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Individual Level Factors Associated with HIV Care Continuum Metrics among MASH Cohort Participants from 2009-2014

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INDIVIDUAL LEVEL FACTORS ASSOCIATED WITH HIV CARE CONTINUUM METRICS AMONG MASH COHORT PARTICIPANTS FROM 2009-2014

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Kristopher Myers

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To: Dean Tomás R. Guilarte
Robert Stempel College of Public Health and Social Work

This dissertation, written by Kristopher Myers, and entitled Individual Level Factors Associated with HIV Care Continuum Metrics Among Mash Cohort Participants From 2009-2014, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Florida International University, 2019

DEDICATION

This dissertation is dedicated to my family. Their unconditional love, patience, and support made this work possible.

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ABSTRACT OF THE DISSERTATION

INDIVIDUAL LEVEL FACTORS ASSOCIATED WITH HIV CARE CONTINUUM METRICS AMONG MASH COHORT PARTICIPANTS FROM 2009-2014

by

Kristopher Myers

Florida International University, 2019

Miami, Florida

Professor Kristopher Fennie, Major Professor

This dissertation assessed the following: 1) the individual-level factors' individual, syndemic, and interactive associations with retention in HIV care; 2) the individual-level factors' individual, syndemic, and interactive associations with adherence among retained persons; and 3) the individual-level factors' individual, syndemic, and interactive associations with viral suppression among retained persons.

In the first study, Non-Hispanic Black race/ethnicity was associated with improved retention (OR=2.44, 95%CI: 1.06–5.75, p≤0.05). "Black-Hispanic" and "Other" racial/ethnic identities were associated with increased retention among participants (OR=4.84, 95%CI: 1.16–25.79, p≤0.05 and OR=7.24, 95%CI: 1.54–54.05p≤0.05, respectively). The interaction between depressive symptoms and alcohol use disorder was significantly and negatively associated with retention in HIV care (OR=0.14, 95%CI: 0.01–1.11, p≤0.10). This negative interaction suggests that the impact of depression on retention differs by alcohol use disorder (or equivalently the impact of alcohol use disorder on retention differs by depression status). The interaction between age and male gender was also negatively associated with retention (OR=0.95,

95%CI: 0.88–1.01, p≤0.10). This suggests that the impact of male gender on retention may be influenced by increased age (or equivalently the effect of age on retention varies by male gender). The interaction between male gender and depression was positively associated with retention (OR=7.17, 95%CI: 0.84–98.49, p≤0.10). Given our understanding of previous literature, we interpreted this as the impact of depression on retention in care is influenced by male gender. In the second study, we determined that cocaine use was significantly and negatively associated with short term adherence when compared to persons who tested negative for cocaine use (OR=0.23, 95%CI: 0.05–0.86, p=0.05) when adjusting for all other factors. Education had a significant negative association with long term adherence (OR=0.73, 95%CI: 0.57–0.91, p=0.01).

In the final study, among 51 retained persons with HIV we determined Non-White race/ethnicity (OR=0.28, 95%CI: 0.05–1.12, p=0.09), education (OR=0.75, 0.52–1.03, p=0.10), and male gender (OR=0.33, 95%CI: 0.09–1.05. p=0.07) were marginally and negatively associated with viral suppression. Collectively, our study findings suggest that multiple individual level factors individually and interactively have a deleterious effect on multiple stages of the HIV care continuum.

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ABBREVIATIONS AND ACRONYMS

ACCESS	AIDS Care Cohort to Evaluate Exposure to Survival Services
AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted odds ratio
AUDIT	Alcohol Use Disorder Identification Test
ART CDC	Antiretroviral Therapy Centers for Disease Control and Prevention
CES-D CI	Center for Epidemiologic Studies Depression Scale Confidence interval
EDM	Electronic Data Monitoring
eHARS	Enhanced HIV/AIDS Reporting System
GEE	Generalized Estimating Equation
HAART	Highly Active Antiretroviral Therapy
HRSA	Health Resources and Services Administration
HIV	Human immunodeficiency virus infection
HIV/RNA	Human immunodeficiency virus infection ribonucleic acid
JHHAA	Johns Hopkins HIV Clinical Cohort
MASH	Miami Adult Study on HIV/AIDS
MEMS	Medication event monitoring system
MMC	Montefiore Medical Center
MSM	Men who have sex with men
NHSS	National HIV Surveillance System
TGA	Transitional Grant Area
US VCCC	United States Vanderbilt Comprehensive Care Clinic

Background

In the United States, approximately 1.1 million persons were living with HIV in 2016 (1). Among persons living with HIV, 40% were engaged in HIV medical care, 37% were prescribed ART, and 30% achieved viral suppression (2). Persons living with HIV who achieve viral suppression can have a nearly normal life expectancy and develop a reduced risk for transmitting HIV to others (3,4). However, every year in the United States, approximately 50,000 persons become infected with HIV (5). Each step along the HIV care continuum (HIV retention in care and adherence to ART) is essential for achieving a suppressed viral load (6). Reduced engagement in HIV medical care has been associated with poor clinical outcomes including reduced retention, poor antiretroviral adherence, virologic failure, and mortality (7). Multiple individual-level factors have been associated with reduced progression along the HIV care continuum (7). Recent literature indicates that to mitigate losses of patient engagement at different stages of the continuum, it is important to focus on individual–level factors at each stage of the continuum (8). According to the behavioral model for vulnerable populations, individual-level factors are stratified into the following categories: traditional factors, vulnerability factors, and enabling factors (9). Traditional factors include demographic information such as age, gender, and race/ethnicity. Vulnerability factors include factors such as mental illness and substance abuse (9). Enabling factors are those that can impede or enhance access to HIV care and include income, insurance, housing, and social support (9).

Recent literature has suggested that education is a socioeconomic vulnerability factor; it was not originally considered such in the behavioral model for vulnerable populations (10). Specific, individual-level factors that have been suggested to impede progress to various stages of the HIV care continuum include depressive symptoms, cocaine use, marijuana use, alcohol use, and cigarette use (11-14). While there are studies assessing individual level traditional factors' and vulnerability factors' association with progression to some stages of the HIV care continuum, there are few assessing specific individual level traditional and vulnerability factors' association with progression throughout the full HIV care continuum. Examining the association of specific individual level traditional and vulnerability factors with progression from one stage to the next and determining what individual-level vulnerability factors are associated with reduced progression can provide valuable insight that can be utilized to determine targets for intervention.

The effect of multiple factors on HIV care continuum metrics is generally assessed individually; however, these factors occur in concert with one another. One type of association that may explain the multifaceted manner in which individual-level characteristics are associated with retention is syndemic or additive association. Syndemic theory, established by Merill Singer, involves a set of mutually enhancing health problems that, working together in a context of harmful social and physical conditions increase vulnerability, and significantly affect the overall disease status of a population (15). Syndemic theory postulates that a constellation of health problems accumulates over a person's lifespan and can amplify the negative impact of one or

more health problems (16). Determining syndemic or additive associations involves determining the sum of multiple factors on a particular outcome (15). These individual-level traditional and vulnerability factors may also be effect modifiers in assessing retention. An interactive association among factors involves the simultaneous, non-additive influence of two or more variables on an outcome (17). Using the syndemic and interactive frameworks is an innovative way of examining the association of individual-level traditional and vulnerability factors on retention in care. Syndemic associations assess if variables in the behavioral model for vulnerable populations work synergistically to impede progression to retention in care. Identifying interactions determined to be significant may lead to conclusions regarding which factors influence the relationship between independent variables and progression to various stages in the HIV care continuum.

This dissertation aimed to determine the individual, syndemic, and interactive associations of cocaine use, alcohol use disorder and depressive symptoms with retention among a cohort of adults living with HIV/AIDS in Miami/Dade between 2009-2014. This dissertation further aimed to determine the individual, syndemic, and interactive associations of cocaine use, alcohol use disorder, depressive symptoms, with ART adherence among a cohort of adults living with HIV/AIDS who have been retained in care in Miami/Dade between 2009-2014. Finally, this study aimed to determine the individual, syndemic, and interactive associations of cocaine use, cigarette smoking, alcohol use disorder, and depressive symptoms on viral

suppression among ART adherent adults living with HIV in Miami/Dade between 2009-2014 in MASH (Miami Adult Study on HIV/AIDS).

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Figures

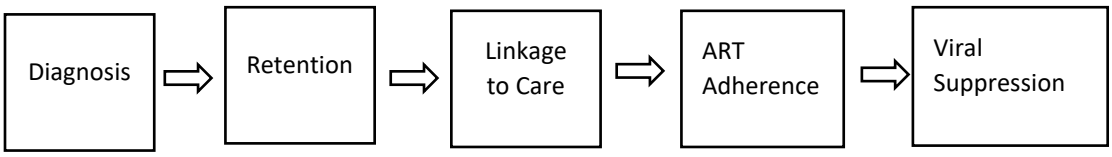

Figure 1: The HIV care continuum. The model has been adapted by the author. Adapted with from original model created by Dr. Gardner (18)

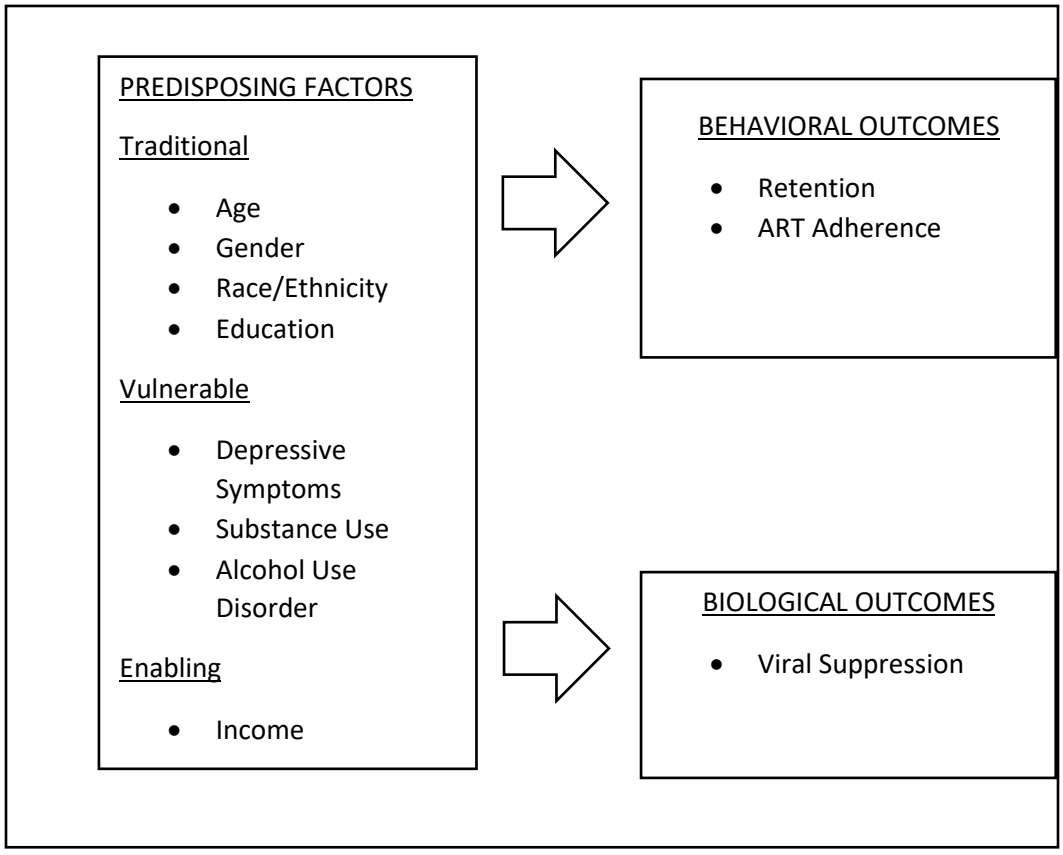

Figure 2: The behavioral model for vulnerable populations. The model has been adapted by the author, with reduced components that influence health behaviors and outcomes. Adapted with from original model created by Christopoulos et al. 2011(9).

Literature Review

Depression and Depressive Symptoms

Although depression has not been studied as a precise variable that effects progression throughout the entire continuum, there are studies that evaluate the association between depression and progression to discrete stages of the HIV care continuum.

In a study conducted by Zuniga and colleagues, researchers attempted to determine the association of depressive symptoms with retention in care among persons living with HIV. The study involved 204 persons who were recruited from public hospital-affiliated outpatient HIV clinics in South Florida from August 2009 to May 2011 (1). The majority of the population was African American (82.9%) and the average for years of education was below the secondary or high school level (11.1±2.1 years of education) (1). Researchers found that increased scores on the somatic symptom scale were positively associated with reduced retention OR=1.604 (95%CI: 1.09,2.37 p= 0.0175) (1). The statistics suggest that as the somatic symptoms suggestive of depression diagnosis increases, so do the odds of having at least one four-month interval with a missed visit (1).

In another study conducted by Gonzalez and colleagues in 2011, they assessed the association between depression and HAART adherence (2). Each unit increase on the Clinical Global Depression Scale score was associated with a 75% increased odds of nonadherence (OR=1.75, 95% CI=1.23–2.48, p=0.002) (2). Each unit increase on the Montgomery Asberg Depression Rating Scale was associated with a 2.6-fold

increase in the odds of HAART nonadherence (OR=2.60, 95% CI=1.45–4.67, p=0.001). The outcome of the logistic regression that assessed the relationship between scores on the Clinical Global Impression Scale for depression and adherence suggests an association between symptoms suggestive of depression diagnosis and adherence (2). The outcome of the logistic regression that assessed the relationship between scores on the Montgomery Asberg Depression Rating scale and adherence suggests an association between depression severity and reduced adherence.

In a study conducted by Carrico et al., they assessed the association between depression and viral load. The results indicated that a higher number of symptoms of depression at baseline predicted a 50% higher mean HIV viral load in the 25 months following baseline ($\beta=0.13$, $p<0.01$); this suggests a relationship between depressive symptoms and increased viral loads.

Current research suggests that symptoms suggestive of depression diagnosis are associated with retention, adherence and viral load(1),(2),(3). There is currently no research that assesses the association between depression and progression through the entire HIV care continuum.

Cocaine

Although cocaine has not been directly studied as it relates to the HIV care continuum, there have been studies assessing the association between cocaine usage and progression to different individual stages of the HIV care continuum.

Althoff and colleagues assessed the association between cocaine use and retention among participants in a multisite study, which assesses jail-release interventions at ten urban US sites. The study found that former inmates who reported cocaine use within the last 30 days were 34% less likely to have visited an HIV provider during days 91–180 after jail release. Cocaine was the only substance significantly associated with reduced retention for this time period (4).

In another study conducted by Gonzalez and his colleagues, researchers assessed the association of multiple drugs on antiretroviral therapy adherence among 121 HIV positive intravenous drug users who were currently receiving opioid dependence treatment. Adherence was defined as the final percent of doses "taken on-time" over the 2-week period and monitored using the medication event monitoring system (MEMS) caps for the ART medication (5). Researchers assessed substance use within the past 30 days which included the following substances: opiates, cocaine, sedatives, alcohol, marijuana, and multiple substances (two or more substances) (5). In the analysis, only cocaine ($\beta = -.22$; $p = .02$) and multiple substance use ($\beta = -.22$; $p = .02$) within the past 30 days were significantly related to decreased HIV medication adherence (5). This indicates that cocaine is negatively associated with ART adherence among HIV positive intravenous drug users (5).

The recent literature also suggests that injection cocaine use is associated with reduced viral suppression. Kerr and colleagues prospectively observed 267 ART naive patients (6). The researchers assessed the association between illicit drug use and viral suppression. Viral suppression was defined as the first instance of achieving

plasma HIV-1 RNA suppression of less than 500 copies/mL and assessed via laboratory data (6). Drug use was determined at baseline in this study. Researchers found that among exclusive cocaine injection users 57.6% (95%CI: 40.6%–75.6%) attained viral suppression at 12 months, while 88.8% (95%CI: 76.2%–96.4%) of non-injecting persons attained viral suppression at 12 months (6). The Kaplan-Meier analysis indicated the differences between these two groups was statistically significant ($p<0.01$) (6).

Current research suggests that cocaine use is associated with reduced retention, adherence, and viral suppression, however, there is no research on the association between cocaine use and HIV testing(4),(5),(6). There is currently no research that directly relates cocaine use with progression through the entire HIV care continuum

Intravenous Drug Use

The literature reveals mixed findings relative to the association between intravenous drug use and progression to the various stages of the HIV care continuum. Recent literature suggests that a lower percentage of HIV infected persons who engage in intravenous drug use progress to the stages of the HIV care continuum when compared to all persons with HIV, specifically among Hispanic Americans, African Americans, and a cohort constructed from 28 jurisdictions within the United States (7-9). Some studies indicate no major percentage differences in progression through the HIV care continuum between those who engage in intravenous drug use

and the overall population with HIV. Researchers found that intravenous drug users with HIV did not progress through the HIV care continuum at reduced percentages when compared to the progression among HIV infected persons overall; this trend was illustrated by a study conducted by the CDC, in which researchers used the National HIV Surveillance System (NHSS) to estimate national progression through the HIV care continuum (10). This trend of similar progression among both groups is illustrated again using NHSS to estimate national progression through the HIV care continuum among African Americans with HIV (11). While these studies indicate percentage differences or similarities for progression through the HIV care continuum's various stages among intravenous drug users as compared to persons with HIV overall, none yielded statistically significant findings.

In a study conducted by Lesko and colleagues using the Johns Hopkins HIV Clinical Cohort (JHHCC), researchers assessed the association between injection drug use on retention, antiretroviral therapy (ART) use, and viral suppression. The cohort consisted of all HIV-infected persons age 18 years and older who enrolled in HIV care at Johns Hopkins outpatient HIV clinic who agreed to share their data. Patients who reported IDU as a likely source of their HIV infection when they registered into care were classified as persons with injection drug use (PWID) (12). The researchers first determined the crude proportion of participants that progressed to each stage in the HIV care continuum and subsequently conducted a binomial logistic regression for each step in the HIV care continuum. The researchers found that among persons who injected drugs in 2010, 77.8% were retained in care, 69.3% were on ART, and

63.3% were virally suppressed. Among persons who did not engage in injection drug use, 82.0% were retained in care, 74.8% were on antiretroviral therapy and 70.1% were virally suppressed (12). Retention was defined as those with greater than or equal to 2 clinic visits at least 90 days apart. ART use was defined as retained patients with at least one ART prescription for more than 30 days between during the calendar year (12). Viral suppression was defined as adherent patients with at least one HIV viral load count ≤400 copies/mL between January 1 and December 31 of 2010 (12). The researchers found a higher percentage of viral suppression and persons on antiretroviral therapy among those who did not use injection drugs; there were no levels of significance attached to these percentages. The researchers found in the unadjusted analysis that intravenous drug use was associated with ART use RR=0.94 (95% CI: 0.89-0.99, p≤.05), retention RR= 0.96 (95% CI: 0.93-0.99, p≤.05), and viral suppression RR=0.96 (95%CI: 0.93- 0.99, p≤.05) in 2010 (12). This indicates that among the JHCC, those who used intravenous drugs were significantly less likely to be retained in HIV care, on ART, or have achieved a state of viral suppression when compared to those who do not engage in intravenous drug use. Other studies corroborate these findings (13-15)

The current research provides mixed findings related to the association between intravenous drug use and progression to the various stages of the HIV care continuum. However, the literature suggests that among persons 18 years and older, intravenous drug use is significantly associated with reduced retention in care,

prescription of ART, and viral suppression, each a vital stage in the HIV care continuum (12,16,17).

Marijuana

In a study conducted in Connecticut involving men who have sex with men, researchers compared the HIV care continuum metrics between heavy marijuana users and intermittent marijuana users. The sample is derived from the uConnect cohort and consisted of 618 African American men who have sex with men (18). When comparing never users to heavy users the researchers noted that heavy marijuana users had 4.18 (95% CI: 1.26- 13.89, $p<.05$) times the odds of being unaware of their HIV positive status than did those who never used drugs (18). The odds ratios for progression to the other stages of the HIV care continuum were not statistically significant. This study indicates that there is not a relationship between marijuana smoking and progression through the various stages of the HIV care continuum. This is currently the only study that assesses marijuana use directly with progression through the HIV care continuum. However, there are other studies that assess the association between marijuana use and progression to discrete stages of the HIV care continuum.

In one study researchers assessed the association between marijuana use and retention in HIV care using a retrospective cohort study design. The examined population were patients at the Vanderbilt Comprehensive Care Clinic (VCCC) (19). Marijuana use was defined as use at least one time in the past week on at least one

screening questionnaire (19). Retention was defined as missed visits in 2012 (19). The researchers found that any marijuana use within the past week was associated with missing next scheduled clinical appointment, RR= 1.37 (95%CI: 1.12, 1.69, $p<0.05$ (19). The association between smoking marijuana and missing the next scheduled clinical appointment was highest among those who smoked marijuana seven times per week, RR=1.67 (95% CI: 1.30, 2.15, $p<0.05$) (19). This study suggests that smoking marijuana within the past week is associated with an increased risk of reduced retention.

In another study, researchers assessed the association between marijuana use and adherence to HAART medication. Researchers separated cannabis users into three groups non-cannabis users, cannabis users, and cannabis dependent users (20). Using the ANOVA analysis researchers found that non-cannabis users (0.97 ± 0.09) had a significantly higher mean adherence (0.93 ± 0.15) than did cannabis users for the four days prior to the examination ($F=3.26$, $p<0.05$) (20). The study implies that cannabis use is associated with reduced adherence to antiretroviral medication.

Another study assessed the association between marijuana use and viral suppression. Sinha and colleagues examined data from the Johns Hopkins HIV Clinical Cohort (JHHCC). Marijuana use was divided into the following categories: 1) no lifetime use, 2) past use, but none in the past 3 months, 3) monthly or less and 4) weekly or daily/almost daily (21). Researchers assessed viral suppression using laboratory records; viral suppression was defined as an HIV-1 RNA $\leq$200 copies/mL. HIV-1 RNAs (21). Researchers determined that having not used marijuana within the

last three months was associated with an increased odds of attaining an undetectable viral load OR=1.45 (95%CI: 1.07–1.96, p<0.05) (21). This study suggests that not using marijuana within the last three months is associated with a greater likelihood of attaining an undetectable viral load.

Although there is scarce literature that relates marijuana use directly to the HIV care continuum, the literature does suggest an association between marijuana use and the multiple stages of the HIV care continuum (retention, adherence, and viral suppression) (19),(20),(21).

Alcohol

Although alcohol use has not been directly studied as it relates to the HIV care continuum, the literature does illustrate that alcohol use is associated with reduced progression to various stages in the HIV care continuum. The majority of studies relating alcohol to HIV care primarily focus on two stages of the HIV care continuum: adherence and viral suppression.

The current literature suggests that studies have noted alcohol use to be negatively associated with multiple stages of the HIV care continuum including: testing, care retention, ART adherence, and viral suppression (22-25). There were few studies that linked alcohol abuse to HIV testing included in the literature that were conducted in the United States.

In a study conducted by Frimpong and colleagues, the researchers examined the correlates of HIV testing. Data from this study are derived from the Los Angeles

County Participant Reporting System (LACPRS). The researchers used the Gelberg-Anderson Behavioral Model for Vulnerable Populations to develop independent variables that may be associated with HIV testing. The model explains the relationships among predisposing, enabling, and need factors that alter health services utilization in the general population (22). Researchers first conducted a chi-squared test and found that alcohol was significantly associated with HIV testing ($p<0.01$), (22).

In a study conducted by Chitsaz and colleagues, researchers attempted to assess the effect of multiple factors on progression through the HIV care continuum among HIV positive prisoners. Alcohol use in the 30 days pre-incarceration was the definition of alcohol use in this study. Linkage was defined as having an HIV care provider in the 30 days prior to incarceration (26). Linkage was not found to be associated with ASI (Addiction Severity Index) alcohol composite score; OR=0.67(95%CI: 0.34-1.31, p=0.238) (26). Other studies in the literature corroborate these findings (4).

The relationship between alcohol use and retention in care has been firmly established by the literature. A study conducted by Cunningham et al. assessed the relationship between alcohol use and retention. Retention was defined as two or more medical visits in the prior 6 months, as this is an established indicator of poor HIV care (23). Heavy alcohol use was defined as drinking five or more drinks of alcohol in one day within the last thirty days (23) The researchers found heavy alcohol use is significantly associated with reduced HIV care visits AOR=1.74 (95%

CI: 1.23-2.45, $p<0.05$) (23). This indicates that heavy alcohol use is significantly associated with poor retention.

The literature also establishes a significant association between alcohol use and ART adherence among HIV infected individuals. Rosen and his colleagues conducted a cross sectional study to determine the relationship between alcohol and ART adherence. To develop a measure that could be extracted from different questions asked at different sites, alcohol use was standardized across sites as the percentage of measured days having used alcohol. Adherence was measured by dividing the total number of openings by the number of prescribed doses for each medication. Alcohol use was determined to be negatively and independently associated with reduced ART adherence. Rosen and his colleagues noted that alcohol use ($\beta=-0.04$, $p<.05$) and the number of days alcohol was used ($\beta=-0.097$, $p<.05$) were both significantly associated with lower adherence (24).

The literature suggests an association between alcohol use and an increased viral load. Wu and colleagues examined the relationship between alcohol use and viral load, independent of adherence to HAART (25). Participant alcohol use was categorized by four response options: every day, a few times a week, a few times a month, and not at all (25). The linear regression, which was adjusted for adherence and demographic covariates, indicated that daily drinkers had nearly a four-fold increase in the odds of detectable viral load OR=3.81 (95%CI: 1.42- 11.48, $p=0.01$)(25).

Alcohol has been assessed as a factor that is associated with multiple HIV care continuum metrics. The literature indicates that alcohol use is associated with reduced retention, decreased adherence, and an increase in the odds of acquiring a detectable viral load (22-25), (26).

Cigarette smoking

There is currently a lack of literature that relates cigarette smoking directly to the HIV care continuum. Individual stages of the HIV continuum have been studied as they relate to cigarette smoking, the majority of these studies are related to adherence and viral suppression.

In one study researchers attempted to determine the relationship between smoking and adherence to HAART. Adherence was defined as (number of bottle openings/number of prescribed doses of lopinavir/ritonavir) x 100 (27). Adherence was monitored using the Medication Event Monitoring System (MEMS). Researchers noticed that smokers took 65% (SE=22.1) of prescribed doses while non-smokers took 84.8% (SE=15.8) (27). These percentages were statistically significant indicating that adherence to ART is less prevalent among cigarette smokers. Researchers, using a multiple linear regression model, found that being a current cigarette smoker is independently associated with poorer ART adherence ($p<0.001$) (27).

Viral suppression, while not indicated to be directly affected by smoking was shown to affect T-cell viability. A T-cell's function is to lyse virally infected cells; an inhibition of this function may cause an increase in viral load (28). In one study

researchers attempted to determine whether T-cell functions, such as the defense against infectious agents, could be altered by the exposure to cigarette smoke extract. Smoke from two Kentucky research cigarettes without filters, 1R4F containing 11 mg tar and 0.8 mg nicotine, was bubbled through 50 ml of cell culture medium at a speed of 5 min per cigarette (28). T-cells were isolated by gradient centrifugation on Ficoll-Paque (28). T-cell viability was determined by activation (CD25 expression). CD25 is a transmembrane protein present on all active T-cells (28). Researchers found cells that were exposed to cigarette smoke extract or CSE had a viability of 69%, while those not exposed had a viability of 76% and both percentages were statistically significant (28). This indicates that T-cells' viability is affected by cigarette smoke exposure and may ultimately lead to an increase in HIV viremia. This study, which utilized data on CD25 expression as a proxy for cell activation after its exposure to CSE, is the first of its kind. This is a relatively new topic of study and more research is necessary to better explain the exact mechanism causing the association between CSE exposure and T cell viability.

Although cigarette use has not been directly studied as it relates to the HIV care continuum, it has been assessed as a factor that is associated with multiple HIV care continuum stages. The literature indicates that cigarette use is associated with reduced adherence and a reduction in T-cell viability which may affect viral load(27)·(28).

Conclusion

Current research suggests that intravenous drug use is significantly and negatively associated with nearly each stage in the HIV care continuum (16). The literature also implies that smoking marijuana is negatively associated with retention and adherence, however, abstinence from marijuana use is positively associated with reduced viral load(19),(20), (21). Alcohol use, although not directly studied, is illustrated to be negatively associated with retention, adherence, and viral suppression (23-25). Cigarette smoking has not been directly studied as an independent variable related to the HIV care continuum, however recent literature suggests that smoking is negatively associated with adherence and viral suppression (27,28). Scarce literature exists relating cigarette smoking, alcohol abuse, marijuana use, and cocaine use directly to the HIV care continuum; this is important as cigarette smoking, alcohol abuse, marijuana use, and cocaine use are highly prevalent behaviors among persons with HIV (29-31). These behaviors may be related to other characteristics of persons with HIV, however, there is a gap in the literature, as there is scarce research directly associating substance use (illicit or legal) in concert with other factors to the progression along the continuum. Another limitation of the majority of these studies is that they do not assess the effect of factors (cigarette smoking, alcohol abuse, marijuana use, and cocaine use) throughout the entire continuum; my study will address this limitation by assessing the effect of these factors throughout the entire continuum. Determining relationships among factors associated with this reduced

progression will provide information that can inform more specific interventions and provide information that can aid prioritization for interventions.

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MANUSCRIPT 1

The Individual, Interactive, and Syndemic Effect of Substance Use, Depression, Education, and Race/Ethnicity on Retention in HIV Care Among MASH Cohort Participants from 2009-2014.

Abstract

Objectives: In this study, we sought to assess the individual-level factors' individual, syndemic, and interactive associations with retention in care. ***Design:*** The sample was derived from the Miami Adult Studies on HIV/AIDS (MASH) cohort study from 2009-2014. The variables were entered into a multiple logistic regression with retention as the outcome to determine which factors were significantly associated with retention. Backward regression, adjusting for all main effects was conducted, to determine which two-way interactions were associated with retention. Multivariable logistic regression was used determine whether number of factors were associated with retention. ***Results:*** Non-Hispanic Black race/ethnicity was associated with improved retention (OR=2.44, 95%CI: 1.06–5.75, p≤0.05). "Black-Hispanic" and "Other" ethnic identities were associated with increased retention among participants (OR=4.84, 95%CI: 1.16–25.79, p≤0.05 and OR=7.24, 95%CI: 1.54–54.05p≤0.05, respectively). The interaction between depressive symptoms and alcohol use disorder was significantly and negatively associated with retention in HIV care (OR=0.14, 95%CI: 0.01–1.11, p≤0.10). The interaction between age and male gender was also

negatively associated with retention (OR=0.95, 95%CI: 0.88–1.01, p≤0.10), and the interaction between male gender and depression was positively associated with retention (OR=7.17, 95%CI: 0.84–98.49, p≤0.10). ***Conclusion:*** Multiple race/ethnicities are associated with improved retention. Multiple factors interact to alter retention in HIV care.

Key words: Epidemiology, HIV, Antiretroviral Therapy

Introduction

Reduced engagement in HIV medical care has been associated with poor clinical outcomes including reduced retention, virologic failure, and mortality(1). Multiple individual-level factors have been associated with reduced progression along the HIV care continuum (1). Recent literature indicates that to mitigate losses of patient engagement at different stages of the continuum, it is highly important to focus on the individual-level factors at each stage of the continuum (2). According to the behavioral model for vulnerable populations, individual-level factors are stratified into the following categories: traditional factors, vulnerability factors, and enabling factors (3). Traditional factors include demographic information such as age, gender, and race/ethnicity. Vulnerability factors include factors such as mental illness and substance abuse (3). Enabling factors are those that can impede or enhance access to HIV care and include income, insurance, housing, and social support (3). Specific, individual-level factors that have been suggested to impede progress to retention

include having less than a high school education, depressive symptoms, cocaine use, marijuana use, and alcohol use (4-7).

Retention is a pivotal component of the HIV care continuum. According to recent literature, retention is defined as two or more HIV-related physician visits or diagnostic tests (CD4 count or viral load tests) in the calendar year at least three months apart (8,9). Recent literature suggests that individual-level traditional, enabling, and vulnerability factors are each associated with retention in HIV care (5,10,11). The effect of multiple factors on retention is generally assessed individually; however, these factors occur in concert with one another. One type of association that may explain the multifaceted manner in which individual-level characteristics are associated with retention is syndemic or additive association.

Syndemic theory, established by Merill Singer, involves a set of mutually enhancing health problems that, working together in a context of harmful social and physical conditions increase vulnerability, and significantly affect the overall disease status of a population (12). Syndemic theory postulates that a constellation of health problems accumulates over a person's lifespan and can amplify the negative impact of one or more health problems (13). Determining syndemic or additive associations involves determining the sum of multiple factors on a particular outcome (12). These individual-level factors may also be effect modifiers in assessing retention. An interactive association among factors involves the simultaneous, non-additive influence of two or more variables on an outcome (14). Using the syndemic and interactive frameworks is an innovative way of examining the association of

individual-level factors on retention in care. Syndemic associations assess if variables in the behavioral model for vulnerable populations work synergistically to impede progression to retention in care. Identifying syndemic associations may provide further evidence of the synergistic effect of individual-level factors on retention in HIV care. Identifying interactions determined to be significant may lead to conclusions regarding which factors influence the relationship between independent variables and progression to retention in HIV care.

In this study, we sought to assess the association of individual-level factors' individual, syndemic, and interactive associations with retention in care. The syndemic and interactive approaches of assessing multiple factors within a population are important for the development of future interventions targeting retention, as a person with HIV is multidimensional and may need more than a single, unimodal intervention.

Materials and Methods

Setting and Population

The sample was derived from the Miami Adult Studies on HIV/AIDS (MASH) cohort study. Further details related to the methodology of the original project can be found in a paper entitled, "Cocaine Use and Liver Disease are Associated with All-Cause Mortality in the Miami Adult Studies in HIV (MASH) Cohort" (15). This is a secondary analysis of a prospective cohort study involving 407 HIV positive individuals residing in the south Florida region. Participants were a

subset of the more than 800 participants from the MASH cohort who have been followed from 2009 - 2014. All independent variables were assessed at baseline and participants were subsequently followed for a one-year period after baseline to determine retention status. All participants provided written consent to participate in the original study (MASH Cohort Study) consistent with the Florida International University Institutional Review Board IRB: 13-0038.

Eligibility Criteria

Participants were eligible to participate if they were (1) eighteen years of age or older, (2) diagnosed with HIV by a standardized testing method, (3) participated in the study from 2009-2014, (4) provided informed consent, (5) and had complete data at baseline.

Measures

The primary outcome of this study was retention in care, defined as two or more HIV-related physician visits or diagnostic tests (CD4 count or viral load tests) during the calendar year at least three months apart (8,9). Those who met this criterion were considered "retained", those who did not, were codified as "not retained". Demographic measures such as age, race/ethnicity, gender, and educational attainment were determined using tools from the Tier 1 Phen X Toolkit designed for NIH clinical trials at the screening phase of the study (16,17). Age, race/ethnicity, and gender were determined using the validated "Current Age, Gender, and Race

Questionnaire" survey from the Tier 1 Phen X Toolkit (16). Education was determined using the validated "Current Educational Attainment Questionnaire" from the Tier 1 Phen X Toolkit (16).

Age was determined in the MASH survey through self-report and calculated from the year of birth. Age was categorized in the current study as follows: "≦ 25", "26-34", "35-44", and "≥45", for the purpose of assessing frequencies among age groups (18). However, age was assessed as a continuous variable in all logistic regressions (19). Race/ethnicity was assessed via self-report and was categorized as: "White (Non-Hispanic)", "Black (Non-Hispanic)", "Hispanic", "Asian", and "Other" (20). Gender was defined as a categorical variable including: "Males", "Females", "Transgender", and "Declined" (21). Education was assessed via self-report. In the current study, educational attainment was assessed using the following categories: "Less than high school education", "High school graduate or equivalent", and "More than high school education" for the purpose of assessing the frequencies of educational attainment of the population (22). However, in the logistic regressions education was assessed as a continuous variable (23).

In the MASH cohort study, the validated Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depression at baseline (24). A score of 16 or higher indicated symptoms suggestive of clinical depression diagnosis, while scores of 15 and below indicated that persons did not have symptoms suggestive of clinical depression diagnosis (25). This variable was coded dichotomously: "Depressed" and "Not Depressed" (25).

Cocaine use and marijuana use were assessed using the Multi-Drug 5 Panel Urine Dip Test Kit (WDOA-754). This test allowed researchers to assess drug use in the past three days. This testing method has been approved by the FDA (26). Cocaine and marijuana use within the past three days were each categorized dichotomously (positive or negative). Alcohol use disorder was determined from the Alcohol Use Disorder Identification Test (AUDIT) at baseline; this form has been validated by Saunders and colleagues (27). This is a 10-item scale in which each question is worth one point. A score of 8 or more is considered indicates symptoms suggestive of alcohol use disorder. Alcohol use disorder was categorized as a dichotomous variable, either as "having alcohol use disorder" or "not having alcohol use disorder (27).

Analysis

First, frequency distributions were examined for the variables (age, race/ethnicity, education, substance use status, and retention status). The bivariate association between these variables and retention was determined using a chi-square test of independence. These variables were subsequently entered into a multiple logistic regression with retention as the outcome to determine which individual-level factors were significantly associated with retention. After determining the individual-level factors associated with retention, all two-way interactions among these factors were included in the logistic regression. Subsequently, backward regression, adjusting for all main effects was conducted, to determine which two-way

interactions were associated with retention. All interactions with $p \leq 0.10$ were included in the final model (28). The threshold of $p \leq 0.10$ was used to determine the exclusion of interactions as the sample size was relatively small and 0.05 would be highly exclusive to interactions of interest (29). To explore the relationship between significant interactive variables and retention, stratified logistic regressions were performed among variables with significant interaction terms. To determine the syndemic or additive association between independent factors and retention, researchers developed a count score of the number of individual-level factors (from 0 to 5).

All variables were categorized dichotomously, whereby a score of five indicates that all factors are present, while a score of zero indicates that none of the factors is present (30). For the purpose of the syndemic analysis, all independent variables not already dichotomous were collapsed into dichotomous variables (30). Education was reduced to two categories ("graduated high school" and "did not graduate high school") (30). Mantel-Haenszel chi-square method was used to test for the association between the number of individual-level factors and retention within the sample. A multivariable logistic regression model was used to determine if number of individual-level factors was associated with retention (30). Odds ratios were reported at 95% confidence intervals to estimate the effect of each variable. Interactions were reported at 90% confidence intervals to estimate the effect of each variable. All statistical analyses were performed using R Version 3.4.1.

Results

A subsample of 407 MASH participants were eligible for this analysis. Table 1 summarizes retention frequencies of participants in the sample as well as their demographic characteristics. Overall, 267 (65.6%) of the HIV infected participants were retained in HIV care, while 140 (34.4%) were not retained. The majority of participants were Non-Hispanic Black persons (n=278, 68.5%). The sample was predominately male (n=263, 65.2%). The majority of persons were 35 years of age or older (n=371, 91.2%). In Table 1, we also present the outcome of the bivariate association between the variables and retention. There were no significant associations.

Table 2 presents model 1 and model 2. In model 1 we summarize results of a logistic regression, that assessed the association between all variables (excluding the interaction terms) and retention in HIV care. Model 1 indicates that race/ethnicity had a significant association with retention. The results suggested that Non-Hispanic Black race/ethnicity was associated with improved retention (OR=2.44, 95%CI: 1.06–5.75, p=0.04). Model 1 also indicates that both “Black-Hispanic” and “Other” racial/ethnic identities were associated with increased retention among participants (OR=4.84, 95%CI: 1.16–25.79, p=0.04 and OR=7.24, 95%CI: 1.54–54.05p=0.02, respectively). White-Hispanic race/ethnicity was not significantly associated with retention in HIV care (OR=1.75, 95%CI: 0.68–4.57, p=0.24). All races/ethnicities were compared to the White Non-Hispanic referent group. Marijuana use, cocaine use

and other demographic factors (education, age, and male gender) were not associated with retention.

Model 2 summarizes the final results of the backward regression which included all single variables and two-way interactions that had a p-value ≤0.10. The interaction between depressive symptoms and alcohol use disorder was significantly and negatively associated with retention in HIV care (OR=0.14, 95%CI: 0.01–1.11, p=0.08). The interaction between age and male gender was also negatively associated with retention (OR=0.95, 95%CI: 0.88–1.01, p=0.10), and the interaction between male gender and depression was positively associated with retention (OR=7.17, 95%CI: 0.84–98.49, p=0.10).

Table 3 presents the outcomes for all stratified analysis (models 3-6). The stratified analysis indicated that among those who tested positive for depression, Non-Hispanic Black race/ethnicity was associated with retention (OR=2.36, 95%CI: 1.02–5.52, p=0.05) (Model 3). Black-Hispanic race/ethnicity and Other race/ethnicity were also associated with retention when compared to their White Non-Hispanic counterparts (OR=5.99, 95%CI: 1.25–44.70, p≤0.04 and OR=6.82, 95%CI: 1.45–50.40, p≤0.03) (model 3). Among those who were not depressed, we found no significant association (model 4). Among males, depression was determined to be positively associated with retention (OR=2.77,95%CI: 1.06–7.46, p=0.04) (model 4). Among females, no variables were determined to be significant (model 5).

"In the syndemic analysis, we determined that 35.14% (n=143) of the participants had two individual-level factors (Table 4). Approximately 31.20%

(n=127) of participants had three factors (Table 4). The ‘four factors’ category contained 12.03% (n=49) of the participants in the sample (Table 4). The ‘five factors’ category included 1.97% (n=8) of the sample (Table 4). The ‘zero factor category’ contained 0.98% (n=4) of the sample (Table 4). Of the 407 participants, 19 were not included in this section of the analysis due to missing values for one of the factors.”. The bivariate association between the number of factors and retention yielded no significant results, nor did the remainder of the syndemic analyses (Tables 4 and 5).

Discussion

While multiple races/ethnicities were associated with improved odds of retention, persons in the Black Non-Hispanic racial/ethnic group had the lowest magnitude of improved odds of retention. The data support previous literature which suggests that Black Non-Hispanic race/ethnicity is associated with a reduced magnitude of improved odds of retention when compared to other racial/ethnic groups (10). A clinical implication of this finding would be to provide retention counseling to Non-Hispanic Black persons who have been recently diagnosed. The study also provides evidence that Black Hispanic persons and persons of the Other race/ethnic groups have a higher odds of retention in HIV care than their Non-Hispanic White counterparts. Current literature supports the finding that Hispanic persons have higher odds of being retained than do Non-Hispanic Blacks or Non-Hispanic Whites (5). There is scarce literature assessing the association of Black

Hispanic race/ethnicity with retention, most literature typically assesses the relationship between general Hispanic ethnicity and retention. More research is necessary to determine the specific factors that contribute to this racial/ethnic group's improved retention. Literature indicates that persons of "Multiple" races/ethnicities have a greater likelihood of achieving retention than do White Non-Hispanic HIV infected persons; which may explain the "Other" racial category's higher association with retention. (31).

The interaction between depression and alcohol use disorder was negatively associated with retention. This negative interaction suggests that the impact of depression on retention differs by alcohol use disorder (or equivalently the impact of alcohol use disorder on retention differs by depression status). Specifically, this finding suggests that the impact of depression on retention in HIV care increases as alcohol use disorder is present (or conversely the impact of alcohol use disorder on retention in HIV is altered if depression is also present). While the literature suggests that depressive symptoms and alcohol abuse reduce retention in HIV care separately, this is the first paper to assess the effect of a two-way interaction between the two variables on retention (4,32). Alcohol has been determined to exacerbate the effect of depression among persons with HIV and increased depressive symptoms have been shown to reduce retention (4,33). In addition, those who abuse alcohol are at increased risk for major depression, and depression is associated with reduced retention (4,34). Recent research related to the direction of causality between alcohol use and depressive symptoms provides inconsistent results (34,35). A clinical

implication of this finding would be to provide depressed HIV positive persons with counseling regarding alcohol use. Another clinical implication may be to screen persons with HIV who have alcohol use disorder for depression during HIV-related visits.

The interaction between age and male gender is also negatively associated with retention. The literature supports the notion that both male gender and increased age reduce retention in care (36,37). This suggests that the impact of male gender on retention may be influenced by increased age (or equivalently the effect of age on retention varies by male gender). Specifically, this finding suggests that the impact of male gender on retention in HIV care is altered as age increases (or conversely the impact of increased age on retention in HIV is altered if male gender is also present). A clinical implication of this finding would possibly be to provide retention related counseling to HIV positive males, specifically among older men, during their initial visit. The interaction between depression and male gender yielded a positive association with retention. While both male gender and depression have been indicated to reduce retention in care among HIV positive persons, some studies indicate that there may be a higher odds of retention among males when compared to females (4,5,38). Given our understanding of previous literature, we interpreted this as the impact of depression on retention in care is improved if male gender is also present(4,5). A clinical implication of this finding would be to provide HIV infected women who are depressed with additional counseling and follow-up regarding HIV-related visits during their initial visit.

To better understand the interactive effects, we conducted stratified analysis which indicated that among those who are depressed, Non-Hispanic Blacks had an increased odds of retention when compared to Non-Hispanic White persons, however, the magnitude of increased odds of retention was larger among other racial/ethnic groups (Black-Hispanic persons and Other persons). This trend is consistent with the current literature (5,31). The reduced magnitude of the association of Non-Hispanic Black race/ethnicity with retention may be related to stigma within the Black community related to HIV care (39). A clinical implication of this finding may be to increase efforts to improve retention among Non-Hispanic Black persons with HIV. The increased retention among the Black Hispanic and other racial/ethnic groups may be the result of specialized care in the Miami-Dade location. Previous literature suggests that bilingual personnel in an HIV care facility increases clinical visits among Hispanic persons with HIV (40). Given the large Hispanic population in Miami, bilingualism is prevalent in most healthcare institutions.

Among males, depression was significantly associated with retention. A positive association between depression and retention in HIV care is presented in the literature, however, a majority of literature does indicate that depressive symptoms are generally negatively associated with retention(4,32). This relationship has not been assessed among an exclusively male group prior to this manuscript (32). Among females, there were no significant associations. Due to the small sample size of non-depressed persons (n=29), we conducted a stepwise regression to reduce overfitting the model by eliminating non-significant parameters (41). Gender was removed from

this particular regression as there were only seven women in this subsample, none of whom tested positive for alcohol use disorder in the non-retained group; which resulted in zero value for one of the cells. Also, among women, none of the cells had over five persons. For most multiple logistic regressions to function, no cells should be zero and at least 80% should be greater than 5, this was not the case when cross-tabulating female gender with alcohol use disorder (42). For the reasons mentioned above the inclusion of gender in the logistic regression that assessed variables' association with retention among the non-depressed would have been inappropriate. Among the non-depressed, there were no significant associations with retention. This model was from the manuscript as it provided no additional information regarding associations among non-depressed persons.

A major strength of this study was a diverse group of HIV infected persons from the Miami-Dade area including Hispanics and Blacks; two groups most affected by HIV in the United States. Despite the strengths of this study, there were limitations. One of the major limitations was a relatively small sample size for these types of analyses, likely contributing to the wide confidence intervals related to some of the point estimates. The small sample size limited the statistical power of the syndemic analysis, which may have contributed to no significant findings.

Conclusion

Overall we found multiple racial/ethnic groups, multiple levels of a traditional factor, are associated with improved retention and also multiple factors interact to alter

retention in HIV care. This trend of ethnic disparities in retention persists among depressed persons living with HIV in this study. This is important because these findings suggest discrepancies among different race/ethnic groups related to retention and clinical practices should be implemented to reduce these discrepancies. We also determined that interactions depression*alcohol use disorder and male gender*age can interact to reduce the likelihood of retention. This is important as barriers that may reduce retention in HIV are not unimodal and can inform clinical practices. The syndemic analysis revealed that most persons who were retained in care had two or three factors that could reduce retention in care. This is also important as it can influence clinical practice to assess patients for more than one factor when attempting to identify factors that may negatively affect persons living with HIV.

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Tables

Table 1: Frequency of Demographic Characteristics and Drug Use Among a Subsample of the MASH Cohort in Miami-Dade County from 2009-2014

Variable	Retained (n=267, 65.60%)	Not Retained (n =140, 34.40%)	Missing	X^2, p-value
	n (row %)	n (row %)		
Race/Ethnicity				
White	14 (50.00%)	14 (50.00%)		
White (Hispanic)	42(59.15%)	29(40.85%)		
Black	187(67.27%)	91(32.73%)		
Black (Hispanic)	12(80.00%)	3(20.00%)		
Other	12(85.71%)	2 (14.29%)		
Missing			1(0.25%)	8.57, 0.07
Gender				
Male	172(65.40%)	91(34.60%)		
Female	91(65.00%)	49(35.00%)		
Missing			4(0.98%)	0.00, 0.99
Age				
≤25	5(83.33%)	1(16.67%)		
26-34	19 (67.86%)	9(32.14%)		
35-44	76(66.09%)	39 (33.91%)		
≥45	165(64.45%)	91 (35.55%)		
Missing			2(0.49%)	1.05, 0.79
Education				
<HS	92(68.15%)	43(33.85%)		
HS	121 (66.12%)	62 (33.88%)		
>HS	49 (60.49%)	32 (39.51%)		
Missing			8 (1.97%)	1.35, 0.51
AUDIT score				
<8	145(63.88%)	82 (36.12%)		
≥8	119(67.61%)	57 (32.39%)		
Missing			4(0.98%)	0.46, 0.50
Cocaine Use				
Positive	67 (68.37%)	31 (31.63%)		
Negative	194 (64.67%)	106 (35.33%)		
Missing			9(2.21%)	0.30, 0.58

Marijuana Use				
Positive	51(58.62%)	36(41.38%)		
Negative	210(67.31%)	102 (32.69%)		
Missing			8 (1.97%)	1.05, 0.21
Depression				
Positive (CES-D score ≥16)	251(66.40%)	127 (33.60%)		
Negative (CES-D score <16)	16(55.17%)	13 (44.83%)		
Missing			0(0.00%)	0.31

Chi squared estimates do not include missing observations

Table 2: Adjusted Odds Ratio (AOR) for Retention Among the MASH Cohort Participants in Miami-Dade, FL from 2009-2014

Variable	Model 1		Model 2	
	AOR	95%CI	AOR	95%CI
Depression				
CES-D Score <15	1.00		1.00	
CES-D Score ≥16	0.53	0.84–4.31	1.20	0.15–6.88
Marijuana Use				
Marijuana Use (-)	1.00		1.00	
Marijuana Use (+)	0.73	0.43–1.27	0.69	0.40–11.21
Alcohol Abuse				
AUDIT Score<8	1.00		1.00	
AUDIT Score≥8	1.17	0.74–1.85	7.39	1.22–68.03
Cocaine Use				
Cocaine (-)	1.00		1.00	
Cocaine (+)	1.15	0.68–1.95	1.18	0.69–2.05
Education (yrs)				
Education	0.91	0.82–1.01	0.90	0.81–1.00
Age (yrs)				
Age	0.98	0.96–1.01	1.02	0.97–1.08
Race/Ethnicity				
White (Non-Hispanic)	1.00		1.00	
White (Hispanic)	1.75	0.68–4.57	1.56	0.61–4.14
Black (Non-Hispanic)	2.44**	1.06–5.75	2.25	0.98–5.31
Black (Hispanic)	4.84**	1.16–25.79	5.37**	1.23–29.96
Other	7.24**	1.54–54.05	6.17**	1.34–47.94
Gender				
Female	1.00		1.00	
Male	0.88	0.55–1.39	1.72	0.34–76.70
Two-Way Interactions				
Depression x Audit			0.14*	0.01–1.11
Depression x Gender			7.17*	0.84–98.49
Age x Gender			0.95*	0.88–1.01

**p-value≤0.05, *p≤0.10
AOR means adjusted odds ratio

Table 3: Adjusted Odds Ratios for Retention Stratified by CES-D Score and Gender from 2009-2014

	Stratified By Depression	
Variable	**Model 3 (CES-D Score ≥16)**	
	AOR	95%CI
Marijuana Use		
Marijuana Use (-)	1.00	
Marijuana Use (+)	0.69	0.39–1.22
Alcohol Abuse		
AUDIT Score<8	1.00	
AUDIT Score≥8	1.00	0.64—1.65
Cocaine Use		
Cocaine (-)	1.00	
Cocaine(+)	1.11	0.64–1.95
Education (yrs)		
Education	0.92	0.83–1.01
Age (yrs)		
Age	0.98	0.95–1.01
Race/Ethnicity		
White (Non-Hispanic)	1.00	
White (Hispanic)	1.67	0.64–4.39
Black (Non-Hisp.)	2.36**	1.02–5.52
Black (Hispanic)	5.99**	1.25–44.70
Other	6.82**	1.45–50.40
Gender		
Female	1.00	
Male	0.98	0.95–1.01

	Stratified by Gender			
	Model 4 (Male)		**Model 5 (Female)**	
	AOR	95%CI	AOR	95%CI
Depression				
CES-D Score <15	1.00		1.00	
CES-D Score ≥16	2.77**	1.06–7.46	0.83	0.11–4.31
Marijuana Use				
Marijuana Use (-)	1.00		1.00	
Marijuana Use (+)	0.72	0.36–1.46	0.66	0.27–1.67
Alcohol Abuse				
AUDIT Score<8	1.00		1.00	
AUDIT Score≥8	1.2	0.69–1.54x10^{3}	1.22	0.53–2.89
Cocaine Use				
Cocaine (-)	1.00		1.00	
Cocaine (+)	1.15	0.61–2.24	1.22	0.45–3.49
Education (yrs)				
Education	0.90	0.79–1.00	0.93	0.76–1.13
Age (yrs)				
Age	0.97	0.93–1.00	1.02	0.97–1.08
Race/Ethnicity				
White (Non-Hispanic)				
White (Hispanic)	1.65	0.47–5.87	1.40	0.30–7.10
Black (Non-Hispanic)	0.51	0.63–6.30	3.00	0.81–11.82
Black (Hispanic)	5.47	0.89–47.94	3.97	0.35–99.48
Other	4.48	0.75–37.71	1.92x10^{7}	0–N/A

**p-value≤0.05, *p≤0.10

Table 4 Frequency Distribution of Factors Among Retained and Not Retained in the MASH Cohort in Miami-Dade County from 2009-2012

(4-Day Adherence)			
Number of Factors	***Frequency (%) of category among retained***	***Frequency (%) of category among non-retained***	***Total Frequency (%) overall***
Zero	1(0.24%)	3(0.74)	4 (0.98%)
One	41 (10.07%)	16 (3.93%)	57 (14.00%)
Two	92 (22.61%)	51 (12.53%)	143 (35.14%)
Three	83 (20.39%)	44 (10.81%)	127 (31.20%)
Four	33 (8.11%)	16 (3.93%)	49 (12.04%)
Five	5 (1.23%)	3 (0.74%)	8 (1.97%)
Missing	12 (2.95%)	7 (1.72%)	19 (4.67%)

Table 5: Adjusted Odds Ratio for the Syndemic Association with Retention (Model 6)

Variable	Exp (Est.)	Exp (CI)
Number of Factors	0.99	0.79-1.24
Age	0.98	0.96-1.01
WH	1.7	0.68-4.39
Black	2.51**	1.09-5.87
BH	4.48	1.08-23.57
Other	7.32**	1.57-54.05
Male Gender	0.89	0.55-1.37

MANUSCRIPT 2

Individual-Level Vulnerability Factors and Their Individual, Syndemic, and Interactive Associations with Adherence in the MASH Cohort Study from 2009-2014

Abstract

Introduction: Adherence is a fundamental component of the HIV care continuum. Achieving effective adherence can be problematic for many, particularly among those exposed to multiple individual level vulnerability factors (i.e. depression, cocaine use, marijuana use, education, and alcohol abuse). Individual-level vulnerability factors rooted in social and behavioral contexts are hypothesized to additively or multiplicatively interact to increase the risk of poorer HIV outcomes. We have examined the frequency distribution of individual-level vulnerability factors and the associations of individual-level vulnerability factors in a syndemic framework on medication adherence measured in the short-term (100% adherence in the last 4-days), and long term (100% adherence in the last 3 months or more). ***Methodology***: The sample was derived from the Miami Adult Studies on HIV/AIDS (MASH) cohort study from 2009-2014. The frequency distribution of variables was first assessed. Variables were entered into a multiple logistic regression with adherence as the outcome to determine which individual-level factors were significantly associated with adherence. Subsequently, backward regression was used to determine two-way interactions associated with adherence. A multivariable logistic regression model was used to test which number of factors were associated with

adherence. ***Results***: Among persons assessed for short term and long term adherence, persons between the ages of 35–44 (80.49% and 65.00%, respectively), White-Hispanic persons (78.26% and 76.17%, respectively), those without alcohol use disorder (77.90% and 67.50%, respectively), and males (76.40% and 67.07%, respectively) had the highest percentages of adherence. Results showed that cocaine use was significantly and negatively associated with short term adherence when compared to persons who tested negative for cocaine use (OR=0.23, 95%CI: 0.05–0.86, p=0.05). Education had a significant negative association with long term adherence (OR=0.73, 95%CI: 0.57–0.91, p=0.01). ***Conclusion***: This study reports findings that cocaine use was negatively associated with short-term adherence, and education was negatively associated with long-term adherence. We determined that White-Hispanic persons, those who did not abuse alcohol, and males had the highest percentages of adherence which provides some insight that may assist in targeted interventions. While certain individual-level vulnerability factors were associated with adherence, an additive or interactive effect was not seen. More research is needed to examine the role of interactions and syndemics on adherence.

Introduction

Achieving viral suppression is the primary goal of antiretroviral therapies (ART). There are multiple steps leading to this outcome, including diagnosis, retention, and antiretroviral therapy adherence. Recent literature suggests that attrition commonly occurs throughout the continuum among persons with HIV (1). Kay and colleagues have emphasized that reducing attrition throughout the continuum requires a focus on individual-level factors (2). According to the behavioral model for vulnerable

populations, individual-level factors are stratified into the following categories: traditional factors, vulnerability factors, and enabling factors (3). Traditional factors include demographic information such as age, gender, race/ethnicity, and education. Vulnerability factors include mental illness and substance abuse (3). Enabling factors can impede or enhance access to HIV care and include income, insurance, housing, and social support (3). Specific individual-level factors that have been suggested to reduce progress to the adherence stage of the HIV care continuum include less than a high school education, depression, cocaine use, marijuana use, and alcohol use (4-7).

Adherence is a fundamental component of the HIV care continuum. Adherence is defined by multiple criteria, as there is no gold standard of measuring adherence in the literature(8). Short term adherence has been defined as not skipping medications in the last 4 days and long term adherence has been defined as not skipping medications within the last three months (9-11). The literature and clinical findings advocate for nearly perfect adherence to HIV antiretroviral therapies, therefore adherence in this study is defined as “never having skipped medications” (8,12).

Although there are studies involving the association between separate individual level vulnerability factors and adherence, the frequency of multiple individual level vulnerability factors within a sample of prospectively followed HIV infected persons has not been fully explored. This distribution must be understood for the purpose of developing a more concise target group for interventions and a clearer comprehension of the distribution of these individual-level vulnerability factors within a vulnerable population.

The association between multiple factors on adherence is typically assessed independently, however, these factors do not occur separately from one another, but in concert with one another in multiple complicated ways. Syndemic and additive associations may explain the complex manner in which individual-level factors are associated with adherence. Syndemic theory; first proposed by Merill Singer, involves a group of reciprocally increasing health problems that work together in a context of harmful social and physical conditions and increase vulnerability. The synergistic effect of these health problems significantly increases the overall disease status of a population (13). Syndemic theory suggests that a collection of health problems accumulates over a person's lifespan and can magnify the negative impact of one or more health problems (14). Determining syndemic or additive associations involves determining the sum of multiple characteristics on a particular outcome (13). An interactive association among factors involves the simultaneous, non-additive influence of two or more variables on an outcome (15). The purpose of this study is to examine the individual, interactive, and syndemic effects of individual-level vulnerability factors on short and long term adherence.

Assessing frequency distributions of individual-level vulnerability factors may provide insight related to the development of a more concise target group for adherence interventions and a clearer comprehension of the distribution of these individual-level vulnerability factors within a vulnerable population(16). Assessing the syndemic associations between individual-level vulnerability factors and adherence may allow determination of whether individual-level vulnerability factors work synergistically to impede progression to adherence among adults with HIV who have been retained in

care(14). Interactive associations may allow researchers to determine the method in which individual-level vulnerability factors influence the relationship between independent variables and progression to adherence among HIV infected adults that have been retained in care(17). Including individual level traditional factors in the assessment of the association between individual-level vulnerability factors and adherence allows researchers to control for demographic factors that could alter the association.

In this study, we evaluate the frequency distribution of individual-level vulnerability factors and the individual, interactive, and syndemic associations between individual-level vulnerability factors and adherence (both short term and long term) to antiretroviral therapies among HIV positive adults that are retained in care.

Methods

Setting and Population

The sample was derived from the Miami Adult Studies on HIV/AIDS (MASH) cohort study. Further details related to the methodology of the original project can be found in a paper entitled, "Cocaine Use and Liver Disease are Associated with All-Cause Mortality in the Miami Adult Studies in HIV (MASH) Cohort" (18). This is a secondary analysis of a prospective cohort study involving 134 HIV positive individuals residing in the south Florida region. Participants were a subset of the more than 800 participants from the MASH cohort who have been followed from 2009 - 2014. All independent variables were assessed at baseline and participants were subsequently followed for a one-year period after baseline to determine retention status. All participants provided

written consent to participate in the original study (MASH Cohort Study) consistent with the Florida International University Institutional Review Board IRB: 13-0038.

Eligibility Criteria

Study participants for this analysis were eligible if (1) they were eighteen years of age or older (2) diagnosed with HIV by a standardized testing method (3) participated in the study from 2009-2014 (4) provided informed consent during the visit or interview (5) retained in HIV care (6) and had complete information for both information gathered at baseline and adherence.

Measures

The primary outcome of this study was adherence, using two time-dependent measures. Short term adherence was defined as not having missed any doses of medication within the last four days (8,9,12). Long term adherence was defined as those who have not missed any medications for 3 months or more (8,10,12). Assessment of adherence was conducted using the validated AIDS Clinical Trial Group (ACTG) survey (8). To determine long term adherence participants were asked, “When was the last time you missed any of your medications”? The response choices to this question were: within the past week, 1-2 weeks ago, 2-4 weeks ago, 1-3 months ago, more than three months ago, and never skip medications. This variable was coded as dichotomous. Persons who answered, “within the last week, “1-2 weeks ago”, “2-4” weeks ago”, “1-3 months ago” were considered non-adherent, those who indicated that they “never skip medications” or “skipped more than 3 months ago” were considered to have attained long term adherence.

Short term adherence was determined by posing the following question "During the past 4 days on how many days have you missed taking all your doses?" Persons who answered, "1", "2", "3", or "4" were coded as non-adherent, those who answered "0" were coded as adherent. A six month time frame between baseline and adherence is generally the time allotted for progression from initiation of the study to adherence when using indirect methods (19). Using a 6-month time period between baseline and adherence standardized the duration of assessment for each participant and therefore reduced the possibility of reverse causation of poor adherence being caused by declining health status (20).

Independent variables included sociodemographic factors such as age, race/ethnicity, and gender. Other variables that were included were education, depressive symptoms, and substance use. Inclusion of these independent variables in the analysis was determined based on the behavioral model for vulnerable populations (3). Age, race/ethnicity, and gender were determined at baseline using the validated survey: Current Age, Gender, and Race Questionnaires (PhenX- Tier 1) (21). Education was assessed at baseline as a categorical variable via the Current Educational Attainment Questionnaire (PhenX Tier 1). Age was determined in the MASH survey from the self-reported year of birth and categorized in the current study as follows: "≤ 25", "26-34", "35-44", and "≥45" (22). However, age was assessed as a continuous variable in all logistic regressions (23).

Race/ethnicity was assessed by posing the following questions to the interviewee: What race do you consider to be? Do you consider yourself Hispanic/Latino? Race/ethnicity was categorized in the current study as: "White (Non-Hispanic)", "Black

(Non-Hispanic)", "Black (Hispanic)", White (Hispanic), "Asian", and "Other" (24). In the current study, Gender was defined as a categorical variable including: "Male", "Female", "Transgender", and "Declined" (25). Education was categorized using the following categories: "Less than high school education", "High school graduate or equivalent", and "More than high school education" (26). In the logistic regressions, years of education was assessed as a continuous variable (27).

In the MASH cohort study, the Center for Epidemiologic Studies Depression Scale (CES-D), a validated depression questionnaire, was used to assess depressive symptoms at baseline. Persons were asked a total of 20 questions that were scored from 0-3 (28). A score of 16 or higher indicates symptoms suggestive of clinical depression diagnosis, while scores of 15 and below indicate that persons do not have symptoms suggestive of clinical depression diagnosis. This variable was coded dichotomously: "Depressed" and "Not Depressed" (28). Cocaine and marijuana use were assessed with validated questionnaires and using the Multi-Drug 5 Panel Urine Dip Test Kit (WDOA-754). This test allowed assessment of drug use within the past three days. This testing method has been approved by the FDA (29). Cocaine and marijuana use within the past three days were categorized dichotomously (positive or negative).

Alcohol use disorder was determined from the Alcohol Use Disorder Identification Test (AUDIT) at baseline; this form has been validated by Saunders and colleagues (30). This is a 10-item test summed to create a score. A score of 8 or more is considered indicative of hazardous or harmful alcohol use. Alcohol dependence was categorized as a dichotomous variable, either as "alcohol dependent" or "not alcohol dependent." (30).

Analysis

Frequencies were determined for variables of interest (age, race/ethnicity, education, substance use status, depression, and adherence status) and Fisher exact tests were used to determine the association between each individual level vulnerability factor and adherence for variables with cell counts less than 5, otherwise, chi-squared tests were used(31). These variables were subsequently entered into a multiple logistic regression with adherence as the outcome using two sets of models, (one for each adherence measure) to determine which individual-level vulnerability factors are significantly associated with adherence. After determining the individual level vulnerability factors associated with adherence, interactions among these factors were included in the logistic regression. To determine the syndemic or additive associations between independent factors and adherence, a count score of the number of individual-level vulnerability factors (from 0-5) and the frequency distribution was determined. All variables (aside from age, race/ethnicity, and gender) were categorized dichotomously, therefore a score of five indicates all factors were present, while a score of zero indicates none of the factors were present (32). For the purpose of the syndemic analysis, all independent variables that were not already dichotomous were collapsed into dichotomous variables (32). Education was reduced to two categories ("graduated high school" and "did not graduate high school") (32). A multivariable logistic regression model was used run to determine if the number of individual-level vulnerability factors is associated with adherence (32). Odds ratios were reported at 95% confidence intervals. These odds ratios

were used to estimate the effect of each variable and their interactions on antiretroviral adherence. All statistical analyses were performed using R Version 3.4.3.

Results

Short Term Adherence

Table 1 summarizes demographic frequencies stratified by short term adherence. Overall there were 134 persons in the sample for short term adherence. Approximately 75.37% (n=101) were non-adherent while 24.63% (n=33) were adherent. The majority of the group were Non-Hispanic Black persons 72.39% (n=97). This group was primarily composed of males (66.42%). The largest age group in the sample (61.65 %, n=82) were composed of those 45 years and older. Most of the participants (63.36 %, n=83) had received a high school education or higher. Most participants (64.18%, n=86). had an did not have alcohol use disorder The majority tested negative for both cocaine and marijuana (77.61%, n=104 and 83.58%, n=112, respectively), and were depressed (72.18%, n=96). There were no significant bivariate associations.

Table 3 presents adjusted and unadjusted odds ratios for variables associated with short term adherence. The results suggested that cocaine use was significantly and negatively associated with short term adherence when compared to persons who tested negative for cocaine use (OR=0.23, 95%CI: 0.05–0.86, p=0.05) when adjusting for all other factors. There were no significant odds ratios among the unadjusted associations. All interaction terms were non-significant at the p>0.10 threshold.

In the syndemic analysis, we determined that 41.05% (n=55) were in the two-factor category; approximately 30.59% (n=41) persons were adherent among those in the

two-factor category and 10.45% (n=14) were non-adherent. Approximately 29.10% (n=39) of participants had three individual level vulnerability factors. In the three-factor category 21.64% (n=29) were adherent and 7.46% (n=10) were non adherent. The one factor category contained 18.66% (n=25) participants (Table 5). Among those in the one factor category, 14.18% (n=19) of persons were adherent while 4.48% (n=6) of persons were non-adherent. The four-factor category contained 8.21% (n=11) of participants. Of the persons with four factors, 6.72% (n=9) of persons were adherent while 1.59% (n=2) of persons were non adherent. The five-factor category contained 0.75% (n=1) of the participants. Three participants, 2.24%, were missing factors and excluded from analysis (Table 5). The syndemic analysis did not yield significant results (Table 6).

Long Term Adherence

Table 2 summarizes demographic frequencies by long term adherence. Overall there were 124 persons that had data for long term adherence. Approximately (33.06%, n=41) of persons in this group were non-adherent, while (66.94%, n=83) were adherent. A large majority, 77.17 %, were African American. The majority were male (66.13%, n=82) and ≥45 years of age (60.98%, n=75). Most had a high school education or greater (63.41%, n=78). The majority did not have alcohol use disorder 64.52% (n=80) and were negative for both cocaine use (76.61%, n=95) and marijuana use (82.26%, n=102). There were no significant bivariate associations between variables and long-term adherence.

Table 4 presents adjusted and unadjusted odds ratios between all variables and ≥3month adherence. The logistic regression suggests that years of education was significantly and negatively associated with long term adherence (OR=0.73, 95%CI:

0.57–0.91, p=0.01) when adjusted for all other factors. Demographic factors such as race/ethnicity and male gender were not associated with adherence. Substance use and alcohol use disorder were not associated with adherence either. There were no significant interactions at the ≤0.10 threshold. Among the unadjusted associations between variables and three-month adherence, education was negatively associated with reduced long-term adherence (OR=0.76, 95%CI: 0.61–0.92, p=0.01) (Table 4).

In the syndemic analysis, 41.13% (n=51) of the participants had two individual-level vulnerability factors (Table 5). Among those in two factor category, 28.23% (n=35) of persons were adherent while 12.90% (n=16) of persons were non-adherent (Table 5). Approximately 29.84% (n=37) of the participants had three individual-level vulnerability factors. Of those in the three-factor category 16.94% (n=21) of persons were adherent while 12.90% (n=16) were non- adherent (Table 5). The one factor category contained 17.74% (n=22) (Table 5). Among those in the one factor category, 12.90% (n=16) of persons were adherent while 4.84% (n=6) were non-adherent. The four factors category contained 8.87% (n=11) (Table 5). Of those in the four factors category, 6.45% (n=8) of persons were adherent while 2.42% (n=3) of persons were non-adherent. The five factors category contained 0.81% (n=1); all persons in this category were adherent (Table 5). The remaining 1.61% (n=2) had missing values and were not included in the syndemic analysis (Table 5). The bivariate analysis between the number of factors and adherence yielded no significant results, nor did the remainder of the syndemic analyses (Table 6).

Discussion

This study presents evidence supporting the negative association between cocaine use and short term adherence and is consistent with the general body of literature(4). Multiple explanations have been offered relating to this association in recent literature. Previous literature indicates that both illicit substance dependence and HIV are associated with neurocognitive impairment(33). These impairments may manifest as reduced attention, processing speed, and memory(33). These HIV-related cognitive impairments may lead to poorer adherence(33). Studies also suggest that psychostimulant use causes less activation in various areas of the brain (i.e. prefrontal cortex, orbitofrontal cortex, anterior cingulate, and posterior parietal region)(33). This reduced activation causes worse performance in memory tasks and therefore reduced adherence(33). Cocaine users with HIV may be at increased risk for neurocognitive impairment, and neurocognitive impairment may partially explain the lower rates of medication adherence observed in cocaine users(33). A clinical implication of this finding is to include substance counseling along with adherence interventions among non-adherent persons with HIV infection (Meade et al. 2011).

Notable similarities and differences in the variable frequencies were noticed when assessing short term and long-term adherence. Among those assessed for short term adherence, the majority were adherent, and also, we noticed the same trend among those assessed for long term adherence. This trend is corroborated with current literature (34). All persons in this sample are retained in care and generally, most persons who are retained in care tend to be adherent (34). This is likely the case because persons who are retained consistently engage in HIV-related care and therefore can be monitored and

influenced by health professionals to engage in proper adherence (35). White-Hispanic persons had the highest levels of adherence for both short term and long-term adherence. Hispanic persons tend to have a percentage of adherence comparable to Non-Hispanic white persons and a higher percentage of adherence when compared to African Americans (36). Specifically, Hispanics of European descent tend to have higher adherence percentages than Black persons and Hispanic persons with origins in Central and South America(37). The reason the White Hispanic group had a higher percentage of adherence than all other groups in this study may be due to bilingualism which has been evidenced to improve HIV care outcomes (38). Given the large Hispanic population in Miami, bilingualism is prevalent in most healthcare institutions. Another reason White Hispanic persons may have higher percentages may be a higher degree of acculturation. Studies have indicated that acculturation may strongly affect health related behavior among minority groups in an Anglo majority host culture (i.e. United States) and specifically compliance with treatment among Hispanic persons(39). This suggests that the White-Hispanics may have a higher degree of acculturation than other minorities in the study, and therefore this could be the reason for a higher adherence percentage among this group compared to all others. Most research assesses Hispanic persons as a general group, therefore more research may be necessary to determine the reason these trends are not found in the Black Hispanic group.

Persons between the ages of 35-44 had a higher short-term adherence percentage than all other age groups, however persons 26-34 had the highest long-term adherence percentage. These persons had an adherence percentage of 100%, however, this group consisted of only 8 participants. A larger group of persons from this age group may be

necessary to develop inferences related to age and long-term adherence. Among groups with a larger number of participants and an actual non-adherent segment, persons between the ages of 35-44 had the highest percentage of long-term adherence. Persons with high levels of adherence are generally older therefore, it is consistent with the literature that the youngest group (≤25) would not have the highest percentage of adherence (40). A number of explanations have been presented to explain this trend. One explanation for the increased percentage of adherence among an older group is that older HIV patients are already familiar with medication usage for chronic diseases and have increased awareness that treatment of HIV requires a high level of medication adherence(41). Another explanation presented by the literature is that older HIV patients have had friends or who passed away from infections associated with HIV/AIDS, principally during the height of the HIV epidemic when treatment options were limited, and this has shaped their desire to maintain control of this disease(41). The oldest group (≥45), did not have the highest percentage of short term or long-term adherence. While this is not consistent with the majority of literature, some literature does corroborate this finding as older patients with evidenced cognitive decline are likely to have poorer adherence (1,42).

Males had a higher percentage of both short term and long-term adherence than did females. This finding is corroborated by the current literature (43). The reasoning offered for this trend is that females report more avoidance coping mechanisms in managing HIV related stress, including the stress that results from publicly taking antiretroviral therapies in public. This may explain more frequent adherence among males than females(44). Another possibility could be the practical barriers to adherence

frequently experienced by women living with HIV such as taking care of a household and children(43)

In both short term and long-term adherence persons who did not have alcohol use disorder had the highest percentages of adherence. The trend of increased percentages of adherence among those who did not have alcohol use disorder when compared to those do not is consistent with current literature (45). While these percentages are not statistically significant, they may be clinically significant in helping researchers develop interventions to improve adherence among persons with HIV. Specifically, persons ≤25, females, and persons who may have symptoms suggestive of alcohol use disorder may need additional counseling and monitoring related to adherence.

Among those assessed for long term adherence, we found that increased education was negatively and significantly associated with adherence. This finding is corroborated in the literature, indicating a statistically significant negative relationship between adherence and years of education completed; however, most literature which assesses the relationship between education and long term adherence generally find that a reduced level of education is associated negatively with long term adherence (46,47). Studies have suggested a potential reason for the negative association between years of education completed and adherence is fear of HIV stigma among more educated persons, resulting in avoidance of HIV clinics and therefore less consistent use of medication(48). Upon assessing the distribution of education relative to other variables, we determined that the majority of persons, 55.55% (n=5), with more than two years of college had alcohol use disorder in this sample. Alcohol abuse has been associated with reduced adherence among persons with HIV(6). We removed this educational class (persons with >2 years

of college) and ran a logistic regression again. Education was no longer significantly and negatively associated with adherence. Please see the supplemental table below (Table 7). These equivocal findings suggest that a more detailed study of the effect of education on adherence is warranted.

There were no significant findings in the syndemic analysis, nevertheless, the distribution of factors is interesting. The majority of persons who had attained short term and long-term adherence were concentrated in the two and three factor categories. This is significant because it suggests that most persons adherent antiretroviral therapy have two to three vulnerability factors that could affect their health outcomes. Assessing the number of vulnerability factors an HIV infected patient has could inform clinical practices and improve care for those with HIV. Determining a threshold or index that sufficiently predicts success along the HIV care continuum, also may be useful.

A major strength of this study was a diverse group of HIV infected persons from the Miami-Dade area including Hispanics and Blacks; two groups most affected by HIV in the United States. Another strength of this study was the multiple variables available in the data allowing assessment of how factors independently affect adherence while controlling for others.

A major limitation was a small sample size for these types of analyses, contributing to the wide confidence intervals around some of the point estimates. The small sample size limited the statistical power of the syndemic analysis, which may have contributed to the null findings. The four and five factor groups for the syndemic comparisons in both the short term and long-term analysis contained 11 and 1 persons, respectively. In an attempt to assess whether the insignificant findings were an artifact of

a small group size the “four” and “five” factor categories were combined in a sensitivity analysis. There were no significant findings; which suggests that the accumulation of individual level vulnerability factors does not additively impact antiretroviral adherence among this group. The syndemic theory suggests that a collection of health-related factors accrues over a person’s lifespan and can increase the negative impact of one or more health problems (14). More research is necessary to determine the specific factors that could accumulate and possibly reduce both short term and long-term adherence. Further research is also needed to assess the manner in which the theory of syndemics applies to adherence to HIV care in a population suffering from disparities.

Conclusion

This study reports findings that cocaine is negatively associated with adherence within the last four days and education was negatively associated with adherence within the last three months. This study also indicates that the distribution of individual-level factors is similar among those with short term and long-term adherence. The majority of these retained subjects were adherent. Adherent persons tended to be older, White-Hispanic, did not have alcohol use disorder, and male. While the findings related to frequency distribution among variables may not be statistically significant, they may be significant in helping researchers develop interventions to improve adherence among persons with HIV. Syndemic and interactive outcomes were not significant and therefore did not provide further insight into the effects of multiple risk factors. Future research is necessary to further assess the relationship between varying levels of substance use,

education and adherence among persons with HIV. Future research is also necessary to assess the syndemic theory's relation to adherence in HIV care.

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Tables

Table 1: Frequency of Demographic Characteristics and Drug Use Among Retained Persons in the MASH Cohort in Miami-Dade County from 2009-2014

	Not Adherent (n=33, 24.63%) last 4 days	Adherent (n=101, 75.37%) last 4 days	Missing	Fisher Exact Test p-value/Chi-Squared
Race/Ethnicity				0.31
White	2 (40.00%)	3 (60.00%)		
White (Hispanic)	5 (21.74%)	18 (78.26%)		
Black	22 (22.68%)	75 (77.32%)		
Black (Hispanic)	1 (50.00%)	1 (50.00%)		
Other	2 (33.33%)	4 (66.67%)		
Missing			0 (0.00%)	
Gender				0.86*
Male	21 (23.60%)	68 (76.40%)		
Female	12 (26.67%)	33 (73.33%)		
Missing			0 (0.00%)	
Age				0.44
≤25	1 (50.00%)	1 (50.00%)		
26-34	1 (12.50%)	7 (87.50%)		
35-44	8 (19.51%)	33 (80.49%)		
≥45	23 (28.05%)	59 (71.95%)		
Missing			1 (0.10%)	
Education				0.83*
<HS	10 (20.83%)	38 (79.17%)		
HS	15 (25.86%)	43 (74.14%)		
>HS	6 (24.00%)	19 (76.00%)		
Missing			3 (2.24%)	
AUDIT score				0.48*
<8	19 (22.10%)	67 (77.90%)		
≥8	14 (29.17%)	34 (70.83%)		
Missing			0 (0.00%)	
Cocaine Use				0.15
Positive	4 (13.79%)	25 (86.21%)		
Negative	29 (27.88%)	75 (72.12%)		
Missing			1 (0.10%)	
Marijuana Use				0.59
Positive	4 (19.05%)	17 (80.95%)		

Negative	29 (25.89%)	83 (74.11%)		
Missing			1 (0.10%)	
Depression				1.00
Positive (CES-D score ≥16)	1(1.04%)	95 (98.96%)		
Negative (CES-D score <16)	32 (84.21%)	6 (15.79%)		
Missing			1 (0.10%)	

*Indicates Chi-squared test, otherwise Fisher exact test used

Table 2: Frequency of Demographic Characteristics and Drug Use Among Retained Persons in the MASH Cohort in Miami-Dade County from 2009-2014

	Not Adherent (n=41, 33.06%) last 3 months	Adherent (n=83, 66.94%) last 3 months	Missing	Fisher Exact Test p-value/Chi-Squared
Race/Ethnicity				0.48
White	2 (40.00%)	3 (60.00%)		
White (Hispanic)	5 (23.81%)	16 (76.19%)		
Black	29 (32.58%)	60 (67.42%)		
Black (Hispanic)	2 (66.67%)	1 (33.33%)		
Other	3 (75.00%)	1 (25.00%)		
Missing			0(0.00%)	
Gender				1.00*
Male	27 (32.93%)	55 (67.07%)		
Female	14 (33.33%	28 (66.67%)		
Missing			0(0.00%)	
Age				0.21
≤25	0 (0.00%)	1 (100.00%)		
26-34	0 (0.00%)	7 (100.00%)		
35-44	14 (35.00%)	26 (65.00%)		
≥45	27 (36.00%)	48 (64.00%)		
Missing			1 (0.01%)	
Education				0.13*
<HS	11 (24.44%)	34 (75.56%)		
HS	18 (33.96%)	35 (66.04%)		
>HS	12 (48.00%)	13 (52.00%)		
Missing			1 (0.01%)	
AUDIT score				1.00*
<8	26 (32.50%)	54 (67.50%)		
≥8	15 (34.09%)	29 (65.91%)		
Missing			0 (0.00%)	
Cocaine Use				0.40*
Positive	7 (25.00%)	21 (75.00%)		
Negative	34 (35.79%)	61 (63.21)		
Missing			1 (0.01%)	

Marijuana Use				0.44*
Positive	9 (42.86%)	12 (57.14%)		
Negative	32 (31.37%)	70 (68.63%)		
Missing			1 (0.01%)	
Depression				0.22
Positive (CES-D score ≥16)	37 (31.62%)	80 (68.38)		
Negative (CES-D score <16)	4 (57.14%)	3 (42.86%)		
Missing			0 (0.00%)	

*Indicates Chi-squared test, otherwise Fisher exact test used

Table 3: Adjusted Odds Ratio (AOR) and Unadjusted Odds Ratio (OR) for 4 Day Adherence Among the MASH Cohort Retained Participants in Miami-Dade, FL from 2009-2012

	(AOR)		(OR)	
Variable	**AOR**	**95%CI**	**OR**	**95%CI**
Depression				
CES-D Score ≥16	1.40	0.19–28.91	2.02	0.33–38.93
CES-D Score <15	Ref.		Ref.	
Marijuana Use				
Marijuana Use (+)	0.74	0.18–2.57	0.67	0.18–2.00
Marijuana Use (-)	Ref.		Ref.	
AUDIT Score				
AUDIT Score≥8	1.50	0.58–3.85	1.45	0.64–3.24
AUDIT Score<8	Ref.		Ref.	
Cocaine Use				
Cocaine (+)	0.24**	0.05–0.86	0.41	0.11–1.18
Cocaine (-)	Ref.		Ref.	
Education (yrs)				
Education	1.02	0.86–1.23	1.01	0.85–1.20
Age (yrs)				
Age	0.98	0.92–1.04	0.99	0.95–1.05
Race/Ethnicity				
White (Hispanic)	3.30	0.03–3.12	0.41	0.05–3.81
Black (Non-Hispanic)	0.37	0.05–3.33	0.44	0.07–3.50
Black (Hispanic)	3.48	0.16–128.56	3.00	0.16–97.62
Other	0.79	0.05–12.87	0.75	0.05–9.59
White (Non-Hispanic)	Ref.		Ref.	
Gender				
Female	1.00		1.00	

Male	0.76	0.30–1.93	0.85	0.38–1.97
Female	Ref.		Ref.	

**p-value≤0.05
*p≤0.10
No significant interactions for Adherence at 4 days

Table 4: Adjusted Odds Ratio (AOR) Unadjusted Odds Ratio (OR)for 3 Month Adherence Among the MASH Cohort Retained Participants in Miami-Dade, FL from 2009-2012

	(AOR)		(OR)	
Variable	**AOR**	**95%CI**	**OR**	**95%CI**
Depression				
CES-D Score ≥16	4.31*	0.81–25.48	2.88	0.61–15.26
CES-D Score <15	Ref.		Ref.	
Marijuana Use				
Marijuana Use (+)	0.72	0.23–2.23	0.61	0.23–1.63
Marijuana Use (-)	Ref.		Ref.	
AUDIT Score				
AUDIT Score≥8	0.98	0.37–2.60	0.93	0.43–2.06
AUDIT Score<8	Ref.		Ref.	
Cocaine Use				
Cocaine (+)	2.15	0.72–7.26	1.67	0.67–4.61
Cocaine (-)	Ref.		Ref.	
Education (yrs)				
Education	0.73**	0.57–0.91	0.76**	0.61–0.92
Age (yrs)				
Age	1.00	0.94–1.07	0.98	0.93–1.04
Race/Ethnicity				
White (Hispanic)	4.75	0.39–60.49	2.13	0.23–16.94
Black (Non-Hispanic)	2.03	0.20–18.85	1.37	0.17–8.76
Black (Hispanic)	0.50	0.01–11.78	0.33	0.01–6.15
Other	1.50	0.09–25.13	0.67	0.05–7.47
White (Non-Hispanic)	Ref.		Ref.	
Gender				
Female	1.00		1.00	
Male	1.21	0.48–3.03	1.02	0.46–2.28
Female	Ref.		Ref.	

**p-value≤0.05
*p≤0.10
No significant interactions for Adherence at 4 days

Table 5: Frequency Distribution of Factors in the MASH Cohort in Miami-Dade County from 2009-2012

(4-Day Adherence)				(3 Month Adherence)			
Number of Factors	**Frequency (%) of category among adherent**	**Frequency (%) of category among non-adherent**	**Total Frequency (%) overall**	**Number of Factors**	**Frequency (%) of category among adherent**	**Frequency (%) of category among non-adherent**	**Total Frequency (%) overall**
One	19 (14.18%)	6(4.48%)	25 (18.66%)	One	6 (4.84%)	16 (12.90%)	22 (17.74%)
Two	41 (30.59%)	14 (10.45%)	55 (41.04%)	Two	16 (12.90%)	35 (28.23%)	51 (41.13%)
Three	29 (21.64%)	10 (7.46%)	39 (29.10%)	Three	16 (12.90%)	21 (16.94%)	37 (29.84%)
Four	9 (6.72%)	2 (1.59%)	11 (8.21%)	Four	3 (2.42%)	8 (6.45%)	11 (8.87%)
Five	1 (0.75%)	0 (0.00%)	1 (0.75%)	Five	0 (0.00%)	1 (0.81%)	1 (0.81%)
Missing	1 (0.75%)	2 (1.49%)	3 (2.24%)	Missing	0 (0.00%)	2 (1.61%)	2 (1.61%)

Table 6: Adjusted Odds Ratio for the Syndemic Association with Adherence in the MASH Cohort in Miami-Dade County from 2009-2014

	Model 1 (4-Day Adherence)		Model 2 (3-Month Adherence)	
Variable	**AOR**	**95%CI**	**AOR**	**95%CI**
Number of Factors				
Number of Factors	0.86	0.52–1.41	0.87	0.55–1.39
Age				
Age	0.99	0.94–1.04	0.98	0.92–1.03
Race/Ethnicity				
White Non-Hispanic	1.00		1.00	
WH	0.37	0.04–3.49	2.03	0.21–16.66
Black	0.39	0.06–3.20	1.27	0.15–8.37
BH	2.83	0.15–93.49	0.32	0.01–5.93
Other	0.73	0.05–9.39	0.64	0.05–7.24
Gender				
Female Gender	1.00		1.00	
Male Gender	0.83	0.35–2.03	1.04	0.45–2.38

Supplemental Table

Table 7: Adjusted Odds Ratio (AOR) Unadjusted Odds Ratio (OR)for 3 Month Adherence Among the MASH Cohort Retained Participants in Miami-Dade, FL from 2009-2012

Variable	AOR	95%CI
Depression		
CES-D Score ≥16	4.82*	0.84–30.51
CES-D Score <15	Ref.	
Marijuana Use		
Marijuana Use (+)	0.40	0.11–1.41
Marijuana Use (-)	Ref.	
AUDIT Score		
AUDIT Score≥8	1.12	0.40–3.34
AUDIT Score<8	Ref.	
Cocaine Use		
Cocaine (-)	Ref.	
Cocaine(+)	2.72	0.86–10.15
Education (yrs)		
Education	0.76	0.56–0.99
Age (yrs)		
Age	0.78	0.56–1.04
Race/Ethnicity		
White (Hispanic)	7.68	0.53–129.98
Black (Non-Hispanic)	2.46	0.23–27.95
Black (Hispanic)	0.58	0.01–16.12
Other	0.90	0.04–17.50
White (Non-Hispanic)	Ref.	
Gender		
Male	1.99	0.37–2.60
Female	Ref.	

**p-value≤0.05
*p≤0.10

MANUSCRIPT 3

The Individual and Interactive Effects of Substance Use, Depression, Education, Race/Ethnicity, and Gender on Viral Suppression Among PLWH Retained in Care

Abstract

Objective*:* To determine significant individual-level (traditional and vulnerability) factors and interactions associated with viral suppression. ***Background***: Achieving viral suppression is the principal goal of antiretroviral therapies (ART). This is the ultimate component of the HIV care continuum; it follows the diagnosis, retention, and adherence stages. Traditional individual-level traditional factors that have been suggested to reduce progression to viral suppression are age, race/ethnicity, and gender. Specific individual-level vulnerability factors that have been demonstrated to reduce progress to the "viral suppression" stage of the HIV care continuum include depression, cocaine use, marijuana use, alcohol use, and tobacco use. These individual-level-factors may individually and interactively reduce progression to viral suppression. ***Methods***: The sample (n= 51) was derived from the Miami Adult Studies on HIV/AIDS (MASH) cohort study from 2009–2014. This is a prospective cohort composed of comprehensively characterized active drug users, with and without HIV infection. Individual-level traditional and vulnerability factors were entered into a multiple logistic regression with viral suppression as the outcome to determine which individual-level factors were significantly associated with

retention. Subsequently, backward regression, adjusting for all main effects was conducted, to determine two-way interactions associated with viral suppression. ***Results***: The sample consisted primarily of 78.43% Non-White persons, males (64.71%), and persons ≥35 years of age (88.24%). Among the adjusted odds ratios Non-White race/ethnicity was marginally and negatively associated with viral suppression (OR=0.23, 95%CI: 0.03–1.10, p=0.08). Among the unadjusted odds ratios Non-White race/ethnicity (OR=0.28, 95%CI: 0.05–1.12, p=0.09), education (OR=0.75, 0.52–1.03, p=0.10), and male gender (OR=0.33, 95%CI: 0.09–1.05. p=0.07) were marginally and negatively associated with viral suppression. No interactions were significant. ***Conclusion***: This study reports findings that indicate male gender, Non-White race/ethnicity, and education are marginally and negatively associated with viral suppression. Future research is necessary to explore the individual and interactive associations between individual-level factors and viral suppression.

Introduction

Achieving HIV viral suppression is the principal goal of antiretroviral therapies (ART)(1). This is the final component of the HIV care continuum; the diagnosis, retention, and adherence stages precede it(1). Recent literature indicates that among all persons who are diagnosed with HIV in the United States, approximately 48% are virally suppressed (2). Kay and colleagues have noted that decreasing attrition throughout the continuum necessitates a focus on individual-level factors (3). According to the behavioral model for vulnerable populations, individual-level factors are divided into the following categories: traditional factors, vulnerability factors, and enabling factors (4).

Traditional factors include demographic information such as age, gender, race/ethnicity, and education. Vulnerability factors include factors such as mental illness and substance abuse (4). Individual-level traditional factors that have been determined to reduce progress to viral suppression are race/ethnicity, gender, and age (5-8). Specific individual-level vulnerability factors that have been demonstrated to reduce progress to the "viral suppression" stage of the HIV care continuum include depression, cocaine use, marijuana use, alcohol use, and cigarette use (9-14). Although substance use generally includes illicit substances and alcohol use in the scope of viral suppression, we included tobacco use as it has been evidenced to reduce T-cell viability and therefore indirectly increase the viral load (4,14)

Viral suppression is a vital component of the HIV care continuum. While there are multiple definitions of viral suppression, we defined viral suppression as an HIV viral load of ≤50 copies per mL during the 12 month follow-up period (15-18). The association between multiple factors on viral suppression is generally assessed individually while adjusting for others, however, these factors do not occur in isolation from one another. They occur in concert with one another in multiple ways. Interactive associations among factors involve the simultaneous, non-additive influence of two or more variables on an outcome (19). The purpose of this brief is to examine the individual and interactive effects of individual-level traditional and vulnerability factors on viral suppression. We hypothesize that multiple individual level traditional and vulnerability factors will be associated with viral suppression. We also hypothesize that there will be an interactive effect among these factors.

Understanding individual-level associations assists researchers in understanding the deleterious effects of specific individual-level factors on viral suppression among persons living with HIV(PLWH) Understanding interactive associations allows researchers to determine putative mechanisms in which individual-level (traditional and vulnerability) factors influence the relationship between independent variables and progression to viral suppression among PLWH that have been retained in care.

Methods

Setting and Population

The sample was derived from the Miami Adult Studies on HIV/AIDS (MASH) cohort study. Further details related to the methodology of the original project can be found in a paper entitled, "Cocaine Use and Liver Disease are Associated with All-Cause Mortality in the Miami Adult Studies in HIV (MASH) Cohort" (20). This is a secondary analysis of a prospective cohort study involving 51 HIV positive individuals residing in the south Florida region. Participants were a subset of the more than 800 participants from the MASH cohort who have been followed from 2009 - 2014. All independent variables were assessed at baseline and participants were subsequently followed for a one-year period after baseline to determine retention status. All participants provided written consent to participate in the original study (MASH Cohort Study) consistent with the Florida International University Institutional Review Board IRB: 13-0038.

Eligibility Criteria

Participants were eligible for this analysis if they were (1) eighteen years of age or older, (2) diagnosed with HIV by a standardized testing method, (3) participated in the study from 2009-2014, (4) provided informed consent, (5) were retained in care for a period ≥3 months during the calendar year in which we assessed viral suppression (6) had complete information gathered at baseline and (7) had complete viral suppression information at the 12 month follow-up period.

Measures

The primary outcome of this study was viral suppression at 12 month follow up. Viral suppression was defined as an HIV viral load of ≤50copies per mL in the calendar year among HIV positive persons on antiretroviral therapies (ART) (16). Those who met this criterion were codified as virally suppressed, and those who did not were codified as not virally suppressed. The time period between baseline and viral suppression was twelve months, as that is the time interval that is generally allotted for progression to viral suppression among persons with HIV (17,18). HIV viral load was determined via laboratory reports and assessed using polymerase chain reaction (RealTime HIV-1 PCR; Abbott Molecular, Des Plaines, IL) after appropriate medical release forms were signed by the parties (21).

Independent variables that were analyzed included sociodemographic factors such as age, race/ethnicity, and gender. Other variables that were included are education, depressive symptoms, and substance use. Inclusion of these independent variables in the analysis was determined according to the behavioral model for vulnerable populations

(4). Age, race/ethnicity, and gender were obtained at baseline using a validated survey: Current Age, Gender, and Race Questionnaires (PhenX- Tier 1). Education was assessed at baseline as a categorical variable via the Current Educational Attainment Questionnaire (PhenX Tier 1) (22).

The Center for Epidemiologic Studies Depression Scale (CES-D), a validated depression scale, was used to assess depression at baseline. Persons were asked a total of 20 questions that were scored from 0-3 (23). A score of 16 or higher indicated symptoms suggestive of clinical depression diagnosis, while scores of 15 and below indicated that persons do not have symptoms suggestive of a clinical depression diagnosis. This variable was coded dichotomously: "Depressed" and "Not Depressed" (23).

Cocaine use and marijuana use were assessed using the Multi-Drug 5 Panel Urine Dip Test Kit (WDOA-754). This test allowed researchers to assess drug use in the past three days. This testing method has been approved by the FDA (24). Cocaine and marijuana use within the past three days were both categorized dichotomously ("positive" or "negative"). Alcohol use disorder was determined from the Alcohol Use Disorder Identification Test (AUDIT) at baseline; this form was validated by Saunders and colleagues (25). This is a 10-item instrument in which each question is worth one point. A score of 8 or more was considered indicative of hazardous or harmful alcohol use. Alcohol dependence was categorized as a dichotomous variable, either alcohol dependent or not alcohol dependent (25).

Tobacco use was determined by a detailed questionnaire of drug, alcohol, and tobacco use in the past six months. The questionnaire queried the type of alcohol or drug of abuse including beer, wine, liquor, marijuana, cocaine, crack, amphetamines, and

tobacco, as well as frequency, quantity, and route of administration. Frequency of use was graded on a numerical scale of 0 = never, 1 = once in the last 30 days, 2 = once/week; 3 = 3-4 times/week, 4 = daily, and 5 = more than daily (26).

Analysis

First, frequencies were obtained for the variables age, race/ethnicity, education, substance use status, depression, and tobacco use status, by viral suppression status. Each variable's association was tested with either a chi-squared test or a Fisher exact test if the variable had a cell value≤5(27). These variables were subsequently entered into a robust multiple logistic regression with viral suppression as the outcome to determine which individual-level factors were significantly associated with viral suppression. We used robust regression due to the small sample size and the effect outliers could potentially have on the regression(28). Subsequently, backward regression, adjusting for all main effects was conducted, to determine which two-way interactions were associated with retention. All interactions with $p \leq 0.10$ were included in the final model (29). Odds ratios were reported at 95% confidence intervals. These odds ratios were used to estimate the effect of each variable and their interactions on viral suppression. All statistical analyses were performed using R Version 3.4.3

Results

Table 1 summarizes viral suppression frequencies of 51 participants in the sample as well as their demographic characteristics. Overall, 50.98% (n=26) were not virally suppressed. The majority of participants were Non-White (Black, Black-Hispanic, and

Other) while the remainder, 21.47% (n=11) were White (Non-Hispanic White and White Hispanic). Approximately 64.71% (n=33) participants were male. The majority of persons were over the age of 35 (88.24 %, n=45) while some were under the age of 35 (11.76%, n=6). Most of the participants had a high school education or some post-secondary education (68.63%, n=35).

Cocaine and marijuana use in the last three days was minimal (17.65%, n=9 and (19.61%, n=10, respectively). The majority of persons did not have alcohol use disorder (66.67%, n=34) and used tobacco at least 3-4 times per week (56.86%, n=29). The majority of persons had depressive symptoms consistent with a diagnosis of depression (94.12%, n=48). Model 1 (Table 1), which illustrates a logistic regression with all individual-level factors excluding interactions, shows there were no significant associations between any individual-level factors and viral suppression among this group. When assessing interactions associated with viral suppression, there were no statistically significant interactions. While there were no statistically significant factors, there were some marginally significant factors at the $p \leq 0.10$ threshold (29). Among the adjusted odds ratios Non-White race/ethnicity was negatively associated with viral suppression (OR=0.23, 95%CI: 0.03–1.10, p=0.08) (Model 1, Table 1). Among the unadjusted odds ratios Non-White race/ethnicity (OR=0.28, 95%CI: 0.05–1.12, p=0.09), education (OR=0.75, 0.52–1.03, p=0.10), and male gender (OR=0.33, 95%CI: 0.09–1.05. p=0.07) were negatively and marginally associated with viral suppression (Model 2, Table 1).

Discussion

Although there were no significant individual-level factors or interactions, there were marginally significant factors associated with viral suppression. Non-White race/ethnicity had a negative and marginally significant association with viral suppression. This finding is corroborated by other studies (5). Recent research has suggested that this disparity may be due to reduced adherence as a result of medical mistrust, and differences in prescribed regimen or setting (30). Another reason for this finding may be stigma. Previous research suggests that stigma may also play a role in reducing viral load among African Americans and Latinos causing many of them not to seek care and therefore maintain a higher viral load(31) More research is necessary to better understand the racial disparities as they relate to viral suppression among persons with HIV (30). Male gender was also negatively associated with viral suppression. Although this is not typical, some literature does corroborate this finding (6,32). Scarce research exists regarding reasoning for the gender differences in viral suppression and most literature attributes these differences to other factors such as gender-specific differences in structural support and homelessness (6,32). Education was negatively associated with viral suppression. Similar, but non-significant trends have been reported in previous literature (33,34). Studies have suggested a potential reason for the negative association between years of education completed and adherence is fear of HIV stigma among more educated persons, resulting in avoidance of HIV clinics and therefore less consistent use of medication(35). Less consistent use of medication would result in reduced viral suppression(36). This association may be due to small cell sizes in this sample. Categories of six, seven, and eight years of education only had one person per category. These small cell sizes can alter

an association(37). After removing these educational categories, education was no longer marginally associated with viral suppression. More research is necessary to further explain this trend.

In the preliminary analysis, researchers found the interaction between alcohol use disorder and education was significantly associated with viral suppression, suggesting that the effect of alcohol use disorder on viral suppression varies according to education level (or equivalently the effect of education on viral suppression varies by alcohol use disorder). An implication of this finding would be to develop more exploratory studies to determine the rationale related to the interaction's positive association with viral suppression. Education may be a significant predictor of later viral suppression because it is capturing the effect of adulthood resource disparities, which could have long-lasting health consequences (30). We also conducted a stratified analysis and recognized a negative association between alcohol use disorder and viral suppression among those with less than a high school education and recognized a slight positive association between alcohol use disorder and viral suppression among those who had a high school education or more. This suggests that alcohol use disorder is especially problematic for persons with HIV and reduced education. Neither association was significant. This interaction was removed due to collinearity with the alcohol use disorder variable as it destabilized the model and it would have been inappropriate to include in the final model(38).

A strength of this study was a diverse group of persons with HIV from the Miami-Dade area including Hispanics and Blacks; two groups most affected by HIV in the United States, as well as the inclusion of participants with multiple individual-level

factors profiles. Another strength of this study was the multiple variables available in the data, allowing assessment of how individual-level factors independently affect viral suppression while controlling for others. An additional strength of this study was the valid measures of vulnerability factors (i.e. substance use confirmed with urine samples).

Despite the strengths of this study, there were limitations. A major limitation was the small sample size. This inhibited our ability to conduct interactive analyses, which in turn limited our understanding of the association between individual-level factors and viral suppression, however, we needed to adhere to the inclusion and exclusion criteria of persons having been retained in care and having complete viral suppression data.

Conclusion

This study reports findings which indicate that male gender, Non-White race/ethnicity, and education are marginally and negatively associated with viral suppression. During the original analysis, researchers found a negative association between alcohol use disorder*education interaction and viral suppression. We also determined that alcohol use disorder is negatively associated with viral suppression among those with less than a high school education. To our knowledge, this is the first manuscript to assess viral suppression within the scope of the behavioral model for vulnerable populations. These findings may inform the development of future viral suppression interventions. Future research is necessary to explore the individual and interactive associations between individual-level factors and viral suppression.

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Tables

Table 1: Frequency Distribution for Viral Suppression Among the MASH Cohort Retained Participants in Miami-Dade, FL from 2009-2014

Variable	Non-Viral Suppressed (n=26, 50.98%)	Virally Suppressed (n=25, 49.02%)	Chi-squared/Fisher exact Test
Race/Ethnicity			0.13
White	3 (27.27%)	8(72.73%)	
Non-White	23 (57.50%)	17 (42.50%)	
Gender			0.11*
Male	20 (60.61%)	13 (39.36%)	
Female	6 (33.33%)	12 (66.67%)	
Age			0.71
≤25	1 (100%)	0 (0.00%)	
26-34	2 (40.00%)	3 (60.00%)	
35-44	11 (57.89%)	8 (42.11%)	
≥45	12 (46.15%)	14 (53.85%)	
Education			0.17
<HS	6 (40.00%)	9 (60.00%)	
HS	12 (46.15%)	14 (53.85%)	
>HS	7 (77.78%)	2 (22.22%)	
AUDIT score			1.00*
<8	17 (50.00%)	17 (50.00%)	
≥8	9 (52.94%)	8 (47.06%)	
Cocaine Use			1.00
Positive	5 (55.56%)	4 (44.44%)	
Negative	20 (48.78%)	21 (51.22%)	
Marijuana Use			0.29
Positive	7 (70.00%)	3 (30.00%)	
Negative	18 (45.00%)	22 (55.00%)	
Tobacco Frequency			0.33
0=none	13 (59.10%)	9 (40.90%)	
1=once in the last 30 days	0 (0.00%)	0 (0.00%)	
2=once per week	0 (0.00%)	0 (0.00%)	

3=3-4 times per week	0 (0.00%)	1 (100.00%)	
4=daily	0 (0.00%)	2 (100.00%)	
5=Multiple times per day	13 (50.00%)	13 (50.00%)	
Depression			0.47
Positive (CES-D score ≥16)	25 (52.08%)	23 (47.92%)	
Negative (CES-D score <16)	1 (33.33%)	2 (66.67%)	

*Indicates Chi-squared test, otherwise Fisher exact test used

Table 2: Adjusted Odds Ratio (AOR) for Viral Suppression Among the MASH Cohort Retained Participants in Miami-Dade, FL from 2009-2014

	Model 1		Model 2	
Variable	**AOR**	**95%CI**	**UOR**	**95%CI**
Depression				
CES-D Score ≥16	0.66	0.02–12.81	0.46	0.02–5.11
CES-D Score <15	Ref.		Ref.	
Marijuana Use				
Marijuana Use (+)	0.30	0.0.–1.92	0.35	0.06.–1.45
Marijuana Use (-)	Ref.		Ref.	
AUDIT Score				
AUDIT Score≥8	0.56	0.11–2.50	0.88	0.27–2.87
AUDIT Score<8	Ref.		Ref.	
Cocaine Use				
Cocaine (+)	1.22	0.18–7.79	0.76	0.17–3.28
Cocaine (-)	Ref.		Ref.	
Education (yrs)				
Education	0.75	0.45–1.14	0.75*	0.52–1.03
Age (yrs)				
Age	1.02	0.94–1.11	1.03	0.96–1.11
Race/Ethnicity				
Non-White	0.21*	0.03–1.10	0.28*	0.05–1.12
White	Ref.		Ref.	
Gender				
Male	0.34	0.05–1.75	0.33*	0.09–1.05
Female	Ref.		Ref.	
Tobacco Frequency				
Tobacco Use (1-5)	1.18		1.09	0.87–1.38
No Tobacco Use	Ref.		Ref.	

**p-value≤0.05, *p≤0.10

Supplemental Tables

Table 3: Frequency Distribution of Factors Among Virally Suppressed and Not Virally Suppressed in the MASH Cohort in Miami-Dade County from 2009-2012

(4-Day Adherence)			
Number of Factors	***Frequency (%) of category among Virally Suppressed***	***Frequency (%) of category among non-Virally Suppressed***	***Total Frequency (%) overall***
One	4 (7.84%)	0.00%	4 (7.84%)
Two	7 (13.73%)	6 (11.76%)	13 (25.49%)
Three	7 (13.73%)	12 (23.53%)	19 (37.26%)
Four	5 (9.80%)	5 (9.80)	10 (19.61%)
Five	1 (1.96%)	1 (1.96%)	2 (3.92%)
Six	1(1.96%)	0 (0.00%)	1 (1.96%)
Missing	0 (0.00%)	2 (3.92%)	2 (3.92%)

Table 4: Adjusted Odds Ratio for the Syndemic Association with Viral Suppression in the MASH Cohort in Miami-Dade County from 2009-2012

Variable	AOR	95%CI
Number of Factors		
Number of Factors	0.91	0.50–1.67
Age		
Age	1.02	0.94–1.10
Race/Ethnicity		
White	1.00	
Non-White	0.31	0.07–1.41
Gender		
Female Gender	1.00	
Male Gender	0.39	0.11–1.44

Discussion

This dissertation sought to investigate the individual-level factors' individual, syndemic, and interactive associations with the multiple stages of the HIV care continuum (retention, adherence, and viral suppression). We determined Non-Hispanic Black race/ethnicity, Black-Hispanic, and Other racial/ethnic identities were associated with increased retention among participants. This study supports previous literature which suggests that Black race is associated with reduced odds of retention when compared to other races/ethnicities and that Black Hispanic persons and persons of the Other race/ethnic group have a higher odds of retention in HIV care than their Non-Hispanic White counterparts (1-3). Several mechanisms have been offered relating to Black persons' reduced retention in HIV care. They include factors related to access (i.e. transportation and lack of qualified medical professionals within reachable distance) and psychosocial factors (i.e. stigma and medical mistrust)(4).

The interaction between depression and alcohol use disorder was negatively associated with retention. This negative interaction suggests that the negative impact of depression on retention differs by alcohol dependence. Alcohol has been determined to exacerbate the effect of depression among persons with HIV and increased depressive symptoms have been shown to reduce retention (5,6). In addition, those who abuse alcohol are at increased risk for major depression, and depression is associated with reduced retention (6,7). Recent research related to the direction of causality between alcohol use and depressive symptoms provides inconsistent results (7,8).

The interaction between age and male gender is also negatively associated with retention. The literature supports the notion that both male gender and increased age

reduce retention in care (9,10). This suggests that the negative impact of male gender on retention may be influenced by increased age (or equivalently the effect of age on retention varies by male gender). The interaction between depression and male gender yielded a positive association with retention. While both male gender and depression have been indicated to reduce retention in care among HIV positive persons, some studies indicate that there may be a higher odds of retention among males when compared to females(9-11).

The stratified analysis suggested that among those who are depressed, Non-Hispanic Blacks have a lower likelihood of being retained in care compared to the White non-Hispanic reference group than do their Black-Hispanic and Other racial/ethnic counterparts. This trend is consistent with the current literature (12,13). The reduced association of Non-Hispanic Black race/ethnicity with retention may be related to stigma within the Black community related to HIV care (14). The increased odds of retention among the Black Hispanic and other ethnic groups may be the result of bilingualism among hospital staff in the Miami-Dade location. Previous literature suggests that bilingual personnel in an HIV care facility increases clinical visits among Hispanic persons with HIV (15). Given the large Hispanic population in Miami, bilingualism is prevalent in most healthcare institutions.

In the second study, we assessed the frequency distributions of individual-level factors and their associations with adherence. Persons between the ages of 35–44, White-Hispanic persons, those without alcohol use disorder, and males had the highest percentages of short term and long-term adherence. Hispanic persons tend to have a similar adherence percentage to Non-Hispanic white persons and a higher percentage of

adherence when compared to African Americans(16) The reason the White Hispanic group had a higher percentage of adherence than the other groups in this study may be due to bilingualism which has been evidenced to improve HIV care outcomes and is generally prevalent in most Miami, Dade healthcare facilities (17). Persons who are monolingual Spanish speakers are at increased risk for poorer HIV outcomes as the linguistic barrier may make it difficult for these persons to understand healthcare materials and instructions written in another language. Bilingual staff at healthcare institutions are capable of addressing these issues(17,18). Males had a higher percentage of both short term and long-term adherence than did females; this finding is corroborated by current literature (19). Persons with high levels of adherence are older in most studies; therefore, it is consistent with the literature that the youngest group (≤25) would not have the highest percentage of adherence (20). However, we noticed that the eldest age group (≥45), did not have the highest percentage of short term or long-term adherence. Some literature does corroborate this finding as older patients with evidenced cognitive decline are likely to have poorer adherence (21,22). The trend of increased percentages of adherence among those who do not engage in alcohol abuse when compared to those who do not is consistent with current literature (23). While these percentages are not statistically significant, the tends determined in this study may aid researchers in developing an integrative intervention framework.

This study presents evidence supporting the negative association between cocaine use and short term adherence and is consistent with the general body of literature(24). A possible mechanism for this association may be neurocognitive decline developed as a result of both cocaine use and the HIV infection(25). Among those assessed for long term

adherence, we found that increased education was negatively and significantly associated with adherence. This finding is corroborated in the literature, indicating a statistically significant negative relationship between adherence and years of education completed; however, most literature which assesses the relationship between education and long term adherence generally find that reduced levels of education are associated negatively with long term retention (26,27). Studies have suggested a potential reason for the negative association between years of education completed and adherence is fear of HIV stigma among more educated persons, resulting in avoidance of HIV clinics and therefore less consistent use of medication(28). However, upon distribution analysis, we determined that a majority of persons with more than two years of education had alcohol use disorder. After removing these individuals from this education category, education was no longer associated with long term adherence. This finding suggests that a high percentage of alcohol use disorder among the few persons with more than two years of college in this sample (n= 10) may have been the cause of this association. These findings suggest that a more comprehensive study of the effect of education on adherence is warranted.

The final study assessed the association between individual-level factors and viral suppression. This study suggests that Non-White race/ethnicity, education, and male gender were marginally and negatively associated with viral suppression. Recent research has suggested that this ethnic disparity related to viral suppression may be due to reduced adherence as a result of medical mistrust, and differences in prescribed regimen or setting (29). Scarce research exists regarding reasoning for the gender differences in viral suppression and the majority of literature attributes these differences to other factors such

as gender-specific differences in structural support and homelessness (30,31). Regarding our findings related to education, similar negative, non-significant trends have been reported in previous literature (32,33). Studies have suggested a potential reason for the negative association between years of education completed and adherence is fear of HIV stigma among more educated persons, resulting in avoidance of HIV clinics and therefore less consistent use of medication(28). Less consistent use of medication would result in reduced viral suppression(34). This association may be due to small cell sizes in this sample only Those categories of six, seven, and eight years of education only had one person per category. These small cell sizes can alter an association(35). After removing these educational categories, education was no longer associated with viral suppression. More research is necessary to further explain this trend.

Researchers also determined the interaction between alcohol use disorder and education was significantly and positively associated with viral suppression, suggesting that the effect of alcohol use disorder on viral suppression varies according to education level (or equivalently the effect of education on viral suppression varies by alcohol use disorder status). An implication of this finding would be to develop more exploratory studies to determine the rationale related to the interaction's positive association with viral suppression. Education may be a significant predictor of later viral suppression because it is capturing the effect of adulthood resource disparities, which could have long-lasting health consequences (26). This interaction was removed due to collinearity (30).

Throughout each of the studies, we notice the association of race/ethnicity with each progression to each stage in the continuum. These associations suggest the need for

patient-centered care for Black persons and Non-White persons overall. Throughout the studies we also notice White-Hispanics attaining increased odds and percentages of retention and adherence. This finding may be supportive of the necessity of bilingualism in HIV care. In the final two studies, gender played an important role. Males had a higher percentage adherence, than did females, however, they had marginally significant lower odds of achieving viral suppression. More research is necessary to understand this occurrence. This finding may suggest that gender-specific assistance is necessary for the adherence and viral suppression stages of the HIV care continuum. According to the literature, improved supportive relationships may improve women's adherence, while improved health literacy could be beneficial in improving male viral suppression(29,36). In the final two studies assessing adherence and viral suppression, persons with less than a high school diploma had a higher percentage of adherent persons and a marginally higher odds of viral suppression than their more educated counterparts. Some literature has indicated that a potential reason for this is the fear of HIV stigma among more educated persons(28). While no particular substance was present as a significant variable at each stage of the HIV care continuum, the use of various substances (interactively or individually) were negatively associated with different stages of the HIV care continuum. In the first study, the alcohol use disorder*depression interaction was negatively associated with retention. In the second study cocaine use was associated with reduced short term adherence. Finally in the original analysis for the third manuscript, researchers determined a negative association between the alcohol use disorder*education interaction. These findings suggests that multiple substances may have deleterious

impacts on progression to different stages of the HIV care continuum and perhaps substance use counseling may be a necessity for persons entering treatment for HIV care.

Researchers also determined multiple interactions associated with various stages of the HIV care continuum, however, none were consistently associated with each stage of the HIV care continuum. Each interaction provides evidence for clinical implications of HIV care. The alcohol use disorder and depression interaction was significantly and negatively associated with retention. This finding provides evidence for the necessity of specialized care (counseling regarding alcohol use) for HIV positive persons who are depressed. The age and male interaction, which was also significantly and negatively associated with retention provides evidence for the necessity of specialized care among older HIV positive males. The male gender and depression interaction, which was positively associated with retention provides evidence for the necessity of patient-centered for HIV positive females who experience depressive symptoms. Although removed due to collinearity within the model, the alcohol use disorder and education interaction was positively associated with viral suppression. This provides evidence that among persons with an alcohol use disorder, those with lower education may need increased counseling related to viral suppression.

The syndemic associations were quite similar throughout the entire study. At each stage in the continuum, the majority of persons who had attained a stage in the HIV care continuum (i.e. retention, adherence, and viral suppression) were concentrated the two and three factors category. This is significant because it suggests that most persons who had progressed to each stage in the continuum had two to three vulnerability factors that could affect their health outcomes. Assessing the number of vulnerability factors an HIV

infected patient has could inform clinical practices and improve care for those with HIV. Determining a threshold or index that predicts success along the HIV care continuum, also may be useful

In sum, multiple races/ethnicities are positively associated with retention with Non-Hispanic Black race/ethnicity having the smallest association. Multiple interactions are associated with retention including depression*alcohol use disorder, age*male gender, and depression*male gender. There are also differential effects of individual-level factors on retention among stratified groups. Cocaine use is negatively significantly associated with short term adherence, while Non-white race/ethnicity and male gender are marginally associated with viral suppression. White Hispanic persons tend to have higher frequencies of both adherence and viral suppression. Collectively these studies suggests that substance use (either interactively or individually) negatively impact progression to retention and adherence. Overall these studies also suggest differential odds of progression to various HIV care continuum stages (retention and viral suppression) by racial/ethnic group. Future research is necessary to further determine the mechanism for the association between these individual level factors (ethnicity and substance use) and progression to various stages in the HIV care continuum. In the syndemic analysis for each stage of the HIV care continuum, all persons who progressed to each stage had at least two to three factors that could affect their health outcomes. Also, in the syndemic analysis, the number of factors was negatively associated with each stage. Although these associations were not significant, these trends could inform clinical practices and improve care for those with HIV.

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Conclusion

Collectively our study suggests that race/ethnicity, gender, alcohol use, substance use, and depression are individually and interactively associated with various stages of the HIV care continuum. Specifically, these findings suggest the negative association between multiple factors and retention (i.e. depression*alcohol use disorder and age*male gender). An implication of these findings is depression counseling for HIV patients who suffer from alcohol abuse disorder and alcohol use disorder screening for HIV patients who suffer from depression. Also, males may require patient coordinated care to ensure retention as they age. Findings also suggest Non-Hispanic Black persons may require improved patient care as the positive association between Non-Hispanic Black race/ethnicity and retention was the lowest when compared to other races/ethnicities. Due to small sample size, we were unable to find more specific information related to these interactions, therefore future research should assess these interactions with larger sample sizes. Cocaine use is negatively associated with short term adherence and an implication would be to include substance counseling along with adherence interventions among non-adherent persons with HIV infection. Future research should assess mechanisms that cause cocaine to be deleterious to short term adherence among PLWH. Other findings in this dissertation also indicated that male gender and Non-White race/ethnicity are marginally associated with reduced viral suppression. This suggests that future research should be focused on the mechanisms that cause this association and a clinical implication is improved patient care among Non-White and male PLWH. Throughout this dissertation race/ethnicity and gender were pertinent factors. In these studies, we notice White-Hispanics attaining increased odds and

percentages of retention and adherence. Further research should assess aspects of acculturation that may be associated with retention and adherence among White Hispanic persons. Males had a higher percentage adherence, than did females, however, they had marginally significant lower odds of achieving viral suppression. Future research should assess mechanisms responsible for gender differences in attaining various HIV care continuum milestones. Syndemic analysis revealed at each stage of the continuum, the majority of persons have two to three vulnerability factors that could alter their progress. An implication of this finding would be an in-depth assessment of patient vulnerability factors for the purpose of coordinating care specifically for each patient. This dissertation emphasizes the need for multifaceted patient centered care among PLWH as these persons are not unimodal, but rather have a multitude of factors that may affect their progression to viral suppression.

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