even if the correlation structure was incorrectly specified [68-72].

The same model was repeated in populations stratified by HIV status so that we could compare which patient-level factors were associated with pharmacotherapy receipt in populations with and without HIV.

All analyses were performed using Stata version 14 (Stata Corp, College Station, TX).

2.3 RESULTS

Study Population

Among 4113 VACS participants, 1722 (42%) self-reported current smoking (n=814 PLWH and 908 HIV-uninfected) and were thus eligible for the present study. Participants in our sample were predominantly black (74%), male (96%), had at least some college or technical school education (89%), and were a mean age of 56 years (Table 2.2).

Compared with HIV-uninfected participants, PLWH had a greater proportion of people reporting black race and earning \$1200-\$24999 annually, lower prevalence of recent non-AIDS malignancy diagnosis, and higher median VACS Index 2.0 score and number of outpatient visits in the last year. PLWH had a lower prevalence of unhealthy alcohol use, moderate-severe depression, recent psychiatric and CVD diagnoses, and lower median number of inpatient visits in the last year relative to uninfected participants (Table 2.2). However, no differences by HIV status were observed in the proportion of participants who were contemplating cessation, median number of previous quit attempts or cigarettes smoked daily (Table 2.2).

Table 2.2: Characteristics of Patients Reporting Current Smoking who Completed VACS Survey between 2012 and 2017, Overall and by HIV Status

	Study Population (n=1722)	HIV+ (n=814)	HIV- (n=908)	<i>p value</i>
SOCIODEMOGRAPHIC FACTORS				
Age, mean (SD)	56.2 (8.3)	56.4 (8.1)	56.1 (8.5)	NS
Male, n (%)	1646 (96)	786 (97)	860 (95)	NS
Race/ethnicity, n (%)				0.01
Black	1280 (74)	623 (77)	657 (72)	
Hispanic	93 (5)	49 (6)	44 (5)	
Other	89 (5)	42 (5)	47 (5)	
White	257 (15)	98 (12)	159 (18)	
Education, n (%)				NS
< High school	104 (6)	49 (6)	55 (6)	
High school grad, GED	647 (38)	290 (36)	357 (39)	
Some college or technical school	779 (45)	374 (46)	405 (45)	
College grad, higher education	184 (11)	97 (12)	87 (10)	
Married or living with partner, n (%)	374 (22)	169 (21)	205 (23)	NS
Annual income, n (%)				0.01
<\$12,000	741 (44)	330 (42)	411 (47)	
\$12,000-24999	485 (29)	259 (33)	226 (26)	
≥ \$25000	443 (27)	200 (25)	243 (28)	
SUBSTANCE USE / MENTAL HEALTH COMORBIDITY				
Audit-C score, median (IQR)	2 (0-5)	2 (0-4)	2 (0-5)	0.05
Unhealthy alcohol use, n (%)	595 (35)	256 (31)	339 (37)	0.01
Substance use in the last year, n (%)				
Marijuana	557 (33)	288 (36)	269 (30)	0.01
Cocaine or crack	447 (26)	202 (25)	245 (27)	NS
Amphetamines	108 (6)	51 (6)	57 (6)	NS
Heroin	128 (8)	57 (7)	71 (8)	NS
Prescription opioids	331 (19)	155 (19)	176 (20)	NS
Depression severity (PHQ-9), median (IQR)	4 (1-9)	4 (1-9)	5 (1-10)	0.01
Moderate to severe depression, n (%)	407 (24)	171 (21)	236 (26)	0.02
Psychiatric disorders, n (%)	781 (48)	296 (38)	485 (57)	<0.001
SMOKING-RELATED COMORBIDITY				
Cardiovascular disease, n (%)	791 (48)	346 (44)	445 (52)	<0.001
Pulmonary disease, n (%)	185 (11)	79 (10)	106 (13)	NS
Non-AIDS malignancies, n (%)	110 (7)	64 (8)	46 (5)	0.03
HIV SEVERITY				
HIV-infected, n (%)	814 (47)			
On antiretroviral therapy, n (%)		762 (94)		
HIV severity				
HIV RNA Viral load, median (IQR)		40 (20-91)		
CD4+ count, median (IQR)		483 (308-691)		
VACS Index 2.0, median (IQR)	42 (33-55)	51 (41.5-63)	35 (29-44)	<0.001
HEALTH CARE UTILIZATION				
Outpatient visits in last year, median (IQR)	4 (2-6)	4 (3-7)	3 (2-5)	<0.001
Inpatient visits in last year, median (IQR)	0 (0-1)	0 (0-0)	0 (0-1)	<0.001

SMOKING-RELATED ATTITUDES / BEHAVIORS

Contemplating to quit, n (%)	1175 (71)	554 (72)	621 (71)	NS
Past quit attempts, median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	NS
Cigarettes smoked daily, median (IQR)	9 (5-12)	8 (5-12)	10 (5-12)	NS
Smoke >1 pack daily, n (%)	63 (4)	27 (4)	36 (4)	NS
Time to first cigarette, n (%)				NS
After 60 minutes	493 (29)	242 (30)	251 (28)	
31-60 minutes	290 (17)	134 (17)	156 (18)	
6-30 minutes	486 (29)	225 (28)	261 (29)	
Within 5 minutes	425 (25)	206 (26)	219 (25)	

Receipt of Smoking cessation pharmacotherapy across HIV status

Overall, the prevalence of receiving any pharmacotherapy was 33% (n=1722); the prevalence of receiving NRT, bupropion, and varenicline was 22%, 9%, and 1%, respectively.

In bivariate comparisons, the prevalence of receiving smoking cessation pharmacotherapy was lower among PLWH than among HIV-uninfected patients (29% vs. 36%, respectively; p=0.004). With regard to specific medications, the proportion receiving NRT was lower among PLWH than uninfected (19% vs. 25%, respectively; p=0.002), no differences were observed in receipt of bupropion (8% vs. 9%; p=NS), and PLWH had a slightly higher proportion of receipt of varenicline than HIV-uninfected participants (1% vs. 0.4%; p=0.03) (Table 2.3).

After adjustment for all covariates, no differences in HIV status were observed in the primary outcome—receipt of any smoking cessation pharmacotherapy. However, PLWH were less likely than HIV-uninfected persons to receive NRT after full adjustment (ARR 0.77, 95% CI 0.67, 0.89). No differences were observed in receipt of bupropion and, due to the small number of observations, the model assessing varenicline receipt did not converge (Table 2.3).

Table 2.3: Associations between HIV status and Receipt of Smoking Cessation Medications among Patients Recruited to VACS (N=1722): Results of Bivariate Comparisons and Adjusted Log-Linear Regression Models

	HIV+ (n=814)		HIV- (n=908)		p-value	Unadjusted relative risk		Adjusted relative risk	
	N	(%)	N	(%)		RR	(95% CI)	ARR*	(95% CI)
Receipt of Smoking Cessation Medications									
Any medication	237	(29)	323	(36)	0.004	0.82	0.71, 0.94	0.90	0.76, 1.07
Nicotine replacement therapy	154	(19)	229	(25)	0.002	0.75	0.58, 0.97	0.77	0.67, 0.89
Bupropion	69	(8)	84	(9)	NS	0.97	0.75, 1.26	1.25	0.87, 1.80
Varenicline	12	(1)	4	(0.4)	0.03	3.02	0.43, 21.00	--	--

* Relative risk of receiving medications for HIV+ relative to HIV- adjusted for age, sex, race/ethnicity, education, income, unhealthy alcohol use, substance use in last year, moderate-severe depression, recent diagnoses for psychiatric disorders, CVD, chronic pulmonary disease and non-AIDS malignancies, VACS Index 2.0, number of inpatient and outpatient visits, contemplation to quit, past quit attempt, and number of cigarettes smoked daily.

Patient-level factors associated with receipt of pharmacotherapy among PLWH

Factors associated with increased likelihood of receiving smoking cessation medications among PLWH included: recently diagnosed psychiatric disorder (ARR 1.34, 95% CI 1.03, 1.73), recently diagnosed pulmonary disease (ARR 1.40, 95% CI 1.03, 1.90), and contemplation to quit (ARR 1.85, 95% CI 1.10, 3.10) (Table 2.4). There were no factors associated with decreased likelihood among PLWH.

Patient-level factors associated with receipt of pharmacotherapy among HIV-uninfected

Factors associated with increased likelihood of receiving smoking cessation medications among HIV-uninfected participants included: black race (ARR 1.25, 95% CI 1.00, 1.57) and “other” race (ARR 1.75, 95% CI 1.24, 2.47) relative to white race, moderate to severe depression (ARR 1.33, 95% CI 1.12, 1.59), recently diagnosed psychiatric disorder (ARR 1.83, 95% CI 1.53, 2.20), contemplation to quit (ARR 1.31, 95% CI 1.14, 1.50), past quit attempt (ARR 2.27, 95% CI 1.57, 3.28), and report of smoking 10-20 cigarettes daily (ARR 1.19, 95% CI 1.06, 1.33) compared to report of smoking <10 cigarettes daily (Table 3). Earning \$1200-24999 in annual income was associated with decreased likelihood of receiving pharmacotherapy relative to earning less than \$1200 annually (ARR 0.84, 95% CI 0.71, 0.98) (Table 2.4).

Table 2.4: Relative Risk for Receipt of Any Smoking Cessation Medication Associated with Patient Characteristics Stratified by HIV Status among Patients Recruited to VACS (N=1722)

	HIV+ ARR* (95% CI)	HIV- ARR* (95% CI)
SOCIODEMOGRAPHIC FACTORS		
Age	1.00 (0.98, 1.01)	0.99 (0.98, 1.00)
Male	1.46 (0.90, 2.37)	0.86 (0.53, 1.37)
Race/ethnicity		
White	Reference	Reference
Black	0.73 (0.48, 1.10)	1.25 (1.00, 1.57)
Hispanic	0.64 (0.36, 1.13)	1.10 (0.72, 1.68)
Other	0.97 (0.53, 1.75)	1.75 (1.24, 2.47)
Education		
< High school	Reference	Reference
High school grad, GED	0.68 (0.32, 1.43)	0.62 (0.35, 1.09)
Some college or technical school	0.69 (0.36, 1.32)	0.72 (0.48, 1.09)
College grad, higher education	0.96 (0.40, 2.28)	0.60 (0.23, 1.54)
Annual income		
<\$12,000	Reference	Reference
\$12,000-24999	0.92 (0.68, 1.23)	0.84 (0.71, 0.98)
≥ \$25000	0.94 (0.68, 1.29)	0.92 (0.77, 1.09)
MENTAL HEALTH / SUBSTANCE USE		
Unhealthy alcohol use	0.99 (0.82, 1.20)	1.05 (0.85, 1.29)
Substance use in the last year	0.97 (0.78, 1.19)	0.86 (0.69, 1.07)
Moderate-severe depression	0.90 (0.76, 1.06)	1.33 (1.12, 1.59)
Psychiatric disorders	1.34 (1.03, 1.73)	1.83 (1.53, 2.20)
SMOKING-RELATED COMORBIDITY		
Cardiovascular disease	1.04 (0.72, 1.50)	0.98 (0.79, 1.21)
Pulmonary disease	1.40 (1.03, 1.90)	1.17 (0.96, 1.43)
Non-AIDS malignancies	1.26 (0.92, 1.72)	1.32 (0.88, 1.99)
HIV SEVERITY		
VACS Index 2.0	0.99 (0.98, 1.01)	1.00 (0.99, 1.00)
HEALTH CARE UTILIZATION		
Outpatient visits in last year		
1 to 2	Reference	Reference
3 to 5	1.28 (0.75, 2.20)	0.92 (0.77, 1.09)
≥6	1.63 (0.95, 2.79)	1.01 (0.87, 1.15)
Inpatient visits in last year		
0	Reference	Reference
1	1.02 (0.71, 1.45)	1.19 (0.87, 1.63)
≥2	1.12 (0.77, 1.64)	0.91 (0.70, 1.18)
SMOKING-RELATED ATTITUDES/ BEHAVIOR		
Contemplation to quit	1.85 (1.10, 3.10)	1.31 (1.14, 1.50)
Past quit attempt	1.31 (0.59, 2.88)	2.27 (1.57, 3.28)
Cigarettes smoked daily		
<10	Reference	Reference
10-20	1.26 (0.81, 1.96)	1.19 (1.06, 1.33)
>20	1.51 (0.73, 3.14)	0.96 (0.76, 1.22)

* Relative risk of receiving medications adjusted for age, sex, race/ethnicity, education, income, unhealthy alcohol use, substance use in last year, moderate-severe depression, recent diagnoses for psychiatric disorders CVD, chronic pulmonary disease, and non-AIDS malignancies, VACS Index 2.0, number of outpatient and inpatient visits, contemplation to quit, past quit attempt, and number of cigarettes smoked daily.

2.4 DISCUSSION

This is the first study to our knowledge to investigate receipt of effective pharmacologic treatment for tobacco use among PLWH who currently smoke, both overall and relative to a matched cohort of HIV-uninfected controls. PLWH were less likely to receive NRT and had comparable rates of receiving other smoking cessation medications to uninfected patients despite the increased dangers of smoking among PLWH. Our findings suggest underutilization of pharmacotherapies generally, and disproportionate underutilization of NRT among PLWH for whom the health risks of smoking are increased.

Of note, over 70% of participants reported contemplating cessation and the median number of previous quit attempts was three in our sample. No significant differences in these characteristics were observed between those with and without HIV, suggesting high levels of readiness to stop smoking across groups. Nonetheless, a small proportion of all patients filled prescriptions for effective pharmacotherapies in the following year. Further work is needed to increase access to these effective medications, especially among highly motivated patients. Promotion of specific medications may also be necessary. Though varenicline has been demonstrated to have the greatest efficacy to promote cessation in populations with and without HIV [23, 47, 49, 73, 74], it was the least received pharmacotherapy. This may relate to the fact that varenicline is still considered a second-line treatment and is strictly controlled within the VHA due to several cases specifically involving veterans in which it potentially exacerbated underlying mental illness [50]. Even though available data have not proven that varenicline causes significant neuropsychiatric adverse events, clinicians should closely monitor patients who are taking varenicline until more is known [75]. And, although NRT was the most frequently received smoking cessation medication, the vast majority of patients did not receive it,

and rates were lower among PLWH than HIV-uninfected patients. Prior studies have demonstrated that PLWH who report smoking have substantial interest in NRT—one conducted in a sample of 60 patients receiving care at an ID clinic in Bronx, New York found that 64% of participants were interested in NRT [39]. Another study conducted among 123 patients from an ID clinic in San Francisco found that 82% of PLWH who were currently thinking about quitting were interested in NRT [30]. Whether there is high interest in NRT among PLWH receiving VHA care who report smoking is unknown, but low rates of NRT across groups and lower rates among PLWH than HIV-uninfected participants in the present study suggest room for improvement with regard to provision of smoking cessation medications.

Patient-level factors associated with the receipt of smoking cessation pharmacotherapy were both similar and different for PLWH and HIV-uninfected groups. Recently documented psychiatric disorder and contemplation to quit were associated with increased likelihood of smoking cessation medication receipt for both patients with and without HIV. However, sociodemographic characteristics (e.g., race and income) appeared to be important predictors of receiving pharmacotherapy in the HIV-uninfected population whereas they were not associated with pharmacotherapy receipt among PLWH. These findings suggest the possibility of inequitable receipt of pharmacotherapy among HIV-uninfected persons. However, given that this sample of HIV-uninfected persons were matched to PLWH in our sample based on age, sex, race, and site of care, it is unclear whether these findings are generalizable to a broader population of HIV-uninfected persons receiving VHA care. Thus, further work is needed to assess patient factors that predict receipt of smoking cessation medication receipt among HIV-uninfected veterans with current smoking in broader samples.

Overall, reasons for differences in smoking cessation medication receipt across HIV status and patient-level predictors identified in the present study are unclear. Factors both inside and outside of the medical encounter may have contributed to these disparities, including patient-level factors (e.g., preferences), provider-level factors (e.g., knowledge and training), and clinical setting (e.g., resources available), many of which were not available measures in our study. For instance, PLWH may be receiving care from providers with different levels of knowledge and training than HIV-uninfected patients or a greater proportion of PLWH may prefer non-pharmacologic options than HIV-uninfected. Unfortunately, we were not able to differentiate such patient and provider-level factors. Similarly in the present study, a recent diagnosis for pulmonary disease among PLWH was associated with increased likelihood of receiving pharmacotherapy. A previous study in VACS found that PLWH with a recent diagnosis for pulmonary disease had nearly five-times the odds of having made a quit attempt in the last year relative to those without such a diagnosis [28]. Thus, it is possible that receiving a diagnosis for a pulmonary disease increases patient readiness to quit smoking. However, it is also possible that identification of a pulmonary condition by a provider may also increase likelihood that the provider gains knowledge about and/or becomes more willing to prescribe pharmacotherapy. Future research is needed to explore patient treatment preferences, as well as provider- and clinic-level factors that are likely influential in patients' receipt of smoking cessation medications.

Interestingly, substance use and depression were not associated with receipt of smoking cessation medications in either PLWH or HIV-uninfected populations despite previous studies citing these as putative barriers to smoking cessation [76-81]. Specifically among PLWH, substance use and depression have been found to be associated with current smoking status,

greater nicotine dependence, and lack of motivation to quit [18, 39, 79-81]. Moderate to severe depression was significantly associated with receipt of pharmacotherapy among the HIV-uninfected group though not among PLWH. Unhealthy alcohol use and substance use in the last year were not associated with smoking cessation medication receipt in either group. Yet, these factors associated with both smoking and HIV-infection may not be translatable to provider-level practices and preferences in offering their patients smoking cessation pharmacotherapies.

Of note, recent diagnosis for CVD was not associated with receipt of smoking cessation pharmacotherapy for either group. Among the many comorbid health conditions afflicting PLWH who smoke, CVD has become of particular concern due to ART-induced metabolic changes, the high prevalence of cardiovascular risk factors in PLWH, and HIV-accelerated inflammatory processes that are believed to promote atherosclerosis [82]. Smoking is a well-known and modifiable risk factor for CVD with marked reductions in CVD and coronary heart disease in PLWH who have successfully quit [55]. Therefore, promoting smoking cessation, as well as greater provision and access to pharmacotherapy is crucial among PLWH who face compounded, health consequences due to smoking.

In addition to limitations regarding measurement of patient-, provider-, and clinic-level factors that may influence receipt of pharmacotherapy, this study is limited in several ways. Specifically, this cohort was comprised of veterans receiving care in the VHA and results may not be generalizable to non-veterans, veterans receiving VHA care who do not match the epidemiologic profile of PLWH receiving VHA care, persons not receiving health care, or to patients with and without HIV receiving care in other health care systems. Additionally, NRT is available over the counter and it is possible that patients had procured smoking cessation

medications in pharmacies outside the VHA. However, due low copayments within the VHA, veterans are less likely to obtain their prescriptions elsewhere [83-85].

Despite these limitations, this study was the first to our knowledge to assess receipt of smoking cessation medications among PLWH and matched HIV-uninfected veterans from nine major U.S. cities. No differences in any pharmacotherapy was observed across HIV status, though PLWH were less likely than HIV-uninfected patients to receive NRT. Further work is needed to ensure access to effective pharmacologic treatments for patients who report smoking, particularly those with HIV for whom the dangers of smoking are great.

3 Chapter 3. RECEIPT OF SMOKING CESSATION MEDICATIONS AMONG PEOPLE WITH AND WITHOUT HIV IN THE VETERANS AGING COHORT STUDY (2003-2018)

3.1 INTRODUCTION

Cigarette smoking is the leading cause of morbidity and mortality worldwide and is highly prevalent among and particularly dangerous for people living with HIV (PLWH) [86-88].

Approximately 45-55% of PLWH currently smoke [16, 87, 89, 90] in contrast to 14% among the general United States (U.S.) population [91]. Smoking cessation medications, such as nicotine replacement therapy (NRT), bupropion, and varenicline, are effective prescription pharmacotherapies approved by the U.S. Food and Drug Administration (FDA) for treatment of tobacco use disorder [45] and have been shown to be similarly effective in promoting cessation for PLWH and those without HIV (PWoH) [22, 23, 25-27]. However, recent evidence suggests that there may be HIV-related disparities in receiving evidence-based pharmacologic treatments [92]. This is concerning because cumulative health impacts of tobacco use and HIV leave PLWH at greater susceptibility and severity of chronic illnesses such as cardiovascular disease [2, 3], chronic obstructive pulmonary disease [4, 5], and cancer [6, 7] relative to PWoH.

There have been multiple changes in recommendations for use of smoking cessation medications for tobacco cessation over the last several decades. The US Public Health Service introduced Clinical Practice Guidelines for providers in 2000 to prescribe at least one smoking cessation medication in the form of NRT or bupropion in the absence of contraindications [93]. These were updated in 2008 to include varenicline, to recommend administering two smoking cessation medications in combination with counseling, and to re-prescribe smoking cessation medications after relapse [45]. Although pharmacotherapy has been standard care in treating

tobacco use disorder for the past two decades, it is unknown how rates of receipt of NRT, bupropion, and varenicline have changed among PLWH compared with the uninfected.

The Veterans Health Administration (VHA) is the nation's largest provider of HIV care and home to the Veterans Aging Cohort Study (VACS). VACS is a multi-site, longitudinal, prospective cohort study of PLWH and HIV-uninfected controls assembled from national VHA data. In the VHA—where veterans with HIV report higher rates of tobacco use than those without HIV and non-veterans [94]—tobacco use reduction is a priority. In 2003, the VHA issued guidance to remove restrictions on prescribing NRT and/or bupropion to increase the access to these highly effective pharmacologic treatments for all patients who smoked [95].

Therefore, the VHA offers an important opportunity to study differences in receipt of smoking cessation medications between PLWH and PWOH longitudinally over a period marked by policy and clinical changes. We used VACS data to assess likelihood of receiving smoking cessation medications, annual rates of receipt, and rate differences among PLWH relative to a PWOH over a 16-year period in a national sample of VHA patients.

3.2 METHODS

Study Data Sources and Sample

This study used VACS data, drawn from national VHA data beginning in 1997. VACS includes all PLWH receiving care in the VHA matched 1:2 to HIV-uninfected patients by five-year blocks of age, race/ethnicity, sex, and site of care [51, 52]. The cohort is updated annually to include veterans with new diagnoses of HIV infection and matched controls receiving care in the same fiscal year.

For the present study, we identified VACS patients with documentation of current smoking in the electronic health record (EHR) resulting from an automated clinical reminder for

tobacco use between January 1, 2003 and December 31, 2018. Clinical reminders are embedded in the EHR and serve to prompt providers to ask their patients about tobacco use. These data have been collected nationally since 1999 and have substantial agreement with smoking status based on survey response [53]. Current smoking status was assigned yearly based on the first EHR-documentation of current smoking in each calendar year. For patients contributing multiple observations, we limited the sample to one observation per person per year and included subsequent observations if they occurred at least 365 days following the one prior.

We linked these data to demographic and pharmacy information extracted from the VHA Corporate Data Warehouse (CDW). The CDW is a national repository that incorporates data from the clinical and administrative systems into one standard database structure for all users of VHA care [57].

Outcomes

The primary outcome of interest was a dichotomous measure identifying receipt of any smoking cessation medications (NRT, bupropion, and varenicline), based on outpatient prescriptions filled from VHA pharmacy data in the EHR 0-365 days following the date documenting current smoking. This outcome measure was generated for each observation in which there was a positive tobacco screen.

In secondary outcomes, we measured receipt of each individual medication 0-365 days following the date of each observation contributed to the data.

Primary Independent Measure

We defined HIV status as having two outpatient or one inpatient diagnostic codes from the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)

for AIDS (042) or HIV (V08), consistent with prior research conducted in the VHA [51]. For patients contributing multiple observations to the data, we updated HIV status accordingly.

Moderator

To reflect changes over time in policies and clinical recommendations regarding smoking cessation medications, we defined time as a continuous measure represented by calendar year.

We assigned each observation to the calendar year in which it was documented.

Covariates

Age at time of each observation (continuous), sex (male versus female), race/ethnicity (Black, Hispanic, other, and white), and site of care were collected via the EHR for each patient. “Other” race included American Indian or Alaska Native, Asian, and Native Hawaiian or Pacific Islander.

Analysis

We summarized characteristics of PLWH and PWoH as individuals and at each observation of the study period. We then compared prevalence of primary and secondary outcomes among all observations by HIV status in bivariate analyses.

In regression analyses, generalized log-linear regression with a modified Poisson working model were used to estimate the relative risk of receiving smoking cessation medications and each individual medication with 95% confidence interval (CI) [70]. Since we allowed patients to contribute to multiple years (given tobacco screens at least a year apart), we clustered by patient and specified an exchangeable correlation structure to account for repeated measures. We also applied a robust sandwich estimator to calculate standard errors, obtain a valid inference for a

large sample and common outcome, and account for misspecification of the correlation structure [68-72].

The inclusion of time in the model allowed us to estimate the relative risk of receiving smoking cessation medications in one calendar year compared with the previous calendar year (annual rate of receipt) among PWOH, holding all other variables constant. Lastly, we included the HIV*year interaction term to estimate the annual rate difference among PLWH relative to PWOH. A significant p-value (<0.05) for the interaction term would indicate that the difference in annual rate of receipt between the two populations is statistically different from zero.

3.3 RESULTS

Between January 1, 2003 and December 31, 2018, 92,632 patients had documentation of current smoking, reflecting 381,637 observations (1-14 per patient) over the 16-year period. Among all patients, 29,086 had documented HIV (31%), contributing 109,473 observations to the analyses. The median number of observations contributed per individual was greater among PWOH than PLWH (median number 4 versus 3, respectively; $p<0.001$).

A summary of patient characteristics of individuals contributing to the data are presented in Table 1, both overall and by HIV status. The population was predominantly male (97.4%) with an average age of 49 years at the time of their first observation. Approximately 50% were Black, reflecting the composition of PLWH who smoke in the VHA. PLWH were more likely to be younger and female, and less likely to have received smoking cessation medications during the study period compared with PWOH, although differences were numerically small. Comparing individual medications, 41% and 43% of PLWH and PWOH, respectively, had received NRT ($p<0.001$); 21% and 24% had received bupropion ($p<0.001$); and 5.3% and 5.2% had received varenicline ($p=0.43$) (Table 3.1).

Table 3.1: Characteristics among VACS Participants who Currently Smoke by Year and HIV Status (N=92,632), between 2003 and 2018

Characteristic	Total population (N=92,632)	HIV+ (n=29,086)	HIV- (n=63,546)	P value
HIV-infected, %	31.4			
*Age, mean (SD)	49.3 (10.4)	49.1 (10.3)	49.4 (10.5)	<0.001
Male, %	97.4	97.1	97.6	<0.001
Race, % Black	49.9	50.3	49.7	0.08
Hispanic	7.4	7.4	7.4	
Other	3.1	3.3	3.1	
White	39.6	39.1	39.9	
Number of observations during the study period, median (IQR)	4 (2, 6)	3 (2, 6)	4 (2, 6)	<0.001
Received SCM during the study period, %	50.2	48.7	50.9	<0.001
NRT	42.6	41.5	43.1	<0.001
Bupropion	23.2	21.0	24.2	<0.001
Varenicline	5.2	5.3	5.2	0.43

*Age reported at first observation for participants contributing more than one observation

Among all observations of current smoking between 2003 and 2018, the proportion receiving any smoking cessation medications within a year of reporting tobacco use increased from 15% to 34% for PLWH and from 17% to 32% among the uninfected (Figure 3.1). In bivariate comparisons, the prevalence of receiving any smoking cessation medication was similar among PLWH and PWOH (28% for both; $p=0.06$). However, there were small, yet statistically significant, differences with regards to specific medications. The proportion that received NRT was greater among PLWH than PWOH (21% vs. 20%, respectively; $p<0.001$). The proportion that received varenicline was also greater among PLWH than PWOH (1.8 vs. 1.6, respectively; $p<0.001$), while the opposite was found in regards to bupropion (9% vs. 10%, respectively; $p<0.001$) (Table 3.2).

Similarly, regression models showed no statistical difference in likelihood of receiving smoking cessation medication between PLWH and PWOH (RR 1.010, 95% CI 0.994-1.026). PLWH were 3.3% more likely to receive NRT (RR 1.033, 95% CI 1.015-1.052) and 15.9% more likely to receive varenicline (RR 1.159, 95% CI 1.086-1.237), but 7.9% less likely to receive bupropion (RR 0.921, 95% CI 0.893-0.950) relative to PWOH.

Rate of receiving smoking cessation medications over time by HIV status

Over the study period, receipt of smoking cessation medications increased by 4.3% and 3.7% per year for PLWH and PWOH, respectively (RR 1.043, 95% CI 1.040-1.047; RR 1.037, 95% CI 1.036-1.038). The rate difference in receiving smoking cessation medications among PLWH was +0.6% greater relative to PWOH (RR 1.006, 95% CI 1.004-1.009) (Table 3.2). Receipt of NRT increased at a similar rate of 5.2% per year across populations (RR 1.052, 95% CI 1.050-1.053).

The annual rate of receiving bupropion was not statistically different from zero for PLWH (RR 1.001, 95% CI 0.994-1.010) and decreased 0.7% per year for PWOH (RR 0.993, 95% CI 0.991-0.996). The rate difference among PLWH was +0.8% greater relative to PWOH (RR 1.008, 95% CI 1.003-1.014) (Table 3.2).

Receipt of varenicline increased by 11.5% and 8.7% per year for PLWH and PWOH, respectively (RR 1.115, 95% CI 1.097-1.133; RR 1.087, 95% CI 1.081-1.093). The rate difference among PLWH was +2.8% greater relative to PWOH (RR 1.028, 95% CI 1.016-1.040) (Table 3.2).

Figure 3.1, A & B: Proportion of VACS Participants who Currently Smoke and Receive Smoking Cessation Medications by HIV Status between 2003 and 2018: Any Smoking Cessation Medications (SCM) and By Individual Medications

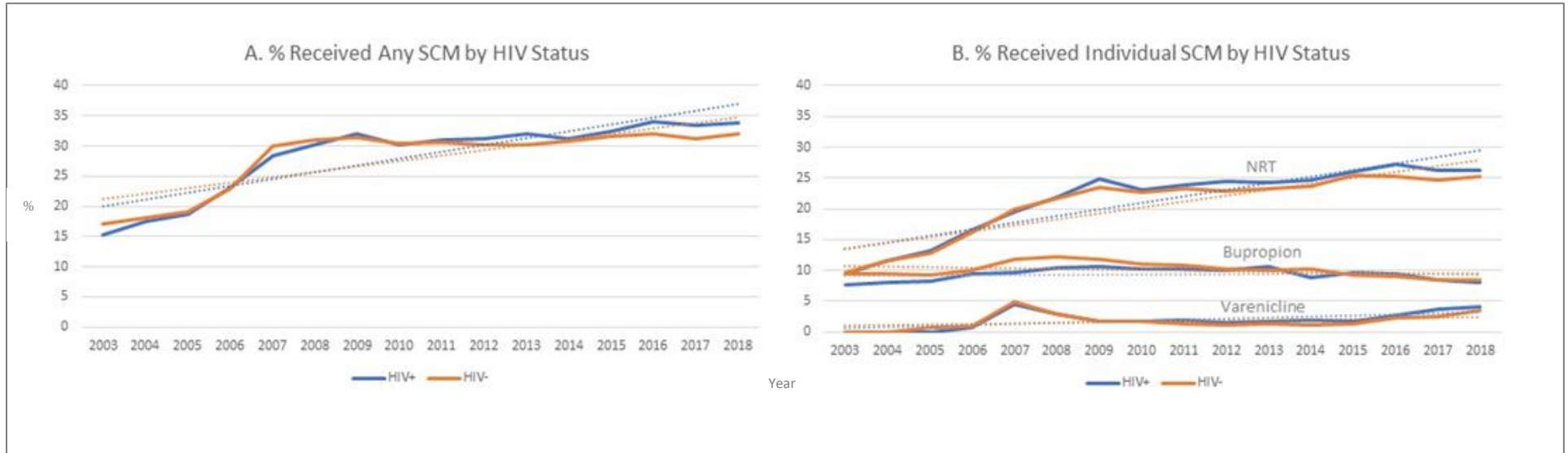


Table 3.2: Bivariate Association and Adjusted Relative Risk between HIV Status and Receipt of Smoking Cessation Medications among VACS Participants who Currently Smoke (N=92,632), between 2003 and 2018

	Bivariate Association and Adjusted Relative Risk of Receiving SCM among All Observations of Current Smoking				Yearly Change in Rates of Receiving SCM among All Observations of Current Smoking		
	HIV+ (*n=109,473)	HIV- (*n=272,164)	P value	^a Relative Risk comparing HIV+ and HIV- (95% CI)	^a Relative Risk per Year for HIV- (95% CI)	^b Relative Risk per Year for HIV+ (95% CI)	^c Relative Risk Difference for HIV+ (95% CI)
Any medication received	28.0%	27.7%	0.06	1.010 (0.994, 1.026)	1.037 (1.036, 1.038)	1.043 (1.040, 1.047)	1.0065 (1.0038, 1.0092)
Nicotine replacement therapy	21.0%	20.3%	<0.001	1.033 (1.015, 1.052)	1.052 (1.050, 1.053)	1.055 (1.050, 1.059)	1.0028 (0.9997, 1.0060)
Bupropion	9.4%	10.1%	<0.001	0.921 (0.893, 0.950)	0.993 (0.991, 0.996)	1.001 (0.994, 1.010)	1.0080 (1.0026, 1.0135)
Varenicline	1.8%	1.6%	<0.001	1.159 (1.086, 1.237)	1.087 (1.081, 1.093)	1.115 (1.097, 1.133)	1.0281 (1.0158, 1.0405)

*n=number of observations

^a Model includes HIV status and year only

^b Addition of RR for HIV- and RR Difference for HIV+

^c Model includes HIV status, year, and interaction term (HIVxYear)

Table 3.3: Characteristics among VACS Participants who Currently Smoke by Year and HIV Status (N=92,632), between 2003 and 2018

	2003		2004		2005		2006		2007		2008		2009		2010	
	HIV+ N=9,367	HIV- N=23,209	HIV+ N=6,786	HIV- N=16,633	HIV+ N=6,941	HIV- N=17,557	HIV+ N=6,854	HIV- N=17,549	HIV+ N=7,272	HIV- N=18,499	HIV+ N=7,233	HIV- N=18,151	HIV+ N=7,205	HIV- N=17,916	HIV+ N=7,137	HIV- N=17,812
HIV+, %	28.8		29.0		28.3		28.1		28.2		28.5		28.7		28.6	
Age, mean (SD)	49.2 (8.2)	49.6 (8.3)	49.5 (8.4)	49.7 (8.8)	50.0 (8.7)	50.3 (9.2)	50.8 (8.8)	51.1 (9.4)	51.2 (8.9)	51.5 (9.3)	51.6 (9.0)	51.9 (9.6)	52.1 (9.2)	52.5 (9.5)	52.6 (9.6)	53.2 (9.8)
Male, %	96.9	97.7	97.2	97.5	97.2	97.4	96.6	97.5	96.9	97.5	97.1	97.5	97.0	97.4	96.8	97.4
Race, %	53.0	50.4	53.2	50.8	54.1	51.5	52.4	51.0	52.6	51.0	52.5	50.7	52.8	51.1	52.8	50.4
Black																
Hispanic	7.8	6.7	7.1	6.7	6.6	6.4	7.1	6.9	7.0	6.4	6.8	6.8	6.7	6.6	6.1	6.6
Other	2.0	2.2	2.1	2.5	2.2	2.5	2.0	2.5	2.5	2.6	2.3	2.5	2.3	2.6	2.4	2.6
White	37.2	40.8	37.6	40.0	37.1	39.7	38.5	39.7	37.9	40.0	38.4	40.0	38.3	39.7	38.7	40.5
Received any medication, %	15.2	17.0	17.4	18.1	18.6	19.1	23.2	22.9	28.4	29.9	30.1	31.0	32.1	31.5	30.2	30.3
NRT	9.5	9.7	11.6	11.5	13.2	12.7	16.6	16.1	19.5	20.0	21.8	21.7	24.8	23.5	23.0	22.6
Bupropion	7.6	9.5	8.1	9.4	8.3	9.3	9.4	10.0	9.7	11.7	10.5	12.2	10.7	11.7	10.3	10.9
Varenicline	0	0	0	0	0	0	0.8	1.0	4.5	4.8	2.9	2.8	1.7	1.7	1.7	1.6
	2011		2012		2013		2014		2015		2016		2017		2018	
	HIV+ N=6,775	HIV- N=17,041	HIV+ N=6,713	HIV- N=16,740	HIV+ N=6,427	HIV- N=16,164	HIV+ N=6,445	HIV- N=15,840	HIV+ N=6,229	HIV- N=15,114	HIV+ N=6,081	HIV- N=14,694	HIV+ N=6,130	HIV- N=14,869	HIV+ N=5,878	HIV- N=14,376
HIV+, %	28.5		28.6		28.5		28.9		29.2		29.3		29.2		29.0	
Age, mean (SD)	53.0 (9.7)	53.7 (9.9)	53.4 (10.1)	54.6 (9.8)	53.8 (10.2)	55.3 (9.9)	54.3 (10.5)	56.0 (10.0)	54.7 (10.8)	56.7 (10.1)	55.3 (10.9)	57.3 (10.1)	56.3 (11.0)	58.3 (10.2)	56.9 (11.2)	59.3 (10.0)
Male, %	96.6	97.4	96.7	97.3	96.9	97.5	96.6	97.3	96.7	97.3	96.4	97.4	96.5	97.3	96.6	97.3
Race, %	52.8	50.8	51.2	51.4	51.7	50.9	50.9	50.8	50.8	52.7	50.6	49.9	50.3	51.4	50.0	51.4
Black																
Hispanic	6.7	6.4	6.6	6.2	6.2	6.3	6.2	6.4	7.0	6.2	6.5	7.0	7.0	7.0	7.0	6.8
Other	2.5	2.8	3.0	2.6	2.8	2.7	3.3	2.7	3.6	2.5	3.1	2.9	3.7	2.8	3.7	2.6
White	38.1	40.1	39.2	39.8	39.3	40.1	39.6	40.1	38.6	38.6	39.7	40.3	39.1	38.8	39.3	39.2
Received any medication, %	31.1	30.7	31.3	30.1	32.1	30.1	31.2	30.9	32.5	31.6	34.1	32.0	33.5	31.2	33.8	32.0
NRT	23.9	23.3	24.5	22.9	24.3	23.3	24.7	23.7	26.0	25.5	27.3	25.3	26.3	24.6	26.2	25.2
Bupropion	10.3	10.8	10.0	10.3	10.7	10.0	8.9	10.3	9.6	9.2	9.4	9.1	8.4	8.5	8.1	8.4
Varenicline	1.8	1.3	1.4	1.1	1.6	1.3	1.9	1.2	1.7	1.3	2.7	2.2	3.6	2.5	4.1	3.4

3.4 DISCUSSION

In this national sample of VHA patients with and without HIV who reported current smoking, receipt of smoking cessation medications nearly doubled during the 2003-2018 study period for both PLWH and PWOH. The majority of this increase appears to be attributable to improved rates of NRT receipt, in particular. Rates of receiving bupropion were similar over the study period for PLWH and slightly decreased for PWOH, but we observed modest gains in receipt of varenicline for both populations. Nevertheless, despite efforts nationally and by the VHA specifically, fewer than 35% of all patients who smoke received smoking cessation medications within a year of reporting current smoking. Though differences between PLWH and PWOH in the rate of increases over time and ultimate rates of receipt were modest, PLWH may be a group in need of specific targeting of smoking cessation medications given the enhanced dangers of smoking for PHW relative to PWOH.

The VHA has made important progress in implementing a number of system-wide interventions to improve patient access to evidence-based tobacco cessation care and pharmacotherapy. The marked increase of smoking cessation medication receipt among VHA patients is likely to reflect the adoption of population-based approaches to tobacco use, such as increased accessibility to NRT (2003), revision of clinical practice guidelines to integrate smoking cessation into primary care (2004), further integration into psychiatric settings (2006), and implementation of computerized clinical reminders to document smoking and performance measures (2009) [95]. Successful performance on VHA's performance measure requires annual documentation that each smoker be given brief counseling, offered medications, and provided a referral for additional services. At the end of the first year of the new performance measure, 75% of current smokers seen in mental health settings were offered smoking cessation

medications to assist with quitting as were 71% of those in nonmental health settings [95]. These adaptations of policy and practice regarding smoking cessation have been shown to be effective in increasing access and receipt of smoking cessation medications, especially NRT. Our findings support that rates of receiving NRT improved most drastically between 2003 and 2009 as NRT became central to VHA smoking cessation efforts, which then expanded to primary care and mental health care settings.

Though considered another first-line therapy, bupropion receipt was similar over time among PLWH and slightly fell among PWOH. Among PLWH, there are several potential interactions between antiretrovirals (ART) and bupropion. For example, ritonavir, lopinavir, tipranavir, and efavirenz can significantly alter plasma concentrations of bupropion [96]. In addition, outside of HIV, bupropion is contraindicated for patients experiencing or being treated for certain mental health and cardiovascular conditions [97, 98]. Therefore, it is possible that a sizeable portion of patients included in this study may experience barriers to receiving bupropion. Despite recent findings that documented mental health conditions were associated with greater likelihood of receiving pharmacotherapy among PLWH and demographically similar PWOH [92, 99], it is unsurprising that NRT continues to be the cessation medication most received.

Certain VHA policies may also limit access of effective smoking cessation treatment in their formulary. This is especially true regarding varenicline and may contribute to its low rates of receipt. Specifically, our study demonstrates that varenicline begins to be received when the FDA approved it for treatment of tobacco use disorder. Over the study period, receipt of varenicline reached its peak in 2007 and then fell sharply in 2008 (4.5% among PLWH and 4.8% among PWOH to 2.9% and 2.8%). This finding potentially coincides with several cases in which

depressed mood, agitation, changes in behavior, and suicidal ideation had been reported in patients attempting to quit smoking while using varenicline [50], prompting an FDA warning. For this reason and situations specifically involving veterans, the VHA has considered varenicline a second-line treatment and strictly controls its use. Although several studies show greater efficacy of varenicline over placebo, bupropion, and single as well as combination NRT in achieving smoking cessation [100-102], and have demonstrated safety [103], provider concerns about its neuropsychiatric effects persist to the detriment of providing a highly effective medication for tobacco use disorder.

Despite great progress over the last 16 years, fewer than 35% of current smokers in our study received smoking cessation medications in any given year, and approximately 50% received them at least once over the entire study period. While adoption of population health approaches to address tobacco use disorder have shown some success, there is considerable room for improvement. Further, additional efforts may be needed to target PLWH due to their increased susceptibility to tobacco-related illnesses. Notably, PWOH contributed more observations to the study data than PLWH, suggesting that they either had more frequent clinic visits or were asked their smoking status through clinical reminder more often than PLWH, despite being otherwise demographically comparable. Continued efforts addressing current smoking among PLWH are needed.

PLWH represent a vulnerable population at higher risk of risks due to smoking because of compounded effects of health factors, putting them at high risk of disease, and social factors, placing them in positions that perpetuate disparities [104, 105]. These include but are not limited to discrimination, stigmatization, and loneliness [106], as well as low income and education levels [31, 107]. In fact, despite comparable and sometimes greater utilization of treatment,

higher rates of smoking persist among PLWH [99, 107]. In July 2012, the VHA created a tobacco cessation handbook specifically for their HIV care providers [98], though further action is needed that focus interventions and resources on PLWH.

This study has several limitations. Specifically, this cohort was comprised of and describes veterans receiving care in the VHA and used data from VACS, which enrolls PWOH matched on age, race/ethnicity, and site of care to PLWH. Thus, results may not be fully generalizable to patients without HIV in the VHA or patients receiving care in other healthcare systems. Additionally, clinical reminder smoking questions and responses, which enabled us to identify veterans with and without HIV who smoke, varied widely by site and over time until October 2018. Despite this variation in implementation, clinical reminders have been found to have substantial agreement with smoking status reported on survey [53].

Smoking cessation medications procured outside the VHA represent another potential opportunity for misclassification. Even though NRT is available over-the-counter and prescriptions can be filled at other pharmacies, veterans are less likely to obtain their medications elsewhere because of low copayments within the VHA [83-85]. Furthermore, the VHA prescription mail order service is highly rated and provides around 80% of VHA outpatient medications [108]. Lastly, it is not clear whether non-receipt of smoking cessation medications was due to patient unwillingness to quit, preference against pharmacotherapy, or missed opportunity for the provider to encourage cessation treatment as this information was not available.

Despite these limitations, our study has several strengths. Our study examines the extent to which PLWH receive smoking cessation medications compared with demographically-similar PWOH in the VHA, the largest system of health care and the largest provider of HIV care in the

U.S. Previous studies have been limited by the number of PLWH receiving care in their health systems, however, at least 25-51% of veterans infected with HIV in care are current smokers [52] allowing for a large evaluation of pharmacotherapy receipt. Additionally, we were able to examine changes in smoking cessation medication receipt over a 16-year period and demonstrate the potential impacts of several VHA-wide interventions to address tobacco use disorder.

In summary, as pharmacotherapy became standard care in treating tobacco use disorders, rates of receiving key medications nearly doubled among PLWH and PWoH in the VHA. Much of this improvement is likely driven by population-based policies that have made NRT more accessible, as rates of other medications exhibited modest changes. This study provides evidence that PLWH appear to be provided the opportunity to receive effective treatment at rates similar to PWoH, though efforts to improve pharmacotherapy receipt should continue for both groups given the known dangers of smoking. Finally, strategies must include a vulnerable population approach in addressing tobacco use among PLWH who represent a subgroup of veterans at higher risk of risks due to smoking relative to PWoH.

4 Chapter 4. PRAGMATIC EFFECTIVENESS OF SMOKING CESSATION MEDICATIONS AMONG PEOPLE LIVING WITH HIV RECEIVING CARE IN THE NATIONAL VETERANS HEALTH ADMINISTRATION

4.1 INTRODUCTION

People living with HIV (PLWH) are disproportionately represented among persons who smoke in the United States (U.S.) and smoking is particularly dangerous for this population [1, 16, 54, 88, 107]. Several studies conducted in large U.S. health systems suggest that PLWH want to stop smoking and receive smoking cessation medications at rates comparable to people without HIV, but are less likely to quit [28, 92, 99]. Smoking cessation medications such as nicotine replacement therapy (NRT), bupropion, and varenicline have known efficacy [109], yet, trials of these principal pharmacotherapies have rarely focused on PLWH or patients with known psychiatric or concurrent addiction behaviors [26, 110-113]. PLWH experience high rates of depression, alcohol use disorder, and other substance use disorders [29, 34, 35], so much of the existing literature ignores the clinical realities of a large segment of this population. Therefore, pragmatic studies of PLWH in real-world clinical settings are needed to understand the effectiveness of smoking cessation medications for PLWH.

The Veterans Health Administration (VHA) is the largest system of health care, the largest provider of HIV care in the United States, and a setting in which a substantial number of patients with HIV receive smoking cessation medications. Since 2006, 12717 PLWH have received NRT, 6760 have received bupropion, and 2469 have received varenicline. Low receipt of varenicline is due to VHA concerns over potential neuropsychiatric effects [50]. Despite its demonstrated superiority in promoting cessation over other pharmacotherapies [49, 101, 102,

114, 115], the VHA considers varenicline a second-line therapy. Thus, the VHA offers a unique opportunity to evaluate the real-world effectiveness of smoking cessation medications among PLWH.

In a national sample of veteran VHA patients with HIV in routine care, we sought to assess whether and which medications are associated with smoking cessation (i.e. change in smoking status from current to former smoker) over a six-year period.

4.2 METHODS

Study Data Sources and Sample

The Veterans Aging Cohort Study (VACS) includes electronic health record (EHR) demographic, clinical, and pharmacy data for all PLWH receiving care in the VHA and is updated annually to include veterans with new diagnoses of HIV infection [51, 52]. These data are drawn from the VHA Corporate Data Warehouse (CDW), a national data repository that mirrors the EHR and incorporates data from the clinical and administrative systems into one standard database structure for all users of VHA care [57].

For the present study, we identified PLWH from VACS who had documentation of current smoking in the EHR resulting from an automated clinical reminder, prompting documentation regarding tobacco use, between January 1, 2013 and December 31, 2018. Utilization of these data to ascertain smoking status have been described in earlier studies and have been shown to have substantial agreement with smoking status based on survey response [53, 116]. In short, patients in primary care and mental outpatient health are screened once a year for current smoking as facilitated by a clinical reminder that is embedded in the EHR, serving to prompt providers to ask their patient about tobacco use. Patients who received a

positive tobacco screen (classified as a current smoker) during the study period and were screened again for tobacco use 9-15 months later were included in the study. Individuals contributed only once to the data at first EHR-documentation of current smoking during the study period.

Outcomes

Among those with current smoking who had a follow-up tobacco screen, we created a dichotomous “smoking cessation” measure that categorized patients into those who changed their smoking status from current smoker to former smoker and those who remained current smokers. If patients had multiple screens documented in the EHR during the follow-up window, we excluded those whose smoking status was not consistently identified as current smoker or former smoker.

Primary independent measure

We used VHA pharmacy data to identify receipt of smoking cessation medications, specifically prescriptions for NRT, bupropion, and varenicline that were filled between the date of initial positive tobacco screen and the date of the subsequent tobacco screen in the follow-up window. We created a categorical variable to compare no medications received (reference) with receipt of single NRT, combination NRT, bupropion, or varenicline. We defined combination NRT as having received two or more forms of NRT (gum, inhaler, lozenge, patch, or spray) during the follow-up window. Bupropion and varenicline categories were defined as having received these medications, even if NRT was also received in the time window.

Covariates

We collected sociodemographic factors such as age, sex (male versus female), race/ethnicity (Black, Hispanic, white, other), and site of care for each patient via the EHR. “Other” race included American Indian or Alaska Native, Asian, and Native Hawaiian or Pacific Islander. Since no measures of income or education are available in administrative data, VHA eligibility status, which reflects dimensions of income, disability status, and health care coverage for veterans, is commonly used as a proxy of socio-economic status [117, 118]. VHA criteria for health care eligibility include either a service-connected disability or low financial resources. Therefore, absence of a service-connected disability is an indicator for low socioeconomic status; these were coded as non-service connected, service connection 50-100%, and service connection <50%. Additionally, no measure of social support exists within the EHR, though marital status has been used as a proxy for this measure in the VHA (married vs. unmarried) [119]. Unmarried status included divorced, never married, separated, single, widowed/widower, and unknown.

Substance use and mental health comorbidity were ascertained through the EHR. We assessed presence of unhealthy alcohol use by combining results from annual VHA implemented alcohol screening using the three-item Alcohol Use Disorders Identification Test Consumption (AUDIT-C) and ICD-9/10 diagnoses for alcohol use disorder (AUD). The AUDIT-C is a brief alcohol screen, which is scored 0-12 (non-drinking to severe unhealthy alcohol use) and validated to identify patients with unhealthy alcohol use; cut-points of 4 for men and 3 for women maximize sensitivity and specificity [58]. We used the AUDIT-C score that occurred most proximal to each initial positive tobacco screen, occurring within 0-365 days prior [119]. Patients with a diagnosis for AUD occurring 0-365 days prior to each initial tobacco screen were also identified as having unhealthy alcohol use. Substance use disorder was similarly defined by ICD-9/10 code for any drug use disorder or dependence. We defined presence of psychiatric

condition if an ICD-9/10 code for bipolar disorder, major/minor depression, post-traumatic stress disorder, schizophrenia, and/or other psychosis occurred 0-365 days prior to initial positive tobacco screen.

HIV severity was measured using the VACS Index 2.0, a composite measure of HIV severity that predicts all-cause mortality, cause-specific mortality, frailty, and other clinical outcomes in PLWH [62]. VACS Index 2.0 includes CD4 cell count and HIV-1 RNA in combination with other disease markers [65-67], and is generated using a combination of administrative, clinical, and laboratory data. Individual components of VACS 2.0, such as HIV viral load and CD4+ count, documented in the EHR closest to date of initial positive tobacco screen, within 365 days prior to 90 days after, was used to calculate the continuous summary score. The wider timeframe was applied to ensure that we include as much lab data as possible in the analysis. Viral load was categorized into undetectable (<40 copies/ml), detectable, and missing. CD4+ count was also categorized into the following groups: <200 cells/ μ L, 200-500 cells/ μ L, >500 cells/ μ L, and missing.

Analysis

We described the demographic and clinical characteristics of the sample, overall and by smoking status at follow-up using chi-square tests of independence, Student's t-test, and Wilcoxon Rank-Sum test as appropriate.

To evaluate which pharmacotherapies were associated with smoking cessation we first conducted bivariate comparisons of the prevalence of receiving different categories of smoking cessation medications using chi-square tests. Subsequently, we fit marginal multivariable log-linear regression models with a Poisson distribution to estimate the unadjusted and adjusted relative risk (RR and ARR, respectively) and 95% confidence interval (CI) associated with

smoking cessation for each medication relative to no medication. Models were adjusted for all measured covariates in the domains already described. We used poisson, rather than logistic regression, because the outcome was expected to be somewhat common, in which case odds ratios may overestimate the associations [69, 70]. To account for the multi-level nature of the data, we clustered by site of care and specified an exchangeable correlation structure. Also, we applied a robust sandwich estimator to calculate standard errors and obtain a valid inference even if the correlation structure was incorrectly specified [68-72].

In additional analyses, we employed inverse probability treatment weighting (IPTW) adjustment, commonly used to estimate causal relationships in observational studies, that assign weights to each treatment relative to the probability of selecting into that treatment given all measured pretreatment covariates [23, 120]. A propensity score was estimated as the probability of receiving each type of pharmacotherapy and a weight was calculated as the inverse of the propensity score. We created a weighted model including all potential confounders to compare average treatment effects (ATE) in the likelihood of each medication (treatment) to change smoking status from current to former smoker compared with no medications (control).

All analyses were performed using Stata version 14 (Stata Corp, College Station, TX).

4.3 RESULTS

Between January 1, 2013 and December 31, 2018, 11915 PLWH had documentation of current smoking. Among these patients, 1239 (10%) had stopped smoking (became former smokers) 9-15 months later. A summary of patient characteristics are presented in Table 4.1, overall and by smoking status. In general, the study population was predominantly male (97%) with an average age of 54.5 years; approximately, 51% were Black, 15% were married, and 49% had a non-service connected disability status. Additionally, 45% of the study population had

unhealthy alcohol use, 18% had a substance use disorder, 50% had a psychiatric disorder, and 41% had undetectable HIV viral load.

When comparing PLWH who continued to smoke to those who had stopped smoking (Table 4.1), those who had stopped were more likely to be older, married, have a higher service connection rating, and a larger proportion were Hispanic (all p-values <0.05). Those who had stopped smoking were also less likely to have unhealthy alcohol use, substance use disorder, and lower HIV viral loads compared with current smokers (all p-values <0.05). Comparing individual smoking cessation medications, 20% and 25% of former smokers and current smokers had received NRT, respectively; 12% and 9% had received bupropion; and 2% and 1% had received varenicline (p<0.001). In both groups, 66% received no smoking cessation medication (Table 4.1).

When comparing the study population by smoking cessation medication (Table 4.2), the treatment groups appeared to be statistically different in all characteristics except for sex and unhealthy alcohol use. Patients who identified as white or were generally healthier were more likely to receive varenicline over patients of color or sicker patients (p<0.001). Those who had a psychiatric diagnosis in the last year were more likely to have received bupropion (p<0.001).

Unadjusted and adjusted relative risks of smoking cessation for single NRT, combination NRT, bupropion, or varenicline compared with receiving no medication were similar (Table 4.3). In the full model that included sociodemographics, substance use variables, presence of psychiatric condition, and HIV viral load, those who received combination NRT had a 3% lower likelihood of smoking cessation compared with those who received no medication (ARR 0.97, 95% CI 0.96, 0.99). However, those who received bupropion had a 3% greater likelihood of smoking cessation compared with those who received no medication (ARR 1.03, 95% CI 1.01,

Table 4.1: Characteristics of PLWH in the VHA who Smoke between 2013 and 2018 (N=11915), by Smoking Status at 9-12 Month Follow-up

	Smoking Status at 9-12 Month Follow-up			
	PLWH with Current Smoking at Initial Screen (n=11915)	Continued Smoking (n=10676)	Stopped Smoking (n=1239)	<i>p value</i>
SOCIODEMOGRAPHIC FACTORS				
Age, mean (SD)	54.5 (10.3)	54.3 (10.2)	55.7 (11.0)	<0.001
Male, n (%)	11508 (97)	10308 (97)	1200 (97)	NS
Race/ethnicity, n (%)				<0.001
Black	6074 (51)	5459 (51)	615 (50)	
Hispanic	779 (7)	664 (6)	115 (9)	
Other	366 (3)	334 (3)	32 (3)	
White	4696 (39)	4219 (40)	477 (39)	
Married, n (%)	1816 (15)	1595 (15)	221 (18)	0.02
VHA Eligibility Status, n (%)				
Non-service connected	5799 (49)	5200 (49)	599 (48)	0.002
Service connection 50-100%	3950 (33)	3493 (33)	457 (37)	
Service connection <50%	2144 (18)	1963 (18)	181 (15)	
Other	22 (0.2)	20 (0.2)	2 (0.2)	
SUBSTANCE USE / MENTAL HEALTH COMORBIDITY				
Unhealthy alcohol use, n (%)	5338 (45)	4816 (45)	522 (42)	0.03
Alcohol use unknown	115 (1)	108 (1)	7 (0.6)	
Substance Use Disorder, n (%)	2170 (18)	2010 (19)	160 (13)	<0.001
Psychiatric disorders, n (%)	5946 (50)	5332 (50)	614 (50)	NS
HIV SEVERITY				
HIV RNA Viral load, median (IQR)	28 (20, 87)	30 (20, 99)	20 (20, 50)	<0.001
Undetectable, n (%)	4892 (41)	4313 (40)	579 (47)	<0.001
Detectable	4523 (38)	4107 (38)	416 (34)	
Missing	2500 (21)	2256 (21)	244 (20)	
CD4+ Count, median (IQR)	544 (344, 768)	543 (340, 764)	555 (371, 788)	NS
>500 cells/μL	5168 (43)	4608 (43)	560 (45)	NS
200-500 cells/μL	3222 (27)	2875 (27)	347 (28)	
<200 cells/μL	1005 (8)	916 (9)	89 (7)	
Missing	2520 (21)	2277 (21)	243 (20)	
VACS Index 2.0, mean (SD)	48.0 (17.2)	48.1 (17.2)	47.2 (17.8)	NS
SMOKING CESSATION MEDICATIONS				
None, n (%)	7834 (66)	7013 (66)	821 (66)	<0.001
Nicotine Replacement Therapy, n (%)	2869 (24)	2623 (25)	246 (20)	
Single NRT	833 (7)	735 (7)	98 (8)	
Combination NRT	2036 (17)	1888 (18)	148 (12)	
Bupropion, n (%)	1052 (9)	908 (9)	144 (12)	
Varenicline, n (%)	160 (1)	132 (1)	28 (2)	

Note: Numbers may vary by category due to missing data. Percentages may not add up to exactly 100 due to rounding

Table 4.2: Characteristics of PLWH in the VHA who Smoke between 2013 and 2018 (N=11915), by Smoking Cessation Medication—No Medication, Single NRT, Combination NRT, Bupropion, and Varenicline

	No Medication (n=7834)	Single NRT (n=833)	Combination NRT (n=2036)	Bupropion (n=1052)	Varenicline (n=160)	<i>p value</i>
SOCIODEMOGRAPHIC FACTORS						
Age, mean (SD)	54.9 (10.4)	54.0 (10.5)	54.0 (9.8)	52.5 (10.4)	53.9 (10.2)	<0.001
Male, n (%)	7574 (97)	814 (98)	1957 (96)	1006 (96)	157 (98)	NS
Race/ethnicity, n (%)						<0.001
Black	3974 (51)	423 (51)	1108 (54)	509 (48)	60 (38)	
Hispanic	532 (7)	42 (5)	119 (6)	79 (8)	7 (4)	
Other	245 (3)	23 (3)	49 (2)	44 (4)	5 (3)	
White	3083 (39)	345 (41)	760 (37)	420 (40)	88 (55)	
Married, n (%)	1191 (15)	119 (14)	303 (15)	174 (17)	29 (18)	<0.001
VHA Eligibility Status, n (%)						<0.001
Non-service connected	3962 (51)	450 (54)	939 (46)	377 (36)	71 (44)	
Service connection 50-100%	2391 (31)	229 (27)	765 (38)	512 (49)	53 (33)	
Service connection <50%	1470 (19)	151 (18)	326 (16)	161 (15)	36 (23)	
Other	11 (0.1)	3 (0.4)	6 (0.3)	2 (0.2)	0 (0)	
SUBSTANCE USE / MENTAL HEALTH COMORBIDITY						
Unhealthy alcohol use, n (%)	3470 (45)	393 (48)	923 (46)	474 (45)	78 (49)	NS
Substance Use Disorder, n (%)	1223 (16)	149 (18)	528 (26)	252 (24)	18 (11)	<0.001
Psychiatric disorders, n (%)	3433(44)	389 (47)	1240 (61)	811 (77)	73 (46)	<0.001
HIV SEVERITY						
VACS Index 2.0, mean (SD)	48.9 (17.8)	49.6 (18.9)	48.8 (16.9)	45.1 (15.8)	43.8 (12.8)	<0.001
HIV RNA Viral load, n (%)						<0.001
Undetectable	3294 (42)	333 (40)	767 (38)	428 (41)	70 (44)	
Detectable	2986 (38)	286 (34)	808 (40)	389 (37)	54 (34)	
Missing	1554 (20)	214 (26)	461 (23)	235 (22)	36 (22)	
CD4+ Count, n (%)						<0.001
>500 cells/μL	3390 (43)	336 (40)	884 (43)	475 (45)	83 (52)	
200-500 cells/μL	2194 (28)	193 (23)	526 (26)	273 (26)	36 (22)	
<200 cells/μL	694 (9)	83 (10)	161 (8)	61 (6)	6 (4)	
Missing	1556 (20)	221 (27)	465 (23)	243 (23)	35 (22)	

Note: Numbers may vary by category due to missing data. Percentages may not add up to exactly 100 due to rounding

1.05). Though few patients received varenicline, those that did had a 7% greater likelihood of smoking cessation compared with those who received no medication (ARR 1.07, 95% CI 1.02, 1.11). There was no statistically significant difference in likelihood of smoking cessation between patients who received single NRT and patients who received no medication (ARR 1.01, 95% CI 0.99, 1.03) (Table 4.3).

Table 4.3: Unadjusted and Adjusted Estimates of Stopping Smoking 9-12 Months after Initial Tobacco Use Screen by Smoking Cessation Medication Received among PLWH in the VHA who Smoke between 2013 and 2018 (N=11915)

	Model 1	Model 2	Model 3	Model 4
	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)	Average Treatment Effect without Adjustment (95% CI)	Average Treatment Effect with Inverse Probability Treatment Weighting (95% CI)
None (Reference)	--	--	--	--
Single NRT	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	0.01 (-0.01, 0.04)	0.02 (-0.01, 0.04)
Combination NRT	0.97 (0.96, 0.98)	0.97 (0.96, 0.98)	-0.03 (-0.05, -0.02)	-0.03 (-0.04, -0.01)
Bupropion	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	0.03 (0.01, 0.05)	0.03 (0.002, 0.05)
Varenicline	1.06 (1.02, 1.11)	1.07 (1.02, 1.11)	0.07 (0.01, 0.13)	0.05 (0.0001, 0.11)

Models 2 and 4 adjusted for sociodemographic characteristics, substance use, psychiatric conditions, and HIV viral load

Results from the propensity score weighted analyses were generally similar. In the full model comparing the treatment group and controls, the average treatment effect based on IPTW indicated that combination NRT resulted in a 3% lower likelihood of smoking cessation (ATE - 0.03, 95% CI -0.04, -0.01) while bupropion resulted in a 3% greater likelihood of cessation (ATE 0.03, 95% CI 0.002, 0.05). Varenicline resulted in a 5% greater likelihood of smoking cessation, though confidence intervals were wide due to the small number of observations (ATE 0.05, 95% CI 0.0001, 0.11). There was no statistically significant difference in likelihood of smoking cessation between patients who received single NRT and patients who received no medication (ATE 0.01, 95% CI -0.01, 0.04) (Table 4.3).

4.4 DISCUSSION

This is the first study to our knowledge to investigate the pragmatic effectiveness of principal smoking cessation pharmacotherapies among a diverse patient population of PLWH who smoke in routine care. Our results suggest that PLWH who had received bupropion and varenicline were more likely to quit smoking compared to those who received no medication, and that those who received single or combination NRT were not. However, clinical indication bias remains difficult to eliminate, especially among those who received varenicline likely due to the small sample size and complicated nature of its prescription in the VHA.

Few studies exist to assess either efficacy or effectiveness of pharmacologic treatments for smoking cessation among PLWH. However, our results agree with existing literature that suggest bupropion and varenicline are effective treatments for tobacco use disorder and are possibly more effective than NRT in promoting smoking cessation. In a prospective cohort study among PLWH, bupropion appeared to be effective in the treatment of tobacco use disorder among PLWH with no interactions with antiretroviral (ART) drugs [25]. Several studies, RCT and observational, suggest that varenicline may be more effective in promoting smoking abstinence over other pharmacotherapies without difference in safety profile among participants on combination ART and those not on ART [23, 27, 110]. One observational study even included patients with known mental health illness [23]. RCTs and observational studies among PLWH receiving NRT, usually in addition to counseling or another intervention, report abstinence rates comparable to general population studies and feasible integration of smoking cessation interventions in clinical HIV treatment settings [22, 26, 121, 122]. Surprisingly, in our study population, single NRT was not shown to be associated with a smoking cessation, and

combination NRT was found to be associated with continued smoking when compared with no medication.

NRT is the most commonly used smoking cessation pharmacotherapy. In our study, it accounted for over 70% of the medications received to quit smoking and is frequently used in combination with other forms of NRT, other pharmacotherapies, and non-pharmacologic treatment [45]. Specifically, the VHA has adopted policies to make NRT more accessible to patients [95] whereas other smoking cessation medications have greater considerations, even restrictions, for its use. Though bupropion is considered a first-line therapy, it has potential interactions with certain forms of ART that providers must consider [96], and is also contraindicated for patients experiencing or being treated for certain mental health and cardiovascular conditions [97, 98]. Despite this, the majority of patients receiving bupropion had a known psychiatric disorder, since it is also used to treat certain forms of depression [123].

Within the VHA, varenicline is a second-line therapy and patients who may be considered to receive varenicline are required to have been previously unsuccessful at quitting with NRT and combination therapies [98]. Therefore, it is possible that the patients receiving NRT products are early in their cessation journey or that those receiving bupropion or varenicline are potentially more motivated to quit. Without pack year data or other measures for smoking intensity or quit motivation, it is difficult to understand the relationship between NRT and smoking cessation found in our study. Future studies with greater availability of refined data regarding tobacco use are needed to further understand associations between smoking cessation medications and smoking cessation among PLWH in pragmatic clinical settings.

Clearly, the principal pharmacotherapies used to treat tobacco use disorder are prescribed differentially in clinical settings and especially within the VHA. We used IPTW to adjust for

confounding by indication and selection bias, although it is possible that these techniques do not fully account for the differences seen in groups receiving each pharmacotherapy. Treatment choice is influenced by a number of factors that relate to smoking cessation, but are often not perfectly recorded or measurable in the types of electronic data sources that were used in our analyses. When these are not measured or not measured precisely, analyses can result in biased estimates, confidence interval undercoverage, and inability to determine causality [124].

Other limitations of this study include misclassification bias. Follow-up tobacco screen from automated clinical indicators in the EHR were used to identify current smokers who changed their smoking status to former smoker. However, it is unclear how this outcome relates to successful cessation and whether these individuals remained former smokers in subsequent screens. Lastly, there is no way to determine whether patients who received medications actually used them or used them correctly. Consequently, we had to assume perfect adherence.

Despite these limitations, this study is a novel examination in the pragmatic effectiveness of the principal pharmacotherapies reflected in the usual practice decisions that providers make to treat tobacco use disorder among a complex and diverse population of PLWH. Our results support findings from prior studies that indicate bupropion and varenicline may be more effective in treating tobacco use disorder over other medications and are both potentially underutilized in the VHA. This practice has implications in the ability to prescribe what has been demonstrated as the most effective medication for treating tobacco use disorder.

5 Chapter 5. CONCLUSIONS

5.1 SUMMARY OF FINDINGS

This dissertation sought to answer three questions regarding PLWH and the receipt of effective pharmacologic treatments for smoking cessation that have not been adequately explored in the literature. This body of work is important for increasing access to and use of smoking cessation pharmacotherapy among PLWH for whom tobacco use is extremely dangerous.

In Chapter 2, we found that PLWH were less likely to receive NRT (though not other medications), compared with those who are HIV-uninfected in a cross-sectional analysis among a cohort of surveyed VACS participants. We also found that, among PLWH, those who had been diagnosed with a psychiatric disorder or pulmonary disease in the year prior to survey were more likely to receive pharmacotherapy compared with those without these diagnoses. PLWH who were contemplating cessation were also more likely to receive these medications compared to those who were not. Importantly, in this surveyed cohort, alcohol use, substance use, and sociodemographic characteristics were not found to be associated with receiving smoking cessation medications despite prior literature suggesting otherwise. Recent diagnosis for CVD was also not found to be associated with received pharmacotherapy, representing missed opportunities to address tobacco use.

Interestingly, in Chapter 3, we found that PLWH were slightly more likely to receive NRT compared with uninfected VACS participants among all observations in which current smoking was documented in the EHR from 2003 to 2018. We also found that the rate of change in receiving any smoking cessation medication per year improved for both populations, though it

was slightly greater among PLWH. Over the study period, receipt of smoking cessation medications, specifically NRT, nearly doubled. No previous studies had examined change in pharmacotherapy receipt over time within a large health care system, and this dissertation provides evidence that PLWH appear to be provided the opportunity to receive effective treatment at rates similar to the uninfected within the VHA.

The discrepancy between the findings in Chapters 2 and 3 underscores the limitations of cross-sectional data and the potential for sampling bias among a surveyed cohort. Possibly, this highlights that changes may have occurred over time in care. However, among individual patients included in the analysis in Chapter 3, a slightly smaller and statistically significant proportion of PLWH received smoking cessation medications during the study period compared with the uninfected (in agreement with the finding in Chapter 2). This suggests that perhaps fewer individuals with HIV are receiving pharmacotherapy, but those who do may be receiving it repeatedly over time.

In Chapter 4, we found that bupropion and varenicline were associated with a change in smoking status from current to former smoker and may be more effective than NRT and combination NRT in promoting cessation among PLWH. Single NRT was not associated with smoking cessation, and combination NRT was found to be associated with remaining a current smoker compared with those who received no medication. However, likely due to complex prescription practices within the VHA and contraindications specific to bupropion and varenicline, clinical indication bias was difficult to eliminate. Still, it is possible that the VHA is underutilizing highly effective medications for the treatment of tobacco use disorder. To the best of our knowledge, we are the first to compare the effectiveness of the principal pharmacotherapies in a routine care setting among PLWH.

5.2 POLICY IMPLICATIONS

There is evidence to suggest that the VHA has made great progress in making smoking cessation a public health priority for their patients with and without HIV, however, this dissertation identified several gaps. First, we found that PLWH were receiving smoking cessation medications at slightly higher rates over the uninfected, but that receipt of pharmacotherapy remains low in general. Also, while there did not appear to be treatment disparities among PLWH on the basis of race/ethnicity, alcohol and substance use, or depression, PLWH who had recently been diagnosed with CVD represent a patient population to which greater attention to tobacco use ought to be paid. Whereas a recent diagnosis for pulmonary disease may prompt receipt for smoking cessation medication, as seen in Chapter 2, so too should a CVD diagnosis.

Second, bupropion and varenicline appear to be underutilized, highly effective smoking cessation medications for the treatment of tobacco use disorder. Even though receipt of NRT has doubled since 2003, many patients are still not being reached, and rates of receiving bupropion and varenicline are lagging. In Chapter 3, we found that rates of receiving bupropion were stagnant among PLWH and decreasing among the HIV-uninfected despite it being associated with a greater likelihood of cessation found in Chapter 4. Our findings also support those of prior studies that suggest varenicline may be the most effective pharmacotherapy in promoting smoking cessation. For this reason, there is evidence to prompt re-examination of VHA policies on varenicline, its guidance for prescription, and its second-line status.

Lastly, given that smoking rates remain exceptionally high among PLWH and cessation illusive (e.g., our study showed only 10% of PLWH stopped smoking 9-12 months after tobacco use screening), standard care services and population health approaches appear inadequate. The

VHA offers the National VA Quitline, the Smokefree VET texting program, and counseling services, but these programs are not tailored to PLWH. Strategies to reduce smoking prevalence and the burden of disease due to smoking must include a vulnerable population approach that includes a greater understanding for the lived experience of PLWH who smoke, better tools for providers that reflect this, and policies that specifically target PLWH.

5.3 FUTURE DIRECTIONS

The population studied in this dissertation was solely comprised of veterans receiving care in the VHA. These examinations must be conducted in other populations of PLWH and in other health care systems. Furthermore, PLWH are not monolithic and there are subgroup analyses that may follow the findings discussed in this dissertation. Although disparities in receiving smoking cessation pharmacotherapy were not found on the basis of alcohol or substance use, future studies may need to investigate strategies to engage people with high alcohol use and injection drug use in effective treatment. Sexual and gender minorities are another highly vulnerable population that have overlapping characteristics related to smoking, HIV infection, substance use and depression that may require further exploration. These groups constitute an intersectionally marginalized population at compounded risk of risks by belonging to several socially stigmatized groups [104, 125, 126].

Moreover, this dissertation focused on patient characteristics at the individual level that may affect receipt of effective pharmacologic treatments to quit smoking. Other factors that are likely to contribute to smoking and cessation behavior include community level factors, which exert great influence among PLWH because of the risk environment in which they live and strong social ties and norms they impart on each other [127, 128]. Interpersonal relationships are also highly determinant of behavioral social norms such as smoking and other addiction

behaviors [39, 128]. Lastly, PLWH in the U.S. are often exposed to a variety of chronic stressors including racism/discrimination, stigmatization, and loneliness [106]. Psychosocial factors such as perceived stress due to racism and stigma—structural issues manifested at the individual level—is further associated with greater engagement in high-risk behaviors as coping mechanisms [129, 130]. High levels of perceived stress are associated with smoking initiation, increased smoking levels, and fewer successful smoking cessation attempts [131]. These domains are not able to be deciphered from the EHR, which was the primary data source for this dissertation, and additional study designs are recommended.

Few studies describe smoking cessation programs targeting PLWH and fewer still openly address these other, more upstream, influences in tobacco use behavior. For example, in one ongoing study titled *Improving the Reach and Effectiveness of Smoking Cessation Services Targeted to Veterans Living with HIV* (NCT04505371), interventionists engage PLWH who smoke in motivational interviewing techniques that cover a range of behaviors including medication adherence, mood/stress management, other substance use and health behaviors. This study will compare standard care services offered by the VHA with this innovative, comprehensive wellness approach tailored to the needs of the participant.

Additionally, qualitative approaches [132] would be of particular value to complement the quantitative, large dataset methods presented in this dissertation. Critical gaps in knowledge remain, as well gaps in appreciation, consideration, and empathy for PLWH who struggle to become and remain smoke-free in the face of many chronic stressors. Mixed methods approaches may better formulate effective smoking cessation strategies, support, and messaging among a vulnerable population in whom the prevalence of smoking is high and the burden is great.

6 REFERENCES

1. Niaura, R., et al., *Human immunodeficiency virus infection, AIDS, and smoking cessation: the time is now*. Clin Infect Dis, 2000. **31**(3): p. 808-12.
2. Sudano, I., et al., *Cardiovascular disease in HIV infection*. Am Heart J, 2006. **151**(6): p. 1147-55.
3. Lifson, A.R., et al., *Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial*. Am J Public Health, 2010. **100**(10): p. 1896-903.
4. Diaz, P.T., et al., *Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers*. Ann Intern Med, 2000. **132**(5): p. 369-72.
5. Crothers, K., et al., *Increased COPD among HIV-positive compared to HIV-negative veterans*. Chest, 2006. **130**(5): p. 1326-33.
6. Kirk, G.D., et al., *HIV Infection Is Associated with an Increased Risk for Lung Cancer, Independent of Smoking*. Clinical Infectious Diseases, 2007. **45**(1): p. 103-110.
7. Sigel, K., et al., *HIV as an Independent Risk Factor for Incident Lung Cancer*. AIDS (London, England), 2012. **26**(8): p. 1017-1025.
8. Gordin, F.M., et al., *Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption*. Am J Respir Crit Care Med, 2008. **178**(6): p. 630-6.
9. Miguez-Burbano, M.J., et al., *Impact of tobacco use on the development of opportunistic respiratory infections in HIV seropositive patients on antiretroviral therapy*. Addict Biol, 2003. **8**(1): p. 39-43.
10. Huttunen, R., T. Heikkinen, and J. Syrjanen, *Smoking and the outcome of infection*. J Intern Med, 2011. **269**(3): p. 258-69.
11. Diaz, P.T., et al., *Respiratory symptoms among HIV-seropositive individuals*. Chest, 2003. **123**(6): p. 1977-82.
12. Turner, J., et al., *Adverse impact of cigarette smoking on dimensions of health-related quality of life in persons with HIV infection*. AIDS Patient Care STDS, 2001. **15**(12): p. 615-24.
13. Crothers, K., et al., *The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans*. J Gen Intern Med, 2005. **20**(12): p. 1142-5.
14. Crothers, K., et al., *Impact of cigarette smoking on mortality in HIV-positive and HIV-negative veterans*. AIDS Educ Prev, 2009. **21**(3 Suppl): p. 40-53.
15. Feldman, J.G., et al., *Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study*. American journal of public health, 2006. **96**(6): p. 1060-1065.
16. Mdodo, R., et al., *Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys*. Ann Intern Med, 2015. **162**(5): p. 335-44.
17. Webb, M.S., et al., *Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum*. Journal of behavioral medicine, 2007. **30**(5): p. 371-383.
18. Burkhalter, J.E., et al., *Tobacco use and readiness to quit smoking in low-income HIV-infected persons*. Nicotine Tob Res, 2005. **7**(4): p. 511-22.

19. Jamal, A., et al., *Current Cigarette Smoking Among Adults - United States, 2016*. MMWR Morb Mortal Wkly Rep, 2018. **67**(2): p. 53-59.
20. Silagy, C., et al., *Nicotine replacement therapy for smoking cessation*. Cochrane Database Syst Rev, 2004(3): p. Cd000146.
21. Hurt, R.D., et al., *A comparison of sustained-release bupropion and placebo for smoking cessation*. N Engl J Med, 1997. **337**(17): p. 1195-202.
22. Ingersoll, K.S., K.L. Cropsey, and C.J. Heckman, *A test of motivational plus nicotine replacement interventions for HIV positive smokers*. AIDS and behavior, 2009. **13**(3): p. 545-554.
23. Ferketich, A.K., et al., *Safety of varenicline among smokers enrolled in the lung HIV study*. Nicotine Tob Res, 2013. **15**(1): p. 247-54.
24. Mercie, P., et al., *Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial*. Lancet HIV, 2018.
25. Pedrol-Clotet, E., et al., *[Bupropion use for smoking cessation in HIV-infected patients receiving antiretroviral therapy]*. Enferm Infecc Microbiol Clin, 2006. **24**(8): p. 509-11.
26. Humfleet, G.L., et al., *A randomized clinical trial of smoking cessation treatments provided in HIV clinical care settings*. Nicotine Tob Res, 2013. **15**(8): p. 1436-45.
27. Cui, Q., et al., *Safety and tolerability of varenicline tartrate (Champix((R))/Chantix((R))) for smoking cessation in HIV-infected subjects: a pilot open-label study*. AIDS Patient Care STDS, 2012. **26**(1): p. 12-9.
28. Shahrir, S., et al., *Contemplation of smoking cessation and quit attempts in human immunodeficiency virus-infected and uninfected veterans*. Subst Abus, 2016. **37**(2): p. 315-22.
29. Tesoriero, J.M., et al., *Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation*. AIDS Behav, 2010. **14**(4): p. 824-35.
30. Marmar, E.M., D. Bahrs, and S. Martinez, *Cigarette smoking and the desire to quit among individuals living with HIV*. AIDS Patient Care STDS, 2002. **16**(1): p. 39-42.
31. *Characteristics associated with HIV infection among heterosexuals in urban areas with high AIDS prevalence --- 24 cities, United States, 2006-2007*. MMWR Morb Mortal Wkly Rep, 2011. **60**(31): p. 1045-9.
32. Frazier, E.L., et al., *Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009-2014*. Preventive Medicine, 2018. **111**: p. 231-234.
33. Gadgeel, S.M. and G.P. Kalemkerian, *Racial differences in lung cancer*. Cancer Metastasis Rev, 2003. **22**(1): p. 39-46.
34. Benard, A., et al., *Tobacco addiction and HIV infection: toward the implementation of cessation programs. ANRS CO3 Aquitaine Cohort*. AIDS Patient Care STDS, 2007. **21**(7): p. 458-68.
35. O'Cleirigh, C., et al., *The unique challenges facing HIV-positive patients who smoke cigarettes: HIV viremia, ART adherence, engagement in HIV care, and concurrent substance use*. AIDS Behav, 2015. **19**(1): p. 178-85.
36. Duval, X., et al., *Living with HIV, antiretroviral treatment experience and tobacco smoking: results from a multisite cross-sectional study*. Antiviral therapy, 2008. **13**(3): p. 389-397.

37. Humfleet, G.L., et al., *Characteristics of HIV-positive cigarette smokers: a sample of smokers facing multiple challenges*. AIDS education and prevention : official publication of the International Society for AIDS Education, 2009. **21**(3 Suppl): p. 54-64.
38. Shuter, J., et al., *Self-efficacy to quit in HIV-infected smokers*. Nicotine Tob Res, 2014. **16**(11): p. 1527-31.
39. Shuter, J., S.L. Bernstein, and A.B. Moadel, *Cigarette smoking behaviors and beliefs in persons living with HIV/AIDS*. Am J Health Behav, 2012. **36**(1): p. 75-85.
40. Encrenaz, G., et al., *Determinants of smoking cessation attempts among HIV-infected patients results from a hospital-based prospective cohort*. Curr HIV Res, 2010. **8**(3): p. 212-7.
41. Hughes, J.R. and P.W. Callas, *Past alcohol problems do not predict worse smoking cessation outcomes*. Drug Alcohol Depend, 2003. **71**(3): p. 269-73.
42. Hall, S.M., *Nicotine interventions with comorbid populations*. Am J Prev Med, 2007. **33**(6 Suppl): p. S406-13.
43. Shuter, J., et al., *Provider beliefs and practices relating to tobacco use in patients living with HIV/AIDS: a national survey*. AIDS and behavior, 2012. **16**(2): p. 288-294.
44. Crothers, K., et al., *Decreased awareness of current smoking among health care providers of HIV-positive compared to HIV-negative veterans*. J Gen Intern Med, 2007. **22**(6): p. 749-54.
45. Clinical Practice Guideline Treating Tobacco, U., L. Dependence Update Panel, and Staff, *A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report*. American journal of preventive medicine, 2008. **35**(2): p. 158-176.
46. (CPH), H.a.S.C.H.W.G.o.t.V.A.C.P.H., *HIV Provider Smoking Cessation Handbook: A Resource for Providers*. U.S. Department of Veterans Affairs Veterans Health Administration, 2012. **IB 10-432**(P96534).
47. Cahill, K., et al., *Pharmacological interventions for smoking cessation: an overview and network meta-analysis*. Cochrane Database Syst Rev, 2013(5): p. Cd009329.
48. Steinberg, M.B., et al., *Abstinence and psychological distress in co-morbid smokers using various pharmacotherapies*. Drug Alcohol Depend, 2011. **114**(1): p. 77-81.
49. Mills, E.J., et al., *Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis*. Ann Med, 2012. **44**(6): p. 588-97.
50. Cantrell, M., et al., *Adverse neuropsychiatric events associated with varenicline use in veterans: a case series*. Issues Ment Health Nurs, 2012. **33**(10): p. 665-9.
51. Fultz, S.L., et al., *Development and verification of a "virtual" cohort using the National VA Health Information System*. Med Care, 2006. **44**(8 Suppl 2): p. S25-30.
52. Justice, A.C., et al., *Veterans Aging Cohort Study (VACS): Overview and description*. Med Care, 2006. **44**(8 Suppl 2): p. S13-24.
53. McGinnis, K.A., et al., *Validating Smoking Data From the Veteran's Affairs Health Factors Dataset, an Electronic Data Source*. Nicotine & Tobacco Research, 2011. **13**(12): p. 1233-1239.
54. Mocroft, A., et al., *Decline in the AIDS and death rates in the EuroSIDA study: an observational study*. Lancet, 2003. **362**(9377): p. 22-9.

55. Petoumenos, K., et al., *Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(*)*. HIV Med, 2011. **12**(7): p. 412-21.
56. U.S. Department of Health and Human Services, H.R.a.S.A., *Guide for HIV/AIDS Clinical Care – 2014 Edition*. Rockville, MD: U.S. Department of Health and Human Services.
57. Price, L.E., K. Shea, and S. Gephart, *The Veterans Affairs's Corporate Data Warehouse: Uses and Implications for Nursing Research and Practice*. Nurs Adm Q, 2015. **39**(4): p. 311-8.
58. Bradley, K.A., et al., *AUDIT-C as a brief screen for alcohol misuse in primary care*. Alcohol Clin Exp Res, 2007. **31**(7): p. 1208-17.
59. Saitz, R., *Clinical practice. Unhealthy alcohol use*. N Engl J Med, 2005. **352**(6): p. 596-607.
60. Kroenke, K., R.L. Spitzer, and J.B. Williams, *The PHQ-9: validity of a brief depression severity measure*. J Gen Intern Med, 2001. **16**(9): p. 606-13.
61. Braun, R., et al., *[Introduction of the 9th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death]*. Z Gesamte Hyg, 1978. **24**(10): p. 793-800.
62. Tate, J.P., J.A.C. Sterne, and A.C. Justice, *Albumin, white blood cell count, and body mass index improve discrimination of mortality in HIV-positive individuals*. Aids, 2019. **33**(5): p. 903-912.
63. Akgün, K.M., et al., *An adapted frailty-related phenotype and the VACS index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals*. Journal of acquired immune deficiency syndromes (1999), 2014. **67**(4): p. 397-404.
64. Akgun, K.M., et al., *Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era*. Crit Care Med, 2013. **41**(6): p. 1458-67.
65. Bebu, I., et al., *The VACS index predicts mortality in a young, healthy HIV population starting highly active antiretroviral therapy*. Journal of acquired immune deficiency syndromes (1999), 2014. **65**(2): p. 226-230.
66. Brown, S.T., et al., *The VACS index accurately predicts mortality and treatment response among multi-drug resistant HIV infected patients participating in the options in management with antiretrovirals (OPTIMA) study*. PloS one, 2014. **9**(3): p. e92606-e92606.
67. Justice, A.C., et al., *Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis*. Journal of acquired immune deficiency syndromes (1999), 2013. **62**(2): p. 149-163.
68. Williams, E.C., et al., *Among patients with unhealthy alcohol use, those with HIV are less likely than those without to receive evidence-based alcohol-related care: A national VA study*. Drug Alcohol Depend, 2017. **174**: p. 113-120.
69. Greenland, S., *Model-based estimation of relative risks and other epidemiologic measures in studies of common outcomes and in case-control studies*. Am J Epidemiol, 2004. **160**(4): p. 301-5.
70. Zou, G., *A modified poisson regression approach to prospective studies with binary data*. Am J Epidemiol, 2004. **159**(7): p. 702-6.

71. Liang, K.-Y. and S.L. Zeger, *Longitudinal Data Analysis Using Generalized Linear Models*. Biometrika, 1986. **73**(1): p. 13-22.
72. Lapham, G.T., et al., *Increased Documented Brief Alcohol Interventions With a Performance Measure and Electronic Decision Support*. Medical Care, 2012. **50**(2): p. 179-187.
73. Brose, L.S., R. West, and J.A. Stapleton, *Comparison of the effectiveness of varenicline and combination nicotine replacement therapy for smoking cessation in clinical practice*. Mayo Clin Proc, 2013. **88**(3): p. 226-33.
74. Kralikova, E., et al., *Fifty-two-week continuous abstinence rates of smokers being treated with varenicline versus nicotine replacement therapy*. Addiction, 2013. **108**(8): p. 1497-502.
75. Ebbert, J.O., et al., *Varenicline for smoking cessation: efficacy, safety, and treatment recommendations*. Patient preference and adherence, 2010. **4**: p. 355-362.
76. Williams, J.M. and D. Ziedonis, *Addressing tobacco among individuals with a mental illness or an addiction*. Addict Behav, 2004. **29**(6): p. 1067-83.
77. Ziedonis, D., et al., *Tobacco use and cessation in psychiatric disorders: National Institute of Mental Health report*. Nicotine Tob Res, 2008. **10**(12): p. 1691-715.
78. Jackson, K.M., et al., *Adolescent alcohol and tobacco use: onset, persistence and trajectories of use across two samples*. Addiction, 2002. **97**(5): p. 517-531.
79. Gritz, E.R., et al., *Smoking behavior in a low-income multiethnic HIV/AIDS population*. Nicotine Tob Res, 2004. **6**(1): p. 71-7.
80. Marshall, M.M., et al., *Tobacco use and nicotine dependence among HIV-infected and uninfected injection drug users*. Addict Behav, 2011. **36**(1-2): p. 61-7.
81. Stewart, D.W., G.N. Jones, and K.S. Minor, *Smoking, depression, and gender in low-income African Americans with HIV/AIDS*. Behav Med, 2011. **37**(3): p. 77-80.
82. Triant, V.A., *Cardiovascular disease and HIV infection*. Current HIV/AIDS reports, 2013. **10**(3): p. 199-206.
83. Borowsky, S.J. and D.C. Cowper, *Dual use of VA and non-VA primary care*. Journal of general internal medicine, 1999. **14**(5): p. 274-280.
84. Kashner, T.M., et al., *Private health insurance and veterans use of Veterans Affairs care. RATE Project Committee. Rate Alternative Technical Evaluation*. Med Care, 1998. **36**(7): p. 1085-97.
85. Wolinsky, F.D., et al., *Veterans' and nonveterans' use of health services. A comparative analysis*. Med Care, 1985. **23**(12): p. 1358-71.
86. Helleberg, M., et al., *Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America*. Aids, 2015. **29**(2): p. 221-9.
87. Asfar, T., et al., *National Estimates of Prevalence, Time-Trend, and Correlates of Smoking in US People Living with HIV (NHANES 1999–2016)*. Nicotine & Tobacco Research, 2021. **23**(8): p. 1308-1317.
88. Palella, F.J., Jr., et al., *Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study*. J Acquir Immune Defic Syndr, 2006. **43**(1): p. 27-34.
89. Weinberger, A.H., et al., *Sex Differences in Tobacco Use Among Persons Living With HIV/AIDS: A Systematic Review and Meta-Analysis*. Journal of acquired immune deficiency syndromes (1999), 2017. **74**(4): p. 439-453.

90. Bien-Gund, C.H., et al., *Persistent Disparities in Smoking Rates Among PLWH Compared to the General Population in Philadelphia, 2009–2014*. *AIDS and Behavior*, 2021. **25**(1): p. 148-153.
91. Cornelius, M.E., et al., *Tobacco product use among adults—United States, 2019*. *Morbidity and Mortality Weekly Report*, 2020. **69**(46): p. 1736.
92. Shahrir, S., et al., *Receipt and predictors of smoking cessation pharmacotherapy among veterans with and without HIV*. *Progress in Cardiovascular Diseases*, 2020.
93. *A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives*. *Jama*, 2000. **283**(24): p. 3244-54.
94. Wilson, S.M., et al., *Veterans Living with HIV: A High-Risk Group for Cigarette Smoking*. *AIDS Behav*, 2017. **21**(7): p. 1950-1955.
95. Hamlett-Berry, K., et al., *Evidence-based national initiatives to address tobacco use as a public health priority in the Veterans Health Administration*. *Military medicine*, 2009. **174**(1): p. 29-34.
96. Hogeland, G.W., et al., *Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects*. *Clin Pharmacol Ther*, 2007. **81**(1): p. 69-75.
97. Wilkes, S., *The use of bupropion SR in cigarette smoking cessation*. *International journal of chronic obstructive pulmonary disease*, 2008. **3**(1): p. 45-53.
98. U.S. Department of Veterans Affairs, V.H.A., *Clinical Public Health, HIV Provider Smoking Cessation Handbook: A Resource for Providers*. Veterans Health Administration, Washington, DC 20420. **IB 10-432; P96534**.
99. Lam, J.O., et al., *Smoking and cessation treatment among persons with and without HIV in a U.S. integrated health system*. *Drug Alcohol Depend*, 2020. **213**: p. 108128.
100. Baker, T.B., et al., *Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial*. *JAMA*, 2016. **315**(4): p. 371-379.
101. Cinciripini, P.M., et al., *Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal*. *JAMA Psychiatry*, 2013. **70**(5): p. 522-33.
102. Jorenby, D.E., et al., *Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial*. *Jama*, 2006. **296**(1): p. 56-63.
103. Anthenelli, R.M., et al., *Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial*. *The Lancet*, 2016. **387**(10037): p. 2507-2520.
104. Link, B.G. and J. Phelan, *Social Conditions As Fundamental Causes of Disease*. *Journal of Health and Social Behavior*, 1995: p. 80-94.
105. Frohlich, K.L. and L. Potvin, *Transcending the known in public health practice: the inequality paradox: the population approach and vulnerable populations*. *Am J Public Health*, 2008. **98**(2): p. 216-21.
106. Pacek, L.R. and R.M. Crum, *A Review of the Literature Concerning HIV and Cigarette Smoking: Morbidity and Mortality, Associations with Individual- and Social-Level*

- Characteristics, and Smoking Cessation Efforts*. *Addiction research & theory*, 2015. **23**(1): p. 10-23.
107. Frazier, E.L., et al., *Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009-2014*. *Prev Med*, 2018. **111**: p. 231-234.
 108. Aspinall, S.L., et al., *Pharmacy Benefits Management in the Veterans Health Administration Revisited: A Decade of Advancements, 2004-2014*. *J Manag Care Spec Pharm*, 2016. **22**(9): p. 1058-63.
 109. Wu, P., et al., *Effectiveness of smoking cessation therapies: a systematic review and meta-analysis*. *BMC Public Health*, 2006. **6**: p. 300.
 110. Mercie, P., et al., *Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial*. *Lancet HIV*, 2018. **5**(3): p. e126-e135.
 111. Tseng, T.Y., et al., *Combining Text Messaging and Telephone Counseling to Increase Varenicline Adherence and Smoking Abstinence Among Cigarette Smokers Living with HIV: A Randomized Controlled Study*. *AIDS Behav*, 2017. **21**(7): p. 1964-1974.
 112. Moadel, A.B., et al., *A randomized controlled trial of a tailored group smoking cessation intervention for HIV-infected smokers*. *J Acquir Immune Defic Syndr*, 2012. **61**(2): p. 208-15.
 113. Lloyd-Richardson, E.E., et al., *Motivation and patch treatment for HIV+ smokers: a randomized controlled trial*. *Addiction*, 2009. **104**(11): p. 1891-900.
 114. Nides, M., et al., *Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up*. *Arch Intern Med*, 2006. **166**(15): p. 1561-8.
 115. Gonzales, D., et al., *Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial*. *Jama*, 2006. **296**(1): p. 47-55.
 116. McGinnis, K.A., et al., *Using the biomarker cotinine and survey self-report to validate smoking data from United States Veterans Health Administration electronic health records*. *JAMIA Open*, 2022. **5**(2).
 117. Williams, E.C., et al., *Variation in documented care for unhealthy alcohol consumption across race/ethnicity in the Department of Veterans Affairs Healthcare System*. *Alcohol Clin Exp Res*, 2012. **36**(9): p. 1614-22.
 118. Young, B.A., et al., *Effects of ethnicity and nephropathy on lower-extremity amputation risk among diabetic veterans*. *Diabetes Care*, 2003. **26**(2): p. 495-501.
 119. Williams, E.C., et al., *Variation in receipt of pharmacotherapy for alcohol use disorders across racial/ethnic groups: A national study in the U.S. Veterans Health Administration*. *Drug Alcohol Depend*, 2017. **178**: p. 527-533.
 120. Robins, J.M., M.A. Hernan, and B. Brumback, *Marginal structural models and causal inference in epidemiology*. *Epidemiology*, 2000. **11**(5): p. 550-60.
 121. Balfour, L., et al., *An HIV-tailored quit-smoking counselling pilot intervention targeting depressive symptoms plus Nicotine Replacement Therapy*. *AIDS Care*, 2017. **29**(1): p. 24-31.
 122. Wewers, M.E., J.L. Neidig, and K.E. Kihm, *The feasibility of a nurse-managed, peer-led tobacco cessation intervention among HIV-positive smokers*. *J Assoc Nurses AIDS Care*, 2000. **11**(6): p. 37-44.

123. Berigan, T.R., *The Many Uses of Bupropion and Bupropion Sustained Release (SR) in Adults*. Prim Care Companion J Clin Psychiatry, 2002. **4**(1): p. 30-32.
124. Austin, P.C. and E.A. Stuart, *Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies*. Stat Med, 2015. **34**(28): p. 3661-79.
125. Bowleg, L., *The problem with the phrase women and minorities: intersectionality-an important theoretical framework for public health*. Am J Public Health, 2012. **102**(7): p. 1267-73.
126. Hatzenbuehler, M.L., J.C. Phelan, and B.G. Link, *Stigma as a fundamental cause of population health inequalities*. American journal of public health, 2013. **103**(5): p. 813-821.
127. Poundstone, K.E., S.A. Strathdee, and D.D. Celentano, *The social epidemiology of human immunodeficiency virus/acquired immunodeficiency syndrome*. Epidemiol Rev, 2004. **26**: p. 22-35.
128. Umberson, D. and J.K. Montez, *Social Relationships and Health: A Flashpoint for Health Policy*. Journal of health and social behavior, 2010. **51**(Suppl): p. S54-S66.
129. Krueger, P.M. and V.W. Chang, *Being Poor and Coping With Stress: Health Behaviors and the Risk of Death*. American Journal of Public Health, 2008. **98**(5): p. 889-896.
130. Earnshaw, V.A., et al., *Stigma and Racial/Ethnic HIV Disparities: Moving Toward Resilience*. The American psychologist, 2013. **68**(4): p. 225-236.
131. Reynolds, N.R., *Cigarette smoking and HIV: more evidence for action*. AIDS Educ Prev, 2009. **21**(3 Suppl): p. 106-21.
132. Wilson, S.M., et al., *Lifetime Smoking Patterns and Preferences for Smoking Cessation Among Women Veterans Receiving Veterans Health Administration Care*. Qual Health Res, 2019. **29**(14): p. 2096-2107.