

SUBSTANCE USE AND ENGAGEMENT ACROSS THE HIV CARE CONTINUUM
AMONG FEMALE SEX WORKERS, A KEY POPULATION IN MALAWI

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ABSTRACT

Kathryn E. Lancaster: Substance use and engagement across the HIV care continuum among female sex workers, a key population in Malawi
(Under the direction of William C. Miller)

The effect of substance use on optimal engagement across the HIV care continuum must be delineated to inform strategies that enhance HIV testing and treatment for female sex workers (FSW), a key population in sub-Saharan Africa for HIV transmission. We characterize the HIV care continuum and evaluate the association between substance use with engagement in HIV testing and treatment among FSW in Lilongwe, Malawi.

From July through September 2014, we enrolled 200 FSW ≥ 18 years using venue-based sampling into a cross-sectional evaluation to assess engagement in the HIV care continuum and substance use. Seropositive FSW, identified using HIV rapid testing, received rapid CD4 counts and viral loads using dried blood spots. We examined the associations of alcohol and marijuana use with lack of HIV infection awareness and sub-optimal HIV treatment outcomes: lack of ART use among ART-eligible and viral nonsuppression.

FSW had a very high HIV seroprevalence of 69%. Sixty-nine percent of HIV-infected FSW had a history of HIV care, 52% reported current ART use, and 45% were virally suppressed. Among HIV-infected FSW, 45% were non-hazardous drinkers, 28% were hazardous drinkers, 12% were harmful drinkers, and 15% were alcohol dependent. We observed a dose-response relationship between increased alcohol use and lack of HIV

infection awareness. The prevalence ratio for lack of HIV infection awareness in multivariable analysis was 1.14 (95% CI: 0.53, 2.45) among current marijuana users. In multivariable analysis, FSW who were harmful drinkers or alcohol dependent were 1.9 (95% CI: 1.0, 3.8) times as likely to not use ART. The bivariable prevalence ratio for FSW nonsuppressed was 2.0 (95% CI: 0.6, 6.5) among harmful drinkers and alcohol dependent FSW. In multivariable analysis, FSW who were currently using marijuana were 1.9 (95% CI: 0.8, 4.6) times as likely to not use ART.

Alcohol use is an influential barrier to achieving optimal HIV testing and treatment outcomes, which are necessary to receive the clinical, immunological, and transmission benefits of therapy. Prioritizing combination interventions to incorporate alcohol risk reduction strategies, in addition to other substances, will improve the uptake of HIV testing and treatment for HIV-infected FSW in Malawi.

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LIST OF ABBREVIATIONS

aPR	Adjusted prevalence ratio
ART	Antiretroviral treatment
AUDIT	Alcohol Use Disorder Identification Test
CAB	Community advisory board
CD4	Cluster of Differentiation 4
CI	Confidence interval
DBS	Dried blood spot
FSW	Female sex worker
HIV	Human Immunodeficiency Virus
HSRC	Health and Population National Health Sciences Research Committee
IQR	Interquartile range
PHQ-9	Patient Health Questionnaire-9
PLACE	Priorities for Local AIDS Control Efforts
PR	Prevalence ratio
PrEP	Pre-exposure prophylaxis
RNA	Ribonucleic acid
STI	Sexually transmitted infections
TasP	Treatment as prevention
TfaC	Theatre for a Change
UNC	The University of North Carolina
WHO	World Health Organization

CHAPTER I: SPECIFIC AIMS

Substance use is highly prevalent among female sex workers (FSW) globally.[1-7] FSW often engage in substance use to facilitate soliciting clients, to self-medicate for depression and to cope with stigma and stress related to sex work.[1, 4, 8-10] Substance using FSW have low condom usage and high rates of sexual abuse and sexually transmitted infections, which all disproportionately place substance using FSW at high-risk for HIV infection.[2, 11-13]

FSW are considered a key population for HIV prevention and treatment, with approximately 60% of FSW undiagnosed and thus unable to be engaged into care and receive antiretroviral treatment (ART). Expanded ART for FSW can improve health outcomes and ultimately onward transmission.[14-16] This success depends on being fully engaged in the HIV care continuum: timely diagnosis, engagement in care, adherence on antiretroviral therapy, and retention.[17-20] Full engagement is a particular challenge among FSWs in sub-Saharan Africa.[14, 21, 22] However to date, there are few interventions linking FSW to HIV testing and care and no interventions specifically focusing on increased access to ART.

Commonly used substances, alcohol and marijuana, may be one important barrier to full engagement for FSW and likely one contributing cause of HIV risk among FSW and their clients. The patterns of substance use and the pathways through which alcohol and marijuana use may affect the HIV care continuum must be clearly delineated to prevent FSW-related HIV acquisition and transmission. We hypothesize that FSW who have a high levels of alcohol and marijuana use, will have less completion of the HIV care continuum

compared to FSW who do not have high levels of alcohol and marijuana use. Identification of the patterns and pathways through which alcohol and marijuana use affects each point along the HIV care continuum will inform strategies to increase access to HIV testing, care, and treatment for FSW.

For this dissertation, we conducted a cross-sectional evaluation to determine whether substance use, particularly alcohol and marijuana, among FSW significantly affects engagement in HIV testing, care, and treatment in Lilongwe, Malawi. In Malawi, the most common substances used are alcohol and marijuana.[23, 24] Recent systematic, nationally representative prevalence estimates for current alcohol and marijuana use are limited; nonetheless alcohol and marijuana are considered acceptable and inexpensive forms of intoxication in Malawi.[24-26] Venue-based recruitment was used to recruit a sample of FSW. Consented FSW participated in a face-to-face survey and received rapid HIV testing. Among the seropositive FSW, CD4 cell count and HIV-1 RNA levels were ascertained. This study was supported by the well-established research infrastructure of UNC Project-Malawi in Lilongwe, Malawi. The specific aims were addressed in three manuscripts:

Aim 1: Characterize the HIV care continuum among FSW in Lilongwe, Malawi.

Overview: We identified 200 FSW using venue-based recruitment to participate in a face-to-face behavioral survey examining HIV testing history and engagement in HIV care and treatment. HIV serostatus was confirmed for all enrolled FSW. Seropositive FSW provide blood samples for ascertaining CD4 counts and plasma HIV-1 RNA levels.

Aim 2: Evaluate and compare the associations of alcohol and marijuana use with HIV testing: awareness of HIV infection. *Overview:* We assessed HIV infection awareness through a behavioral survey collecting HIV testing history. Women will received

HIV rapid testing to confirm HIV serostatus. We examined the relationships between alcohol and marijuana use, alone and together, and HIV infection awareness.

Aim 3: Evaluate and compare the associations of alcohol and marijuana use with engagement into HIV treatment: current use of ART among ART eligible FSW and viral suppression. *Overview:* Among women who are seropositive, virological and immunological status was determined. FSW eligible for ART was based on Malawi's Ministry of Health ART eligibility definition.[27] Among the FSW that have initiated ART, ART adherence was assessed based on the primary goal of ART– viral suppression.[28]

This dissertation is one of the first studies to assess the impact alcohol and marijuana use along each stage of the HIV care continuum among FSW, a key population disproportionately affected by HIV. A future combination intervention increasing both substance use treatment and access to HIV testing and treatment for FSW will be informed by this study.

CHAPTER II: BACKGROUND AND SIGNIFICANCE

HIV prevalence among FSW in sub-Saharan Africa

HIV prevalence among FSW remains disproportionately high despite decades of prevention activities. FSW have been a key prevention population for the HIV epidemic since the 1980's.[29] Yet, these women still are disproportionately more likely to acquire HIV than all other women of reproductive age.[29-34] Globally, the burden of HIV among FSW is approximately 12%. When compared to other regions, Sub-Saharan Africa holds the highest HIV prevalence among FSW, at approximately 37%.[30] FSW within generalized epidemics in sub-Saharan Africa have more than 12-times increased odds of living with HIV when compared to all women.[30] FSW in Malawi carry one of the highest burdens of HIV at an estimated 70%.[30]

Despite nearly 20 years of prevention efforts, FSW in sub-Saharan Africa continue to experience high incidence of HIV.[14, 30, 35] The heightened risk for HIV acquisition and transmission among FSW functions through a complex lattice of behavioral, biological, and structural risks.[36] Behavioral risk factors at the individual level are varied and numerous.[32] FSW have high-risk sexual exposures— high rates of unprotected sex,[11, 31, 37, 38] anal sex,[39, 40] different sexual partners,[6, 41] concurrent sexual partners,[6, 32, 42] and substance use.[2, 4, 8, 13] Biologically, the burden of sexually transmitted infections (STI), besides, HIV, in FSW is high. Generally at any point in time, two-thirds of FSW in sub-Saharan Africa have a curable STI.[32] This high prevalence of STIs and the synergist relationship between HIV and STIs only compounds the risk of HIV transmission.[43]

Indirectly, structural risk factors further exacerbate HIV acquisition and transmission as FSW are more likely to experience stigma and discrimination reducing their ability to access HIV care and treatment services.[14, 30, 36, 44] Furthermore, the illicit nature, organization, and power dynamics of sex work limits FSW's ability to negotiate for safer sexual practices.[35, 36] Prevention activities must be complemented with novel combination interventions, addressing behavioral, biological, and structural risk factors, for HIV-infected FSW in order to prevent further HIV transmission.

FSW access to HIV care and treatment

HIV-infected FSW infrequently access HIV care and treatment services. Alarming, only one-third of FSW in sub-Saharan Africa receive adequate HIV prevention services, even fewer access HIV care and treatment services.[14, 21] Approximately 60% of FSW in the region are unaware of their HIV infection and most FSW only learn of their infection at antenatal care clinics during pregnancy.[14, 21]

A situation analysis conducted by the Family Planning Association of Malawi in 2011, reported nearly 70% of the 913 FSW interviewed were unaware of their current HIV infection.[41] Qualitative findings revealed that the majority of FSW avoided receiving HIV testing and counseling out of fear for their results. Similar to other countries in the region, most FSW were aware of their HIV infection due to mandatory testing during pregnancy. The most common reason for voluntary HIV testing was because of frequent illnesses or deterioration of health.[41] Identifying HIV-infected FSW is only the first of several critical steps of accessing HIV care and treatment.

The proportion of FSW who are eligible or have access to ART is scarcely evaluated or documented.[14] Despite the recognition that linking newly diagnosed FSW to HIV care

and treatment can decrease morbidity and mortality, and ultimately onward transmission,[14-16] no interventions specifically focusing on increased access to ART for FSW in sub-Saharan Africa were identified in a recent systematic review.[14] The full effect of expanded ART cannot be achieved unless the myriad of barriers for engagement into care are FSW are identified and addressed.

Barriers of engagement into HIV care and treatment for FSW in sub-Saharan Africa are poorly understood. Although the challenges of engagement in care and treatment are well-described for many HIV-infected persons in sub-Saharan Africa,[45, 46] FSW experience unique barriers that may further complicate HIV care. The multilevel barriers for full engagement into the HIV care continuum among FSW have been documented in other HIV prevalent settings. Figure 2.1 depicts an adaption of the social ecological framework describing structural, work environment, interpersonal, and individual level barriers identified among FSW in similar settings that are likely exacerbating HIV risk and limiting their ability to seek HIV testing, care and treatment in sub-Saharan Africa.

Structural level barriers arising out of the illegal nature of their work, cultural factors, geographic, lack of economic and educational opportunities, and discrimination from community and healthcare providers likely force FSW out of the HIV care continuum.[15, 16, 29, 32, 33, 44] The work environment where FSW solicit clients further impedes their ability to seek HIV care and treatment. FSW who are street-based have higher prevalence of sexual risk behaviors and likely are less engaged for HIV care and treatment as most HIV surveillance activities focus on venue-based FSW.[47] Many FSW endure violence from a multitude of sources, whether it be from paying clients or police.[1, 2, 8, 13, 48] Additionally, availability of condoms and other forms of HIV prevention or treatment are

particularly limited for FSW.[11, 31, 37] At the interpersonal level, the FSW-client partnership dyads, FSW-stable partnership dyads, and gender norms influence the ability to negotiate condom use, the potential for intimate partner violence, and number of partners.[12, 36, 42, 49-53] The lack of social support networks for FSW precludes HIV prevention and treatment behaviors.[54-56] FSW experience individual level barriers to care, including substance use and depression.[2, 4, 38] Furthermore, biologically, FSW who have STI co-infections are disproportionately at more risk for HIV, making it more challenging for them to remain fully engaged in the HIV care continuum.[32, 43] The specific multilevel barriers to engagement into HIV care and treatment, although well described in other high HIV prevalence settings, are poorly described for FSW in sub-Saharan Africa and must be identified to develop effective combination prevention and treatment interventions.

Substance use among FSW

Substance use is prevalent and likely an important barrier to engagement into the HIV care continuum among FSW in sub-Saharan Africa. FSW have higher rates of substance use, including alcohol and marijuana, when compared to the general population due to their occupational and environmental factors.[4, 13] In Malawi, nearly 45% of FSW report consuming 4 to 5 bottles of alcoholic beverages per day, which puts these women at great risk for alcohol dependency.[8, 41, 57] Despite the recognition of high prevalence of alcohol use among FSW, alcohol use among FSW is rarely systematically measured.[4, 58] Alcohol use is generally documented as lifetime use or general use, with studies rarely utilizing standardized and reliable screening tools, such as the Alcohol Use Disorder Identification Test (AUDIT), to assess the frequency and severity of alcohol use behaviors. The use of these validated tools can assist with the comparability of alcohol use studies

among FSW, in addition to more accurately examining the relationship between alcohol use and HIV care and treatment among FSW.

The hazardous effects of alcohol use among HIV-infected individuals, not engaging in sex work, has been well documented. Among the general population, alcohol use severely affects utilization of HIV care.[59-62] The majority of longitudinal cohort studies have shown decreased ART adherence among HIV-infected individuals with alcohol use disorders. However the measurement of alcohol use disorders substantially differed, by assessing heavy drinking, hazardous drinking or severe drinking.[60, 63, 64] Additionally, the culmination of these results are further complicated by the differing measures of ART adherence: self-report, pill counts, or MEMS caps. Even after accounting for HAART adherence, alcohol consumption is biologically associated with high viral load and other poor immunologic and virological outcomes.[65, 66] Furthermore, hazardous drinking generally impairs cognitive functions and judgment, making it increasingly difficult to manage ART adherence and many other aspect of HIV care and treatment.[59, 61]

Heavy use of marijuana, similar to alcohol, adversely affect decision-making, cognitive functions, and memory.[67, 68] These adverse effects negatively likely negatively influence the necessary health seeking behavior for managing HIV care and treatment, including ART adherence.[69-71] However, evidence is remains unclear if marijuana also precludes HIV specific health care utilization given the apparent lack of estimates of marijuana use. Marijuana use estimates among FSW in Malawi are absent, nonetheless, marijuana is highly produced and a cheap form of intoxication.[24, 25, 72] Substance use of both alcohol and marijuana are likely one major threat to improving linkage to HIV testing, care, and treatment among FSW.

Conceptual framework

This dissertation is guided by self-regulation and coping theories that individuals engage in substance use to help cope with negative life events and dysregulate emotional states brought on by sex work, which in turn may influence HIV health seeking behaviors.[73-75] We have developed a multidimensional conceptual model focused on the potential impact of alcohol and marijuana use on engagement in key HIV care continuum outcomes: HIV testing, ART initiation and ART adherence, and viral suppression among FSW (Figure 2.2). The model depicts the influence of individual, social, and structural factors on each other, while simultaneously affecting alcohol and marijuana use among FSW. The factors in grey are unmeasured factors, while the factors in black were measured through this study. For this dissertation, we explore the relationship between alcohol and marijuana use and engagement in HIV testing and treatment, while controlling for other measured individual, social, and structural factors. We hypothesize that FSW who have a high levels of alcohol and marijuana use, will have less completion of the HIV care continuum compared to FSW who do not have high levels of alcohol and marijuana use.

Preliminary studies

In 2009, the UNC developed and implemented Priorities for Local AIDS Control Efforts (PLACE) in Lilongwe to assess key HIV transmission networks, including FSW, for the Ministry of Health.[76] Of these, approximately 65% were bottle stores or bars/taverns and 23% were hotels, guest houses, or rest houses. Among women (n=427) interviewed at these sites, 76% reported engaging in sex for pay in the past 4 weeks and 61% self-identified as a sex worker.

The Family Planning Association of Malawi in 2011 conducted a situation analysis of the magnitude and behavioral patterns of FSW.[41] An estimated 20,000 FSW work in

Malawi, with 3,500 FSW in Lilongwe. FSW were mostly 20-24 years old, found at bars, bottle stores, and guesthouses, and would take clients to nearby cars or rest houses. Few problems were identified for enrolling FSW; however, the length of the survey had to be strongly considered as to not serve as a participation disincentive.

In 2008, UNC Project assessed HIV prevalence in Malawi using multiple surveillance data sources.[77] Among FSW, the HIV prevalence was 74%. Only 10% of FSW reported condom use with their last sexual partner. About 70% of FSW reported ever being tested for HIV. In 2013, Theatre for a Change, a non-governmental organization and partners with UNC Project-Malawi, provided 1,213 FSW at approximately 25 different identified venues with health services in their mobile clinic. Services included STI testing, family planning, psycho-social support, contraception and condoms. These activities and the collaboration between UNC Project and Theatre for a Change demonstrate our ability to reach the FSW population in Lilongwe. Given the high burden of HIV infection, the FSW are clearly a key population for HIV prevention and treatment research.

Key informant interviews were conducted with FSW community liaisons in 2014 by UNC Project assessed marijuana and alcohol prevalence among FSW in Lilongwe. Respondents agreed that both marijuana and alcohol use are common within Lilongwe and particularly among FSW. Marijuana is considerably cheaper than alcohol and FSW often smoke marijuana in between clients while working or as a leisure activity when not working. In general, the respondents reported that FSW who engaged in alcohol consumption would also engage in marijuana use, yet, the patterns and frequency of using both marijuana and alcohol together have not been clearly delineated.

Innovation

Acceptability, feasibility, and efficacy of HIV treatment as prevention strategies among FSW is unknown. ART significantly reduces HIV transmission among monogamous, serodiscordant couples through decreased viral load in genital secretions.[18] The community-level effect of treatment as prevention is highly dependent on the success of identifying, linking to care, and initiating early ART among HIV-infected persons.[19, 20, 78, 79] However, FSW substantially differ from the predominately monogamous heterosexual couples of HPTN 052.[18]

As previously mention, FSW tend to engage in high risk sexual behaviors, including – high rates of unprotected sex,[11, 31, 37, 38] anal sex,[39, 40] different sexual partners,[6, 41] and concurrent sexual partners.[6, 32, 42] Additionally, FSW have higher rates of STI co-infections.[32, 43] The combination of these factors making FSW one of the hardest to reach populations for HIV care and treatment. FSW have low levels of engagement into care and have the potential to transmit drug resistant HIV if adequate viral suppression is not achieved.[14, 21, 80, 81] To maximize the benefits of treatment as prevention strategies, strategies to keep FSW engaged into the HIV care continuum must be identified.

Understanding substance use's influence on the HIV continuum of care will inform future treatment as prevention interventions for FSW. FSW are an important contributor to HIV transmission, affecting the global HIV epidemic, making FSW in crucial need for “treatment as prevention” strategies.[19, 82] Modeling shows that prioritizing treatment access to FSW could influence HIV transmission, if FSW are appropriately engaged into care and adhere to treatment.[19] Given the negative effect of substance use on engagement in HIV care combined with a high prevalence of substance use among FSW, substance use could prevent the success of treatment as prevention interventions. Successfully identifying

the impact of substance use on each point along the HIV care continuum will lead to future combination interventions that focus on substance use treatment and increasing access to HIV testing, care, and treatment among FSW.

Actively identifying FSW in the field to provide rapid CD4 testing will facilitate immediate HIV care referral. Approaches to streamline HIV services for FSW are imperative. Rapid point-of-care CD4 testing has the great potential to improve immediate decision-making, patient management, and referral for hard-to-reach FSW. The PIMA analyzer has been validated in several resource-limited settings to identify ART-eligibility.[83-86] When compared to a standard FACSCalibur platform the PIMA CD4 counts had no significant difference.[84, 85] The use of PIMA in mobile HIV testing and counseling settings in South Africa improved linkages to HIV care among HIV-infected individuals.[87] Provision of CD4 testing in the field to FSW may alleviate testing burden not only for FSW, but also for centralized clinic-based laboratories. To date, point-of-care CD4 has yet to be employed for FSW in the field.

FSW will continue to disproportionately affect the global HIV epidemic, if left behind. FSW will not benefit immunologically and clinically if they remain outside the HIV care continuum.[88, 89] Furthermore, they may continue to transmit the virus and as mathematical modeling has shown, FSW significantly affect the HIV epidemic.[14, 19, 90] Increasing access to ART for FSW would have a significant effect on the HIV transmission in high HIV prevalent settings. In 2013, the WHO's recommended CD4 threshold for ART initiation increased to 500 cells/mm³. [91] Theoretical models conducted in Kenya, reveal that expanding ART access to both FSW and their male clients who met the new WHO treatment guidelines could avert a third of new HIV infections among FSW and their clients

within the next decade.[92] Directing HIV prevention efforts to FSW is an essential cost-efficient use of already limited health systems and financial resources and additionally can dramatically reduce HIV transmission rates for all subpopulations.[93, 94] However, this reduction is largely dependent on FSW receiving a timely diagnosis, engaging in care, adhering to ART, and retaining in HIV care.

Summary

Understanding the impact of alcohol and marijuana use has on the HIV care continuum among FSW will provide empirical evidence for developing and enhancing treatment as prevention strategies for FSW in sub-Saharan Africa. The results from this study will have significant implications for the design of a combination intervention that focuses on substance use treatment and increasing access to HIV testing and treatment among FSW.

Figure 1. Barriers to engagement into the HIV care continuum among FSW

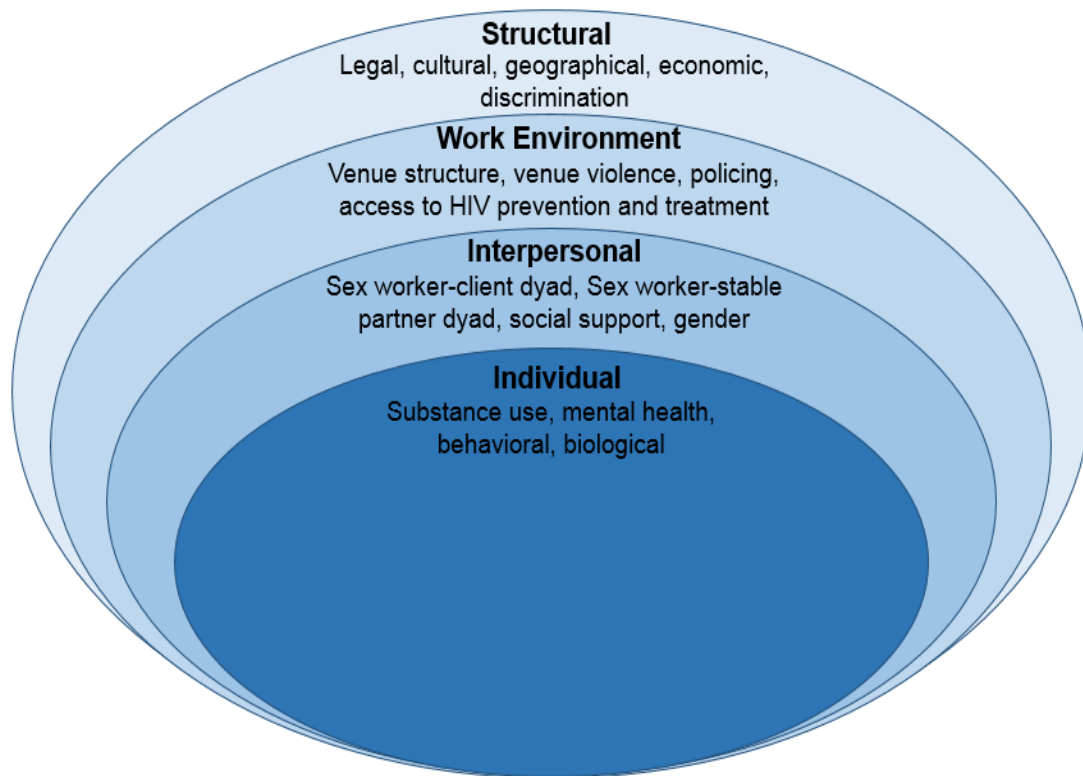
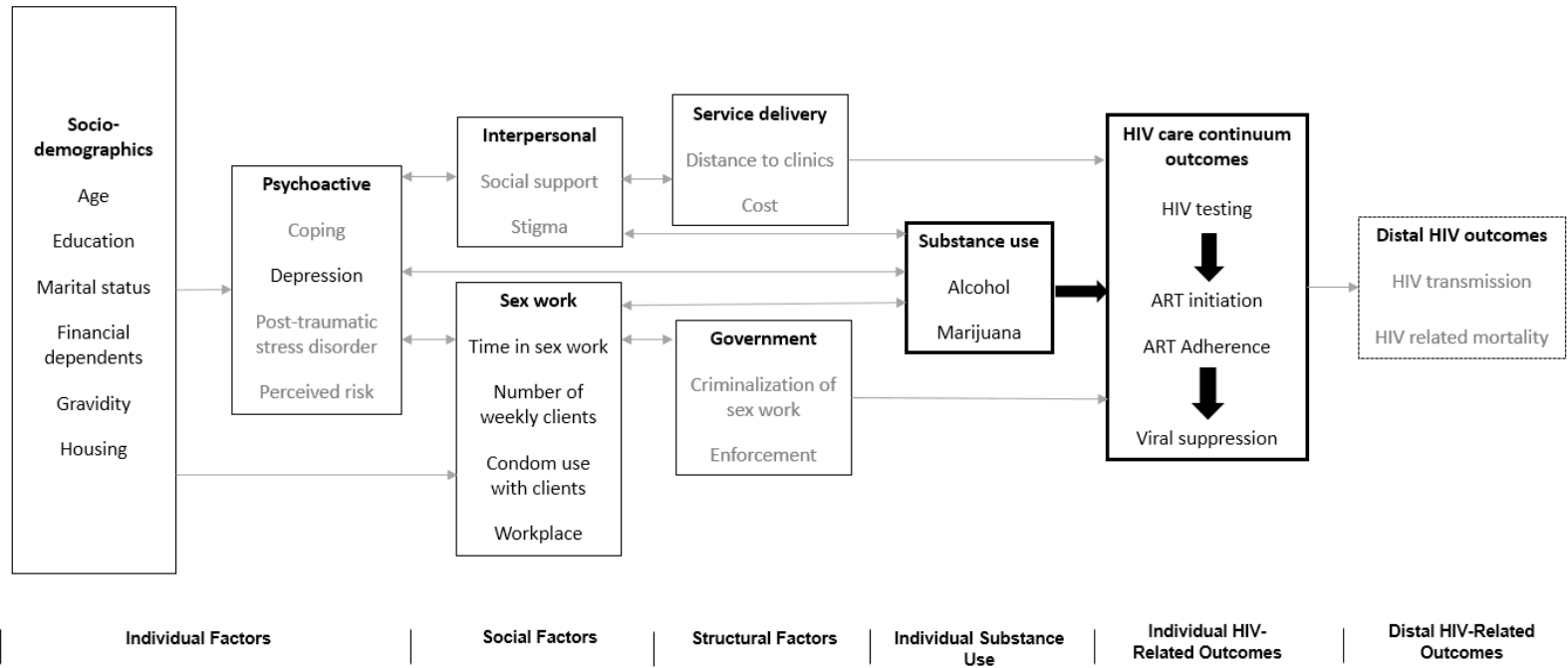


Figure 2. Conceptual framework for the impact of substance use on engagement in key HIV care continuum outcomes



CHAPTER III: RESEARCH DESIGN AND METHODS

Study design overview

To evaluate whether substance use, particularly alcohol and marijuana, significantly affects engagement in HIV testing and treatment among FSW, we conducted a cross-sectional evaluation of FSW in Lilongwe, Malawi. We used venue-based recruitment to recruit a sample of FSW. All consented FSW participated in a face-to-face survey and received rapid HIV testing. Among the seropositive FSW, we obtained CD4 cell counts and HIV-1 RNA levels. We designed and implemented this study through a collaboration between The University of North Carolina at Chapel Hill, UNC Project Malawi, and Theatre for a Change, a non-governmental organization in Malawi.

The research protocol, survey, and consent forms were reviewed and approved by the Institutional Review Board at the University of North Carolina and the Malawi Ministry of Health and Population National Health Sciences Research Committee (HSRC). All participants provided written informed consent prior to completing study activities. All study related activities were conducted in a safe and private location.

Study setting

Lilongwe is located in the Central Region of the Republic of Malawi (Figure 3.1). Nested within the district is Malawi's administrative capital, Lilongwe City, with an estimated population of 1,346,360 persons. The Malawian law does not explicitly criminalize sex work; however, "the keeping of brothels" and "living on the earnings of prostitution or influencing others to engage in prostitution" is illegal.[41] Law enforcers

often perform night raids to arrest persons loitering in entertainment and public places, and FSW are most commonly arrested.[41] To navigate the potential legal implications of working with FSW, community engagement activities were undertaken within the well-established infrastructure of UNC Project-Malawi.

UNC Project-Malawi provided an extensive research platform in Lilongwe, including a permanent research team, field workers, health care professionals, and an infrastructure that will support the implementation of this study. For over twenty years, UNC and the Malawi Ministry of Health have collaborated on research, care, and training programs in Lilongwe. UNC Project-Malawi has a large, diverse and most importantly, active community advisory board (CAB). The CAB is made up of participants in clinical trials, people living with HIV, and local community members, including traditional, civic, political, and religious community leaders.

This study also reflected a partnership with the non-governmental organization, Theatre for a Change (TfaC). Since 2003, TfaC has worked to empower women and girls and to develop programs focused on sex workers and their clients, sexually exploited children, pre-service and in-service teachers and primary school children. TfaC has far-reaching relationships with local stakeholders, including chiefs, police, NGOs, United Nations agencies and government ministries.

UNC Project-Malawi provided the necessary infrastructure to navigate the complex and hard-to-reach FSW networks of Lilongwe. UNC Project-Malawi was the optimal site for implementing our study.

Study procedures

Pre-implementation activities

In May 2014, prior to study recruitment, we held a stakeholder meeting with queen mothers in Lilongwe. Queen mothers are mentor FSW who live at venues where FSW solicit sex. At this meeting, 24 queen mothers attended, representing 23 different venues in Lilongwe. During the stakeholder meeting, we informed the queen mothers about this study and its procedures. We provided a forum for concerns to be raised and addressed. Also, through UNC Project Malawi, our study was presented and discussed during the monthly community advisory board (CAB) meeting.

Community mapping and venue identification

From July 2014 through September 2014, we systematically recruited FSW using venue-based sampling. Our outreach team comprised peer FSW, HIV testing counselors, interviewers, a study nurse, and male driver in a mobile clinic. We developed the list of venues, in collaboration with Theatre for a Change and sex work stakeholders, where FSW are known to solicit sex. . Brief face-to-face interviews were conducted with representatives or management from the identified venues to obtain characteristics of the venue, patrons, and alcohol availability. Permission to recruit participants, in addition to commitment of ensuring safety of outreach team, was obtained from venue management. Brief face-to-face interviews with people who are socializing at the venue were conducted to confirm whether or not FSW have solicited sex at the venue.

Identification and recruitment of participants

To systematically identify FSW, we used venue-based recruitment to identify FSW. These methods have documented success with identification of hidden populations, including FSW.[12, 95-98] Women at a venue were approached by a member of our outreach team

and asked if they were willing to participate in screening for an HIV research study. After verbal consent was obtained, women were brought to a confidential location outside received a brief screening survey to assess eligibility for participation.

Selection criteria

We used the 2011 Family Planning Association of Malawi's definition of sex work, as someone "who had received money in exchange for sex either regularly or occasionally up to 12 months prior to the survey".

Inclusion criteria

- Female age ≥ 18 years
- Self identifies as someone who has received money in exchange for sex either regularly or occasionally up to 12 months prior to the date of the survey
- Willingness to complete survey, undergo HIV testing and counseling and provide blood sample

Exclusion criteria

- Female < 18 years
- Male
- Incapable of providing informed consent

Informed consent

If willing and eligible, FSW were asked to provide written informed consent for participation in the study. The interviewer explained the purpose of the research study and criteria for participation. During the informed consent process, the interview described the procedures the procedures, the risks and benefits of participation, the duration of participation, and the steps taken to protect confidentiality. Participants provided their

signature on the consent form. Non-literate participants were asked to document their understanding and consent with a mark (e.g., an X or thumbprint) in the presence of a literate third-party, impartial witness. FSW participants who are non-literate chose a literate third-party witness whom they feel comfortable disclosing their participation in the study. Copies of the consent form were offered to the participants.

Protection of human subjects

The research protocol was reviewed by the Institutional Review Board at the University of North Carolina and the Malawi Ministry of Health and Population National Health Sciences Research Committee (HSRC). All procedures conformed to U.S. and Malawian ethical standards for human subjects research. This study received approval from the Institutional Review Board at the University of North Carolina on December 7, 2013 (IRB#: 13-3283). Approval from the HSRC was received on March 11, 2014 (Protocol#: 1224).

Data collection

Consented FSW then received a face-to-face behavioral survey on substance use including alcohol and marijuana use, HIV testing history, HIV infection awareness, engagement in HIV care, and ART use. We assessed HIV serostatus for all consented FSW. Per Malawian National HTC guidelines, FSW received serial HIV-antibody rapid tests, Determine HIV-1/2 and Uni-Gold rapid HIV-antibody. Pre- and post-HIV test counseling, clinic referral, and risk reduction counseling was administered, and both male and female condoms were offered.

For FSW with confirmed HIV infection, another finger stick was performed to collect blood for CD4 measurement and plasma HIV-1 RNA levels. CD4 measurement was obtained using the Pima CD4TM, a self-contained, cartridge-based test platform with results

available in approximately 20 minutes.[84, 99] The results were provided to the participant and a trained study nurse was available to assist the participant with interpretation of these results.

Dried blood spots (DBS) were collected to determine HIV-1 RNA concentrations. DBS is an effective method for measuring plasma HIV-1 RNA levels.[100-102] Samples were kept in drying boxing with a humidity indicator card to monitor moisture levels, until they were brought to the UNC Project laboratory. HIV-1 RNA levels were available for women within 4 weeks of DBS collection and results were provided by a trained study nurse.

Aim 1: Characterize the HIV care continuum among FSW in Lilongwe, Malawi

HIV care continuum assessments

HIV diagnosis: We asked FSW to report the date and results of their most recent HIV test to determine new vs. previous diagnosis. We defined a new HIV diagnosis as FSW who were seropositive, based HIV rapid testing, and self-reported being HIV negative at their most recent HIV test (or never testing previously). We defined a previous diagnosis as those reporting being HIV-positive at their most recent test.

History of HIV care: For FSW who were self-reported being HIV-positive, we asked “Have you ever seen an HIV health care provider?” FSW who responded yes to the question or reported current ART use were classified as having a history of HIV care. All other FSW were classified as not having a history of HIV care.

Current ART use: FSW who were previously diagnosed were asked the question “Are you currently on ART?” Those who responded yes were defined as being on ART. All other FSW were considered not on ART.

ART eligibility: FSW were considered ART-eligible if they reported current ART use, had CD4 ≤ 500 cells/mm³ following the Malawi national guidelines, were currently pregnant or breastfeeding, or had a pregnancy after July 2011 following Option B+ policy. All other FSW were classified as ART-ineligible.

ART adherence: For the FSW who reported being on ART, we asked the question “In the last 4 weeks, when was the last time you missed taking any of your anti-HIV medications?” with the response options as: within the past week; 1-2 weeks ago; 2-4 weeks ago; or never skipped medications in the last 4 weeks.

Viral suppression: For all confirmed seropositive FSW, viral load was assessed. We defined FSW as virally suppressed with an HIV-1 RNA ≤ 5000 copies/mL and defined as undetectable with an HIV-RNA ≤ 550 copies/mL, which are the recommended thresholds when using fingerstick DBS.[47, 103]

Covariates

We obtained data on demographic characteristics and sexual risk behaviors, which included: age (18-24, 25-29, ≥ 30 years),[104] years in sex work (<1, 1.0-1.9, 2.0-2.9, ≥ 3.0 years),[105] weekly number clients (<10, 10-19, 20-29, ≥ 30 clients),[106] and condom use during vaginal sex with clients in prior 7 days (consistent use, inconsistent use).[106]

Sensitivity analyses

In addition to our primary analysis of the characterizing the HIV care continuum, we conducted two separate sensitivity analyses to address apparent discrepancies across key continuum indicators in a small number of FSW. In the first sensitivity analysis, FSW who were virally suppressed but self-reported not previously diagnosed were re-assigned as seronegative to account for the possibility of false-positive HIV rapid tests. In the second

sensitivity analysis, FSW who were virally suppressed but whose self-reports suggested they had not been previously diagnosed or did not report current ART use were re-assigned to categories in which they were assumed to be previously diagnosed, have a history of care, and be current ART users. After we re-classified these FSW, we then re-calculated the key continuum outcomes and compared with our primary analysis.

Aim 2: Evaluate and compare the associations of alcohol and marijuana use with lack of awareness of HIV infection

Alcohol use assessment

Alcohol use will be captured using the World Health Organization's Alcohol Use Identification Test (AUDIT).[107-110] The AUDIT measures alcohol use behaviors and alcohol use disorder symptoms (Table 3.1). The AUDIT is a screening tool for hazardous drinking, which is a pattern of drinking that poses high risk of future damage to physical or mental health. This screening tool has been validated in various populations and has been widely used to screen for hazardous drinking in sub-Saharan Africa.[111, 112] The AUDIT is a brief 10 question survey that consists of questions related to specific domains, like hazardous alcohol use, alcohol dependence symptoms, and harmful alcohol use. Each of the 10 questions has a set of responses with a corresponding score of 0 to 4. Scores are added from each question resulting in one composite score ranging from 0 to 40. A score of 8 or above indicates hazardous drinking, with an average sensitivity of the 90% and specificity of 80% varying among populations and countries. The WHO recommends shifting the cut-off for indication of hazardous drinking to a score of 7 to increase the sensitivity among women.[110] Therefore, FSW with an AUDIT score of 7 will be indicative of hazardous drinking.

Marijuana use assessment

Marijuana use was measured in terms of reported lifetime marijuana use and number of days using marijuana within the past 30 days (Table 3.2). Current marijuana use was defined as at least one day of marijuana use within the prior 30 days.

HIV history and infection assessments

To measure HIV infection awareness, we asked FSW to report the results of their last HIV test. FSW who were HIV-seropositive and self-reported themselves as HIV-negative from last HIV test, never receiving their results from an HIV test, or never previously tested for HIV were considered unaware of HIV infection.

Covariates

We used directed acyclic graphs, based on the literature, to identify a minimally sufficient adjustment set of covariates to include in our analysis of the associations between alcohol and marijuana use, alone and together, with lack of HIV infection awareness. Covariates examined -included age (18-24, 25-29, ≥ 30 years), education (never attended school/only primary school, any secondary school/more school), marital status (never married, cohabitating/married, separated/divorced/widowed), housing (private house, bottle shop/bar, hotel/guesthouse), gravidity (no previous pregnancies, any previous pregnancies), financial dependents (no dependents, any dependents), probable depression measured by the Patient Health Questionnaire-9 (PHQ9 < 10 , PHQ9 ≥ 10), [113-115] and treatment for an STI in the prior 12 months (no, yes). We also examined years in sex work (< 1 , 1.0-1.9, 2.0-2.9, ≥ 3.0 years), location for soliciting paying sexual partners (bar/bottle shop, other), weekly number of clients (< 10 , 10-19, 20-29, ≥ 30 clients), condom use during vaginal sex with clients in prior 7 days (consistent use, inconsistent use), ever had a client that demanded not

using a condom during vaginal sex (no, yes), alcohol use prior to last vaginal sex with client (no, yes), and any marijuana use prior to last vaginal sex with client (no, yes). Categorization of the covariates were based on interpretability and replicability.

Aim 3: Evaluate and compare the associations of alcohol and marijuana use with engagement into HIV treatment: current use of ART among ART eligible FSW and viral suppression

Alcohol use assessment

Alcohol use was assessed as previously presented in aim 2.

Marijuana use assessment

Marijuana use was assessed as previously presented in aim 2.

HIV treatment assessments

We asked FSW to report the date and results of their most recent HIV test to determine new vs. previous diagnosis. We defined a new HIV diagnosis as FSW who were seropositive, based HIV rapid testing, and self-reported being HIV negative at their most recent HIV test (or never testing previously). We defined a previous diagnosis as those reporting being HIV-positive at their most recent test.

We measured reported current ART use among all ART eligible FSW. ART eligibility was defined as those reporting current ART use, a CD4 ≤ 500 cells/mm³ following the Malawi national guidelines, currently pregnant or breastfeeding, or any pregnancy after July 2011 following Option B+ policy.[116] Option B+ provides confirmed HIV-infected pregnant and breastfeeding women lifelong ART regardless of CD4 count or clinical stage. FSW who answered no to the question “Are you currently on ART?” were defined as not using ART.

We measured HIV-1 RNA concentration for viral suppression. FSW were classified as virally nonsuppression with an HIV-1 RNA >5000 copies/mL which is the recommended thresholds when using fingerstick DBS.[47, 103]

Covariates

We used directed acyclic graphs, based on the literature, to identify minimally sufficient adjustment set of covariates to include in our models examining the associations between alcohol and marijuana use with sub-optimal HIV care and treatment outcomes. The covariates we examined- included age (18-24, 25-29, ≥ 30 years), education (never attended school/only primary school, any secondary school/more school), marital status (never married, cohabitating/married, separated/divorced/widowed), housing (private house, bottle shop/bar, hotel/guesthouse), gravidity (no previous pregnancies, any previous pregnancies), financial dependents (no dependents, any dependents), probable depression measured by the Patient Health Questionnaire-9 (PHQ9 <10, PHQ9 ≥ 10),[113-115] and treated for an STI in the prior 12 months (no, yes). We also examined years in sex work (<1, 1.0-1.9, 2.0-2.9, ≥ 3.0 years), location for soliciting paying sexual partners (bar/bottle shop, other), weekly number clients (<10, 10-19, 20-29, ≥ 30 clients), condom use during vaginal sex with clients in prior 7 days (consistent use, inconsistent use), paying sexual partner demanded not using a condom for vaginal sex (no, yes), and alcohol use prior to last vaginal sex with client (no, yes) Categorization of the covariates were based on interpretability and replicability.

Data management and analysis

Data management

Data was derived from two source: face-to-face behavioral survey and laboratory data. Survey data and laboratory results were entered using Open Data Kit Collect on an encrypted and password protected study android-based tablet by the principal investigator or

study staff. All entered data was uploaded to the password-protected UNC Project shared server daily. Data was housed at UNC Project-Malawi in Lilongwe, an HPTN/ACTG/MTN site, and the University of North Carolina at Chapel Hill. All data collected underwent quality assurance and quality control testing adapted from HPTN/ACTG studies. Study staff developed and implemented a system to track all questionnaires. All FSW participants were assigned a unique study identification number that was used for this study. Survey data and biological data were linked through this study identification number.

Aim 1: Characterize the HIV care continuum among FSW in Lilongwe, Malawi

Statistical analyses

We used frequency distributions and descriptive statistics to characterize the study population. Proportions and associated 95% confidence intervals (CI) were computed for HIV serostatus and three key outcome of the HIV care continuum: history of HIV care, current ART use, and virally suppressed. We characterized these continuum indicators using two different approaches. The first approach is estimated using all HIV-infected FSW as the denominator, which provides information about opportunities for HIV transmission from FSW to their sexual partners. The second approach is estimated using the number of HIV-infected FSW achieving the prior step in the continuum, which more directly highlights healthcare delivery gaps for HIV prevention and treatment services. For example, within the second approach, the proportion of FSW who have a history of care has the denominator of FSW who reported being previously diagnosed. In addition to these analyses of the three primary continuum outcomes (history of care, current ART use, and viral suppression), we also assessed ART use in relation to ART eligibility, and ART adherence among those on ART.

We explored a demographic characteristics and transmission risk behaviors associated with HIV care continuum outcomes. A parsimonious set of demographic and transmission risk behaviors were established based on literature review and sample size considerations and included: age,[104] years in sex work,[105] weekly number clients,[106] and condom use during vaginal sex with clients in prior 7 days.[106] The HIV care continuum outcomes assessed were a) previous diagnosis (vs. new diagnosis) among all HIV-infected FSW, b) history of HIV care (vs. no history of care) among those previously diagnosed, c) reported current ART use (vs. no current ART use) among those previously diagnosed and ART-eligible. We examined associations using Poisson regression models with robust variance estimates to estimate prevalence ratios (PR) with 95% confidence intervals.[117]

Aim 2: Evaluate and compare the associations of alcohol and marijuana use with lack of awareness of HIV infection

Statistical analyses

Characteristics, history of HIV testing, and substance use were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables.

We conducted analyses for the associations of alcohol and marijuana use with the primary outcome of lack of HIV infection awareness. We developed a product interaction term to assess the association between alcohol and marijuana use together and lack of HIV infection awareness. We used Poisson regression with robust variance estimates to estimate bivariable and multivariable prevalence ratios (PR) with 95% confidence intervals (CI), due to problems with consistent convergence of log-binomial regression models.[118, 119] The

prevalence ratio is the proportion of participants that have the outcome (D+) among exposed (E+) over the proportion of people that have the outcome (D+) among unexposed (E-).

$$Prevalence\ Ratio = \frac{P(D + | E+)}{P(D + | E-)}$$

Prevalence ratios are interpretable, less biased, and in comparison to odds ratios, the PR tends to be more consistent when estimating the total effect.[120-122] In order to estimate the total effect of these associations, additional covariates were examined as possible confounders and effect measure modifiers.

Potential confounders were assessed one-by-one, and retained in final adjusted multivariable models if removal resulted in a >10% change in the prevalence ratio estimate. Interactions were only considered for variables of interest that met positivity assumptions and were retained in the final adjusted multivariable models if they had public health relevance and reached statistical significance at alpha=0.10. Collinearity was evaluated in the model using Pearson's correlation coefficient; none of the covariates showed significant correlation (p-value ≥0.5).

Aim 3: Evaluate and compare the associations of alcohol and marijuana use with engagement into HIV treatment: current use of ART among ART eligible FSW and viral suppression

Statistical analyses

We summarized the characteristics, substance use, and engagement in HIV treatment using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables.

We conducted separate analyses for the associations of alcohol and marijuana use with the primary outcomes of lack of ART use and viral nonsuppression. We used Poisson regression with robust variance estimates to estimate bivariable and, when sample size

permitted, multivariable prevalence ratios (PR) with 95% confidence intervals (CI).[118, 119]

We assessed potential confounders one-by-one, and retained in the final adjusted multivariable models if removal resulted in >10% change in estimate. Interactions were only considered for variables of interest that met positivity assumptions and retained in final adjusted multivariable models if they reached statistical significance at $\alpha=0.10$ and considered to have public health relevance. Collinearity was evaluated in the model using Pearson's correlation coefficient, though, none of the covariates showed significant correlation ($p \text{ value} \geq 0.5$).

Limitations

Specific limitations to each aim are incorporated within the discussions of chapters 4 through 6. Here we present certain limitations that applied to the implementation and design of all our aims.

Challenges associated with recruiting FSW

During the community mapping activities, we engaged with venue owners to inform them that we were conducting a substance use and sexual health study among women patrons. We alleviated any resistance owners had by study staff showing up announced. We were also aware of the difficulties identifying FSW and subsequently obtaining their consent to participate in the survey while they were working. The duration of the survey was kept manageable, as not to serve as a disincentive for participation. We also conveyed the benefits of receiving HIV testing on site, particularly among FSW who are unaware of their infection, and CD4 cell counts among HIV infected FSW not on ART.

Self-report of substance use

The measure of substance use was based on self-report. Given the need for social acceptance, this measurement may be susceptible to social desirability bias and recall bias. We incorporated strategies in survey administration to minimize these potential biases, such as the use of trained interviewers, building rapport, and reassuring confidentiality throughout the survey.

Generalizability of results

All FSW who are enrolled in this study were enrolled at venues where they were be soliciting clients. Therefore, street-based FSW were likely not included in our sample. These FSW may fundamentally be different than those in our study, in terms of their HIV risk structure and health seeking behaviors. We made sure that our results did not inappropriately generalize FSW outside of our study sample.

Figure 3. Map of Lilongwe, Malawi



Table 1. Measurement of alcohol use

Question	Response (score)
Alcohol Use Disorder Identification Test (AUDIT)	
<i>Composite score</i>	
How often do you have a drink containing alcohol?	Never (0) Once a month or less (1) 2 to 4 times a month (2) 2 to 3 times a week (3) 4 times or more a week (4)
How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2 drinks (0) 3 or 4 drinks (1) 5 or 6 drinks (2) 7, 8, or 9 drinks (3) 10 or more drinks (4)
How often do you have six or more drinks on one occasion?	Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4)
How often during the last year have you found that you were not able to stop drinking once you had started?	Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4)
How often during the last year have you failed to do what was normally expected from you because of drinking?	Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4)
How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4)
How often during the last year have you had a feeling of guilt or remorse after drinking?	Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4)
How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never (0) Less than monthly (1) Monthly (2) Weekly (3) Daily or almost daily (4)

<p>Have you or someone else been injured as a result of your drinking?</p>	<p>No ⁽⁰⁾ Yes, but no in the last year ⁽²⁾ Yes, during the last year ⁽⁴⁾</p>
<p>Has a relative, friend, or a doctor or other health worker been concerned about your drinking or suggested that you cut down on your drinking?</p>	<p>No ⁽⁰⁾ Yes, but no in the last year ⁽²⁾ Yes, during the last year ⁽⁴⁾</p>

Table 2. Measurement of marijuana use

Question	Response
Marijuana use	
Have you ever used marijuana?	Yes No
In the past 30 days, how many days have you used marijuana?	0 – 30 days
On the days that you used marijuana on about how many times did you use marijuana per day?	0 – 30 times

CHAPTER IV: THE HIV CARE CONTINUUM AMONG FEMALE SEX WORKERS, A KEY POPULATION IN LILONGWE, MALAWI

INTRODUCTION

HIV prevalence among female sex workers (FSW) remains disproportionately high despite decades of prevention activities.[29-34] Globally, the HIV prevalence among FSW is 12%, with a higher prevalence of 37% in sub-Saharan Africa. HIV-infected FSW have a higher number of sexual partners compared to other women of reproductive age, increasing the likelihood of HIV acquisition, as well as transmission to their clients and onward transmission from clients to other sexual partners.[30, 123] Effective interventions are clearly needed to reduce HIV acquisition and transmission from this key population.

Anti-retroviral therapy (ART) sharply reduces HIV morbidity, mortality, and transmission.[18, 124] To experience these benefits of ART, HIV-infected persons must be diagnosed and receive HIV care and treatment. The HIV care continuum is a commonly used framework that provides cross-sectional descriptions of population-level engagement in HIV testing, care, and treatment. [12, 20] If HIV-infected FSW fail to attain optimal outcomes along this “HIV continuum,” they will not receive the clinical benefits of HIV care and treatment, and also will likely continue to transmit HIV.[19, 125]

The HIV care continuum has not been well characterized in FSW.[125, 126] Estimates of ART initiation, adherence, and treatment outcomes among this key population in sub-Saharan have been derived predominately from small, intensively followed cohorts whose experiences may not be representative of FSW more generally.[126] Without

estimates of engagement in HIV care and treatment among FSW outside of these intensively followed cohorts, the unmet needs of this population are difficult to assess.

We conducted the first study to characterize the HIV care continuum among FSW in Lilongwe, Malawi, where the FSW HIV prevalence (70%) is one of the highest globally.[30] In addition to quantifying the continuum, we examined the associations between continuum outcomes and both demographic characteristics and transmission risk behaviors.

METHODS

Study procedures

We designed and implemented this study through a collaboration between The University of North Carolina at Chapel Hill, UNC Project Malawi, and Theatre for a Change (TfaC), a non-governmental organization in Malawi with far-reaching relationships with local sex work stakeholders including FSW, chiefs, police, local NGOs, and Malawian government ministries. This study is a descriptive, cross-sectional biological and behavioral survey among FSW in Lilongwe, Malawi. FSW were systematically recruited using venue-based sampling. Venue-based sampling has documented success with identification of hidden populations, including FSW.[12, 95-98] Our reach team comprised of HIV testing counselors, interviewers, a study nurse, male driver for the mobile clinic, and a peer FSW to facilitate approaching women at the venues. In collaboration with TfaC, we developed the list of venues where FSW are known to solicit sex.

From July through September 2014, FSW were recruited from 23 different venues within Lilongwe; most venues were bars and bottle shops. Women at a venue were approached by a member of our outreach team and asked if they would like to participate in a research study for FSW. We used the 2011 Family Planning Association of Malawi's

definition of sex work, as someone “who had received money in exchange for sex either regularly or occasionally up to 12 months prior to the survey”. Women were eligible for enrollment if they were at least 18 years of age and self-reported as a FSW. All FSW provided written informed consent.

All consenting FSW completed a structured behavioral survey to obtain detailed information on demographics, pregnancy history, transmission risk behaviors, HIV testing history, and engagement in HIV care and treatment. The survey was translated from English to Chichewa, the predominant language in Malawi, and back translated. The survey was available in both languages to all FSW.

HIV serostatus was confirmed for all participating FSW using Malawian National HIV Testing and Counseling guidelines, which indicate serial HIV-antibody rapid tests, Determine HIV-1/2 and Uni-Gold rapid HIV-antibody. Pre- and post-HIV test counseling, clinic referral, and risk reduction counseling were administered, and both male and female condoms were offered. FSW were defined as HIV seronegative with a negative Determine HIV-1/2 test result or HIV seropositive with positive Determine HIV-1/2 and Uni-Gold test results.

For FSW with confirmed HIV infection, another finger stick was performed to collect blood for CD4 measurement and plasma HIV-1 RNA levels. CD4 measurement was obtained using the Pima CD4TM, a self-contained, cartridge-based test platform with results available in approximately 20 minutes.[84, 99] The results were provided to the participant and a trained study nurse was available to assist the participant with interpretation of these results.

Dried blood spot (DBS) were collected to determine HIV-1 RNA concentrations.[100-102] Samples were kept in drying boxing with a humidity indicator card to monitor moisture levels, until they were brought to the UNC Project laboratory. HIV-1 RNA levels were available for within 4 weeks of DBS collection and results were provided by a trained study nurse.

All FSW confirmed HIV seropositive were referred to Lighthouse Trust HIV Clinic in Lilongwe for medical care and treatment. All study-related activities were conducted in a safe and private location.

Data collection

To assess whether women testing positive were newly (vs. previously) diagnosed, FSW were asked to report the date and results of their most recent HIV test. FSW who were seropositive and self-reported being HIV negative at their most recent HIV test (or never testing previously) were defined as a new HIV diagnosis; those reporting being HIV-positive at their most recent test were classified as previously diagnosed. Previously diagnosed FSW who responded yes to the question “Have you ever seen an HIV health care provider?” or reported current ART use were classified as having history of HIV care. Previously diagnosed FSW who answered yes to the question “Are you currently on ART?” were classified as being on ART. ART-eligible FSW were defined as those reporting current ART use, a CD4 ≤ 500 cells/mm³ following the Malawi national guidelines, currently pregnant or breastfeeding, or any pregnancy after July 2011 following Option B+ policy.[116] The Option B+ policy provides confirmed HIV-infected pregnant and breastfeeding women lifelong ART regardless of CD4 count or clinical stage. ART adherence was assessed based on responses to the question “In the last 4 weeks, when was the last time you missed taking any of your anti-HIV medications?” (within the past week; 1-2 weeks ago; 2-4 weeks ago; or

never skipped medications in the last 4 weeks). All HIV-infected FSW provided blood specimens for HIV-1 RNA levels. FSW were defined as virally suppressed with an HIV-1 RNA ≤ 5000 copies/mL and defined as undetectable with an HIV-RNA ≤ 550 copies/mL, the recommended thresholds when using fingerstick DBS.[47, 103]

Data analyses

We used frequency distributions and descriptive statistics to characterize the study population. Proportions and associated 95% confidence intervals (CI) were computed for HIV serostatus and three key outcome of the HIV care continuum: history of HIV care, current ART use, and virally suppressed. We characterized these continuum indicators using two different approaches. The first approach, which provides information about opportunities for HIV transmission from FSW to their sexual partners, is estimated using all HIV-infected FSW as the denominator. The second approach, which more directly highlights healthcare delivery gaps for HIV prevention and treatment services, is estimated using the number of HIV-infected FSW achieving the prior step in the continuum. For example, under the second approach, the proportion of FSW who have a history of care has the denominator of FSW who reported being previously diagnosed. We report separately the small proportion of discrepancies across the three key continuum outcomes. In addition to these analyses of the three primary continuum outcomes, we also assessed ART use in relation to ART eligibility, and ART adherence among those on ART.

Demographic characteristics and transmission risk behaviors associated with HIV care continuum outcomes were explored. A parsimonious set of demographic and transmission risk behaviors were established based on literature review and sample size considerations, which included: age (18-24, 25-29, ≥ 30 years),[104] years in sex work (<1,

1.0-1.9, 2.0-2.9, ≥ 3.0 years),[105] weekly number clients (≤ 19 , ≥ 20 clients),[106] and condom use during vaginal sex with clients in prior 7 days (consistent use, inconsistent use).[106] The question used to assess condom use was “How often did you use condoms during vaginal sex with a paying sexual client in the last 7 days?” Responses included never, rarely, sometimes, most times, and always. FSW who responded always were classified as having consistent use and all other responses were classified having inconsistent use. The three key HIV care continuum outcomes assessed were a) previous diagnosis (vs. new diagnosis) among all HIV-infected FSW, b) history of HIV care (vs. no history of care) among those previously diagnosed, c) reported current ART use (vs. no current ART use) among those previously diagnosed and ART-eligible. We examined associations using Poisson regression models with robust variance estimates to estimate prevalence ratios (PR) with 95% confidence intervals.[117]

Sensitivity Analyses

We conducted two sensitivity analyses to address apparent discrepancies across key continuum indicators in a small number of FSW. First, FSW who were virally suppressed but self-reported not previously diagnosed were re-assigned as seronegative to account for the possibility of false-positive HIV rapid tests. Second, FSW who were virally suppressed but whose self-reports suggested they had not been previously diagnosed or did not report current ART use were re-assigned to categories in which they were assumed to be previously diagnosed, have a history of care, and be current ART users. Following re-classifications of these FSW, we re-calculated the key continuum outcomes.

All statistical analyses were conducted using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Ethics Statement

Ethics approval was obtained from the Malawi Ministry of Health and Population National Health Sciences Research Committee (HSRC) and the University of North Carolina-Chapel Hill Institutional Review Board.

RESULTS

Among the total study population (n=200), the median age was 24 years (IQR: 22-28). Most (66%) had not completed primary school and the majority (81%) were separated, divorced, or widowed (Table 1). Approximately 60% reported currently living in a bar or bottle shop, and 90% solicited clients at these venues. The median duration of exchanging sex for money was 3 years (IQR: 1-5). The median reported number of clients in the past 7 days was 21 (IQR: 10-35). Nearly three quarters reported consistent condom use during vaginal sex with clients in the past 7 days.

HIV diagnosis

The HIV seroprevalence was very high (69%, 95% CI: 62, 75%, n=138). Among the HIV-infected FSW, 20% (95% CI: 13, 26%, n=27) were newly diagnosed (Table 2); of these, 74% (95% CI: 54, 89%, n=20) had tested negative previously, 19% (95% CI: 6, 38%, n=5) had never tested, and 7% (95% CI: 1, 24%, n=2) had tested but not received results (results not shown). Among newly diagnosed FSW that had previously tested negative, the median time since last HIV test was 11 months (IQR: 3-17). The median CD4 among all newly diagnosed FSW was 464 cells/mm³ (IQR: 276-632) and median viral load was 44, 846 copies/ml (IQR: 5,981- 202,395). Among previously diagnosed HIV-infected FSW, median time since diagnosis was 14 months (IQR: 4-44). The median CD4 was 528 cells/mm³ (IQR: 355-747).

History of HIV care

Among all HIV-infected FSW, 69% (95% CI: 61, 76%, n=95) had a history of HIV care, as determined by report of ever seeing an HIV care provider or current ART use (Figure 1A). Among FSW previously diagnosed, 86% (95% CI: 78, 92%, n=95) had a history of HIV care (Figure 1B).

Current ART use

Among the 52% (95% CI: 44, 61%, n=72) of all HIV-infected FSW who were currently on ART (Figure 1A), adherence was suboptimal: 33% (95% CI: 23, 45%) reported skipping pills within the past 4 weeks (results not shown). Three fourths (76%, 95% CI: 66, 84%, n=72) of FSW previously diagnosed with a history of care reported current ART use (Figure 1B).

About half of all HIV-infected FSW (48%; 95% CI: 35, 56%, n=66) reported no current ART use; their median CD4 was 478 cells/mm³ (IQR: 321-656). Of those that reported no current ART use, 62% (95% CI: %, n=41) were eligible for ART, with 42% (95% CI: 26, 58%, n=17) newly diagnosed and 59% (95% CI: 42, 74%, n=24) previously diagnosed. Among the previously diagnosed with no current ART use and ART eligible (n=24), 92% (95% CI: 73, 99%, n=22) had a CD4 \leq 500 cells/mm³ with an additional 8% (95% CI: 1, 27%, n=2) that were ART-eligible based on Option B+ (currently pregnant, currently breastfeeding, or any pregnancy after July 2011).

Viral suppression

Approximately half (45%, 95% CI: 36, 54%, n=62) (Figure 1A) of all HIV-infected FSW were virally suppressed (\leq 5000 copies/mL) and 38% had an undetectable viral load (\leq 550 copies/mL). Among previously diagnosed FSW (n=111), half had undetectable viral

loads (median viral load= 0 copies/ml IQR: 0- 31,295) (Table 2). Of the FSW who reported current ART use, 86% (95% CI: 76, 93%, n=62) had viral loads \leq 5000 copies/mL (Figure 1B). Seven women (5%) of all HIV-infected FSW were identified as virally suppressed but did not report current ART use or previous HIV diagnosis.

Sensitivity analyses

Among the seven FSW who were virally suppressed but did not report experience with “upstream” continuum indicators, four reported previous diagnosis and a history of care but no current ART use, and three had no indication of previous diagnosis, history of care, or current ART use based on self-report.

In the first sensitivity analysis that re-classified the three FSW that self-reported not being previously diagnosed as seronegative, the HIV seroprevalence was similar to the seroprevalence of the primary analyses. Of all the 200 FSW enrolled in our study, 68% were seropositive (95% CI: 61, 74%).

In the second sensitivity analysis that re-classified these seven FSW as being previously diagnosed, with a history of care and current ART use, the overall proportions achieving the HIV care continuum outcomes were similar to those obtained in the main analyses. Of all HIV-infected FSW, 72% (95% CI: 64, 80%) had a history of care, 57% (95% CI: 49, 66%) reported current ART use, and 50% (95% CI: 41, 59%) were virally suppressed. Among previously diagnosed FSW (83%, (95% CI: 75, 89%), 88% (95% CI: 80, 93%) had a history of care. Of those with a history of care, 79% (95% CI: 70, 87%) FSW currently ART using and among those with current ART use, 87% (95% CI: 78, 94%) were virally suppressed.

Factors associated with HIV care continuum outcomes

In multivariable analyses (Table 3), there was little to no association between age, duration in sex work, number of weekly clients and condom use and the key HIV care continuum outcomes: previously diagnosed, history of HIV care, and current ART use.

FSW who were younger (18-24 years: APR: 0.74, 95% CI: 0.30, 1.84; 25-29 years: APR: 0.84, 95% CI: 0.34, 1.91) and reported ≤ 19 clients per week (APR: 0.67, 95% CI: 0.33, 1.36) were less likely to be previously (vs. newly) diagnosed. FSW who were engaged in sex work for < 1.0 year (APR: 1.81, 95% CI: 0.62, 5.33) or 1.0-1.9 years (APR: 2.04, 95% CI: 0.85, 4.94) were more likely to be previously diagnosed. FSW who reported inconsistent condom use with clients in the prior 7 days were 1.65 (95% CI: 0.70, 3.47) times as likely to be previously diagnosed when compared to FSW who reported consistent condom use.

FSW who were 25-29 years were 0.89 (95% CI: 0.73, 1.14) times as likely to have a history of care (vs. no history of care) than FSW who were ≥ 30 years old. FSW that were engaged in sex work for 1.0-1.9 years (APR: 0.84, 95% CI: 0.463, 1.12) and reported inconsistent condom use (APR: 0.90, 95% CI: 0.75, 1.01) were less likely to have a history of HIV care. FSW who reported ≤ 19 clients per week were 1.12 (95% CI: 0.96, 1.30) times as likely to have a history of care compared to FSW who reported ≥ 20 clients per week.

FSW who were younger and engaged in sex work for less than 3 years were less likely to have current ART use when compared to FSW who were ≥ 30 years old and engaged in sex work for ≥ 3 years. FSW who reported ≤ 19 clients per week were 1.10 (95% CI: 0.88, 1.38) times as likely to have a history of care compared to FSW who reported ≥ 20 clients per week. FSW who reported inconsistent condom use with clients in the prior 7 days were 1.08

(95% CI: 0.84, 1.38) times as likely to be previously diagnosed when compared to FSW who reported consistent condom use.

DISCUSSION

In this study, FSW in Lilongwe, Malawi were heavily HIV burdened, with one-fifth of HIV-infected FSW being previously unaware of their HIV infection. Although most HIV-infected FSW reported seeing an HIV healthcare provider at least once, only half reported current ART use. More encouragingly, among FSW on ART, over four-fifths were virally suppressed, the ultimate goal for clinical and transmission outcomes. Both HIV-infected and HIV-uninfected FSW in our sample were highly active and engaging in high-risk sexual behaviors. Among HIV-infected FSW, transmission risk behaviors were not statistically associated with being previously diagnosed, having a history of HIV care, or current use of ART.

Despite continued HIV prevention efforts in Malawi, the HIV seroprevalence among this sample of FSW in Lilongwe remains consistent with estimates from nearly a decade ago. The 2006 bio-behavioral surveillance survey among 273 FSW from six urban centers of Malawi, including Lilongwe, identified 71% of FSW as HIV-infected.[127] We expected the FSW prevalence to have fallen along with the national HIV prevalence.[127] Malawi's adult HIV prevalence has steadily declined from its peak of 18% in 2000 to 11% in 2010 among adults, including 13% among adult women.[128] Our prevalence may be an overestimate for all FSW in Malawi, given all the FSW were recruited within venues in Lilongwe, the capital and second largest city in Malawi. However, current national HIV prevalence estimates among FSW are unavailable for comparison. The consistently high HIV prevalence among FSW in Malawi over the past decade highlights the importance of

combination behavioral, biomedical, and structural HIV prevention and treatment efforts for both HIV-uninfected and infected FSW.

The proportion of FSW newly diagnosed, as part of our study, has serious consequences for both FSW and their sexual partners. Establishing a timely HIV diagnosis for highly active FSW is absolutely critical.[129] FSW who remain unaware of their HIV infection miss opportunities for entry into HIV care, leading to later ART initiation, higher risk for HIV clinical progression, and ongoing transmission.[130] The time between tests identified in our study highlights the need for frequent outreach to encourage rapid HIV testing to capture highly active FSW at most risk for ongoing HIV transmission.

Overall in this sample, about half of HIV-infected FSW were not on ART and therefore not receiving the full clinical, immunological, and transmission prevention benefits of therapy. Despite the recognition that timely uptake of ART can improve health outcomes and decrease onward transmission,[14-16] there are currently no interventions specifically focusing on increased access and adherence to ART for FSW in sub-Saharan Africa.[14] However, the recent expansions of ART may increase ART initiation among FSW. Since 2011, Malawi has provided lifelong ART for all women who are pregnant or breastfeeding for the prevention of mother-to-child transmission under Option B+.[29] In addition to Option B+, Malawi has implemented earlier initiation of ART (CD4 count ≤ 500 cells/mm³) in April 2014.[131] Further expansion of ART initiation should be prioritized to reach all HIV-infected FSW in Malawi.

FSW face a complex lattice of individual, social, and structural barriers to HIV care and ART uptake with the goal for viral suppression. For example, FSW are highly stigmatized, experiencing discrimination and violence, which can have damaging effects on

access to HIV care and treatment.[11, 36, 132] Furthermore, FSW often use alcohol as a means to facilitate sex work.[4] This high-risk alcohol consumption impairs judgment and cognitive function, making it even more challenging for FSW to access care and initiate ART.[59, 61] The specific barriers affecting ART uptake among FSW in sub-Saharan Africa are poorly described. Successfully identifying the impact of these barriers on ART uptake in sub-Saharan Africa, including Malawi, can inform tailored multilevel combination interventions focused on increasing access and uptake of ART, and ultimately viral suppression, for HIV-infected FSW.

Within our sample of FSW, we identified little to no association between transmission risk behaviors and key HIV care continuum outcomes. These results are in contrast to observed reductions in sexual risk behaviors following HIV diagnosis,[133] initiation of HIV care and treatment among non-FSW populations.[134-136] The null association between behaviors and continuum outcomes in our FSW population may be due to the nature of their work: because their livelihoods depend on high-risk sexual behaviors, FSW may face greater difficulty in reducing transmission risk behaviors following diagnosis and engagement in care than do other populations.[30]

Another important unmet need identified in the study is prevention for HIV-uninfected FSW. HIV-uninfected FSW within our sample are at increased risk for HIV acquisition due to their numerous weekly clients and inconsistent condom use and are in need of a tailored comprehensive package of interventions. Pre-exposure prophylaxis (PrEP) has emerged as an effective biomedical intervention to prevent HIV infection.[137] Although it has not yet been evaluated specifically among FSW, PrEP could provide a highly effective prevention strategy for at risk FSW. Given the multilevel HIV risks FSW face, PrEP must be

complemented with other proven effective interventions, such as community empowerment and testing and treatment strategies to reduce HIV incidence in FSW and their clients.[138] Comprehensive prevention packages that incorporate PrEP delivery must be developed and rigorously evaluated among FSW.

In this study, the HIV care continuum provided a valuable framework for describing HIV testing, care, and treatment cross-sectionally among FSW in Lilongwe, Malawi; however, the framework fails to fully capture the dynamic nature of FSW's engagement in the trade and with HIV prevention and care services. For example, the traditional continuum framework does not explicitly describe important processes, such as care re-engagement and viral re-suppression that may occur for some HIV-infected FSW.[126] A related limitation is that we assessed HIV care history but not current HIV care status; therefore, we were unable to determine whether suboptimal ART use among ART-eligible FSW was due to care disengagement or rather failures in ART initiation/re-initiation among FSW who were currently in care. Prospective, longitudinal studies that can better enumerate dynamic, multidirectional movement would provide additional, useful understanding of HIV testing, care, and treatment of FSW.

The outcomes we used to describe the HIV care continuum were mostly reliant on self-report and thus subject to misclassification. In particular, our estimated proportion of newly diagnosed FSW may be an overestimate of new diagnoses if women were uncomfortable reporting their known HIV-positive status. Additionally, FSW who were previously diagnosed but not on ART may have felt it more socially desirable to report not being previously diagnosed and therefore unable to be on ART. Furthermore, FSW who were virally suppressed but did not report engaging in "upstream" care continuum outcomes

may have been concerned about reporting HIV status awareness while continuing to be engaged in sex work. This apparent discrepancy related to virally suppressed FSW that are reportedly unengaged in HIV care and not on ART, which may be partially explained by the possibility that some small percentage were elite controllers,[139] has been seen previously among FSW in Zimbabwe.[140] Clinical records could potentially have provided more reliable diagnosis and ART use data; however, such data are not readily available in Malawi.

This study was the first to characterize key HIV care continuum outcomes among a sample of FSW in Lilongwe, Malawi—where the HIV prevalence among FSW remains among the highest globally. HIV-burdened FSW in sub-Saharan Africa are severely understudied and underserved, leading to limited understanding of and attention to their HIV testing, care, and treatment engagement. Our study suggests an enormous need for integrated behavioral, biomedical, and structural approaches for both HIV-infected and HIV-uninfected FSW to improve clinical outcomes and prevent onward transmission.

Table 3. Characteristics of female sex workers in Lilongwe, Malawi, July-September 2014

	Total Population (n=200)		HIV seronegative (n=62)		HIV seropositive (n=138)	
	n	(%)	n	(%)	n	(%)
Age (years)						
18-24	101	(51)	44	(71)	57	(41)
25-29	54	(27)	10	(16)	44	(32)
≥30	45	(22)	8	(13)	37	(27)
Nationality						
Malawian	195	(98)	62	(100)	133	(96)
Other	5	(2)	0	(0)	5	(4)
Education						
Never attended school	15	(7)	5	(8)	10	(7)
Some primary	117	(59)	36	(58)	81	(59)
Completed primary	20	(10)	3	(5)	17	(12)
Some secondary	44	(22)	15	(24)	29	(21)
Completed primary	4	(2)	3	(5)	1	(1)
Marital status*						
Never married	28	(14)	13	(21)	15	(11)
Married (legal or traditional) or co-habiting	9	(4)	3	(5)	6	(4)
Separated, divorced, or widowed	162	(81)	45	(73)	117	(85)
Housing						
Private house	27	(13)	10	(16)	17	(12)
Bar or Bottle shop	115	(58)	35	(57)	80	(58)
Guesthouse or hotel	58	(29)	17	(27)	41	(30)
Number of pregnancies						
0	15	(7)	4	(6)	11	(8)
1	56	(28)	19	(31)	37	(27)
≥2	129	(65)	39	(63)	90	(65)
Duration of sex work (years)*						
<1.0	25	(12)	10	(16)	15	(11)
1.0-1.9	39	(20)	15	(24)	24	(17)
2.0-2.9	34	(17)	12	(19)	22	(16)
≥3.0	100	(50)	23	(37)	77	(56)
Location for soliciting clients						
Bar or bottle shop	181	(91)	57	(92)	124	(90)
Other	19	(9)	5	(8)	14	(10)
Number of clients per week*						
<10	43	(21)	16	(27)	27	(20)
10-19	45	(23)	12	(19)	33	(24)
20-29	52	(26)	19	(31)	33	(24)
≥30	58	(29)	14	(23)	44	(32)

Condom use with paying sexual partners in past 7 days[†]

Inconsistent	49 (24)	13 (21)	36 (26)
Consistent	151 (76)	49 (79)	102 (74)

*Missing data due to not knowing or refused to answer: marital status: n=1; number of years exchanging sex for money: n=2; number of paying sexual partners in past 7 days: n=2

[†]Inconsistent includes FSW who responded “never”, “rarely”, “sometimes”, or “most times”; Consistent includes FSW who responded “always”.

Table 4. HIV testing history, CD4 count, and VL at the time of cross-sectional survey by new and previous HIV diagnosis for female sex workers, (n=138)

	New HIV diagnosis (n=27)	Previous HIV diagnosis (n=111)
	Median (Interquartile Range)	
Time since last HIV test (months)*	11 (3-17)	14 (4-44)
CD4 count, cells/mm ³	464 (276-632)	528 (355-747)
Viral load, copies/ml	44, 846 (5,981- 202,395)	0 (0- 31,295)

*Among those who report previously testing negative

Figure 4. HIV Care Continuum among HIV-infected female sex workers, Lilongwe, Malawi (n=138). A) Among all HIV-infected FSW; B) Among FSW achieving prior step.

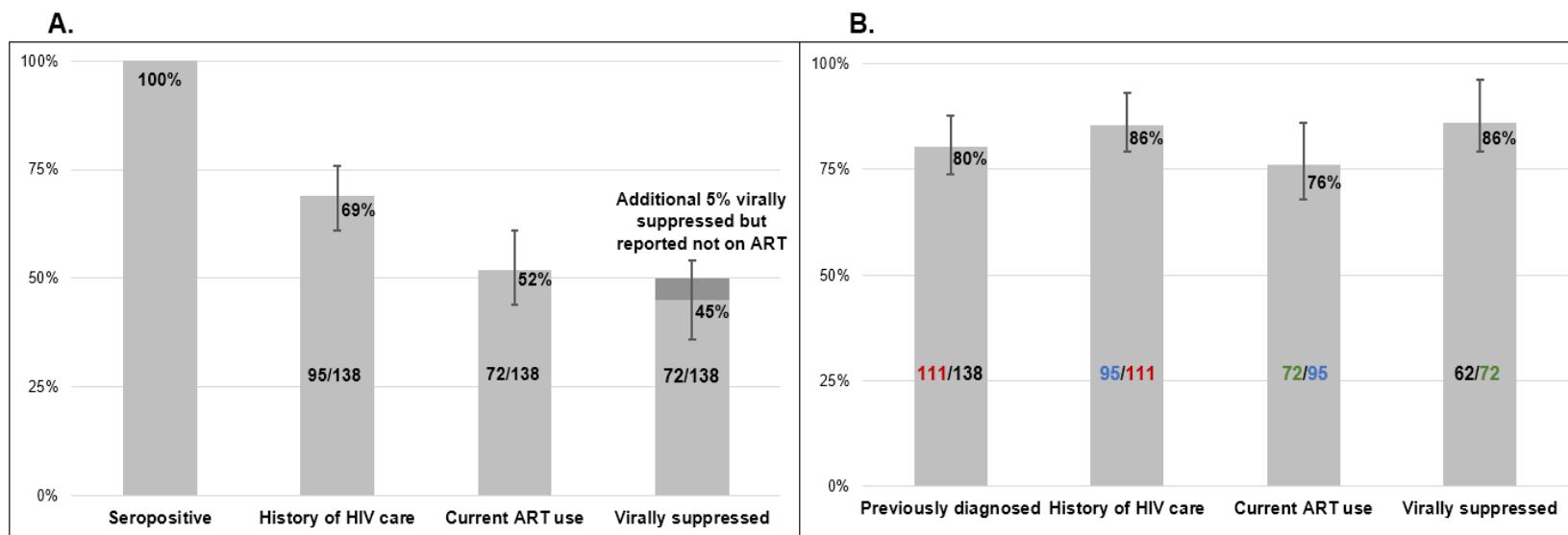


Table 5. Associations of demographic and transmission risk behaviors with HIV care continuum outcomes (previously HIV diagnosed, history of HIV care, and current ART use) among HIV-infected female sex workers in Lilongwe, Malawi

Characteristic	Previously HIV diagnosed n=138		History of HIV care n=111		Current ART use n=96	
	PR (95% CI)	APR* (95% CI)	PR (95% CI)	APR* (95% CI)	PR (95% CI)	APR* (95% CI)
Age (years)						
18-24	0.89 (0.40, 2.01)	0.74 (0.30, 1.84)	0.91 (0.78, 1.07)	0.99 (0.86, 1.14)	0.90 (0.67, 1.17)	0.98 (0.74, 1.31)
25-29	0.84 (0.35, 2.02)	0.81 (0.34, 1.91)	0.87 (0.72, 1.04)	0.89 (0.73, 1.08)	0.88 (0.67, 1.17)	0.93 (0.70, 1.23)
≥30	1.00	1.00	1.00	1.00	1.00	1.00
Duration of sex work (years)						
<1.0	1.58 (0.60, 4.19)	1.81 (0.62, 5.33)	1.02 (0.83, 1.25)	1.02 (0.83, 1.12)	0.78 (0.49, 1.25)	0.81 (0.49, 1.33)
1.0-1.9	1.73 (0.78, 3.83)	2.04 (0.85, 4.94)	0.79 (0.58, 1.09)	0.84 (0.63, 1.12)	0.82 (0.56, 1.20)	0.91 (0.62, 1.33)
2.0-2.9	0.81 (0.25, 2.58)	0.91 (0.28, 2.88)	0.95 (0.76, 1.17)	0.93 (0.75, 1.15)	0.87 (0.62, 1.21)	0.87 (0.60, 1.24)
≥3.0	1.00	1.00	1.00	1.00	1.00	1.00
Number of clients per week						
≤19	0.64 (0.31, 1.33)	0.67 (0.33, 1.36)	1.13 (0.98, 1.31)	1.12 (0.96, 1.30)	1.11 (0.89, 1.39)	1.10 (0.88, 1.38)
≥20	1.00	1.00	1.00	1.00	1.00	1.00
Condom use**						
Inconsistent	1.42 (0.70, 2.86)	1.65 (0.79, 3.47)	0.94 (0.77, 1.14)	0.90 (0.75, 1.01)	1.12 (0.88, 1.43)	1.08 (0.84, 1.38)
Consistent	1.00	1.00	1.00	1.00	1.00	1.00

PR: Prevalence Ratio; APR: Adjusted Prevalence Ratio; CI: Confidence Interval

*adjusted for all other variables in table

†Inconsistent includes FSW who responded “never”, “rarely”, “sometimes”, or “most times”; Consistent includes FSW who responded “always”.

CHAPTER V: SUBSTANCE USE AND AWARENESS OF HIV INFECTION AMONG HIV-INFECTED FEMALE SEX WORKERS IN LILONGWE, MALAWI

Introduction

Female sex workers (FSW) have been a key focus for HIV prevention efforts for over three decades; however, these women remain disproportionately at risk for acquiring HIV.[29-34] The global burden of HIV among FSW is approximately 12%.[30] The prevalence among FSW is even higher in sub-Saharan Africa, at approximately 37%.[14, 30, 35] In Malawi, the HIV prevalence among FSW is about 70%, the highest FSW prevalence globally.[30, 141] To prevent ongoing transmission and successfully engage in HIV care and treatment, FSW must be aware of their HIV infection.

Timely HIV testing and infection awareness is the pivotal first step for successful engagement in HIV care and treatment and subsequent improvements in health outcomes. Currently, the World Health Organization (WHO) currently recommends that HIV testing for high risk persons, such as FSW, should occur at least every 12 months.[142] Yet, many FSW do not access HIV testing and counseling fearing a positive result.[41] Among FSW who are aware of their HIV infection, many learn it as a result of testing during pregnancy. The most common reason for voluntary HIV testing is frequent illness or deterioration of health.[41] The barriers to HIV testing for hard-to-reach FSW in sub-Saharan Africa must be delineated to improve uptake of HIV care and treatment and prevent ongoing transmission.

Substance-using FSW in the region use alcohol most commonly.[4, 143, 144] FSW often engage in alcohol use to facilitate soliciting sex and cope with stressors associated with sex work.[3, 4] In Malawi, nearly 45% of FSW report consuming four to five bottles of

alcoholic beverages per day, which puts these women at serious risk for alcohol dependency.[8, 41, 57] Alcohol use negatively affects health care utilization and likely serves as a barrier to HIV infection awareness.[58, 145] To date, the association between alcohol use and HIV testing, particularly among FSW in sub-Saharan Africa, has rarely been examined.[146]

Marijuana is widely used in sub-Saharan Africa, including among FSW.[2, 143, 147, 148] FSW in South Africa are significantly more likely to use marijuana when compared to non-sex worker females, with two thirds reporting marijuana use.[3] Estimates of marijuana use among FSW in Malawi are lacking, nonetheless, marijuana is widely available and inexpensive.[24, 25, 72] Marijuana use impairs cognitive functions and judgment, which may in turn adversely affect HIV-related health seeking decision making and likely subsequent delay of HIV infection awareness. [69-71] However, the relationship of marijuana use with HIV testing and infection awareness specifically among FSW is unknown.

In this study, we examined associations between alcohol and/or marijuana use and lack of awareness of HIV infection among FSW in Lilongwe, Malawi. We also describe history of HIV testing among HIV-infected FSW.

Methods

Study setting and participants

This study was conducted in Lilongwe, the central region of the Republic of Malawi. The study population included FSW, defined per the Family Planning Association of Malawi as someone “who had received money in exchange for sex either regularly or occasionally up to 12 months prior to the survey”, who were at least 18 years of age, and able to speak English or Chichewa, the predominant local language.

Study design

Our study was guided by self-regulation and coping theories that individuals engage in substance use to help cope with negative life events and dysregulate emotional states brought on by sex work, which in turn may influence HIV health seeking behaviors.[73-75] We designed and implemented this study through a collaboration among the University of North Carolina-Chapel Hill, UNC Project-Malawi, and Theatre for a Change (TfaC), a non-governmental organization in Malawi with far-reaching relationships with local stakeholders including sex workers, chiefs, police, other NGOs, United Nations agencies, and government ministries. We employed a cross-sectional design to systematically recruit FSW using venue-based sampling, a strategy with documented success in identifying hidden populations, such as FSW.[12, 95-98] Using a mobile van, we recruited FSW using an outreach team comprised of a peer FSW, HIV testing counselors, interviewers, a study nurse, and male driver. The list of venues was developed in collaboration with TfaC. Prior to recruitment, stakeholder meetings with FSW community leaders known as “Queen Mothers” were held in conjunction with TfaC and the UNC Project-Malawi community advisory board to navigate the legal and social networks involved with sex work. FSW were recruited for participation from July to September 2014 from 23 different venues, primarily bars and bottle shops, within Lilongwe.

Data collection

All consenting FSW received a behavioral survey. With the behavioral survey, we obtained detailed information on self-reported alcohol and marijuana use and HIV testing history, as well as sociodemographic information, number of pregnancies, depression, and sex work factors (length of time in sex work, number of weekly clients, condom use, and

location of soliciting sex). The survey was translated from English to Chichewa and back-translated. The survey was available in both languages to all participants.

HIV serostatus was assessed for all participating FSW. Per Malawian National HTC guidelines, FSW received serial HIV-antibody rapid tests, Determine HIV-1/2 and Uni-Gold rapid HIV-antibody. Pre- and post-HIV test counseling, clinic referral, and risk reduction counseling were administered, and both male and female condoms were offered.

Substance use assessments

Alcohol use was assessed using the WHO's Alcohol Use Disorders Identification Test (AUDIT).[110, 149, 150] The AUDIT is an internationally-validated screening tool that measures alcohol use behaviors and alcohol use disorder symptoms.[111, 112] The AUDIT comprises 10 questions related to specific domains, like hazardous drinking, harmful drinking, and alcohol dependence symptoms. Hazardous alcohol use is an alcohol consumption pattern that increases the risk of harmful consequences of the person or others. Harmful alcohol use is an alcohol consumption pattern that leads to adverse physical and mental health outcomes. Alcohol dependence is a condition in which a person experiences a strong desire to drink and difficulty controlling alcohol use. Each of the 10 questions has a set of responses with a corresponding score of 0 to 4. Scores from each question are added, resulting in one composite score ranging from 0 to 40, with higher scores correlated to having an alcohol use disorder. FSW with an AUDIT score of 0 to 6 will be indicative of abstinence or non-hazardous drinking, 7 to 15 of hazardous drinking, 16 to 19 of harmful drinking, and ≥ 20 of possible alcohol dependency.[110]

Marijuana use was measured in terms of reported lifetime marijuana use and number of days using marijuana within the past 30 days. Current marijuana use was defined as at least one day of marijuana use within the prior 30 days.

HIV infection awareness assessment

To measure HIV infection awareness, we asked FSW to report the results of their last HIV test. FSW who were HIV-seropositive and self-reported themselves as HIV-negative from last HIV test, never receiving their results from an HIV test, or never previously tested for HIV were considered unaware of HIV infection.

Covariates

We used directed acyclic graphs, based on the literature, to identify a minimally sufficient adjustment set of covariates to include in our analysis of the associations between alcohol and marijuana use, alone and together, with lack of HIV infection awareness. Covariates examined included s age (18-24, 25-29, ≥ 30 years), education (never attended school/only primary school, any secondary school/more school), marital status (never married, cohabitating/married, separated/divorced/widowed), housing (private house, bottle shop/bar, hotel/guesthouse), gravidity (no previous pregnancies, any previous pregnancies), financial dependents (no dependents, any dependents), probable depression measured by the Patient Health Questionnaire-9 (PHQ9 < 10 , PHQ9 ≥ 10), [113-115] and treatment for an STI in the prior 12 months (no, yes). We also examined were years in sex work (< 1 , 1.0-1.9, 2.0-2.9, ≥ 3.0 years), location for soliciting paying sexual partners (bar/bottle shop, other), weekly number of clients (< 10 , 10-19, 20-29, ≥ 30 clients), condom use during vaginal sex with clients in prior 7 days (consistent use, inconsistent use), ever had a client that demanded not using a condom during vaginal sex (no, yes), alcohol use prior to last vaginal sex with client

(no, yes), and any marijuana use prior to last vaginal sex with client (no, yes). Categorization of the covariates were based on interpretability and replicability.

Statistical analysis

Sociodemographic characteristics, sexual history, history of HIV testing, and substance use were summarized using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables.

We conducted analyses for the associations of alcohol and marijuana use with the primary outcome of lack of HIV infection awareness. We developed a product interaction term to assess the association between alcohol and marijuana use together and lack of HIV infection awareness. We also explored the association between alcohol and marijuana use and time since most recent HIV testing (≤ 12 months vs. ≥ 12 months) among FSW unaware of their HIV infection. We used Poisson regression with robust variance estimates to estimate bivariable and, when sample size permitted, multivariable prevalence ratios (PR) with 95% confidence intervals (CI), due to problems with consistent convergence of log-binomial regression models.[118, 119]

Potential confounders were assessed one-by-one, and retained in final adjusted multivariable models if removal resulted in a $>10\%$ change in the prevalence ratio estimate. Interactions were only considered for variables of interest that met positivity assumptions and were retained in the final adjusted multivariable models if they had public health relevance and reached statistical significance at $\alpha=0.10$. Collinearity was evaluated in the model using Pearson's correlation coefficient; none of the covariates showed significant correlation ($p\text{-value} \geq 0.5$).

All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA).

Ethics

The research protocol, survey, and consent forms were reviewed and approved by the Institutional Review Board at the University of North Carolina and the Malawi Ministry of Health and Population National Health Sciences Research Committee (HSRC). All participants provided written informed consent prior to completing study activities. All study related activities were conducted in a safe and private location.

Results

Of the total study population of 200 FSW, 138 (69%) had confirmed HIV infection (Table 1). About half (41%) of those HIV-infected were between the ages of 18 and 24 years and most (66%) never attended school or received only primary school. Most (85%) were separated, divorced, or widowed, and approximately 60% lived in a bar or bottle shop. Nearly all (92%) HIV-infected FSW had at least one previous pregnancy. A quarter (24%) of HIV-infected FSW had received treatment for an STI in the prior 12 months per self-report. The median time exchanging sex for money was 3 years (interquartile range: 1-6) and the median number of clients per week was 21 (IQR: 10-35). About two-thirds (64%) reported ever having a client who demanded not using a condom during vaginal sex. Nearly a third (30%) reported alcohol use prior to last vaginal sex act with a client, with less than 10% reporting any marijuana use prior to last vaginal sex act with a client.

HIV testing and infection awareness

Of those HIV-infected, 111 (80%, 95% CI: 73, 87%) were aware of their HIV infection (Table 2). Among the 20% who were unaware of being HIV-infected, 20 (74%) had tested negative previously, 5 (19%) had never been tested, and 2 (7%) had been tested but had never received results.[141] The majority of unaware HIV-infected FSW had tested

most recently more than 12 months prior (41%), followed by 32% testing within 6 months prior. About three-fourths (77%) received the last HIV test at a governmental health center.

Substance use

Using the AUDIT scale, less than half (45%) of all HIV-infected FSW were non-hazardous drinkers, while 28% were hazardous drinkers, 12% were harmful drinkers, and 15% were alcohol dependent (Table 3). FSW who were unaware of their HIV infection were more likely to be harmful drinkers (19%) or dependent drinkers (26%) when compared to FSW who were aware of their HIV infection. The proportion of FSW reporting current marijuana use was similar among FSW unaware (23%) and aware of their HIV infection (26%). The proportion of both harmful and dependent alcohol drinking and current marijuana use was also comparable among FSW who were unaware (11%) and aware (8%) of their HIV infection.

Substance use and HIV infection awareness

Among HIV-infected FSW, dose-response relationship was observed for alcohol use and lack of HIV infection awareness (Table 4). When compared to non-hazardous drinkers, FSW who were hazardous drinkers (adjusted PR: 1.24, 95% CI: 0.46, 3.37) or harmful drinkers (adjusted PR: 2.72, 95% CI: 0.97, 7.60) were more likely to be unaware of their HIV infection, in multivariable analysis including adjusting for duration in sex work, alcohol use prior to last vaginal sex with a client, and number of clients per week. FSW who were likely dependent drinkers were 2.99 (95% CI: 1.31, 6.81) times as likely to be unaware of their HIV infection compared to FSW with non-hazardous drinkers, after adjusting for duration in sex work, alcohol use prior to last vaginal sex with a client, and number of clients per week. Specifically among FSW who were unaware of their HIV infection and previously tested,

FSW who were harmful drinkers or alcohol dependent were 0.91 (95% CI: 0.45, 1.85) times as likely to most recently receive an HIV test in the prior 12 months than FSW who were nonhazardous or hazardous drinkers in bivariable analysis.

Comparing current to non-current marijuana use, the prevalence ratio of lack of HIV infection in multivariable analysis was 1.14 (95% CI: 0.53, 2.45), adjusting for marital status and number of clients per week. In bivariable analysis comparing harmful/alcohol dependence and current marijuana use to non-hazardous/hazardous drinking and no current marijuana use, the prevalence ratio was 1.82 (95% CI: 0.59, 5.59).

Discussion

In this population of HIV-infected FSW in Lilongwe, surprisingly a majority of HIV-infected FSW were aware of their HIV infection. However, among those that were unaware of their HIV infection, a considerable proportion had previously tested more than 12 months prior to our study. Nearly half of HIV-infected FSW reported at least hazardous and harmful alcohol consumption, with many dependent drinkers. We observed a dose-response relationship between increased levels of alcohol use and lack of HIV infection awareness. FSW who were dependent drinkers were significantly more likely to be unaware of their HIV infection compared to FSW with non-hazardous alcohol consumption patterns. Marijuana use, alone and together with alcohol use, was uncommon and weakly associated with lack of HIV infection awareness.

The proportion of HIV-infected FSW in our Lilongwe sample who were unaware of their HIV infection was unexpectedly lower when compared to previous estimates among FSW in sub-Saharan Africa. Up to 60% of HIV-infected FSW in sub-Saharan Africa are unaware of their HIV infection, with most FSW only learning of their infection at antenatal care clinics during pregnancy.[22, 151] In Malawi, a 2011 national-level size estimation,

enumerating the number of active FSW, reported that nearly three-quarters of all FSW were unaware of their HIV status.[41] Unfortunately, HIV testing to determine current HIV infection was not conducted, therefore the proportion of unaware HIV-infected FSW could not be estimated, limiting the ability to explore the potential impact of not knowing one's infection on care and forward transmission. Our sample of FSW in Lilongwe was recruited from venues identified by our implementing partner, TfaC. It is likely that FSW within our sample may have previously participated in TfaC sexual and reproductive health promotion programs, therefore, may be more likely to be aware of their HIV infection. Furthermore, the large majority of our FSW reported previous pregnancies and may have undergone compulsory HIV testing as part of antenatal care.

FSW unaware of their HIV infection were testing infrequently, as the majority had previously tested more than 12 months prior to our study. The WHO recommends high-risk persons should receive HIV testing at least every 12 months.[142] Most of the FSW in our study that were unaware of their HIV infection had a previous HIV test outside of the WHO recommended HIV testing period. Strategies that increase the frequency of testing, such as venue-based HIV testing, must be implemented to reach FSW and improve HIV infection awareness.

Notably, a sizeable proportion of those HIV-infected and unaware of their HIV infection had previously tested negative six months prior to our study. It is possible that this proportion of FSW had recently acquired HIV and therefore less opportunity for becoming aware of their HIV infection. Given these likely recent HIV infections, FSW in Malawi should be encouraged to receive HIV testing and counseling more frequently than every 12 months to prevent ongoing transmission and access timely HIV care and treatment. HIV-

infected FSW who delay HIV testing may not adequately engage in HIV care and treatment and continue to unknowingly transmit HIV through high-risk sexual behaviors. However, previously in our study, we found little difference in sexual risk behaviors between HIV-uninfected and infected FSW.[141] Given the continued engagement in sexual risk behaviors, it will be imperative for FSW to receive a timely HIV diagnosis and infection awareness to then engage in proper HIV care and treatment.

Alcohol use among HIV-infected FSW in Lilongwe was prevalent. The high prevalence of alcohol use among HIV-infected FSW may be due to living and working in an environment where alcohol is readily available. The majority of HIV-infected FSW in our sample reported currently living and soliciting sex at a bar or bottle shop FSW in similar settings who worked at bars or other alcohol venues were more likely to consume alcohol or binge drink when compared to FSW not working in alcohol serving venues.[4, 8, 11] The prevalence of alcohol use may have been lower if more non-venue-based FSW had been included in our sample; regardless, our prevalence is consistent with previous high prevalence estimates of alcohol use among FSW recruited within the larger community and clinic settings in sub-Saharan Africa.[4, 143, 152, 153] To reduce the prevalence of alcohol use, FSW in Lilongwe should be reached using a venue-based approach for alcohol risk reduction efforts.

We found in this population that increased alcohol consumption was associated with lack of HIV infection awareness. Although scarcely examined, one study in Kenya among FSW found that harmful alcohol drinkers (AUDIT score 7-15) were more likely to self-report never having been tested HIV, compared to hazardous alcohol drinkers (AUDIT score 16-19).[146] However, this study was restricted to FSW who drank regularly with hazardous or

harmful drinking (AUDIT scores ranging from 7 to 19). Our results not only suggest a relationship between alcohol dependence and lack of HIV infection awareness among HIV-infected FSW in Lilongwe, but a dose-response relationship between increased alcohol use and lack of HIV infection awareness.

Our association between alcohol use and lack of HIV infection awareness may be due to alcohol use influencing sexual risk behaviors leading to increased recent HIV infections and less time to obtain HIV testing.[4, 8, 34, 152, 154] However, among those that were unaware of their HIV infection and previously tested, we found little to no association between alcohol use and receiving an HIV test in the prior 12 months. Therefore it is likely more plausible that alcohol use adversely influences health seeking behaviors and therefore inhibits HIV testing and HIV infection awareness.[58, 145] Alcohol use likely predates lack of awareness of HIV infection for FSW within our sample of unaware HIV-infected FSW, regardless of the cross-sectional nature of our study, as alcohol use was ascertained prior to determination of HIV among those reporting previously never testing or HIV-negative. Targeted alcohol reduction interventions must be explored as a means to expand HIV infection awareness for FSW.

Among HIV-infected FSW in Lilongwe, current marijuana was uncommon. Our results add to the limited knowledge base documenting marijuana use among FSW sub-Saharan Africa. Research on marijuana use among FSW has predominantly occurred in urban areas of South Africa.[143, 155] FSW in South Africa report marijuana as the most commonly used substance behind alcohol, with approximately 70% reporting marijuana use.[143, 155] It is possible that FSW in our sample were more likely to use alcohol than marijuana since alcohol may be more readily available given our sample of FSW recruited

from mainly alcohol-serving venues. Our estimate of current marijuana use may be an underestimate of marijuana use among FSW in Malawi not living or working in alcohol-serving venues.

Marijuana use, alone or together with alcohol use, was weakly associated with HIV infection awareness. A qualitative study among street-based FSW using marijuana found that most FSW reported receiving an HIV test at some point but some reported never testing for HIV.[155] The most commonly mentioned barriers to HIV testing for FSW were negative treatment by health care professionals and limited HIV testing locations.[155] These non-substance-use-related barriers highlight the multilevel nature of barriers to HIV testing among FSW and may account for our lack of association between marijuana use and HIV infection awareness among HIV-infected FSW in Lilongwe. It is also possible that severe marijuana use, which was not examined within our study, may more directly affect HIV infection awareness. Future research with improved marijuana use assessments are needed to examine the frequency, duration, and severity of marijuana use.

These findings emphasize the importance of improving HIV testing uptake to increase infection awareness as a first step to engaging in HIV care and treatment and improving health outcomes for HIV-infected substance-using FSW in Malawi. Targeted strategies including venue-based HIV testing and counseling, are necessary to better reach alcohol-using FSW for frequent and consistent HIV testing to deliver a timely HIV diagnosis and infection awareness. Venue-based alcohol reduction strategies must be explored to mitigate alcohol use and to expand HIV infection awareness among highly active FSW in Malawi.

Table 6. Characteristics of HIV-infected female sex workers in Lilongwe, Malawi, July-September 2014, n=138

	n	(%)
Age (years)		
18-24	57	(41)
25-29	44	(32)
≥30	37	(27)
Education		
Never attend or only primary school	91	(66)
Any secondary or more school	47	(34)
Marital status		
Never married	15	(11)
Married (legal or traditional) or co-habiting	6	(4)
Separated, divorced, or widowed	117	(85)
Housing		
Private house	17	(12)
Bar or bottle shop	80	(58)
Guesthouse or hotel	41	(30)
Number of pregnancies		
0	11	(8)
≥1	127	(92)
Number of financial dependents		
0	6	(4)
≥1	132	(96)
Depression		
No probable depression	125	(91)
Probable depression	13	(9)
Treated for an STI in prior 12 months		
No	105	(76)
Yes	33	(24)
Duration of sex work (years)		
<1.0	15	(11)
1.0-1.9	24	(17)
2.0-2.9	22	(16)
≥3.0	77	(56)
Location for soliciting clients		
Bar or bottle shop	124	(90)
Other	14	(10)
Number of clients per week ^a		
<10	27	(20)
10-19	33	(24)
20-29	33	(24)
≥30	44	(32)
Condom use with client in past 7 days		
Inconsistent	36	(26)
Consistent	102	(74)

Ever had a client demand not using a condom during vaginal sex		
No	50	(36)
Yes	88	(64)
Alcohol use prior to last vaginal sex with client		
No	97	(70)
Yes	41	(30)
Drug use prior to last vaginal sex with client		
No	129	(93)
Yes	9	(7)

^a Missing data due to not knowing or refused to answer: number of clients in past 7 days: n=1

Table 7. Frequency and history of HIV testing by HIV infection awareness among previously tested HIV-infected female sex workers in Lilongwe, Malawi, July-September 2014

	All (n=133)		Unaware of HIV infection (n=22)		Aware of HIV infection (n=111)	
	median	(IQR)	median	(IQR)	median	(IQR)
Number of lifetime HIV tests	2	(2-4)	3	(2-4)	2	(2-4)
	n	(%)	n	(%)	n	(%)
Time since last HIV test (months)						
≤ 6	42	(32)	7	(32)	35	(32)
6.1-11.9	26	(27)	6	(27)	20	(18)
≥ 12.0	65	(49)	9	(41)	56	(50)
Location of most recent HIV test ^a						
Health center, governmental	95	(71)	17	(77)	78	(70)
Private clinic	13	(10)	1	(5)	12	(11)
HIV/AIDS comprehensive care and treatment clinic	7	(5)	0	(0)	7	(6)
Other	16	(12)	4	(18)	12	(11)

IQR: interquartile range

^a Missing due to not knowing most recent HIV test location, n=2

Table 8. Patterns of alcohol and marijuana use by HIV infection awareness among previously tested HIV-infected female sex workers in Lilongwe, Malawi, July-September 2014

Substance use	All (n=138)	Unaware of HIV infection (n=27)	Aware of HIV infection (n=111)
	n (%)	n (%)	n (%)
<i>Alcohol use (AUDIT)</i>			
Non-hazardous drinking (score 0-6)	62 (45)	9 (33)	53 (47)
Hazardous drinking (score 7-15)	39 (28)	6 (22)	33 (30)
Harmful drinking (score 16-19)	17 (12)	5 (19)	12 (11)
Alcohol dependence (score ≥ 20)	20 (15)	7 (26)	13 (12)
<i>Marijuana use</i>			
No current marijuana use	105 (76)	20 (74)	85 (77)
Current marijuana use ^a	33 (24)	7 (26)	26 (23)
<i>Alcohol and marijuana use</i>			
Non-hazardous/hazardous drinking and no current marijuana use	80 (58)	11 (41)	69 (63)
Harmful/alcohol dependent and no current marijuana use	25 (18)	9 (33)	16 (14)
Non-hazardous/hazardous drinking and current marijuana use	21 (15)	4 (15)	17 (15)
Harmful/alcohol dependent and current marijuana use	12 (9)	3 (11)	9 (8)

AUDIT= Alcohol Use Disorder Identification Test

^a Current use defined as reported use in past 30 days

Table 9. Associations of alcohol and marijuana use, alone and together, with lack of HIV infection awareness (n=138)

	Unaware of HIV infection	
	Unadjusted PR (95% CI)	Adjusted PR (95% CI)
<i>Alcohol use (AUDIT)</i>		
Non-hazardous drinking (score 0-6)	1.00	1.00
Hazardous drinking (score 7-15)	1.06 (0.341, 2.75)	1.24 (0.46, 3.37) ^a
Harmful drinking (score 16-19)	2.03 (0.78, 5.25)	2.72 (0.97, 7.60) ^a
Alcohol dependence (score ≥20)	2.41 (1.03, 5.64)	2.99 (1.31, 6.81) ^a
<i>Marijuana use</i>		
No current marijuana use	1.00	1.00
Current marijuana use	1.11 (0.52, 2.40)	1.14 (0.53, 2.45) ^b
<i>Alcohol and marijuana use</i>		
Non-hazardous/hazardous drinking and no current marijuana use	1.00	
Harmful/alcohol dependent and no current marijuana use	2.62 (1.23, 5.59)	-
Non-hazardous/hazardous drinking and current marijuana use	1.39 (0.49, 3.91)	-
Harmful/alcohol dependent and current marijuana use	1.82 (0.59, 5.59)	-

PR=prevalence ratio; CI=confidence interval; AUDIT= Alcohol Use Disorder Identification Test

^a Adjusted for duration in sex work (years), alcohol use prior to last vaginal sex with client, and number of clients per week

^b Adjusted for marital status and number of clients per week

CHAPTER VI: THE ASSOCIATION BETWEEN SUBSTANCE USE AND SUB-OPTIMAL HIV TREATMENT OUTCOMES AMONG HIV-INFECTED FEMALE SEX WORKERS IN LILONGWE, MALAWI

Introduction

Substance use is highly prevalent among female sex workers (FSW) globally.[1-7] FSW often engage in substance use to facilitate soliciting clients and to cope with stigma and stress related to sex work.[1, 4, 8-10] Substance-using FSW have particularly low condom usage and high rates of sexual abuse and sexually transmitted infections (STI), which disproportionately place substance-using FSW at high risk for HIV infection.[2, 11-13]

FSW are a key population affected by HIV. The global HIV prevalence among FSW is 12%, with a prevalence of 37% among FSW in sub-Saharan Africa.[30] The HIV prevalence is highest among FSW in Malawi, with approximately 70% of FSW living with HIV.[141] To improve health outcomes and ongoing transmission, HIV-infected FSW must use antiretroviral therapy (ART) and become virally suppressed. Engagement in HIV treatment may be a particular challenge among FSW in sub-Saharan Africa.[14, 21, 22]

For FSW, one potential barrier to engagement in HIV treatment is substance use. The heavy use of alcohol and/or marijuana, the most commonly used substances in Malawi, severely affects cognitive functions, such as decision-making and memory.[59, 61, 67, 68] Lack of these cognitive skills may make it increasingly difficult for substance users to manage their HIV treatment.[59, 61, 69-71] Substance-using FSW who are not successfully engaged in HIV treatment will not benefit immunologically or clinically and may continue to transmit HIV to their sexual partners. To improve health outcomes and reduce ongoing

transmission, the impact of substance use on engagement in HIV treatment among FSW must be understood.

For this study, we examined the association between alcohol and marijuana use and sub-optimal HIV treatment outcomes: lack of ART use among ART-eligible and viral nonsuppression, among HIV-infected FSW in Lilongwe, Malawi.

Methods

Study setting and participants

This study was conducted in Lilongwe, Malawi, where a 2011 situation analysis estimated 3,500 FSW working. Our study population included women who were at least 18 years of age, were either aware or unaware of their HIV status, able to speak English or Chichewa, the predominant local language, and self-identified as a FSW using the 2011 situation analysis definition (“received money in exchange for sex either regularly or occasionally up to 12 months prior to the survey”).

Study design

Our study was designed and implemented through a collaboration between University of North Carolina-Chapel Hill, UNC Project-Malawi, and Theatre for a Change, a non-governmental organization in Malawi. We used a cross-sectional design systematically recruiting FSW using venue-based sampling, a well-documented successful strategy for identifying hidden population, such as FSW.[12, 95-98] We identified FSW using an outreach team made up of HIV testing counselors, interviewers, a study nurse, a male driver, and a peer FSW, to assist with approaching women at the venues. Through July and September 2014, we recruited FSW for participation from 23 different venues within Lilongwe that were primarily bars and bottle shops.

Data collection

All consenting FSW completed a behavioral survey seeking detailed information on alcohol and marijuana use and HIV treatment engagement. We also obtained sociodemographics factors, number of pregnancies, number of financial dependents, depression, previous STI treatment and sexual history. The survey was translated and back translated from English to Chichewa. The survey in both languages was available to all FSW.

We used the Malawian National HIV Testing and Counseling guidelines to assess and confirm serostatus for all participating FSW. FSW received serial HIV-antibody rapid tests, Determine HIV-1/2 and Uni-Gold rapid HIV-antibody. Based on the national guidelines, persons with serodiscordant test results underwent tiebreaker tests using Determine and Uni-Gold parallel testing. We administered pre- and post-testing counseling, clinic referral, and risk reduction counseling. We also offered male and female condoms to all FSW participants.

For all confirmed HIV-seropositive FSW, we obtained CD4 measurements and plasma HIV-RNA levels. CD4 measurement was obtained using a fingerstick blood sample and the Pima CD4TM analyzer, a self-contained, cartridge-based test platform with results available in approximately 20 minutes.[84, 99] We provided CD4 results using a trained study nurse to assist with interpretation of these results.

Dried blood spots (DBS) were collected using fingerstick to determine HIV-1 RNA concentrations.[100-102] DBS samples were stored in drying boxing with a humidity indicator card to monitor moisture levels, until they were brought to the UNC Project

laboratory. We obtained HIV-1 RNA levels within 4 weeks of DBS collection and a trained study nurse provided and explained results to FSW.

Substance use assessment

We measured alcohol use using the World Health Organization's (WHO) Alcohol Use Identification Test (AUDIT).[110, 149, 150] The AUDIT is an internationally-validated screening tool that measures alcohol use behaviors and alcohol use disorder symptoms.[111, 112] The AUDIT comprises 10 questions related to specific domains, such as hazardous drinking, harmful drinking, and alcohol dependence symptoms. Hazardous alcohol use is an alcohol consumption pattern that increases the risk of harmful consequences of the person or others. Harmful alcohol use is an alcohol consumption pattern that leads to adverse physical and mental health outcomes. Alcohol dependence is a condition in which a person experiences a strong desire to drink and difficulty controlling alcohol use. Each of the 10 questions has a set of responses with a corresponding score of 0 to 4 that sums to a single composite score ranging from 0 to 40, with higher scores correlated to having an alcohol use disorder. For this analysis, FSW with an AUDIT score of 0 to 6 was considered indicative of abstinence or non-hazardous drinking, 7 to 15 of hazardous drinking, 16 to 19 of harmful drinking, and ≥ 20 of alcohol dependency.[110]

Marijuana use was assessed by reports of lifetime marijuana and number of days using marijuana within the past 30 days. We defined current marijuana use as FSW who reported using marijuana at least one day within the prior 30 days.

HIV treatment assessments

We asked FSW to report the date and results of their most recent HIV test to determine new vs. previous diagnosis. We defined a new HIV diagnosis as FSW who were

seropositive, based HIV rapid testing, and self-reported being HIV negative at their most recent HIV test (or never testing previously). We defined a previous diagnosis as those reporting being HIV-positive at their most recent test.

We assessed reported current ART use among all ART eligible FSW. ART eligibility was defined as those reporting current ART use, a CD4 ≤ 500 cells/mm³ following the Malawi national guidelines, currently pregnant or breastfeeding, or any pregnancy after July 2011 following Option B+ policy.[116] Option B+ provides confirmed HIV-infected pregnant and breastfeeding women lifelong ART regardless of CD4 count or clinical stage. FSW who answered no to the question “Are you currently on ART?” were classified as not using ART.

We measured HIV-1 RNA concentration for viral suppression. FSW were classified as nonsuppressed with an HIV-1 RNA >5000 copies/mL which is the recommended threshold when using fingerstick DBS.[47, 103]

Covariates

We used directed acyclic graphs, based on the literature, to identify minimally sufficient adjustment sets of covariates to include in our models examining the associations between alcohol and marijuana use with sub-optimal HIV treatment outcomes. The covariates we examined included age (18-24, 25-29, ≥ 30 years), education (never attended school/any primary school, any secondary school/more school), marital status (never married, cohabitating/married, separated/divorced/widowed), housing (private house, bottle shop/bar, hotel/guesthouse), gravidity (no previous pregnancies, any previous pregnancies), financial dependents (no dependents, any dependents), probable depression measured by the Patient Health Questionnaire-9 (PHQ9 <10 , PHQ9 ≥ 10),[113-115] and treated for an STI in

the prior 12 months (no, yes). We also examined were years in sex work (<1, 1.0-1.9, 2.0-2.9, ≥ 3.0 years), location for soliciting paying sexual partners (bar/bottle shop, other), weekly number clients (<10, 10-19, 20-29, ≥ 30 clients), condom use during vaginal sex with clients in prior 7 days (consistent use, inconsistent use), paying sexual partner demanded not using a condom for vaginal sex (no, yes), and alcohol use prior to last vaginal sex with client (no, yes). Categorization of the covariates was based on interpretability and replicability.

Statistical analysis

We summarized the characteristics, substance use, and engagement in HIV treatment using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables.

We conducted separate analyses for the associations of alcohol and marijuana use with the primary outcomes of lack of ART use and nonsuppression. Poisson regression with robust variance estimates was used to estimate bivariable and, when sample size permitted, multivariable prevalence ratios (PR) with 95% confidence intervals (CI).[118, 119]

We assessed potential confounders one-by-one, and retained them in the final adjusted multivariable models if removal resulted in a >10% change in estimate. Interactions were only considered for variables of interest that met positivity assumptions and were considered to have public health relevance; they were retained in final adjusted multivariable models if they reached statistical significance at $\alpha=0.10$. Collinearity was evaluated in the model using Pearson's correlation coefficient; none of the covariates showed significant correlation (p value ≥ 0.5).

All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA).

Ethics statement

Ethics approval was obtained for all study-related procedures and materials from the Malawi Ministry of Health and Population National Health Sciences Research Committee (HSRC) and the University of North Carolina-Chapel Hill Institutional Review Board. All participants provided written informed consent prior to completing study activities. All study-related activities were conducted in a safe and private location.

Results

Among the 200 enrolled FSW, 111 (56%) were previously diagnosed and confirmed HIV-infected. Of those previously diagnosed, 96 (86%) were considered eligible for ART. Among those ART-eligible, the median age was 26 (IQR: 23-30). Approximately 70% never attended school or received only primary schooling and 87% were separated, divorced, or widowed (Table 1). Over half (58%) were living at a bar or bottle shop. Almost all had a previous pregnancy (92%) and at least one financial dependent (96%). About 10% were considered depressed based on the PHQ-9 criteria. Three fourths self-reported receiving treatment for an STI in the prior 12 months. The median time exchanging sex for money was 3 years (interquartile range: 1-6) and number of clients per week was 20 clients (IQR: 10-35). Nearly one quarter (23%) reported inconsistent condom use with clients in the prior 7 days and 58% reported ever having a client demand not using a condom during vaginal sex.

Among those eligible for ART, 29% (n=28) reported using alcohol prior to their last vaginal sex act with a client (Table 1). Overall among ART-eligible FSW, over half (52%) had AUDIT scores ≥ 7 . One-third (30%) had patterns of hazardous drinking. Over 20% were heavily consuming alcohol, 10% were harmful drinkers and 12% were alcohol dependent. Twenty one percent of all ART-eligible FSW reported current marijuana use.

Of those eligible for ART (n=96), 25% (n=24) were not using ART and 75% (n=72) reported using ART. FSW not using ART had a lower median CD4 count (391, IQR: 261-474) and higher median viral load (86,345, IQR: 26,319-337,689) when compared to FSW who were using ART (Figure 1).

The prevalence of ART non-use was 38% (n=8) among those who were harmful drinkers or alcohol dependent and 21% (n=16) among those who were non-hazardous or hazardous drinkers (Table 2). In bivariable analysis, the prevalence ratio for no ART use among ART-eligible was 1.8 (95% CI: 0.9, 3.6) for harmful drinkers or alcohol dependent FSW compared to non-hazardous or hazardous drinkers. In multivariable analyses, FSW who were harmful drinkers or alcohol dependent were 1.9 (95% CI: 1.0, 3.8) times as likely to not use ART compared to FSW who were not hazardous or hazardous drinkers, adjusting for number of clients per week, housing, and duration in sex work.

Among the 72 FSW using ART, 14% (n=10) were nonsuppressed and 86% (n=62) were virally suppressed at the time of this study. Of those using ART, the prevalence of nonsuppressed FSW was 23% (n=3) among those who were harmful drinkers or alcohol dependent and 12% (n=7) among those who were non-hazardous or hazardous drinkers. The prevalence ratio for FSW nonsuppressed was 2.0 (95% CI: 0.6, 6.5) among harmful drinkers and alcohol dependent FSW compared to non-hazardous or hazardous drinkers in bivariable analysis.

Of those ART-eligible, the prevalence of FSW not using ART was 35% (n=7) among current marijuana users. The prevalence ratio of not using ART among ART-eligible FSW was 1.5 (95% CI: 0.8, 3.2) among current marijuana users compared to non-hazardous or hazardous drinkers, in bivariable analysis. Upon adjusting for treatment for an STI in prior

12 months, FSW who were currently using marijuana were 1.9 (95% CI: 0.8, 4.6) times as likely to not use ART compared to FSW who were not currently using marijuana.

In bivariable analysis, FSW who were currently using marijuana were 0.5 (95% CI: 0.1, 3.6) times as likely to be virally nonsuppressed compared to FSW who were not currently using marijuana.

Discussion

In our study, we identified a modest proportion of ART-eligible FSW who did not report ART use. We found that heavy levels of alcohol use, such as harmful drinking or alcohol dependence, and marijuana use are associated with sub-optimal engagement in HIV treatment among HIV-infected FSW. Specifically, FSW who were harmful drinkers or alcohol dependent were significantly more likely to not use ART. Among FSW in our study, current marijuana use was uncommon but was associated with not using ART.

About three-quarters of ART-eligible FSW were using ART. This high level of ART use is likely a result of scaled-up ART coverage in Malawi. ART coverage has expanded in Malawi through the provision of ART to all pregnant or breastfeeding HIV-infected women (Option B+) beginning in July 2011 and earlier initiation of ART (CD4 count ≤ 500 cells/mm³) in April 2014.[131] Given this recent expansion of ART in Malawi, we expected most ART-eligible FSW in our sample to report ART use.

For the remaining ART-eligible FSW that were not using ART, we were unable to determine the timing for ART-eligibility. Our study began shortly after the expanded ART guidelines were implemented in Malawi. The FSW we identified as ART-eligible through our study may have previously been ineligible to initiate ART due to a high CD4 count. Among FSW that were aware of their HIV status and identified through our study as ART-

eligible, the most commonly reported reason for not being on ART was a prior high CD4 count.[156]

Within our study, heavy alcohol use was associated with lack of ART use among ART-eligible FSW. The adverse influence of alcohol use on ART use has been well-documented globally.[60, 157, 158] Alcohol use may impede ART use through several plausible pathways. First, alcohol intoxication impairs memory, organizational skills, judgement and other cognitive abilities likely resulting in lack of ART initiation or treatment interruptions.[59, 61, 67, 68, 157] Lacking cognitive skills from heavy alcohol use may not only impede a person's health-care seeking behavior but may also influence health-care providers' decision for providing ART. Health-care providers may withhold providing ART to heavy alcohol users, despite eligibility, because heavy alcohol users are viewed as incapable to competently use ART.[159] Further influencing treatment among alcohol users are the beliefs that ART medications should not be mixed with alcohol and therefore ART should be not be used when consuming alcohol.[160, 161] In the context of our study, the mechanisms that most influence the relationship between alcohol use and lack of ART are unknown, and future work is needed to improve ART uptake among ART-eligible FSW in Malawi.

To our knowledge, this study is one of the first to examine alcohol use and viral suppression among FSW in sub-Saharan Africa. Alcohol use among HIV-infected persons in sub-Saharan Africa has been identified as an important predictor of viral nonsuppression.[60, 159] Viral nonsuppression is generally a result of poor ART adherence among persons on ART. However, alcohol may have a direct effect on viral nonsuppression by increasing HIV viral replication.[162-164] Regardless of the mechanism, targeted interventions for HIV-

infected FSW should focus on alcohol reduction and ART adherence to improve viral suppression and health outcomes, and to prevent ongoing transmission.

FSW often use alcohol to facilitate sex work and to cope with their work and high-risk environments.[1, 4, 8-10] The observed prevalence of heavy alcohol use may be driven by FSW living at alcohol-serving venues. Given the strategy used for recruitment, nearly all of the FSW in our sample reported living and soliciting sex in a bar or bottle shop. In similar studies, FSW who worked at bars or other alcohol venues were more likely to consume alcohol or binge drink when compared to FSW not working in alcohol-serving venues.[4, 8, 11]

Marijuana use was not as common as alcohol use among FSW in Lilongwe. Our results contribute to the limited knowledge of marijuana use among FSW in sub-Saharan Africa, which has primarily come from urban areas of South Africa.[3, 155] Approximately 70% of FSW in South Africa report using marijuana.[3] Marijuana use was noticeably higher among FSW in South Africa than our sample of FSW in Malawi. The lower prevalence of marijuana use observed in our study may be due to our sample of FSW, who were predominantly living at alcohol-serving venues. Marijuana use may be more common among FSW who are not living in environments where alcohol is readily available.

Within our sample of FSW, marijuana use influences ART use however, the prevalence of virally non-suppressed FSW that reported current marijuana use was too low to draw meaningful conclusions of this relationship. The pathways of both alcohol and marijuana use affecting HIV treatment are analogous. Similar to alcohol, marijuana use affects cognitive functions that are necessary for decision-making and judgement.[59, 61, 67, 68, 158] In addition to impairments of cognitive skills, heavy marijuana use does negatively

affect ART adherence.[71, 165] Although not presented as part of this analysis, the majority of marijuana users were less likely to be heavy drinkers, perhaps suggesting that heavy alcohol use may play a more important role on viral nonsuppression than current marijuana use. For our present study, we only examined current marijuana use, so it is possible that severe marijuana use could negatively influence HIV treatment, specifically viral nonsuppression, for FSW in Malawi.[165] More thorough examinations of the frequency, duration of use, and dependent symptoms of marijuana use and longitudinal assessments of viral load among FSW would provide insight on the impact of heavy marijuana use, along with concurrent alcohol use, on HIV treatment outcomes.

Although this is the first study to examine the association between alcohol and marijuana use and sub-optimal HIV treatment outcomes among FSW in Malawi, the size of our sample is small and does not represent all HIV-infected FSW in Malawi. Our modest sample size resulted in decreased estimate precision, limited power to detect small differences, and decreased ability to control confounding in multivariable analyses. Our sample of FSW in Lilongwe were recruited from venues identified by our implementing partner, TfaC. Since 2007, TfaC has implemented behavior change and advocacy programs to reduce poor sexual and reproductive health outcomes for FSW in Malawi. It is likely that FSW within our sample may have previously participated in these programs, and therefore were not representative of more difficult-to-reach FSW in Malawi. Despite these shortcomings, our study is the first to highlight the negative influence of substance use on HIV treatment outcomes for FSW in Malawi.

Among HIV-infected FSW in Malawi, heavy alcohol use is common and associated with lack of ART use. To improve HIV treatment engagement, targeted interventions for

HIV-infected FSW should prioritize the reduction of alcohol use, along with other substances. Further evaluations on the frequency and severity of marijuana use are needed to determine the additional role marijuana may play on sub-optimal HIV treatment outcomes. ART uptake strategies are critically needed for alcohol-using, ART-eligible FSW to induce viral suppression and ultimately, improve health outcomes and reduce transmission.

Table 10. Characteristics and substance use of ART-eligible female sex workers in Lilongwe, Malawi, July-September 2014, (N=96)

	n	(%)
Age (years)		
18-24	37	(39)
25-29	32	(34)
≥30	27	(28)
Education		
Never attend or only primary school	66	(69)
Any secondary or more school	30	(31)
Marital status		
Never married	10	(10)
Married or co-habiting	3	(3)
Separated, divorced, or widowed	83	(87)
Housing		
Private house	13	(14)
Bar or bottle shop	56	(58)
Guesthouse or hotel	27	(28)
Number of pregnancies		
0	8	(8)
≥1	88	(92)
Number of financial dependents		
0	4	(4)
≥1	92	(96)
Depression		
No probable depression	87	(91)
Probable depression	9	(9)
Treated for an STI in prior 12 months		
No	72	(75)
Yes	24	(25)
Duration of sex work (years)		
<1.0	11	(11)
1.0-1.9	15	(16)
2.0-2.9	17	(18)
≥3.0	53	(55)
Location for soliciting clients		
Bar or bottle shop	11	(11)
Other	85	(89)
Number of clients per week ^a		
<10	19	(20)
10-19	22	(23)
20-29	27	(28)
≥30	27	(28)
Condom use with client in prior 7 days		
Inconsistent	22	(23)
Consistent	74	(77)

Ever had a client demand not using a condom during vaginal sex		
No	40	(42)
Yes	56	(58)
Alcohol use prior to last vaginal sex with client		
No	68	(71)
Yes	28	(29)
<i>Substance use</i>		
Alcohol use (AUDIT)		
Non-hazardous drinking (score 0-6)	46	(48)
Hazardous drinking (score 7-15)	29	(30)
Harmful drinking (score 16-19)	10	(10)
Alcohol dependent (score \geq 20)	11	(12)
Marijuana use		
No current marijuana use	76	(79)
Current marijuana use ^b	20	(21)

^a Missing data due to not knowing or refused to answer: number of clients in past 7 days: n=1

^b Current use defined as reported use in past 30 days

Figure 5. CD4 (A.) count and viral loads (B.) at the time of cross-sectional survey by reported ART use among ART-eligible HIV-infected female sex workers, (n=96); Box plots showing median (line), interquartile range (IQR; box), minimum (lower whiskers), and maximum (upper whiskers)

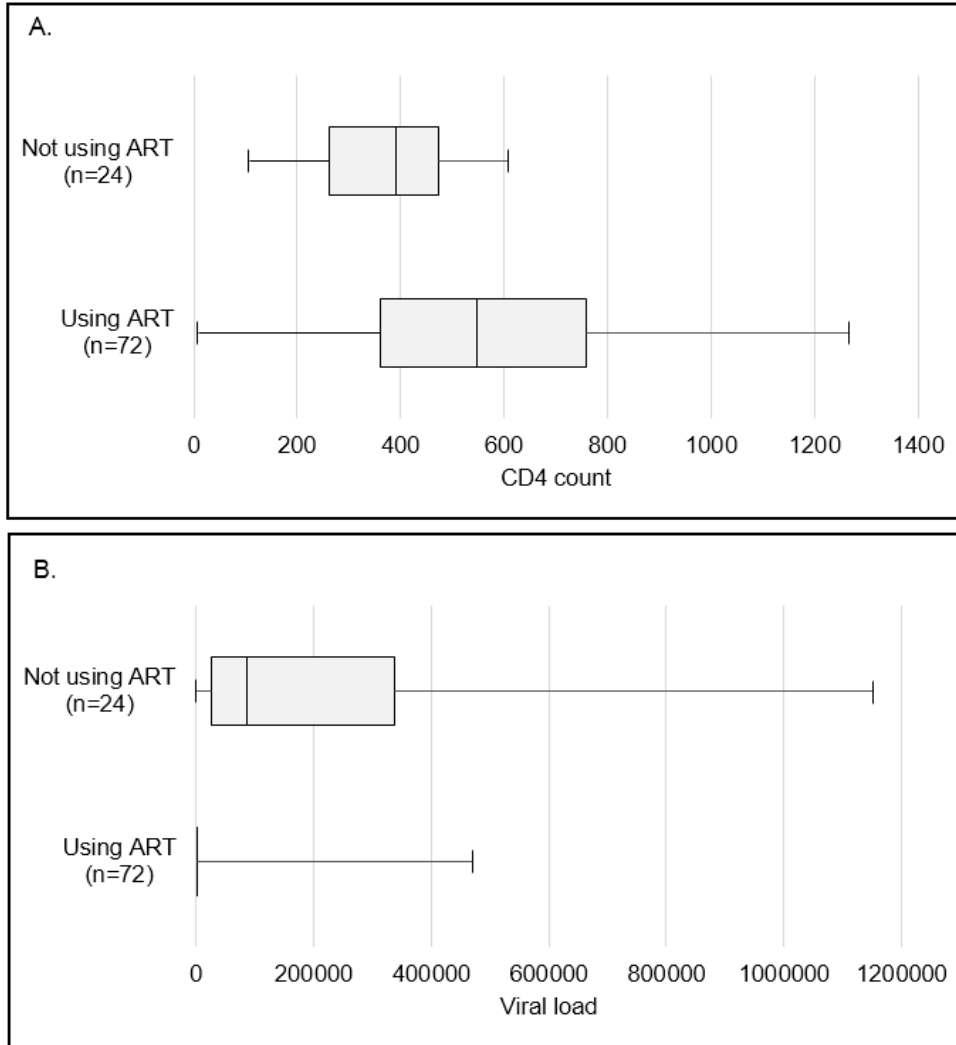


Table 11. Prevalence and association of alcohol and marijuana use with sub-optimal HIV care and treatment outcomes (not using ART and virally non-suppressed) among HIV-infected female sex workers in Lilongwe, Malawi

	Reported ART use (N=96)		Not using ART		Viral suppression (N=72)		Virally non-suppressed	
	Not using ART (n=24)	Using ART (n=72)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)	Virally non-suppressed (n=10)	Virally suppressed (n=62)	Unadjusted PR (95% CI)	Adjusted PR (95% CI)
<i>Alcohol use (AUDIT)</i>								
Non-hazardous/hazardous (score ≤15)	16 (21)	59 (79)	1.0	1.0	7 (12)	52 (88)	1.0	1.0
Harmful/alcohol dependent (score ≥16)	8 (38)	13 (62)	1.8 (0.9, 3.6)	1.9 (1.0, 3.8) ^b	3 (23)	10 (77)	2.0 (0.6, 6.5)	--
<i>Marijuana use</i>								
No current marijuana use	17 (23)	59 (78)	1.0	1.0	9 (15)	50 (85)	1.0	1.00
Current marijuana use ^a	7 (35)	13 (65)	1.5 (0.8, 3.2)	1.9 (0.8, 4.6) ^c	1 (8)	12 (92)	0.5 (0.1, 3.6)	--

PR=prevalence ratio; CI=confidence interval; AUDIT= Alcohol Use Disorder Identification Test

^a Current use defined as reported use in past 30 days

^b Adjusted for number of clients per week, housing, and duration in sex work (years)

^c Adjusted for treatment for an STI in the prior 12 months

CHAPTER VII: DISCUSSION AND CONCLUSION

Substance use is highly prevalent among FSW globally.[1-7] For FSW, substance use is often used to facilitate sex work and to cope with the stigma and stress associated with sex work.[1, 4, 8-10] However, substance use can subsequently lead to high-risk sexual behaviors and increased HIV acquisition.[2, 11-13]

The HIV prevalence among FSW is 12% globally and 37% in sub-Saharan Africa.[30] FSW in Malawi have the highest HIV prevalence of nearly 70%.[141] Given this very high prevalence, FSW must engage in HIV care and receive ART. The expansion of ART for FSW can dramatically improve health outcomes and reduce onward transmission.[14-16] To achieve the numerous benefits of expanded ART, HIV-infected FSW must receive a timely diagnosis, engage in care, adhere to treatment, and become virally suppressed.[19, 125] Yet, little is known about FSW's ability to engage in HIV testing, care, and treatment.[125, 126]

Substance use is likely an influential barrier to HIV testing and treatment outcomes for FSW in sub-Saharan Africa. Clearly delineating the effect of substance on optimal engagement will inform strategies to enhance access to HIV testing, care, and treatment for FSW. This dissertation was designed and implemented to evaluate whether commonly used substances significantly affects engagement in HIV testing and treatment among FSW in Lilongwe, Malawi.

Summary of findings

Our work was conducted in a population of 200 FSW in Lilongwe, Malawi, where the HIV burden is one of the highest globally. We sought to evaluate and compare the associations between substance use and engagement within each stage along the HIV care continuum among FSW, a key population disproportionately affected by HIV. For our study, we conducted a behavioral survey, HIV rapid testing, CD4 cell count assessments, and HIV-1 RNA levels measurements to achieve our three aims.

In our first aim, we characterized the HIV care continuum for our sample of FSW in Malawi. Our studies was one of the first studies to characterize the HIV care continuum among this key population. Among our sample of 200 FSW, we found the HIV seroprevalence was very high at 69% (n=138), with 20% as newly diagnosed through our study. Among all HIV-infected FSW, nearly 70% reported a history of care, over 50% reported current ART use, and 45% were virally suppressed. Specifically among the FSW who reported current ART use, we identified 86% were virally suppressed at the time of our study. We also observed that transmission risk behaviors, such as duration in sex work, number of weekly clients, inconsistent condom use during vaginal sex with clients, were not associated with the HIV care continuum outcomes.

For our second aim, we focused on the relationship between alcohol and marijuana use, alone and together, with HIV infection awareness among HIV-infected FSW in Lilongwe, Malawi. Of the 138 HIV-infected FSW, 80% were aware of their HIV infection and 20% were unaware of their HIV infection. Alcohol use was very common among HIV-infected FSW in our sample. We identified a dose-response relationship between increased alcohol use and lack of HIV infection awareness. In multivariable analysis, alcohol dependency was associated with lack of HIV infection awareness, adjusting for adjusting for

duration in sex work, alcohol use prior to last vaginal sex with a client, and number of clients per week. Among our sample of HIV-infected FSW, marijuana use, alone and together with alcohol, was not significantly associated with lack of HIV infection awareness.

For our third aim, we evaluated the association between alcohol and marijuana use and sub-optimal HIV treatment outcomes, including lack of ART use among ART-eligible and viral nonsuppression, among HIV-infected FSW in Lilongwe, Malawi. Among the FSW who ART-eligible, only about 30% were not using ART. Of the HIV-infected FSW, heavy levels of alcohol use, including harmful drinking and alcohol dependency, and current marijuana use associated with sub-optimal HIV treatment outcomes. Specifically, FSW who were harmful drinkers or alcohol dependent were two times as likely to not use ART compared to FSW who were not hazardous or hazardous drinkers, adjusting for number of clients per week, housing, and duration in sex work. Marijuana use was uncommon, with only 20% of ART-eligible FSW reporting current marijuana use. However, marijuana use was weakly associated with using ART among ART-eligible FSW in Lilongwe, Malawi.

Public health implications

Together, our three studies have contributed to our understanding of the co-occurring substance use and HIV epidemics among the understudied and underserved FSW in sub-Saharan Africa. Our findings emphasize that despite decades of prevention activities, FSW in Malawi remain heavily burdened by HIV.[127] Substance use, specifically alcohol use, among FSW is common and is an important barrier to achieving optimal HIV care continuum outcomes necessary for optimizing health outcomes and preventing ongoing transmission.

Given the exceedingly high prevalence of HIV among FSW, Malawi must consider the adoption of targeted universal testing and treatment strategies for FSW. HIV testing is the critical initial step towards engaging in HIV care and treatment. Frequent HIV testing for

FSW is necessary for a timely diagnosis and prevention of ongoing transmission. FSW who remain unaware of their HIV infection miss opportunities for HIV care entry, resulting in later initiation of ART and increased risk for AIDS progression.[130] The proportion of FSW in our study who tested outside the current recommendation of yearly HIV testing, underscores the need for frequent outreach to encourage rapid HIV testing to capture highly active FSW.

Most ART-eligible FSW in our sample were using ART. Expanded ART programs in Malawi have been successful in improving access to ART for HIV-infected persons, including FSW. These programs have included the provision of ART to all pregnant or breastfeeding HIV-infected women (Option B+) beginning in July 2011 and early initiation of ART (CD4 count ≤ 500 cells/mm³) in April 2014.[131] The expansion of ART is likely responsible for our high proportion of HIV-infected ART-eligible FSW receiving ART.

Initiation of ART for all HIV-infected FSW in Malawi is critical for the prevention of ongoing transmission to HIV-uninfected partners. Among all the HIV-infected FSW in our study, nearly half were not on ART and therefore, not receiving the numerous clinical, immunological, and transmission benefits of therapy. Timely uptake of ART can dramatically improve health outcomes and prevent onward transmission.[14-16] Interventions are urgently needed that focus on increasing access and adherence to ART for FSW in sub-Saharan Africa.

Our findings highlight that substance use, particularly alcohol use, is common. Overall within our sample, many FSW were consuming alcohol with a substantial proportion consuming alcohol heavily. In general, FSW have higher rates of hazardous alcohol consumption patterns than the general population due to their specific occupational and environmental factors.[4, 20, 46] Alcohol serving venues tend to be the location where FSW

solicit clients, in return making alcohol easily accessible.[4, 29, 166] Abstaining from alcohol consumption is challenging as male clients typically purchase alcohol prior to sexual activity with the FSW.[167-169] Alcohol consumption also serves as a coping mechanism for FSW, as a way to handle stress associated from their work.[4, 169, 170] Identification of heavy alcohol use provides a point of intervention for FSW in Malawi.

We observed that heavy alcohol use leads to lack of HIV infection awareness, low ART use among ART-eligible, and viral nonsuppression. Optimal ART use and viral suppression are necessary for the success of treatment as prevention interventions. In light of newly identified biomedical prevention interventions, there is increasing interest of preventing HIV at the population level by treating HIV-infected individuals.[171] Modeling shows that prioritizing ART uptake to FSW could have a significant effect on HIV transmission, if FSW properly engage and adhere to treatment.[19] Given our documented association between heavy alcohol use and sub-optimal HIV testing and treatment outcomes, heavy alcohol use will likely prevent the potential success of treatment as prevention interventions. Strategies that improve uptake of HIV testing, care, and treatment and address substance use must be strongly considered FSW in Malawi.

Our findings improve the limited existing knowledge of marijuana use among FSW in sub-Saharan Africa. Marijuana use was uncommon among our sample FSW and was weakly associated between marijuana use and HIV testing and treatment. This was unexpected given marijuana use, like alcohol use, can affect engagement in HIV prevention and treatment services by decreasing cognitive abilities. The weak association may likely be the result of our selection of FSW. FSW in our sample were predominantly living and working at bars and bottle shops where alcohol is more readily available than marijuana. Additionally, our

estimate of marijuana use was based on current marijuana use which limited our ability to measure the severity of marijuana use. Our results encourage careful consideration for the best approaches for designing studies focused on marijuana use and engagement in HIV testing, care and treatment among FSW.

Future directions

Prospective, longitudinal national surveillance programs will be critical to estimate the dynamic, multidirectional movement of engaging in HIV testing, care, and treatment for both venue-based and street-based FSW in Malawi. The HIV care continuum provides an informative framework for cross-sectionally characterizing HIV testing, care, and treatment. Unfortunately, this framework, alone, cannot appropriately capture the dynamic nature of engaging and disengaging in sex work and HIV prevention and care services. Qualitatively, we found that FSW in Lilongwe engage and disengage with sex work multiple times throughout their young lives. Furthermore, the traditional continuum framework does not clearly characterize important processes, such as care re-engagement and viral re-suppression that may occur for some HIV-infected FSW.[126] Enhanced national surveillance programs for FSW in Malawi will provide a better understanding and monitoring of the HIV epidemic and engagement in HIV testing, care, and treatment.

A better understanding is needed of the underlying pathways of the relationships of substance use and engagement in HIV testing, care, and treatment among FSW. Additional research should employ longitudinal assessments of substance use engagement throughout the HIV care continuum. In particular, future work should examine how substance use changes over time during sex work, document the duration and severity of substance use. Further research should also determine appropriate points of substance use focused interventions to improve uptake of HIV testing, care, and treatment among FSW.

Additionally, research should include various FSW typology, such as venue-based and street-based FSW. Including these types of FSW will assess potential differences by type of the association between substance use and HIV care continuum outcomes. Together, these future studies can inform combination substance use and HIV treatment as prevention interventions for FSW.

Interventions are urgently needed for FSW in Malawi to reduce substance use and promote a timely HIV diagnosis, engagement in care, adherence to ART, and viral suppression. The design of combination interventions must utilize the most strategic approaches to maximize uptake of effective substance use and HIV treatment strategies. One approach may be integrating substance use treatment into current HIV prevention and treatment services. Successfully integrating these services will benefit service providers and reduce costs within this already resource-limited settings. An additional approach if resources allow, these interventions should employ a venue-based approach to provide substance use treatment and HIV testing, care, and treatment for FSW. Targeted strategies for highly active FSW within venues must be explored and implemented to effectively reach FSW.

Conclusions

Substance use is common among FSW in Malawi, where the HIV prevalence among FSW remains the highest globally. Alcohol use, in particular, is an important barrier to reaching optimal HIV care continuum outcomes. Increasing levels of alcohol use is associated with lack of HIV infection awareness. FSW who are heavy alcohol users, such as harmful drinkers and alcohol dependent, are more likely to not use ART and be virally nonsuppressed. Further evaluations on the frequency and severity of marijuana use are needed to determine the additional affect marijuana may have on HIV testing and treatment.

FSW in Malawi with sub-optimal HIV testing and treatment outcomes will not receive the full clinical, immunological, and transmission prevention benefits of therapy. Targeted combination interventions for HIV-infected FSW must prioritize the reduction of alcohol use, along with other substances, to optimize HIV testing and treatment for FSW.

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