UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Assessing the role of alcohol and intimate partner violence on HIV care and viral suppression in Uganda

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Public Health (Global Health)

by

Amanda Pearl Miller

Committee in charge:

University of California San Diego

Professor Jennifer A. Wagman, Co-Chair
Professor Anita Raj

San Diego State University

Professor Eileen V. Pitpitan, Chair
Professor Susan M. Kiene
Professor María Luisa Zúñiga

2021

The dissertation of Amanda Pearl Miller is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

_____

_____

_____

_____
Co-chair

_____
Chair

University of California San Diego

San Diego State University

2021

DEDICATION

This work is dedicated to those who have always supported me and believed in me. My parents have always instilled a sense of curiosity and inquisitiveness that led me to an interest in science and research. They have and continue to encourage me to aim high and pursue my dreams even when the challenge seemed daunting.

This work is also dedicated to my husband and best friend, Jamie, who supported my decision to return to school to pursue my doctorate and has been a constant source of encouragement throughout this journey.

The rest of my family as well as my close friends have also been instrumental in my success and growth. I am forever indebted to the amazing people with which I share this life journey: WVV, AMV, ECW, REW, BAB (RJM, STP, CDP) KCS, JKV, RTM, LWM, JWM, MMB, VLN, BEB, HDF, CEDS, MDS, KSC.

Finally, this work is dedicated to my daughter, Grace. May she always feel supported to pursue her own big dreams.

EPIGRAPH

"The idea that some lives matter less is the root of all that is wrong with the world."
— **Paul Farmer**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
AUDIT	Alcohol Use Disorder Identification Test
GEE	Generalized Estimating Equations
IPTCW	Inverse Probability of Treatment and Censoring Weights
IPV	Intimate Partner Violence
IRB	Institutional Review Board
PEth	Phosphatidylethanol
PLWH	Persons living with HIV
RCCS	Rakai Community Cohort Study
TasP	Treatment as Prevention
VIF	Variance Inflation Factor
WLWH	Women living with HIV

ACKNOWLEDGEMENTS

There are many mentors and teachers that helped me along the way on this journey and I would like to take the opportunity to thank them for their time and insight. First, I would like to thank my dissertation committee. Without their guidance and feedback, I would not have been able to complete this work. Drs. Anita Raj, Susan M. Kiene and Maria Zuniga provided invaluable guidance and mentorship; my chairs, Drs Jennifer Wagman and Eileen V. Pitpitan went above and beyond, supporting not only my research but also my professional growth and development to help me pursue my larger career goals. Furthermore, as my primary mentor and advisor, I would like to thank Dr. Wagman for her support and guidance throughout the duration of the PhD program. I would also like to thank Dr. George Rutherford, whose mentorship during my master's program and time working at UCSF was instrumental in me pursuing a PhD.

I would also like to thank my friends and family for the endless support they have provided. I know that I have been distracted and busy these last few years and I thank you for the efforts you have made through visits and phone calls as well as your understanding when we haven't been able to attend something due to my school schedule. It takes a village to earn a PhD. Without the love and support of my friends and family I could not have done it. I am especially grateful for my husband, Jamie, who was willing to relocate so that I could go back to

school and has supported me throughout this four-year journey. I love you, my dear.

Chapter 1, in part has been submitted for publication of the material at it may appear in Alcoholism: Clinical and Experimental Research, 2021, Miller, A.P., Pitpitan, E. V., Kiene, S.M., Raj, A., Jain, S., Zuniga, M. L., Nabulaku, D., Nalugoda, F., Ssekubugu, R., Nantume, B., Kigozi, G., Sewankambo, N. K., Kagaayi, J., Reynolds, S. J., Grabowski, M. K., Wawer, M., & Wagman, J.A. The dissertation author was the primary investigator and author of this paper.

Chapter 2 in part is currently being prepared for submission for publication of the material in Journal of the International AIDS Society, 2021, Miller, A.P., Pitpitan, E. V., Kiene, S.M., Raj, A., Jain, S., Zuniga, M. L., Nabulaku, D., Nalugoda, F., Ssekubugu, R., Nantume, B., Kigozi, G., Sewankambo, N. K., Kagaayi, J., Reynolds, S. J., Grabowski, M. K., Wawer, M., & Wagman, J.A. The dissertation author was the primary investigator and author of this paper.

Chapter 3 is co-authored, with Pitpitan, E. V., Kiene, S.M., Raj, A. and Wagman, J.A. The dissertation author was the primary investigator and author of this paper.

VITA

2009	Bachelor of Arts, University of California Santa Barbara
2011	Master of Science, University of California San Francisco
2013-2016	Research Assistant, University of California San Francisco
2016-2017	Research Analyst, RTI International
2017-2021	Research Assistant, University of California San Diego
2021	Doctor of Philosophy, University of California San Diego/San Diego State University

PUBLICATIONS

1. **Miller AP**, Ziegel L, Mugamba S, Kyasanku E, Wagman J, Nkwanzi-Lubega V, et al. Not enough money and too many thoughts: Exploring perceptions of mental health in two Ugandan districts through the mental health literacy framework. Qualitative Health Research.

2. Sileo KM, **Miller AP,** Huynh TA, Kiene SM. A systematic review of interventions for reducing heavy episodic drinking in sub-Saharan African settings. Plos One. 2020;15(12).

3. **Miller AP**, Pitpitan E, Nabukalu D, et al. Transactional sex, alcohol use and intimate partner violence against women in the Rakai region of Uganda. AIDS and Behavior. 2020.

4. Wagman JA, Nabukalu D, **Miller AP**, Wawer MJ, Ssekubugu R, Nakowooya H, et al. Prevalence and correlates of men's and women's alcohol use in agrarian, trading and fishing communities in Rakai, Uganda. PLoS One. 2020;15(10):e0240796.

5. Sileo KM, **Miller AP,** Wagman JA, Kiene SM. Psychosocial interventions for reducing alcohol consumption in sub-Saharan African settings: a systematic review and meta-analysis. Addiction. 2020.

6. **Miller AP**, Kintu M, Kiene SM. Challenges in measuring depression among Ugandan fisherfolk: a psychometric assessment of the Luganda version of

the Center for Epidemiologic Studies Depression Scale (CES-D). BMC Psychiatry. 2020;20(1).

7. **Miller AP**, Malekinejad M, Horváth H, Blodgett JC, Kahn JG, Marks SM. Healthcare facility-based strategies to improve tuberculosis testing and linkage to care in non-U.S.-born population in the United States: A systematic review. PLOS ONE. 2019;14(9).

8. Breuer C, Bloom B, **Miller AP**, Kigozi G, Nakyanjo N, Ddaaki W, et al. "The Bottle Is My Wife": Exploring Reasons Why Men Drink Alcohol in Ugandan Fishing Communities. Social Work in Public Health. 2019:1-16.

9. Parriott A, Malekinejad M, **Miller AP**, Marks SM, Horvath H, Kahn JG. Care Cascade for targeted tuberculosis testing and linkage to Care in Homeless Populations in the United States: a meta-analysis. BMC Public Health. 2018;18(1).

10. Marseille E, Mirzazadeh A, Biggs MA, **Miller AP**, Horvath H, Lightfoot M, et al. Effectiveness of School-Based Teen Pregnancy Prevention Programs in the USA: a Systematic Review and Meta-Analysis. Prev Sci. 2018.

11. Parriott A, Malekinejad M, **Miller AP**, Horvath H, Marks SM, Kahn JG. Yield of testing and treatment for tuberculosis among foreign-born persons during contact investigations in the United States: A semi-systematic review. PLoS One. 2018;13(7):e0200485.

12. Malekinejad M, Parriott A, **Viitanen AP,** Horvath H, Marks SM, Kahn JG. Yield of community-based tuberculosis targeted testing and treatment in foreign-born populations in the United States: A systematic review. PLoS One. 2017;12(8):e0180707.

13. Mirzazadeh A, Biggs MA, **Viitanen A**, Horvath H, Wang LY, Dunville R, et al. Do School-Based Programs Prevent HIV and Other Sexually Transmitted Infections in Adolescents? A Systematic Review and Meta-analysis. Prev Sci. 2017.

14. Chesang K, Hornston S, Muhenje O, Saliku T, Mirjahangir J, **Viitanen A,** et al. Healthcare provider perspectives on managing sexually transmitted infections in HIV care settings in Kenya: A qualitative thematic analysis. PLOS Medicine. 2017;14(12).

15. **Viitanen AP,** Colvin CJ. Lessons learned: program messaging in gender-transformative work with men and boys in South Africa. Global Health Action. 2015;8(1).

FIELDS OF STUDY

Major Field: Public Health

Studies in Global Health

Professors J.A. Wagman and E.V. Pitpitan

ABSTRACT OF THE DISSERTATION

Assessing the role of alcohol and intimate partner violence on HIV care and viral suppression in Uganda

by

Amanda Pearl Miller

Doctor of Philosophy in Public Health (Global Health)

University of California San Diego 2021
San Diego State University 2021

Professor Eileen V. Pitpitan, Chair

Professor Jennifer A. Wagman, Co-Chair

Background: HIV, alcohol use and intimate partner violence (IPV) are critical interrelated public health issues in the Rakai region of Uganda. There is a

growing evidence base that suggests that alcohol use adversely impacts HIV treatment outcomes. Findings regarding the effects of alcohol use on viral suppression have been inconclusive. Similarly, experiencing IPV is also associated with poor treatment outcomes. Although IPV and alcohol use are frequently co-occurring, their combined effects on treatment outcomes has not been explored.

Objective: To assess how alcohol use and IPV independently (aims 1 and 2, respectively) and as co-occurring issues (aim 3) relate to HIV treatment outcomes among persons living with HIV (PLWH) participating in the Rakai Community Cohort Study (RCCS).

Methods: Data from two consecutive rounds (2017-2020) of the RCCS, a prospective population-based HIV surveillance study, were analyzed. Multivariable models were built to explore associations between past year alcohol use, IPV and current ART use and viral suppression (<=1000 copies/mL) To explore the relationship between alcohol use and the HIV treatment outcomes (aim 1), Generalized Estimating Equations were built to adjust for correlations from within person observations at two visits with analyses run overall and stratified by sex. Prospective associations between IPV and the HIV outcomes among women were explored using logistic regression models weighted with inverse probability weights (aim 2). Mediation and moderation analyses were performed to explore temporal pathways between IPV, alcohol use and the HIV outcomes (aim 3).

Results: For aim 1, the sample consisted of 3,823 PLWH. Alcohol use was associated with significantly worse treatment outcomes among women but not men. Among alcohol users, experiencing alcohol-related consequences was associated with worse outcomes among men but not women. In aim 2, among women reporting past year sexual activity at baseline (n=1,923), experiencing IPV was not associated with worse treatment outcomes. None of the mediating or moderated pathways explored in aim 3 were significant.

Conclusions: Alcohol use should be a target of intervention to improve HIV treatment outcomes. Given the frequent co-occurrence of HIV, alcohol use and IPV in this setting more research is needed to understand how these variables relate

INTRODUCTION

Uganda has one of the highest rates of per capita alcohol consumption in the world (1). In the fishing villages along the Rakai/Masaka border, where the greatest burden of HIV in Uganda exists (median HIV prevalence is 42%), heavy drinking is common among alcohol users, with 52% of women and 62% of men self-reporting consumption of unsafe levels of alcohol (2, 3). Alcohol use is also common among persons living with HIV (PLWH); a community survey In Rakai found that 57% of PLWH reported past year alcohol use (2, 4). At the same time, in Rakai, nearly half (49.8%) of women report having experienced some form of intimate partner violence (IPV) (defined as physical, sexual or verbal violence from an intimate partner) in their lifetime (5).

Extensive global health research suggests HIV infection, alcohol use and IPV are critical interrelated public health issues. In many settings, alcohol use has been linked to violent behavior and increased engagement in risky sexual behavior (e.g., condomless sex), both of which increase risk for HIV infection (6, 7). IPV can increase risk of HIV infection directly (e.g., forced intercourse) and indirectly (e.g. reduced ability to safely negotiate condom use)(8). HIV prevalence in Rakai is three times higher (19.7%) than the national average (6.2%)(9). IPV is also common (10) and associated with both alcohol use and HIV incidence (3, 7, 11). While there is substantial evidence that alcohol use and IPV increase risk for HIV acquisition (10, 12, 13), less is known about associations between IPV and alcohol

use and the HIV care and treatment continuum. There is also a paucity of data exploring the likely synergistic effects of co-occurring alcohol use and IPV on these outcomes in this setting, despite evidence that alcohol use by one or both partners often precedes instances of IPV (14). Evidence from Rakai and elsewhere in sub-Saharan Africa (SSA) suggests the relationship between HIV and IPV is bidirectional; IPV is a risk factor for HIV and rates of IPV among HIV-positive women are higher than their HIV-negative counterparts (15-20). The role of alcohol use as a driver of the HIV epidemic in this context is also well established by quantitative and qualitative data (11, 21-23). A number of theories describing the bidirectional relationships between HIV, IPV and alcohol use exist (24-28).

In the era of test and treat, which are the current treatment guidelines in Uganda, HIV treatment is initiated at the time of HIV positive diagnosis, reducing barriers in linkage to care and treatment initiation. This dissertation examines the effects of alcohol use and experiences of IPV (independently and together) on the HIV treatment cascade at two points: current ART use and viral suppression.

The following comprise the specific research aims for this dissertation:

Aim 1 (Chapter 1). Estimate associations between past year alcohol use and experiencing alcohol-related consequences (e.g., unsteady gait, shaky

hands the morning after drinking) in the past year and HIV treatment outcomes among PLWH residing in Rakai.

Aim 2. (Chapter 2) Estimate prospective associations between past year IPV and HIV treatment outcomes among women living with HIV (WLWH) residing in Rakai.

Aim 3. (Chapter 3) Explore how alcohol use and IPV together are related to HIV treatment outcomes through prospective mediated and moderated pathway analyses.

Each chapter is written as a standalone manuscript with its own abstract, introduction, methods, results and discussion. The achievement of these aims was facilitated by access to data collected from the two most recent rounds of the parent study, The Rakai Community Cohort Study (RCCS), which is funded through the following mechanisms: NIAID (5U01AI100031, PI: Gray), NICHD (5R01HD070769; PI: Wawer), NIMH (5R01MH099733; PI: Wawer) and Gates Foundation.

Background on RCCS Dataset

Study Setting**:** Rakai is a rural district in the central region of Uganda with a population of 518,008 residents (2014 census)(29). The first AIDS case in Uganda

was diagnosed in Rakai in 1982 and it remains one of the areas most heavily affected by HIV in the country. Today, HIV prevalence within the district varies substantially with the fishing villages, considered HIV hotspots, approaching 42% prevalence; overall the district prevalence (19.7%) is more than three times the national prevalence (6.2%)(3, 9). The early presence of AIDS in Rakai prompted the establishment of the Rakai Health Sciences Program (RHSP) in 1987 through a collaborative partnership between Makerere University, Columbia University, Johns Hopkins University, the International Centre for Excellence Research (ICER) and the Division of Intramural Research at the National Institutes of Allergy & Infectious diseases (NIAID). In 1994, RHSP established the RCCS.

Data sources: The RCCS is the parent study of the proposed research. RCCS is a longitudinal population based open-cohort study that collects household health data annually in 40 communities throughout the district. The survey cycle is continuous, with each round of data collection in a given community typically happening 12-18 months apart. Although the RCCS is a longitudinal study, variables of interest were only added in the two most recent rounds, precluding the inclusion of additional rounds of data in our analysis. For this reason, analysis was restricted to rounds 18 (Aug. 2016-May 2018) and 19 (May 2018-November 2020). First, a household census is conducted in each community and the population is enumerated. All consenting adults (15-49 years of age) are eligible for study participation. The survey collects data on sociodemographic

characteristics, healthcare utilization, sexual networks and behavioral characteristics for members of included households and offers HIV testing. Additional details on the RCCS study design and implementation have been detailed by Wawer et al. (30).

Data collection/consent: RCCS data collectors are fluent in the local language, Luganda, and have received training in research ethics. Surveys are conducted by researchers who are the same sex as the participant. Data is collected on electronic tablets. Written informed consent is obtained from all participants prior to participation. In addition to the survey, participants are asked to provide a sample for HIV testing and provided with HIV counseling and testing services. If an individual tests positive they are offered ART initiation. Viral load data is collected by lab technicians at laboratories throughout the district every six months as part of routine monitoring for PLWH currently on ART.

Significance of this Research

This dissertation addresses multiple pervasive interrelated public health issues in Uganda (harmful alcohol use, IPV and poor HIV treatment outcomes) and addresses critical gaps in the literature.

A. Alcohol use and IPV are both independently associated with delays throughout the HIV care continuum

Antiretroviral therapy (ART) can reduce an individual's HIV viral load to a level that is undetectable (i.e. virally suppressed), significantly diminishing the likelihood of HIV transmission (31). After a number of clinical trials demonstrated the efficacy of treatment as prevention (TasP) (32-34), the Joint United Nations Programme on HIV/AIDS (UNAIDS) unveiled its current HIV prevention framework: the 95-95-95 targets. This framework aims to achieve 95% coverage at three steps in the HIV care continuum by 2030: (1) 95% of those infected aware of their status, (2) 95% of PLWH who are aware of their status are on ART and (3) 95% of those on ART achieving viral suppression. Achieving timely linkage to ART and viral suppression among PLWH is imperative to secondary HIV prevention efforts and good HIV treatment outcomes. Achieving viral suppression in Rakai is especially critical to prevention efforts because the HIV epidemic is generalized and hyper-endemic (prevalence >15%), self-reported condom use in primary partnerships is low and having multiple concurrent sexual partners is common. The literature (which has primarily come from high income countries) suggests that alcohol use and IPV are both independently associated with delays throughout the HIV care continuum (35-39). However, there is a dearth of literature on how alcohol use and IPV impact engagement in the HIV care continuum in Uganda and a paucity of data (globally) on the combined effects of alcohol use and IPV on HIV care and treatment outcomes. Given that IPV frequently occurs in the context of

alcohol use (7), determining if alcohol use and IPV have an additive effect on HIV care and treatment outcomes may inform if IPV should be addressed in interventions addressing alcohol use among PLWH in this setting-[=

B. The use of virologic outcomes to monitor viral suppression is novel in this setting

While the existing literature has consistently found an association between alcohol use and decreased engagement and retention in the HIV care continuum (37, 40-42), findings on the effect of alcohol use on disease progression (using either immunologic and virologic markers) have been mixed and inconclusive, warranting additional research (15, 43, 44). To date, most research examining the effects of alcohol use on HIV disease progression in SSA have relied on immunological monitoring (CD4 T-cell count) for HIV (41, 43, 45, 46). In recent years, a consensus has emerged that when feasible, virologic monitoring should be implemented to monitor HIV disease progression because identifying virologic failure is critical to accurate identification of ART treatment failure(47). By using virologic outcomes, findings from this work can provide more accurate estimates of associations between alcohol use, IPV and treatment failure in Uganda (47).

CHAPTER 1: Alcohol use and alcohol-related consequences are associated with poor HIV care and poor treatment outcomes among persons living with HIV in the Rakai region of Uganda

Abstract

Background: Alcohol use is common among persons living with HIV in Uganda and associated with poor HIV care and treatment outcomes; findings regarding the relationship between alcohol use and viral suppression have been less conclusive. To date, most research examining the effects of alcohol use on HIV treatment outcomes in Africa have relied on immunological monitoring.

Methods: Data from two consecutive rounds (2017-2020) of the Rakai Community Cohort Study, a prospective population-based HIV surveillance study in the Rakai region, Uganda, were analyzed. Multivariable models (GEE) were used to estimate longitudinal associations between alcohol use and alcohol-related consequences and HIV treatment outcomes (current antiretroviral therapy use (ART) and viral suppression) for the overall sample and stratified by sex, adjusting for repeated measurement.

Results: The sample consisted of 3,823 persons living with HIV. Over half (55%) of participants reported past year alcohol use at baseline; 37.8% of alcohol users reported at least one related negative consequence, such as falling down or

shaky hands the morning after drinking. A greater proportion of non-drinkers (compared to drinkers) were represented in both treatment outcomes. Past year alcohol use was significantly associated with decreased odds of current ART use and viral suppression. Among male alcohol users, experiencing alcohol-related consequences was significantly associated with decreased odds of current ART use and viral suppression. For any alcohol use, a significant natural indirect effect supported mediation by ART use in the overall sample.

Conclusions: Alcohol use is adversely associated with current ART use and viral suppression. Findings related to viral load suggest that ART may mediate the relationship between alcohol use and viral suppression. Alcohol consumption should be a target of intervention among persons living with HIV in Uganda to improve care continuum outcomes and support secondary prevention efforts.

Key words: Uganda, Alcohol, HIV care continuum, viral suppression, treatment adherence

Introduction

More than half (52.6%) of Uganda's citizens aged 15 years and older consume alcohol, and its use is a major public health concern (1). Among those who drink alcohol, 56.9% consume at least 60 grams (equivalent to six standard drinks) or more of unmixed alcohol on at least one occasion in the past 30 days (1) and per capita annual consumption is 50% higher than the average individual for the WHO Africa region (9.5 liters compared to 6.3 liters) (1). In Uganda there are also pronounced differences in alcohol use by gender with men being more likely consume alcohol and to engage in heavy drinking. Two-thirds of men (68.8%) who use alcohol report engaging in heavy episodic drinking (defined as at least 60 grams of pure alcohol on at least one occasion in the past 60 days) while only one-third of women (32.6%) who drink alcohol report this same behavior (1). Men in Uganda are also more likely to report experiencing consequences related to their alcohol use, such as drinking on the job or getting into a fight while under the influence (48). These gendered differences in alcohol use and drinking patterns are culturally engrained and socially enforced (49, 50). In Uganda, rates of alcohol use disorder and physical alcohol dependence are nearly twice that of the overall African region (1) and in 2017, alcohol use was ranked the 5th highest contributing risk factor of disability adjusted life years (DALYs) (a measure of disease burden) in the country (51). There is also considerable overlap between the disease burden of alcohol use and HIV, another prevalent public health issue in Uganda.

National prevalence of HIV in Uganda is 6.2% (52) and an estimated 32.2% of those persons living with HIV (PLWH) had a biomarker related to unhealthy drinking, Phosphatidylethanol (PEth) ≥ 50 mg/mL (53). In Rakai, a district of roughly a half million residents in southwestern Uganda (54), HIV prevalence exceeds the national average at 7.9% (52), including a prevalence as high as 42% in the fishing communities that lie along the shores of Lake Victoria at the district border (3). Overall, 57% of PLWH residing in the district and participating in a previous survey reported past year alcohol use (4).

Alcohol use is a widely recognized risk factor for HIV infection (55, 56) and a robust global evidence base suggests that among PLWH, alcohol use can adversely impact engagement in HIV care and antiretroviral treatment (ART) outcomes throughout the HIV care continuum (see **Figure 1**) (57). After testing positive for HIV, alcohol use is associated with delayed linkage to care services and delayed initiation of ART (38). Among those on ART, alcohol use is associated with worse retention and non-adherence to a treatment regimen (36, 37). Some studies have found a relationship between any level of alcohol use and non-adherence to ART (36) while others have found threshold effects among heavy drinkers (58). Some of this non-adherence is intentional, driven by fears of "alcohol-ART interaction intoxication" beliefs (59) but doses are also unintentionally forgotten or missed due to intoxication (36). While the existing

literature has consistently found an association between alcohol use and decreased engagement and retention in the HIV care and treatment continuum (37, 40-42), findings on the relationship of alcohol use to HIV disease progression (using either immunologic and virologic markers) have been mixed (15, 43, 44).

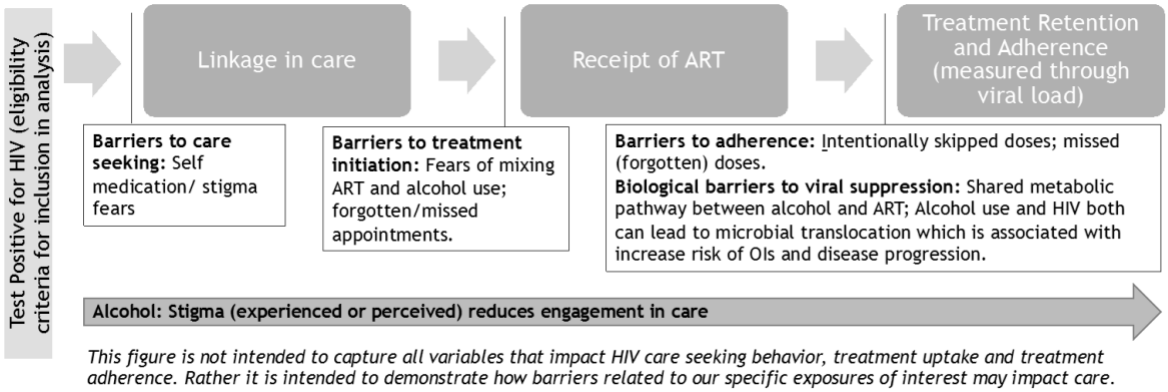

Figure 1. Conceptual Model Depicting Alcohol-Related Risk Factors for Poor HIV Care and Treatment Outcomes

HIV disease progression is the progression of an infected individual from asymptomatic to severely immunocompromised and ultimately meeting clinical diagnostic criteria for Acquired Immunodeficiency Syndrome (AIDS). Disease progression is measured through immunological (depletion of CD4 T-cell count) and/or virologic (increased viral load per milliliter of blood) markers indicative of compromised immune response and increased viremia, respectively. Early initiation of ART can halt disease progression and when taken consistently and correctly, ART can reverse disease progression, suppressing viral load. Progression of HIV disease can be directly affected by alcohol use through biological

mechanisms. For example, there is evidence that both alcohol use and HIV cause microbial translocation and markers of translocation are associated with increased opportunistic infections and HIV disease progression (60-62). Another potential biological pathway for alcohol use to impact disease progression is through its shared metabolic pathway with ART medications (63). The relationship between viral load and alcohol use may also be mediated by treatment adherence, and as alluded to above, alcohol has been reported to be associated with non-compliance to medication regimens (63, 64). Out of five recent prospective cohort studies examining alcohol use and HIV disease progression, after controlling for ART, only one study (65) found a positive association between heavy alcohol use and increased risk of detectable viral load (44). The other four studies (66-69), which used immunologic markers (CD4 cell count) to measure HIV disease progression, found no effect of heavy alcohol use after controlling for ART. These studies were all conducted in the United States, a setting that differs drastically from sub-Saharan Africa both in term of HIV care and treatment options as well as patterns of alcohol use. In the test-and-treat era, where linkage to HIV care and initiation of ART occur simultaneously, when an individual receives a positive HIV diagnosis, viral suppression can more readily be thought of as a measure of treatment success/failure than disease progression.

To date, most research examining the effects of alcohol use on HIV disease progression in sub-Saharan Africa have relied on immunological monitoring (CD4

T-cell count) (41, 43, 45, 46). In recent years, a consensus has emerged that when feasible, virologic monitoring should be implemented because virologic failure provide a more accurate identification of ART treatment failure (47). When taken consistently and correctly, ART can reduce an individual's HIV viral load to a level that is undetectable (i.e. viral suppression), significantly diminishing the likelihood of HIV transmission (70). After several clinical trials demonstrated the efficacy of treatment as prevention (TasP) (32-34), the Joint United Nations Programme on HIV/AIDS (UNAIDS) unveiled its current HIV prevention framework: the 95-95-95 targets. This framework aims to achieve 95% coverage at three steps in the HIV care continuum by 2030: (1) 95% of those infected aware of their status, (2) 95% of PLWH who are aware of their status on ART and (3) 95% of those on ART achieving viral suppression.

Achieving timely (i.e. as soon as possible after diagnosis) linkage to ART and viral suppression among PLWH is imperative to both secondary HIV prevention efforts as well as individual HIV treatment outcomes. A recent paper by Puryear et al. examined associations between alcohol use and heavy drinking on three HIV continuum outcomes (previous HIV diagnosis/aware of status, ART use, and viral suppression (using a cut off of <500 viral copies/mL)) in a large sample from 28 East African study sites across Kenya and Uganda (71). Alcohol users were less likely to know their HIV status and if positive, were less likely to be on ART. Among those on ART, alcohol use was not significantly associated with viral suppression

except among those who were classified as very high-level alcohol users. They also examined viral suppression among PLWH regardless of ART use and found a significant association between any alcohol use and viral suppression. The authors concluded ART use may be mediating the relationship between viral suppression and alcohol use in their sample. While this study included a very large population-based sample (118,923), and rigorous alcohol use measures and virologic outcomes (e.g., viral load) for treatment adherence, the analysis conducted was cross-sectional and the data was collected prior to the rollout of universal test-and-treat programs in Uganda, a policy which aims to test all individuals at risk for HIV infection and initiate those with a positive test onto antiretroviral therapy immediately, regardless of viral load or CD4 cell count.

The present study builds upon the existing literature and fills a gap in knowledge regarding the relationships between alcohol use and HIV treatment outcomes by exploring prospective associations between alcohol use and two important steps in the HIV care and treatment continuum (current use of ART, and achievement of viral suppression) using data from two consecutive rounds of the Rakai Community Cohort Study (RCCS) in Uganda. Achieving viral suppression in Rakai is important because this is one of many regions in the world with a heavy burden of both HIV and heavy, problematic drinking and the findings can inform potential avenues of intervention in other regions. The results are especially critical to support Uganda's National HIV strategic prevention efforts due to the district's

high HIV prevalence. We propose three broad hypotheses. First, we predict that alcohol use will be positively associated with not being on ART, and not being virally suppressed (defined as <=1000 copies/mL in accordance with Uganda's Ministry of Health). Second, there will be sex differences in alcohol use that may result in differential impacts on the HIV outcomes of interest. Finally, we hypothesize that worse HIV outcomes will be associated with reporting past year alcohol-related consequences (e.g., waking up with shaky hands the morning after drinking). This will be the first study in Rakai to look at viral suppression in data collected *after* the rollout of universal test-and-treat in the district in 2016. It is worth noting that while current treatment guidelines recommend initiation of ART upon linkage to care, this does not always occur; however it occurs most of the time. By using virologic outcomes (as opposed to immunologic outcomes), the findings from this study can provide more accurate estimates of the relationship between alcohol use and HIV treatment in Uganda (47).

Materials and Methods

Study Design and Data Collection:

The design and data collection methods of the RCCS have been described in detail in previous publications (30). In brief, the RCCS is an open cohort longitudinal HIV surveillance study currently in its 20th continuous round of data collection, with ongoing data collection since 1994. The present study involves secondary data analysis of rounds 18 and 19. Typically, data collection across

communities takes approximately a little over one year with the next round occurring in a given community 12-18 months later. The two visits data collection occurred between August 2016 – March 2020 when Uganda declared a national Lockdown due to the COVID-19 pandemic. At the time of analysis for the current study, data collection had not resumed; therefore, six trade communities (communities where buying and selling of services and goods is the most common self-reported primary profession) typically included in the RCCS that had not participated yet in round 19 were excluded from the analytic sample. The full sample of participants in round 18 was 19,795. Given the research focus on the relationship between alcohol use and HIV treatment outcomes, the current sample focused on participants living with HIV (known positives and those testing positive in Rakai Community Cohort Study) at round 18 creating a sample of 3,283 individuals.

The survey is conducted across 40 communities in Rakai district with roughly 20,000 residents participating in each round. A household census proceeds each round of the survey in order to identify eligible participants. Following the census, residents between the ages of 15 and 49 years who are present and provide written informed consent are invited to participate in the RCCS survey, which covers sociodemographic and behavioral characteristics, characteristics and health care utilization (inclusive of HIV services). HIV rapid testing is performed and post-test HIV counseling and referral to care and ART treatment initiation is

provided. Ethical approval for the RCCS has been granted by the Johns Hopkins School of Public Health's institutional review board (IRB), Columbia University's IRB, Western IRB, the Uganda Virus Research Institute's Research and Ethics Committee and the Uganda National Council for Science and Technology.

Measures The primary independent variable of interest was "any alcohol use", a dichotomous variable measured by the question, "Have you drunk any alcohol in the past year, for instance, beer, wine, waragi or other spirits, or home-made beer?" The second major independent variable of interest was the number of alcohol-related consequences (indicators of harmful drinking, heavy drinking and alcohol dependence) experienced in the past 12 months (unsteady gait, fell over, got angry, got violent/got into a fight, had difficulty speaking, forgot some of the things that you did or that happened while you were drinking, had shaking hands the next morning, felt ashamed of something that you did while drinking). Two of these items, "got into a fight" and "had shaky hands the next morning" were adapted measures from the Michigan Alcoholism Screening Test, a validated alcoholism screening tool (72). The other six consequences which were developed specifically for the RCCS were designed to capture aspects of harmful alcohol use and proxies of alcohol dependence as described in the previous research (48). Responses to these questions were tallied into a new variable, "number of past year consequences experienced" and a dichotomous categorical variable "no consequences vs. any consequences" was created.

Dependent variables. The two dependent variables pertained to steps in the HIV care and treatment continuum. The first outcome, "Current ART use" was a dichotomous variable measured by a yes/no response to the question, "Are you currently taking antiretrovirals?". The second outcome was the major variable of interest, viral suppression, which was collected as a continuous variable, viral load, and dichotomized per Ugandan ministry of health guidelines for viral suppression, defined as a viral load ≤1000 viral copies per mL of blood (73).

Covariates. Sociodemographic covariates included sex (male, female), community type (agricultural, fishing, trade), marital status (currently married, previously married, never married), education (no formal education, primary school or higher), employment (defined as the primary occupation of bar/restaurant worker, fishermen, trade/shopkeeper, agriculture/housework, other), religion (Christian, Muslim, other/no religion), age, and household socioeconomic status (an index based on dwelling attributes such as the presence of modern building materials and divided into tertiles for low, middle, high). As a study focused on alcohol use, we also controlled for other substance use, and specifically use of one or more drugs (marijuana, amphetamines, aero fuels ["glue"], mayirungi (a leaf that is chewed with stimulant properties), and/or heroin collapsed into (any/no past year drug use) in the past 12 months.

Data Analysis

All analyses were conducted in SAS studio (74). The data was inspected for errors, omissions, and data outside the limit ranges. Next, "baseline" (round 18) sociodemographic and independent variables of interest were analyzed, using descriptive statistics, to characterize the analytic sample overall and explore differences by participant sex. Descriptive analysis included frequencies for dichotomous and categorical variables, measures of central tendency for continuous outcomes and stratified bivariate analysis of covariates by sex using χ^2 analysis and 2 sample T-test. Multicollinearity was assessed by examining the intercorrelations between the predictor variables in the model as well as the tolerance and variance inflation factor (VIF).

To test the hypotheses, correlates of the two HIV treatment outcomes (current ART use and viral suppression) were examined longitudinally, using multivariable logistic regression models. Generalized Estimating Equations (GEE) were built using the proc genmod function in SAS and the logit link and binomial distribution adjusting for correlations from within person observations at the two visits. To identify potential bias due to loss-to-follow-up, sociodemographic and drug use covariates identified a priori from the literature were compared for participants that were retained at round 19 and those that were not. (Participation in the RCCS open cohort varies from year to year due to short- and long-term mobility; seventy one percent of those who participated at round 18

also participated in round 19.) This was done for the overall sample as well as for men and women separately. Any variables that were statistically significantly different by retention status using an alpha of 0.05 were included as covariates in multivariable models. Analyses also examined potential covariates by testing associations between these same sociodemographic and drug use variables and each of the outcome variables. Covariates were included in multivariate analysis if they differed by retention status and/or were significantly associated with the outcome using an alpha of 0.05. A stratified analysis by sex was also conducted to explore differences in HIV care outcomes by this variable. Finally, all multivariable models were rerun among alcohol users, this time with the other main independent variable of interest, past year alcohol related consequences (no consequences vs. any consequences), to evaluate associations between alcohol related consequences and the outcomes. Each outcome was analyzed among all PLWH to best capture the absolute associations between alcohol use and alcohol related consequences and the treatment outcomes of interest.

Multicollinearity

VIF and tolerance for independent variables with all three outcome models and intercorrelations between independent variables suggested that there was little multicollinearity between variables. All VIF were approximately 1, no tolerance values were <0.1 and no correlations were >0.7.

Missing data

We encountered a negligible number of missing responses/observations for one of the two HIV outcomes, viral suppression (0.44% of observations missing this outcome), as well as one of the covariates, household SES (1.2%). The source and impact of missing data was not explored further for these three variables, given the small proportion of missing observations.

To improve readability, for the remainder of the paper, round 18 will be referred to as "baseline" and round 19 will be referred to as "follow-up". Tables showing differences in sociodemographic and behavioral characteristics by retention status, overall and for men and women separately can be found in **Appendix File 1**.

Results

Descriptive Characteristics of the Sample at Baseline

Table 1 describes relevant baseline characteristics for the total sample as well as the characteristics of males and females separately, with all differences across the sexes being statistically significant. Just over half of the sample (55%) reported past year alcohol use at baseline, including 72% of men and 44% of women. Among alcohol users, 38% reported experiencing any alcohol-related consequences in the past 12 months, with significantly higher rates for men (42%) than women (31%). Regarding demography, over half of study participants

resided in the fishing communities with only 6% from trade communities. Half of participants (50%) fell into the "high" socioeconomic status (SES) category. Housework (47.3%) and fishing (46.1%) were the most common professions among women and men, respectively. Past year drug use was uncommon but men were much more likely to report this behavior than women (11% versus 1%, respectively). Men were more likely to be married than women (66% versus 55%).

Figure 2 shows the proportion of persons reporting each treatment outcome at round 18 (baseline), overall, and by alcohol use status. A greater proportion of persons who did not report alcohol use in the past year (85.0%) were currently on ART treatment than those who did (78.3%) ($p<0.0001$). The same pattern was observed for viral suppression; a smaller proportion of alcohol users were virally suppressed (80.9%) than non-alcohol users (86.5%) ($p<0.0001$).

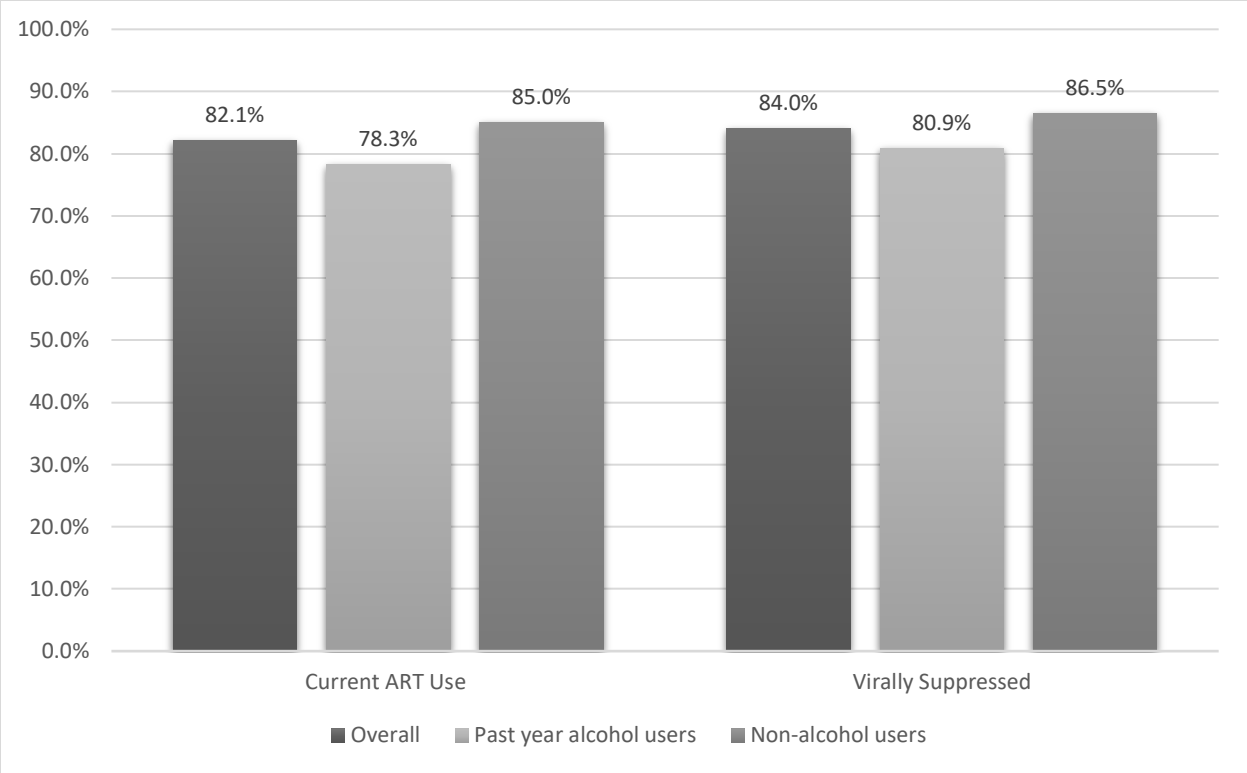

Figure 2. Proportion of PLWH Reporting Current ART Use and Viral Suppression by Past Year Alcohol Use Status.

Multivariate analysis of alcohol use on HIV care continuum outcomes and disease progression

Tables 2a and 2b, present multivariate analyses of the association between past year alcohol use and current ART use, and past year alcohol use and level of viral suppression, respectively. These data are presented for the full sample, and then for men and for women separately and all analyses are adjusted for relevant covariates.

As shown in Table 2a, PLWH who reported past year alcohol use had lower odds of currently being on ART than those who reported no past year alcohol use (OR 0.72, 95% CI 0.60-0.85), p<0.0001). When stratified by sex, this relationship was still significant for both men and women. Table 2b uses the same structure as Table 2a to present data regarding the relationship between viral suppression and past year drinking among PLWH. Here past year alcohol use was significantly inversely associated with viral suppression (OR 0.73 95% CI 0.62-0.87 p=0.0004), as hypothesized. However, when stratifying by sex, only women showed a significant lower odds ratio for this relationship.

Multivariate analysis of alcohol use consequences on HIV care continuum outcomes and disease progression

Tables 3a and 3b, respectively, summarize multivariate analysis results of the association between past year experiences of alcohol-related consequences and current ART use, and viral suppression among individuals in the sample who reported alcohol use in the 12 months. These data are presented for the full sample, and then for men and for women separately and all analyses are adjusted for relevant covariates.

As shown in Table 3a, persons who reported past year alcohol-related consequences had lower odds of current ART use than those who reported no consequences (OR 0.73 95% CI 0.59-0.90, p=0.0036). When stratified by sex, only

men showed a significantly lower OR for the association between alcohol-related consequences and current ART use. Similarly, Table 3b presents results regarding the relationship between experiences of alcohol-related consequences and viral suppression. Experiencing past year alcohol-related consequences was significantly associated with lower odds of viral suppression (OR 0.69 95% CI 0.57-0.85, p=0.003); again, this finding only statistically significant for men and not women. Among women living with HIV, differential loss to follow up by alcohol consequences was observed in the RCCS. There was a higher prevalence of consequences among women lost to follow up than women retained, and this difference was statistically significant (34.3% viral suppression 24.9%, p=0.0005); significant differential loss to follow up among male alcohol users was not observed.

Discussion

The present study, which is the first to use longitudinal data to explore associations between alcohol use and ART use and treatment outcomes in the context of Uganda's current HIV treatment guidelines (i.e. universal treatment and a threshold for viral suppression consistent with Ugandan Ministry of Health protocol) found that alcohol use and alcohol-related consequences were significantly associated with lower likelihood of current ART use as well as poorer treatment outcomes. The present analysis confirmed many, but not all of the hypotheses, including finding clinically significant differences in viral load (i.e. the

achievement of viral suppression) by alcohol use status. Observed significant inverse associations between past year alcohol use and current ART use were driven by the relationships between these variables in men and women while significant inverse associations between viral suppression and alcohol use were driven by the relationship between these variables in women. Significant inverse associations between alcohol-related consequences and the HIV outcomes were driven by the relationships between these variables in men. These findings have important public health implications and address existing gaps in understanding the effects of alcohol use on HIV care and treatment outcomes. Following we present insights on the public health implications of the study.

Alcohol use was associated with lower odds of current ART use among both men and women in the sample. Uganda's current HIV treatment guidelines recommend initiation of ART in all patients, regardless of disease status, meaning all patients diagnosed as HIV positive should immediately be linked into HIV care and initiated on ART. In previous studies. associations between alcohol use and delayed HIV care-seeking have been observed (37, 38, 75); the implementation of test and treat and immediate initiation of ART should reduce barriers to treatment and opportunities for delayed treatment initiation. Despite all data in the study being collected after the roll out of test and treat, alcohol users were less likely to report current ART use, which could be the product of declining to

initiate ART, failure to pick up ART medication and attend follow up appointments and/or choosing to discontinue treatment.

When studying the relationship between alcohol use and viral suppression among all PLWH, regardless of current ART use, we found that those reporting any alcohol use were significantly less likely to be virally suppressed. Prior studies have found that ART use mediated the relationship between alcohol use and viral suppression (63, 64). To explore this possibility, mediation tests were performed in our own sample for both exposures (data not shown). For any alcohol use, a significant natural indirect effect supported mediation by ART use in the overall sample. Among alcohol users, ART use did not mediate the relationship between consequences and viral suppression. The findings are consistent with Puryear et al (2020), who observed a significant association between viral suppression and alcohol use when looking in their overall sample, but not when controlling for ART use (71). Another longitudinal cohort study in an ART naïve sample in Uganda found no association between unhealthy alcohol use (defined in this study as PEth levels indicative of at least two drinks a day or an AUDIT-C score meeting criteria for alcohol use disorder) and decline in CD4 count (a measure of HIV disease progression); the authors determined that the relationship between these two variables was clinically insignificant (43). This finding does not necessarily conflict with our own findings because the outcomes are different; they found no association between alcohol use and HIV disease progression and we found an

association between alcohol use and failure to achieve viral suppression. Still, additional research is warranted to further disentangle the relationship between alcohol use, ART use, and viral suppression, preferably through the use of more precise measures such as biomarkers for ART adherence and a validated alcohol use measure like the AUDIT.

In stratified analysis both men and women who used alcohol in the past year had lower odds of viral suppression, but this relationship was only statistically significant among women. It is possible that the lack of significant association between alcohol use and viral suppression among men is a product of the alcohol use measure itself not being sensitive enough to detect differences. Ideally, alcohol use is measured by a validated scale that allows for differentiation of drinking behaviors, such as the Alcohol Use Disorder Identification Test (AUDIT) to detect problematic alcohol use (76) or a measure that captures drinking patterns and quantity and frequency of consumption. In Uganda, persons who drink tend to drink heavily (77), so the measure is more sensitive in this context than others, but this variable still captures a wide range of alcohol use behaviors from very low risk (e.g. ceremonial drinking on special occasions) to very high risk (e.g. regular binge drinking). The lack of precision regarding alcohol use behaviors captured by this variable may have reduced our ability to detect a significant association if the relationship between alcohol use and viral suppression is

strongest among those in the heaviest drinking categories, as has been observed in previous studies (64, 71, 78).

Among alcohol users, those reporting at least one past year alcohol-related consequence were less likely to currently be on ART than those reporting none; when stratified by sex this relationship was only significant among men. When examining viral suppression among the overall sample of alcohol using PLWH (regardless of ART use), a significant effect of consequences was observed. Again, this relationship was only significant among men. A number of previous studies have found that individuals in the heaviest drinking categories are the least likely to achieve viral suppression, and a recent biomarker study in Uganda found that men are more likely than women to underreport unhealthy levels of drinking (53). If this extends to reporting of alcohol-related consequences, men in the sample may have actually experienced a greater number of consequences than reported which would bias the estimates towards the null. Furthermore, the finding related to the relationship between alcohol-related consequences and VS (which was significant among all PLWH but not mediated by ART use) suggests that other unmeasured confounders (e.g. mental health) may be the key to better understanding this pathway.

In Uganda, men are not only more likely than women to drink, they are also more likely to consume hazardous amounts of alcohol, a trend seen globally (77).

These gendered differences in alcohol consumption are most pronounced in societies with greater gender inequality (79). The lack of significant association between alcohol-related consequences and both HIV treatment outcomes among women may be a product of different gendered patterns of drinking. Social norms around alcohol use in Uganda dictate gendered differences in where and how one can consume alcohol. Prior work in Rakai has found that it is less socially acceptable for women to consume alcohol than men (49); furthermore men in more rural (i.e., traditional) areas of Uganda have agency to consume alcohol outside of the household at drinking establishments, whereas women's alcohol use is typically constrained to drinking at home with friends and family (including their spouse) (50). Still, we found that women who reported any past year alcohol use were statistically significantly less likely to currently be on ART and be virally suppressed, suggesting differences in HIV treatment outcomes by alcohol use status. Women who report any level of alcohol use in Rakai may have less heterogeneity in their drinking behaviors than men (i.e., they may mostly be low level users) or they may be underreporting their alcohol related consequences for social desirability, diminishing differences between the categories of alcohol user. Another possible explanation for the lack of significant relationships between alcohol related consequences and the outcomes observed in women could be the significant differential loss to follow up among female alcohol users; women experiencing consequences were less likely to be retained than those not reporting consequences.

This analysis identified alcohol use as an important barrier to achieving optimum HIV care and treatment outcomes in Uganda. It provides timely estimates for treatment coverage in an area heavily impacted by the HIV epidemic and explores differences in the relationship between alcohol and these outcomes by sex. These findings have important implications for public health planning because alcohol use is a modifiable risk behavior and the findings inform points in the care and treatment continuum that can be intervened on for improved outcomes. The negative association between alcohol use and current ART use suggests that interventions to address alcohol use among PLWH should occur as early in the care and treatment cascade as possible (i.e. at the point of HIV testing) in order to facilitate immediate uptake of care. Our recent qualitative work in the region suggests that immediately after receipt of HIV test results is an optimum time to screen for and intervene on harmful drinking (80). Women living with HIV indicated such an intervention would be acceptable and that people's willingness to implement lifestyle changes immediately after receiving their results (in order to improve health outcomes, either to continue to stay negative or live as healthily as possible with HIV) offers a unique window of susceptibility to behavior change. Counseling around the harms of alcohol use is already discussed by healthcare providers once an individual is engaged in routine HIV care, so this would involve extending alcohol related counseling by introducing it at an earlier stage in the continuum: time of diagnosis. Among men who consume

alcohol we observed worse outcomes among those experiencing consequences related to their alcohol use, suggesting that men who consume enough alcohol to experience these consequences should be screened for alcohol misuse and a priority population for alcohol interventions. More rigorous alcohol measures in this setting are needed to clearly distinguish types of drinker and further identify highest priority populations.

To date there is limited evidence available regarding the effectiveness of interventions to address alcohol use among PLWH and even fewer studies looking at this problem in Africa (81, 82). Additional work is needed to adapt and pilot effective interventions to reduce risky alcohol consumption or treat alcohol use disorders from other settings. Findings from prior work suggests a balance needs to be struck between not overburdening the primary healthcare system (i.e., limiting the additional time and effort an integrated intervention demands of health care providers) while also ensuring intervention dose is large enough to be effective.

This study had a number of limitations related to variable availability. All of the outcomes and risk factors except for viral load were self-reported measures, subject to bias. Validated measures for harmful and hazardous alcohol use (e.g. Alcohol Use Disorders Test) were not available and the included alcohol use variables may not have been sensitive enough to identify differences by alcohol

use status in the study sample. In addition, variables from important domains that may confound the relationship between alcohol use and the HIV outcomes of interest (such as measures of impulsivity (83) and mental health (84, 85)) were not available, which may result in unmeasured (and therefore uncontrolled) confounding in the analysis. We were also not able to control for time since diagnosis in the models. RCCS is an open cohort study; although HIV tests are performed at each visit, there is no way of knowing if the oldest available test on file for an individual in the RCCS dataset is their first positive test. Finally, the associations reported in this paper should be interpreted with caution; they are odds ratios and may not approximate the relative risk. Despite these limitations, the study had a number of strengths including the large sample size, use of virologic outcomes to measure HIV disease progress, use of two consecutive time points of data and the timeliness of the presented findings which reflect current treatment guidelines and protocol.

This study confirms that alcohol use is adversely associated with current ART use and HIV treatment failure. The relationship between alcohol use and HIV outcomes differed by gender and this should be considered in the development of future interventions, which should focus on intervening on alcohol use at time of HIV diagnosis. Among alcohol users, experiencing alcohol related consequences is also associated with not currently being on treatment and not being virally suppressed. Findings related to viral load suggest that ART may

mediate the relationship between alcohol use and viral suppression. Alcohol consumption should be a target of intervention among PLWH in Uganda, especially those recently diagnosed as HIV-positive to improve their health as well as regional HIV care continuum outcomes and support secondary prevention efforts.

Table 1. Baseline (round 18) characteristics of PLWH participating in the Rakai Community Cohort Study, Overall and Stratified by Sex

Characteristic	**Overall (n=3283)**	**Men (n=1310)**	**Women (n=1973)**	**P-value for Chi²**	**Chi²**
Past year alcohol use				<0.0001	258.7
Yes	2877 (55.5%)	949 (72.4%)	867 (43.9%)		
No	2400 (45.5%)	361 (27.6%)	1106 (56.1%)		
Alcohol-related consequences				<0.0001	32.1
None	1127 (62.2%)	532 (58.2%)	595 (68.7%)		
Any	685 (37.8%)	414 (43.8%)	271 (31.3%)		
Mean Age (SD)	34.5 (7.5)	36 (7.0)	33.6 (7.6)	<0.0001	t= 9.9
Residence				<0.0001	62.3
Agrarian	1305 (39.8%)	439 (33.5%)	866 (43.9%)		
Trade	200 (6.1%)	54 (4.12%)	146 (7.4%)		
Fishing	1778 (54.2%)	817 (62.4%)	961 (48.7%)		
Education				<0.0001	18.8
No School/Primary	1036 (31.6%)	470 (35.9%)	566 (28.7%)		
Secondary or above	2247 (68.4%)	840 (64.1%)	1407 (71.3%)		

Table 1 cont'd. Baseline (round 18) characteristics of PLWH participating in the Rakai Community Cohort Study, Overall and Stratified by Sex

Characteristic	Overall (n=3283)	Men (n=1310)	Women (n=1973)	P-value for Chi^2	Chi^2
HH SES				0.0003	16.1
High	1631 (50.3%)	595 (46.9%)	1036 (52.5%)		
Middle	579 (17.9%)	219 (17.2%)	360 (18.3%)		
Low	1033 (31.9%)	456 (35.9%)	577 (29.2%)		
Occupation				<0.0001	154.2
Housework	1209 (36.8%)	276 (21.1%)	933 (47.3%)		
Trade/shopkeeper	556 (16.9%)	146 (11.2%)	410 (20.8%)		
Bar/Restaurant worker	268 (8.2%)	collapsed into "other"*	261 (13.2%)		
Fisherman	605 (18.4%)	604 (46.1%)	collapsed into "other"*		
Other	645 (19.7%)	284 (21.7%)	369 (18.7%)		
Religion				0.0005	15.2
Christian	2891 (88.1%)	1188 (90.7%)	1703 (86.3%)		
Muslim	370 (11.3%)	113 (8.6%)	257 (13.0%)		
None/Other	22 (0.7%%)	9 (0.7%)	13 (0.7%)		

Table 1 cont'd. Baseline (round 18) characteristics of PLWH participating in the Rakai Community Cohort Study, Overall and Stratified by Sex

Characteristic	Overall (n=3283)	Men (n=1310)	Women (n=1973)	P-value for Chi^2	Chi^2
Any Drug Use**				<0.0001	171
Yes	165 (5.0%)	146 (11.2%)	19 (1.0%)		
No	3118 (95.0%)	1164 (88.9%)	1954 (99.0%)		
Marital Status				<0.0001	43.1
Currently Married	1956 (59.6%)	867 (66.2%)	1089 (55.2%)		
Previously Married	1124 (34.2%)	363 (27.7%)	761 (38.6%)		
Never Married	203 (6.2%)	80 (6.1%)	123 (6.2%)		
No	3118 (95.0%)	1164 (88.9%)	1954 (99.0%)		

Table 2a-b. Multivariate GEE of the Relationship between Past Year Alcohol Use and Treatment Outcomes

2a. Past Year Alcohol Use and Current ART Use

2a. Past Year Alcohol Use and Current ART Use

	Overall[A] (n=3,285)				Men[B] (n=1,311)				Women[C] (n=1,974)			
	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value
Alc.												
Yes	-0.33	0.09	0.72 (0.60-0.85)	0.0001	-0.31	0.14	0.73 (0.59-1.07)	0.0286	-0.34	0.11	0.71 (0.58-0.88)	0.0018
No	--	--	1.00	--	--	--	1.00	--	--	--	1.00	--

2b. Past Year Alcohol Use and Viral Suppression

	Overall[G] (n=3,285)				Men[H] (n=1,311)				Women[I] (n=1,974)			
	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value
Alc.												
Yes	-0.31	0.09	0.73 (0.62-0.87)	0.0004	-0.24	0.13	0.79 (0.61-1.08)	0.0698	-0.32	0.11	0.72 (0.58-0.89)	0.0031
No	--	--	1.00	--	--	--	1.00	--	--	--	1.00	--

A: visit no, marital status, HH SES, occupation, sex, drug use, residence

B: visit no, marital status, HH SES, drug use

C: visit no, marital status, age, occupation

D: visit no, marital status, residence, occupation, sex, drug use

E: visit no, marital status, age, drug use

F: visit no, marital status, age, residence, occupation

Table 3a-b. Multivariate GEE of the Relationship between Experiencing Alcohol-related Consequences and Treatment Outcomes

3a. Alcohol-related Consequences and Current ART Use

	All alcohol users[A] (n=2,014)				Men[B] (n= 1,004)				Women[C] (n=1,010)			
	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value
Consq.												
None	--	--	1.00	--	--	--	1.00	--	--	--	1.00	--
Any	-0.31	0.11	0.73 (0.59-0.90)	0.0036	-0.37	0.15	0.60 (0.46-0.79)	0.0003	-0.29	0.10	1.09 (0.79-1.52)	0.5739

3b. Alcohol-related Consequences and Viral Suppression

	All alcohol users[D] (n=2,014)				Men[E] (n= 1,004)				Women[F] (n=1,010)			
	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value	B	SE	OR (95% CI)	P value
Consq.												
None	--	--	1.00	--	--	--	1.00	--	--	--	1.00	--
Any	-0.37	0.10	0.69 (0.57-0.85)	0.0003	-0.37	0.13	0.69 (0.54-0.88)	0.0034	-0.27	0.17	0.76 (0.54-1.07)	0.1120

A: visit no, marital status, HH SES, occupation, sex, drug use, residence

B: visit no, marital status, HH SES, drug use

C: visit no, marital status, age, occupation

D: visit no, marital status, residence, occupation, sex, drug use

E: visit no, marital status, age, drug use

F: visit no, marital status, age, residence, occupation

Acknowledgements

This work, in part has been submitted for publication of the material at it may appear in Drug and Alcohol Dependance 2021, Miller, A.P., Pitpitan, E. V., Kiene, S., Raj, A., Jain, S., Zuniga, M. L., Nabulaku, D., Nalugoda, F., Ssekubugu, R., Nantume, B., Kigozi, G., Sewankambo, N. K., Kagaayi, J., Reynolds, S. J., Grabowski, M. K., Wawer, M., & Wagman, J. The dissertation author was the primary investigator and author of this paper. Protected time to complete this project was provided by National Institute of Alcohol Abuse grants F31AA028198-01 (PI: Miller).

CHAPTER 2: In the Era of Universal Test and Treat, Intimate Partner Violence is not associated with poor HIV treatment outcomes in the Rakai region of Uganda

Abstract

Introduction: IPV is a pervasive public health issue that disproportionately burdens WLWH Despite literature supporting the relationship between IPV victimization and poor HIV care and treatment outcomes, with much of the evidence coming from high income countries, cross-sectional analyses and non-current treatment protocols, important gaps in the existing body of evidence exist. The present study explores associations between IPV and HIV treatment outcomes under current HIV treatment guidelines in Uganda.

Methods: Data collected in two consecutive rounds (August 2016-November 2020) of the Rakai Community Cohort Study (RCCS), an open cohort HIV surveillance study conducted in the Rakai region of Uganda, were analyzed. IPV and other correlates of two HIV treatment outcomes (current ART use and viral suppression) were examined longitudinally, using logistic regression and adjusting for outcome variables at baseline. To address differences in retention by IPV, as well as confounding, estimated propensity scores were used to create inverse probability of treatment and censoring weights (IPTCW) which were applied to the final regression models.

Results: The sample consisted of 1,923 WLWH. One-third (34.6%), 26.5%, 13.5% of participants reported past year verbal, physical and sexual IPV at baseline. At baseline, a greater proportion of persons who did not experience past year physical IPV (81.3%) were currently on ART treatment than those who did (77.1%) (p=0.0387). The same pattern was observed for viral suppression; a smaller proportion of those who experienced physical IPV were virally suppressed (79.4%) than those who did not (84.3%) (p=0.0117). The proportion achieving viral suppression also significantly differed by exposure to verbal IPV (p=0.0302). After application of weights, none of the forms of IPV were associated with lower odds of ART use or viral suppression.

Conclusions: IPV is a critical public health issue among WLWH, but it does not appear to be a barrier to ART use or viral suppression in the sample. Uptake of universal test and treat guidelines may have reduced barriers to HIV treatment. Given the prevalence of IPV. interventions to address it in this population are needed. Additional work exploring if specific subgroups of WLWH experience IPV related barriers to care is needed.

Keywords: HIV, treatment adherence, Uganda, Viral Suppression, Intimate Partner Violence

Introduction

Intimate partner violence (IPV), defined as physical, sexual or verbal violence perpetrated by an intimate partner, is a pervasive public health issue that disproportionately burdens women. Globally, 30% of women have experienced IPV in their lifetime and this estimate is even higher in sub-Saharan Africa where 36.6% of women report having experienced IPV in their lifetime (86). Experiencing IPV can adversely affect physical, sexual and mental health outcomes (87-90); in its most severe forms, IPV can lead to death. Globally, 38% of female murders are committed at the hands of a male intimate partner (86) and IPV is also a risk factor for suicide (91). IPV is also inextricably linked to HIV, another prevalent public health issue that disproportionately burdens women.

The relationship between IPV and HIV is bidirectional. IPV can increase risk of HIV infection directly (e.g., forced intercourse) and indirectly (e.g. reduced ability to safely negotiate condom use) (8). Women who are living with HIV are also more likely to experience IPV (15, 19, 20) and the literature suggests that experiencing IPV is associated with delayed and decreased engagement throughout the HIV care continuum. A 2015 meta-analysis by Hatcher et al. looking at the impact of IPV victimization on engagement and retention in HIV care found a statistically significant association between experiencing IPV and lower odds of current ART receipt (OR 0.79, 95% CI 0.64 – 0.97, p=0.012), lower odds of ART adherence (OR 0.48, 95% CI 0.30 – 0.75, p=0.044) and lower odds of

viral suppression (OR 0.64, 95% CI 0.46–0.90, p=.114) (39). Several causal pathways have been identified to explain poor engagement and retention in the HIV care continuum among victims of IPV (see **figure 3**).

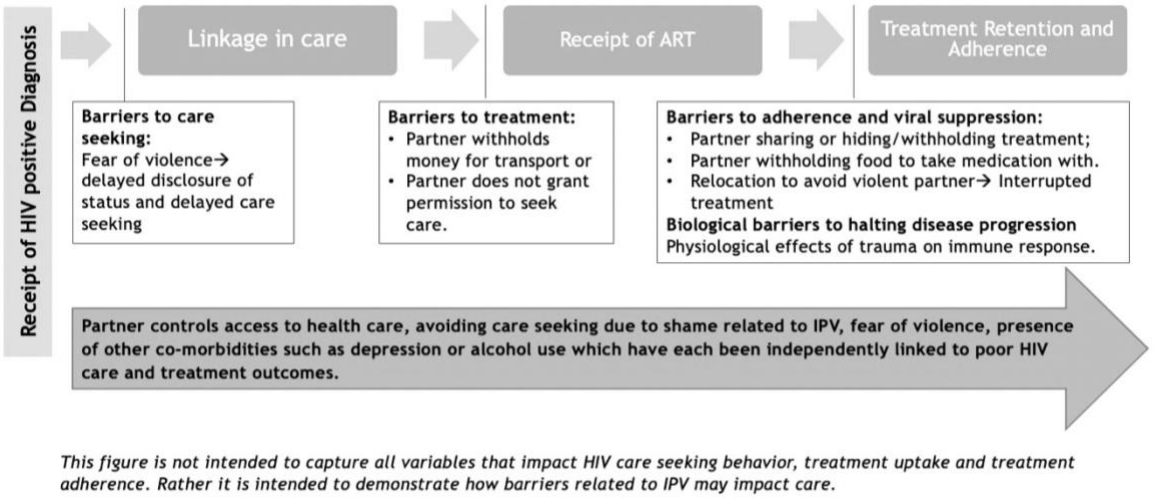

Figure 3. Conceptual Model Depicting IPV-related Risk Factors for Poor HIV Care and Treatment Outcomes

Fear of violence may lead victims of IPV to delay or refrain from disclosing their positive status to their partners, which can lead to delays in initiating care and poor adherence, as personal safety (and hiding one's HIV positive status) is prioritized over treatment adherence (92). Studies looking at the effect of experienced trauma and engagement in HIV care support this link between IPV victimization and delayed initiation of ART and non-adherence. A 2004 study found that any lifetime experience of physical or sexual violence was associated with declining ART use among women who were medically eligible to initiate treatment (93) and a 2006 study found increased likelihood of non-adherence to

ART with each additional lifetime experience of trauma (94). Additional potential drivers of non-engagement and non-adherence that persist across the care and treatment continuum among those experiencing IPV include a controlling partner limiting access to care and avoiding care seeking due to shame and denial around the experienced abuse (95, 96).

In the Rakai region of Uganda, both IPV and HIV are critical public health issues. HIV prevalence exceeds the national average (6.2%) at 7.9% with some deeply affected fishing communities experiencing a median prevalence of 49% among women (3, 97). Nearly half (49.8%) of women in the region report having experienced some form of IPV in their lifetime (5) and one in five (21%) women report experiencing some form of IPV in the past year (98). Prior mixed-methods work in the region found that any form of IPV in the past year reduced engagement in HIV care by 49-56% and ART use by 50-73% among women 30 years of age and older, but did not significantly effect among women under 30 years of age (99). However, this data was collected between 2008-2013, which precedes the rollout of current treatment guidelines in Rakai. Women participating in the qualitative component (conducted in 2017) of this mixed-methods study reported IPV as a consequence for taking their ART and indicated that threats of violence contributed to non-adherence (99).

Despite a robust body of literature supporting the relationship between IPV victimization and poor HIV care and treatment outcomes, important limitations and gaps in the existing body of evidence exist. The 2015 review by Hatcher et al. described above did not identify any longitudinal studies and the majority of included studies were conducted in a single high income country, the United States (39). Understanding the relationship between IPV and HIV treatment outcomes in sub-Saharan Africa, a setting experiencing the largest generalized HIV epidemic where young women and girls experience high-risk of both IPV and HIV is important for public health planning efforts, in terms of improving treatment outcomes, promoting secondary prevention via viral suppression and improving delivery of trauma informed care. The present analysis addresses this urgent gap by exploring associations between experiences of IPV and two HIV treatment outcomes using data from two rounds of an ongoing HIV surveillance cohort in Rakai, Uganda. The data were collected after the rollout of universal test and treat (a policy which aims to test all individuals and initiate those with a positive test onto ART immediately, regardless of viral load or CD4 cell count), allowing us to explore associations between experiences of violence and treatment outcomes in the context of current treatment guidelines. We focus exclusively on experiences of IPV among women, because although men can and do experience IPV, the overwhelming majority of IPV is experienced by women and perpetrated by men (both generally and in the study setting) (100, 101). Furthermore, prior work in Rakai found a low prevalence of female physical IPV

perpetration (3%) and the majority of those reporting perpetration (80%) also reported recent IPV victimization (101), which suggests this may have been self-defense. We hypothesize that women experiencing any form of IPV (verbal, physical or sexual) will be less likely to report current ART use and be less likely to be virally suppressed relative to women who report no past year IPV.

Materials and Methods

Data Collection:

The RCCS is a longitudinal open cohort HIV surveillance study and its data collection methods have been described in detail in previous publications (30). The survey, which is conducted across 40 communities in Rakai district with roughly 20,000 residents participating in each round, is currently in its 20th round of data collection. RCCS is implemented in two phases; first a household census is conducted in order to identify eligible participants. During the census, all persons residing in a household are enumerated (whether present or not) and information on life events (births, deaths), housing characteristics and resident mobility are collected. The RCCS survey is conducted following the census; residents between the ages of 15 and 49 years who are present and provide written informed consent are invited to participate. The survey covers a wide range of sociodemographic and behavioral characteristics, including sexual risk behaviors, ART use, family planning and health care utilization (inclusive of HIV

services). HIV rapid testing is also performed and post-test HIV counseling, ART treatment initiation and referral to ongoing care is provided. Ethical approval for the RCCS has been granted and renewed on an ongoing basis by the Johns Hopkins School of Public Health's institutional review board (IRB), Columbia University's IRB, Western IRB, the Uganda Virus Research Institute's Research and Ethics Committee and the Uganda National Council for Science and Technology.

Analytic Sample:

The present study involves secondary analysis of data collected in two consecutive rounds of the RCCS. Data collection for RCCS typically occurs in a given community every 12-18 months. Round 18 was conducted from August 2016 to May 2018. Data collection for Round 19 began in June of 2018 but was halted in March 2020 due to the national lockdown in Uganda for the COVID-19 pandemic. Data collection resumed in August of 2020 and concluded in November of the same year. Given the focus on the relationship between IPV and HIV treatment outcomes, the analytic sample focused on women living with HIV (known positives and those testing positive in RCCS) at round 18 who reported an intimate partnership in the past 12 months (individuals who do not report a past year intimate partnership are not asked questions regarding past year IPV), creating a sample of 1,923 individuals.

Measures

Primary exposures. The primary exposures of interest pertained to past year experiences of three categories of IPV: physical, sexual and verbal. Ten adapted questions were used from the Conflict Tactics Scales (CTS) (102), a validated measure that has previously been used for IPV research in this setting. The three forms of IPV were measured by asking, "In the past 12 months has your partner…":

Verbal IPV (1 item) "verbally abused or shouted at you?"

Physical IPV (6 items) "pushed, pulled, slapped, held you down?"; "punched you with fist or something that could hurt you?"; "kicked or dragged you?"; "tried to strangle or burn you?"; "threatened you with a knife, gun, other weapon?"; and "attacked you with knife, gun, other weapon?"

Sexual IPV (3 items) "used verbal threats to force you to have sex;" "physically forced you to have sex;" or "coerced you to perform other sexual acts when you did not want to."

The formatting of this question differed between rounds 18 and 19. In round 18, participants were asked to answer the ten IPV questions in relation to a specific intimate partner (starting with current/most recent). They were asked to recall this

information for up to four past year partners. Responses were collapsed across partners, where a "yes" response to an item with one partner indicated a yes for that type of IPV. The responses for the six physical IPV items and four sexual IPV items were then further collapsed so that an individual who responded yes to any of the six physical IPV items was a "yes" for past year physical IPV, and similarly, an affirmative response to any of the three forms of sexual violence was a "yes" for past year sexual IPV. In round 19, participants were asked each of the ten IPV items only once, regarding all partners in the past year. Responses to the six physical IPV items and three sexual IPV items were still collapsed to create single measures for each form of IPV, "any past year physical IPV?" (yes/no) and any past year sexual IPV?" (yes/no).

Dependent variables. The two dependent variables pertained to HIV treatment outcomes. The first outcome, "Current ART use" was a dichotomous variable measured by a yes/no response to the question, "Are you currently taking antiretrovirals?". The second outcome was the major variable of interest, viral suppression, defined per Ugandan ministry of health guidelines as a viral load less than or equal to 1000 viral copies per mL of blood (73). This variable was collected as a continuous variable, viral load, but dichotomized to increase clinical meaningfulness.

Covariates. Covariates were identified *a priori* from the literature and included community type (agricultural, fishing or trade), occupation (housework, bar/restaurant worker, trade/shopkeeper, other profession) marital status (currently married or not married), age and household socioeconomic status (a index based on dwelling attributes such as the presence of modern building materials and electricity and divided into tertiles for low, middle, high).

Data Analysis

All analyses were conducted in SAS studio (74). The data were inspected for errors, omissions, and data outside the limit ranges. Next, "baseline" (round 18) sociodemographic and independent variables of interest were analyzed, using descriptive statistics, to characterize the analytic sample. Descriptive analysis included frequencies for dichotomous and categorical variables and measures of central tendency for continuous outcomes. Multicollinearity was assessed by examining the intercorrelations between the exposure variables in the model as well as the tolerance and variance inflation factor (VIF).

RCCS is an open cohort study but efforts are made to retain participants from year to year through the census screening activities that precede each survey round. However, round 19 was interrupted by the COVID-19 lockdown which may have adversely impacted follow-up. We looked for differences by retention status by our main outcome variable, viral suppression as well as the

three main exposures, verbal, physical and sexual IPV. Chi-squared analysis was performed to identify any differences in retention by IPV exposure status. Statistically significant differences were observed for physical IPV. We also observed significant differences in retention by a number of covariates: age, marital status, community type and household SES. To address attrition as well as confounding, estimated propensity scores were used to create inverse probability of treatment weights (IPTW) and inverse probability of censoring weights (IPCW) which were combined and applied to the final regression models. Both stabilized and unstabilized IPTWs were applied and compared. Outcomes from stabilized models are reported.

To test the hypotheses, correlates of the two HIV treatment outcomes (current ART use and viral suppression) were examined longitudinally, using logistic regression and adjusting for outcome variables at baseline. First directed acyclic graphs were used to identify the minimally sufficient set of baseline covariates to adjust for to reduce bias from measured confounders. A variable was considered a confounder if it was predictive of both the exposure and outcome and was not on the causal pathway between exposure and outcome. Next, propensity scores were created based on these measured confounders: age, household socioeconomic status, marital status and residence. To create the propensity scores for the IPTWs, an exposure logistic regression model was used where identified confounders were regressed on each IPV exposure of interest. Next,

propensity scores for the IPCWs, were created by regressing the identified confounders on censoring status. These two weights were then combined to create a single weight that addressed bias from both censoring and the potential confounders (known as inverse probability of treatment and censoring weights, IPTCWs). Finally, logistic regression models were built to obtain odds ratios with the IPTCWs using the proc genmod function in SAS and the logit link and binomial distribution.

Multicollinearity

All VIF were less than 2, no tolerance values were <0.1 and no correlations were >0.7, suggesting that there was little multicollinearity between variables.

Missing data

We encountered missing observations for one of the two HIV outcomes: VS (0.43% of observations missing this outcome). We also encountered a single missing observation for one of the covariates: household SES (0.04%). The source and impact of missing data was not explored further for these two variables, given the small proportion of missing observations. Participation in this open cohort varies from year to year; sixty three percent of those who participated at round 18 also participated in round 19.

Results

Descriptive Characteristics of the Sample at Baseline

Table 4 describes relevant baseline characteristics of the study sample. Just over 1/3 of participants reported experiencing past year verbal IPV (34.6%). Past year physical and sexual IPV were reported by 26.5% and 13.5% of participants, respectively. Mean age of participants was 32.8 years (SD 7.2 years). The largest proportion of participants (45.9%) resided in fishing communities. Most (61.8%) were currently married and most (72.0%) had attended at least some of secondary school. The majority (56.3%) of participants were classified as having high socioeconomic status and the most common occupation among participants was housework (45.1%).

Figures 4a and 4b show the proportion of women reporting each HIV treatment outcome (current ART use and viral suppression, respectively) at baseline by exposure to each form of IPV. A greater proportion of persons who did not experience physical IPV in the past year (81.3%) were currently on ART treatment than those who did (77.1%) (p=0.0387). The same pattern was observed for viral suppression; a smaller proportion of those who experienced physical IPV were virally suppressed (79.4%) than those who did not (84.3%) (p=0.0117). Across sexual and verbal IPV, we saw the same trend: persons experiencing both forms of IPV were less likely to be on ART and less likely to be virally suppressed than their counterparts who did not. However, these differences were not significant for

either treatment outcome by exposure to sexual IPV and only viral suppression significantly differed by exposure to verbal IPV (p=0.0302).

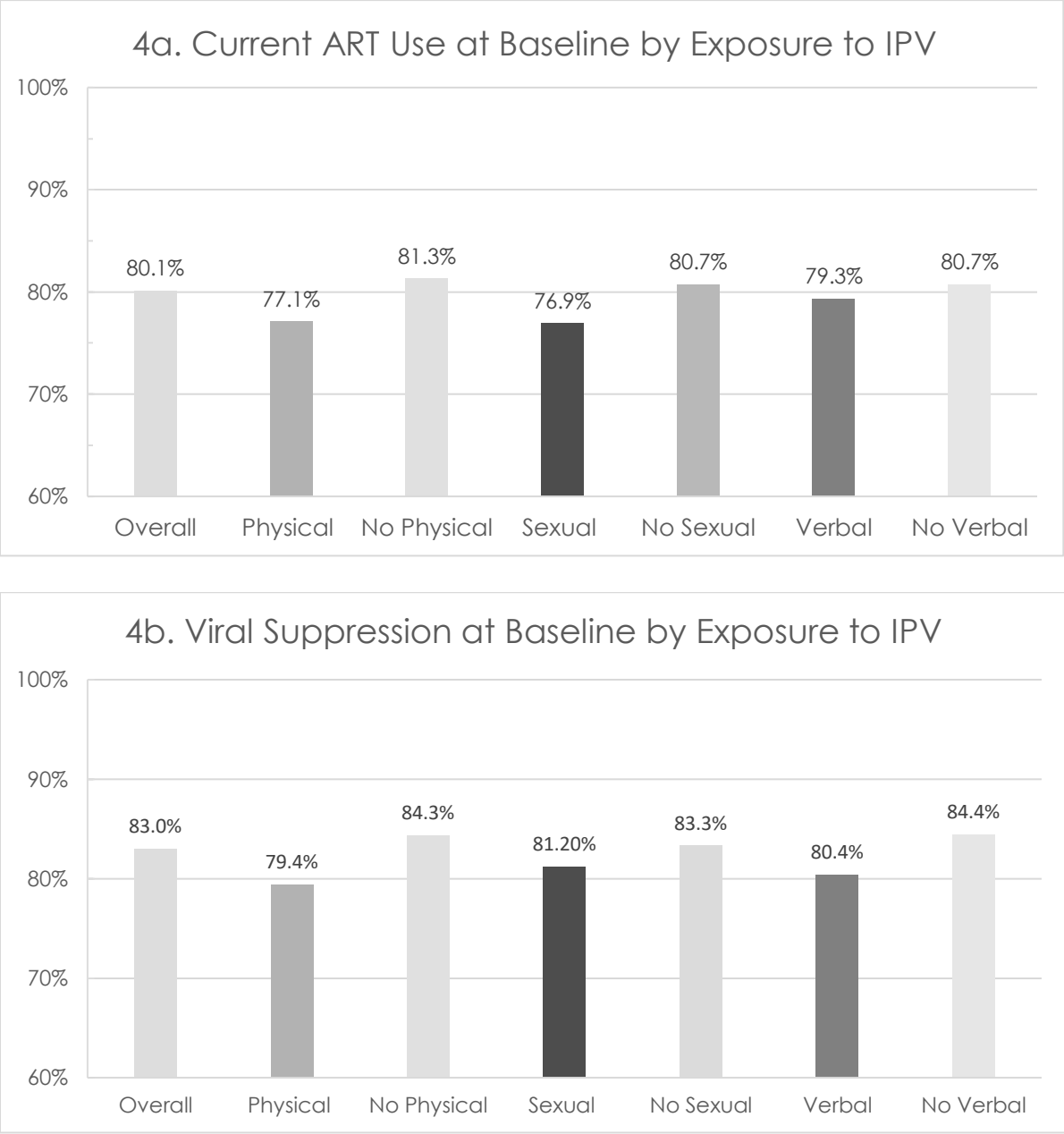

Figure 4a-b. Proportion with Treatment Outcomes at baseline by Exposure to IPV

Adjusted Regression Analysis Weighing on Propensity Scores for HIV outcomes by exposure to IPV.

Tables 5 summarizes the adjusted regression analysis weighing on propensity scores for the association between past year experiences of IPV and current ART use and viral suppression among women. After application of stabilized IPTCWs, none of the three IPV exposures were significantly associated with the two HIV treatment outcomes of interest. All observed associations between IPV and the outcomes were highly insignificant in the adjusted analysis with odds ratios that were near one.

Discussion

The present study, which explored associations between experiences of IPV among WLWH and treatment outcomes in the context of Uganda's current HIV treatment guidelines found that IPV was not significantly associated with lower odds of current ART use or viral suppression. The findings do not confirm our hypotheses and are inconsistent with findings from Hatcher et al.'s meta-analysis (39). Although Hatcher et al.'s meta-analysis found significant associations between IPV and treatment outcomes, the individual studies included in the review had less conclusive results. Of the five identified studies that measured self-reported "current ART use" in a similar format to our question, none found a statistically significant association with IPV (103-107). Of the seven studies that measured viral suppression, only three found a statistically significant association

between viral suppression and IPV (105-111). It is also important to note that most of the studies in this review were from high income settings and relied on cross-sectional data, limiting their generalizability to the experiences of WLWH in Uganda. The findings are also inconsistent with previous longitudinal work in Rakai by Wirtz et al. which found significant associations between IPV and ART use among women over 30 years of age (99).

Although not the focus of the present analysis, we ran the models in older and younger age strata (results not shown) to see if similar age-related patterns were observed in our sample, but associations remained insignificant across strata. The ever-evolving HIV care and treatment landscape is one possible explanation for observed differences between the relationship between IPV and HIV treatment outcomes in our study and those observed by Wirtz et al. in the same setting. In 2016, Uganda aligned their national HIV treatment guidelines with the universal test and treat approach (112). Under this model, persons are offered ART initiation the day they receive their positive diagnosis; previously persons were referred to HIV care and treatment initiation was delayed until an individual's CD4 t-cell count reached a certain threshold. These additional steps between point of diagnosis and initiation of ART were identified in earlier work as barriers to care seeking and optimal treatment engagement for women experiencing violence (39). For example, a woman fearful of revealing her HIV positive status to her partner may delay disclosure and care-seeking (113). Once disclosure occurred,

depending on her mobility and agency in the relationship, her partner may prohibit her from accessing care and initiating treatment. Provision of ART at the point of diagnosis greatly may reduce the number of barriers incurred to engage in care and initiate treatment.

Findings have been mixed regarding the relationship between IPV and treatment outcomes in other recent studies in sub-Saharan Africa since the implementation of test and treat. A longitudinal study in South Africa looking at associations between IPV, depression and alcohol use and HIV care and treatment outcomes among mothers found that IPV did not adversely impact treatment adherence over time (114). Conversely, a recent cross-sectional study from Malawi looking at IPV in dyads found significant associations between IPV victimization and self-reported non-adherence to ART (115). In this study, the authors found the strongest association to non-adherence among participants experiencing bidirectional violence (i.e.., when a person is both a perpetrator and victim). Recent work elsewhere in Uganda suggests that bidirectional IPV is common (115). This phenomenon has not been explored in Rakai for a couple of decades (101) and shifting gender norms may have impacted patterns and directionality of IPV; if women experiencing bidirectional IPV are at greatest risk of poor treatment outcomes, the inclusion of data collection around bidirectional IPV in the future may help to identify a subset of WLWH who are most likely to experience IPV-related barriers to care.

In the weighted models we saw no difference in the HIV outcomes, indicating that women in the sample who experienced IPV were viral suppression comparable to those not experiencing IPV. It is possible that partner support of ART adherence in serodiscordant couples may have also shifted as a result of advances in HIV treatment. It is now known that adherence to HIV treatment can reduce an individual's viral load to an undetectable level, reducing the risk of HIV transmission to close to zero (70). Qualitative work with WLWH who experience IPV in this setting could shed light on how IPV currently impacts HIV care seeking behavior and if this has changed in response to changing treatment guidelines.

This analysis had several limitations. The measures for IPV and current ART use were self-reported and subject to reporting bias. Additionally, the IPV variable was asked differently in the two rounds and it is possible that this change may have altered reporting; prevalence was higher in the baseline round when persons were asked about individual partners and there is evidence that people have better recall when prompted to remember specific details (116). Finally, the COVID-19 lockdown occurred in the middle of data collection for round 19. However, given that we would anticipate an increase in IPV and additional barriers to treatment adherence under the lockdown and the findings were null, the lockdown does not appear to have impacted the results. The analysis also had a number of strengths. The data were collected and analyzed in the context

of current treatment guidelines allowing us to consider the policy implications of our results. Viral load data, which was used to measure viral suppression in the study sample, is not prone to measurement bias due to underreporting of missed doses. Finally, we looked at recent experiences of IPV which reduces the potential time delay between experiences of IPV and the treatment outcomes.

To understand the absolute association of IPV and HIV treatment outcomes, the present paper looks at IPV without considering a frequently occurring co-morbidity that is associated with poor treatment outcomes, alcohol use (see Chapter 1). Although we did not see a significant association between various forms of IPV and the treatment outcomes, additional work is needed to identify whether IPV among specific subsets of women (e.g., women who use alcohol) is a driver of worse treatment outcome. Collection of data on the occurrence of bidirectional IPV in this setting as well as qualitative work with IPV-experiencing WLWH would also be informative in further disentangling the relationship between IPV and HIV treatment outcomes.

Despite the lack of significant relationship between IPV and HIV treatment outcomes in our study, IPV remains a critical public health issue disproportionately burdening WLWH. Severe IPV among WLWH has been associate with a twofold increase in odds of all-cause mortality (117). Reducing experiences of IPV in this setting is a public health priority and interventions are needed to address this

health issue among WLWH. More work is needed to understand if IPV is associated with worse treatment outcomes among specific high-risk groups of women.

Table 4. Baseline Characteristics of WLWH participating in Round 18 of the Rakai Community Cohort Study

Characteristic		**Overall (n=1,923)**
Any Past Year Verbal IPV		
	Yes	665 (34.6%)
	No	1427 (65.4%)
Any Past Year Physical IPV		
	Yes	510 (26.5%)
	No	1413 (73.5%)
Any Past Year Sexual IPV		
	Yes	260 (13.5%)
	No	1663 (86.5%)
Mean Age (SD)		32.8 (SD 7.2)
Residence		
	Agrarian	721 (37.5%)
	Trade	320 (16.6%)
	Fishing	882 (45.9%)
Education		
	No School/Primary	539 (28.0%)

Table 4 cont'd. Baseline Characteristics of WLWH participating in Round 18 of the Rakai Community Cohort Study

Characteristic		**Overall (n=1,923)**
	Secondary or above	1384 (72.0%)
HH SES		
	High	1082 (56.3%)
	Middle	323 (16.8%)
	Low	517 (26.9%)
Occupation		
	Housework	867 (45.1%)
	Trade/shopkeeper	444 (23.1%)
	Bar/Restaurant Worker	272 (14.1%)
	Other	340 (17.7%)
Marital Status		
	Currently Married	1188 (61.8%)
	Previously Married	643 (33.4%)
	Never Married	92 (4.78%)

Table 5. Prospective Logistic Regression Weighing on Propensity Score Examining the Relationship between IPV and HIV Treatment Outcomes (n=1,923)

		Current ART Use				Achievement of Viral Suppression			
				Odds Ratio				Odds Ratio	
Form of IPV		**B**	**SE**	**(95% CI)**	**P value**	**B**	**SE**	**(95% CI)**	**P value**
Verbal									
	Yes	0.01	0.00	1.01 (1.00-1.02)	0.1237	0.00	0.01	1.00 (0.98-1.02)	0.8554
	No	--	--	1.00	--				
Physical									
	Yes	0.00	0.01	1.00 (0.99-1.01)	0.6145	0.00	001	0.99 (0.98-1.01)	0.9743
	No	--	--	1.00	--	--	--	1.00	--
Sexual									
	Yes	-0.01	0.01	0.99 (0.97-1.01)	0.4935	-0.01	0.01	0.99 (0.97-1.01)	0.4570
	No	--	--	1.00	--	--	--	1.00	--

PS weighted for age, marital status, household SES and community type and censoring

Acknowledgements

This work, in part is currently being prepared for submission for publication of the material in Journal of the International AIDS Society, 2021, Miller, A.P., Pitpitan, E. V., Kiene, S., Raj, A., Jain, S., Zuniga, M. L., Nabulaku, D., Nalugoda, F., Ssekubugu, R., Nantume, B., Kigozi, G., Sewankambo, N. K., Kagaayi, J., Reynolds, S. J., Grabowski, M. K., Wawer, M., & Wagman, J. The dissertation author was the primary investigator and author of this paper. Protected time to complete this project was provided by National Institute of Alcohol Abuse grants F31AA028198-01 (PI: Miller).

CHAPTER 3: Exploring pathways between alcohol use, intimate partner violence and HIV treatment outcomes in the Rakai region of Uganda

Abstract

Objective: Prospectively explore mediating and moderating process between alcohol use, intimate partner violence (IPV) and two HIV treatment outcomes (current ART use and viral suppression) among WLWH in Rakai, Uganda.

Design: Pathway analysis of two consecutive rounds of data collected from the Rakai Community Cohort study, an open-cohort longitudinal HIV surveillance study.

Methods: To explore the pathway mediated by IPV, logistic regression models were estimated for each of the HIV outcome variables with alcohol use as the exposure and IPV as the mediating variable. To explore the pathway mediated by alcohol use, models were estimated for each of the HIV outcome variables with IPV as the exposure and alcohol use as the mediating variable. To test the moderation hypotheses, three sets of interaction terms were tested for each outcome. All moderation models were prospective and measured with the HIV outcomes at follow up. Interactions were considered significant at p=0.05.

Results: The sample consisted of 1923 WLWH. Just under half (47%) reported past year alcohol use at baseline; past year IPV was reported by 37%. A total of four mediation and four moderation models were built. None of the four mediation pathways analyses yielded significant effects. Of the four moderation analyses, no significant statistical interactions were observed.

Conclusions: These findings could be attributed to the absence of any true causal effect, measurement error, and/or incorrect model specification. given the frequent co-occurrence of HIV, alcohol use and IPV in this setting more research is needed to understand how these variables are related.

Key words: Uganda, Alcohol, IPV, syndemic, moderation, mediation, viral suppression, HIV

Introduction

Alcohol use, intimate partner violence (IPV) victimization, and HIV are intrinsically linked public health issues that disproportionately burden women compared to men. The association between any two of these issues is bidirectional, with each mutually serving as a risk factor for the other. For example, a robust global body of evidence suggests that alcohol is a risk factor for both HIV infection (55, 56) and IPV victimization among women. Alcohol use and alcohol use disorders are also more prevalent among persons living with HIV (compared to persons not living with HIV) (118), and there is evidence that subsequent alcohol use after incidences of violence can be used as a coping mechanism among women experiencing IPV (119). IPV can increase a woman's risk of HIV infection through direct (e.g., forced intercourse) and indirect (e.g. reduced ability to negotiate safer sex practices such as condom use) pathways (8), and women living with HIV (WLWH) are at increased risk of experiencing IPV (15, 19, 20). A body evidence suggests that public health issues not only co-occur but exacerbate one another.

In 1994, Merrill Singer coined the term syndemic to explain how substance use, violence and HIV/AIDS (SAVA syndemic) are mutually entwined epidemics that put African American women at disproportionate risk of HIV (120). The syndemic conceptual framework posits that some co-occurring epidemics have an effect on health outcomes by synergistically interacting and exacerbating

one another. To date, this framework has mainly been applied to understand frequently co-occurring HIV risk factors in populations in the United States (U.S.) at high risk of HIV, such as men who have sex with men (121), men of color (122) and female sex workers (123). It has also been applied to understand barriers to HIV care and treatment in the U.S. (124, 125).

The evidence base establishing alcohol use and IPV victimization as synergistic and interrelated health issues that each serve as risk factors for HIV is well established (119). However, despite evidence that each independently and adversely impacts outcomes throughout the HIV care and treatment continuum, there is less research simultaneously examining the effects of alcohol use and IPV on HIV care seeking behaviors (e.g., initiation of ART). Alcohol use is associated with delays in testing and care seeking and suboptimal treatment adherence (44). Similarly, a 2015 systematic review found that IPV is associated with barriers to optimum care throughout the HIV care continuum starting from delayed disclosure of HIV positive status to partners, to non-adherence of antiretroviral therapy (39). However, most of the IPV studies captured in the review were conducted in high income countries, were cross-sectional in nature, and were conducted in the context of outdated treatment guidelines.

In Uganda, which experiences a generalized HIV epidemic (prevalence of 6.2%)(97), heavy alcohol use is common among those that consume alcohol (1).

In the fishing villages along the Rakai/Masaka border, where the greatest burden of HIV exists (median HIV prevalence among women is 49%), the majority of persons who drink consume hazardous levels of alcohol and there is substantial overlap between the occurrence of IPV, alcohol use and HIV (2, 3). The role of alcohol use as a driver of the HIV epidemic in this context is well established by quantitative and qualitative data (11, 21-23). Qualitative research with WLWH in Rakai suggests that alcohol use by one or both partners often precedes instances of IPV (14). Among WLWH who consume alcohol in this setting, 31% report experiencing an alcohol-related consequence (indicators of harmful drinking, heavy drinking and alcohol dependence) in the past year, suggestive of harmful or hazardous drinking (see CHAPTER 1). Recent analyses from the current dissertation exploring associations between alcohol use and HIV treatment outcomes in Rakai found that women who reported past year alcohol use were less likely to report current ART use and less likely to be virally suppressed (see CHAPTER 1). In another recent analysis from this dissertation, we explored prospective associations between experiences of IPV and HIV treatment outcomes in the same study sample (see CHAPTER 2). In these analyses, we did not find a significant association between experiences of IPV and the outcomes (current ART use and viral suppression) after adjusting for potential confounders. This is in contrast to prior longitudinal research in Rakai that did find a significant association between treatment adherence and experiences of IPV in some age strata (99). To date, the effects of co-occurring alcohol use and IPV on HIV

treatment outcomes has not been explored in this setting. There is a need to understand the temporal nature of how these two frequently co-occurring conditions relate to HIV treatment outcomes. Specifically, research is needed to examine how or for whom alcohol use and IPV affect treatment outcomes.

The present analysis fills a gap in the literature by applying mediation and moderation analysis to inform how and for whom the two variables impact HIV treatment outcomes. We will explore longitudinal pathways between alcohol use and IPV and two HIV treatment outcomes (i.e., current ART use and viral suppression) with the aim of disentangling the temporal nature of the relationship between these variables in women. When examining moderator effects, we examined them between the exposure variables contemporaneously at baseline, as well as prospectively with the moderator occurring at follow-up to explore all temporal pathways (i.e., co-occurring alcohol use and IPV at baseline, alcohol use at baseline and subsequent experiences of IPV at follow-up and IPV at baseline and subsequent alcohol use at follow up). To explore mediation, we examined both IPV and alcohol mediated pathways with both of the HIV outcomes. A total of four mediation models were tested; alcohol mediated pathways between (1) IPV and current ART use and (2) IPV and viral suppression as well as IPV-mediated pathways between (3) alcohol use and current ART use and (4) alcohol use and viral suppression. These exploratory analyses were conducted using data from two consecutive rounds of the Rakai Community

Cohort Study which were conducted after the roll out of universal test and treat, Uganda's current HIV treatment guidelines. Exploring these mediating and moderating effects, will disentangle the temporal nature of the relationship between these variables and allow for estimation of direct and indirect causal effects between alcohol use, IPV and the HIV treatment outcomes.

Materials and Methods

Study Design and Data Collection:

Detailed description of RCCS study design and data collection methods have been described in detail in previous publications (30). The RCCS is an open cohort longitudinal HIV surveillance study that has been continuously collecting data since 1994. Each round of data collection includes roughly 20,000 participants and typically takes 12-18 months as the survey moves through forty communities in the Rakai region. Data collection is currently in its 20th round; the present study involves secondary data analysis of the two most recently completed rounds (18 and 19). Each round consists of a household census to identify eligible participants, followed by a survey. Residents between the ages of 15 and 49 years who are present and provide written informed consent are invited to participate in the survey, which covers sociodemographic and behavioral characteristics as well as health care utilization (inclusive of HIV services). HIV testing and counseling, referral to care and ART treatment initiation are also

provided. Ethical approval for the RCCS has been granted by the Johns Hopkins School of Public Health's institutional review board (IRB), Columbia University's IRB, Western IRB, the Uganda Virus Research Institute's Research and Ethics Committee and the Uganda National Council for Science and Technology.

Analytic Sample:

The present study involves secondary analysis of data collected in Rounds 18 and 19 of the RCCS. Round 18 was conducted from August 2016 to May 2018. round 19 began in June of 2018 but was abruptly stopped in March 2020 due to the national COVID-19 lockdown in Uganda. Data collection resumed in August of 2020 and concluded in November of 2020. To improve readability, for the remainder of the paper, round 18 will be referred to as "baseline" and round 19 will be referred to as "follow-up". Given the focus on the relationship between alcohol use, IPV and HIV treatment outcomes among women, the analytic sample focused on women living with HIV (known positives and those testing positive in RCCS) at baseline who reported an intimate partnership in the past 12 months (individuals who do not report a past year intimate partnership are not asked questions regarding past year IPV), creating a sample of 1,923 individuals.

Measures

Primary exposures/mediators. "Any past year alcohol use", was a dichotomous variable measured by the question, "Have you drunk any alcohol in

the past year, for instance, beer, wine, waragi or other spirits, or home-made beer?"

"Any past year IPV" is a composite variable comprised of ten adapted questions from the Conflict Tactics Scales (CTS) (102). IPV was measured by asking, "In the past 12 months has your partner…": "verbally abused or shouted at you?"; "pushed, pulled, slapped, held you down?"; "punched you with fist or something that could hurt you?"; "kicked or dragged you?"; "tried to strangle or burn you?"; "threatened you with a knife, gun, other weapon?"; and "attacked you with knife, gun, other weapon?"; "used verbal threats to force you to have sex?" "physically forced you to have sex?;" or "coerced you to perform other sexual acts when you did not want to?"

The formatting of this question differed between baseline and follow up. At baseline, participants were asked to answer the ten IPV questions in relation to a specific intimate partner (starting with current/most recent). They were asked to recall this information for up to four past year partners. Responses were collapsed across partners, where a "yes" response to an item with one partner indicated a yes for that type of IPV. The responses were then further collapsed so that an individual who responded yes to any item was a yes to "any past year IPV". At follow-up, participants were asked each of the ten IPV items only once, regarding

all partners in the past year. Responses to the ten were still collapsed to create single measures, "any past year IPV?" (yes/no).

Dependent variables. The first outcome, "current ART use" was a dichotomous variable measured by a yes/no response to the question, "Are you currently taking antiretrovirals?". Viral suppression, the primary outcome of interest, was collected as a continuous variable, viral load, and dichotomized per Ugandan ministry of health guidelines for viral suppression, defined as a viral load ≤1000 viral copies per mL of blood (73).

Covariates. Seven baseline sociodemographic characteristics were included in the analyses to control for potential confounding, including, age, community type (agricultural, fishing, trade), marital status (currently married, previously married, never married), education (no formal education, primary school or higher), employment (defined as the primary occupation of bar/restaurant worker, fishermen, trade/shopkeeper, agriculture/housework, other), religion (Christian, Muslim, other/no religion), and household socioeconomic status (a three category index based on dwelling attributes and divided into tertiles for low, middle, high).

Data Analysis

Analyses were performed using SAS studio (74). Data were inspected for errors, omissions and outliers. Descriptive statistics were used to characterize the analytic sample. Descriptive analysis included frequencies for dichotomous and categorical variables and measures of central tendency for continuous variables. Multicollinearity was assessed by examining the intercorrelations between the predictor variables in the model as well as the tolerance and variance inflation factor (VIF).

To test the mediation hypotheses, four logistic regression models were estimated (see Figures 5-8) using the approach described by Vanderweele (126). To explore the pathway from alcohol use to the outcomes mediated by IPV, prospective models were estimated for each of the HIV outcome variables with alcohol use as the exposure and IPV as the mediating variable. To explore the pathway from IPV to the outcomes mediated by alcohol use, models were estimated for each of the HIV outcome variables with IPV as the exposure and alcohol use as the mediating variable. Causal mediation models were estimated in SAS using the PROC CAUSALMED function. To meet the assumptions required to interpret the results causally, models included adjustments at baseline for potential (1) exposure-outcome confounding (2) mediator-outcome confounding and (3) exposer-mediator confounding. These potential confounders were identified *a priori* from the literature. Direct acyclic graphs were used to test the fourth assumption, that no mediator-outcome confounders were

included that were affected by the exposure. Outcome and mediator variables in all models were from follow-up while exposure and covariates were from baseline data. All models also adjusted for mediator and outcome values at baseline. Ninety fifth percentile bootstrap confidence intervals and odds ratio estimates were obtained.

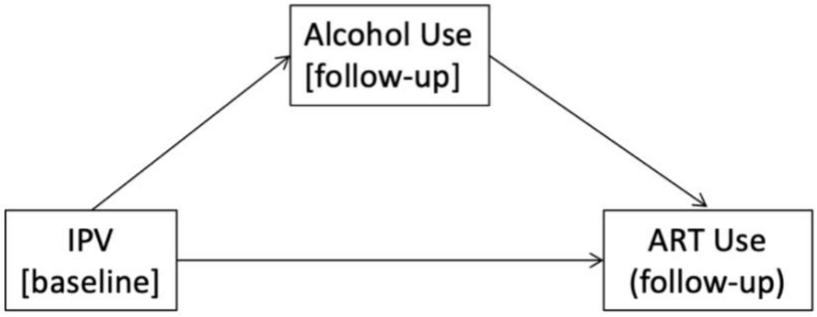

Figure 5. Alcohol Use as a Mediator of the Relationship between IPV and ART Use

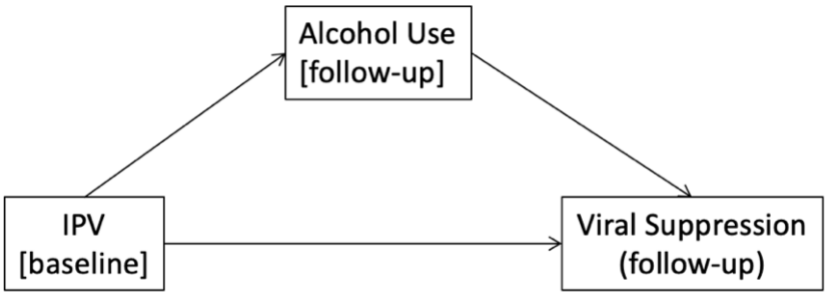

Figure 6. Alcohol Use as a Mediator of the Relationship between IPV and Viral Suppression

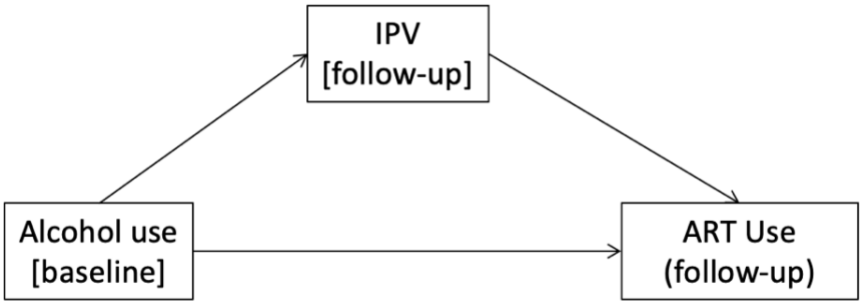

Figure 7. IPV as a Mediator of the Relationship between Alcohol Use and ART Use

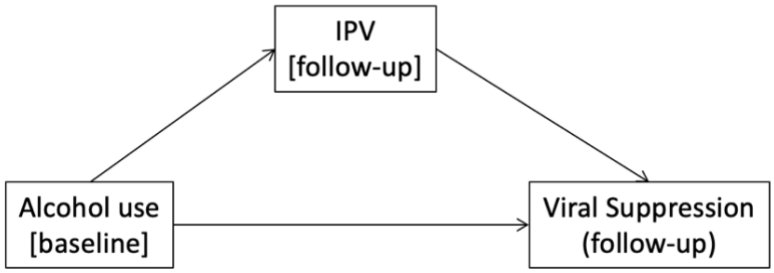

Figure 8. IPV as a mediator of the Relationship between Alcohol Use and Viral Suppression

To test the moderation hypotheses, three sets of interaction terms were tested for each outcome. Models were built using the proc genmod function in SAS and the logit link and binomial distribution to obtain odds ratios. All moderation models were prospective and measured associations between exposures and interaction terms with the HIV outcomes at follow up. The first two models tested two-way interaction between IPV X alcohol use both measured at baseline (for each outcome); the next two models were estimated to test the two-

way interactions between IPV at baseline and alcohol use at follow up (for each outcome). The third set of two models tested two-way interactions between alcohol use at baseline X IPV at follow up. All models were adjusted for covariates and outcome at baseline. Interaction terms were considered significant at alpha of 0.05. An alpha of 0.05 was used to determine significance of other associations.

Multicollinearity

All VIF were less than 2, no tolerance values were <0.1 and no correlations were >0.7, suggesting that there was little multicollinearity between variables.

Missing data

We encountered missing observations for one of the two HIV outcomes: VS (0.43% of observations missing this outcome). We also encountered a single missing observation for one of the covariates: household SES (0.04%). The source and impact of missing data was not explored further for these two variables, given the very small proportion of missing observations. Participation in this open cohort varies from year to year; sixty three percent of those who participated at baseline also participated at follow up.

Results

Descriptive Characteristics of the Sample at Baseline

Table 6 describes baseline characteristics of the analytic sample. Just under half of the sample (47%) reported past year alcohol use at baseline; past year IPV was reported by 37%. Among those reporting past year IPV at baseline, nearly half (49.2%) reported alcohol use preceding the most recent episode of IPV. Regarding demography, most study participants resided in the fishing communities (46%) or agrarian communities (38%), with only 17% residing in trade communities. Most participants (62%) were currently married. The common profession among women was housework (45%) and more than seven in ten had completed some or all of secondary school (72%). The proportion of reported use of other drugs (apart from alcohol) was very small, with less than 1% of women reporting this behavior in the past year at baseline.

Mediated Pathway Analysis of the relationship between alcohol use, IPV and the HIV treatment outcomes

Tables 7a-7d, summarize the results from the four mediated pathway analyses between past year alcohol or IPV at baseline and current ART use or viral suppression at follow-up. Adjusted Odds Ratios, bootstrap corrected 95% confidence intervals and p-values are reported for the total, direct effect and natural indirect effects for each model. All models were adjusted for potential confounders, outcome, and mediator at baseline. None of the pathways across the four models were found to be statistically significant at $p<.05$.

Prospective Moderation Analysis of Alcohol Use, IPV and Current ART Use

Tables 8a-c, summarize multivariate logistic regression results of prospective moderation analyses of past year alcohol use and past year IPV on the first outcome, current ART use. The following interactions were explored: alcohol use and IPV at baseline, alcohol use at baseline and IPV at follow-up, IPV at baseline and alcohol use at follow-up. Beta, standard error and p-values are reported for each model. All models adjusted for the following at baseline: SES, residence, age, marital status, education, religion, viral suppression

As shown in Tables 8a-c, in adjusted models the main effects (alcohol use and IPV), as well as the interaction terms were not statistically significant in any of the models.

Prospective Moderation Analysis of Alcohol Use, IPV and Viral Suppression

Tables 9a-c, summarize multivariate logistic regression results of prospective moderation analyses of past year alcohol use and past year IPV on the main outcome, viral suppression. The following interactions were explored: alcohol use and IPV at baseline, alcohol use at baseline and IPV at follow-up, IPV at baseline and alcohol use at follow-up. Beta, standard error, odds ratio, 95% confidence interval and p-values are reported for each model. All models adjusted for the following at baseline: SES, residence, age, marital status, education, religion, viral suppression

As shown in Tables 9a-c, in adjusted models we observed no significant interaction effects. We observed a significant main effect of alcohol use in the model looking at alcohol use at baseline moderated by IPV at follow up (Table 9b, aOR 2.25 95% CI 1.05-4.77, p=0.0375) but this relationship was no longer significant after removing the insignificant interaction term (p=0.1525)

Discussion

This paper applied moderation and mediation analysis to explore temporal pathways between alcohol use, IPV and two HIV treatment outcomes: current ART use and viral suppression. No statistically significant mediating or moderating effects were observed across models. These findings might be attributed to several factors, including, the absence of any true causal effect, measurement error, and/or incorrect model specification. Causal mediation analysis relies on strong assumptions around correct model specification that cannot be violated if the resulting direct and indirect effects are to be interpreted causally. Vanderwheele (2016), identifies four confounding assumptions for causal mediation; a mediation model must (i) control for confounders between control and outcome, (ii) control for confounders between mediator and outcome, (iii) control for confounders between exposure and mediator and (iv) no mediator-outcome confounder should be controlled for that is itself affected by the exposure (126). Violation of any of these assumptions, through model

misspecification or unmeasured confounding could produce misleading results. While DAGS were used to identify confounding variables a priori, it is possible that potential unmeasured confounders that are established in the literature, like depression (127, 128) as well as unknown confounders biased the estimates in the present analyses.

Measurement error and misclassification could also have produced misleading results that were biased towards the null. All the measures in the model except for viral suppression were self-reported and subject to measurement error (e.g., under-reporting due to social desirability bias). Instead of a validated measure of hazardous drinking or alcohol use disorder (such as the AUDIT (76)) or a biomarker for alcohol consumption (such as Phosphatidylethanol (PEth)), we relied on self-reported past year alcohol consumption, a measure that does not account for the frequency or quantity of alcohol consumed. The lack of precision of this variable may have obscured the ability to measure the true relationship between alcohol use and the other variables of interest. As an example, the measure of alcohol consumption used in this study is unable to distinguish between persons who, for example, drank once at a religious ceremony in the past year vs. heavy drinkers) Similarly, the IPV questions did not capture frequency of IPV. Edits to the IPV items between baseline and follow up could have produced misclassification of this exposure. In the baseline round, participants were asked about experiences of violence with specific partners. At follow up

they were asked about experiences of IPV with any past year partner. There is evidence that recall is improved when people are asked to think about the details of a specific scenario (116). The prevalence of IPV was lower at follow-up and it is unclear if this was a result of reduced IPV, or the use of a less sensitive measure of IPV. Regardless of which IPV measure (baseline or follow-up) produced a more precise estimate, this potential misclassification is a threat to the findings of the analyses. Though not applied here, Vanderwheele and Le Cessie have developed advanced methods to correct measurement error as a source of bias to direct, indirect and mediated effects and these could be applied in future analyses (129, 130).

Finally, temporality is critical to causal inference and causal mediation analysis specifically. The present paper only observes two time points one year apart. The recall period for the exposure/mediators of interest is "past year". These measurement time points may be too far apart and the recall period too vast to capture the effects we were interested in exploring. Of course, it is possible that the models were correctly specified no mediation or moderation effects were observed simply because these effects did not exist. Much of the previous work affirming a relationship between IPV and alcohol use and HIV care and treatment outcomes has been cross-sectional (i.e. associational) and has not reflected current ART treatment guidelines. Advancements in ART have led to simpler (such as single dose daily) and more tolerable (i.e., with fewer side effects) treatment

regimens (131). Furthermore, the advent of test and treat introduced same day diagnosis and initiation of treatment, reducing the number of steps (and opportunities to delay) to link into care and treatment. These changes in the treatment landscape may have reduced barriers to ART use and viral suppression which could explain the lack of observed significant effects between the exposures and outcomes of interest.

The results of the present study should be viewed in light of its limitations. Concerns regarding the operational definitions (precision of measurement changes in the items used at the two time points) of the key variables have been described above. However, the present study is novel in its application of both moderation and mediation analysis to explore pathways between alcohol use, IPV and HIV treatment outcomes in sub-Saharan Africa. It adds to a sparse evidence base of the application of these methods in this setting. Additionally, this paper is timely, capturing HIV outcomes under current treatment guidelines.

The findings were inconclusive; given the high prevalence and co-occurrence of HIV, alcohol use and IPV in this setting and the public health burden attributed to each of these issues, more research is needed to understand how these variables are related. Future studies should use more rigorous alcohol use and IPV measures that capture frequency, quantity, type and severity. Data collection should also focus on shorter recall periods (e.g., two weeks, past month)

to narrow the temporal window and improve recall. Finally, qualitative research among WLWH is needed to understand perceived barriers to treatment adherence related to IPV and alcohol use.

Table 6. Baseline characteristics of WLWH participating of the Rakai Community Cohort Study, overall and stratified by sex

Characteristic		Overall (n=1,923)
Any Alcohol Use		
	Yes	905 (47.1%)
	No	1018 (52.9%)
Alcohol use before most recent IPV*		
	Yes, one or both partners	353 (49.2%)
	No	364 (50.8%)
Any IPV		
	Yes	716 (37.2%)
	No	1207 (62.8%)
Mean Age (SD)		32.8 (SD 7.2)
Residence		
	Agrarian	721 (37.5%)
	Trade	320 (16.6%)
	Fishing	882 (45.9%)

Table 6 cont'd. Baseline characteristics of WLWH participating of the Rakai Community Cohort Study, overall and stratified by sex

Characteristic		Overall (n=1,923)
Education		
	No School/Primary	539 (28.0%)
	Secondary or above	1384 (72.0%)
HH SES		
	High	1082 (56.3%)
	Middle	323 (16.8%)
	Low	517 (26.9%)
Occupation		
	Housework	867 (45.1%)
	Trade/shopkeeper	444 (23.1%)
	Bar/Restaurant Worker	272 (14.1%)
	Other	340 (17.7%)
Religion		
	Catholic	1230 (64.0%)
	Muslim	354 (18.41%)

Table 6 cont'd. Baseline characteristics of WLWH participating of the Rakai Community Cohort Study, overall and stratified by sex

Characteristic		Overall (n=1,923)
	Muslim	354 (18.41%)
	Other	339 (17.6%)
Any Drug Use		
	Yes	18 (0.9%)
	No	1905 (99.1%)
Marital Status		
	Currently Married	1188 (61.8%)
	Previously Married	643 (33.4%)
	Never Married	92 (4.78%)

**only asked of persons who report past year IPV*

Table 7a-d. Mediated Pathway Analyses

7a. IPV mediated pathway between any alcohol use at baseline and current ART Use at Follow-up (n=1,009)

	OR (Bootstrap bias corrected 95% CI)	P-value
Total Effect	1.45 (0.54-3.72)	0.4187
Direct Effect	1.51 (0.56-3.84)	0.3819
Natural Indirect Effect	0.96 (0.89-1.05)	0.2095

adjusted for the following at baseline: SES, residence, age, marital status, education, religion, art use, IPV

7b. IPV mediated pathway between any alcohol use at baseline and viral suppression at Follow-up (n=998)

	OR (Bootstrap bias corrected 95% CI)	P-value
Total Effect	1.50 (0.73-2.93)	0.2817
Direct Effect	1.55 (0.76-3.04)	0.2562
Natural Indirect Effect	0.97 (0.90-1.03)	0.2536

adjusted for the following at baseline: SES, residence, age, marital status, education, religion, viral suppression, IPV

Table 7a-d cont'd. Mediated Pathway Analyses

7c. Alcohol mediated pathway between any IPV at baseline and current ART use at Follow-up (n=1,086)

	OR (Bootstrap bias corrected 95% CI)	P-value
Total Effect	1.59 (0.64-4.22)	0.3220
Direct Effect	1.59 (0.64-4.14)	0.3259
Natural Indirect Effect	1.00 (0.93-1.09)	0.9262

adjusted for the following at baseline: SES, residence, age, marital status, education, religion, viral suppression, alcohol use

7d. Alcohol mediated pathway between any IPV at baseline and viral suppression at Follow-up (n=1,076)

	OR (Bootstrap bias corrected 95% CI)	P-value
Total Effect	1.25 (0.62-3.09)	0.5251
Direct Effect	1.28 (0.64-3.08)	0.4897
Natural Indirect Effect	0.98 (0.90-1.01)	0.3308

adjusted for the following at baseline: SES, residence, age, marital status, education, religion, viral suppression, alcohol use

Table 8a-c. Prospective Moderated Pathway Analysis for Current ART Use

8a. Assessing moderation between alcohol use and IPV at baseline and current ART use at follow-up (n=1,086)

	Beta	SE	OR	95% CI	P-value
Alcohol use	-0.0621	0.439	0.94	(0.40-2.22)	0.8875
IPV	-0.1834	0.512	0.83	(0.31-2.27)	0.7201
Alc*IPV	1.2116	0.740	3.36	(0.79-14.32)	0.1015

8b. Assessing moderation between alcohol use at baseline and IPV at follow up and current ART use at follow-up (n=1,009)

	Beta	SE	OR	95% CI	P-value
Alcohol use	0.1769	0.449	1.19	(0.50-2.88)	0.6934
IPV	-0.9728	0.538	0.38	(0.16-1.30)	0.1403
Alc*IPV	0.8584	0.757	2.36	(0.54-10.40)	0.2566

8c. Assessing moderation between IPV at baseline and alcohol use at follow up and current ART use at follow-up (n=1,086)

	Beta	SE	OR	95% CI	P-value
Alcohol use	0.0834	0.430	1.09	(0.49-3.66)	0.8462
IPV	0.2892	0.515	1.34	(0.47-2.52)	0.5744
Alc*IPV	0.3156	0.730	1.37	(0.33-5.74)	0.6656

All models adjusted for the following at baseline: SES, residence, age, marital status, education, religion, art use

Table 9a-c. Prospective Moderated Pathway Analyses for Viral Suppression

9a. Assessing moderation between alcohol use and IPV at baseline and viral suppression at follow-up (n=1,086)

	Beta	SE	OR	95% CI	P-value
Alcohol use	0.3071	0.375	1.36	(0.65-2.83)	0.4125
IPV	0.0375	0.409	1.04	(0.47-2.31)	0.9270
Alc*IPV	0.3725	0.610	1.45	(0.44-4.79)	0.5412

9b. Assessing moderation between alcohol use at baseline and IPV at follow up and viral suppression at follow-up (n=1,009)

	Beta	SE	OR	95% CI	P-value
Alcohol use	0.8045	0.837	2.24	(1.05-4.77)	0.0375
IPV	0.2877	0.496	1.33	(0.50-3.52)	0.5617
Alc*IPV	-1.0909	0.663	0.34	(0.09-1.23)	0.0917

9c. Assessing moderation between IPV at baseline and alcohol use at follow up and viral suppression at follow-up (n=1,086)

	Beta	SE	OR	95% CI	P-value
Alcohol use	0.0968	0.378	1.10	(0.52-2.31)	0.7980
IPV	0.5120	0.430	1.67	(0.72-3.87)	0.2336
Alc*IPV	-0.5136	0.612	0.60	(0.18-1.98)	0.4012

Acknowledgements

This work is co-authored, with Pitpitan, E. V., Kiene, S., Raj, A., Wagman, J. The dissertation author was the primary investigator and author of this paper. Protected time to complete this project was provided by National Institute of Alcohol Abuse grants F31AA028198-01 (PI: Miller).

CHAPTER 4: Summary, Implications and Future Recommendations

Summary of Findings

In chapter 1, associations between two alcohol measures and two HIV outcomes (current ART use and viral suppression) were estimated using generalized estimating equations to obtain odds ratios. The hypotheses were that both alcohol measures would be associated with worse HIV outcomes and that there would be differences in observed associations by sex. To explore possible differences by sex, analyses were performed overall and stratified by sex. Most of these hypotheses were confirmed. There were clinically significant differences in viral load (i.e., the achievement of viral suppression) by alcohol use status. There were also differences in observed relationships by sex. Significant inverse associations between any past year alcohol use and current ART use were driven by the relationships between these variables in both men and women while significant inverse associations between viral suppression and past year alcohol use were driven by the relationship between these variables in women. A significant natural indirect effect supported mediation by ART use in the overall sample.

Among alcohol users, associations between the experience of alcohol-related consequences and the HIV outcomes were estimated. Significant inverse associations between alcohol-related consequences and the HIV outcomes

were driven by the relationships between these variables in men. These differences by sex could be attributed to differences in gendered drinking patterns in Uganda as well as the alcohol measures. Among alcohol users, ART use did not mediate the relationship between consequences and viral suppression.

In chapter 2, prospective associations between three forms of IPV (physical, sexual, and verbal) and the same two HIV outcomes among WLWH were examined by fitting logistic regression models with stabilized inverse probability of treatment and censoring weights (IPTCW) to obtain odds ratios. The application of IPTCWs allowed us to adjust for measured confounders and censoring (loss to follow up) in a single summary weight. We hypothesized that all three IPV measures would be associated with worse HIV outcomes at follow up. After application of stabilized IPTCWs, none of the three IPV exposures were significantly associated with current ART use or viral suppression. All observed associations between IPV and the outcomes were highly insignificant in the adjusted analyses with odds ratios that were near zero.

In chapter 3, mediating and moderating processes between alcohol use, IPV and two same two HIV outcomes among WLWH were explored. This analysis was exploratory in nature and not driven by hypotheses. IPV was a composite variable indicating past year experience of any of the three forms of IPV in

chapter 2. To explore the pathway mediated by IPV, logistic regression models were estimated for each of the HIV outcome variables with alcohol use as the exposure and IPV as the mediating variable. To explore the pathway mediated by alcohol use, models were estimated for each of the HIV outcome variables with IPV as the exposure and alcohol use as the mediating variable. To test the moderation hypotheses, three sets of interaction terms were tested for each outcome. None of the four mediation pathways analyses yielded significant direct or indirect effects. Of the six moderation analyses, no significant statistical interactions were observed.

Public Health Implications

IPV, alcohol use and HIV are interrelated, frequently co-occurring issues in Uganda and these findings have important public health implications for HIV programmatic planning. The present study was the first to explore associations between alcohol use, IPV and current ART use and viral suppression in the context of Uganda's current HIV treatment guidelines (i.e., universal treatment and a threshold for viral suppression consistent with Ugandan Ministry of Health protocol). While a robust body of literature suggests that alcohol use (44) and IPV (39) may be associated with worse HIV care and treatment outcomes, many of these studies were conducted under outdated treatment guidelines, which has implications for care and treatment access. Additionally, many used cross-

sectional data and were conducted in drastically different study settings (e.g., the United States). Furthermore, despite alcohol use and IPV being frequently co-occurring health issues there is a dearth of literature exploring the temporal nature of their relationship and their potentially synergistic effects on HIV treatment outcomes. Therefore, findings from this work are timely and can inform interventions aimed at improving HIV treatment outcomes in Uganda.

Alcohol use and alcohol-related consequences were significantly associated with lower likelihood of current ART use and viral suppression. Alcohol use was associated with lower odds of current ART use among both men and women. Uganda's current HIV treatment guidelines recommend initiation of ART in all patients, meaning all patients diagnosed as HIV positive should immediately be linked into HIV care and initiated on ART the same day they are diagnosed. In previous studies conducted prior to the scale up of test and treat, associations between alcohol use and delayed HIV care-seeking have been observed (37, 38, 75); the implementation of test and treat should reduce barriers to treatment and opportunities for delayed treatment initiation. Despite data in the present study being collected after the roll out of test and treat, alcohol users were still less likely to report current ART use, which could be the product of declining to initiate ART, failure to pick up ART medication and attend follow up appointments and/or choosing to discontinue treatment. These findings suggest that alcohol use is an

important barrier to achieving optimum HIV care and treatment outcomes in Uganda.

Alcohol use is a modifiable risk behavior that can be intervened on. The negative association between alcohol use and current ART use suggests that interventions to address alcohol use among PLWH should occur as early in the care and treatment cascade as possible (i.e., at the point of HIV testing and initiation of treatment) to facilitate immediate uptake of care. Our recent qualitative work with WLWH in the area found that individuals are often willing to implement lifestyle changes at time of diagnosis and indicated general acceptability of an alcohol use intervention integrated into testing services (80). Among male alcohol users, those reporting any alcohol-related consequences (indicators of harmful drinking, heavy drinking and alcohol dependence) were less likely to report current ART use or be virally suppressed, suggesting that men who consume enough alcohol to experience these consequences should be screened for alcohol misuse and a priority population for alcohol interventions in this setting.

Findings from chapter 2 were inconclusive. We did not observe a causal effect of past year experiences of any form of IPV on current ART use or viral suppression. It is possible that this was the result of no true causal effect. Many of

the IPV-related barriers to ART initiation identified in prior studies (such as delayed care seeking for fear of disclosure of HIV positive status to one's partner and subsequent delayed care seeking, partner limiting access to transportation to clinic to initiate treatment) are overcome through access to treatment at the time of diagnosis. Beyond a sensitivity analysis stratified by age group, our analysis did not explore if specific groups of women (e.g. sex workers) who experienced IPV were at greater risk of poor HIV outcomes. IPV is a prevalent and serious public health issue in its own right that disproportionately burdens WLWH. Integration of services to address IPV into HIV care and treatment should be a priority regardless of its effect (or potential lack of effect) on HIV treatment outcomes.

Findings from chapter 3 should were also inconclusive. We did not observe any significant mediated or moderated pathways between IPV, alcohol use and current ART use or viral suppression. These findings might be attributed to several factors, including, the absence of any true causal effect, measurement error, and/or incorrect model specification. Potential sources of measurement error, unmeasured confounding and model misspecification are described in detail in chapter 3. Given the high prevalence and co-occurrence of HIV, alcohol use and IPV in this setting and the public health burden attributed to each of these issues, more research is needed to understand how these variables are related. Null findings for aims two and three should be considered inconclusive and we outline suggested next steps for research under "recommendations for future work"

Recommendations for Future Work

Insignificant findings across all three chapters could be a product of the measures used. We did not have access to validated alcohol use measures or (e.g., AUDIT to detect problematic alcohol use (76)) or biomarker data. We were reliant on self-reported use (which is subject to social desirability bias) and our primary alcohol use measure, "any past year alcohol use", which groups those who ceremoniously drink once a year in the same group as binge drinkers, may not have been sensitive enough to capture differences in viral suppression among men. More rigorous alcohol use measures in this setting are needed to clearly distinguish types of drinker and further identify highest priority populations.

The IPV measures used were adapted from the conflict tactics scale, a validated IPV measures used globally (102). However, the questions were asked differently across the two rounds and this could have impacted recall and reporting. At baseline individuals were asked about experiences of IPV with specific partners and at follow up they were asked about any IPV with any past year partner. There is evidence that recall is improved when individuals are asked about more specific experiences (116). The prevalence of IPV at follow-up was lower than at baseline and this could have been a product of this discrepancy in survey formatting. Future data collection should seek to maintain the same

question format across rounds to remove this potential source of bias. This will also facilitate the inclusion of additional time points in prospective analyses and allow for clinically meaningful outcomes such as durable viral suppression to be measured. The addition of questions that capture the frequency and severity of IPV experienced as well as instances of bidirectional IPV are also needed to determine if specific populations of women experiencing IPV have worse HIV treatment outcomes. Finally, qualitative work with WLWH who experience IPV is needed to shed light on how IPV currently impacts HIV care seeking behavior and if this has changed in response to changing treatment guidelines.

Additional studies exploring pathways between alcohol, IPV and HIV care and treatment outcomes are needed to further disentangle the relationship between these variables. Future pathway analyses should utilize data collected more frequently and with shorter recall periods (e.g., two weeks, past month) to narrow the temporal window and improve recall. Finally, qualitative research among WLWH is needed to understand perceived barriers to treatment adherence related to IPV and alcohol use.

This dissertation addresses gaps in the literature regarding the relationship between alcohol use, IPV and HIV treatment outcomes. It contributes to the sparse evidence base on this topic in sub-Saharan Africa and provides

meaningful recommendations for next steps in future research and HIV program development.

APPENDICES

Supplemental Table 1. Comparison of Sociodemographic and Behavioral Characteristics at Baseline by Retention Status, overall (Chapter 1)

		RETAINED N (%)	NOT RETAINED N (%)	P-value for Chi2
Past Year Alcohol Use				0.0026
	Yes	756 (58.6%)	1060 (53.2%)	
	No	535 (41.4%)	932 (46.8%)	
Alc consequences				0.1166
	none	448 (59.4%)	679 (64.2%)	
	1	114 (15.1%)	138 (13.0%)	
	2+	192 (25.5%)	241 (22.8%)	
Mean age	years	33.5	36.1	<0.0001
Residence				0.3249
	Agrarian	496 (38.4%)	809 (40.6%)	
	Trade	75 (5.8%)	125 (6.28%)	
	Fishing	720 (55.8%)	1058 (53.1%)	

Supplemental Table 1 cont'd. Comparison of Sociodemographic and Behavioral Characteristics at Baseline by Retention Status, overall (Chapter 1)

		RETAINED N (%)	NOT RETAINED N (%)	P-value for Chi2
Education				0.6665
	No School	413 (32.0%)	623 (31.3%)	
	Primary or above	878 (68.0%)	1369 (68.7%)	
HH SES				0.6364
	High	653 (51.3%)	978 (49.6%)	
	Middle	225 (17.7%)	354 (18.0%)	
	Low	395 (31.0%)	638 (32.4%)	
Occupation				0.0055
	Housework	427 (33.1%)	782 (39.3%)	
	Trade/shopkeeper	225 (17.4%)	331 (16.6%)	
	Bar/Restaurant Worker	260 (20.1%)	345 (17.3%)	
	Fisherman	118 (9.1%)	150 (7.5%)	
	Other	261 (22.2%)	384 (19.3%)	
Religion				0.0872
	Catholic	847 (65.6%)	1364 (68.5%)	
	Other	444 (34.4%)	628 (31.5%)	
Any Drug Use				0.0691

Supplemental Table 1 cont'd. Comparison of Sociodemographic and Behavioral Characteristics at Baseline by Retention Status, overall (Chapter 1)

		RETAINED N (%)	NOT RETAINED N (%)	P-value for Chi2
Any Drug Use				0.0691
	Yes	76 (5.9%)	89 (4.5%)	
	No	1215 (94.1%)	1903 (95.5%)	
Marital Status	Currently Married	741 (57.4%)	1215 (60.0%)	0.0402
	Not Married	550 (42.6%)	777 (40.0%)	
Mean time since dx	Days	1337 (1601.5)	2028 (1840.0)	<0.0001
Sex				0.0006
	M	562 (43.5%)	748 (37.6%)	
	F	729 (56.5%)	1244 (62.5%)	

Supplemental Table 2. Comparison of Sociodemographic and Behavioral Characteristics at Baseline by Retention Status (Chapter 2)

		RETAINED N (%)	NOT RETAINED N (%)	P-value for Chi2
Physical IPV				0.0032
	Yes	260 (23.9%)	250 (29.9 %)	
	No	827 (76.1%)	586 (70.1%)	
Sexual IPV				0.3485
	Yes	140 (12.9%)	120 (14.4%)	
	No	947 (87.1%)	716 (85.7%)	
Verbal IPV				0.6459
	Yes	276 (25.4%)	220 (26.3%)	
	No	811 (74.6%)	616 (73.7%)	
Alcohol Use				
Before IPV	Yes	193 (50.9%)	160 (47.3%)	0.3377
	No	186 (49.1%)	178 (52.7%)	
Mean age	years	31.3	34.7	<0.0001
Residence				<0.0001

Supplemental Table 2 cont'd. Comparison of Sociodemographic and Behavioral Characteristics at Baseline by Retention Status (Chapter 2)

		RETAINED N (%)	NOT RETAINED N (%)	P-value for Chi2
	Agrarian	474 (42.7%)	247 (29.6%)	
	Trade	68 (6.3%)	252 (30.1%)	
	Fishing	545 (51.0%)	337 (40.3%)	
Education				0.0606
	No School	323 (29.7%)	216 (25.8%)	
	Primary or above	764 (70.3%)	620 (74.2%)	
HH SES				<0.0001
	High	554 (52.0%)	528 (63.2%)	
	Middle	193 (17.8%)	130 (15.6%)	
	Low	340 (31.3%)	177 (21.2%)	
Occupation				<0.001
	Housework	535 (49.2%)	332 (39.7%)	
	Trade/ shopkeeper	232 (21.3%)	212 (25.4%)	
	Bar/Restaurant Worker	130 (12.0%)	142 (17.0%)	
	Other	190 (17.5%)	150 (17.9%)	

Supplemental Table 2 cont'd. Comparison of Sociodemographic and Behavioral Characteristics at Baseline by Retention Status (Chapter 2)

		RETAINED N (%)	NOT RETAINED N (%)	P-value for Chi2
Religion				0.1090
	Catholic	712 (65.5%)	518 (62.0%)	
	Other	375 (34.5%)	318 (38.0%)	
Any Drug Use				0.3832
	Yes	12 (1.1%)	6 (0.7%)	
	No	1075 (98.9%)	830 (99.3%)	
Marital Status	Currently Married	706 (65.0%)	482 (57.7%)	0.0011
	Not Married	381 (35.1%)	354 (42.3%)	

REFERENCES

1. WHO. Global status report on alcohol and health 2014: Country Profiles for WHO Regions. Geneva, Switzerland: World Health Organization; 2018.

2. Tumwesigye NM, Atuyambe L, Wanyenze RK, Kibira SP, Li Q, Wabwire-Mangen F, et al. Alcohol consumption and risky sexual behaviour in the fishing communities: evidence from two fish landing sites on Lake Victoria in Uganda. BMC Public Health. 2012;12:1069.

3. Chang LW, Grabowski MK, Ssekubugu R, Nalugoda F, Kigozi G, Nantume B, et al. Heterogeneity of the HIV epidemic in agrarian, trading, and fishing communities in Rakai, Uganda: an observational epidemiological study. The Lancet HIV. 2016;3(8):e388-e96.

4. Rakai Health Sciences Program. Report to the World Bank: Comprehensive Report on Combination HIV Prevention Impact Evaluation in Rakai District, Uganda. Available upon request.; 2014.

5. Kouyoumdjian FG, Calzavara LM, Bondy SJ, O'Campo P, Serwadda D, Nalugoda F, et al. Risk factors for intimate partner violence in women in the Rakai Community Cohort Study, Uganda, from 2000 to 2009. BMC Public Health. 2013;13:566.

6. Weinsheimer RL, Schermer CR, Malcoe LH, Balduf LM, Bloomfield LA. Severe intimate partner violence and alcohol use among female trauma patients. . The Journal of Trauma. 2005;58:22-9.

7. Zablotska IB, Gray RH, Koenig MA, Serwadda D, Nalugoda F, Kigozi G, et al. Alcohol use, intimate partner violence, sexual coercion and HIV among women aged 15-24 in Rakai, Uganda. AIDS Behav. 2009;13(2):225-33.

8. WHO. Intimate Partner IVolence and HIV/AIDS. Geneva, Switzerland: World Health Organization; 2004.

9. Mafigiri R, Matovu JK, Makumbi FE, Ndyanabo A, Nabukalu D, Sakor M, et al. HIV prevalence and uptake of HIV/AIDS services among youths (15-24 Years) in fishing and neighboring communities of Kasensero, Rakai District, South Western Uganda. BMC Public Health. 2017;17(1):251.

10. Kouyoumdjian FG, Findlay N, Schwandt M, Calzavara LM. A systematic review of the relationships between intimate partner violence and HIV/AIDS. PLoS One. 2013;8(11):e81044.

11. Zablotska IB, Gray RH, Serwadda D, Nalugoda F, Kigozi G, Sewankambo N, et al. Alcohol use before sex and HIV acquisition: a longitudinal study in Rakai, Uganda. AIDS. 2006;20(8):1191-6.

12. Maman S, Campbell J, Sweat MD, Gielen AC. The intersections of HIV and violence: directions for future research and interventions. Soc Sci Med. 2000;50(4):459-78.

13. Wagman JA, King EJ, Namatovu F, Kiwanuka D, Kairania R, Semanda JB, et al. Combined Intimate Partner Violence and HIV/AIDS Prevention in Rural Uganda: Design of the SHARE Intervention Strategy. Health Care Women Int. 2016;37(3):362-85.

14. Miller AP, Ddaaki W, Bloom BE, Nakyanjo N, Ddaaki W, Kigozi G, et al. Perspectives of Women living with HIV on addressing violence and use of alcohol during HIV services: Qualitative findings from fishing communities in Uganda VIolence Against Women. under review.

15. Campbell JC, Baty ML, Ghandour RM, Stockman JK, Francisco L, Wagman J. The intersection of intimate partner violence against women and HIV/AIDS: a review. Int J Inj Contr Saf Promot. 2008;15(4):221-31.

16. Fonck K, Leye E, Kidula N, Ndinya-Achola J, Temmerman M. Increased risk of HIV in women experiencing physical partner violence in Nairobi, Kenya. AIDS Behav. 2005;9(3):335-9.

17. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntryre JA, Harlow SD. Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. The Lancet. 2004;363(9419):1415-21.

18. Jewkes R, Nduna M, Levin J, Jama N, Dunkle K, Khuzwayo N, et al. A cluster randomized-controlled trial to determine the effectiveness of Stepping Stones in preventing HIV infections and promoting safer sexual behaviour amongst youth in the rural Eastern Cape, South Africa: trial design, methods and baseline findings. Trop Med Int Health. 2006;11(1):3-16.

19. Maman S, Mbwambo JK, Hogan NM, Kilonzo GP, Campbell JC, Weiss E, et al. HIV-positive women report more lifetime partner violence: findings from a voluntary counseling and testing clinic in Dar es Salaam, Tanzania. Am J Public Health. 2002;92(8):1331-7.

20. Li Y, Marshall CM, Rees HC, Nunez A, Ezeanolue EE, Ehiri JE. Intimate partner violence and HIV infection among women: a systematic review and meta-analysis. J Int AIDS Soc. 2014;17:18845.

21. Bonnevie E, Kigozi G, Kairania R, Ssemanda JB, Nakyanjo N, Ddaaki WG, et al. Alcohol use in fishing communities and men's willingness to participate in an alcohol, violence and HIV risk reduction intervention: qualitative findings from Rakai, Uganda. Culture, Health & Sexuality. 2019:1-17.

22. Miller AP, Kigozi G, Bonnevie E, Nakyanjo N, Ddaaki W, Ssekyewa C, et al., editors. HIV+ women's perspectives on integrating screening and a brief intervention (SBI) for harmful alcohol use into routine HIV post-test counseling in Ugandan fishing villages:

assessing acceptability and identifying barriers to implementation. [THPEC286]. International AIDS Conference; 2018 July 23-27; Amsterdam, Netherlands.

23. Mbulaiteye S, Ruberantwari A, Nakiyingi J, Carpenter L, Kamali A, Whitworth J. Alcohol and HIV: a study among sexually active adults in rural southwest Uganda. International Journal of Epidemiology. 2000;29(5):911-5.

24. Hofer-Szabó G., Rédei M., LE.. S. The Principle of the Common Cause. Cambridge University Press: Cambridge University Press; 2013.
25. Khantzian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry. 1997;4(5):231-44.

26. Klostermann K.C., W. F-S. Intimate partner violence and alcohol use: Exploring the role of drinking in partner violence and its implications for intervention. Aggression and Violent Behavior. 2006;11(6):587-97.

27. Leonard K.E., B.M. Q. Drinking and marital aggression in newlyweds: an event-based analysis of drinking and the occurrence of husband marital aggression. . J Stud Alcohol 1999;60(4):537-45.

28. Overup CS, DiBello AM, Brunson JA, Acitelli LK, Neighbors C. Drowning the pain: intimate partner violence and drinking to cope prospectively predict problem drinking. Addict Behav. 2015;41:152-61.

29. Statistics UBo. The National Population and Housing Census 2014 – Area Specific Profile Series, Kampala, Uganda. Kampala, Uganda; 2017.

30. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Paxton L, Berkley S, et al. A randomized, community trial of intensive sexually transmitted disease control for AIDS prevention, Rakai, Uganda. AIDS. 1998;12(10):1211-25.

31. WHO. Antiretroviral treatment as prevention (TASP) of HIV and TB. Geneva, Switzerland; 2012.

32. Baeten JM, Grant R. Use of antiretrovirals for HIV prevention: What do we know and what don't we know? Current HIV/AIDS Reports, 10, 2, 142–51. 2013;10(2):142-51.

33. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505.

34. Cohen MS, McCauley M, Gamble TR. HIV treatment as prevention and HPTN 052. Current Opinion in HIV & AIDS. 2012;7(2):99-105.

35. Monroe AK, Lau B, Mugavero MJ, Mathews WC, Mayer KH, Napravnik S, et al. Heavy Alcohol Use Is Associated With Worse Retention in HIV Care. J Acquir Immune Defic Syndr. 2016;73(4):419-25.

36. Hendershot CS, Stoner SA, Pantalone DW, Simoni JM. Alcohol use and antiretroviral adherence: review and meta-analysis. J Acquir Immune Defic Syndr. 2009;52(2):180-202.

37. Vagenas P, Azar MM, Copenhaver MM, Springer SA, Molina PE, Altice FL. The Impact of Alcohol Use and Related Disorders on the HIV Continuum of Care: a Systematic Review : Alcohol and the HIV Continuum of Care. Curr HIV/AIDS Rep. 2015;12(4):421-36.

38. Samet JH, Freedberg KA, Stein MD, Lewis R, Savetsky J, Sullivan L, et al. Trillion virion delay: time from testing positive for HIV to presentation for primary care. Arch Intern Med. 1998;158(7):734-40.

39. Hatcher AM, Smout EM, Turan JM, Christofides N, Stockl H. Intimate partner violence and engagement in HIV care and treatment among women: a systematic review and meta-analysis. AIDS. 2015;29(16):2183-94.

40. Azar MM, Springer SA, Meyer JP, Altice FL. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. Drug Alcohol Depend. 2010;112(3):178-93.

41. Kahler CW, Liu T, Cioe PA, Bryant V, Pinkston MM, Kojic EM, et al. Direct and Indirect Effects of Heavy Alcohol Use on Clinical Outcomes in a Longitudinal Study of HIV Patients on ART. AIDS Behav. 2017;21(7):1825-35.

42. Wandera B, Tumwesigye NM, Nankabirwa JI, Kambugu AD, Parkes-Ratanshi R, Mafigiri DK, et al. Alcohol Consumption among HIV-Infected Persons in a Large Urban HIV Clinic in Kampala Uganda: A Constellation of Harmful Behaviors. PLoS One. 2015;10(5):e0126236.

43. Hahn JA, Cheng DM, Emenyonu NI, Lloyd-Travaglini C, Fatch R, Shade SB, et al. Alcohol Use and HIV Disease Progression in an Antiretroviral Naive Cohort. J Acquir Immune Defic Syndr. 2018.

44. Williams EC, Hahn JA, Saitz R, Bryant K, Lira MC, Samet JH. Alcohol Use and Human Immunodeficiency Virus (HIV) Infection: Current Knowledge, Implications, and Future Directions. Alcohol Clin Exp Res. 2016;40(10):2056-72.

45. Wandera B, Tumwesigye NM, Nankabirwa JI, Kambugu AD, Mafigiri DK, Kapiga S, et al. Hazardous alcohol consumption is not associated with CD4+ T-cell count decline among PLHIV in Kampala Uganda: A prospective cohort study. PLoS One. 2017;12(6):e0180015.

46. Samet JH, Cheng DM, Libman H, Nunes DP, Alperen JK, Saitz R. Alcohol consumption and HIV disease progression. J Acquir Immune Defic Syndr. 2007;46(2):194-9.

47. Rowley CF. Developments in CD4 and viral load monitoring in resource-limited settings. Clin Infect Dis. 2014;58(3):407-12.

48. Wagman JA, Nabukalu D, Miller AP, Wawer MJ, Ssekubugu R, Nakowooya H, et al. Prevalence and correlates of men's and women's alcohol use in agrarian, trading and fishing communities in Rakai, Uganda. PLoS One. 2020;15(10):e0240796.

49. Breuer C, Bloom B, Miller AP, Kigozi G, Nakyanjo N, Ddaaki W, et al. "The Bottle Is My Wife": Exploring Reasons Why Men Drink Alcohol in Ugandan Fishing Communities. Soc Work Public Health. 2019;34(8):657-72.

50. Wolff B, Busza J, Bufumbo L, Whitworth J. Women who fall by the roadside: gender, sexual risk and alcohol in rural Uganda. Addiction. 2006;101(9):1277-84.

51. Institute for Health Metrics and Evaluation. Country Profiles: Uganda Seattle: IHME; 2020 [Available from: http://www.healthdata.org/uganda.

52. Ugandan Ministry of Health. UGANDA POPULATION-BASED HIV IMPACT ASSESSMENT: UPHIA 2016-2017: Extended Summary Sheet: Preliminary Findings. 2018.

53. Magidson JF, Fatch R, Orrell C, Amanyire G, Haberer JE, Hahn JA, et al. Biomarker-Measured Unhealthy Alcohol Use in Relation to CD4 Count Among Individuals Starting ART in Sub-Saharan Africa. AIDS Behav. 2019;23(6):1656-67.

54. Uganda Bureau of Statistics. The National Population and Housing Census 2014 – Area Specific Profile Series, Kampala, Uganda. Kampala, Uganda; 2017.

55. Rehm J, Shield KD, Joharchi N, Shuper PA. Alcohol consumption and the intention to engage in unprotected sex: systematic review and meta-analysis of experimental studies. Addiction. 2012;107(1):51-9.

56. Fisher JC, Bang H, Kapiga SH. The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies. Sex Transm Dis. 2007;34(11):856-63.

57. Rehm J, Probst C, Shield KD, Shuper PA. Does alcohol use have a causal effect on HIV incidence and disease progression? A review of the literature and a modeling strategy for quantifying the effect. Popul Health Metr. 2017;15(1):4.

58. Samet JH, Horton NJ, Meli S, Freedberg KA, Palepu A. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. Alcohol Clin Exp Res. 2004;28(4):572-7.

59. Kalichman SC, Grebler T, Amaral CM, McNerey M, White D, Kalichman MO, et al. Intentional non-adherence to medications among HIV positive alcohol drinkers: prospective study of interactive toxicity beliefs. J Gen Intern Med. 2013;28(3):399-405.

60. Marchetti G, Bellistri GM, Borghi E, Tincati C, Ferramosca S, La Francesca M, et al. Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. AIDS. 2008;22(15):2035-8.

61. Balagopal A, Philp FH, Astemborski J, Block TM, Mehta A, Long R, et al. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. Gastroenterology. 2008;135(1):226-33.

62. Cassol E, Malfeld S, Mahasha P, van der Merwe S, Cassol S, Seebregts C, et al. Persistent microbial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. J Infect Dis. 2010;202(5):723-33.

63. Hahn JA, Samet JH. Alcohol and HIV disease progression: weighing the evidence. Curr HIV/AIDS Rep. 2010;7(4):226-33.

64. Baum MK, Rafie C, Lai S, Sales S, Page JB, Campa A. Alcohol use accelerates HIV disease progression. AIDS Res Hum Retroviruses. 2010;26(5):511-8.

65. Deiss RG, Mesner O, Agan BK, Ganesan A, Okulicz JF, Bavaro M, et al. Characterizing the Association Between Alcohol and HIV Virologic Failure in a Military Cohort on Antiretroviral Therapy. Alcohol Clin Exp Res. 2016;40(3):529-35.

66. Kowalski S, Colantuoni E, Lau B, Keruly J, McCaul ME, Hutton HE, et al. Alcohol consumption and CD4 T-cell count response among persons initiating antiretroviral therapy. 2012;61(4):455-61.

67. Ghebremichael M, Paintsil E, Ickovics JR, Vlahov D, Schuman P, Boland R, et al. Longitudinal association of alcohol use with HIV disease progression and psychological health of women with HIV. AIDS Care. 2009;21(7):834-41.

68. Chander G, Lau B, Moore RD. Hazardous alcohol use: a risk factor for non-adherence and lack of suppression in HIV infection. 2006;43(4):411-7.

69. Cook JA, Burke-Miller JK, Cohen MH, Cook RL, Vlahov D, Wilson TE, et al. Crack cocaine, disease progression, and mortality in a multicenter cohort of HIV-1 positive women. AIDS. 2008;22(11):1355-63.

70. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med. 2016;375(9):830-9.

71. Puryear SB, Balzer LB, Ayieko J, Kwarisiima D, Hahn JA, Charlebois ED, et al. Associations between alcohol use and HIV care cascade outcomes among adults undergoing population-based HIV testing in East Africa. AIDS. 2020;34(3):405-13.

72. Selzer ML. The Michigan alcoholism screening test: the quest for a new diagnostic instrument. Am J Psychiatry. 1971;127(12):1653-8.

73. PEPFAR. Standard Operating Procedures on Viral Load Monitoring for ICAP Clinical Staff and Health Care Workers: A Template for Coutnry Adaptation. 2016.

74. SAS Institute Inc. SAS University Edition. Cary, NC.: SAS Institute Inc. .

75. Williams EC, McGinnis KA, Edelman EJ, Matson TE, Gordon AJ, Marshall BDL, et al. Level of Alcohol Use Associated with HIV Care Continuum Targets in a National U.S. Sample of Persons Living with HIV Receiving Healthcare. AIDS Behav. 2019;23(1):140-51.

76. Babor TF, de la Fuente JR, Saunders J, Grant M. AUDIT. The Alcohol Use Disorders Identification Test. Guidelines for use in primary health care. Geneva, Switzerland: World Health Organization; 1992.

77. WHO. Global status report on alcohol and health 2018. Geneva, Switzerland.: World Health Organization, ; 2018.

78. Miguez MJ, Shor-Posner G, Morales G, Rodriguez A, Burbano X. HIV treatment in drug abusers: impact of alcohol use. Addict Biol. 2003;8(1):33-7.

79. Wilsnack RW, Wilsnack SC, Kristjanson AF, Vogeltanz-Holm ND, Gmel G. Gender and alcohol consumption: patterns from the multinational GENACIS project. Addiction. 2009;104(9):1487-500.

80. Miller AP, Ddaaki W, Bloom BE, Wirtz AL, Nakyanjo N, Kigozi G, et al. Perspectives of Women living with HIV on addressing violence and use of alcohol during HIV services: Qualitative findings from fishing communities in Uganda Violence Against Women. 2021; Forthcoming.

81. Sileo KM, Miller AP, Wagman JA, Kiene SM. Psychosocial interventions for reducing alcohol consumption in sub-Saharan African settings: a systematic review and meta-analysis. Addiction. 2020.

82. Sileo K, Miller AP, Huynh TA, Kiene S. A systematic review of interventions for reducing heavy episodic drinking and related outcomes in sub-Saharan African settings. PLOS ONE. 2020.

83. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995;51(6):768-74.

84. Spitzer RL. Patient Health Questionnaire (PHQ). New York: New York State Psychiatric Institute 1999.

85. Radloff LS. The CES-D Scale. Applied Psychological Measurement. 2016;1(3):385-401.

86. WHO. Global and reginal estimate of violence against women: prevlaence and health effects of intimate partner violence and non-partner sexual violence. Geneva: WHO; 2013.

87. Delara M. Mental Health Consequences and Risk Factors of Physical Intimate Partner Violence. Mental Health in Family Medicine. 2016.

88. Coker AL, Davis KE, Arias I, Desai S, Sanderson M, Brandt HM, et al. Physical and mental health effects of intimate partner violence for men and women. American Journal of Preventive Medicine. 2002;23(4):260-8.

89. Ellsberg M, Jansen HAFM, Heise L, Watts CH, Garcia-Moreno C. Intimate partner violence and women's physical and mental health in the WHO multi-country study on women's health and domestic violence: an observational study. The Lancet. 2008;371(9619):1165-72.

90. Sarkar NN. The impact of intimate partner violence on women's reproductive health and pregnancy outcome. J Obstet Gynaecol. 2008;28(3):266-71.

91. MacIsaac MB, Bugeja LC, Jelinek GA. The association between exposure to interpersonal violence and suicide among women: a systematic review. Aust N Z J Public Health. 2017;41(1):61-9.

92. Hatcher A, Woollett N, Pallitto C, Mokoatle K, Delany- Moretlwe S, Macphail C. Bidirectional links between HIV and intimate partner violence in pregnancy: implications for prevention of mother-to-child transmission. . J Int AIDS Soc 2014.

93. Cohen MH, Cook JA, Grey D, Young M, Lawrence HH, Tien P, et al. Medically eligible women who do not use HAART: the importance of abuse, drug use, and race. American Journal of Public Health. 2004;94(7).

94. Mugavero M, Ostermann J, Whetten K, Leserman J, Swartz M, Stangl D, et al. Barriers to antiretroviral adherence: the importance of depression, abuse, and other traumatic events. AIDS Patient Care STDS. 2006;20(6):418-28.

95. McCauley J, Yurk RA, Jenckes MW, Ford DE. Inside 'Pandora's box': abused women's experiences with clinicians and health services. J Gen Intern Med 1998;13:549-55.

96. Lichtenstein B. Domestic violence in barriers to health care for HIV-positive women. AIDS Patient Care STDS. 2006;20(2):122-32.

97. Uganda Ministry of Health;. UGANDA POPULATION-BASED HIV IMPACT ASSESSMENT (UPHIA) 2016-2017: Final Report. Kampala: Ministry of Health; 2019 July 2019.

98. Sabri B, Wirtz AL, Ssekasanvu J, Nonyane BAS, Nalugoda F, Kagaayi J, et al. Intimate partner violence, HIV and sexually transmitted infections in fishing, trading and agrarian communities in Rakai, Uganda. BMC Public Health. 2019;19(1):594.

99. Wirtz A, Nakyanjo N, Wagman J, Gray R, Ssekubugu R, Serwadda D, et al. The effects of intimate partner violence on HIV care and ART use in Rakai, Uganda. International AIDS Conference; July 25, 2018; Amsterdam, Netherlands 2018.

100. Reed E, Gupta J, Silverman JG. Understanding sexual violence perpetration. JAMA Pediatr. 2014;168(6):581.

101. Koenig MA, Lutalo T, Zhao F, Nalugoda F, Wabwire-Mangen F, Kiwanuka N, et al. Domestic violence in rural Uganda: evidence from a community-based study. Bull World Health Organ. 2003;81(1):53-60.

102. Straus MA. Measuring intrafamily conflict and violence. The conflict tactics (CT) scales. . Journal of Marriage and the Family 1979(41):75-88.

103. Kalokhe AS, Paranjape A, Bell CE, Cardenas GA, Kuper T, Metsch LR, et al. Intimate partner violence among HIV-infected crack cocaine users. AIDS Patient Care STDS. 2012;26(4):234-40.

104. Ramachandran S, Yonas MA, Silvestre AJ, Burke JG. Intimate partner violence among HIV-positive persons in an urban clinic. AIDS Care. 2010;22(12):1536-43.

105. Illangasekare S, Tello M, Hutton H, Moore R, Anderson J, Baron J, et al. Clinical and mental health correlates and risk factors for intimate partner violence among HIV-positive women in an inner-city HIV clinic. Womens Health Issues. 2012;22(6):e563-9.

106. Siemieniuk RA, Krentz HB, Miller P, Woodman K, Ko K, Gill MJ. The clinical implications of high rates of intimate partner violence against HIV-positive women. J Acquir Immune Defic Syndr. 2013;64(1):32-8.

107. Blackstock OJ, Blank AE, Fletcher JJ, Verdecias N, Cunningham CO. Considering care-seeking behaviors reveals important differences among HIV-positive women not engaged in care: implications for intervention. AIDS Patient Care STDS. 2015;29 Suppl 1:S20-6.

108. Espino SR, Fletcher J, Gonzalez M, Precht A, Xavier J, Matoff-Stepp S. Violence screening and viral load suppression among HIV-positive women of color. AIDS Patient Care STDS. 2015;29 Suppl 1:S36-41.

109. Blank AE, Fletcher J, Verdecias N, Garcia I, Blackstock O, Cunningham C. Factors associated with retention and viral suppression among a cohort of HIV+ women of color. AIDS Patient Care STDS. 2015;29 Suppl 1:S27-35.

110. Sullivan KA, Messer LC, Quinlivan EB. Substance abuse, violence, and HIV/AIDS (SAVA) syndemic effects on viral suppression among HIV positive women of color. AIDS Patient Care STDS. 2015;29 Suppl 1:S42-8.

111. Rose RC, House AS, Stepleman LM. Intimate partner violence and its effects on the health of African American HIV-positive women. Psychological Trauma: Theory, Research, Practice, and Policy. 2010;2(4):311-7.

112. Ministry of Health U, ;. Consolidated Guidelines for the Prevention and Treatment of HIV and AIDS in Uganda. Kampala: Ministry of Health; 2020.

113. Tam M, Amzel A, Phelps BR. Disclosure of HIV serostatus among pregnant and postpartum women in sub-Saharan Africa: a systematic review. AIDS Care. 2015;27(4):436-50.

114. Rotheram-Borus MJ, Weichle TW, Wynn A, Almirol E, Davis E, Stewart J, et al. Alcohol, But Not Depression or IPV, Reduces HIV Adherence Among South African Mothers Living with HIV Over 5 Years. AIDS Behav. 2019;23(12):3247-56.

115. Bulamba R, Miller A, Mugamba S, Nakigozi G, Kigozi G, Kigozi G, et al. Drivers and risk factors of Intimate Partner Violence (IPV) perpetration and victimization in a Uganda based urban community cohort study. 24th International Summit on Violence, Abuse and Trauma; September 5-9, 2019; La Jolla, California: Institute on Violence, Abuse and Trauma (IVAT); 2019.

116. Bachman R, Saltzman LE. Violence Against Women: Estimates From the Redesigned Survey, Special Report,. Washington, D.C.: U.S. Department of Justice, Bureau of Justice Statistics; 1995.

117. Closson K, McLinden T, Parry R, Lee M, Gibbs A, Kibel M, et al. Severe intimate partner violence is associated with all-cause mortality among women living with HIV. AIDS. 2020;34(10):1549-58.

118. Duko B, Ayalew M, Ayano G. The prevalence of alcohol use disorders among people living with HIV/AIDS: a systematic review and meta-analysis. Subst Abuse Treat Prev Policy. 2019;14(1):52.

119. Devries KM, Child JC, Bacchus LJ, Mak J, Falder G, Graham K, et al. Intimate partner violence victimization and alcohol consumption in women: a systematic review and meta-analysis. Addiction. 2014;109(3):379-91.

120. Singer M. AIDS and the health crisis of the U.S. urban poor; the perspective of critical medical anthropology. Soc Sci Med. 1994;39(7):931-48.

121. Tsai AC, Burns BF. Syndemics of psychosocial problems and HIV risk: A systematic review of empirical tests of the disease interaction concept. Soc Sci Med. 2015;139:26-35.

122. Wilson PA, Nanin J, Amesty S, Wallace S, Cherenack EM, Fullilove R. Using syndemic theory to understand vulnerability to HIV infection among Black and Latino men in New York City. J Urban Health. 2014;91(5):983-98.

123. Buttram ME, Surratt HL, Kurtz SP. Resilience and syndemic risk factors among African-American female sex workers. Psychol Health Med. 2014;19(4):442-52.

124. Quinn KG, Reed SJ, Dickson-Gomez J, Kelly JA. An Exploration of Syndemic Factors That Influence Engagement in HIV Care Among Black Men. Qual Health Res. 2018;28(7):1077-87.

125. Mizuno Y, Purcell DW, Knowlton AR, Wilkinson JD, Gourevitch MN, Knight KR. Syndemic vulnerability, sexual and injection risk behaviors, and HIV continuum of care outcomes in HIV-positive injection drug users. AIDS Behav. 2015;19(4):684-93.

126. VanderWeele TJ. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health. 2016;37:17-32.

127. Cichowitz C, Maraba N, Hamilton R, Charalambous S, Hoffmann CJ. Depression and alcohol use disorder at antiretroviral therapy initiation led to disengagement from care in South Africa. PLoS One. 2017;12(12):e0189820.

128. Hartka E, Johnstone B, Leino EV, Motoyoshi M, Temple MT, Fillmore KM. A meta-analysis of depressive symptomatology and alcohol consumption over time. Br J Addict. 1991;86(10):1283-98.

129. VanderWeele TJ, Valeri L, Ogburn EL. The role of measurement error and misclassification in mediation analysis: mediation and measurement error. Epidemiology. 2012;23(4):561-4.

130. le Cessie S, Debeij J, Rosendaal FR, Cannegieter SC, Vandenbroucke JP. Quantification of bias in direct effects estimates due to different types of measurement error in the mediator. Epidemiology. 2012;23(4):551-60.

131. Lee WK, Milloy MJS, Nosova E, Walsh J, Kerr T. Predictors of Antiretroviral Adherence Self-efficacy Among People Living With HIV/AIDS in a Canadian Setting. J Acquir Immune Defic Syndr. 2019;80(1):103-9.