Using Routinely Collected EHR Data to Optimize Patient Care, Refine Clinical Care Guidelines, And Inform Healthcare Policies for Vulnerable or Low-Resource HIV Patients

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Abstract

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Despite major achievements in HIV care over the last several decades, more effort is needed to improve service delivery to low-resource and vulnerable communities. Observational data from routine clinical sources represent a source of information for optimizing HIV care in settings where large, randomized trials are not feasible, or for populations typically excluded from clinical trials. This research used observational data from the centralized iSante EHR for Haitian HIV patients enrolled in care, as well as the CFAR Network of Integrated Clinical Systems (CNICS) electronic medical records-based network which integrates clinical data from HIV-infected persons in the United States. The specific aims included: defining the association between early linkage to care and various types of substance use; determining the causal effect of extending ART (antiretroviral therapy) prescription lengths on retention in care; assessing the potential subgroup differences in the effect of increasing ART prescription length and exploring refining existing ART guidelines. We found that those with substance use entered care earlier than those who did not report substance use, extending ART intervals causes an increase in retention in care; this effect does differ across patient subgroups, though a uniform ART guideline remains appropriate. This research provided insight into how to optimize care for key populations in efforts to reach national and global HIV care benchmarks.

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Chapter 1: Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) launched 90-90-90 targets in 2014 with the aim to diagnose 90% of all HIV-positive persons, provide antiretroviral therapy (ART) for 90% of those diagnosed, and achieve viral suppression for 90% of those treated by 2020[1]. These represented challenging targets, especially for low-resource countries or areas with particularly vulnerable populations[2,3]. UNAIDS strategy outlines even more ambitious targets of 95-95-95 to be achieved by 2030. ***More work is clearly warranted to achieve these service delivery goals.*** Differentiated models of care is an evolving strategy to move past the "one size fits all" approach to care that was characteristic of earlier HIV treatment models at the start of the HIV/AIDS epidemic[4–6]. Health system challenges are no longer about finding effective treatments for HIV, but rather delivering care and treatment to those most in need, those patients for whom traditional care delivery models are not optimal and who often contribute to the ongoing HIV epidemic due to poor disease management. Health systems are also tasked with delivering services more efficiently into order to reach universal treatment at a lower cost per person, since new resources for further scaling up treatment have been flat in recent years.

Traditional care models are particularly challenging for patients with co-occurring health conditions as well as those whose health care is affected by social and non-clinical factors that hinder the ability to engage in care on a routine basis[7–9]. Substance use disorders, such as drug and alcohol dependencies, often inhibit patients from reliably seeking follow up care after HIV diagnosis or during the lifelong HIV treatment process.[10–13] In some regions, injection drug using populations represent a substantial portion of the HIV patient population and when care models are ill fitting, then clients are unable to achieve the desired state of undetectable viral load, thus limiting progress towards the 90-90-90 targets[2,14,15]. ***Patients with co-occurring substance use***

thereby signify a critical subpopulation of HIV patients that demands more research attention for improved care delivery.

In settings where increasing numbers of HIV patients are enrolled in resource-limited healthcare systems, **strategies to improve patient outcomes while also alleviating strain on care delivery systems are paramount.** Multi-month scripting (MMS) is such a strategy and is a HIV care policy becoming increasingly common in the global health arena[4,5,16]. The effectiveness of this strategy has not yet been empirically evaluated within a causal framework[5]. Does MMS contribute to improved retention by decreasing access barriers, or are patients who are more likely to be retained those who are prescribed MMS? Early studies suggest an association between MMS and increased retention in care[17], but research is needed to ascertain the causal impact of extending ART prescriptions on treatment adherence. The causal effect estimate is critical, as the positive outcomes observed in several of the reported observational studies could be due to selection bias since adherent patients are preferentially prescribed longer ART intervals.

Improving HIV treatment and care in these populations is vital for meeting 95-95-95 targets. In settings where resources are limited or for patient populations frequently excluded from clinical trials, ***research should capitalize on available health infrastructure to meet the needs of HIV patient populations where and when appropriate***. Treatment and care policies are often informed by clinical trials that are resource intensive, unsustainable, and of limited generalizability to many patient populations[8,18,19]. Using data from routine sources, such as electronic health records, provides cost efficient, accurate, and timely information for the patient population engaged in care.

SPECIFIC AIMS

Aim 1: Define the association between early entry into care and various types of substance use. HIV care remains a challenge for vulnerable populations even in higher resource settings, such as urban areas in the US. HIV patients with comorbid substance use issues are more likely to disengage from formal care systems relative to the general population[10–12,20]. This aim will assess the probability of early entry to care (enrolling in care with CD4 counts above 350 vs CD4 counts below 350) for patients with documented drug or alcohol dependencies and identify how patient characteristics of age, sex, and race effect this probability. It is hypothesized that those reporting current substance use will be linked to care with lower CD4 counts than those who do not use illicit substances or high volumes of alcohol, but this relationship may vary depending on substance type.

Aim 2: Estimate the causal effect of increasing ART prescription lengths on retention in care and define ART prescription lengths at which retention appears to be maximized. Longer ART intervals are hypothesized to increase treatment adherence by reducing the time and travel burden of treatment, thus making HIV care and ART regimens more easily integrated into the daily lives of HIV patients. This aim employs an analytic strategy to obtain a causal estimate of the effect of extending ART prescription lengths on retention in care, a proxy for treatment adherence[21]. This work will inform a population-based recommendation for an optimal ART prescription length for new ART patients in Haiti.

Aim 3: Evaluate potential heterogeneity in retention in care with increasing ART prescription lengths for specific Haitian HIV patient subgroups and determine if a targeted algorithm for optimal ART prescription intervals is preferable to a uniform, population-based strategy. Current ART treatment guidelines encourage all eligible HIV patients on ART to be put on prescription intervals longer than one month, yet most guidelines do not specify the

appropriate length of prescription intervals or inform providers if or how prescription interval lengths should vary based on patient characteristics[5]. This aim tests if the effect of extending ART prescription intervals on retention in care differs by patient subgroups and if this difference warrants specific ART prescription length recommendations based on key patient characteristics.

INNOVATION

This dissertation uses methods to yield empirically robust findings from routine clinical data sources. Aim 1 capitalizes on medical record data to characterize the timing of entry into care for an often challenging to engage patient population. Aims 2 & 3 use instrumental variable analysis to identify the causal effect of extending ART prescription intervals, a novel application of this analytic technique for evaluating the effectiveness of this differentiated care strategy.

The proposed analyses highlight the importance of creating and bolstering high quality health information systems. We use two rich EHR systems to answer the research questions of interest. The analysis will use data from the centralized iSante EHR for Haitian HIV patients enrolled in care, as well as the CFAR Network of Integrated Clinical Systems (CNICS) electronic medical records-based network which integrates clinical data from HIV-infected persons in the US. This research promotes the support of routine data sources by showcasing how these sources have clinical *and* research benefit. Investment in health information systems allows research to leverage the experience of many patients to inform clinical decisions and healthcare policies.

This research uses examples from a domestic and international setting. Although healthcare systems differ between the US and low-resource countries such as Haiti, lessons learned

in one situation may have broader applicability to other settings. The methods for assessing the proposed aims could be applied to other data systems or other regions facing similar HIV care and treatment challenges. As the 95-95-95 targets are globally focused, it is important to illustrate solutions to HIV service delivery shortcomings in a variety of contexts. It is also important to consider the levels of application to which this research can inform. This research is innovative in that it tackles key issues at the individual, group, and national levels with the goals of addressing individual care trajectories, clinical care guidelines, and healthcare policies.

CONCEPTUAL FRAMEWORK

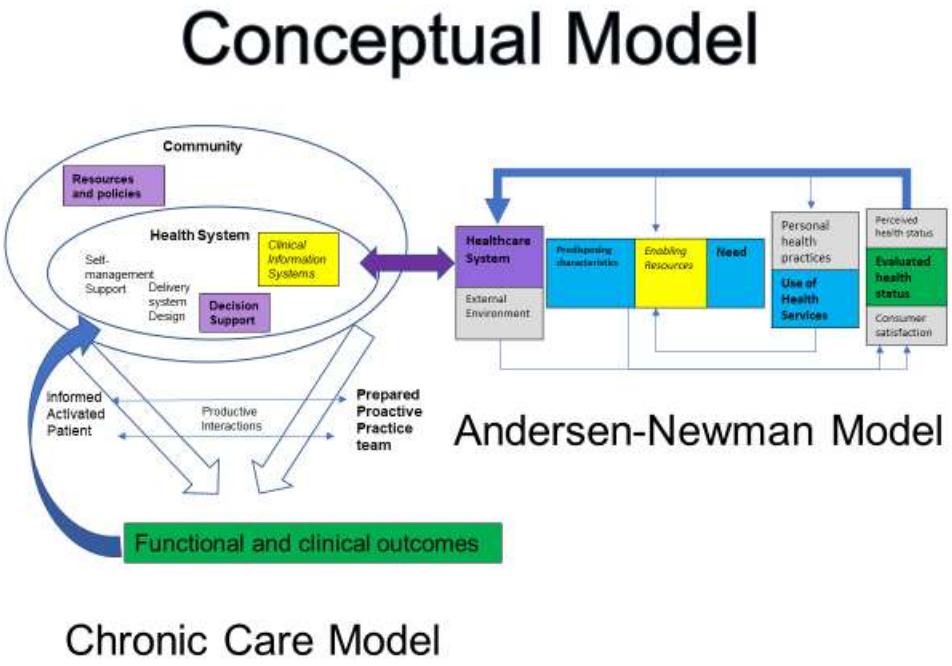


Figure 1. Conceptual Model: Chronic Care Model and Anderson-Newman Model

This research draws upon the Andersen-Newman model for healthcare seeking behavior and the Chronic Care Model for organizing care for chronic health conditions. The Andersen-Newman model posits that individual predisposing factors, such as age and gender; enabling

factors, such as financial resources or care coverage, and individual-level need characteristics, such as disease severity or comorbidity, are associated with the utilization of health care services[22,23]. This use of services, in addition to personal heath practices, contribute to both perceived and clinically measured health status[23–25]. This model, however, lacks a feedback mechanism from evaluated health status back to the healthcare system and broader environment in which individuals seek health. The research addressed in this proposal seeks to use information on individual level characteristics (blue boxes) and evaluated health outcomes (green boxes) from routine EHR systems to inform the healthcare environment with which an individual interfaces (**Aims 1 & 3**).

This research will also bridge the Andersen-Newman individual level model to the Chronic Care Model (CCM), a more population-based model of care. The CCM details how the community and healthcare system contribute to prepared and proactive practice teams that, with productive interaction with patients, promote positive functional and clinical outcomes[26–28]. The research will demonstrate how clinical outcomes observed in EHR systems can be used to optimize components of the health community and the health system (purple boxes). Specifically, this research aims to equip clinicians with enhanced decision support and health policymakers with robust information regarding specific HIV care strategies (**Aims 2 & 3**).

Capitalizing on the synergy between these two conceptual models is critical for advancing HIV care delivery. As previously noted, HIV is a life-long condition that is well-managed with good adherence to effective medication regimens, making the condition appropriate for a chronic care model[29,30]. However, there are HIV+ individuals and subpopulations for which traditional care delivery models are not working[9,31]. Since the purview of this proposal is using routine clinical data systems for refining HIV care for vulnerable or low-resource populations, the inclusion and consideration of infrastructure constraints (existing clinical information systems) and individual

level constraints (enabling or disabling resources such as access to accessory care services for substance use treatment or distance to a healthcare facility) (yellow boxes) is essential for a comprehensive model of care for these populations.

Chapter 2: Substance Use and HIV Stage at Entry into Care and Among People With HIV

INTRODUCTION

In the era of universal treatment for HIV, increasing attention has been focused on the HIV continuum of care from diagnosis to linkage and retention in care, initiation of antiretroviral therapy (ART), and achievement of HIV viral suppression[1,2]. Timely diagnosis and engagement in care are key to maximizing the benefit of ART, minimizing the long-term negative consequences of HIV, and the success of a treatment as prevention approach[32–34]. In the United States (US), it is estimated that only 86% of people with HIV (PWH) have been diagnosed, and only 64% have been linked to care[35]. Although these proportions change over time, they are well under both national and international HIV targets[2].

Traditional care models may pose challenges for PWH affected by factors that hinder the ability to engage in care on a routine basis[7–9]. Drug and alcohol use disorders often prevent PWH from reliably seeking follow-up care after HIV diagnosis or during the lifelong HIV treatment process[10–13]. In some regions, PWH who inject drugs represent a substantial portion of the HIV-infected population, to which studies have attributed ongoing HIV transmission and limited progress towards global HIV targets[2,14,15]. Research is needed to better define the challenges and optimal approaches to improve care delivery to individuals with co-occurring substance use.

Factors that have been associated with delayed HIV testing and linkage to care include younger age, Black or Hispanic race/ethnicity, lower socioeconomic status, and HIV testing without co-located HIV care services[32,34,36,37]. However, these studies are somewhat dated as testing policies have continued to evolve, and the role of substance use has been less extensively examined[10,38]. Little is known about the impact of specific substances or combinations of substances on the timing of linkage to care. Information regarding the relationship between substance use by substance type and early stages of the HIV care continuum is limited. In this study, we used comprehensive clinical data from a geographically diverse cohort of PWH to characterize the effect of specific substances and multi-substance use on the timing of entry into HIV care.

We conducted this study to identify factors among PWH in real-world settings associated with differential engagement in early steps of the HIV care cascade, particularly the impact of substance use. By examining when in their course of HIV disease PWH initiate care, we can better understand the impact of factors such as substance use on the initial HIV care cascade steps of testing and linkage. Additionally, care policies no longer target testing to high-risk groups but instead encourage HIV testing for everyone[39]. Better understanding of factors associated with entry into care, can help guide approaches and policies to improve HIV testing and linkage.

We examined the association between entry into care at earlier or later stages of HIV disease, defined by higher vs. lower CD4 counts, and substance and/or high-risk alcohol use. We hypothesized that PWH reporting current substance use would be less likely to initiate care early (at higher CD4 counts) than PWH who do not use substances or high-risk alcohol. We further hypothesized that this relationship would vary depending on substance type and frequency of use, as well as different between sociodemographic sub-groups.

METHODS

Data Source

The Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort is a longitudinal observational study of adult PWH receiving care at eight clinical sites across the US from 1995 to the present[38,40]. The CNICS cohort is geographically diverse with demographic and clinical characteristics similar to the overall population of PWH in the US[35]. Comprehensive clinical data collected through electronic medical records and other institutional data systems undergo rigorous quality assessment, are harmonized in a central repository, and are updated on a quarterly basis[40]. These data include demographic information, laboratory data, antiretroviral medication data, and diagnosis data including diabetes, hypertension, cardiovascular disease, mental illness, and substance use. Additionally, symptoms and behaviors are self-reported longitudinally by the CNICS clinical assessment of patient-reported measures and outcomes (PROs) using validated instruments including the PHQ-9 for depression[41], the AUDIT-C (Alcohol Use Disorders Identification Test) for alcohol use[42], and the ASSIST (modified Alcohol, Smoking, and Substance Involvement Screening Test) for substance use[43]. The CNICS clinical assessment of PROs are administered approximately every 6 months[44] via tablets as part of routine clinical care.

Study Population

We examined all PWH newly enrolling in HIV care in the CNICS cohort from January 1, 2010 to September 30, 2019. We included PWH enrolled in CNICS in or after 2010 in order to reflect current treatment and clinical care practices. PWH with evidence of previous HIV care prior to CNICS entry (e.g. historical ART or undetectable viral loads) were excluded. The analytic sample included PWH who completed the CNICS clinical assessment of PROs within the first 12

months of entry into care. Initiation of the clinical assessment varied across sites (median year of initiation 2011) so study period start date also varied by site.

Statistical Analysis

We conducted a cross-sectional analysis of HIV disease stage measured by CD4 count at the time of care initiation as the primary outcome of interest. Early entry into care was defined as starting clinical care for HIV with a CD4 cell count ≥350 cells/mm^3 compared to later entry into care defined by CD4 cell count <350; CD4 cut points were informed by previous research and clinical relevance[10,45–48].

Substance use, the primary predictor of interest, was obtained from PROs using the AUDIT-C and ASSIST instruments. The first AUDIT-C and ASSIST completed within the first year of care was used as a proxy of substance and alcohol use at the time of entry into care. High-risk alcohol use was defined by AUDIT-C scores of greater than or equal to 4 for men and 3 for women[49]. Methamphetamine, cocaine/crack, illicit opioid, and marijuana use were each categorized into three mutually exclusive categories: never used, past use, and current use.

Covariates of interest, including sex, age, race/ethnicity, current depressive symptoms (measured by the PHQ-9), mental health diagnoses, and CNICS site, were included in all statistical models as adjustment variables. For mental health diagnoses, we categorized PWH into one of three hierarchical groups[50]: 1) any psychotic disorder, bipolar disorder, and/or personality disorders with or without depression and/or anxiety, 2) depression and/or anxiety only, 3) no history of mental illness as documented within the first 6 months of entry into care. The HIV acquisition risk factor of injection drug use (IDU) was not included in the models due to collinearity with substances and difficulty of interpretation of substance coefficients in the presence of this variable. An indicator variable representing men who have sex with men (MSM)

was included as an HIV risk factor in the multiple substance model so that we could characterize the relationships of interest among two distinct male populations (MSM and non-MSM men) as substance use and HIV care seeking behaviors differ between these populations[51–53].

We compared the prevalence of use for each of the substances of interest at early or later initiation of care using chi square tests for categorical variables and t-tests for continuous variables. Analyses employed logistic regression models and relative risk regression models to determine factors associated with early entry into care compared to later entry into care; relative risk estimates from a generalized linear model with Poisson family and log link[54] were compared with the odds ratios obtained in the logistic regression models to aid in interpretability of associations since the outcome was common[55]. All models used robust standard errors. Analyses were completed in Stata 14 (StataCorp 2015).

Single substance models

Categorical parametrizations of substance use (never used, past use, current use) for methamphetamine, cocaine/crack, illicit opioid, and marijuana, and a binary parameterization of high-risk alcohol use (high-risk drinking vs. no high-risk drinking) were used to construct five separate, single-substance models. Additional analytic models included two-way multiplicative interaction terms for each substance of interest with age, sex, and race/ethnicity.

To address the impact of substance use frequency on the outcome, we included a second set of single substance models with measures of substance use frequency. These models included continuous variables for days of use in the last 30 days with adjustment for use of other substances (binary indicators of never/ever use for each substance).

Multiple substance model

Finally, an analytic model including all reported substances and high-risk alcohol use was evaluated to assess the impact of concurrent use of substances on entry into care. In addition to adjusting for other current substance use, a multiple substance use indicator variable was included for any combination of substances or high-risk alcohol (not for specific combinations). Previous studies have suggested that multiple substance use is common among PWH[38]. An indicator for men who have sex with men (MSM) was also included in this model.

Sensitivity analyses

Sensitivity analyses were conducted with: 1.) other CD4 cut points (e.g. 500 cells/mm^3), 2.) adjustment for other factors of interest that may potentially impact the relationship under examination such as year of entry into CNICS, enrollment in substance use treatment programs, hepatitis C virus coinfection, and other comorbidities (e.g. ADI, diabetes, hypertension, etc.), 3.) linear regression models with continuous CD4 as the outcome, and 4.) models that varied the PRO window of eligibility. We also conducted a stratified analysis by HIV risk factors (MSM, IDU, heterosexual sex, or other/unknown; MSM who were also IDU were categorized into the MSM risk factor group) to assess the relationship between substance use and early entry into care for these specific populations.

RESULTS

Among 5,017 PWH who enrolled in care from January 2010 through September 2019, the majority were male (86%) with a mean age of 40 years (standard deviation (SD): 12). Mental health diagnoses and past or current substance use were more prevalent than reported within the general US population[56]. As shown in Table 1, demographic characteristics and substance use varied by early or later entry into care in unadjusted analyses.

In the single substance models, we found a significant association between current methamphetamine use (OR=1.52, 95% Confidence Interval (CI): 1.23 – 1.88; RR=1.14, 95% CI: 1.07 – 1.22), as well as past and current cocaine and past and current marijuana use (ORs= 1.20, 1.43, 1.19, 1.33, respectively; RRs=1.07, 1.13, 1.07, 1.12) and increased likelihood of early entry into care (CD4 count $\geq$350 cells/mm^3) compared with PWH who reported no use of those substances. Associations between early initiation into care and past methamphetamine use, past and current illicit opioid use, and high-risk alcohol consumption were not statistically significant (Table 2).

Results of single substance models that included two-way interaction terms for each substance with age, sex, and race/ethnicity produced similar effect estimates for each specific substance and none of the interaction terms in any of the models were statistically significant (data not shown), demonstrating no effect modification for any substance by demographic characteristics.

In single substance models including measures of substance use frequency within the last 30 days, we found no statistically significant effects of larger frequency of substance use on early entry into care compared to lower frequency of use. There did not appear to be a strong dose response relationship between substance use and early care entry for any of the substances (Table 3).

In the model that included all substances, the statistically significant relationships between early entry into care and current methamphetamine, cocaine/crack, and marijuana use remained and the magnitude of the associations did not change; after accounting for use of other substances, current methamphetamine (OR=1.52, 95% CI: 1.16 – 1.98; RR=1.14, 95% CI: 1.05 – 1.23), cocaine (OR=1.44, 95% CI: 1.07 – 1.93; RR=1.12, 95% CI: 1.02 – 1.23), and marijuana (OR=1.27,

95%CI: 1.04 – 1.53; RR=1.09, 95% CI: 1.02 – 1.18) use were associated with earlier entry into care compared to PWH who did not use these substances in adjusted analyses. Past use of any of the substances was no longer associated with timing of care entry when controlling for use of the other substances and high-risk alcohol use (Table 4).

In the full model, we found a significant association between older age, male with no reported sex with men, Black race, and Hispanic ethnicity and lower likelihood of early entry into care. Men who have sex with men were more likely to enter care with higher CD4 counts than men who did not report same-sex sexual relationships. Those with mental health diagnoses were more likely to enter care early than those without mental health diagnoses. Current depressive symptoms were not independently associated with early care initiation when controlling for the other covariates. (Table S1)

Sensitivity analyses using different specifications of the outcome variable and inclusion of additional comorbidity and adjustment covariates yielded similar results to the models described above (data not shown). Variation of the time window in which a PRO assessment was attributed to baseline substance use and alcohol consumption also did not affect the results. Patterns in the associations between substance use and early entry into care were also similar in analyses stratified by HIV risk factor (MSM, IDU, heterosexual sex) (Tables S2-S4); the magnitude of associations in the smaller risk factor groups (IDU and heterosexual sex) were similar to those in the main analyses, however due to small sample sizes the confidence intervals were wide and the effect measures for the substances did not achieved statistical significance except for past use of marijuana and illicit opioids among the heterosexual risk group (Table S4).

DISCUSSION

Contrary to our hypotheses, we found that PWH who reported current methamphetamine, cocaine/crack, or marijuana use were more likely to enter care at an earlier stage of HIV disease than those who did not report use of these substances. However, the magnitude of the observed effects was modest. We did not find an association between illicit opioid or high-risk alcohol use and stage of disease at entry into care. Reported associations between early entry into care and substance or high-risk alcohol use did not differ by demographic characteristics, including age, sex, and race/ethnicity, nor by HIV risk factor.

A possible explanation for our findings is that HIV testing continues to be targeted to persons at higher risk of HIV infection, such as those with certain substance use disorders[51,57], and that recommendations for universal testing for HIV have not been fully adopted in clinical practice[39]. People who report substance use may be more likely to be tested for HIV than those who do not report these behaviors[51,58,59], and more frequent testing can lead to earlier diagnosis of HIV and entry into care. This trend towards selective testing could be driven in part by self-selection by individuals with known HIV risk factors as education regarding high-risk behaviors can increase motivation for testing[51,57,60], and by clinicians who may be reluctant to routinely test all patients for HIV due to lack of awareness of newer testing guidelines or perceived capacity to integrate routine testing into practice[59].

In addition, substance use may increase engagement with the health care system due to exacerbation of underlying health conditions, overdose, injuries related to impairment [61–63], and/or substance use treatment, that provide more opportunities for testing and care initiation. Previous studies have found an association between physical health comorbidities and substance use[61,63], which may prompt greater interaction with the health care system. While we controlled for hypertension, diabetes, and hepatitis C coinfection in sensitivity analyses, there may be additional

health conditions that influence early entry into care in our study that we did not take into account. Additionally, clinical outreach programs targeting people who are homeless may bring certain subsets of people into clinical settings at earlier HIV disease stages, and the relationship between homelessness and substance use is well-established[64]..

There are limitations of this study. We were interested in examining factors associated with entry into care and therefore excluded PWH with documented evidence of prior treatment. However, there is the possibility of misclassification if evidence of prior treatment was not well-documented. Second, detailed substance use information was obtained from the CNICS clinical assessment of PROs, and not all PWH have PRO assessments within the first year of care. This could result in potential for selection bias if those with substance or alcohol use disorders and lower CD4 counts were less likely to receive PRO assessments systematically across CNICS clinics. However, sensitivity analyses using varying time windows for PRO completion, including18 and 24 months, found very similar results, reducing our concern about selection bias. Additionally, PROs are only available in English, Spanish, and Amharic, so not all PWH may have been able to complete a PRO in their preferred language. Third, the timing of starting PRO assessment at sites varied so not all sites contributed participants throughout the entire study period. Fourth, the prevalence of illicit opioid use in the CNICS cohort is low, so non-significant results between illicit opioid use and stage of entry into care may, in part, be due to power issues. Finally, findings may not generalize to other treatment contexts as a large proportion of PWH in the CNICS cohort live in urban and suburban settings.

This research has notable strengths too, including detailed substance use information using validated instruments collecting current and past substance use; demographic, clinical, and geographic diversity; and data reflecting clinical practice in the current treatment era.

This study provides insight as to the impact of specific substance use, as well as high-risk alcohol, on the HIV stage at which a person enters care for HIV. Early entry into care among PWH who use substances suggests that HIV testing may still be differentially offered to people with known HIV risk factors in routine care and in targeted outreach, and that individuals with substances use disorders may be more likely to be tested and linked to care due to increased interactions with the healthcare system. It is likely that a combination of factors is driving the associations we observed. Our findings also indicate that there is room for improvement in testing and linkage to care overall and in particular among those without documented risk factors for HIV.

TABLES

Table 1. Demographic and clinical characteristics including substance use of PWH in this study categorized by CD4 count at enrollment in care.

PWH Characteristics	Overall (N=5,017)	HIV Severity		
		CD4<350 cells/mm^3 (N=1,945)	CD4≥350 cells/mm^3 (N=3,072)	P-value*
Age in years, mean (SD)	40.2 (11.9)	40.9 (11.7)	39.2 (12.1)	<0.01
Male, N (%)	4,333 (86.4)	1,669 (85.8)	2,664 (86.8)	0.35
Race, N (%)				<0.01
White	2,149 (42.8)	378 (37.9)	1,411 (45.9)	
Black	1,670 (33.3)	748 (38.5)	922 (30.0)	
Hispanic	850 (16.9)	336 (17.3)	514 (16.7)	
Other	348 (6.9)	123 (6.3)	225 (7.3)	
Mental Health Diagnoses, N (%)				<0.01
No mental health diagnoses	2,747 (54.8)	1,153 (59.3)	1,594 (51.9)	
Depression and/or anxiety only	1,801 (35.9)	634 (32.6)	1,167 (38.0)	
Psychosis, bipolar, personality disorders (with or without depression and/or anxiety)	469 (9.4)	158 (8.1)	311 (10.1)	
Methamphetamines/crystal				<0.01
Never used	3,136 (64.6)	1,299 (69.4)	1,837 (61.6)	
Past use	1,142 (23.5)	140 (21.9)	732 (24.6)	
Current use	576 (11.9)	164 (8.8)	412 (13.8)	
Cocaine/Crack				<0.01
Never used	2,678 (54.7)	1,123 (59.3)	1,555 (51.8)	
Past use	1,809 (36.9)	639 (33.7)	1,170 (39.0)	
Current use	410 (8.4)	133 (7.0)	277 (9.2)	
Marijuana				<0.01
Never used	1,461 (29.8)	645 (33.8)	816 (27.2)	
Past use	1,666 (34.0)	637 (33.4)	1,029 (34.4)	
Current use	1,775 (36.2)	624 (32.7)	1,151 (38.4)	
Illicit Opioids				0.02
Never used	3,832 (82.8)	1,477 (84.8)	2,355 (81.7)	
Past use	645 (13.9)	217 (12.5)	428 (14.8)	
Current use	149 (3.2)	48 (2.8)	101 (3.5)	
High-risk Alcohol Consumption				0.01
High-risk drinking	3,859 (78.1)	1,530 (80.0)	2,329 (77.0)	
No high-risk drinking	1,080 (21.9)	383 (20.0)	697 (23.0)	
HIV Risk Factor				
Men who have Sex with Men (MSM)	3,222 (64.2)	1,182 (60.8)	2,040 (66.4)	<0.01
Injection Drug Use (IDU)	557 (11.1)	207 (10.6)	350 (11.4)	0.41
Heterosexual	1,008 (20.1)	465 (23.9)	543 (17.7)	<0.01

*Comparing PWH populations with CD4<350 and CD4≥350 cells/mm^3.

Table 2. Associations between substance use and early entry into care[1] (individual models for each substance) in adjusted analyses[2]

Substance	OR	P-value	95% CI	RR	P-value	95% CI
Methamphetamines (ref. Never used)						
Past use only	1.09	0.29	0.93 – 1.27	1.03	0.28	0.98 – 1.09
Current use	*1.52*	*<0.01*	*1.23 – 1.88*	*1.14*	*<0.01*	*1.07 – 1.22*
Cocaine/Crack (ref. Never used)						
Past use only	*1.20*	*0.01*	*1.05 -1.37*	*1.07*	*0.01*	*1.02 – 1.12*
Current use	*1.43*	*<0.01*	*1.14 – 1.79*	*1.13*	*<0.01*	*1.05 – 1.22*
Marijuana (ref. Never used)						
Past use only	*1.19*	*0.02*	*1.03 – 1.38*	*1.07*	*0.02*	*1.01 – 1.14*
Current use	*1.33*	*<0.01*	*1.14 – 1.55*	*1.12*	*<0.01*	*1.05 – 1.19*
Illicit Opioids (ref. Never used)						
Past use only	1.12	0.22	0.93 – 1.34	1.03	0.22	0.98 – 1.10
Current use	1.22	0.28	0.85 – 1.74	1.07	0.25	0.95 – 1.20
High-risk Alcohol Consumption (ref. No high-risk drinking)						
High-risk drinking	1.12	0.11	0.97 – 1.30	1.04	0.12	0.99 – 1.10

[1] Early entry into care define as entering care with CD4 counts $\geq$ 350 cells/mm^3
[2] All models adjusted for sex, age, race/ethnicity, current depressive symptoms, mental health diagnoses, and treatment site

Table 3. Single-substance models with frequency of use within the past 30 days and association with early entry into care[1,2].

Substance[3]	OR	P-value	95% CI	RR	P-value	95% CI
Methamphetamines	1.10	0.24	0.94 – 1.30	1.03	0.22	0.98 – 1.07
Cocaine/Crack	0.87	0.31	0.67 – 1.14	0.96	0.36	0.87– 1.05
Marijuana	0.94	0.12	0.87 – 1.02	0.98	0.11	0.95– 1.00
Illicit Opioids	0.80	0.16	0.58– 1.10	0.93	0.19	0.83 – 1.04
Alcohol	1.00	0.80	0.97 – 1.02	1.00	0.82	0.99 – 1.00

[1] Early entry into care define as entering care with CD4 counts $\geq$350 cells/mm^3
[2] All models adjusted for sex, age, race/ethnicity, current depressive symptoms, mental health diagnoses, treatment site, and use of other substances
[3] Substances are measured by days of use within the past month (range 0-30).

Table 4. Associations between substance use and early entry into care[1] in adjusted analyses[2,3]

Substance	OR	P-value	95% CI	RR	P-value	95% CI
Methamphetamines (ref. Never used)						
Past use only	0.96	0.67	0.79 – 1.16	0.99	0.69	0.92 – 1.05
Current use	*1.52*	*0.00*	*1.16 – 1.98*	*1.14*	*<0.01*	*1.05 – 1.23*
Cocaine (ref. Never used)						
Past use only	1.15	0.10	0.97 – 1.37	1.05	0.10	0.92 – 1.12
Current use	*1.44*	*0.02*	*1.07 – 1.93*	*1.12*	*0.01*	*1.02 – 1.23*
Marijuana (ref. Never used)						
Past use only	1.10	0.27	0.92 – 1.30	1.04	0.23	0.98 – 1.11
Current use	*1.27*	*0.02*	*1.04 – 1.53*	*1.09*	*0.01*	*1.02 – 1.18*
Illicit Opioids (ref. Never used)						
Past use only	1.04	0.73	0.85 – 1.27	1.01	0.79	0.94 – 1.08
Current use	1.02	0.94	0.68 – 1.53	1.00	0.95	0.89 – 1.14
High-risk Alcohol Consumption (ref. No high-risk drinking)						
High-risk drinking	1.17	0.12	0.96 – 1.42	1.05	0.12	0.99 – 1.23

[1] Early entry into care define as entering care with CD4 counts $\geq$350 cells/mm^3
[2]All substances included in the same analytic model
[3] All models adjusted for sex, age, race/ethnicity, MSM, current depressive symptoms, mental health diagnoses, and treatment site

Supplementary Table 1. Associations[1] between PWH Characteristics and Early Entry into Care[2]

Substance	OR	P-value	95% CI	RR	P-value	95% CI
Male, Not MSM (ref. Female)	0.68	<0.01	0.54- 0.85	0.86	0.01	0.79- 0.94
MSM	1.33	<0.01	1.14-1.56	1.12	<0.01	1.05- 1.19
Age	0.99	0.01	0.98-0.99	0.99	0.01	0.99- 0.99
Race/ethnicity (ref. White)						
Black	0.80	0.01	0.67-0.94	0.92	0.01	0.86 – 0.98
Hispanic	0.79	0.01	0.66 – 0.95	0.92	0.02	0.86-0.98
Current depressive symptoms (PHQ-9 Score)	0.96	0.11	0.90- 1.01	0.98	0.12	0.97- 1.0
Mental Health Diagnosis (ref. No Mental Health Diagnosis)						
Depression and/or Anxiety	1.26	<0.01	1.09 -1.46	1.09	<0.01	1.03-1.15
Any psychotic, bipolar, or personality disorder	1.42	0.01	1.10 -1.82	1.13	<0.01	1.04- 1.22

[1] Adjusted for all substances and treatment site

[2] Early entry into care define as entering care with CD4 counts ≥350 cells/mm^3

Supplementary Table 2. Associations between substance use and early entry into care[1] (individual models for each substance) in adjusted analyses[2] among those with Men who have Sex with Men HIV acquisition risk factor

Substance	OR	P-value	95% CI	RR	P-value	95% CI
Methamphetamines (ref. Never used)						
Past use only	1.12	0.24	0.93 – 1.35	1.04	0.23	0.98 – 1.11
Current use	*1.52*	*<0.01*	*1.16 – 1.98*	*1.14*	*<0.01*	*1.05 – 1.22*
Cocaine/Crack (ref. Never used)						
Past use only	*1.21*	*0.03*	*1.02-1.43*	*1.07*	*0.03*	*1.01– 1.13*
Current use	*1.36*	*0.04*	*1.02 – 1.81*	*1.11*	*0.03*	*1.01 – 1.21*
Marijuana (ref. Never used)						
Past use only	1.05	0.609	0.87 – 1.27	1.02	0.58	0.95 – 1.10
Current use	*1.26*	*0.02*	*1.04 – 1.52*	*1.09*	*0.02*	*1.01 – 1.16*
Illicit Opioids (ref. Never used)						
Past use only	1.17	0.20	0.92 – 1.51	1.05	0.19	0.98 – 1.13
Current use	1.39	0.25	0.79 – 2.47	1.11	0.20	0.95 – 1.30
High-risk Alcohol Consumption (ref. No high-risk drinking)						
High-risk drinking	1.15	0.11	0.97 – 1.38	1.05	0.11	0.99 – 1.11

[1] Early entry into care define as entering care with CD4 counts $\geq$ 350 cells/mm^3
[2] All models adjusted for age, race/ethnicity, current depressive symptoms, mental health diagnoses, and treatment site

Supplementary Table 3. Associations between substance use and early entry into care[1] (individual models for each substance) in adjusted analyses[2] among people with injection drug use HIV acquisition risk factor (IDU)

Substance	OR	P-value	95% CI	RR	P-value	95% CI
Methamphetamines (ref. Never used)						
Past use only	1.26	0.42	0.71 – 2.19	1.06	0.54	0.87 – 1.29
Current use	1.83	0.06	0.99– 3.40	1.20	0.08	0.98 – 1.48
Cocaine/Crack (ref. Never used)						
Past use only	1.00	0.99	0.61-1.67	0.99	0.94	0.84– 1.18
Current use	1.24	0.54	0.63 – 2.41	1.07	0.50	0.87 – 1.33
Marijuana (ref. Never used)						
Past use only	1.18	0.56	0.68 – 2.05	1.06	0.59	0.87 – 1.29
Current use	1.19	0.54	0.67- 2.12	1.06	0.55	0.87 – 1.30
Illicit Opioids (ref. Never used)						
Past use only	0.79	0.27	0.51 – 1.20	0.91	0.24	0.79 – 1.06
Current use	1.21	0.57	0.63 – 2.30	1.06	0.53	0.88 – 1.28
High-risk Alcohol Consumption (ref. No high-risk drinking)						
High-risk drinking	1.09	0.72	0.68 – 1.74	1.04	0.66	0.88 – 1.22

[1] Early entry into care define as entering care with CD4 counts $\geq$ 350 cells/mm^3
[2] All models adjusted for sex, age, race/ethnicity, current depressive symptoms, mental health diagnoses, and treatment site

Supplementary Table 4. Associations between substance use and early entry into care[1] (individual models for each substance) in adjusted analyses[2] among those with heterosexual sex HIV acquisition risk factor

Substance	OR	P-value	95% CI	RR	P-value	95% CI
Methamphetamines (ref. Never used)						
Past use only	1.17	0.45	0.76 – 1.80	1.06	0.49	0.89 – 1.27
Current use	1.93	0.15	0.78– 4.73	1.25	0.11	0.95 – 1.65
Cocaine/Crack (ref. Never used)						
Past use only	1.27	0.14	0.92-1.75	1.10	0.16	0.96– 1.27
Current use	1.13	0.66	0.65 – 1.97	1.05	0.67	0.84 – 1.32
Marijuana (ref. Never used)						
Past use only	*1.60*	*<0.01*	*1.17 – 2.18*	*1.23*	*<0.01*	*1.07 – 1.41*
Current use	1.38	0.07	0.98- 1.94	1.16	0.06	0.99 – 1.35
Illicit Opioids (ref. Never used)						
Past use only	*2.13*	*0.01*	*1.23 – 3.70*	*1.32*	*<0.01*	*1.11 – 1.57*
Current use	0.64	0.39	0.24 – 1.74	0.81	0.53	0.50 – 1.32
High-risk Alcohol Consumption (ref. No high-risk drinking)						
High-risk drinking	098	0.88	0.70 – 1.37	0.99	0.89	0.85 – 1.15

[1] Early entry into care define as entering care with CD4 counts $\geq$ 350 cells/mm^3
[2] All models adjusted for sex, age, race/ethnicity, current depressive symptoms, mental health diagnoses, and treatment site

Chapter 3: Estimating the Effect of Increasing Prescription Intervals on Retention in Care for HIV Patients

INTRODUCTION

The last several decades have seen great strides in therapeutic regimens for HIV, leading to improved survival and quality of life for HIV patients[65,66]. However, achieving optimal health status at the population level requires both excellent therapeutic options as well as effective delivery models. These issues of care delivery are especially salient for vulnerable populations and low-resource settings where managing an increasing number of people living with HIV and addressing high rates of attrition at all stages along the care continuum is particularly challenging[16]. Managing HIV patient care during crises such as global pandemics involve even more challenges.

The differentiated care approach has emerged as a promising way to address the challenges of providing effective ART treatment for individuals with HIV[31,67]. One differentiated care strategy is to increase the prescription length, number of days of medication supplied, of ART for stable patients from previously standard 1-month medication dispenses. This strategy has been promoted within PEPFAR programs since 2016 and shows great promise[4,5,16]. Increased prescription intervals, also known as multi-month scripting (MMS), are intended to increase treatment adherence by reducing the amount of disruption to patients' everyday lives[4,31,68]. Additionally, in settings where increasing numbers of HIV patients strain resource-limited healthcare systems, strategies to improve patient outcomes while also reducing the burden on care delivery systems are paramount. MMS, by definition of the longer prescription intervals, requires fewer human resources than the standard of care (shorter dispense lengths of one to three months in many contexts) due to reduced interactions between patients and the healthcare delivery system. If longer prescription intervals improve patient outcomes compared to the standard of care, or is

at least non-inferior, MMS presents an opportunity to maintain patient care quality, while decreasing the resources needed to sustain HIV care programs.

The effectiveness of MMS, or extending prescription interval length, in routine settings has not been empirically evaluated within a causal framework[5]. Studies suggest an association between MMS and increased retention in care[17,69], but additional research is needed to ascertain the causal impact on treatment adherence, especially outside the context of randomized-trials. The question remains whether longer prescription lengths lead to better retention due to its increased convenience for patients or are people selected for longer intervals those mostly likely to be adherent. Existing studies of MMS effectiveness using routine data are limited by selection bias – patients given longer prescription interval lengths are those who are believed to be stable and to have a high likelihood of succeeding. This study employs a statistical approach designed to address inherent selection bias in ART prescription lengths and estimate a causal effect of increasing prescription intervals for new ART patients.

Historically, HIV treatment guidelines and HIV care policies were derived from clinical trial data[18,19,70]. However, clinical trials are expensive, time intensive, and often of limited generalizability to vulnerable populations as these populations are difficult to recruit into research studies[18,71,8]. For resource constrained settings or for populations not represented in the clinical trial literature, observational data from routine clinical sources represent a source of information for optimizing HIV care based on empirical trends[72,73]. The current study uses an existing, robust clinical data system to evaluate this strategy at national level.

The current COVID-19 pandemic makes it more imperative to investigate the causal effect of extending ART prescription intervals. Reducing interactions with the healthcare system helps minimize COVID-19 exposure for both clinical providers and patients, HIV patients with low CD4

counts and not yet on ART potentially representing a high-risk group for COVID-19 morbidity and mortality due to compromised immune systems[74]. However, the risk of COVID-19 exposure for patients must be weighed against the risk for increased opportunity for HIV care attrition if ART prescription intervals are maximized. Evaluating the impact of longer ART prescription intervals on retention is now more critical than ever.

This study provides a novel and timely contribution to literature regarding the impact of this specific differentiated care strategy and how this strategy may be best applied to a HIV patient population in Haiti. This information is vital for Haitian policy makers who wish to estimate the effect of this strategy as well as for policy makers from other settings who are considering adopting this strategy as a part of their HIV strategic planning or COVID-19 response. Our study estimates the causal effect of increasing ART prescription lengths on retention in care and provides evidence for prescription lengths at which retention appears to be maximized.

METHODS

Data source

This study used the iSante HIV-specific electronic health record (EHR) data from Haiti. iSanté supports retrospective data entry from forms used in the clinic as well as interactive, point-of-care use[75,76]. iSante is a networked system of longitudinal clinical encounter data used in more than 100 health facilities where HIV care and treatment are available to Haitian HIV patients[77]. iSante includes information about patient demographics, laboratory history/results, diagnosis history, treatment history, and pharmacy records, as well as data fields for counseling and referrals recieved[75,78]. All records from health facilities with out-of-date data, defined as having less than

90% of patient visit forms saved to the iSante consolidated server within 90 days of the patient's visit[77], were excluded from the analysis for data quality control purposes.

Inclusion criteria

Our sample included ART-naïve HIV patients enrolled in iSante who started ART on or after January 1st, 2017 and could have been followed for 13-months (to assess 1-year retention with a 30-day grace period) after their initial ART dispense. In 2016, Haiti updated its County Operational Plan to include guidelines that encouraged all eligible patients to be put on MMS regimens instead of standard 1-month medication dispenses[79]. Patients were included after the full 2016 calendar year to account for delays in guideline implementation across facilities nationally. Patients on any ART regimen (first, second, or third line) were included in the analysis; patients who never started ART were excluded.

Variables

Haitian ART guidelines during this time period encouraged MMS after patients were demonstrated to be stable on ART for 6 months[79], but in practice MMS was often used before 6 months as evidenced in the EHR data. The primary exposure was ART prescription length in days, as obtained from pharmacy records. To assign patients' exposure status, we calculated the average prescription length over the first 6 months of treatment and applied that as their prescription length of interest. Initial prescription lengths may be significantly shorter than subsequent ones as clinicians may test patient tolerability to specific ART drugs and monitor for evidence of toxicity[80]. We chose not to classify the exposure based on the interval for dispense most immediately preceding the 6-month point as attrition early in treatment can be high[77] and we wanted to estimate

the effect of increasing prescription length on retention among a more representative sample of new ART patients.

The outcome of interest for this study was a binary measure of retention in care (retained vs. not retained). Retention in care, or timely ART pickup, was defined picking up an ART prescription within 30 days of the scheduled ART pickup after one year in treatment (12-month follow-up). Retention in care was used as a proxy for treatment adherence[21], and therefore viral suppression[10], for this study. iSante does include information on laboratory values for HIV viral load, yet viral load testing is not consistent in clinical practice in Haiti and viral load tests are often backlogged at national labs in low-resource countries[81]. Although viral suppression is the gold standard for treatment success[1,10,82], this variable in the Haitian context was less desirable due to a high level of missing data.

Patient characteristics of sex, age, World Health Organization (WHO) stage, Body Mass Index (BMI) category, and isoniazid (TB treatment and prevention medication) at ART initiation were included in all models, in addition to a categorical variable for facility ownership (public, private, and mixed) and facility network. The WHO stage and BMI category variables included a "missing" indicator if there was insufficient evidence in the medical record to ascertain these characteristics, but complete information existed for the other key demographics, as well as exposure and outcome variables.

Data analysis

To estimate the causal impact of MMS, or prescription length, on retention in care, we employed an instrumental variable (IV) analysis using a 2-stage residual inclusion (2SRI) approach for non-linear models[83,84]. IV analysis is used to account for unmeasured confounding

by using a variable called an instrument that isolates the average direct effect of the treatment or exposure variable on the outcome, independent of the unobserved sources of variability that may also be associated with exposure.

The instrumental variable approach was used to address potential patient selection into specific prescription lengths given that MMS is a treatment strategy that is not randomly applied to patients; patient characteristics likely drive whether a patient gets MMS and therefore the length of the ART interval. Further, MMS is patient-centered by design[4,5,31] so the we would expect patient characteristics to determine "exposure" to this strategy. However, we do not yet know the direction in which unobserved patient characteristics effect the likelihood of exposure to MMS or the influence of these characteristics on the relationship of MMS and health-related outcomes like ART retention. Instrumental variables allow us to estimate the causal effect of MMS on outcomes in the presence of this non-random assignment to treatment strategies.

The instruments used were the mean and standard deviation of a facility's ART prescription length for new ART patients within the 6-month window in which the patient received their initial ART prescription. Average prescription intervals (for all HIV patients treated at that facility) do vary significantly across facilities represented in the iSante database. We checked the balance of measured patient-level covariates across levels of the instruments and assessed the strength of the instruments in predicting ART prescription length in the first stage model.

Standardized residuals from the first stage treatment model were included in the second stage outcome model along with squared terms for both the residuals and exposure variables to improve model fit. Bootstrapping with 1,000 iterations was conducted to achieve valid standard errors with the 2-stage models. We assessed the goodness-of-fit of the second stage outcome model using the Pearson correlation test to assess any linear relationship between the raw-scale

predictions and residuals and the Hosmer-Lemeshow test in which we plotted mean residuals across deciles of Xβ to determine if there were any systematic patterns in the residuals[85].

We calculated the marginal effects on one-year retention of increasing current, observed prescription lengths by 30 days with 95% confidence intervals (Figure 1). In addition, we graphed the probabilities of retention from the adjusted model at the observed prescription lengths of 10-180 days, as well as predicted probabilities of retention if current prescription intervals were increased (Figure 2).

RESULTS

Our analyses are based on the experience of 21,880 patients. The majority of patients were female (61.2%), between 25-54 years of age (73.4%), and of normal BMI (46.9%). Approximately half of the patients were treated with Isoniazid for TB management and most were classified as WHO stage 1 or 2 (early HIV/AIDS stages) at ART initiation. The average ART prescription length was 42.5 days with range of 6-192 days. (Table 1)

Patient level covariates were balanced between the instrument levels when the instruments were bifurcated at their medians. The instruments improved balance between the patient level covariates compared to the treatment variable of ART prescription lengths, suggesting these instruments are valid in this setting. The instruments were also strong in the first stage models; highly predictive of individual ART prescription length. The second stage, or outcome model, performed well on diagnostic goodness-of-fit tests.

We found that longer ART prescription lengths for ART naïve patients increase the probability of retention at 12-months after treatment initiation. The marginal effect of increases to prescription lengths was greatest for shorter prescription lengths, particularly for prescription

lengths of 60 days or less, though the effect persisted until approximately 110 days. Figure 1 presents the marginal effects on retention of increasing prescription lengths by 30 days (i.e. comparing retention outcomes if those on 60-day prescription intervals were moved to 90-day intervals). Estimates above the zero-line indicate an improvement (increase) to retention compared to shorter prescription lengths by 30-days; estimates below the zero-line indicate detriment (decrease) to retention compared to shorter prescription lengths. We observed gains to retention until approximately 4-months (110 days), at which point, the benefits to retention appears no longer statistically significant. Increasing prescription lengths for those already receiving 150-day prescriptions lengths or longer was demonstrated to have a potentially negative effect on the probability of retention. (Figure 1)

For observed ART prescription lengths, we noted that probability of retention in the adjusted models was highest among those with prescription lengths of 120 days, with the steepest increases to retention occurring between prescriptions of 10-90 days (blue line in Figure 2). When we added the marginal effects of a 30-day prescription increase to the probability of retention at observed prescription lengths, we see a significant improvement to retention for those currently receiving prescriptions less approximately than 135 days. After 135 days, there appears to be no significant additional benefits to retention if prescription lengths are increased. For patients already receiving prescription lengths of 135 days or longer, there appears to be a *decrease* in the probability of retention if prescription lengths are increased, though there is not enough evidence to rule a true negative (or positive) effect due to insufficient power at the right tail of the prescription length distribution of this population.

DISCUSSION

Based on a synthesis of our findings, it appears that prescription lengths of 3-4 months for new ART patients may result in the highest probability of retention at 12-months. The most significant gains to retention occur with increases to ART prescription length for current prescription lengths less than 90 days. We estimated the marginal effect of increasing prescription length by 30 days to be beneficial (higher likelihood of retention) until approximately 4 months. We conclude that increasing ART prescription lengths for new ART patients who would receive prescriptions up to 135 days shows a clinical benefit in terms of retention in care after 1-year of treatment.

Many current guidelines recommend waiting until 6 months of treatment before starting patients on MMS regimens[70,79], yet our findings suggest a clinical benefit to starting longer prescription lengths soon after ART initiation for clinically stable patients where the potential of ART toxicity has been ruled out. Other studies assessing MMS have used enrollment in treatment for 6 months as an inclusion criteria[31,69], as this is noted in some country guidelines for MMS[79]. However, we felt that this does not address the fact that ART attrition can be quite high in the beginning stages of treatment[77]; iSante records indicate that many facilities do not wait until 6 months to employ longer ART prescription intervals for many patients .

The ability to interpret estimates from an IV regression as causal hinges on the strength of the instrument(s) employed in the analysis. The chosen instruments in this study performed well in routine assessments of IV strength. Additionally, pharmacy records in iSante, which determined ART prescription lengths, are highly reliable[86] and not subject to large errors in measurement. Regional (or facility) rates of a procedure or medical practice have been used as valid instruments in other studies using instrumental variable analysis to assess the casual effect of medical treatments[87]. A possible limitation is that these instruments could be associated with the outcome

of retention on ART for reasons other than choice of exposure (prescription length). If facilities that report higher rates of MMS are also facilities that are more patient-centered or sensitive to patient needs, a hallmark of the MMS strategy, this may increase patient retention in care regardless of ART interval length.

There are a few additional limitations to our study. We included patients for whom we had complete data for our variables of interest (outcome of retention, as well as demographics and key clinical characteristics); patients without complete data were excluded from the analysis. Incomplete patient data may signal differences in clinical care practices that are associated with both ART prescription length and retention in care. The conclusions from this study are limited to ART naïve patients; our analyses to do not assess the effect for increasing ART prescription lengths for those with lengthy history of ART. Furthermore, as Haiti widens its application of universal HIV treatment guidelines, the profile of new ART patients may continue to evolve, and these findings may not be generalizable to future patients.

Physician discretion is currently used to determine specific ART prescription interval length for MMS patients in Haiti. This leads to large variation in ART prescription intervals even among patients with similar characteristics. Translating the current findings into policies which inform individual treatment plans has benefits to patients as well. Starting patients on ART intervals based on national recommendations can help inform patient expectations for their treatment plans. Guideline-informed ART intervals can be used as a talking point for bolstering provider-patient communication to enhance care experience and possibly lead to better retention[88]. Provider-patient communication is a critical component to high quality clinical interactions[89,90] and this is especially important in HIV care where patients are involved in lifelong clinical management of their condition.

This research also promotes the support of routine data sources by showcasing how these sources have research advantage, in addition to clinical benefit. Investment in health information systems has sustainable application for clinical tasks and patient management as well as research that can refine these same clinical practices. This advantage is especially notable during global pandemics where clinical practice may be forced to adapt rapidly to changing circumstances to protect patients and providers. Descriptive analyses from iSante indicate that the mean proportion of ART prescriptions that are greater than 3-months and greater than 6-months have increased significantly since COVID-19 was confirmed in Haiti. HIV care providers should be aware of the possibility of a reduction to retention when extending prescription lengths among new ART patients already receiving prescriptions of 4-months or longer. Additional efforts to maintain retention in care for new ART patients may be especially warranted during the pandemic with the associated increase in longer ART prescription intervals.

This study demonstrates a positive effect of increasing ART prescription lengths on retention in care for new ART patients. This differentiated care strategy appears to benefit patients at care initiation and need not be delayed for 6 months unless clinically indicated. The largest gains to retention were observed for patients receiving prescriptions of 3 months or less. Due to a small number of patients with prescriptions lengths of longer than 4 months, the confidence intervals of the estimated marginal effects among those with already longer intervals are much wider than for the estimates of increasing prescription lengths for shorter ART intervals. There is preliminary evidence that increasing prescription lengths beyond 4 months could result in reduced likelihood of retention, but further research is needed. As longer ART prescription intervals become more common practice, it will become more feasible to precisely estimate the effect of extending prescription lengths at the upper end of the spectrum, and to assess for evidence of a point of

diminishing return or even harm. Extending ART prescription intervals is an effective service delivery strategy that improves care retention for new ART patients, especially those who may receive shorter ART prescription durations in settings not adopting this differentiated care strategy.

TABLES AND FIGURES

Table 1. Patient Characteristics and Clinical Indicators

PATIENT CHARACTERISTICS AND CLINICAL INDICATORS	N (%)- TOTAL N=21,880
Female	13,595 (62.1)
Age Category	
<15	1,014 (4.6)
15-24	2,838 (13.0)
25-34	6,968 (31.9)
35-54	9,083 (41.5)
55+	1,977 (9.0)
BMI Category	
Underweight <18.5	3,339 (15.3)
Normal weight 18.5-<25	10, 259 (46.9)
Overweight 25-<30	2,527 (11.6)
Obese ≥30	862 (3.9)
Missing height and/or weight data	4,893 (22.4)
WHO Stage	
1	8,702 (39.8)
2	5,274 (24.1)
3	3,180 (14.5)
4	1,087 (5.0)
Missing WHO stage assessment and/or relevant data to construct WHO stage from record	3,637 (16.6)
Isoniazid for TB management	11,563 (52.9)
Average ART prescription length in days within first 6 months of treatment – mean (SD)	42.5 (26.3) Range: 6-192
Healthcare Facility (site for ART initiation) Ownership	
Public	8,392 (38.4)
Private	8,547 (39.1)
Mixed	4,758 (21.8)
Not-classified	182 (0.8)

Figure 1. Changes to Retention with Increasing Prescription Length by 30 Days

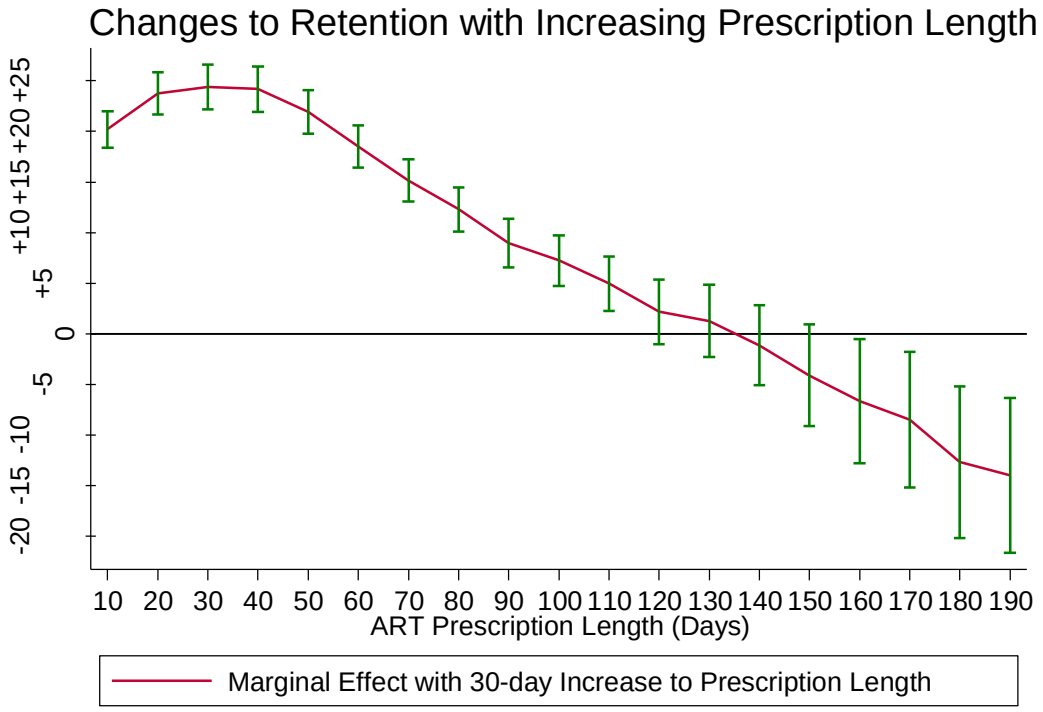
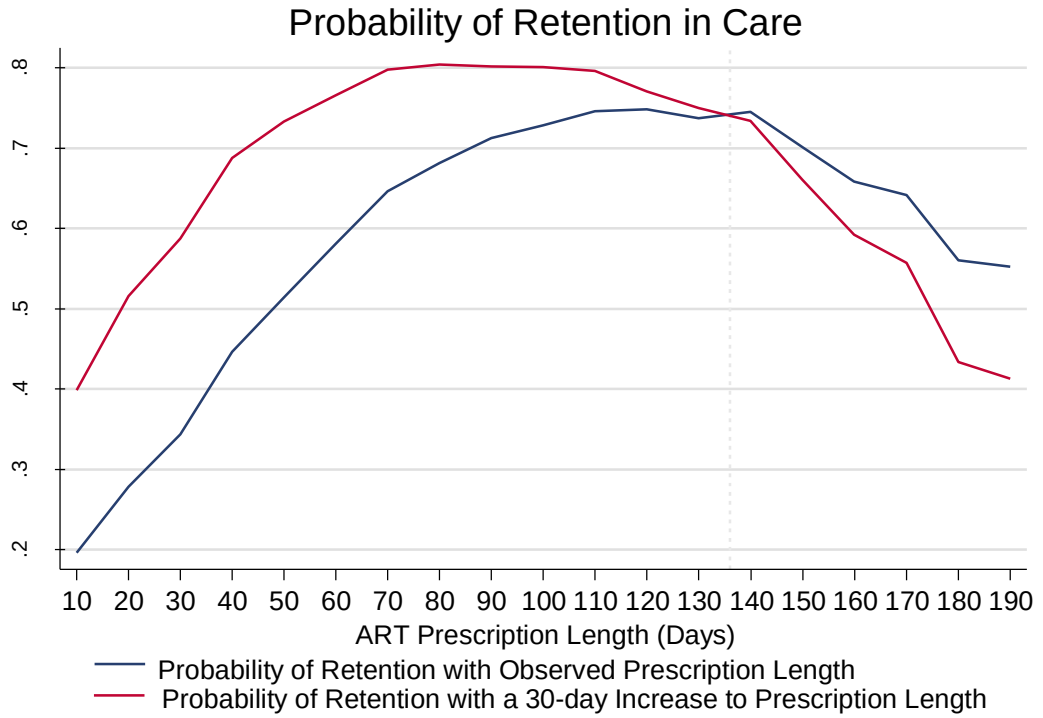


Figure 2. Probabilities of Retention at Observed ART Intervals and Extensions of 30-days



Chapter 3: A Sub-group Evaluation of the Multi-Month Prescribing Strategy for Differentiated HIV Care: Is personalization of care guidelines warranted in Haiti?

INTRODUCTION

Differentiated care strategies are rapidly becoming the norm for HIV care delivery globally[5,67]. Eligibility criteria for HIV care have expanded and there is increased focus on how to best implement treatment and support services for all people with HIV(PWH)[6]. One differentiated care approach has been to increase (ART) prescription lengths to several month intervals to ease the demands on patients' time in obtaining prescription refills[4,67]. This approach also benefits healthcare systems that are managing care for an increasing number of PWH by reducing the human resources required to sustain care delivery. Studies have demonstrated that longer ART prescription intervals may be clinically beneficial for patient outcomes; longer ART intervals are associated with increased probability of retention in care and viral suppression[17,69].

Building upon an interest in further reducing barriers to ART retention and prior experience in informally implementing MMS in some clinics, the MSPP formally endorsed MMS for patients who were "clinically and virologically stable," defined as being on ART for at least 6 months with no emergent opportunistic infections or evidence of a detectable viral load, in the November 2016 national ART guidelines. The guidelines, however, do not state precise prescription lengths or specify tailored recommendations based on patient characteristics. Previous research by the research team has demonstrated that increasing ART prescription length improves the likelihood of retention in care for most patients. Our previous research estimated that increasing ART prescription length by 30 days would have improved the likelihood of retention by up to 23% points for patients with ART prescriptions of between 20 and 50 days, and that all patients with prescriptions of up to 130 days would have benefited from longer intervals[91]. The causal estimates

from that research represented population-averaged intervention effects; the current study aims to address whether the effect on retention differed by various patient subgroups.

Subgroup analyses are common in the medical literature; they build upon existing evidence by adding a focus on particular groups of interest, potentially leading to more nuanced, appropriate policy than a population wide-recommendation[92]. Treatment or intervention effects may differ by patients and across different populations, this is referred to as heterogeneity [83,93]. There are important clinical implications for characterizing this heterogeneity for certain treatment guidelines. Clinicians may find that information from subgroup analyses can be more interpretable than deriving information for an individual patient using data from a population-based model[94,95]. Evidence informed policies for specific patient groups can alleviate some of the clinical decision-making burden providers face when deciding between a range of treatment options for a given patient[96]. In many low and middle-income countries (LMICs), a low number of doctors per capita and task sharing with lower-level cadres of health workers[97,98] make protocolized guidelines desirable for consistent, evidence-informed care pathways.

Subgroup analyses are made possible by the availability of data from data-rich systems with large amounts of information, such as regional or national electronic health records. Clinical trials are not often powered for subgroup analyses which reduce the analytic sample size[99,100], so subgroup analyses from observational datasets represent important contributions to the literature about the effect of specific clinical strategies or treatment protocols. Finally, subgroup analyses are helpful to prepare for and manage specific patient populations where medication supply chain needs, provider time demands, and facility procedures may differ for different treatment options optimized to certain patient groups.

This study explores heterogeneity in retention in care with increasing ART prescription lengths for specific Haitian HIV patient subgroups and evaluates if a targeted algorithm for optimal ART prescription intervals is preferable to a uniform, population-based strategy in Haiti. This information will be useful for clinician decision-making and for policy makers in defining whether sub-group recommendations are warranted within Haiti's national ART guidelines.

METHODS

This study used the iSanté HIV-specific electronic health record (EHR) from Haiti. Our sample included ART-naïve HIV patients enrolled in iSanté who started ART on or after January 1st, 2017 and could have been followed for 13-months (to assess 1-year retention with a 30-day grace period) after their initial ART dispense. Details regarding the dataset and inclusion criteria for this research are documented in previous work[91].

Variables

The primary exposure was ART prescription length in days, as obtained from pharmacy records. To assign patients' exposure status, we calculated the average prescription length over the first 6 months of treatment and applied that as their prescription length of interest. Initial prescription lengths tend to be significantly short, so that clinicians can closely monitor patients for ART toxicity, side effects, and patient tolerance to their ART regimens [80]. Haitian ART guidelines during the time period of this analysis encouraged MMS after patients were demonstrated to be stable on ART for 6 months[79], but in practice MMS was often used before 6 months as evidenced in the EHR data. We chose not to classify the exposure based on the interval length following the 6-month point, as was done in other studies[69], since attrition early in treatment can be high[77] and we wanted to estimate the effect of increasing prescription length on retention

among a more representative sample of new ART patients. Also, there is high within-person variability in dispense lengths for patients during the first 6 months, therefore selecting a single dispense within this window could result in estimation that would possibly not be representative of a patients early ART care history.

The outcome of interest for this study was a binary measure of retention in care 12 months after starting ART (retained vs. not retained). Retention in care, or timely ART pickup, was defined as picking up an ART prescription within 30 days of the scheduled ART pickup after one year in treatment. Retention in care was used as a proxy for treatment adherence[21], and therefore viral suppression[10], for this study. This outcome was used and described in greater detail in our previous work estimating the causal effect of extending ART prescription intervals on retention[91].

Patient characteristics of sex, age, World Health Organization (WHO) stage, Body Mass Index (BMI) category at ART initiation were included the models. WHO Stage is a proxy for HIV disease severity based on patient clinical characteristics such as CD4 count and the presence of opportunistic infections[101]. We also added an indicator for whether the patient had received appropriate, guideline-informed TB management at ART initiation. Appropriate TB management was defined as being treated for active TB or receiving Isoniazid (INH) for TB prophylaxis. In addition, we included categorical variables for facility ownership (public, private, and mixed) and facility network to account for differences in clinical practices and guideline implementation. The WHO stage and BMI category variables included a "missing" indicator if there was insufficient evidence in the medical record to ascertain these characteristics, but complete information existed for the other key demographics, as well as exposure and outcome variables.

Data analysis

We employed an instrumental variable (IV) analysis using a 2-stage residual inclusion (2SRI) approach for non-linear models[83,84] to estimate the causal effect of increasing ART prescription length on ART retention, by patient subgroup. The instrument used was the mean facility-level ART prescription length for new ART patients within the 6-month window in which the patient received their initial ART prescription. We checked the balance of measured patient-level covariates across levels of the instrument and assessed the strength of the instruments in predicting ART prescription length in the first stage model.

Standardized residuals from the first stage treatment model were included in the second stage outcome model. Bootstrapping with 1,000 iterations was conducted to achieve valid standard errors with the 2-stage models. We assessed the goodness-of-fit of the second stage outcome model using the Pearson correlation test to assess any linear relationship between the raw-scale predictions and residuals and the Hosmer-Lemeshow test in which we plotted mean residuals across deciles of $X\beta$ to determine if there were any systematic patterns in the residuals[85].

To identify subgroups in which to explore heterogeneity, we implemented a double-lasso regression method[102,103] for variable selection to determine which patient characteristics would define the subgroups. The lasso (least absolute shrinkage and selection operator) is a type of regression method designed to improve the prediction accuracy and interpretability of regression models by selecting a subset of the available covariates that exhibit the strongest effects[102]. We first used a data-driven penalization lasso approach for predicting ART prescription length in days and then a regularized logistic regression model for the outcome of retention. The first stage model included all possible interactions between the instrument with patient characteristics (sex, age, WHO stage, and BMI) and second stage models included interactions with the same patient-level variables and ART prescription length. Main effects of the patient characteristics, TB management,

and facility-level variables were not penalized in either model. Interactions that were selected by the lasso algorithm in either model were included in the IV analysis.

All included interaction terms were tested for significance jointly across all levels of the variable after the second stage model in the IV analysis. Significant interaction terms indicated characteristics in which treatment heterogeneity existed for this patient population. Patient characteristics that were in statistically significant interaction terms then defined the patient subgroups of interest. We estimated the marginal effect of a 30-day increase to ART prescription length to retention in care for each of these patient subgroups using the margins post-estimation command following the second stage IV model and compared these marginal effects across groups.

We conducted a secondary analysis among the subgroups identified in our primary analysis to test if the effects of extending ART prescriptions by 30 days differed across different observed ART prescription intervals. We estimated the effects of increasing ART prescription length for patient subgroups among three observed prescription length categories: less than 60 days, 60-90 days, and more than 90 days in length. These categories were informed by our previous work demonstrating the population-averaged effect of increases to ART prescription length differed across these three categories[91].

RESULTS

The demographic and clinical characteristics of the 21,880 ART naïve patients in the study population included in this analysis is described elsewhere[91].

Interactions with all the patient-level variables were selected via the double-Lasso selection process and were included in the following IV analysis in both the first and second stage models. Patient level covariates were balanced between the instrument levels when the instrument was

divided at the median. The instrument was strong in the first stage models; highly predictive of individual ART prescription length. The second stage, or outcome model, performed well on diagnostic goodness-of-fit tests.

In the adjusted outcome model, only the interactions between ART prescription and WHO stage were statistically significant. There was evidence for heterogeneity in the effect of extending ART prescription intervals on retention in care among WHO stages. This selected characteristic of WHO stage, as operationalized in our analyses, defined 4 unique patient subgroups. Within the 4 subgroups, we observed improvements to the likelihood of retention in care at 1-year with increased ART prescription lengths for all groups with statistically significant marginal effects (Figure 1). The effects ranged from a 14.7%-point increase to retention with a 30-day extension of the ART prescription interval for patients in WHO stage 1 to a 21.6%-point increase to the likelihood of retention for those in WHO stage 3. The increases to retention for Stages 2 and 3 patients were significantly greater than the increases for Stage 1 patients; the changes to retention for Stage 4 patients were not statistically significantly different than the changes for either of the other three stages.

We conducted our secondary analysis among the WHO stage groups and the prespecified ART prescription length categories. Patients in all WHO stage groups were estimated to have statistically significant improvements to retention with increased ART prescription length across all three ART length categories (Figure 2). Effects ranged from 10.7%-points for WHO stage 3 patients with ART prescriptions more than 90 days in length to 22.7%-points for with 60-90 day prescription lengths in WHO stage 4. For ART prescription length categories of less than 60 days and 60-90 days, patients in WHO stages 2 and 3 had significantly larger increases to the likelihood of retention compared to those in WHO stage 1. For those patients currently on prescription lengths

of more than 90 days, there was no difference to the increases to retention across the WHO stage groups. Overall, the benefits to retention were smallest among the subgroups with prescription lengths in that ART length category.

DISCUSSION

The statistically significant effects demonstrated improvement to the likelihood of retention in care with 30-day increases ART prescription length and were of similar magnitude across the patient subgroups. Although treatment heterogeneity was observed, the improvements to retention were not different enough to warrant further exploration of a targeted ART prescription length policy based on patient characteristics. As noted in our secondary analysis, the overlapping confidence intervals for the many of the subgroups suggest similar trends across patient groups and observed ART prescription lengths up to 90 days.

This study had several limitations, some of which are related to our data source and methodological approach in estimating the causal effect of increasing ART prescription length on retention (IV analysis) and are described in previous work[91]. Lasso regression selects the variables with the strongest effects on the outcome[102,104], not necessarily the variables most commonly used to consider treatment options in clinical practice. Variable selection by this process may not be intuitive for clinicians. To note, we did not identify gender, sex, age, or BMI as variables to evaluate for heterogeneity in the intervention effect. The variables in which we identified heterogeneity in the intervention effect are highly dependent on this specific Haitian population. Populations with different distributions of patient demographic and clinical characteristics would likely see different subgroups emerge from a similar analytic approach; targeted policies around optimal ART prescription length based on subgroup defining characteristics could be warranted in other settings. Also, we were unable to precisely estimate the effect of increasing ART prescription

within the defined subgroups at longer ART prescription lengths (longer than 4 months as suggested by our previous analyses) due to limitations in sample size.

However, our approach capitalized on a large patient population for most of the other subgroups and was able to provide insight into whether further refinement of ART guidelines for Haiti was justifiable. There is a need to balance optimizing individual or patient subgroup outcomes with ease in guideline and policy implementation and monitoring. A general, uniform policy relating to clinical guidelines appears to be suitable for Haiti. The iSanté EHR allows for the consideration of individual characteristics linked to specific health outcomes and this availability of data allows analysts to run sub-group analyses in order to shape guidelines, however, in many settings, the receipt of monitoring information for analysts is most common in the aggregate [31,79,105]. Additionally, a general guideline, one ART interval length recommendation for all patients, lends well to economic evaluations at the national level[106,107], where the subgroup defining characteristics may be hard to quantify for an entire population. This general strategy could be desirable for other countries that wish to adopt extended ART intervals as a part of their national strategic plan to manage HIV.

These results also provide salient information for care delivery systems in the context of the COVID-19 pandemic and the health system challenges it has engendered. The COVID-19 pandemic has threatened the ART medication supply for over 70 countries due to severely reduced land and air transport serices[108]. If medication supplies are limited, our analyses may suggest prioritizing longer ART intervals for groups that would likely experience the most clinical benefit from extended prescription lengths, such as those in more severe HIV.

Future research regarding subgroup analysis may be used characterize the effect of extending ART prescription lengths among critical populations, such as men who have sex with

men, commercial sex workers, and people who inject drugs, to achieve more ambitious 95-95-95 targets for 2030[109]. These populations are often disproportionally burdened by HIV and frequently experience social and structural barriers to care that hinder ART initiation and ART retention[110,111]. The effect of extending ART intervals among HIV risk category groups represents area of future research to explore in Haiti. Although iSanté does capture information on transmission risk category, the completeness of this data field can be highly variable and also subject to social desirability bias, however, other health information systems may capture this information more consistently and could evaluate the effect of extended ART prescription intervals on these populations specifically.

The patient subgroups of WHO stage experienced a benefit of extending ART intervals to retention in care at 1-year. Though the effect may differ slightly by WHO stage, the effects went in the same direction and were of similar magnitude. Therefore, a standardized recommendation for ART prescription length is appropriate for Haiti treatment guidelines. Based on our previous population-based analysis[91], starting new ART patients on ART intervals of 3-4 months in length, after the possibility of medication toxicity has been ruled out, should be appropriate for most patient groups. Our results are additionally consistent with our previous analysis in that those already on longer ART prescription intervals may not experience as much of a benefit to retention as those on shorter prescription lengths.

FIGURES

Figure 1. Effects of a 30-day Increase to ART Prescription Length on Retention in Care for WHO Stage patient subgroups

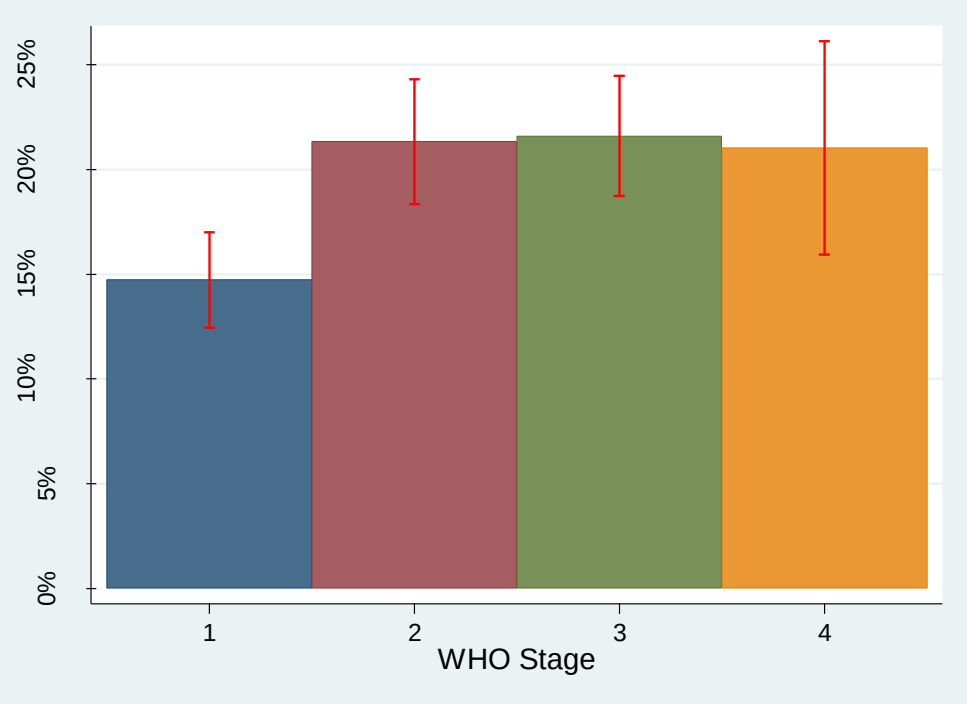
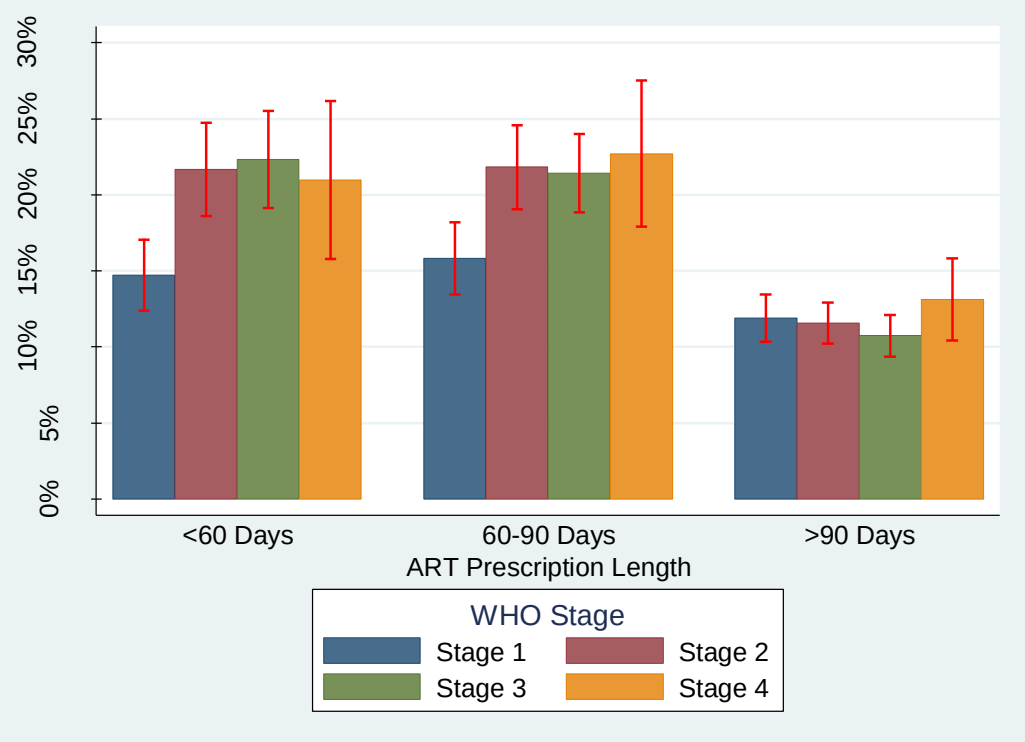


Figure 2. Effects of a 30-day Increase to ART Prescription Length on Retention in Care across 3 ART Prescription Length Categories.



Chapter 5: Conclusions

Improving HIV service delivery is vital for reaching global HIV testing and treatment targets, especially for populations with competing health demands or limited resources. As of 2019 globally, 81% of those with HIV knew their HIV status, 82% of those who knew their HIV status were on ART, and 88% of people on ART were virally suppressed[112]. These estimates fall short of the 90-90-90 targets for 2020 and are well below the more ambitious 95-95-95 targets for 2030[2]. These estimates vary greatly across settings and subpopulations; in areas and for populations for whom these estimates are low, testing and treatment models need to better adapt to the needs of the populations which they serve. Differentiated care strategies highlight interventions that address coexisting health conditions and limited resources of patients and healthcare facilities and identify populations for whom care models could be enhanced to increase linkage to care, retention on ART, and ultimately viral suppression[5,6]. Achieving viral suppression benefits the individual patient by reducing risk of mortality and opportunistic infections and the population by decreasing the likelihood that viral transmission will occur[45]. Using routine data sources which include people frequently excluded or specifically precluded from clinical trials can help refine these differentiated care strategies to further improve care along the HIV treatment cascade with the goal of viral suppression and improved health on an individual and population level.

SUMMARY OF FINDINGS

In this research, we focused on two key patient populations: vulnerable populations (vulnerable due to competing health challenges such as substance use) and low-resource populations (low resource in terms of individual patient resources and limited health system resources that often characterize many low and middle-income countries). For the population of people with HIV (PWH) who also report substance use, this research indicates some positive signs

of testing outreach as illustrated by entry into care at earlier stages of disease than people not reporting substance use. This may signal that community outreach and improved testing in clinics are successful at engaging those in need of HIV care services who have known HIV risk factors. HIV testing is likely differentially offered to people with these known factors. Additionally, those with substance use disorders may have increased interactions with the healthcare system due to their substance use and resulting health consequences and may experience more opportunities to be tested for HIV. Many studies have noted lower rates of retention in care among those with substance use disorders[11,20,38,50], this research suggests that this reduction in retention may not be due to increased disease severity at care initiation. There may not be as much of a problem at the front end of the care continuum with linkage to care, but more with continuity of care once linked. This highlights the need to bolster HIV treatment with ancillary services, not necessarily more HIV-related services, to improve retention in care for PWH and substance use disorders. These findings also suggest room for improvement in testing among those vulnerable to HIV, but without more common HIV risk factors, in increased efforts towards universal testing of HIV for entire populations.

For low-resource populations and settings, such as Haiti, this research found that the differentiated care strategy of extending ART prescription lengths improves retention in care for most new ART patients. The optimal interval for ART prescriptions is about 3-4 months in length; the largest gains when extending ART prescription intervals are observed for patients currently receiving ART prescription of 3 months or less. As longer prescription lengths are becoming more common due to changes in clinical care guidelines[69,79], this research provides evidence that benefits to retention can be expected with these changes. Healthcare systems looking to care for a larger number of patients more efficiently can employ this extended prescription interval strategy

for many patients without fear of compromising clinical outcomes. However, this research did highlight the need for supporting efforts to ensure retention if prescription lengths are extended beyond 5 months, after which extending prescription intervals may have a detrimental effect on retention. This may be especially salient considering the current COVID-19 pandemic where many healthcare systems are attempting to maximize prescription intervals to protect patients and care providers. Retention with longer ART intervals can vary across patient subgroups, though the effects are in the same direction and are of similar magnitude, thereby signaling that a uniform strategy for optimal ART intervals is appropriate for Haiti.

IMPLICATIONS OF THIS RESEARCH

This research is an illustration in the use of routine data systems to support clinical decision-making for patients who may not be represented in clinical trials. Use of observational data from these routine systems, like EHRs, is an economical use of a health information system that is typically used as a point-of-care clinical tool. Using available information from EHRs also represents an efficient use of donor organization or tax dollars that supported the development of these systems[75]. Although randomized control trials are often touted as the gold standard for casual inference and clinical care guidelines, this research demonstrates the use of large observational datasets with strong claims of external validity, and the application of rigorous statistical methods in order to offer robust findings which provide insight for healthcare guidelines and policies for a broad range of patients.

This research provides actionable information for care delivery guidelines. It signals the need for increased HIV testing among all patients engaged in care, despite the documented challenges that providers face when providing testing counseling to patients without more common HIV risk factors[59]. It provides refinement of existing ART and MMS guidelines in Haiti to specify

a recommended ART prescription length of 3-4 months for new ART patients. This research also demonstrates that a uniform, population-based ART guideline is suitable for Haiti, thus simplifying the guideline implementation process and allowing some room for physician autonomy and independent decision making for their patients.

Finally, this research contributes towards efforts to improve population health by optimizing care for individual HIV patients who require lifelong interaction with the healthcare system. The intersection of the two conceptual models on which this work was based[113,114], allows for the contextual consideration of caring for people with HIV both from the individual perspective and the healthcare system perspective. This research considers the experience of many patients to inform individual care pathways and provide a missing feedback mechanism to healthcare systems so that these systems may better adapt to the needs of PWH.

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