Influence of attendance at a clinic service for high-risk women on HIV prevention: A longitudinal study in Kampala, Uganda

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STATEMENT OF OWN WORK

I, Ivan Kasamba, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: _ [redacted] ____Date: _____20/09/2020__________________

ABSTRACT

Background: HIV/AIDS continues to be a major public health threat. Globally, there has been notable progress towards reaching people for HIV testing and treatment, as well as in the development of effective prevention tools. But preventing new HIV infections remains a key challenge, particularly among populations at the most risk including female sex workers and their sexual partners. Reducing HIV transmission in these populations requires combined HIV prevention options not only to be available, but also sufficiently used over time. However, regular attendance at clinic facilities, and use of HIV services by female sex workers is affected by persistent and common barriers including high mobility, stigmatisation, and discrimination in health-care settings. The aim of this thesis is to examine the effect of irregular exposure to a package of HIV prevention interventions among women at high risk of HIV in Uganda.

Methods: A cohort of HIV-negative women at high risk of HIV was scheduled to attend dedicated clinic services once every three months within the Good Health for Women Project in Kampala, Uganda. An initial cohort of women was enrolled between April 2008 and May 2009 and followed-up (cohort 1). Alongside cohort 1, a second cohort was enrolled from January 2013, and followed-up (cohort 2). At each scheduled clinic visit, participants were offered a combination HIV prevention package that included risk reduction counselling, STI management, and HIV testing. Based on these data, I analysed (i) trends in HIV incidence following enrolment and the influence of missed scheduled visits on HIV incidence trends. In addition, multiple imputation of time-to-event was used to assess the influence of attrition over time on incidence; (ii) the association of the number of missed scheduled visits with subsequent HIV risk; (iii) the association of the number of missed scheduled visits with subsequent proximate determinants of HIV risk (sexually transmitted infections (STIs), alcohol use, inconsistent condom use with paid sex). The analyses were censored at 29th August 2017.

Results: Of the 3084 HIV-negative women enrolled, 2206 (71.5%) had at least one follow-up visit. HIV incidence declined rapidly following enrolment from 6.1/100 person-years in ≤6 months to 2.0/100 at year 3 in cohort 1 (p-value<0.001), and from 3.8/100 to 1.8/100 in cohort 2 (p-value=0.04). HIV incidence was associated with the prior number of missed scheduled visits (adjusted hazard ratio=1.40; 95%CI 0.93-2.12 for 1-2 missed visits versus none, and 2.00 (95%CI 1.35-2.95) for ≥3 missed visits versus none; p-trend=0.001). Missed visits were associated with increased detection of STIs, and increased reporting of daily alcohol use at the subsequent visit attended, but not with reported consistency of condom use with paid sex.

Conclusion: The increased HIV risk when high-risk women interrupted their regular exposure to combination HIV prevention was most likely attributed to untreated STI. But the absence of a concurrent change in pattern of inconsistent condom use with paid sex could additionally suggest influence of contextual factors on HIV risk. HIV programmes need to routinely monitor the individual-level exposure to and use of complementary HIV interventions among high-risk women, as well as actively facilitate their attendance of effective intervention packages at regular intervals. For those unable to regularly attend services at health facilities, HIV programmes must adopt innovative ways to deliver combination intervention packages, incorporating STI management and risk reduction counselling and using mobile clinics, clinic vouchers, or even leveraging technology.

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ACRONYMS AND ABBREVIATIONS

ANC	Antenatal Care
ART	Antiretroviral Therapy
CI	Confidence Interval
FSWs	Female Sex Workers
GBV	gender-based violence
HR	Hazard Ratio
HIV	Human Immunodeficiency Virus
HCT	HIV Counselling and Testing
IEC	Information Education Communication
LSHTM	London School of Hygiene and Tropical Medicine
MSV	Missed Study Visit
MI	Multiple Imputation
OR	Odds Ratio
PrEP	pre-exposure prophylaxis
PYR	person-years of observation
SRH	Sexual and Reproductive Health
STI	Sexually Transmitted Infection
SWs	Sex Workers
SSA	Sub-Saharan Africa
MOT	Modes of Transmission of HIV
UK	United Kingdom
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNCST	Uganda National Council of Science and Technology
UPHIA	The Uganda Population-Based HIV Impact Assessment
UVRI	Uganda Virus Research Institute

VCT	Voluntary Counselling and Testing
WHO	World Health Organization

CHAPTER 1: BACKGROUND

1.1 Introduction

This chapter provides the background for the thesis before introducing its aims and objectives. The background includes the epidemiology of human immunodeficiency virus (HIV) in the general population and among female sex workers (FSWs), and why prevention of HIV among FSWs is urgently needed in sub-Saharan Africa. I discuss the key determinants of HIV infection among FSWs, the evidence for prevention interventions and their scale-up. Then, I highlight the contribution of this thesis in improving our understanding of HIV prevention among women at high risk of HIV exposure in settings with high HIV prevalence.

1.1.1 The global HIV epidemics

Despite substantial progress in understanding the prevention and treatment of HIV infection, HIV continues to be a major public health threat globally. There has been a substantial increase in the proportion of people initiated on antiretroviral therapy (ART), which has reduced HIV-related morbidity and mortality. Of the 38.0 million (95% confidence interval (CI): 31.6–44.5 million) people estimated to be living with HIV in 2019, 67% were on ART compared to 25% of those in 2010[1]. In the same period, annual estimated HIV-related deaths were estimated to have declined by 52% in absolute terms to 690,000 (95% CI: 500,000–970,000) in 2019[1].

Early initiation and effective use of ART has a clinical benefit to the individual, and is of public health benefit by reducing infectiousness of HIV[2]. As such, the 90-90-90 Joint United Nations Programme on HIV/AIDS (UNAIDS) targets became a key focus of the global HIV response i.e. that 90% of people living with HIV know their HIV status, 90% of those who know their HIV-positive status are on sustained ART and 90% of people on treatment have suppressed viral loads to undetectable levels[3]. These UNAIDS targets have been updated to 95-95-95 for 2030[3]. However, although ART scale-up has been the central focus in national HIV programmes, the HIV prevention benefits of increased ART coverage at the global level have not been realised. The estimated number of new infections was 1.7 million (95% CI: 1.2–2.2 million) in 2019, far from the UNAIDS target of 500,000 by 2020[4].

Substantial declines in new HIV infections require not only treatment as prevention but also high coverages of effective prevention interventions, particularly among people at the highest risk of HIV exposure[5]. The sub-optimal coverage of primary prevention may partly explain the shortcomings of HIV treatment as prevention at the population level, in addition to difficulties in early diagnosis of HIV and subsequently sustaining those infected on ART for effective viral suppression[6,7]. For example, while Uganda is one of the few countries in sub-Saharan Africa that have achieved the 90-90-90 targets for the year 2020, there has not been an accompanying substantial decline in the number of new infections[4,8]. In 2019, estimates showed 75% of people living with HIV to have suppressed viral loads, above the 2020 target of 73%[4]. But the current estimate of 50,000 new infections remains high and has not substantially declined in the recent years[8].

1.1.2 The HIV epidemics and sex work in sub-Saharan Africa

Sub-Saharan Africa remains the epicentre of the global HIV epidemic. Despite only 12% of the global population living in the region, estimates for 2019 show that 67% of the global number of people living with HIV, 57% of the number of new infections, and 64% of the number of HIV-related deaths were in sub-Saharan Africa[4]. Most east African countries have generalised epidemics (i.e. HIV has spread to substantial levels across the general population), most southern Africa countries have “generalized, hyper endemic” (i.e. HIV prevalence exceeds 15% in the adult population), and many West African countries have low-level epidemics (i.e. HIV prevalence has not spread to substantial levels in the general population)[9,10]. Some countries, such as Burundi and Côte d'Ivoire, have concentrated epidemics, where HIV is very low in the general population but has spread rapidly in key populations such as sex workers[10]. Across these HIV epidemic contexts, as the overall number of new HIV infections reduces as a result of interventions new infections become more concentrated in key populations defined by UNAIDS to include injecting drug users, men who have sex with men, and sex workers and their sexual partners.

Recent UNAIDS estimates for 2019 show that 62% of new HIV infections globally were in key populations despite these populations being only a relatively small proportion of the general population[4]. However, key populations accounted for 28% of new infections in 2019 in eastern and southern Africa, the region most affected by the HIV epidemic. In this region, sex workers have a disproportionately high HIV prevalence compared to other key populations (Figure 1.1). In addition, sex work remains a key HIV epidemic driver sustaining the transmission of HIV and other sexually transmitted infections in the region[11-15]. This is primarily because of the transmission dynamics where an infection of HIV or other STIs can quickly lead to multiple infections including secondary transmissions because of the high rates concurrent sexual relationships.

Figure 1.1 HIV prevalence by key populations in eastern and southern Africa, 2015–2019

Sex work is commonly defined as the exchange of sexual services for money, favours, or goods[16,17]. In sub-Saharan Africa, it can be difficult to differentiate “sex work” from the more common and socially acceptable “transactional sex”. Social science and epidemiological reviews of literature on sex work and transactional sex in sub-Saharan Africa suggest that in “sex work” the sexual services are immediately compensated and explicit, while the material gains in “transactional sex” are usually implicit, not necessarily tied directly to the sex and often there is emotional intimacy[18-21]. Sex work in the region is diverse and takes various forms with entertainment places such as bars, hotels, and streets being the predominant locations for soliciting clients[20].While some people might easily self-identify as sex workers, others who have paid sex with non-intimate partners might be reluctant to self-identify as “sex workers” or do not consider themselves as “sex workers” although they could overtime self-identify as sex workers[22]. In particular, people might not self-identify if they occasionally sell sex in exchange for money, have a limited number of regular partners providing material or cash support, or are employed in entertainment places but supplement incomes with paid sex to patrons. A respondent-driven sampling survey of 2387 young women who sell sex conducted in 2017 in Zimbabwe found that although young women who were reluctant to self-identify as sex workers were less likely to access services, they had similar HIV risk determinants as those who self-identified as sex workers[22].

Systematic reviews have consistently showed sub-Saharan Africa as having the highest HIV prevalence among female sex workers (FSWs) globally[11,23,24]. In the most recently updated estimates up to September 2017, the HIV prevalence was 33.3% (95%CI: 29.2-37.6%) from 15 eastern and southern Africa countries, and 20.1% (95%CI: 16.7-23.8%) from 14 west and central Africa countries[24]. This implies that FSWs are more likely to be living with HIV than women of reproductive age in the same populations: 4.5 times more likely in eastern and southern Africa and 8 times in west and central Africa.

Although recent HIV incidence data among FSWs in sub-Saharan Africa remain sparse, the most recent estimates indicate that HIV incidence is still high. For example, in the Zimbabwe's National Sex Work programme data covering all provinces, HIV incidence among FSWs was 9.8/100 (95%CI: 7.1-15.9) person-years of observation (PYR) in clinic visits between 2009 and 2014[25]. In Tanzania, HIV incidence based on data from a cross-sectional sample of 1914 FSWs recruited in 2013 from 7 geographical regions was estimated at 12.6/100 PYR (CI not reported)[26]. In cohort studies from other eastern Africa countries, HIV incidences were: 3.5/100 (95% CI: 1.6-5.4) PYR at the one-year follow-up in Rwanda (recruitment between October 2006 and August 2007)[27], and 4.8/100 (95% CI: 4.2-5.5) PYR after a median of 16 months in Kenya (recruitment: 1993-2007)[28]. In the Ugandan cohort study on which this thesis is based, HIV incidence between 2008 and 2010 was estimated at 3.7/100 (95% CI: 2.7-5.0)[29].

The high HIV incidence among FSWs implies that FSWs are at an elevated risk of HIV exposure. While the high turnover of sexual partners increases the cumulative risk of HIV acquisition among FSWs, it is also likely to facilitate rapid onward transmission to other sexual partners for every new infection where condoms are not correctly and consistently used[14,20]. Further, persons in extended sexual networks containing FSWs and their clients are subsequently at risk of HIV and other sexually transmitted infections (STIs). For example, qualitative studies among regular and intimate sexual partners of FSWs have reported low condom use within these relationship, and may have other concurrent sexual partners who are at risk due to this[30,31]. Therefore, urgent and effective prevention and control of HIV infection among FSWs is needed to reach the global epidemic control[3,32].

1.1.3 HIV epidemic and sex work in Uganda

Uganda has a mature generalised HIV epidemic with an estimated 1.5 (95% CI: 1.4-1.6) million people living with HIV in 2019[33]. HIV prevalence is estimated as 7.5% (95% CI: 6.9-8.1) among women and 4.3% (95% CI: 3.9-4.7) among men aged 15-49 years according to the Uganda Population-Based HIV Impact Assessment (UPHIA) survey conducted between 2016 and 2017[34]. The most recent HIV prevalence suggests some decline from that reported in the 2011 Uganda Aids Indicator Survey (8.3% and 6.1% for women and men, respectively) which used similar methodology to UPHIA[35]. Besides HIV prevalence being higher in women than men, women living in urban areas have a higher HIV prevalence than those in rural areas (9.8% in urban areas, 6.7% in rural areas). The number of new HIV infections among adults has decreased from an estimated 80,000 in 2011 to 46,487 in 2018 according to The Uganda HIV and AIDS Country Progress Report 2019[8]. The declines have been mainly attributed to an intensified combination of HIV interventions at the general population level including: behavioural change communication and provision of condoms, HIV testing and counselling, and provision of safe male circumcision services, accompanied by increased ART coverage[36,37]. The adoption of the initiative to treat all persons living with HIV regardless of disease stage and the recent introduction of pre-exposure prophylaxis (PrEP) particularly for key populations could further decrease HIV incidence once widely available and sufficiently used[38]. By March 2018, only an estimated 3000 people are recorded to have received PrEP which had been introduced in 35 sites in Kampala and Wakiso district[8].

The Uganda National HIV strategic plan 2015-2020 has recognised key populations including FSWs as critical in the country's HIV control[39]. Whereas HIV prevalence is high among key populations that commonly overlap with sex work (i.e fisher folk (22%), truck drivers (25%), and uniformed personnel (18%)), it is disproportionately higher among sex workers[39]. A systematic review of epidemiological data on FSWs in Uganda up to March 2015 estimated that between 32% and 52% of FSW were living with HIV in 7 identified studies; 3 in Kampala, 1 in south-western and 3 in northern Uganda[40]. Thus, HIV prevalence among FSWs is estimated to be 4-7 times that among adult women in the general population. Further, the Uganda Modes of Transmission (MOT) analyses estimated 11% of all new infections in 2008 to have been due to sex workers, clients and their other sexual partners[41]. The MOT estimates are based on a static mathematical model computing the fraction of all new HIV infections that is acquired by a specific risk group[42]. Specifically, the adult population is divided into risk groups and parameterized using data on population sizes of each risk group, their prevalence of HIV and other STI as well as sexual behaviour[42]. However, arguments against the MOT method suggest that it underestimates the contribution of sex work in sub-Saharan Africa, particularly in the medium to long-term[14,43]. Mishra and colleagues have provided alternative estimates of new HIV infections due to sex work as 14%-38% in sex work settings with moderate-to-high condom use, or 60%-88% in settings with no interventions, using model simulations with data from Kenya, Burkina Faso and Benin[43].

Contextual factors contribute to the vulnerability of sex workers to HIV infection. Using multiple data sources, the Uganda AIDS Commission estimated a population size of about 55,000 FSWs in Uganda[44] while a survey using capture-recapture methods estimated 3.3% of the female adult population in Kampala (between 10,000 and 16,000) to be FSWs[45]. This is likely to be an under-estimate since FSWs are a socially stigmatized and hidden population. Some women are engaged in sex work through formal organised structures (for example, in brothels or massage parlours) while others work independently, solicit sex through mobile phones, and combine sex work with other work[46,47]. However, sex work based around entertainment places (bars and/or night clubs) is most dominant, with that in lodges and on the street also common, particularly among those who are young and new to sex work[46,47]. According to the Uganda Penal Code, sex work is criminalised, with both the selling and buying of sex, and sex work-related activities such as facilitating sales, brothel ownership or pimping considered illegal[48]. Socially, sex workers are also stigmatised and discriminated against in addition to experiencing a high prevalence of rape and client-initiated gender-based violence (GBV)[30,49].

1.1.4 Determinants of HIV infection among sex workers

Several interrelated factors underlie the heightened HIV risk among women who sell sex, particularly in sub-Saharan Africa. While most of these factors relate to the context within which sex work takes place, the contextual factors act through proximate determinants such as behavioural characteristics, which in turn influence biological HIV determinants[20,50,51]. Biologically, HIV is transmitted when there is an unprotected sexual or blood contact with a person living with HIV who has unsuppressed HIV viral load[52,53]. However, the number of unprotected sexual contacts with a person living with HIV ("effective sexual contacts") increases the cumulative risk of HIV transmission to a susceptible individual. FSWs are characterised with having several sexual relationships with casual, regular and intimate partners, concurrently and over time[20]. While data on HIV prevalence among male partners to FSWs is limited, social science studies have reported that male partners often engage in high risk sexual behaviour including having multiple partners, high alcohol use, and inconsistent condom use[30,54]. These reported behaviours might suggest a high background of HIV prevalence among male partners to FSWs, which can expose HIV-negative FSWs to many effective sexual contacts.

The high prevalence of STIs among FSW in sub-Saharan Africa likely elevates the efficiency of HIV acquisition per sexual act with effective contacts[20,26,55,56]. A systematic review of behavioural risk factors of FSWs in sub-Saharan Africa reported that between half and two-thirds of FSWs had a curable STI at any given time, while 30% had reactive syphilis results and at least 10% had an active ulcerative STIs[20]. In Uganda and other settings, ulcerative STIs such as herpes simplex virus type 2 have been characterized to be common among FSWs (for instance, 80% in Uganda and 60% in Tanzania) and to substantially increase the risk of HIV transmission through increased viral shedding[26,57,58]. Overall, concurrent STIs increase HIV risk through three main biological mechanisms: (i) by disrupting the epithelial surface of the genital tract facilitates access to target cells beneath, (ii) through blood contact through ulcerating STI, and (iii) by increased viral shedding in the genital tract[59,60]. Therefore, concurrent STIs are likely to contribute substantially to the disproportionate HIV burden among FSWs, which underlines regular screening and treatment as a critical component of HIV programming for FSWs.

At the individual level, sexual behaviours influence HIV risk through having direct effects on the biological mechanisms discussed above: i.e exposure to effective sexual contacts and efficiency of HIV acquisition per contact due to presence of an STI or condom use. For example, where a susceptible individual has been exposed to an HIV infectious person the use of a condom can physically limit efficiency of HIV acquisition. Systematic reviews of effectiveness of condom use in HIV sero-discordant heterosexual couples globally have concluded that always using condoms reduced the risk of HIV transmission by between 70% and 95% when exposed to HIV but studies did not account for the correct use of condoms[61-63]. Among FSWs, however, correct and consistent condom use is typically difficult to achieve and maintain because of a combination of individual, interpersonal and other contextual factors. For example, FSWs have reported depending on substances to cope with the difficult work environments and the stigma associated with sex work[47,64-66]. However, substance abuse is associated with negative health consequences such as poor decision-making in sexual interactions, physical and sexual violence, incorrect and inconsistent condom use, and consequently HIV incidence[29,49,65,67-70]. In addition, FSWs have reported inconsistent condom use because clients often offer higher payment for condomless sex[20,50].

At the contextual level, the social stigma, criminalisation of sex work and mobility are key determinants of HIV risk among sex workers. This adverse social environment fosters high rates of physical and sexual violence and other long-term effects such as depression and mental illness associated with violence[20,70,71]. In addition, sex work is characterised by high mobility of sex workers (in search of new opportunities) and sometimes their clients (such as truck drivers)[20,50]. The effect of mobility on HIV risk is mainly modified by the epidemiological context (i.e. prevalence of HIV, STIs and sexual behaviour) of the environments to which sex workers have moved[50]. While mobility could affect the probability of exposure to an infected person, it could also interrupt access to targeted prevention services including STI management, HIV counselling and testing, and access to condoms[72]. Such contextual factors as discussed above can influence the proximate HIV determinants at individual and partner-levels, which in turn affect the more direct biomedical determinants, consequently impacting on HIV acquisition. Therefore, HIV control in sex work requires identifying and scaling up combinations of interventions that can act at multi-levels of HIV risk determinants.

1.1.5 HIV prevention interventions for sex workers

A range of interventions exist to reduce the risk of HIV infection among FSWs. Evidence in different settings suggests that HIV interventions targeting FSWs are most effective when individual biomedical, behavioural, and socio-structural components are combined and context-specific[73-78]. While these components of prevention programmes are mainly targeted at affecting proximate determinants such as inconsistent condom use and STI coinfection, the ultimate effect is biological: reducing efficiency of HIV transmission, exposure to HIV, and infectiousness of STIs or HIV if already infected. Given that FSWs often continue to have several concurrent sexual partners, systematic reviews have consistently identified priority HIV interventions as those that subsequently reduce efficiency of transmission such as STI management, condom promotion and distribution, and risk-reduction counselling (i.e reducing hazardous alcohol use)[73,74,76,77,79].

For STI management, no primary study has yet sufficiently demonstrated clear evidence for effectiveness of STI management on HIV risk among FSWs[80-85]. In 1995, a community randomised controlled trial (RCT) in Mwanza, Tanzania (where about 10% of the study population were sex workers or bar workers) showed that HIV incidence reduced by 38% (95%CI: 21%-58%) in the intervention communities offered syndromic STI management compared to control communities during a two-year follow-up period[86]. Other authors have also suggested that STI screening and treatment included in targeted HIV prevention packages might have contributed substantially to the reduced HIV prevalence or incidence among FSWs after introducing intervention studies for controlling sexually transmitted diseases[72,77,79].

Biomedical interventions could be critical components of targeted HIV programmes once incorporated into existing prevention packages for FSWs, by substantially reducing the efficiency of both HIV acquisition and transmission. Few studies to date have evaluated the effectiveness of ART-based biomedical interventions (pre- and post-exposure prophylaxis) among FSWs, but there is strong evidence of effectiveness in discordant couples, and men who have sex with men[87-89]. A comprehensive review of HIV prevention interventions which could be applicable to FSWs found the effectiveness of PrEP to range from 39% to 75% in populations that did not explicitly enrol FSWs but included women[73]. Several African countries including Uganda have recently started phased rolling out of PrEP for populations at substantial risk in their national HIV programmes, but coverage remains low to yet have a substantial impact on new HIV infections[4,8]. In Uganda, at least 3000 people at high risk of HIV had received PrEP by March 2018 from 35 sites in Kampala and Wakiso district, but these have been slowly expanded to other regions since then[8]. While acceptability of PrEP has been reported to be high once FSWs become aware of it, there are barriers that could affect PrEP uptake and adherence including: stigma because of its resemblance of HIV pills, concerns about side effects, and the requirement for daily use[90-92]. Nevertheless, integrating PrEP into existing primary prevention and treatment services could lead to increased impact of sex work programmes in the control of HIV.

In addition to sex worker-focused interventions, HIV prevention among FSWs can also benefit from the reduced HIV infectiousness among their non-paying and men who commonly buy sex such as long-distance truck drivers, uniformed personnel and fisher folks in Uganda. However, there is limited epidemiological data relating HIV interventions among sexual partners of FSWs and HIV prevention among FSWs. But population-based longitudinal studies in eastern and southern Africa have shown differential impacts of intensive combination HIV prevention efforts between men and women, which is mainly explained by differences in engagement with HIV prevention and treatment services[93,94]. In these studies, women were more likely than men to test for HIV, initiate ART early and sustain treatment to achieve viral suppression, which resulted into steeper HIV incidence declines over time among men than women in both Uganda (54% vs 32%) and South Africa (62% vs 34%)[93,94]. Similarly, the risk of HIV acquisition among FSWs in high HIV prevalence settings might decrease further by reducing HIV incidence and the infectiousness of clients and other sexual partners through, say, improved viral suppression and voluntary medical male circumcision.

Behavioural interventions have also been found to be effective in HIV prevention among FSWs in low and middle-income countries, typically enabling correct and consistent condom use, peer education on sexual health, HIV counselling and testing and reducing alcohol and drug use[73-77,95]. In sub-Saharan Africa, the most recent systematic review of HIV interventions among FSWs published in 2017 identified 25 epidemiological studies, of which all included peer educators and the provision of condoms[74]. Specifically, reported consistent condom use among FSWs was increased as a result of venue-based condom distribution, peer-led condom promotion sessions including the use of social media platforms and short message services. Specifically, observational studies in sub-Saharan Africa have consistently found evidence for an association between increased reported condom use and a reduction in either STIs or HIV infection among FSWs[82,84,85,96-99]. In addition, WHO brief interventions for hazardous and harmful alcohol use were effective in reducing self-reported alcohol misuse, sexual violence, and increasing reported consistent condom use, as observed in RCTs among sex workers in Mombasa (Kenya)[93,94] and Pretoria (South Africa)[100]. For example, in the Kenyan study of 818 FSWs identified as hazardous or harmful drinkers, the intervention of six sessions of alcohol harm reduction counselling every month was associated with a substantial reduction in self-reported alcohol use[101], and sexual violence from clients[101,102], and a reduction in engagement in sex work[102].

Cumulatively, evidence now recognises that the effectiveness of behavioural and biomedical interventions among FSWs can be modified by contextual factors, highlighting the need for social and structural interventions[50,78,103,104]. These social-structural interventions to address underlying factors vary greatly including: mobilising sex workers to act together through peer educators, community ownership involving police and legal systems, ensuring sustainability of resources for mass condom distribution, and providing sex-worker-friendly health services in order to improve service access and utilisation[103-107]. Broadly defined as community empowerment, these approaches have been found to be effective for HIV prevention in systematic reviews and meta-analyses of studies among sex workers in low and middle income countries[24,50,78,106]. In particular, community empowerment-based HIV prevention interventions were associated with a more than three-fold increase in the odds of reported consistent condom use with clients as well as a one-third reduction in the odds of HIV infection among FSWs[106]. However, the influence of community mobilisation on the effectiveness of individual-level interventions remains to be better understood. In Africa, however, systematic reviews of community empowerment for FSW-targeted interventions have found that these approaches have been typically limited to peer-education and engagement of communities, but little on community ownership[78,105]. Recently initiated studies on community empowerment interventions in sub-Saharan Africa such as "Project Shikamana" are likely to provide much needed evidence for their delivery and effectiveness in this setting[108].

1.1.6 Regular attendance of targeted HIV services for sex workers

The accelerated downward trajectory of HIV in key populations will depend on sustaining adequate geographic coverage and intensity of targeted cost-effective services[14,109,110]. As such, the limited coverage and scope of sex work-focused HIV services in most of Africa calls for an urgent scale-up of targeted comprehensive HIV prevention, testing, and treatment[111]. Among people with ongoing HIV risk, however, not only should effective interventions be available, affordable and acceptable but there is need to sustain the demand for these interventions to support consistent use of prevention practices[112,113].

Peer-mediated combined HIV prevention packages for FSWs are conventionally delivered through clinic facilities, perhaps because of the convenience of offering multiple services in a single facility[114]. Given that the prevention needs for FSWs are likely to vary and change over the long-term, consistent prevention practices and use of biomedical interventions require the regular contact of FSWs with service providers. World Health Organization (WHO) recommends that sex workers should test for HIV at least annually for early diagnosis and if HIV-negative, to receive ongoing health education[115]. While HIV testing is a key component of combined HIV prevention package, in practice it has usually been emphasised as an entry point into HIV care and treatment services[116]. Thus, studies about the engagement of FSWs with HIV services have mainly focused on reaching UNAIDS 90-90-90 targets[117-121]. Although adequate engagement with HIV care services can foster better health for FSWs and reduce transmission to sexual partners, several researchers have argued that focusing on effective HIV treatment alone is not sufficient to accelerate declines in HIV infections[6,110]. For a sustainable HIV response in sex work, the focus on effective HIV treatment requires an equally effective ongoing exposure of sex workers and their clients to targeted prevention services.

Experience from targeted HIV programmes and empirical data has shown that ongoing exposure of FSWs to interventions can be limited by sub-optimal attendance to clinic-based services[25,28]. FSWs can fail to attend HIV services, attend services irregularly, or withdraw from targeted HIV programmes over a variety of reasons including: stigma and discrimination faced in health care settings, high levels of mobility, unfamiliarity with available services, low risk perception, and hazardous alcohol use[11,72,114,122]. Although loss to follow-up is usually acknowledged in cohort studies as likely to lead to biased HIV incidence estimates, the epidemiological consequences of inconsistent exposure to HIV prevention services among women at high risk of HIV have received little attention and hence, not fully understood. The insufficient attention given to facilitating women at high risk of HIV acquisition to regularly engage with health services might be partly due to there being limited empirical data[117,119,120]. To reinforce the importance of consistent exposure to effective interventions, it might be necessary to demonstrate how prolonged duration without attending targeted HIV services is associated with subsequent increase in HIV risks, and possible pathways of risk.

1.2 Study rationale

The UNAIDS HIV prevention 2020 framework considers adequate coverage and consistent use of effective interventions in populations at the greatest HIV risk as critical to reaching the global target of 200,000 new adult infections by 2030 from 2 million infections in 2010[110,123]. If the epidemiological consequences of inconsistent exposure to HIV prevention services among women at high risk are better understood, an important feature of targeted HIV programming can better be strengthened. When women at high risk are consistently exposed to targeted interventions, there can be opportunities to reinforce messages for safe behavior and to detect and treat STIs earlier[76,77,124]. In addition, regular testing for HIV can facilitate early diagnosis of HIV and initiation of ART. Thus, strengthening the consistency of exposure to combination HIV prevention either at the clinic facility or through mobile clinic outreach could maximise the impact of sex work HIV programming.

By understanding how individual proximate determinants such as condom use or detection with an STI change after missing visits to a dedicated clinic facility, we could assess whether the intervention is sustainable during interruptions in exposure. In addition, this enables us to identify which components of the HIV package might be sustainable despite intermittent clinic attendance. In addition, this association of missing a visit and subsequent proximate determinants aids in identifying possible pathways for increased risk of HIV infection and consequently, enable better delivery of targeted interventions.

Given that the targeted HIV programme offered a wide range of services for women at high risk of HIV infection, tying the characteristics of participants associated with attending subsequent visits to services offered can clarify key programme components that facilitate subsequent clinic attendance. This knowledge should guide the design, implementation of effective programmes and efforts to intensify comprehensive HIV programmes for women at high risk of HIV infection resulting into improved HIV-related outcomes.

1.3 Overall aims and objectives

The aim of this thesis is to examine the effect of irregular exposure to a package of interventions to prevent HIV acquisition on HIV risk among women at high risk of HIV. To better understand this relationship between regular exposure to interventions and HIV prevention, I examined the influence of missed scheduled visits on HIV incidence trends, on individual-level HIV risk, and on key proximate risk determinants - inconsistent condom use, STIs, and daily alcohol use.

This aim is addressed by analysing longitudinal cohort data with repeated measures collected in an HIV programme for women at high risk of HIV in Kampala, Uganda (The Good Health for Women Project)[57]. The high-risk women were predominantly self-identified sex workers, and women working in entertainment settings such as waitresses in bars or night clubs, who have sex in exchange for money.

The findings in this thesis can contribute to efforts for maximising the impact of HIV interventions over time and strengthening HIV programming for women at high risk of HIV. For example, an increase in a risk determinant (e.g. STI incidence or inconsistent condom use) after interrupting exposure to HIV interventions would highlight the need to facilitate regular exposure to the intervention for high-risk women, for example through increased use of mobile clinics.

Specific objectives

The specific objectives are:

Objective 1: To examine the trends in HIV incidence and key HIV risk determinants among women at high risk of HIV enrolled and scheduled to attend clinic services once every three months within the Good Health for Women Project between March 2008 and August 2017. In interpreting the HIV incidence trends, I assess the influence of missing scheduled visits and participant attrition over time.

Objective 2: To investigate the association of the number of missed scheduled clinic visits between two successive visits attended with subsequent HIV risk among women at high risk of HIV enrolled and followed-up in the Good Health for Women Project between March 2008 and August 2017.

Objective 3: To investigate the association of the number of missed scheduled visits between two successive visits attended with and subsequent key determinants of HIV risk (sexually transmitted infections (STIs), alcohol use, inconsistent condom use with paid sex) among women at high risk of HIV enrolled and followed-up in the Good Health for Women Project between March 2008 and August 2017.

1.4 Structure of thesis

This thesis is organised following the research paper style format. Chapter 1 and Chapter 2 provide the background and a review of peer-reviewed literature on routine exposure to HIV interventions among female sex workers, respectively. Chapter 3 presents an overview of the Good Health for Women Project (GHWP) study on which the articles in this thesis are based. This chapter describes the study population, enrolment and follow-up procedures, and the components of the targeted HIV prevention and treatment offered through the GHWP.

Chapters 4-6 incorporate the research articles presenting the key results of this thesis which address the objectives of the thesis. Since each research article was prepared independently, some of the information is inevitably repeated across the articles. The text of the articles in this thesis is as published, but references to tables and figures have been edited to represent the broader chapters in which they are presented. In a few cases, words have been edited to allow the thesis to be coherent.

The references of the articles have been maintained as stand-alone at the end of the articles for ease reference. However, references from other sections of the thesis which are not part of the research articles are combined into a general reference chapter (Chapter 8).

Lastly, Chapter 7 brings together the findings from preceding chapters to provide an overview of the significance and implications findings for HIV prevention among women at high risk of HIV infection and estimating the timing of HIV seroconversion in assessing HIV incidence in the presence of intermittent attendance HIV testing.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

In this chapter, I review and synthesise research on indicators to measure exposure to HIV interventions among FSWs, and the relationship between these measures of exposure and HIV prevalence and incidence. In addition, I assess the evidence for the relationship between the measures of exposure and proximate determinants for HIV risk: STIs, reported consistent condom use and alcohol use.

2.2 Regular exposure to HIV prevention and treatment services

As discussed in chapter 1, sub-optimal exposure to HIV interventions for women at high risk can reduce the impact of effective interventions for prevention and treatment of HIV. In HIV-positive individuals, indicators for exposure are typically related to the steps of the HIV care cascade such as whether the individual knows her HIV status, are in care, initiated on ART, or retained in care[118,125-128]. For example, in a systematic review on the engagement of FSWs living with HIV along the HIV care cascade, Mountain et al. identified 39 studies globally, of which 24 were from 5 African countries that included at least one element of the cascade: ever ART use, current ART use, post-ART loss to follow-up and death, adherence to ART, and viral suppression[125].

In HIV-negative FSWs, studies in sub-Saharan Africa have argued that substantially impacting HIV infection requires targeted geographic and most-at-risk coverage, as well as adequate intensity through combining intervention components[14,77,129]. FSWs in high HIV transmission settings also require regular exposure to effective interventions given that they have an ongoing risk of being exposed to an infectious sexual partner. I define exposure to an HIV intervention to occur when there is contact between a FSW and providers of HIV services or peer facilitators ultimately aimed at influencing at least one proximate determinant for HIV infection among FSWs. In the context of sustained HIV prevention over time among FSWs, consequences of irregular exposure to effective interventions following an initial contact with targeted HIV programming remain to be well understood.

2.3 Measurement of HIV intervention exposure among female sex workers

2.3.1 Systematic search strategy

In this review, I aimed to examine whether there was a relationship between indicators for exposure to HIV prevention interventions and either HIV infection or key proximate HIV risk determinants (STIs, consistent condom use with paid sex, and alcohol misuse) among sub-Saharan African female sex workers. To do this, I followed guidelines from the preferred reporting items for systematic review and meta-analysis (PRISMA) checklist. I carried out a systematic search on the 20th December 2018 for peer-reviewed published articles on HIV prevention interventions among FSWs in sub-Saharan Africa in PUBMED and EMBASE. For each bibliographical database, both Medical Subject Headings (MeSH) and free-text words were used. The following key search terms were used (sex work OR sex workers OR female sex workers OR FSW OR Commercial sex workers OR CSW OR high risk women OR women at high risk) AND (visits OR sessions OR events OR intervention) AND (HIV OR incidence OR prevalence OR consistent condom use OR STI OR alcohol) AND (Africa). Initially, relevant articles were required to have an indicator to measure exposure to HIV prevention interventions, and outcomes of either HIV infection or HIV risk determinants. However, individual intervention studies identified were further examined for an indicator to measure of exposure to interventions among FSWs given that these studies were scarce.

Eligibility criteria were: i) articles in which authors compared either HIV prevalence or incidence, or HIV risk determinants, by an indicator measure of exposure to an HIV intervention strategy; ii) quantitative data analysis based on cross-sectional, case-control, or cohort designs; iii) publication by December 2018. There were no restrictions by whether the article was based on survey, population or facility data. Reference lists of systematic reviews on the effectiveness of HIV prevention interventions among FSWs in sub-Saharan Africa were searched to identify additional eligible papers.

2.4 Systematic search findings

The search strategy identified 57 potentially eligible studies. Examination of the full text of the eligible studies and additional papers from systematic reviews identified 10 of these as eligible (Figure 2.1). For articles using the same measure of exposure and study population, only one of the articles with more informative data was selected. The 10 studies came from: Kenya (4), Democratic Republic of Congo (1), South Africa (1), Cote d'Ivoire (1), Uganda (1), and Zimbabwe (2). Five were prospective studies, one was a cohort analysis of programme data for FSW consultations with no scheduled visits but participants were encouraged to attend every 6 months, and 4 were post-intervention cross-sectional surveys.

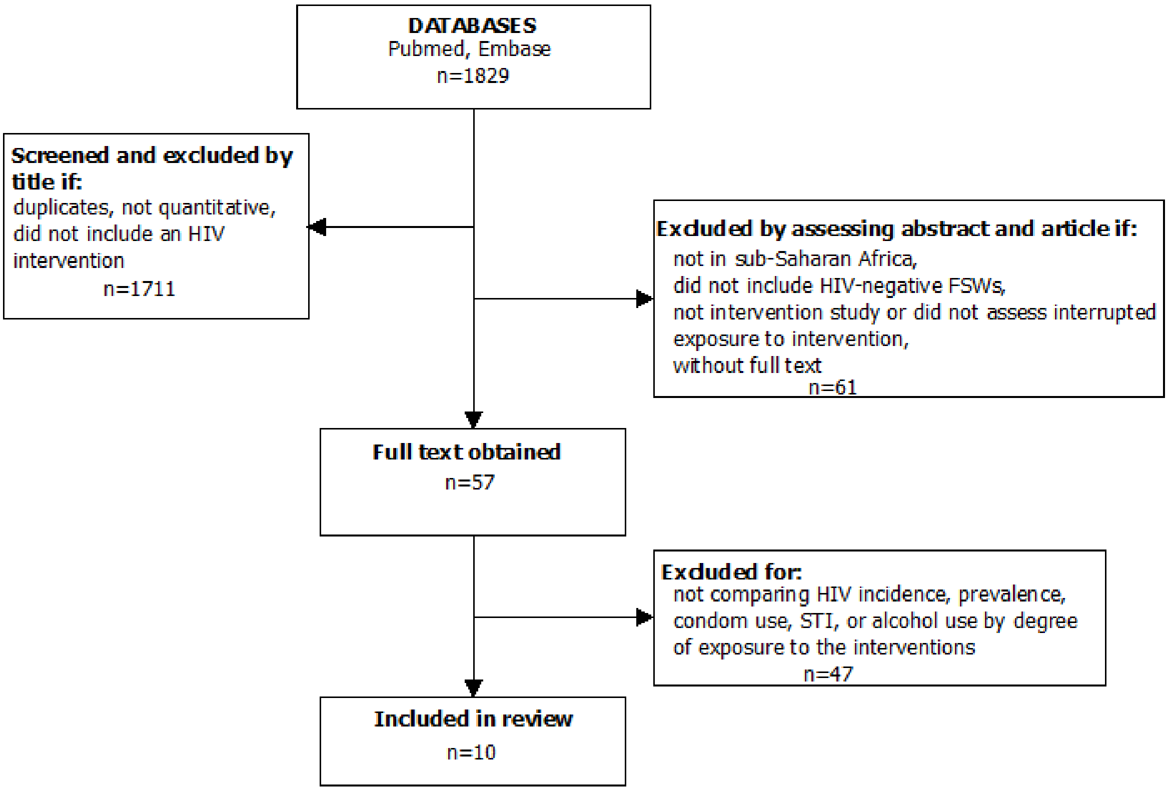

Figure 2.1: Flow chart for systematic selection of studies which reported an indicator to measure exposure to HIV prevention interventions among female sex workers in sub-Saharan Africa.

2.4.1 Exposure to HIV interventions defined

From the literature search, a limited number of studies on HIV interventions among FSWs reported on an indicator to measure exposure levels to a given intervention. From the studies identified, FSWs had contact with HIV services from through attending at least one of the following: a static clinic facility, drop-in centre, mobile services, outreach services, or homes of FSWs. FSWs who attended a dedicated static clinic facility were offered a wider range of health services than at outreach services, which included risk reduction counselling, HIV testing, STI screening and treatment, as well as condom promotion and provision. While outreach services limit the range of health services that can be offered, they can enable reaching FSWs who are unable to attend facility-based services due to various reasons. However, peer-mediated outreach services to venues where FSWs solicit clients were commonly used as a gateway for FSWs to attend static facility-based services but also to test for HIV.

The measures of exposure to HIV interventions were defined in varying ways across the studies. The variation in definitions was dependent on the study design and what components of HIV intervention were offered in the study setting. For example, while some studies considered the number of visits to a study clinic in a specific timeframe, the duration or gap between visits, or the proportion of all scheduled visits attended over the study period, others reported on having had a contact with a peer educator or number of peer-education sessions in a given timeframe.

2.4.2 Measures of exposure to HIV intervention in longitudinal studies

In five longitudinal studies, measures of exposure to HIV interventions were defined for each individual using her repeated visits to the study clinic (Table 2.1). In these studies, intervention exposure was defined in one of two approaches. First, as a proportion of the total number of scheduled visits to the clinic that were attended over the study period or within a specific timeframe for each participant[29,80,98]. The other approach defined intervention exposure using the duration between successive clinic visits attended by a given participant[28,82].

Defined elsewhere as `visit adherence'[130], the proportion of total number of scheduled visits attended by a given participant is the most predominantly used measure in longitudinal studies. This measure is usually expressed with the number of visits attended by the participant as the numerator and the total number of scheduled visits as the denominator[29,80,98]. As an example for `visit adherence', a longitudinal study of FSWs in the Democratic Republic of Congo (DRC) defined visit adherence for each enrolled participant over a 3-year observation period[98].Visit adherence was then categorised as ≥90%, 76-90%, 50-75% or <50% of the clinic visits. If each participant has large number of repeated visits attended or a similar number of expected visits, then small differences in the number of missed visits between participants do not substantially vary visit adherence. However, estimated visit adherence can vary substantially with small differences in the number of missed visits between participants if participants have considerably varying expected number of visits i.e are under observation for remarkably different durations.

A summary of visit adherence and its association with HIV-related outcomes would be appropriate for comparison between studies with similar clinic visit scheduling and study durations. Another key limitation for estimating visit adherence originates from varying patterns of visit attendance over time for an individual. An individual can attend visits regularly during some periods of study observation and irregularly during others. Allowing for the timing of visit attendance at different time-points instead of a cumulative measure enables to better understand the relationship of visit attendance with subsequent HIV-related outcomes. This relationship between a time-varying visit attendance and HIV-related outcomes is examined in this thesis.

In one study the measure of visit adherence was modified to measure exposure in the most recent timeframe[80]. In this longitudinal study of FSW in Côte d'Ivoire, FSWs had monthly scheduled visits for health talks, condoms and STD treatment, and HIV serological assessment every six months for a maximum of 42 months of follow-up. Intervention exposure was defined as the number of visits attended out of the five scheduled visits before their first and last assessment[80]. HIV incidence, the prevalence of STIs, and frequency of condom use reported at their last assessment were compared between women who attended at least 4 out of the 5 scheduled visits (80%) and those who attended three or less visits. Although this definition was used to assess influence of intervention exposure in the most recent time interval on HIV incidence, STIs, and reported frequency of condom use, it discarded exposure prior to most recent time interval. A participant can vary her attendance over the observation period, which could influence outcomes differently.

Two separate longitudinal studies among FSWs in South Africa and Kenya used the time duration between successive clinic visits attended by a given participant to define intervention exposure[28,82]. In both studies, participants were scheduled to attend clinic visits once every month. Defining intervention exposure this way allowed for a time-varying measure for each individual across the observation period. In the South African study where participants were given presumptive STI treatment every month at the clinic for nine months, Steen et al. defined a binary variable for intervention exposure showing whether the interval between successive visits was less or more than a threshold of 1.3 months[82]. Instead of the 1.3 months threshold, a Kenyan study which also scheduled monthly visits with up to 176 months of follow-up reported applying a threshold of 60 days[28]. Since defining exposure based on duration between successive visits requires only visits which are attended, this definition can be used in HIV programmes where there is no scheduling of visits. However, a measure of the duration since the last visit attended should be known.

In summary, intervention exposure in longitudinal studies can be defined as either a fixed proportion of visits attended over the study period or a time-varying measure representing the duration between successive visits for a given participant. While the fixed proportion provides a single useful summary over time, the time-varying measure of exposure at time-points is a more accurate reflection the extent of exposure over the study period.

Table 2.1: Summary of studies which reported on a measure of exposure to HIV prevention interventions among female sex workers in sub-Saharan Africa

First Author/ Location	Sample definition	Design	Sample size/ study duration	Frequency of visits/ HIV intervention and procedures	Primary objective of study	Measure of intervention exposure, timeframe/ analysis	Outcomes compared by measures of intervention exposure
Laga 1994[98] Democratic Republic of Congo (DRC)/ Congo, Kinshasa	Self-identified as FSWs	Prospective cohort	531 initially HIV seronegative FSWs followed for up to 3 years	Monthly follow-up visits. Monthly: interviews, individual health education, free condoms. 3-monthly: screening and syndromic management of STI, group sessions for condom promotion	Effect of a programme of STD treatment combined with condom promotion on HIV-1 incidence	Fixed variable: proportion of scheduled monthly appointments attended, over study period. 6-monthly HIV incidence Seroconversion assumed mid-point between first positive and last negative tests	HIV incidence: Attended ≥90% of their clinic appointments: 2·7/100 person-years; 76-90%:7·1/100 person-years; 50-75%: 20.3/100 person-years; <50% : 44.1/100 person-years; p<0·0001. Trends remained after controlling for reported condom use and number of clients. Overall HIV incidence 8·0/100 person-years. Condom use and STIs: Regular attendance associated with consistent condom use, regular STI management (crude analysis)
Ghys 2001[80] Cote d'Ivoire, Abidjan.	FSWs	Randomised Controlled Trial (RCT) intervention study. 273 in the intensive strategy, examined regardless STI symptoms; 269 in basic STD	542 HIV seronegative or HIV-2 seropositive FSWs from a cross-sectional study (October 1992-May 1994) followed up for up to 42 months.	Monthly visits where FSWs received health education talks, condoms and a new sexual activity log booklet, screened and treated for STIs. Then, every 6 months assessment of HIV/STD outcomes until a maximum of 42 months.	To determine impact of an integrated prevention approach on the incidence of HIV infection	Fixed variable showing the number of visits attended out of the five scheduled visits before their first or last outcome assessment.	HIV incidence: Attended ≥4/5 programmed visits before their last outcome assessment: 4.6/100 person-years, Attended ≤3/5:13.0/100 person-years; p=0.04. Overall HIV incidence: 8.5/100 person-years (95% CI:5.8-12.4) STIs (≥4/5 Vs ≤3/5 visits): C. trachomatis (1.2 versus 5%), N. gonorrhoeae (3.6 versus 9.8%), T. vaginalis (10.8 versus 9.8%), Genital ulcers (1.1 versus 0%).

		screening and treatment strategy	(n=220 with outcome assessment)				Reported consistent condom use (≥4/5 Vs ≤3/5 visits): (82.6 versus 79%)
Graham 2013[28] Kenya, Mombasa.	Female Sex Workers (FSWs) defined as women accepting cash or gifts in exchange for sex	Prospective cohort	1,513 HIV seronegative FSWs enrolled into the cohort during 1993-2007 with ≥1 follow-up visit	Monthly follow-up visits. Standardized physical examination, screening and syndromic management of STI, HIV testing. Risk-reduction counselling and free condoms for all.	Association between sexual risk behaviour and HIV incidence; influence of cohort attrition.	Time-varying indicator for whether a visit occurred after a gap in attendance of more than 60 days (no vs yes) (seroconversion assumed mid-point between first positive and last negative tests) Cox regression adjusted for potential confounders (Fixed and time-varying socio-demographic and behavioural characteristics).	HIV incidence: Gap in attendance>60 days Vs gap≤60 days (reference) aHR: 0.30 (0.22–0.42), p<0.001 (adjusted for fixed and time-varying characteristics). Overall HIV incidence 198/4150 person-years 4.8/100 person-years (95%CI: 4.2-5.5). Median follow-up time=16.2 months, range:0.4-176.8.
Steen 2000[82] South Africa, Free State mining town.	High-risk women included FSWs or reporting at least 3 regular/ non-regular multiple partners, recruited from entertainment places frequented by miners.	Prospective cohort	407 HIV seronegative and women living with HIV followed up for 9 months. The intervention conducted between October 1996-June 1997	Monthly interviews, examination and presumptive treatment for STIs at a mobile clinic, syndromic STI management, prevention education and condoms were offered. Peer outreach workers in recruitment and providing information on risk reduction, availability and advantages of services.	Assessing the impact of STD treatment and prevention services	Time-varying indicator of whether the interval between two successive visits was less than or at least 1.3 months. Repeated measurement analysis used to compare STD prevalence rates at follow-up visits to baseline rates.	Prevalence of STIs The prevalence of all STIs at follow-up were significantly lower than that at baseline for intervals between visits of <1.3 months

Vandepitte 2013[29] Uganda, Kampala	Self-reporting FSWs and/or employed in entertainment facilities (95% reported sex work)	Prospective cohort	646 HIV negative, Recruited April 2008-April 2009), median follow-up time of 2.1 years (range 0.1-3.0)	Once every 3 months visits, interviews, HIV counselling and testing, family planning, antenatal services, STI screening and syndromic treatment, primary health care	Determinants of HIV seroconversion and HIV incidence changes over time during follow-up	Fixed variable: proportion of scheduled monthly appointments attended over the study period Attended scheduled visits (%): 100%, 75-99%, 50-74%, 25-49%, <25% Seroconversion assumed mid-point between first positive and last negative tests	HIV incidence: 100% of visits attended: 3.2/100 person-years; 75-99%: 3.2/100 person-years; 50-74%: 4.3/100 person-years; 25-49%: 5.5/100 person-years <25% : 40.5/100 person-years; p=0·15.
Hargreaves 2015[25] Zimbabwe, All provinces	Participants self-identified as FSW consulting at an HIV programme	Ongoing HIV programme for FSWs: Sisters with a Voice" (Sisters) HIV prevention and sexual and reproductive health services	13,360 women, 31,389 visits to the Zimbabwe' s National Sex Work programme, 2009 – 2014 in 26 sites.	No active follow-up of participants FSW consultations and weekly outreach services: HIV testing, STI treatment, family planning, HIV prevention education, condoms, and legal services. Peer educators and community mobilization and empowerment activities. Group meetings once a month. HIV negative women were encouraged to retest every 6 months. At each consultation, data were collected on sociodemographic characteristics, HIV testing and ART history	To estimate HIV incidence and intervention uptake	Fixed variable showing whether FSW reported testing for HIV within 6 months before the first visit. Cohort analysis approach Seroconversion assumed mid-point between first positive and last negative tests	HIV incidence: 9.8/100 person-years (67 cases/686 person-years) HIV testing<6months: 7.3/100 person-years (95% CI: 4.9–13.4) ≥6 months: 11.0/100 person-years (95% CI: 6.9–20.8) Never:11.9/100 person-years (95% CI: 8.7-17.9) 9.8 per 100 person-years of follow-up (95% CI: 7.1 to 15.9)
Luchters 2008[131]	FSW (women	FSW consultation	Samples of 503 and 506	Peer-mediated one-on-one or weekly-group sessions,	To evaluate	Fixed variable: Reported number of peer-education	HIV prevalence: ≥4 sessions: 25%; 1–3 sessions: 34%

Kenya, Mombasa	who reported having received money or gifts in exchange for sex in the past year)	s and weekly outreach services	HIV seronegative and FSW living with HIV in 2000 and 2005, respectively	mostly in the houses of FSW or at a drop-in centre. Condoms, Voluntary counselling and testing (VCT) services and health information, education and communication (IEC) materials were distributed at drop-in centres and by mobile VCT services. Peer-educators referred FSWs for STI treatment. Study also included peer-mediated drama, role playing exercises, use of picture codes (visual images used for engaging discussion on sensitive topics) and video sessions.	the impact of five years of peer-mediated STI/HIV prevention interventions	sessions attended in the past six months: ≥4 sessions and 1–3 sessions. Crude prevalence Fitted logistic model for behaviour and STI outcomes, adjusted for age, marital status, education, place of work.	Consistent condom use (≥4 Vs 1–3 sessions): 93% (66/71) Vs, 80% (59/74) aOR:3.3 (95% CI: 1.0–10.8) ≤ 4 sexual partners in past week (≥4 Vs 1–3 sessions): 53% (39/74) Vs 30% (21/71), aOR:0.4 (95% CI: 0.2–0.9) Curable STIs; syphilis, gonorrhoea or trichomoniasis (≥4 Vs 1–3 sessions): 14% (10/69) Vs 22% (16/73)
Ndori 2018[117] Zimbabwe, Three sites: Mutare, Victoria Falls, Hwange	FSWs (reported exchanging sex for money in the past 30 days)	Respondent driven sampling survey at the beginning and after implementing intensified community mobilization activities. Ongoing “Sisters with a Voice” (Sisters) HIV prevention and sexual	Samples of 870 HIV seronegative and FSW living with HIV in 2011, 915 in 2015	Intensified community mobilization providing peer-delivered activities biweekly instead of monthly, additional peer educators, trained public sector health workers, monthly meetings with clinic staff and peer educators	To compare key indicators related to FSW health seeking behaviour and sexual behaviour in 2011 and 2015.	Fixed variable: Reported HIV testing ≤6 months among HIV-negative FSWs. Reported visiting the Sisters clinic ≤6 or 12 months. Reported contact with a peer educator ≤6 or 12 months. Reported receiving condoms from the Sisters clinic or peer-educators ≤12 months.	HIV prevalence: higher in 2011 than 2015 for Hwange and Victoria Falls (51.0% vs 41.3%; 69.6% vs 62.1%). In Mutare, 50.6% in 2011 and 63.7% in 2015. Consistent results after adjusting for socio-demographic factors The number of clinic visits steadily increased from 204 FSWs in 2010 to 3,130 in 2015; proportions of FSWs reported to have visited Sisters clinic in last 12 or 6 months: range 18.8%-31.6% in 2011, 47.0%-77.9% in 2015. Proportion reported to receive condoms from the Sisters clinic: Higher in 2015 than in 2011 Contact with a peer educator in the last 12 or 6 months: 31.1%-36.9% in 2011, 20.4%-30.3% in 2015.

		and reproductive health services				Reported being aware of their status, enrolled in HIV care, or on ART among FSWs living with HIV. Observed clinic visits attended at the Sisters clinic in each year. Prevalence comparisons between 2011 and 2015, logistic regression adjusted for age, duration in sex work and education.	Proportion of HIV-negative FSWs who reported having an HIV test ≤6 months across the 3 sites increased from a range of 13.4%-25.1% in 2011 to 78.1%-80.8% in 2015. Among FSWs living with HIV and aware: more likely to report being on ART in 2015 than in 2011 for Victoria Falls and Mutare. While no difference in Hwange Consistent condom use with clients in the past month: no evidence for a difference between 2011 and 2015.
Prakash 2018[129] Kenya, Nairobi.	FSWs (reporting to have exchanged sex for gifts, or materials or cash), recruited from settings known for sex work	Intervention cross-sectional surveys using snowball sampling; covered by HIV prevention programme for key populations in Nairobi implemented by the Sex Worker's Outreach Project (SWOP)	A sample of 1357 HIV seronegative and FSW living with HIV	Peer-led services providing health education, distributing condoms and lubricants, providing support at times of violence and refer them to the nine NGO-run and other government clinics currently offering prevention and care services in Nairobi.	To examine the relationship between FSW programme exposure levels and HV-related outcomes.	Level of exposure: (i) Intensive ("Yes" to all: contact with peer educators; received condoms through the programme; and visits to clinics exclusively meant for sex workers.); (ii) Moderate ("Yes" to one or two options); (iii) None ("No" to all options). Multivariate logistic regression was carried out.	Not exposed to any programme: 35% Moderate: 24% Intensive exposure: 41% Consistent condom use: FSWs with intensive programme exposure more likely to report consistent condom use with occasional clients (AOR: 1.57; 95% CI: 1.08–2.31) than FSWs with no (reference) STIs: to seek treatment for STIs (AOR: 3.37; 95%CI: 1.63–7.02) than FSWs with no (reference) or moderate exposure.
Ngugi 2007[132]	FSWs defined as women	Follow-up resurvey of participants	172 HIV seronegative women	During the RCT: monthly visits with antibiotic prophylaxis to prevent	To examine the	Comparison of trial and post-trial resurvey data on condom use	Condom use with clients: Individual changes in condom use with clients were sustained after trial termination, in fact, condom use continued

Kenya, Nairobi	reported to have received money or gifts in exchange for sex the last month	one year after termination of RCT.	participated in follow-up resurvey	STIs, peer- and clinic-based counselling, symptomatic and asymptomatic STI management, every 3 months HIV counselling and testing. After trial termination: Only quarterly peer-led FSW meetings continued, and distribution of condoms in sex work settings.	sustainability of behavioural changes after trial termination	(measurements based on semi-quantitative scale of 0-5)	to increase (from an average of 3.7/5 to 4.3/5; $p<0.001$).

2.4.3 Measures of exposure to HIV intervention in cross-sectional surveys

Two studies aimed to assess whether the reductions in risky behaviours observed during a given RCT (on the effectiveness of monthly STI treatment in preventing STIs) were sustained one year after completion of the trial[132,133]. To do this, individual-level behaviours were compared between the period of the trial and at the follow-up behavioural survey conducted one year later. The in-between period can be considered as an indicator of no or reduced intervention exposure after a period of intensive exposure to monthly interventions during the trial, which included monthly clinic-based counselling sessions, condom supply and STI testing and treatment. While with this indicator proportions of outcomes can be compared during and after the trial, there is no way to assess the association for the degree of intervention exposure with the outcomes.

Three cross-sectional studies assessed intervention exposure among women sampled from geographical settings where a targeted HIV intervention was offered[117,129,131]. Depending on the components of the targeted intervention and how frequently these were delivered, indicators for intervention exposure included reported number of clinic visits, reported number of times a participant was contacted by peer-educators or received condoms through the programme within a given timeframe[117,124,129,131]. For example, in one cross-sectional survey of 506 FSWs recruited using snowball sampling in Mombasa, Kenya intervention exposure was defined by the reported number of peer-education sessions attended in the past 6 months[131]. Outcomes of HIV prevalence, frequency of condom use, sexual partners in past week, and curable STIs (syphilis, gonorrhoea, trichomoniasis) were compared across unexposed participants, those who had attended 1–3 sessions, and those with at least 4 sessions[131].

In another example, four indicators of exposure to HIV services were examined among FSWs in three sites covered by the national Sisters with a Voice (“Sisters”) programme of Zimbabwe[117]. This programme offers free HIV prevention and clinical services to FSWs in Zimbabwe supported by a network of trained peer-educators[25,134]. Intervention exposure was compared between two respondent driven sampling surveys with sample sizes of 836 FSWs in 2011 and 913 FSWs in 2015[117]. The indicators which were defined over the last 12 months in 2011 and over the last 6 months in 2015 included: having visited the “Sisters” clinic, had contact with a peer educator, and having received condoms from “Sisters” clinic. An additional indicator for intervention exposure in this study was self-reporting of HIV testing in the last 6 months. Such measures used in both examples for the Kenyan and Zimbabwean studies discussed above can be good proxies for intervention exposure in the most recent timeframe considered but ignore intervention exposure in the prior periods.

2.5 Measuring HIV intervention exposure in this thesis

In this thesis, I adopt the time-varying measure based on the duration between successive visits attended, as did Steen et al. in the South African study and Graham et al. in the Kenyan study[28,82]. This measure can allow the examining of changes in visit attendance within an individual over time since individuals can vary their attendance to HIV services over the study period. In addition, a time-varying measure over the observation period enables controlling for the effect of temporal changes in the characteristics of individuals while in follow-up as well as for autocorrelation that occurs with repeated outcome measures.

Whereas the measure for duration between visits only requires completed visits, it fails to explicitly account for the impact of missed scheduled visits on outcomes given the scheduling practices of the GHWP study. Although participants were scheduled to attend the GHWP clinic on a particular date, a visit window was used to determine whether the participant missed or attended the visit (14 days before and 76 days after the scheduled date). Participants were then traced if they missed two or more consecutive visits. Therefore, to account for missed visits I expressed the duration between successive visits in terms of the number of missed scheduled visits in that interval.

2.6 The relationship between interrupted intervention exposure and HIV infection

In this section, I review the relationship between measures of exposure to targeted HIV interventions and HIV infection among FSWs. Seven studies were identified which examined the relationship between an indicator of intervention exposure and HIV infection among FSW in sub-Saharan Africa[25,28,29,97,98,117,131].

2.6.1 The relationship between intervention exposure and HIV incidence

In 4 out of 5 studies with an outcome of HIV incidence, the findings suggest a negative association between a measure of exposure to HIV interventions and HIV incidence[25,29,80,98]. Only 1 of the 5 studies showed findings for an association between a time-varying measure and HIV incidence[28]. While this[135135135135135] study presented an adjusted association, all other 4 studies only showed HIV incidence across the categories of the measure of intervention exposure. Notably, none of the studies was specifically designed to examine measures of intervention exposure and HIV incidence.

In the Cote d'Ivoire study, HIV incidence was higher among women who attended <4 out of the 5 monthly visits before their last 6-monthly assessment than among those who attended ≥4 of the 5 scheduled monthly visits (13.0/100 versus 4.6/100 person-years, p=0.04)[80]. Only half of the participants were followed-up to at least one outcome assessment scheduled for every 6 months (284/542; 52%), indicating high attrition. The authors attributed the considerable attrition to high mobility among FSWs and the burdensome research procedures. High levels of attrition can substantially affect HIV incidence estimates if attrition is related to risk for HIV infection[136]. Further, the relationship of visits attended in the recent timeframe and HIV incidence may have been affected by confounding since the results were not adjusted for confounding. Furthermore, estimating HIV incidence by intervention exposure in the most recent timeframe only assumes that the risk of HIV acquisition during this period is similar across the study for all participants, which may not be the case. Hence, defining a time-varying intervention exposure over the whole observation period is likely to appropriate the varying risk of HIV over time.

After defining a time-varying measure of intervention exposure in the Kenyan study, durations of >60 days between successive visits were associated with reduced HIV risk when compared to durations of ≤60 days (adjusted hazard ratio=0.30; 95% CI:0.22–0.42; p<0.001)[28]. In this study of 1513 HIV seronegative women enrolled and followed-up the overall HIV incidence was 4.8/100 person-years (95%CI: 4.2-5.5). Of the women enrolled into the cohort, 64.0% were lost to follow-up after a median follow-up of 16.2 months. Although the authors did not suggest any possible reasons for the negative association of the duration between successive visits and HIV risk, it is plausible that women with a self-perception of being at lower risk might have found it unnecessary to consecutively attend scheduled visits. However, this finding should be interpreted with care since this study was not designed to examine intervention exposure, but rather the time-varying exposure was only adjusted for in the primary analyses. The time-dependent variables which were fitted in the multivariable model such as the behavioural characteristics and STI occurrence can be on the causal pathway to HIV risk (Figure 2.2)[137]. Therefore, time-dependent variables should be lagged in multivariable models examining the association between interrupted intervention exposure and subsequent HIV risk[138]. In addition, a dose-response relationship would have aided our interpretation of the study findings[137,139].

Although a fixed proportion of visits attended by a given individual was used as an indicator for intervention exposure, the DRC study found that HIV incidence was lower among those with a greater proportion of clinic appointments attended, which remained after adjusting for condom use frequency and number of clients. HIV incidence was 2·7/100 person-years among FSWs who attended ≥90% of their monthly appointments, 7·1/100 person-years with 76-90% attendance, 20·3/100 person-years with 50-75% attendance, and 44·2/100 person-years with less than 50% attendance (p-value for trend<0.001)[98]. The authors attributed this to more consistent condom use and earlier STI management among regular clinic attenders, but there is a possibility for selection bias. For example, HIV incidence can be over-estimated if participants at the most risk are also largely mobile and attend clinic appointments less often. Nevertheless, a similar finding for the dose-response relationship between the proportion of clinic appointments attended and HIV incidence was observed in the Ugandan cohort on which this thesis is based, although the wide 95% confidence intervals suggest low statistical power[29]. In the Sisters' HIV programme in Zimbabwe, HIV incidence was lower in FSWs who reported to have tested for HIV within the last 6 months at baseline than those who had tested more than 6 months ago or among those who had never tested[25]. HIV incidence was 7.3/100 person-years (95% CI: 4.9–13.4) in those tested within 6 months, 11.0/100 person-years (95% CI: 6.9–20.8) in those with at least 6 months ago, and 11.9/100 person-years (95% CI: 8.7–17.9) in those who had never tested for HIV[25]. However, assuming a fixed indicator for HIV testing does not allow for the possibility of varying levels of testing in different timeframes over time.

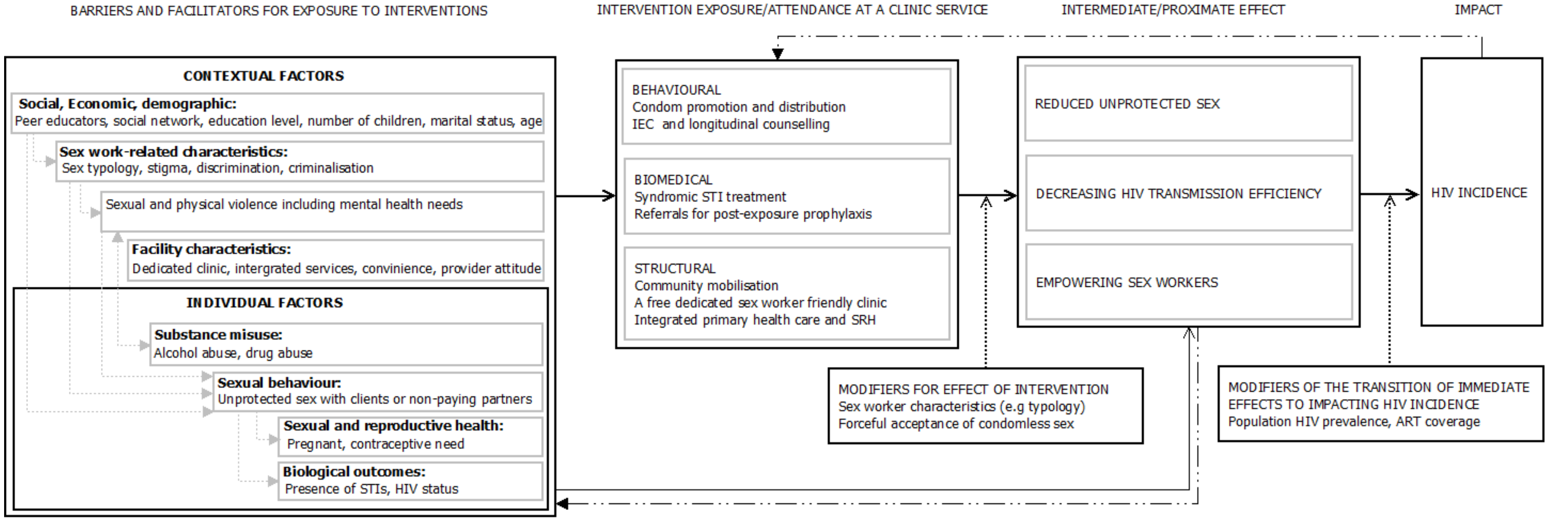

Figure 2.2: Conceptual framework for the relationship between intervention exposure through attendance at a clinic service and HIV incidence among women at high risk of HIV infection. Notes: STI-sexually transmitted infection; IEC-information education communication; SRH-sexual and reproductive health; HIV-Human Immunodeficiency Virus

2.6.2 The relationship between intervention exposure and HIV prevalence

Pre- and post- intervention cross-sectional surveys can provide further insights into the association between indicators for intervention exposure and HIV-related outcomes[7,57]. However, only one post-intervention cross-sectional survey examined the relationship between an indicator for intervention exposure and HIV prevalence, but the data appeared to be consistent with no differences. In this Kenyan survey conducted after five years of a peer-mediated intervention, FSWs who attended at least 4 peer-education sessions in the past 6 months appeared to have a lower HIV prevalence (24.6%, 17/69) than those with 1-3 sessions (34.3%, 25/73), and those without any peer-education sessions (34.8%; 124/356)[131]. However, the authors attributed the weak evidence for an association between peer-education sessions and HIV prevalence to a small sample size and potential confounding factors. Another key limitation might be that post-intervention cross-sectional surveys are subject to reverse causality[137]. For example, participants diagnosed with HIV might already be attending HIV care and see no need of regularly attend peer-mediated education sessions, which can over-estimate HIV prevalence among those with fewer education sessions.

The relationship between regular exposure to interventions and HIV infection is likely to be explained by changes in individual behavioural or biomedical factors. In the next sections, I discuss evidence for the relationship between indicators of intervention exposure and proximate HIV risk determinants of consistent condom use and STIs.

2.7 The influence of intervention exposure on subsequent consistent condom use

Four studies examined the relationship between at least one indicator for intervention exposure and condom use at the individual level[80,82,129,131].

At the individual level, three of four studies consistently reported that regular exposure (clinic visits and peer-educator sessions) was associated with a higher likelihood for reporting consistent condom use with clients. For example, the odds of reported consistent condom use with clients were 3 times higher (adjusted Odds Ratio (aOR)=3.3; 95%CI: 1.0-10.8) in FSWs who attended ≥4 peer-education sessions in the past 6 months than those who attended 1-3 sessions in the Mombasa, Kenya study[131]. However, in the Cote d'Ivoire study there was no association between the number of visits attended out of 5 monthly visits before their first 6-monthly assessment and consistent condom use with clients[80].

The findings in the Cote d'Ivoire study are not easily comparable to those in other studies because of many study differences including how the indicators of intervention exposure were defined and intensity of the HIV intervention in the given setting. For instance, to compare characteristics of two studies; the Cote d'Ivoire study was longitudinal, defined exposure basing on clinic visits, but used a fixed indicator of number of monthly visits attended prior to first assessment (assessed once every 6 months of follow-up). Defining a time-varying indicator instead may have utilised the temporal data across all assessments for a given participant. While the Mombasa, Kenya study was a cross-sectional survey and defined exposure basing on the number of peer-education sessions in the last month, which examines the intervention exposure in the most recent timeframe. However, this being a cross-sectional study is subject to reverse causality between attending peer-educator sessions and reported consistent condom use with clients in the last month.

The finding observed in the Mombasa study showing a positive association between peer-education sessions and reported consistent condom use with clients is consistent with evidence observed within the Avahan India AIDS Initiative programme[103,124]. Within this large-scale targeted HIV intervention for high-risk populations, a cross-sectional study in Karnataka, India (a sample of 775 FSWs) found a positive association between reported consistent condom use with clients and increased number of contacts by project staff in the last month (classified as: Zero, 1-5, ≥5 times) and condom demonstrations witnessed by FSWs in the past month (classified as: Zero, 1, 2, ≥3)[124]. However, the authors for this study suggested that there could be a threshold at which point increased intervention exposure might not improve the level of condom use, which warrants further investigation.

2.8 The influence of intervention exposure on subsequent detection of STIs

STIs can increase the efficiency of sexual transmission of HIV from an unprotected encounter with an infected sexual partner, making the timely treatment of STIs a critical component for an effective HIV intervention[140]. Four studies had consistent conclusions for a likely relationship between regularity of intervention exposure and decreased STI detection despite having varying indicators for intervention exposure[80,82,98,131]. However, none of these four studies which reported on this relationship adjusted for confounding. For example, in the Cote d'Ivoire study, the prevalence of Neisseria gonorrhoea and Chlamydia trachomatis was lower among women who attended 4 of the 5 monthly visits before their first 6-monthly assessment than among those who attended <4 visits (Neisseria gonorrhoea: 3.6 and 9.8%; Chlamydia trachomatis: 1.2% and 5%;

respectively)[80]. However, a similar prevalence by intervention exposure was observed for Trichomonas vaginalis and genital ulcers. Similarly, in the Mombasa, Kenya study the combined prevalence of syphilis, Neisseria gonorrhoea and Trichomonas vaginalis was lower among FSWs who attended at least 4 peer-education sessions in the past 6 months than those with 1-3 sessions (14%, 10/69 and 22%, 16/73, respectively)[131]. These findings suggest that frequent contact between FSWs and peer-educators, which could subsequently facilitate better attendance at health service points can be a critical in targeted HIV interventions including in reducing the efficiency of STIs to transmit HIV.

2.9 The influence of population-level intervention exposure on consistent condom use

Two studies were identified which assessed the relationship between changes in intervention exposure at the population-level and condom use[117,132].

In the Zimbabwean study, community mobilization activities in three sites were intensified beginning from 2011 to increase FSWs' use of clinical services and adoption of safer behaviours. The authors reported that there was no accompanying increase in reported consistent condom use with clients despite an increase in the exposure to HIV services as indicated by routine Sisters' clinic data, and self-reported data on: contact with peer educators, receiving condoms from the clinic and HIV testing in the last 6 months from the 2011 and 2015 surveys[117]. For example, the proportion of FSWs reported to have visited the Sisters clinic in the three sites increased from a range of 18.8%-31.6% in 2011 (over the last 12 months) to 47.0%-77.9% in 2015 (over the last 6 months). The design of this study limits its ability to relate changes in intervention exposure and condom use at the individual-level. The absence or presence of differences in proportions reporting condom use between time points do not necessarily reflect behavioural change at the individual-level but rather changes in the characteristics of the population.

The second study among Kenyan FSWs in Nairobi was designed to assess whether individual changes in sexual behaviour could be sustained after termination of a RCT interrupted regular exposure to intensive HIV interventions[132]. During this RCT of monthly antibiotic prophylaxis to prevent STIs and HIV, all participants were offered a clinic-based combination of HIV services including risk reduction counselling and STI management for a median follow-up period of two years. Based on a resurvey conducted one year after trial termination, the authors for the study concluded that individual changes in condom use with clients were sustained with basic quarterly peer-led meetings and condom distribution in entertainment places. This conclusion is consistent with the information-motivation-behavioural skills conceptual framework for behavioural change.

The framework suggests that individuals can maintain behavioural patterns once they are well informed about HIV prevention, are motivated to act, and acquire the necessary behavioural skills[141]. However, the evidence in this Nairobi, Kenya study showing sustained condom use after interrupted exposure contrasts that noted earlier from the three studies which concluded that regular exposure was associated with a higher likelihood for reporting consistent condom use with clients. It is likely that participants in this study may have had a sufficiently long follow-up period necessary to sustain behavioural skills. Given that this inconsistence in findings is based on analyses which did not appropriately allow for confounding, further assessment of the relationship between interrupting intervention exposure at the individual-level and subsequent reports of inconsistent condom use is necessary.

2.10 Conclusion

The potential impact of targeted interventions for women at high risk of HIV could be reduced when there is insufficient coverage and routine exposure to facilitate consistent intervention use. Although scale-up of effective HIV programming for people at high risk has received attention, routine exposure is not well understood. As a result, there is limited guidance on this key feature of HIV programming for people with ongoing HIV risk. This review finds that there is a small number of studies which have examined a measure of intervention exposure in Africa. Across the studies, measures of exposure varied from the number of visits to the clinic or peer-education sessions in a specific timeframe, the proportion of all scheduled visits attended over the study period, duration between successive visits attended or interruption of some routine exposure.

Overall, evidence suggests that the more FSWs were exposed to an intervention component during a specific timeframe or over all scheduled visits, the lower the HIV incidence and prevalence. However, the evidence for this relationship was inconsistent in cohort studies which reported a time-varying or fixed measure of intervention exposure in the most recent timeframe. Targeted HIV programming for women at high risk of HIV could be informed with a better understanding of the temporal association between interrupting intervention exposure and subsequent HIV risk. This subsequent HIV risk might, in turn, be preceded by changes in either proximate determinants for HIV infection such as inconsistent condom use or STIs, or underlying factors associated or concomitant with the interruption of routine intervention exposure. For example, a FSW could experience an increased HIV risk if she moves from a geographical setting with a low risk of being exposed to an infected sexual partner to that with a high risk of being exposed to an infected partner despite maintaining a similar level of inconsistent condom use with clients.

A key limitation in the studies that compared reported frequency of condom use with clients and STIs by measures of intervention exposure was that of failure to report appropriately adjusted associations, particularly because of low statistical power. In addition, time-varying measures for intervention exposure and subsequent proximate determinants can be more informative in understanding the relationship and consequently mitigating associated HIV risks.

CHAPTER 3: METHODS

3.1 Introduction

This chapter provides a detailed description of the study on which the thesis is based. The PhD uses secondary longitudinal data collected prospectively through the Good Health for Women Project (GHWP). Within this project, a cohort was setup to study the epidemiology of HIV and other STIs among women at high risk of acquiring or transmitting HIV infection. The details of the study population, setting, recruitment, and design as well as data preparation and analysis are described in the sections that follow.

3.2 Study population

The GHWP was designed to offer sexual and reproductive health services to women at high risk of HIV infection within Kampala, the capital city of Uganda. In particular, the target population consisted of women either part-time or full-time earning their living by selling sex in known locations, along streets and around entertainment places. These locations included clusters of bars, night clubs, lodges, brothels and guest houses providing rooms for sex work, and street spots frequented by sex workers. In addition, women employed in entertainment facilities such as waitresses or karaoke singers were considered to be at high risk given that some were likely to recruit men for paid sex to supplement their income.

Prior to setting up the GHWP, several consultations about the feasibility and acceptability of the project were made with members of the target population, members of the local community and other stakeholders such as bar owners and managers. Subsequently, a mapping exercise was carried out to determine the specific areas most concentrated with the target population in search of clients. Figure 3.1 shows the location of common entertainment places frequented by sex workers in Kampala.

3.3 Study Setting

A convenient and accessible location for the target population was chosen to establish the study clinic facility in a densely populated slum area in southern Kampala. In this target setting, a local NGO, Women at Work International, had already been offering health education and condom promotion to female sex workers since 2004. The first people invited to attend the GHWP clinic were peer-educators trained by Women at Work International, who subsequently recruited other women in sex work or employed in entertainment facilities within settings where sex work is concentrated. Additional peer educators were selected as more women were enrolled. Those selected as peer educators were offered a monthly allowance of 50,000 Ugandan shillings (currently equivalent to £11).

From March 2008 the GHWP study clinic started offering sexual and reproductive health care to the target women, and primary health care to the women and their children aged less than five years. Initially, the study area covered two of the five divisions of Kampala (Makindye and Rubaga) but was later expanded to include women from other divisions (Figure 3.1).

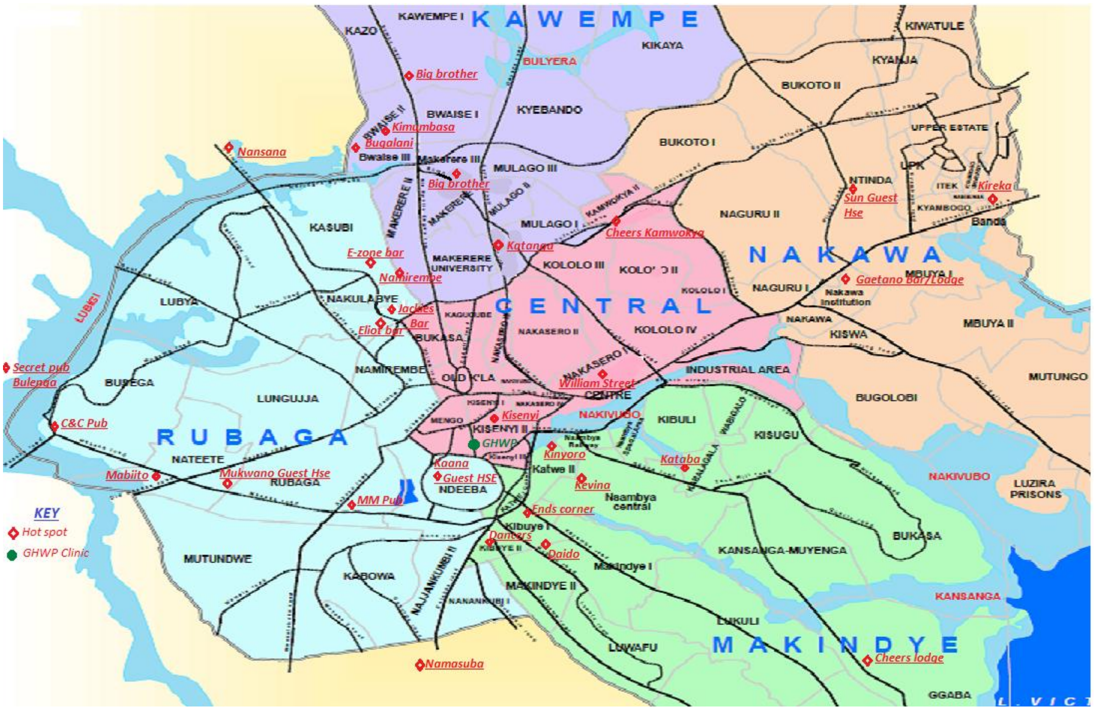

Figure 3.1: Map of Kampala, Uganda showing the study area, and the location of common entertainment places frequented by sex workers across the five divisions.

3.4 Study Design

This study is observational with longitudinal data prospectively collected at the study clinic from all enrolled women. The women comprising this cohort were initially screened and enrolled between March 2008 and May 2009 (cohort 1). Following enrolment, participants were scheduled to attend study visits at the clinic at a frequency of once every 3 months. To provide HIV prevention and care services to more women, the second enrolment of participants started in January 2013 (cohort 2) on an ongoing basis and identical follow-up procedures as cohort 1.

3.5 Screening, enrolment and follow-up

3.5.1 Screening

Women were recruited by peer educators from settings known for sex work in Kampala. Field workers met the recruited women at their locations of work to assess whether they were eligible to attend the study clinic. Those successful with this pre-screening were invited to attend the GHWP clinic with an appointment card. At the clinic, trained nurse-counsellors undertook the consent procedures, which included explaining the objectives, procedures, services offered and re-screening of potential participants.

Women were eligible to be enrolled into cohort if they were aged $\geq$18 years, and acknowledged working as sex workers or self-reported earning money, goods or other favours by having sex with men in the last 12 months, or were employed in surrounding entertainment facilities, for example, as waitresses in bars, nightclubs or massage parlours known for sex work activities. Women aged 15-18 years and having children or pregnant or catering for own livelihood were also considered eligible.

3.5.2 Data collection at enrolment and follow-up

Women were enrolled after consenting by way of signing or thumb printing the consent form. At enrolment and the three-monthly follow-up visits, data were recorded using standardized interviewer-administered structured questionnaires on socio-demographic characteristics, sexual behavioural, alcohol and illicit drug use, reproductive health and STI symptoms. Since January 2015, demographic and behavioural data including sexual behaviour, alcohol and drug use were collected annually. Data on reproductive health and STI symptoms were collected once every three months from all women. In addition, a genital examination was conducted (using a speculum) and a syndromic approach to management of STIs was applied.

Women were asked to provide a urine sample for pregnancy test if not visibly pregnant or reported their last menstruation period to have occurred more than 4 weeks ago or unsure about the last menstruation dates. All participants were counseled for HIV prior to drawing blood samples for HIV-1 testing at enrolment and among previously confirmed HIV negative women at follow-up. This blood sample was also used for Syphilis serology in all women and HIV virological tests among women diagnosed with HIV at least every 6 months. For all tests, the Uganda Ministry of Health guidelines were followed.

3.5.3 Study retention through active participant follow-up

To ensure high retention, group meetings were held every 14 days at the study clinic with women who had scheduled visits within the following month, those who missed their scheduled visits since the last meeting, and peer educators. These sessions include health education on HIV and STIs. In addition, participants were actively followed-up with those who had consecutively missed two or more scheduled study visits contacted by phone or traced in the community (either at their workplace or home) through a peer educators or local council members of their respective area and subsequently invited to attend the clinic at an appointed time.

Figure 3.2 shows the number of women attending at least once in each year at the study clinic between 2008 and 2017, by the cohort in which they were enrolled. There has been attrition over time in both cohort 1 and 2. In cohort 1, there was a sharp drop in the total number of participants who attended in 2013. This is likely explained by a combination of removing transport refund from January 2013 and temporarily stopping the monthly allowance given to peer-educators from January 2013 up to the end of that year. Not only do peer educators in this study facilitate recruitment, they also encourage women to attend upcoming study visits through reminders and active follow-up.

In the most recent time period, over half of the participants attending any given recent year in cohort 1 were living with HIV. Similarly, in cohort 2 there are more HIV-negative women unable to attend the following year than women living with HIV. In addition, HIV-negative women were more likely to miss subsequent scheduled study visits than women living with HIV. Missing of subsequent visits more commonly occurred in the period after cohort 2 was introduced.

The differences in attendance by HIV-status in the most recent calendar period may be a result of availing ART at the study clinic starting January 2013. Whereas, the differences in attendances between pre- and post-cohort 2 period is mainly explained by the stopping of transport refund for participants in January 2013 despite re-introducing the payment of monthly allowances to peer educators. This thesis concentrates on HIV-negative women as the aim is to contribute towards a better understanding of the influence of interrupting routine exposure to a basic combination HIV prevention package on HIV prevention among women at high risk.

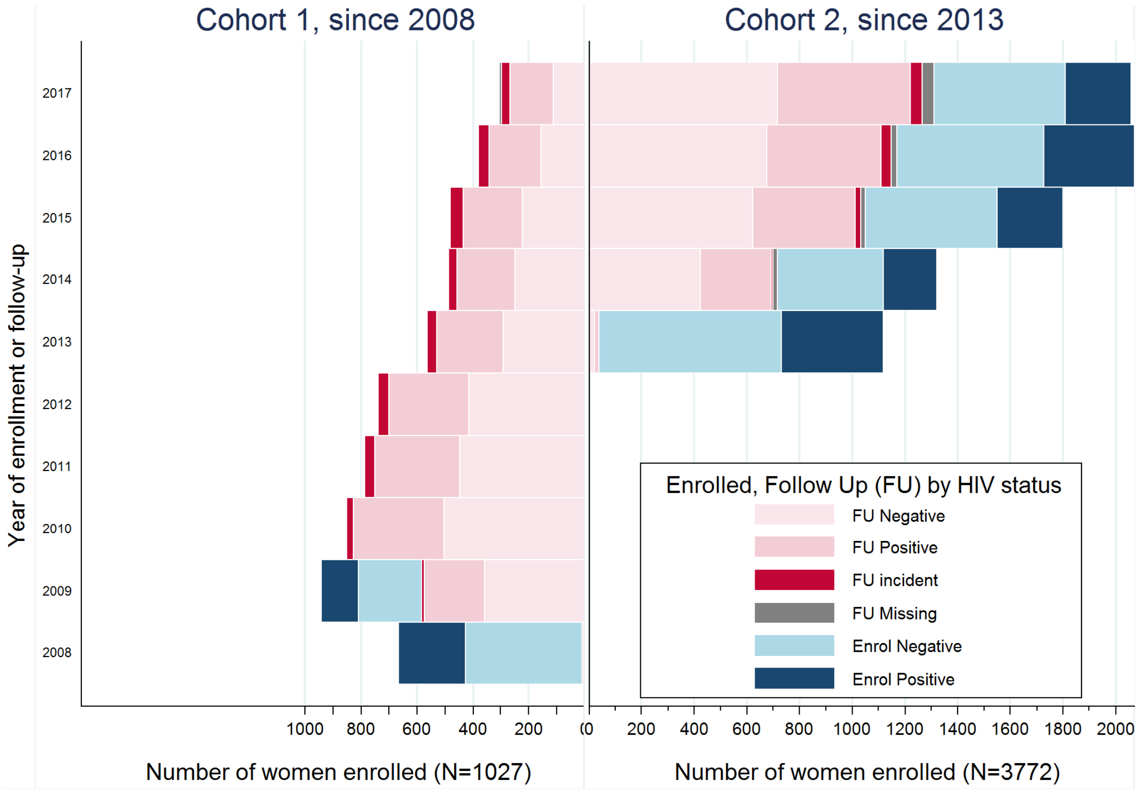

Figure 3.2: The number of women attending the study clinic at least once in each year between 2008 and 2017, by the cohort in which they were enrolled. Notes: FU – followed up at that time point, Enrol – enrolled at that time point, Incident–sero-converters at a given time point, FU positive would include women who tested positive at enrolment and those who seroconverted during the previous year, The FU missing category shows women who attended a visit but no available data records.

3.6 Targeted HIV prevention intervention

To reduce the risk of HIV acquisition and transmission among women at high risk, the GHWP concurrently implemented multiple interventions comprising of behavioural, biomedical and structural components. Figure 3.3 shows the multiple HIV intervention components for women at high risk which the GHWP has been offering since March 2008. In brief, the GHWP offers a range of free sex work-friendly clinic-based services as well as outreach services. The bi-weekly outreach services for women at high risk were restricted to voluntary HIV counselling and testing, and distribution of condoms to locations with concentrations of sex work.

At each visit to the study clinic, all women were offered a combined HIV prevention and treatment package which included sexual health education, counselling on HIV prevention and harmful substance use, HIV counselling and testing (HCT), screening and treatment for diagnosed STIs, and promotion as well as provision of condoms. Nurse-counsellors and peer educators also demonstrated the correct use of condoms in group sessions. However, specific components of the prevention package were emphasised for participant depending on their responses to the behavioural questionnaires, test results for HIV and syphilis, and clinical outcomes including syndromic diagnosis of STIs. For example, participants who reported consistent condom use or non-drinkers were encouraged to maintain this behaviour, whereas inconsistent condom users or harmful drinkers were supported to acknowledge their behaviour and its possible consequences, and to take immediate steps to adopt safer behaviours. Participants were also given information on existing HIV prevention products and services such as post-exposure prophylaxis (PEP), and referred to providers for PEP and other services such as gender-based violence interventions when needed.

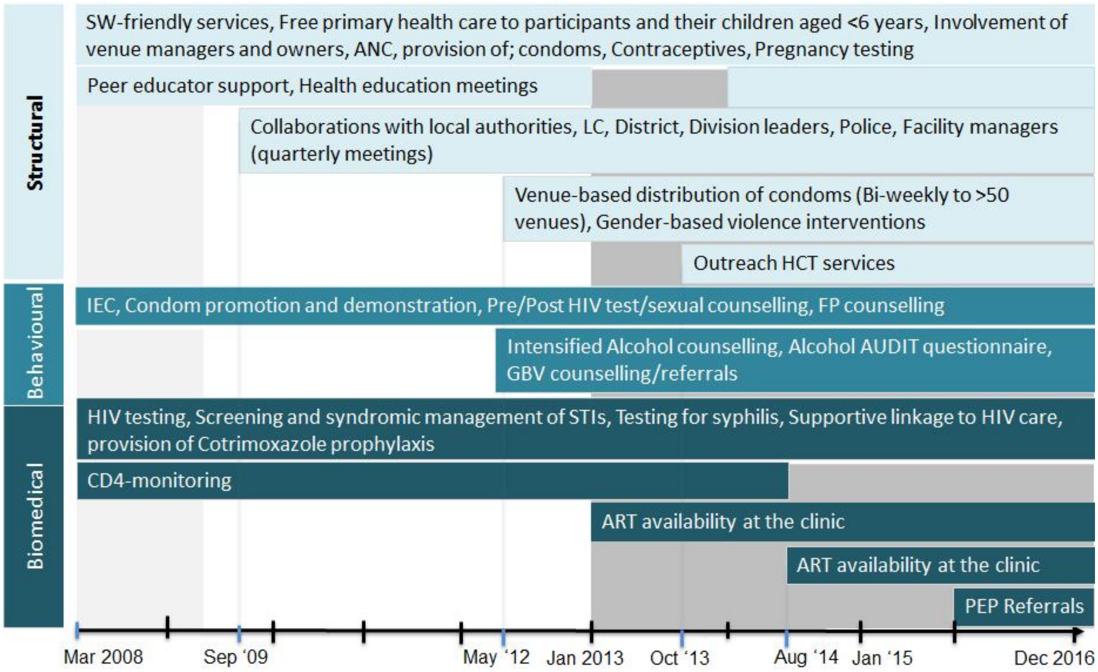

Figure 3.3: Multiple intervention components classified into Biomedical, behavioural, and structural interventions offered by the Good Health for Women Project since March 2008

Interventions for women diagnosed with HIV

Participants diagnosed with HIV received HIV-positive prevention counselling in addition to the above interventions which are applicable. From 2008 to January 2013, CD4 count tests were conducted for participants with confirmed HIV infection and if eligible for ART, participants were pre-counselled on ART at the clinic and accompanied to an HIV-care centre of their choice for ART initiation. In January 2013, ART became available at the GHWP clinic. From August 2014 all participants with HIV were encouraged to start ART regardless of CD4 cell counts in line with Uganda Ministry of Health guidelines.

Laboratory Testing for HIV, syphilis, and pregnancy

The GHWP established a laboratory at the study clinic to conduct tests such as HIV rapid tests, malaria smears, syphilis serology, and urine analysis for pregnancy. This enabled rapid delivery of test results to participants at the same visit of testing.

Testing for HIV followed the Uganda Ministry of Health algorithm for HIV testing. HIV screening was performed using Determine HIV-1/2 (Abbott Diagnostics, UK). Before 2013, reactive results were confirmed using two EIA tests (Vironostika Uniform II plus O, Murex HIV 1.2.0), then a Western Blot Test. Butfrom2013, confirmation was done using Stat-PakdipstickHIV-1/2(Chembio Diagnostics, US) and discordant samples were further tested with the Uni-Gold HIV-/2 (Trinity Biotech, Ireland).

Testing for syphilis was carried out every 6 months using a rapid plasma reagin (RPR Biotec) test and Treponema pallidum hemagglutination (TPHA Biotec) test, with active syphilis having positive tests for both RPR and TPHA. A rapid pregnancy test was performed for all women not visibly pregnant or reported their last menstruation period to have occurred more than 4 weeks ago or unsure about the last menstruation dates.

3.7 Data management and preparation

Key aspects of data management for this thesis were:

1) Changes in the study procedures since the cohort was established, which affected the way data was collected and recorded. These are illustrated in Figure 3.4 and include:

(i) The expansion of the cohort to allow more people at high risk of HIV to access services at the clinic in January 2013 necessitated trimming of the questionnaires to reduce on time spent on a given participant.

(ii) The introduction of the electronic data capture in January 2015 rather than recording on paper forms then later entering data into computers.

2) The data was captured at different points and by different project staff as the participant went through the procedures, which paused multiple points for errors including related to data entry. For example, there were four main paper questionnaires captured by at least two project staff (data on sociodemographic, alcohol, reproductive health, and STIs) and participants' data could be captured through these questionnaires but there were also records at the triage, in the laboratory, and the PEPFAR programme data. However, the collection of data at multiple points for a given participant attending a study visit aided data checking for missing data and subsequent data cleaning.

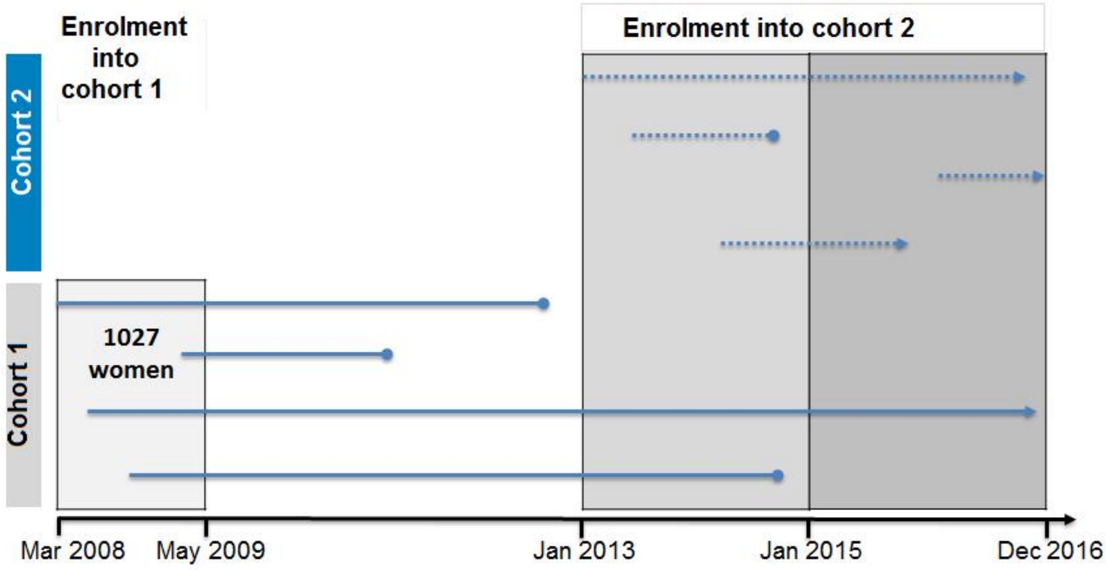

Figure 3.4: An illustration of initial cohort enrolment (March 2008, cohort 1), the expansion of the cohort (January 2013, cohort 2) and the change from recording data on paper forms to electronic data capture (January 2015). Notes: The blue lines are examples of women enrolled and followed-up; Solid lines were enrolled 2008/9 in Cohort 1, Dotted were enrolled in Cohort 2)

Data cleaning and linking datasets

The quality of the data was rigorously checked at different levels for accuracy and completeness. First, I developed a list of unique personal identifiers for all participants who had ever been enrolled into the cohort using all the available data. The unique personal identifiers consistent of three variables: the screening number, the identification number, and the date of enrolment (Figure 3.5). Checking and cleaning these unique identifiers was crucial so as to link data sets across the clinic since different data sets used either screening or identification number. For example, the right length and formats for the identifiers were checked and corrected.

Before merging data sets from the different questionnaires at the same visit for enrolment and follow-up, I checked and corrected errors in typos of unique identifiers in the partial datasets. This required simultaneously cross-checking with data from all the different points of capture at the clinic. It sometimes required obtaining hard copies or tracing backup copies of electronic data entry and re-uploading, whichever was applicable, where complete questionnaires of a visit for a participant(s) were missing.

I also checked and ensured that the data collected for a given variable prior and post-2013 were consistent in terms of the actual question asked, response categories and associated category codes. When the cohort was expanded in January 2013 to allow more people to access services at the clinic, the data collection instruments were trimmed to reduce on the time spent on a single participant at the clinic (which made it necessary to trim the amount of data collected per participant). In addition, some of the response categories had been expanded or coded differently from the prior-2013 period or the period pre-electronic data capture.

For each variable, I checked whether the data represents the appropriate categories and whether the variable had missing data. This also required cross-checking with data from other sources including hard-copies, where that was not applicable. For example, missing HIV status at a given clinic visit or inconsistent HIV data across visits could be resolved using data recorded on laboratory forms.

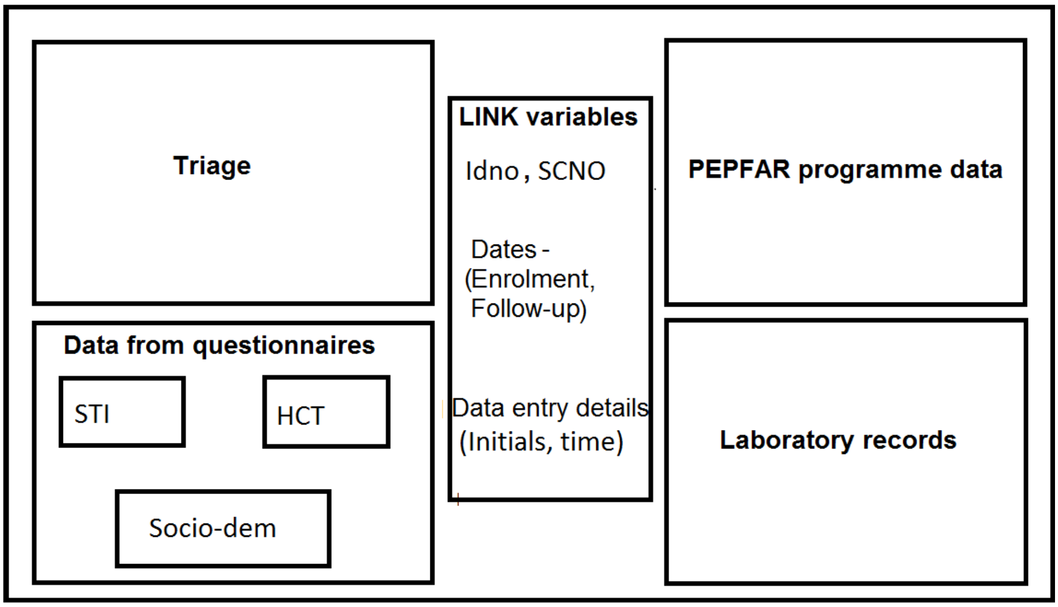

Figure 3.5: An illustration of the different points of data capture across the study clinic from which data was obtained to check for data quality and the link variables that where utilised as unique identifiers and in data cleaning. Notes: Idno – Unique Identifiers, SCNO – Screening number, STI – sexually Transmitted Infections and reproductive health data, HCT – HIV counselling and Testing, Socio-dem – Socio-demographic and behavioural characteristics.

3.8 Ethical considerations

This study was approved by the Science and Ethics Committee of the Ugandan Virus Research Institute, the Uganda National Committee for Science and Technology and the Ethics Committee of the London School of Hygiene and Tropical Medicine.

3.9 Role of the candidate

The candidate decided on the research objectives for the thesis, led the team of data team, worked with programmers and the Good Health for Women Project (GHWP) staff to improve the data capture systems and subsequently, an improve quality of data collected. I carried out routine checks to identify areas of data collection and management that needed urgent improvements. For example, in the case of electronic data capture, I developed a data audit system, suggested the initiation of creation of local backup copies to prevent complete data loss, cleaned and setup a master copies for linking data across the GHWP clinic, developed real-time checks for data, completeness, accuracy, and consistency. I led the development of Standard operating procedures for data management. I guided the mobilisation team in setting up a system to capture key data on tracking of participants who missed scheduled visits.

I prepared the pooled data for analysis, I led out rigorous data management with support from the GHWP team, analysed the data, and drafted the manuscripts. I also shared copies of the manuscripts with co-authors and incorporated feedback. I then identified journals for submission and submitted manuscripts to journals. At all stages, I received guidance from my supervisors.

CHAPTER 4: HIV INCIDENCE AMONG WOMEN AT HIGH RISK OF HIV INFECTION ATTENDING A DEDICATED CLINIC IN KAMPALA, UGANDA: 2008-2017

Introduction

This chapter presents results on HIV incidence trends following enrolment of high-risk women (predominantly sex workers) into the Good Health for Women Project (GHWP), where they are offered a free package of effective HIV prevention interventions at every three-monthly visit attended. Given the sub-optimal attendance of scheduled visits, the influence of missing scheduled visits on the interpretation of incidence trends is also examined. Thus, objective 1 is addressed. The findings were published in the Journal of Sexually Transmitted Diseases in June 2019[142].

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RESEARCH PAPER COVER SHEET

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Thesis Title	Influence of attendance at a clinic service for high-risk women on HIV prevention: A longitudinal study in Kampala, Uganda		
Primary Supervisor	Helen Weiss		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Journal of Sexually Transmitted Diseases		
When was the work published?	01 Jun 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led the team of data managers, programmers, clinic staff in improving the data capture systems and subsequently the quality of data collected. I carried out routine checks to identify areas of data collection and management that needed improvements such as a data audit system, creation of local data backups to prevent data loss, linkage of data across the study clinic, developing real-time checks for data completeness, accuracy and consistency. Led the development of standards operating procedures for data management using electronic at the site. I guided the mobilisation team in setting a system to capture key data about tracking for participants who missed visits. I led the preparation of the manuscript, developing the aims, analysed the data, and drafting the manuscript. I made revisions based on feedback from co-authors, identified a journal and submitted the manuscript. I received guidance from my supervisors at the different stages. I also collected supplementary data from different data points of the study clinic, and pooled together data. I led the data team and worked with the study clinic staff in detailed data cleaning, management and rigorous data checks.

SECTION E

Student Signature	[redacted]
Date	3rd August 2020

Supervisor Signature	Helen Weiss
Date	September 22nd 2020

4.1 ARTICLE

4.1.1 Abstract

Background: High attrition and irregular testing for HIV in cohort studies for high-risk populations can bias incidence estimates. We compare incidence trends for high-risk women attending a dedicated HIV prevention and treatment clinic, using common methods for assigning when seroconversion occurs and whether seroconversion occurs among those with attrition.

Methods: Between April 2008-May 2009 women were enrolled into cohort 1 and from January 2013 into cohort 2, then scheduled for follow-up once every three months. Incidence trends based on assuming a mid-point in the seroconversion interval were compared to those of assigning a random-point. We also compared estimates based on the random-point with and without multiple imputation (MI) of sero-status for participants with attrition.

Results: By May 2017, 3084 HIV-negative women had been enrolled with 18,364 clinic visits. Before attrition, 27.6% (6,990/25,354) were missed visits. By August 2017, 65.8% (426/647) of those enrolled in cohort 1 and 49.0% (1194/2437) in cohort 2 were defined with attrition. Among women with ≥1 follow-up visit, 93/605 in cohort 1 and 77/1601 in cohort 2 seroconverted. Periods with longer seroconversion intervals appeared to have noticeable differences in incidences when comparing the mid-point and random-point values. MI for attrition is likely to have overestimated incidence following escalated attrition of participants. Based on random-point without MI for attrition, incidence at end of observation was 3.8/100 person-years in cohort 1 and 1.8/100 in cohort 2.

Conclusion: The random-point approach attenuated variation in incidence observed using mid-point. The high incidence after years of ongoing prevention efforts in this vulnerable population should be investigated to further reduce incidence.

Key words: HIV, incidence, high-risk, imputation, Uganda

4.1.2 Introduction

Monitoring HIV incidence rates over time facilitates informed public health decisions on HIV prevention and treatment. Longitudinal studies are commonly used to estimate incidence rates where test dates are scheduled at fixed time intervals of, say, every month or year[1]. The timing of a new infection can be assumed to be within the seroconversion interval of the last-negative and first-positive test dates, as either the mid-point or a random-point value. Recently, these two popular approaches for identifying the timing of seroconversion in estimating incidence rates have been discussed but little is still known about how these approaches influence interpretation of HIV incidence trends under different circumstances in cohorts for women at high risk of HIV[2].

Globally, HIV risk was 13 times higher among female sex workers (FSWs) than among other adult women[3]. HIV incidence in FSW studies in eastern and southern Africa is as high as 9.8/100 person-years[4]. In Uganda, where adult female HIV prevalence is 7.5%, the estimated prevalence among FSWs varies between 32%-52%[5,6].

Using data on HIV-1-specific immunoglobulin G (IgG) levels that indicates if a patient was infected recently, assuming the mid-point value while estimating incidence was appropriate for cohort studies with regular testing intervals[7]. However, a recent simulation study estimating incidence trends demonstrated that, in the presence of missed scheduled testing, the mid-point approach leads to an artefactual clustering of seroconversion times in the middle of the observation period[2]. As a result, incidence rates are under-estimated at the beginning and at the end of the observation period, and over-estimated in the middle. For example, incidence rates at the end of the observation period were in error of 27% for a simulated cohort with a 40-59.9% testing rate. An alternative approach that randomly assigns the timing of seroconversion within the seroconversion interval produced less biased incidence trend estimates[2].

Several factors can lead to varying visit attendance rates during observation. In follow-up studies of long durations, later observation periods usually have poorer attendance rates than earlier ones, partly due to participation fatigue[8]. Changes in certain cohort activities such as removing transport refund can also influence levels of attendance during those periods. In particular, cohorts for high-risk populations are vulnerable to missing visits and prematurely discontinuing participation (attrition) because of the high mobility of participants, and transport costs among other reasons[9,10]. The longer seroconversion intervals due to missed visits create larger uncertainty over when the event occurs, and attrition leads to uncertainty of whether the event occurs for participants defined with attrition. These uncertainties can compromise the interpretations of HIV incidence trends[8]. Participants with attrition are usually censored at their last observation, while assuming their risk of infection at censoring is the same as that in those under observation at that time-point. If this assumption is violated, for instance if women who discontinue are at a higher risk of HIV than those who remain in the study, then there is potential for bias in incidence estimates. Given the cohort experience of participants without attrition who have similar characteristics as those with attrition, using multiple imputation (MI) to predict unobserved HIV sero-status and timing of seroconversion for women with attrition could improve the accuracy of incidence estimates[11].

In this paper, we aim to compare HIV incidence trends based on three approaches: (1) estimating the date of seroconversion within the seroconversion interval using mid-point; (2) estimating the date of seroconversion within the seroconversion interval using the random-point method; and (3) predicting the time-to-event data using MI for women with attrition. These comparisons are performed in the epidemiological context of a dedicated clinic which has been providing services to women at high risk of HIV in Kampala, Uganda since 2008.

4.1.3 Methods

Cohort description

The Good Health for Women Project (GHWP) is a stand-alone clinic offering free services to women at high risk of HIV-infection in Kampala, Uganda[12]. Briefly, peer educators recruited other women involved in commercial sex or employed in an entertainment facility within mapped sex work hotspots (e.g., clusters of bars, night clubs, lodges and guest houses providing rooms for sex work, street spots frequented by sex workers). Outreach workers visited these women at their workplace to assess eligibility. Women were eligible if aged ≥18 years and reported engaging in commercial sex (self-identified FSWs or received money, goods, or other favours in exchange for sex) or employed in an entertainment facility. Women <18 years were eligible if pregnant, had a child, or provided for their own livelihood. Those eligible were invited to attend the clinic for screening and enrolment.

Women were initially enrolled into cohort 1 between April 2008 and May 2009 and continually scheduled for follow-up once every three months. Previous publications on this cohort have examined prevalence of HIV and other STIs at baseline[12], HIV incidence and risk factors using data up to March 2011[13], and the epidemiology of alcohol use until September 2013[14]. Cohort 2 was started in January 2013 with continuous enrolment of participants and identical follow-up procedures as cohort 1. This paper considered follow-up visits up to 29th August 2017 for both cohorts.

Study intervention

The programme integrates sex worker friendly HIV and sexual and reproductive health services, including offering free general health care for participants and their children aged <5 years old. Figure 2.2 (Chapter 2) shows a summarised conceptual framework guiding the GHWP intervention derived from the standard framework for preventing HIV acquisition in FSWs developed by WHO. The intervention can be categorised into three broad components (behavioural, biomedical, structural) aiming at three broad categories of immediate outcomes: reducing unprotected sex; decreasing HIV transmission efficiency; and empowering FSWs[15,16]. The horizontal arrows depict the link from the intervention to the intermediate effects, which in turn determine the impact on HIV acquisition and transmission. The vertical arrows show the factors that can influence the immediate intervention effects, and the transition to HIV prevention indicators. To ensure high cohort retention, group meetings were held every 14 days with women who had scheduled visits within the following month. Participants with two or more missed visits were contacted by phone or visited and encouraged to attend.

Data

At every visit, HIV testing was performed using determine HIV-1/2 (Abbott Diagnostics, UK) for screening and a reactive result was confirmed by Stat-Pak dipstick HIV-1/2 (Chembio Diagnostics, US). The Uni-Gold HIV-1/2 (Trinity Biotech, Ireland) was used as a tie breaker if Determine and Stat-Pak were discordant. At every visit, trained nurse-counsellors administered structured questionnaires to collect data on socio-demographic characteristics, sexual behaviour, reproductive health, alcohol use, and illicit drug use.

Statistical analysis

Analyses were restricted to HIV-negative women enrolled before May 2017 to allow for follow-up visits for all participants. In estimating incidence, the endpoint for calculating person-years at risk was the earliest of i) estimated HIV seroconversion date for seroconverters or ii) last HIV-negative test date for non-seroconverters.

HIV seroconversion date was estimated using (a) mid-point between last-negative and first-positive HIV test dates; (b) random-point method. The random-point method assumed seroconversion to be a random date from a uniform distribution bounded by the last-negative and first-positive test dates. To account for the variability of using a random date, multiple imputations were made, and incidence rates over time were estimated each time and averaged at each time-point for all iterations.

To assess the potential consequence of attrition on incidence trends, we imputed the unobserved HIV sero-status then obtained timing for seroconversion for participants with attrition. Several methods for imputing unobserved time-to-event endpoints have been published[17,18]. Since our interest is incidence trends evaluated at time intervals of follow-up, we applied an MI approach that models the probability of seroconversion within each time interval given that the participant was HIV-negative up to the start of that interval. In this approach the follow-up period is divided into discrete intervals of time and logistic regression used to impute sero-status sequentially in each interval. Then, the imputed sero-statuses are mapped back to the time-scale by allocating a random time within the seroconversion interval, and censoring at each participant's expected complete follow-up time for imputed non-seroconverters. Estimates were based on 200 imputations. The log of incidence rates at each time-interval were estimated separately in each imputed dataset, then averaged using Rubin's rules[19]. Statistical tests assessing whether the age-adjusted incidence trends changed over time in each imputed dataset were combined after normalisation using Wilson-Hilfertytransformation[20].

The imputation model included factors associated with both attrition and HIV incidence in this analysis. To improve imputation accuracy of sero-status, we included as a-priori the age, and time-varying characteristics of: frequency of alcohol consumption, reporting paid sex, condom use frequency with paid sex and number of partners in the last month in the imputation models. To identify factors associated with attrition, the outcome was time-to-attrition, and follow-up was right-censored at last observation. A participant had attrition if their last study attendance was 12 months or more prior to the administrative censoring date, consistent with what has been used in other studies. To investigate factors associated with attrition and then incidence, hazard ratios (HRs), and associated 95% confidence intervals (CI) and p-values were estimated using Cox regression models. Age-adjusted models were fitted separately for each factor and independently associated sociodemographic factors (p-value≤0.15) were determined. These were then adjusted for behavioural and reproductive health factors that remained statistically significant at 15% level. Time-changing variables were fitted using the most recent reports at each visit.

Analyses were performed separately for each cohort because of the potential variation in exposures due to the five-year gap between the starts of the two cohorts. For each cohort, estimates of incidence trends from three models were compared: 1) Without MI using mid-point; (2) Without MI using random-point; (3) MI using random-point. Changes in incidence trends were assessed using Poisson regressions models by testing the inclusion of a linear and a quadratic trend with time in models adjusted for current age. Stata 14 (StataCorp, Tx) was used for all analyses.

4.1.4 Results

HIV prevalence at enrolment was 37.0% (380/1027) in cohort 1 and 35.4% (1335/3772) in cohort 2. Table 4.1 shows enrolment characteristics for the 3084 HIV-negative women. Overall, the mean age was 26.2 years (SD: 6.3) with over 80% having ≥1 child. Most (58.0%) reported their only source of income as sex work, and 37.2% reported having another job in addition to sex work.

Attrition and missed visits

The percentage of women with ≥1 follow-up visit was 93.5% (605/647) in cohort 1 and 65.7% (1601/2437) in cohort 2. A total of 32,762 visits (Cohort 1:17,970; Cohort 2:14,792) were expected while 18,364 (Cohort 1: 9,504; Cohort 2: 8,860) were made. Before attrition, 6,990 visits (Cohort 1:3,324; Cohort 2:3,666) were missed and 7,408 (Cohort 1: 5142; Cohort 2: 2266) after attrition. Table 4.2 shows study participation and the supplementary Table C.1 shows the factors associated with attrition. Attrition was independently associated with follow-up characteristics of having no child, being pregnant, recruiting clients on phone, and reporting no illicit drug use in the last 3 months in cohort 1 and younger age, not using oral contraceptives, and less frequent paid sex in the last year in cohort 2. The percentage of participants attending each visit with ≥1 missed visits since the previous attendance in cohort 1 was stable at 10% until year four, when this proportion increased to an average of 30% for all the visits after year four (Figure 4.1). In cohort 2, this proportion was stable at 30% for all the visits following enrolment.

HIV incidence

Among 2206 HIV-negative participants with ≥1 follow-up visit, 170 were observed to seroconvert within 5540 person-years. Without MI, the mid-point and random-point incidence trends were similar in the first four years of enrolment and at years 7 and 8 of cohort 1 (Figure 4.2a). At the introduction of cohort 2 in January 2013, corresponding to years 5 and 6, the random-point method attenuated the variation observed using mid-point estimation (Figure 4.2a). The median length of the seroconversion interval was 3.4 months (IQR: 3.0-7.1) for cohort 1 participants whose last-negative test date occurred before January 2013, and 10.1 months (IQR: 5.8-18.3) between January 2013 and December 2014, and 3.9 months (IQR: 2.5-5.5) after January 2015. In cohort 2 the median was 14.9 months (IQR: 4.7-26.9) between January 2013 and December 2014, and 5.6 months (IQR: 3.2-7.7) after January 2015. In cohort 2 without MI, incidence based on mid-point increased between the first and second intervals peaked at year two then decreased steeply at the end of the observation period, while that based on random-point dropped from its peak at the first interval and decreased further in the last interval (Figure 4.2b).

In cohort 1, incidences based on MI using random-point estimation for attrition were higher than without MI (using either method), particularly starting from year five. In cohort 2, the overlapping 95% CIs for incidences are consistent with no differences between MI and without MI approaches.

Based on random-point without MI for attrition, there was a sharp fall in incidence from 6.1/100 person-years within the first six months to 2.5/100 in the following six months, and then 2.0/100 at year three in cohort 1(age-adjusted trend p-value<0.001). After the fourth year, incidence increased to 3.8/100 person-years at the end of the observation period but there was weak evidence to suggest a changing trend (age-adjusted p-value=0.15). In cohort 2, incidence declined from 3.8/100 person-years in the first 6 months to 1.8/100 in year 3 (age-adjusted p-value=0.04).

4.1.5 Discussion

Our findings suggest that the variations in incidence patterns observed with assigning mid-points within seroconversion intervals were attenuated if random-points were assigned instead.With long seroconversion intervals spanning the observation period, incidences based on mid-point were lower at the beginning and at the end of the observation than in the middle where incidence peaked (cohort 2). Where long seroconversion intervals were concentrated in the middle of observation periods with short seroconversion intervals, there were larger fluctuations in incidences over time during that middle period using the mid-point than the random-point approach (cohort 1). MI for unobserved HIV sero-status and time-to-seroconversion for women defined with attrition showed noticeably higher incidences than without MI following an escalated attrition of participants (year 5 in cohort 1 and year 1 in cohort 2).

An incidence peak in the middle of the observation period and lower incidence at the beginning and at the end using the mid-point approach is consistent with results from a recent simulation study where incidence was underestimated at the beginning and at the end of the observation and overestimated in the middle[2]. This mid-point behaviour is a result of clustering of the seroconversion timing in the middle of the observation period. The authors observed this pattern with a large extent of missed scheduled test dates irrespective of the true incidence trend, cohort type and number of scheduled test dates. However, they described incidence patterns where irregular HIV testing spans the entire observation period, similar to what we observe in cohort 2. Conversely, in their study the random-point assignment of seroconversion date which was less restrictive than the mid-point showed less biased incidence trends.

Cohort 1 had much longer seroconversion intervals in the period spanning year 5 and 6 than during the first four years and years 7 and 8. This resulted in similar incidences for the random-point and mid-point approaches in the period with shorter seroconversion intervals and noticeable differences in the period with longer seroconversion intervals. In 2013 and 2014, peer-educators who were instrumental in study recruitment involving high-risk populations were not paid allowances. This, together with not providing transport compensation for participants, had a negative effect on visit attendance leading to longer seroconversion intervals and a subsequent clustering of seroconversion timing at year 5 but offset at the following year.

Although participants in years 7 and 8 had irregular visit attendance similar to that in years 5 and 6, they had shorter seroconversion intervals suggesting that the length of the seroconversion intervals rather than irregular visit attendance determine the extent of differences between the two approaches. If for some reason there is irregular visit attendance in general but the seroconversion intervals are shorter, then there would be little differences between the approaches.

In both cohorts, the higher MI-based than non-MI incidences following escalated attrition of participants suggests attrition of more-risky participants, given previously reported characteristics. However, it is likely that the estimated MI-based incidences following marked attrition may be overestimated if some participants dropped-out because they perceived themselves to be low-risk, for example, exited sex work but reported high-risk behaviours at the prior visit. For cohort 1, escalated attrition occurred at a time-point corresponding to the estimated mean duration of risk behaviours for FSWs in Africa of 5.5 years, as reported in a review of duration of risk behaviours in key populations[21]. Overall, these MI-based estimates suggest that incidences obtained without MI may have been underestimated following escalated attrition.

A key limitation in this study is the use of self-reported data in predicting sero-status for women with attrition, which data is subject to social desirability and can ultimately affect MI-based incidence estimates. Also, some women defined with attrition in our study may be accessing services elsewhere including private services, may have exited sex work, or are living less-risky lifestyles yet their un-observed predicted sero-status is based on previously reported high-risk behaviours. Therefore, combined with the lack of proper data on the reasons for exit and data on mortality, the MI-based incidences may have been over-estimated. In addition, missing data in some women, which was used to perform MI, could potentially skew conclusions. However, we assumed these data were missing completely at random because most of the missingness was due to the electronic data capture system failing to capture data at roll-out during cohort 2.Nonetheless, it is unlikely that these observations could have substantially changed our conclusions.

In conclusion, the random-point approach reduced the improbable fluctuations in incidence and incidence patterns observed with mid-point in the presence of long seroconversion intervals. Based on random-point without MI, the HIV incidence declines in the three years following enrolment of 67% in cohort 1 and 53% in cohort 2 were substantial but incidence remains high. The declines in HIV incidence over time are likely due to the ongoing interventions but the high incidence rates after years of potential exposure to the intervention suggests a need for further strengthening the intervention efforts in this cohort. In particular, the factors influencing the slight rise in incidence after four years among cohort 1 participants are not well understood, but these changes coincide with the period with substantial proportions of missed visits. We are currently examining some of these factors in more detail. Despite the importance of tracking HIV incidence trends in this vulnerable population, there was paucity of recent incidence data with which to compare our findings[10,21,22]. In choosing how to assign the seroconversion timing and interpreting the resulting incidence patterns, it is important to consider the changes in the extent of missed visits and length of seroconversion intervals over time.

Table 4.1: Characteristics at enrolment for HIV-negative women enrolled into the GHWP between 31st March 2008 and 1st May 2017, and a comparison of women who remained in each cohort with those defined with attrition.

Characteristic at enrolment		Cohort1			Cohort2		
		All	Successfully followed, n (%)	Loss to follow-up, n (%)	All[1]	Successfully followed, n (%)	Loss to follow-up, n (%)
Total		647	221	426	2437	1243	1194
Age in years	<24	291 (45.0)	92 (41.6)	199 (46.7)	1059 (44.6)	528 (43.5)	531 (45.6)
	25-34	298 (46.1)	107 (48.4)	191 (44.8)	1008 (42.4)	511 (42.1)	497 (42.7)
	35+	58 (9.0)	22 (10.0)	36 (8.5)	310 (13.0)	174 (14.3)	136 (11.7)
					60		
Highest education level	Less than primary	284 (43.9)	99 (44.8)	185 (43.4)	907 (40.8)	458 (41.8)	449 (39.8)
	Completed Primary	281 (43.4)	96 (43.4)	185 (43.4)	940 (42.2)	443 (40.4)	497 (44.1)
	Completed Secondary Ordinary level	82 (12.7)	26 (11.8)	56 (13.1)	378 (17.0)	196 (17.9)	182 (16.1)
					212		
Marital status	Widowed/divorced	417 (64.5)	147 (66.5)	270 (63.4)	1447 (60.7)	723 (59.3)	724 (62.3)
	Currently married	52 (8.0)	19 (8.6)	33(7.7)	163 (6.8)	86 (7.1)	77 (6.6)
	Never married	178 (27.5)	55 (24.9)	123 (28.9)	772 (32.4)	410 (33.6)	362 (31.1)
					55		
Number of children	None	85 (13.1)	16 (7.2)	69 (16.2)	399 (17.0)	211 (17.6)	188 (16.3)
	One	169 (26.1)	63 (28.5)	106 (24.9)	612 (26.1)	296 (24.7)	316 (27.5)
	At least 2	393 (60.7)	142 (64.3)	251 (58.9)	1337 (56.9)	690 (57.6)	647 (56.2)
					89		
Source of income	Sex work alone	379 (58.6)	133 (60.2)	246 (57.7)	1371 (57.9)	732 (60.6)	639 (55.1)
	Sex work and other job	242 (37.4)	80 (36.2)	162 (38.0)	876 (37.0)	430 (35.6)	446 (38.5)
	No sex work	26 (4.0)	8 (3.6)	18 (4.2)	119 (5.0)	45 (3.7)	74 (6.4)

[1]Most of the missing data were due to programming errors in the electronic data capture systems, which was rolled-out starting in January 2015.

					71		
Where paying clients are recruited from	Bar, club or restaurant	334 (52.7)	117 (54.2)	217 (51.9)	1062 (48.1)	564 (49.0)	498 (47.1)
	Street	82 (12.9)	32 (14.8)	50 (12.0)	693 (31.4)	381 (33.1)	312 (29.5)
	Several avenues	218 (34.4)	67 (31.0)	151 (36.1)	452 (20.5)	205 (17.8)	247 (23.4)
	missing	13	5	8	230		
Pregnancy status	Not pregnant	585 (90.4)	197 (89.1)	388 (91.1)	2273 (96.8)	1161 (98.1)	1112 (95.5)
	Pregnant	62 (9.6)	24 (10.9)	38 (8.9)	76 (3.2)	23 (1.9)	53 (4.5)
					88		
Current contraceptive use	none or other	364 (56.3)	124 (56.1)	240 (56.3)	1449 (65.7)	724 (66.1)	725 (65.4)
	oral cc	63 (9.7)	20 (9.0)	43 (10.1)	142 (6.4)	79 (7.2)	63 (5.7)
	inject	158 (24.4)	53 (24.0)	105 (24.6)	538 (24.4)	270 (24.6)	268 (24.2)
	Pregnant	62 (9.6)	24 (10.9)	38 (8.9)	76 (3.4)	23 (2.1)	53 (4.8)
					232		
Frequency of paid sex in the last 12 months at enrolment	Less than once a week/None	92 (14.2)	29 (13.1)	63 (14.8)	308 (12.8)	127 (10.4)	181 (15.4)
	At least once a week	256 (39.6)	89 (40.3)	167 (39.2)	689 (28.7)	353 (28.9)	336 (28.5)
	Daily	299 (46.2)	103 (46.6)	196 (46.0)	1404 (58.5)	743 (60.8)	661 (56.1)
					36		
Number of sexual partners in the last month	<5	208 (32.1)	67 (30.3)	141 (33.1)	545 (24.6)	241 (22.0)	304 (27.0)
	5-19	200 (30.9)	74 (33.5)	126 (29.6)	471 (21.2)	246 (22.5)	225 (20.0)
	At least 20	239 (36.9)	80 (36.2)	159 (37.3)	1203 (54.2)	606 (55.4)	597 (53.0)
					218		
Number of paying partners in the last month	<5	227 (35.1)	80 (36.2)	147 (34.5)	562 (25.4)	249 (22.8)	313 (27.9)
	5-19	193 (29.8)	64 (29.0)	129 (30.3)	457 (20.7)	237 (21.7)	220 (19.6)
	At least 20 or cannot remember	227 (35.1)	77 (34.8)	150 (35.2)	1193 (53.9)	604 (55.4)	589 (52.5)
					225		
Condom use frequency with paid sex in the last month	Inconsistent	214 (33.1)	75 (33.9)	139 (32.6)	969 (43.4)	496 (45.0)	473 (41.9)
	Consistent (always)	359 (55.5)	127 (57.5)	232 (54.5)	1007 (45.1)	487 (44.2)	520 (46.1)
	No paid sex	74 (11.4)	19 (8.6)	55 (12.9)	255 (11.4)	120 (10.9)	135 (12.0)
					206		

Alcohol consumption frequency	Non-drinker	160 (24.7)	51 (23.1)	109 (25.6)	531 (23.0)	280 (23.9)	251 (22.0)
	Non-daily drinker	332 (51.3)	115 (52.0)	217 (50.9)	886 (38.4)	427 (36.5)	459 (40.3)
	Daily drinker	155 (24.0)	55 (24.9)	100 (23.5)	892 (38.6)	463 (39.6)	429 (37.7)
					128		
Binge drinking in last 3 months	Non drinker	160 (24.7)	51 (23.1)	109 (25.6)	530 (22.6)	280 (23.6)	250 (21.6)
	No binging	325 (50.2)	114 (51.6)	211 (49.5)	396 (16.9)	179 (15.1)	217 (18.8)
	Binged	162 (25.0)	56 (25.3)	106 (24.9)	1414 (60.4)	725 (61.2)	689 (59.6)
					97		
Illicit drug use in last 3 months	No	529 (81.8)	170 (76.9)	359 (84.3)	1548 (69.6)	782 (71.3)	766 (68.0)
	Yes	118 (18.2)	51 (23.1)	67 (15.7)	676 (30.4)	315 (28.7)	361 (32.0)
					213		
When the participant last tested prior to enrolment	>1 year ago or never	408 (63.1)	138 (62.4)	270 (63.4)	582 (24.8)	268 (22.3)	314 (27.4)
	7-12 months ago	110 (17.0)	36 (16.3)	74 (17.4)	294 (12.5)	151 (12.6)	143 (12.5)
	<6 months ago	129 (19.9)	47 (21.3)	82 (19.2)	1470 (62.7)	783 (65.1)	687 (60.1)
					91		
Ever experienced gender based violence by type of partner	Never				1308 (59.3)	606 (55.7)	702 (62.8)
	Marital or non-paying partners				458 (20.8)	240 (22.1)	218 (19.5)
	Paying clients				397 (18.0)	218 (20.0)	179 (16.0)
	Several of above/DK				43 (1.9)	24 (2.2)	19 (1.7)
	missing				231		

Table 4.2: Study participation and follow-up status at each time interval by when participants were enrolled (cohort 1 or 2)

	Cohort 1							Cohort 2						
	Retention		Status at the end follow-up					Retention		Status at the end follow-up				
Time interval (years)	Women expected at the start of each interval	Cohort retention at end of interval†, n (%)	Women without a single follow-up visit	HIV-negative followed-up to end of interval	Attrition by end of interval⁑	Administratively censored	HIV incident cases (Sero-converters)	Women expected at the start of each interval*	Cohort retention at end of interval†, n (%)	Women without a single follow-up visit	HIV-negative followed-up to end of interval	Attrition by end of interval⁑	Administratively censored	HIV incident cases (Sero-converters)
Enrolled	647	647 (100.0)	42	-	-	-	-	2,437	2437 (100.0)	836	-	-	-	-
0 - 0.5	647	582 (90.0)	-	570	23	-	12	2,338	1692 (72.4)	-	1,332	134	120	15
0.5 - 1	647	563 (87.0)	-	540	19	-	11	2,065	1197 (58.0)	-	997	150	171	14
1 - 2	647	524 (81.0)		485	39	-	16	1,731	650 (45.4)		488	211	272	26
2 - 3	647	491 (75.9)	-	444	32	-	8	1,026	450 (43.9)	-	254	77	142	15
3 - 4	647	429 (66.3)	-	375	63	-	7	676	300 (44.4)	-	41	11	236	7
4 - 5 ‡	647	375 (58.0)	-	313	54	-	8							
5 - 6	647	331 (51.2)	-	264	44	-	4							
6 - 7	647	267 (41.3)	-	189	64	-	12							
7 - 8	647	203 (31.4)	-	116	46	18	9							
End of follow-up			-	-		110	6							

Cohort 1 was a closed cohort, Cohort 2 was an open cohort.

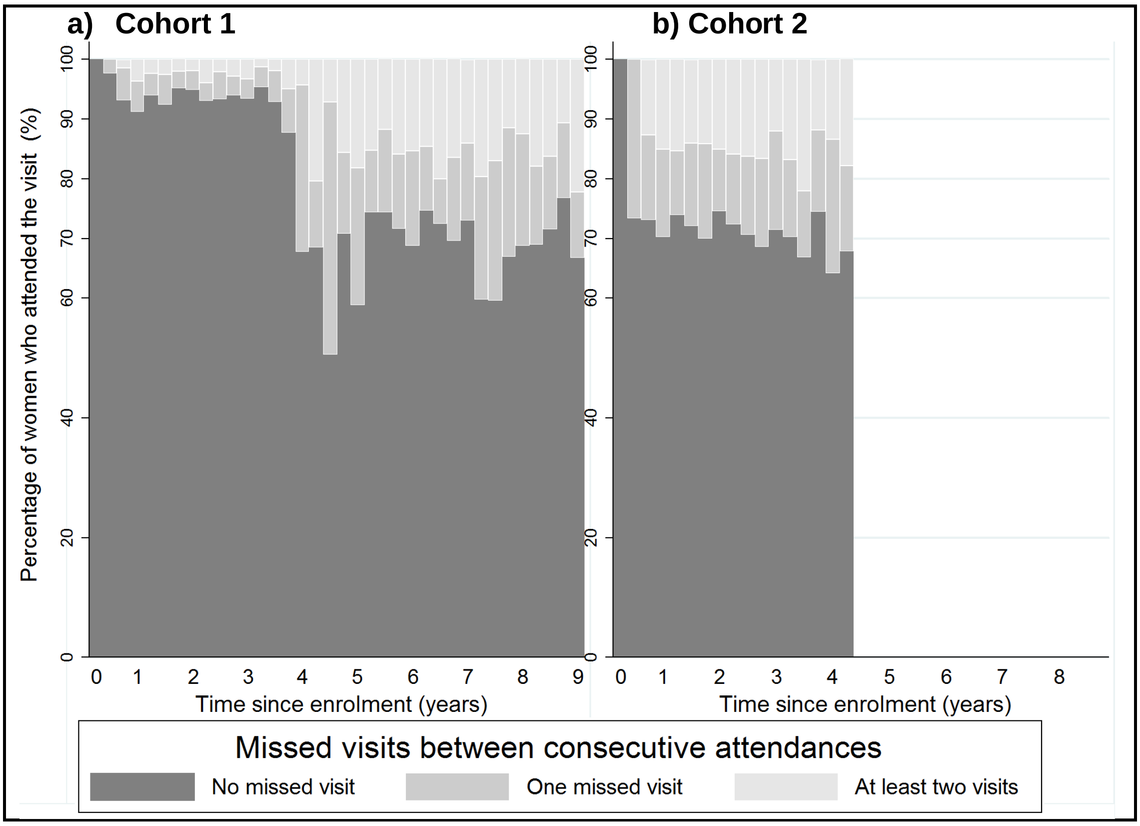

Figure 4.1: Distribution for the number of missed visits between consecutive visits attended following enrolment by cohort of enrolment.

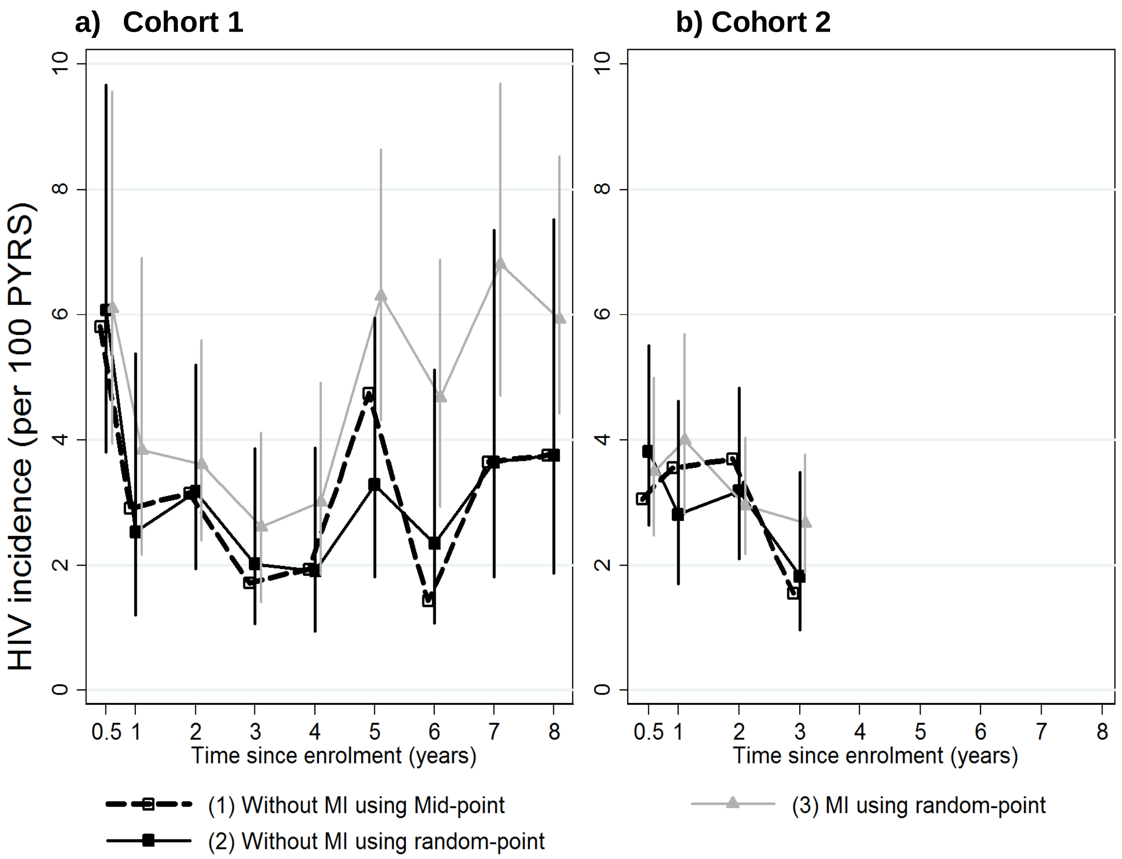

Figure 4.2: Compares HIV incidence trends based on three methods, by cohort: 1) Without multiple imputation (MI) for attrition using the mid-point method; (2) Without MI

using random-point; (3) With MI for attrition using random-point. 95% Confidence intervals are shown only for the preferred method of random-point. *Notes: MI was based on 30 imputed datasets and combined rates using Rubin's rules. The imputation model for MI included age, number of partners in the last month, reporting paid sex, frequency of condom use in the last month with paid sex, frequency of alcohol consumption, source of income, number of children and marital status. Random-point estimation of the seroconversion date was based on 200 imputations, more than 3 times imputations required for convergence. 95% confidence intervals are shown for only random-point estimation of HIV seroconversion with and without MI. Missing data in some of the variables in the imputation model were mainly because some data was not captured as electronic data capture was being rolled-out in January 2015. Therefore, we assumed that this data was missing completely at random (MCAR), and multiple imputation that involved these variables was not conducted for these women.*

Table 4.3: HIV incidence rates and associated 95% confidence intervals (CI) for each of the three analytic methods, by time since enrolment for each cohort.

	Cohort 1			Cohort 2		
Years since enrolment	Mid-point without multiple imputation [per 100 pyr (95% CI)]	Random-point without multiple imputation [per 100 pyr (95% CI)]	Random-point with multiple imputation [per 100 pyr (95% CI)]	Mid-point without multiple imputation [per 100 pyr (95% CI)]	Random-point without multiple imputation [per 100 pyr (95% CI)]	Random-point with multiple imputation [per 100 pyr (95% CI)]
Combined	3.1 (2.5-3.8)	3.1 (2.5-3.8)	4.8 (4.2-5.5)	3.0 (2.4-3.8)	3.0 (2.4-3.8)	3.2 (2.7-3.8)
0.5	5.8 (3.6 - 9.3)	6.1 (3.8 - 9.7)	6.1 (3.9 - 9.6)	3.1 (2.0 - 4.6)	3.8 (2.6 - 5.5)	3.5 (2.5 - 5.0)
1	2.9 (1.5 - 5.8)	2.5 (1.2 - 5.4)	3.8 (2.2 - 6.9)	3.5 (2.3 - 5.5)	2.8 (1.7 - 4.6)	4.0 (2.8 - 5.7)
2	3.1 (1.9 - 5.1)	3.2 (2.0 - 5.2)	3.6 (2.4 - 5.6)	3.7 (2.5 - 5.4)	3.2 (2.1 - 4.8)	3.0 (2.2 - 4.0)
3	1.7 (0.9 - 3.4)	2.0 (1.1 - 3.9)	2.6 (1.4 - 4.1)	1.5 (0.8 - 3.1)	1.8 (1.0 - 3.5)	2.7 (1.9 - 3.8)
4	1.9 (1 - 3.9)	1.9 (0.9 - 3.9)	3.0 (1.9 - 4.9)			
5	4.7 (2.9 - 7.7)	3.3 (1.8 - 5.9)	6.3 (4.3 - 8.6)			
6	1.4 (0.5 - 3.8)	2.3 (1.1 - 5.1)	4.7 (2.9 - 6.9)			
7	3.7 (1.8 - 7.3)	3.6 (1.8 - 7.3)	6.8 (4.7 - 9.7)			
8	3.8 (1.9 - 7.5)	3.8 (1.9 - 7.5)	5.9 (4.4 - 8.5)			

Pyr – person-years of observation, 95% CI – 95% confidence intervals

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CHAPTER 5: MISSED STUDY VISITS AND SUBSEQUENT HIV INCIDENCE AMONG WOMEN IN A PREDOMINANTLY FEMALE SEX WORKER COHORT ATTENDING A DEDICATED CLINIC SERVICE IN KAMPALA, UGANDA

Introduction

This chapter uses longitudinal data from the Good Health for Women Project (GHWP) to address thesis objectives 2. Here, findings on the association of the number of missed scheduled clinic visits with subsequent HIV risk among HIV-negative women are presented. These results show the influence of interrupting exposure to an HIV prevention package on HIV risk among high-risk women. These findings were published in Journal of Acquired Immune Deficiency Syndromes in December 2019[143]

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SECTION A – Student Details

Student ID Number	323362	**Title**	Mr.
First Name(s)	Ivan		
Surname/Family Name	Kasamba		
Thesis Title	Influence of attendance at a clinic service for high-risk women on HIV prevention: A longitudinal study in Kampala, Uganda		
Primary Supervisor	Helen Weiss		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?	Journal of Acquired Immune Deficiency Syndromes		
When was the work published?	01st December 2019		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	**Yes**	Was the work subject to academic peer review?	**Yes**

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led the team of data managers, programmers, clinic staff in improving the data capture systems and subsequently the quality of data collected. I carried out routine checks to identify areas of data collection and management that needed improvements such as a data audit system, creation of local data backups to prevent data loss, linkage of data across the study clinic, developing real-time checks for data completeness, accuracy and consistency. Led the development of standards of operations for data management using electronic at the site. I guided the mobilisation team in setting a system to capture key data about tracking for participants who missed visits. I led the preparation of the manuscript, developing the aims, analysed the data, and drafting the manuscript. I made revisions based on feedback from co-authors, identified a journal and submitted the manuscript. I received guidance from my supervisors at the different stages. I oversaw the data management and data cleaning.

SECTION E

Student Signature	
Date	3rd August 2020

Supervisor Signature	Helen Weiss
Date	September 22nd 2020

5.1 ARTICLE

5.1.1 Abstract

Background

There is limited evidence on the relationship between sustained exposure of female sex workers (FSWs) to targeted HIV programmes and HIV incidence. We investigate the relationship between the number of missed study visits within each episode of two consecutively attended visits (missed study visits) and subsequent HIV risk in a predominantly FSW cohort.

Methods

Women at high-risk of HIV are invited to attend an ongoing dedicated clinic offering a combination HIV prevention intervention in Kampala, Uganda. Study visits are scheduled once every three months. The analysis included HIV-seronegative women with ≥1 follow-up visit from enrolment (between April 2008 and May 2017) to August 2017. Cox regression models were fitted adjusted for characteristics on sociodemographic, reproductive, behavioural, and sexually transmitted infections (through clinical examination and serological testing for syphilis).

Findings

Among 2206 participants, HIV incidence was 3.1/100 (170/5540) person-years (95%CI: 2.6-3.5). Incidence increased from 2.6/100 person-years (95%CI: 2.1-3.2) in episodes without a missed study visit, to 3.0/100 (95%CI: 2.2-4.1) for 1-2 missed study visits, and 4.3/100 (95%CI: 3.3-5.6) for ≥3 missed study visits. Relative to episodes without a missed study visit, the hazard ratios (adjusted for confounding variables) were 1.40 (95%CI 0.93–2.12) for 1-2 missed study visits, and 2.00 (95%CI 1.35–2.95) for ≥3 missed study visits (p-trend=0.001).

Conclusion

Missing study visits was associated with increased subsequent HIV risk. Although several factors may underlie this association, the finding suggests effectiveness of targeted combination HIV prevention. But exposure to targeted interventions needs to be monitored, facilitated and sustained in FSWs.

Key words

HIV, HIV incidence, missed study visits, Female sex workers, sub-Saharan Africa

5.1.2 Introduction

Combination HIV prevention programmes targeting sex workers are cost-effective, especially in settings with high HIV incidence and prevalence among sex workers[1,2]. However, when HIV prevention in sex work is not sustained in these settings, there can be rapid HIV acquisition and onward HIV transmission beyond female sex workers (FSWs) and their clients to the wider population[3]. In Uganda, a systematic review of epidemiological data among FSWs showed an estimated HIV prevalence in the range of 32%-52%, which is 4-7 times that in adult women in the general population[4,5]. While there is sufficient evidence that supports effectiveness of multicomponent targeted HIV interventions for FSWs, sustaining exposure to these interventions remains a major challenge[6-9].

WHO recommends routinely offering evidence-based comprehensive HIV prevention services to key populations such as FSWs, which includes HIV Counselling and Testing (HCT), and diagnosis and treatment of sexually transmitted infections (STIs)[10]. This regular exposure to services is likely to reinforce behavioural messages, to facilitate community empowerment, and to detect and treat STIs early among FSWs[8,11]. Furthermore, regular exposure to HCT can facilitate earlier initiation of antiretroviral treatment during the acute and early infectious phases of HIV.

Notwithstanding the limited coverage for FSW-targeted services across Africa, several factors exist at multiple levels that facilitate or deter FSWs from utilising services[12-14]. The most commonly identified contextual factors are stigma, discrimination, and criminalisation, and their associated consequences[13-15]. However other contextual factors such as the high mobility among sex workers have been identified to delay the utilisation of services[15,16]. These contextual factors typically act through the individual factors such as perceptions of HIV risk and importance of services as well as behavioural (sexual and substance abuse), reproductive and biological characteristics (Figure 1)[13,14]. At the same time, these key determinants of service utilisation are also important risk factors for HIV infection among FSWs[17-19].

Although there is growing interest in improving service utilisation among FSWs, it remains unclear how recent levels of service attendance are associated with subsequent HIV risk[15,20,21]. Using the proportions of study visits completed, research has linked reduced incidence of HIV and other STIs among FSWs to amount of exposure to targeted HIV interventions such as peer-mediated HIV education, condom promotion, risk-reduction interventions, and presumptive treatment for STIs[22-24]. However, assessment of the HIV risk associated with prior recent levels of service attendance may offer better evidence for risk associated with intervention exposure since an individual's level of attendance can vary over time and for different reasons. If we understand this relationship better, we could then inform the design and scale-up of appropriate interventions in sex work.

In a Kenyan FSW cohort with monthly clinic visits followed for a median of 16.2 months, a time-varying preceding gap in clinic attendance of ≥60 days was associated with reduced HIV risk[25]. But this variable of preceding gap in clinic attendance in this study was only considered as a confounding variable and thus, warrants further investigation as a main exposure of interest. As a main exposure, a different approach that considers the conceptual interrelationships with potential confounders and their relationship with HIV risk should be applied. Furthermore, instead of assigning the date of seroconversion as mid-point between the last-negative and first-positive test dates we assigned a random date in this interval, thereby reducing on the artefactual clustering of seroconversion times in the middle of observation periods with missed scheduled testing[26,27].

Therefore, the aim of this study was to examine the association between the number of missed study visits (MSV) within episodes of two consecutively attended visitsand subsequent HIV risk in a predominantly FSW cohort attending a dedicated clinic in Kampala, Uganda.

5.1.3 Methods

Study population

Between March 2008 and May 2009 (cohort 1), the Good Health for Women Project (GHWP) enrolled women acknowledging being FSWs or working in entertainment facilities such as bars, night clubs, or lodges (women at high-risk of HIV infection) in Kampala, Uganda[28]. Participants were scheduled to attend the study clinic once every three months, which is consistent with the Uganda Ministry of Health guidelines for HCT of key populations[29]. From January 2013 (cohort 2), more participants were continuously enrolled into GHWP alongside cohort 1 participants.

The procedures for recruiting, screening, enrolling and following-up of cohort 1 participants have been described in detail elsewhere[28]. But identical procedures were followed for cohort 2. Briefly, outreach workers visited and assessed study eligibility for women at high-risk of HIV-infection who had been recruited by peer-educators or contacted through evening community-outreach HCT sessions. Women were eligible if they were involved in commercial sex (self-identified FSWs or received money, goods, or other favours in exchange for sex) or employed in entertainment facilities within mapped sex work hotspots (clusters of bars, night clubs, lodges and guest houses providing rooms for sex work, street spots frequented by sex workers). Those who were eligible were invited to attend the study clinic for rescreening and study enrolment.

Targeted intervention

The GHWP intervention follows the WHO standard framework for HIV prevention in FSWs; aiming at reducing condomless sex, decreasing HIV transmission efficiency, and empowering FSWs[30]. This intervention integrates sex worker-friendly HIV services with other sexual and reproductive health services and offers free general healthcare for participants and their children aged<5 years old. Table 5.1 shows the detailed components of the intervention broadly classified as structural, behavioural and biomedical.

At each visit, HIV preventive behaviours were promoted to each participant, but the content of the counselling sessions depended on each participant's behavioural responses, outcomes of clinical examinations, and serological test results. Low risk participants were encouraged to maintain behaviour while those with risky behaviours were supported to acknowledge the behaviour and its possible consequences. In addition, high risk participants were encouraged to take immediate steps to reduce the risk associated with behaviours such as harmful alcohol use or inconsistent condom use. Depending on their identified needs, participants were also counselled on a wide range of other physical and psycho-social issues including their general health, family, spiritual needs and employment.

To ensure high retention, group meetings were held every 14 days at the study clinic with women who had scheduled visits within the following month. Participants with two or more consecutively missed study visits were contacted by phone or traced in the community (either at their workplace or home) through a peer leader or the local council member of the respective area and then invited to attend the clinic at an appointed time.

Data

At the clinic, trained nurse-counsellors used structured questionnaires to collect data on socio-demographics, sexual behaviour, reproductive health, substance abuse (alcohol use and illicit drug use). Data were collected only at enrolment for: age, education level, source of income (sex work alone or sex work and other jobs), place of client recruitment (street, bar, club or restaurant, and several avenues) and number of children. While data collected at enrolment and follow-up visits included marital status, and behavioural variables such as alcohol use, illicit drug use, number of sexual partners, number of paying sexual partners, frequency of condom use with clients, report of any paid sex in the last month, as well as contraceptive use and pregnancy. Pregnancy was determined using human chorionic gonadotropin (hCG) urine sample tests or visible pregnancy.

A participant had an STI if they had an active syphilis infection (Rapid Plasma Reagin titres≥1:8 and positive Treponema Pallidum Haemagglutination Assay based on serology tests done at six-month intervals or had any of the STI symptoms of abnormal vaginal discharge, genital ulcer disease syndrome, or pelvic inflammatory disease. Between 2008 and 2010, endocervical and vaginal swabs were also used to detect neisseria gonorrhoea, chlamydia trachomatis, mycoplasma genitalium, and bacterial vaginosis.

Outcome variable

The primary outcome was HIV seroconversion which was defined as a negative test result at a given visit attended followed by a positive result at the subsequent visit. Testing for HIV followed the Uganda MoH algorithm for HIV testing. According to this algorithm, HIV screening was performed using Determine HIV-1/2 (Abbott Diagnostics, UK). Before 2013, reactive results were confirmed using two EIA tests (Vironostika Uniform II plus O, Murex HIV 1.2.0), then a Western Blot Test. But from 2013, confirmation was done using Stat-Pak dipstick HIV-1/2 (Chembio Diagnostics, US) and discordant samples were further tested with the Uni-Gold HIV-/2 (Trinity Biotech, Ireland). Participants were included in this analysis if they tested HIV-negative at enrolment and had at least one follow-up visit by 29th August 2017 (administrative censoring date). The total person-years (pyr) for each participant were calculated from their enrolment date to the earliest of (i) estimated date of seroconversion for seroconverters or (ii) last known HIV-negative test date for non-seroconverters. The approach for estimating the date of seroconversion is described under the statistical analysis section.

Exposure variable

The number of missed study visits within each participant's episodes of two consecutively attended visits was used to define the exposure of interest. This exposure variable is a proxy for the extent of exposure to and engagement with the combined components of the HIV intervention offered at the clinic. We classified a scheduled study visit as missed if the participant did not attend the study clinic within 14 days before and 76 days after the scheduled visit date. At each follow-up visit, the number of scheduled visits that the participant consecutively missed since the previous visit attended was calculated, resulting in a time-varying exposure variable. However, since the exposure variable is likely to have sparse data for higher numbers of missed study visits, we categorised the counts of MSV into three levels: (i) no missed visit, (ii) 1-2 MSV, (iii) ≧3 MSV.

Statistical analysis

The total person-years of observation for each participant were split according to their number of episodes of attendance represented by the time period between two consecutively attended visits. Each episode was then assigned an appropriate category for the three-level MSV variable defined above. There would be increased uncertainty for the date of seroconversion during episodes with missed study visits while estimating the person-years for seroconverters. To address this potential concern, the date of seroconversion was assigned as a random date from a uniform distribution bounded by the last-negative and first-positive test dates. In addition, the variability due to assigning a random date was accounted for by multiple imputations (200 imputations). For each set of imputed seroconversion dates the HIV incidence rates, crude and adjusted Hazard Ratios (HR) were calculated and combined using Rubin's rules31.

To facilitate identifying potential confounders for the association between MSV and HIV incidence we examined factors associated with MSV using repeated measures ordered logistic regression. In this model, the three-level MSV variable was fitted as the outcome. Within-woman clustering due to repeated measures was accounted for using random-effects. We also examined factors associated with HIV-infection.

All models included an indicator variable for cohort (1 or 2) and age group a priori. The incidence analysis was performed in three stages: firstly, the association between MSV and HIV seroconversion was examined using Cox regression models that included the cohort indicator and age. Secondly, socio-demographic, behavioural, reproductive health, and STIs characteristics were added individually to the base model in order to assess whether the crude association persisted. Thirdly, the final model was adjusted for variables that were likely confounders of the MSV and HIV seroconversion relationship (i.e. at least a 10% change in the log transformed MSV effects). As a sensitivity analysis, results from the final model were compared to those where analyses were restricted to women with at least 6 months of observation time. This is because HIV incidence peaked within the first six months, yet participants were less likely to miss scheduled visits during this period than later periods27. After performing an interaction of MSV with the cohort indicator variable in the final model adjusted for other confounders, results were also compared for the two cohorts.

Figure 5.1 shows the relationship between MSV and subsequent HIV risk, and the relationships across factors controlled for in the regression model. While behavioural factors and detection of STIs can influence attendance at the study clinic, attendance can also influence reported behavioural and STI outcomes. As a result, the Cox regression model adjusted for time-dependent variables at the preceding visits. Ordered categorical variables in the model were assessed for extra-linear variability using likelihood ratio tests by comparing models with variables as categorical versus a linear fit. Analyses were performed using STATA 14 (StataCorp, College Station, TX).

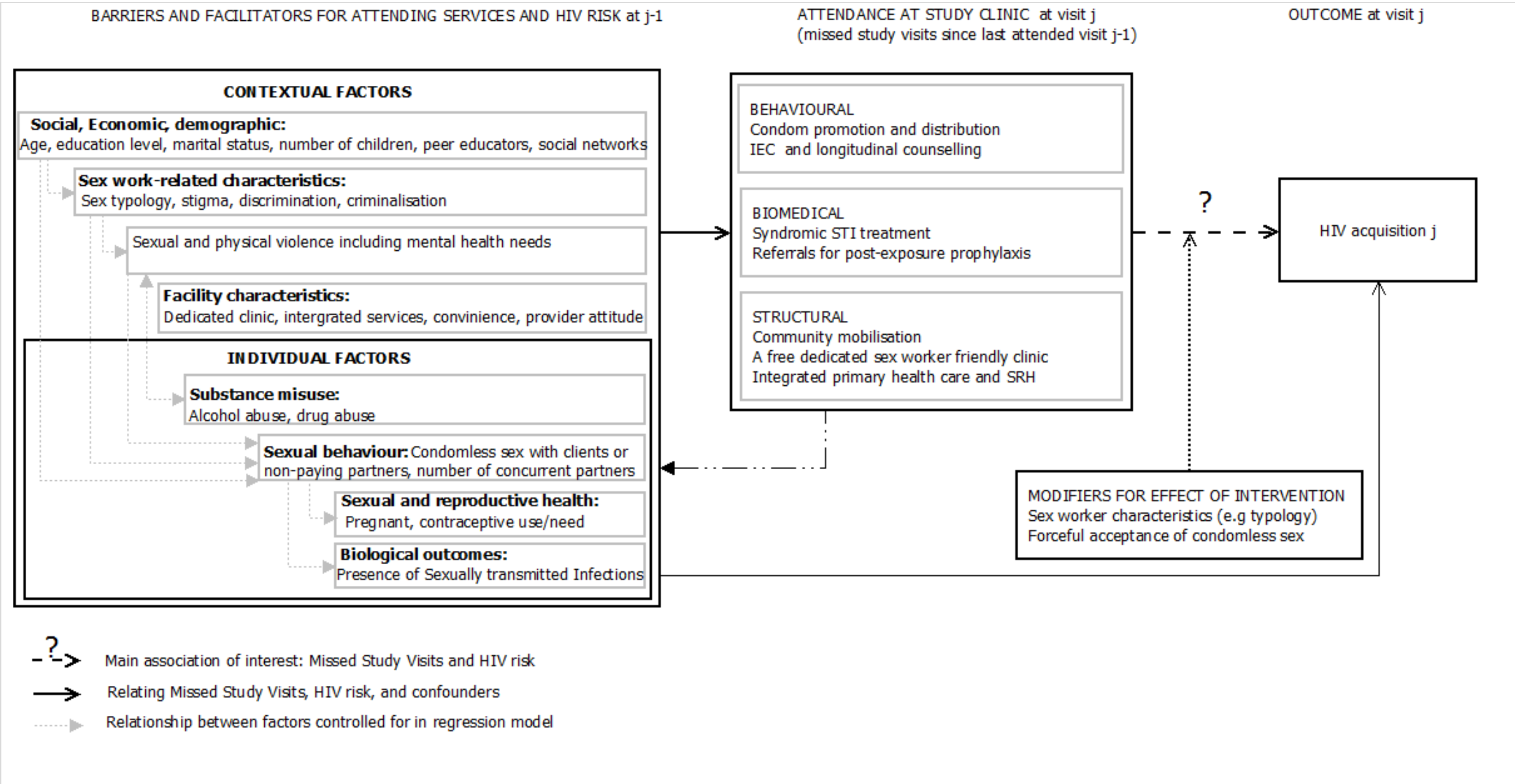

Figure 5.1: Conceptual framework linking factors leading to missed study visits and subsequent HIV risk used to fit the Cox regression model within the GHWP. STI, sexually transmitted infection; IEC, information education communication; SRH, sexual and reproductive health; HIV, Human Immunodeficiency Virus.

Table 5.1: The HIV prevention and treatment intervention available at the GHWP by type of intervention

Type of intervention	Components	Delivery
Behavioural	Condom promotion, demonstration, and free condom distribution	Each visit
	Sexual counselling	Each visit
	Excessive alcohol use counselling including the AUDIT[1] questionnaire as part of the motivational interviewing	Each visit
	Knowledge of HIV status through HIV testing	Each visit, and at moonlight outreaches to sex work hotspots
	If diagnosed with HIV, offered positive prevention strategies, treatment adherence counselling, and HIV care	Each visit, and at ART refill visits
	Information sharing and health education	Each visit, and at the group meetings held fortnightly for participants with upcoming visits
	General counselling services	Each visit
Biomedical	Syndromic management of Sexually Transmitted Infections	Each visit
	Referrals to other collaborating service providers for participants in need of post-exposure prophylaxis	As needed
	Antiretroviral Therapy (ART)[2] treatment if diagnosed with HIV	As needed
Structural	Access to a free sex worker friendly dedicated clinic	As needed
	Sexual and reproductive health services including antenatal care and contraceptive provision	Every visit, and as needed
	Free general health care and their children aged <5 years old	As needed
	Support by peer support network	As needed
	Outreach HIV Counselling and Testing, and supply of condoms and health information at the sex work hotspots	Two nights a week, with a team that includes peer educators, venue managers, and study staff
	Community mobilization involving police, venue managers and owners, and local authorities	Quarterly meetings
	Protection services and referrals to community-based organizations in case of gender-based violence	As needed

[1]Alcohol Use Disorders Identification Test (AUDIT) was initiated in April 2012 but there was ongoing risk-reduction counselling. [2]ART became available at the clinic in January 2013 (eligibility: CD4 cell counts <350 cells/µl, and from August 2014, for all diagnosed with HIV regardless of CD4 cell count), but prior to that participants with CD4 cell count below 250 cells/µl were referred to HIV care providers.

5.1.4 Results

Cohort characteristics

Of the 3084 HIV-negative women enrolled at the clinic, 2206 (71.5%) attended ≥1 follow-up visit after enrolment: 93.5% (605/647) in cohort 1 and 65.9% (1601/2437) in cohort 2. Between the first enrolment (April 2008) and end of follow-up (Aug 2017), a total of 24,476 visits (cohort 1: 12,786, cohort 2: 11,690) had been scheduled by the last visit of each participant with ≥1 follow-up visit. Of these, 17,486 (71.4%) scheduled visits (cohort 1: 9,462, cohort 2: 8,024) were attended. The median number of visits attended per participant was 15 (IQR: 8-22) in cohort 1 and 4 (IQR: 2-6) in cohort 2.

Table 5.2 compares enrolment characteristics for HIV-negative women with and without a follow-up visit. In the multivariable analysis (Supplementary Table C.1), the factors associated with having no follow-up include: younger age, fewer children, street-based recruitment of clients, not on oral contraceptives, less frequent paid sex, and consistently using condoms with clients in the last month

HIV incidence

Among women with ≥1 follow-up visit, we observed 5540 person-years and 170 (7.7%) seroconversions, giving an incidence rate of 3.1/100 person-years (95%CI: 2.6-3.5). Overall incidence was similar in the two cohorts (cohort 1: 93 seroconversions; incidence=3.1/100 person-years; cohort 2: 77 seroconversions; incidence=3.0/100 person-years). HIV incidence declined following enrolment, from 3.6/100 person-years within the first year, 2.8/100 person-years in the second year, and 2.5/100 person-years beyond 2 years of follow-up.

Figure 5.2 shows that episodes of two consecutively attended visits during which HIV was diagnosed are longer (have their distribution more skewed to the right) than those with HIV-negative test results at both attended visits. After restricting to episodes with ≥3 MSV, the median number of MSV within each participant's period of two consecutively attended visits was 4 MSVs (Interquartile range: 3-6) while one person had the longest episode of 30 missed visits (Figure 5.2). In examining the potential confounders for the association of MSV and HIV seroconversion (Supplementary Table C.2), there was evidence that the odds of being in higher categories of MSV than in lower categories were independently associated with: enrolment in cohort 2, longer follow-up, incomplete ordinary secondary education level, street-based recruitment of clients, being pregnant, reporting no paid sex within the last month, alcohol consumption, illicit drug use in last three months, and having no STI at the previous visit.

Table 5.2: Comparing the enrolment characteristics for HIV-negative women with and without a follow-up visit.

Characteristic	Follow-up status, n (%)		
	At least one follow-up	No follow-up visit	p-value
Number enrolled	2206	878	
SOCIO-DEMOGRAPHIC			
Age in years			<0.001
<24	891 (41.0)	459 (54.1)	
25-34	985 (45.3)	321 (37.8)	
35+	299 (13.7)	69 (8.1)	
missing	31	29	
Highest education level			0.94
Less than primary	863 (41.3)	328 (42.0)	
Completed Primary to incomplete O level	889 (42.6)	330 (42.3)	
Completed Secondary Ordinary level above	336 (16.1)	123 (15.7)	
missing	118	97	
Marital status			0.01
Widowed/divorced	1381 (63.2)	484 (57.1)	
Currently married	148 (6.8)	67 (7.9)	
Never married	654 (30.0)	296 (34.9)	
missing	23	31	
Number of children			<0.001
None	297 (13.7)	187 (22.4)	
One	542 (25.1)	239 (28.7)	
At least 2	1322 (61.2)	407 (48.9)	
missing	45	45	
Source of income			0.01
Sex work alone	1227 (56.5)	523 (62.1)	
Sex work and other job	844 (38.8)	276 (32.8)	
No sex work	102 (4.7)	43 (5.1)	
missing	33	36	
Where paying clients are recruited by participants			<0.001
Bar, club or restaurant	1040 (50.9)	356 (45.4)	
Street	472 (23.1)	291 (37.1)	
Several avenues	532 (26.0)	138 (17.6)	
missing	162	93	
REPRODUCTIVE HEALTH			
Pregnancy status			0.02
Not pregnant	2048 (94.8)	812 (96.9)	
Pregnant	112 (5.2)	26 (3.1)	
missing	46	40	
Current contraceptive use			<0.001
none or other	1285 (61.7)	531 (68.9)	
oral cc	170 (8.2)	34 (4.4)	
inject	514 (24.7)	180 (23.3)	
Pregnant	112 (5.4)	26 (3.4)	
missing	125	107	

Table 5.2 (*Continued*): Comparing the enrolment characteristics for HIV-negative women with and without a follow-up visit.

Characteristic	Follow-up status, n (%)		
	At least one follow-up	No follow-up visit	p-value
BEHAVIOURAL CHARACTERISTICS			
Frequency of paid sex in the last 12 months			<0.001
Less than once a week/None	275 (12.6)	125 (14.6)	
At least once a week	735 (33.5)	210 (24.5)	
Daily	1181 (53.9)	522 (60.9)	
missing	15	21	
Number of partners in the last month			0.07
<5	563 (27.0)	189 (24.3)	
5-19	499 (23.9)	170 (21.8)	
At least 20 or Cannot remember	1022 (49.0)	420 (53.9)	
missing	122	99	
Number of paying partners in the last month			0.10
<5	587 (28.2)	204 (26.3)	
5-19	488 (23.4)	162 (20.8)	
At least 20	1009 (48.4)	411 (52.9)	
missing	122	101	
Condom use frequency with paid sex in the last month			0.09
Inconsistent	883 (42.2)	297 (38.0)	
Consistent (always)	969 (46.3)	397 (50.8)	
No paid sex	241 (11.5)	88 (11.3)	
missing	113	96	
Alcohol consumption frequency			0.46
Non-drinker	488 (22.8)	203 (24.9)	
Non-daily drinker	891 (41.6)	327 (40.2)	
Daily drinker	762 (35.6)	284 (34.9)	
missing	65	64	
Binge drinking within the last 3 months			0.01
Non drinker	489 (22.7)	201 (24.2)	
No binging	557 (25.8)	164 (19.7)	
Binged	1112 (51.5)	466 (56.1)	
missing	48	47	
Illicit drug use in last 3 months			0.45
Not used drugs in last 3 months	1513 (72.5)	562 (72.1)	
Non-daily drug user	129 (6.2)	58 (7.4)	
Daily drug user	444 (21.3)	159 (20.4)	
missing	120	99	
			<0.001
HIV TESTING HISTORY			
>1 year ago or never	788 (36.5)	202 (24.3)	
7-12 months ago	309 (14.3)	95 (11.4)	
<6 months ago	1064 (49.2)	535 (64.3)	
missing	45	46	
SEXUALLY TRANSMITTED INFECTIONS (STIs) §			
No STI	1349 (63.2)	592 (72.8)	<0.001
With STI	787 (36.8)	221 (27.2)	

§STI variable was a composite variable combining data on STI symptoms from clinical examination and test results for STI for syphilis.

The number of MSVs seem to be positively correlated with HIV incidence. HIV incidence was 2.6/100 person-years (95%CI: 2.1-3.2) during episodes without missed visits, 3.0/100 person-years (95%CI: 2.2-4.1) in episodes with 1-2 MSV, and 4.3/100 person-years (95%CI: 3.3-5.6) in episodes with ≥3 MSV (p-value for trend=0.003; Table 5.3).

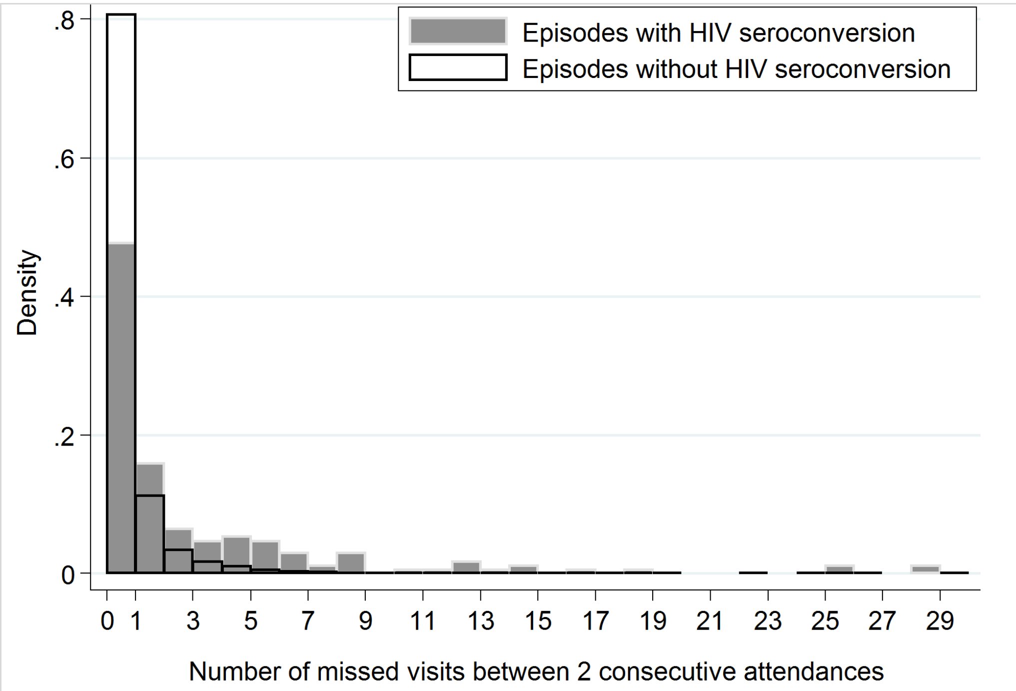

Figure 5.2: Distribution for the number of missed study visits within each participant's episodes of two consecutively attended visits by HIV seroconversion status in the episodes.

The number of MSVs remained correlated with subsequent increase in HIV risk even after taking account of differences in cohort of enrolment, age of participant, education level, having a stable sexual partner, location for recruiting clients, current type of contraceptive, the number of men with paid sex in the last month, frequency of condom use during paid sex, frequency of alcohol consumption and having a current STI (Table 5.3).

In this multivariable model, episodes with 1-2 MSV were associated with 40% higher risk of HIV-infection (aHR=1.40, 95%CI: 0.93–2.12) than episodes without a MSV, but the evidence for this association was weak. However, episodes with ≥3 MSV had twice the risk of HIV-infection (aHR=2.00, 95%CI 1.35–2.95) compared to that in episodes without a MSV. Further, there was strong evidence in favour of the risk of HIV infection increasing with the increasing number of MSV within episodes; p-value for trend=0.001and p-value for extra-linear variability=0.91.

The evidence for the association between MSV and increased HIV incidence remained when analyses were restricted to follow-up of >6 months (p-value for trend<0.001; aHR=1.61 (95%CI: 1.00-2.58) for 1-2 MSV, and aHR=2.05 (95%CI: 1.31-3.22) for ≥3 MSV). But the estimated effect for the 1-2 MSV category was stronger in this restricted analysis. Although there was no evidence that the effect of MSV differed by cohort (p-value for interaction=0.24), the results are also shown by cohort in Supplementary Table C.3.

Other factors independently associated with increased risk of HIV incidence included: not having a stable sexual partner, recruiting clients from the street, not being pregnant and inconsistent condom use with clients.

Table 5.3: Crude and adjusted association of the number of missed visits between successively attended visits and HIV seroconversion based on Cox regression model.

Characteristic	New HIV cases/pyr (Rate/100 pyr)	Crude Hazard Ratio (95% CI)	P-value	Adjusted Hazard Ratio (95% CI)	P-value
Overall (both cohort)	170/5540 (3.1)				
Number of visits missed between attendances					
No missed visit	81 /3106 (2.6)	1	0.003†	1	0.001†
One/two missed visit(s)	38 /1250 (3.0)	1.18 (0.80-1.74)		1.40 (0.93-2.12)	
At least 3 missed visits	51 /1180 (4.3)	1.77 (1.23-2.54)		2.00 (1.35-2.95)	
SOCIO-DEMOGRAPHIC					
Cohort of enrolment					
Cohort 1	93 /3003 (3.1)	1	0.45	1	0.43
Cohort 2	77 /2537 (3.0)	0.87 (0.61-1.24)		0.85 (0.56-1.27)	
Calendar period††					
Jan 2013-Dec 2014	46 /1394 (3.3)	1	0.16		
Jan 2015-Aug 2017	65 /2138 (3.0)	0.99 (0.64-1.55)			
Apr 2008-Dec 2012	59 /2007 (2.9)	1.09 (0.70-1.70)			
Age in years					
<25	53 /1562 (3.4)	1	0.49	1	0.37
25-34	92 /2955 (3.1)	0.96 (0.68-1.35)		0.86 (0.60-1.24)	
At least 35	25 /994 (2.5)	0.76 (0.46-1.24)		0.80 (0.48-1.33)	
With a stable sexual partner*					
Yes	113/3959 (2.9)	1	0.01	1	0.003
No	57 /1211 (4.7)	1.55 (1.13-2.14)		1.75 (1.23-2.50)	
Highest education level at enrolment					
Incomplete primary level	74 /2361 (3.1)	1	0.93	1	0.24
Completed Primary to incomplete O level	70 /2267 (3.1)	0.97 (0.70-1.35)		1.06 (0.76-1.49)	
Completed Secondary O'level above	25 /792 (3.2)	1.00 (0.63-1.57)		1.20 (0.75-1.92)	
Marital status*					
Widowed/divorced	112/3325 (3.4)	1	0.33		
Currently married	28 /1150 (2.4)	0.77 (0.50-1.17)			
Never married	30 /1044 (2.9)	0.81 (0.54-1.22)			

Table 5.3 (*Continued*): Crude and adjusted association of the number of missed visits between successively attended visits and HIV seroconversion with based on Cox regression model.

Characteristic	New HIV cases/pyr (Rate/100 pyr)	Crude Hazard Ratio (95% CI)	P-value	Adjusted Hazard Ratio (95% CI)	P-value
Number of children*					
None	21 /583 (3.6)	1	0.41		
One	42 /1247 (3.4)	0.94 (0.56-1.59)			
At least 2	107/3665 (2.9)	0.81 (0.51-1.30)			
Source of income*					
Sex work alone	74 /2241 (3.3)	1	0.13		
Sex work and other job	73 /2416 (3.0)	0.94 (0.68-1.31)			
No sex work	23 /851 (2.7)	0.89 (0.54-1.45)			
Recruitment of clients*					
Bar, club or restaurant	76 /2717 (2.8)	1	0.01	1	0.004
Street	46 /888 (5.2)	1.78 (1.23-2.57)		1.89 (1.27-2.80)	
Several avenues	48 /1634 (2.9)	1.07 (0.75-1.54)		0.98 (0.68-1.42)	
REPRODUCTIVE HEALTH					
Current contraceptive use*					
none or other	100/3160 (3.2)	1	0.001	1	<0.001
oral cc	12 /526 (2.3)	0.73 (0.40-1.33)		0.70 (0.38-1.28)	
inject	56 /1378 (4.1)	1.29 (0.93-1.80)		1.35 (0.96-1.88)	
Pregnant	2 /397 (0.5)	0.16 (0.04-0.66)		0.13 (0.03-0.55)	
BEHAVIOURAL CHARACTERISTICS					
Number of sexual partners*					
<5	77 /2765 (2.8)	1	0.30		
5-19	32 /1119 (2.9)	0.97 (0.64-1.49)			
At least 20 or cannot remember	61 /1543 (4.0)	1.29 (0.90-1.84)			
Number of men the participant had paid sex within the last month*					
<5	79 /2816 (2.8)	1	0.14	1	0.29
5-19	27 /1089 (2.5)	0.84 (0.54-1.32)		0.70 (0.43-1.14)	
At least 20 or cannot remember	60 /1522 (3.9)	1.29 (0.90-1.85)		0.96 (0.62-1.47)	

Table 5.3 (*Continued*): Crude and adjusted association of the number of missed visits between successively attended visits and HIV seroconversion with based on Cox regression model.

Characteristic	New HIV cases/pyr (Rate/100 pyr)	Crude Hazard Ratio (95% CI)	P-value	Adjusted Hazard Ratio (95% CI)	P-value
Condom use frequency with paid sex in the last month*					
Inconsistent	72 /1616 (4.5)	1	0.01	1	0.002
Consistent (always)	55 /2223 (2.5)	0.56 (0.40-0.80)		0.51 (0.35-0.74)	
No paid sex	43 /1601 (2.7)	0.64 (0.43-0.96)		0.76 (0.48-1.20)	
Alcohol consumption frequency*					
Non-drinker	49 /1870 (2.6)	1	0.30	1	0.41
Non-daily drinker	68 /2202 (3.1)	1.17 (0.81-1.70)		1.17 (0.79-1.73)	
Daily drinker	53 /1418 (3.7)	1.37 (0.92-2.04)		1.34 (0.87-2.07)	
Binge drinking in last 3 months*					
Non-drinker	48 /1847 (2.6)	1	0.21		
No binging	58 /1617 (3.6)	1.41 (0.95-2.07)			
Binged	64 /2039 (3.1)	1.14 (0.78-1.67)			
Illicit drug use in last 3 months*					
No	122/3949 (3.1)	1	0.34		
Yes	48 /1260 (3.8)	1.18 (0.84-1.66)			
SEXUALLY TRANSMITTED INFECTIONS (STIs)*§					
No STI	109/4033 (2.7)	1	0.01	1	0.12
With STI	61 /1471 (4.1)	1.49 (1.09-2.05)		1.31 (0.93-1.85)	

Adjusted for: Cohort of enrolment, Age at follow-up in years, having a stable sexual partner (both married and un-married), highest education level at enrolment, where clients are recruited from, current contraceptive use, condom use frequency with paid sex in the last month at follow-up, alcohol consumption frequency at follow-up, and presence of a sexually transmitted infection at follow-up. †test for linear trend. Pyr – person years of observation. ††The calendar period of January 2013-December 2014 was common to both cohorts (cohort 1 and cohort 2) since cohort 2 was initiated in January 2013 and was, therefore, used as the reference category. §STI variable was a composite variable combining data on STI symptoms from clinical examination and test results for STI for syphilis. *Data collected at enrolment and follow-up study visits.

5.1.5 Discussion

Our findings demonstrate the importance of ensuring sustained exposure to combined HIV prevention interventions targeting women at high-risk of HIV-infection in the prevention of HIV. Sustained exposure is not only likely to reinforce prevention interventions but also facilitate earlier initiation of antiretroviral treatment (ART) among those recently infected with HIV. Participants attending the clinic had access to a range of services including HIV and other sexual health and reproductive services. At every visit, participants attended counselling sessions where they were encouraged to modify or maintain behaviours depending on their interview responses, results from clinical examinations, and serological test. Participants diagnosed with STIs were additionally given treatment. Therefore, MSV within episodes of consecutive attendances was a proxy for recent degree of exposure to combined HIV prevention interventions.

Compared to episodes without MSV, those with 1-2 MSV had 40% higher risk of HIV-infection while those with ≧3 MSV had twice the risk. This dose-response relationship further supports the effectiveness of combination HIV prevention interventions among FSWs for improved HIV-related outcomes such as consistent condom use with clients, earlier treatment of STIs, and consequently lower HIV infection[6,7,32,33]. However, this effectiveness is dependent on good programme adherence.

Additionally, our findings are consistent with studies that have suggested a link between the amount of exposure to HIV interventions and improved HIV-related outcomes[22-24]. Most notable is a study in Côte d'Ivoire that conducted health talks, provided condoms, treated STIs at monthly clinic visits and serological tests every six months[24]. In this study, HIV incidence was 4.6/100 person-years for women who attended 4 of the 5 scheduled visits before their last assessment and 13.0/100 person-years among those who attended fewer visits[24]. But a time-varying preceding gap in clinic attendance of ≥60 days was associated with reduced HIV risk in a Kenyan FSW cohort with monthly clinic visits[25]. While the authors did not offer a reason for this association, it is likely that participants who missed the monthly visits may have had low risk perception and therefore, saw no need to regularly attend visits. Additionally, the variable indicating a preceding gap was correctly analysed as a confounder but where it is the main exposure of interest, the time-varying variables in that analysis represent potential mediating factors. Thus, these mediating factors underestimate the overall effect of preceding gap.

In our study, the mechanisms through which MSV within episodes of consecutive visit attendances influence HIV infection may be explained by interconnected factors operating at the structural, behavioural, and biomedical levels.

i) Structural factors: HIV determinants such as high mobility, economic difficulties and risky work environments of FSWs may underlie the risk associated with MSV. While the ability to take risks (being a more risky individual) could influence an individual to be mobile in search of work, mobility itself can affect the risk of HIV if there is risk of HIV associated with the new environment/place (i.e the new place has high HIV prevalence, low condom use, and low ART coverage or adherence). A previous qualitative study in this cohort reported that participants commonly moved to fishing communities for extended periods in search of clients[16]. These communities have been linked with high HIV prevalence and incidence yet the fishermen usually preferred condomless sex, thus increasing HIV vulnerabilities for the mobile participants[34].

Other findings in this cohort are a signal to the potential economic pressures facing participants to not only deter them from accessing the much-needed clinic services but also affecting their ability to refuse sex with a client paying more for non-condom use. For example, when transport refund for participants was stopped in January 2013 the rate of MSV among those attending each visit increased substantially from 10% to 30%[27]. Furthermore, some 5% of participants reported lack of transport as a cause for missing two or more consecutive visits based on records of 342 HIV-negative women contacted between October and December 2015.

The social components of targeted HIV interventions such as peer outreach are not only critical in facilitating clinic attendance but are also associated with increased consistent condom use among FSWs[19,21]. Some of the participants with MSV might also have had limited engagement with peer-educators as well as with outreach services, particularly participants working in isolation like street or phone-based FSWs. Yet our findings show that street-based FSWs were more likely to miss study visits and to acquire HIV-infection than those who recruit clients from facilities such as bars or clubs. Among other reasons, street-based FSWs in this cohort as in other studies report a particularly higher risk of sexual or physical violence and exploitation by clients and law enforcers than venue-based FSWs[17,19,35]. Consequently, they are likely to be at a greater risk for STIs and HIV than those based in facilities. Further, participants starting out in sex work are usually young and without social support networks to help them manage daily risks, including getting support for attending clinic visits[17]. These young participants are likely to be more isolated, more stigmatised and to be highly vulnerable[35-38]. Therefore, targeted programmes should work with potentially isolated groups of women at high-risk of HIV (such as the highly mobile or young women) to develop better delivery models for services, which models could include scaling-up and intensifying mobile night clinics and intensifying peer outreach[21,39,40].

ii) Behavioural factors: Regular attendance of a dedicated clinic creates opportunities for reinforcing individual behavioural change messages among women at high-risk of HIV. HIV prevention behaviour can be achieved and sustained when participants are continually provided with appropriate information, are motivated to act, and enabled to obtain behavioural skills. These are key elements of information-motivational-behavioural skills model that has been proposed for antiretroviral therapy adherence but can also be applied for behavioural change among women at high-risk of HIV[41]. In our study, trained counsellors provide information on HIV prevention to participants through interactive sessions. Similar interactive sessions have been credited by FSWs in Zimbabwe for improving awareness of self-care as well as prevention and treatment of HIV and STIs[20]. Also, during ongoing risk-reduction counselling sessions in our study participants are motivated to improve or maintain healthy behaviours. This motivation may not only facilitate the adoption of healthy behaviours but may also influence participants to regularly attend the clinic. Attending follow-up visits at the clinic was associated with higher parity, being on oral contraceptives, and having had an STI at the previous visit, which factors also reflect some underlying motivations related with the services offered at the clinic. According to the information-motivational-behavioural model, ongoing information on HIV prevention and motivation to stay healthy would act through acquired behavioural skills such as correct use of condoms to influence HIV incidence.

Therefore, participants who miss study visits are likely to also miss opportunities for reinforcing HIV risk-reduction behaviours. In addition, the HIV risk associated with MSV may increase where the participant's decision to attend the clinic is influenced by new intimate relationships. When participants start new intimate relationships they might be afraid to associate with the clinic and they could be stopped by spouses from attending the dedicated clinic. In participants who missed ≥2 consecutive visits, 10% reported the reason as being in a new stable relationship or being stopped by a spouse. In this cohort as elsewhere, it is not uncommon for some of these new relationships to involve paying clients who transitioned into regular partnerships[17,35]. These partnerships have not only been associated with limited condom use which is usually seen as a sign of mistrust within intimate relationships across Africa, but also with high HIV burdens[17,42].

iii) Biomedical factors: Regular attendance of a dedicated clinic enables timely access to biomedical interventions for prevention, treatment, and care. For example, 18% of all syndrome-based STIs might not have been detected if FSWs had not attended the clinic in a large study in Southern India on the impact of peer outreach on clinic utilisation reported[144]. Similarly, the clinical examination at our study clinic is likely to facilitate earlier diagnosis and treatment of STIs for those regularly attending the clinic. As a result, earlier treatment would reduce the efficiency of STIs for HIV transmission.

Despite the substantial decline in HIV incidence following enrolment that was recently observed in this cohort, the incidence remained high and persisted over time[27]. HIV incidence also remained high during episodes with no MSV although it was substantially lower in these episodes compared to those with at least 3 MSV. This persistently high HIV incidence despite combined HIV prevention efforts may suggest presence of potential barriers in HIV control among women at high-risk of HIV in this cohort. Among other factors, HIV control may be hindered by common barriers reported across studies in Africa such as accepting offers of sex without condoms for more money, hazardous alcohol use, and sexual and physical violence among women at high-risk of HIV[35,43-46]. To further interrupt the spread of HIV through sex work, there is a need to strengthen targeted HIV prevention efforts by integrating promising direct biomedical interventions such as PrEP, strengthening risk-reduction interventions for substance abuse and perhaps implementing mental health interventions[47-50]. These individual level interventions should be further supported by structural interventions such as community empowerment that ensure that targeted services are supplied and delivered to all women at high-risk of HIV. Community empowerment conceptualised as an active involvement of sex workers and the community in targeted activities could also reduce on the interconnected HIV risk factors of; social stigmas, discrimination and violence[6,8,51]. More importantly, there is need to monitor and strengthen regular engagement between women at high-risk of HIV and service providers including their attendance at clinic services in the design and implementation of HIV prevention interventions. Intensified peer outreach is associated with improved clinic utilisation among FSWs and may be particularly important among isolated groups such as street-based FSWs[20-22].

We note some key limitations. The measurement of MSV and seroconversion within the same episode could lead to some misclassification for the timing of seroconversions in the episodes with MSV if seroconversion occurred earlier before the missed visits. However, we assigned the timing of seroconversion as a random date rather than the commonly used mid-point to reduce on the potential for over estimation of HIV risk during episodes with MSVs[26,27]. Also, the number of events per predictor variable (EPV) in the multivariable model was relatively low (8.5) compared to the recommended minimum EPV of 10[52]. While this low EPV can affect model-based inferences, the strong evidence for the association between MSV and HIV incidence in both the simple and multivariable models suggests that our conclusions could be valid. Similarly, data on some important risk factors such as duration of sex work was not collected, meaning that this association could be confounded. Further, the study did not fully record reasons for MSV and on a longitudinal basis which would have facilitated better understanding of what underlies the HIV risk associated with MSV.

In conclusion, the need for scaling-up targeted combination HIV prevention and treatment interventions for FSWs has been emphasised but this study stresses the importance of monitoring, facilitating, and sustaining exposure to these services once women at high-risk of HIV have been linked to services. Sustained exposure reinforces HIV prevention and facilitates earlier initiation of ART among those recently infected with HIV. Therefore, HIV programmes should include moving a wider scope of services to HIV vulnerable women who are unable or unwilling to attend clinic services, particularly those working outside of established venues such as street based FSWs.

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CHAPTER 6: MISSED STUDY VISITS AND SUBSEQUENT HIV RISK DETERMINANTS AMONG A PREDOMINANTLY FEMALE SEX WORKER COHORT ATTENDING A DEDICATED CLINIC SERVICE IN KAMPALA, UGANDA

Introduction

In Chapter 5, I found an association between the number of missed scheduled visits and subsequent HIV risk among high-risk women, underscoring the need for regular exposure to an effective HIV package among high-risk women. In this chapter I present results that might the potential pathways for the association between the number of missed scheduled visits and subsequent HIV risk, hence addressing thesis objectives 3. A manuscript was submitted to Journal of Acquired Immune Deficiency Syndromes.

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SECTION A – Student Details

Student ID Number	323362	**Title**	Mr.
First Name(s)	Ivan		
Surname/Family Name	Kasamba		
Thesis Title	Influence of attendance at a clinic service for high-risk women on HIV prevention: A longitudinal study in Kampala, Uganda		
Primary Supervisor	Helen Weiss		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Stage of publication	**Undergoing revision**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I led the team of data managers, programmers, clinic staff in improving the data capture systems and subsequently the quality of data collected. I carried out routine checks to identify areas of data collection and management that needed improvements such as a data audit system, creation of local data backups to prevent data loss, linkage of data across the study clinic, developing real-time checks for data completeness, accuracy and consistency. Led the development of standards of operations for data management using electronic at the site. I guided the mobilisation team in setting a system to capture key data about tracking for participants who missed visits. I led the preparation of the manuscript, developing the aims, analysed the data, and drafting the manuscript. I made revisions based on feedback from co-authors, identified a journal and submitted the manuscript. I received guidance from my supervisors at the different stages. I oversaw the data management and data cleaning.

SECTION E

Student Signature	[redacted]
Date	3rd August 2020

Supervisor Signature	Helen Weiss
Date	Sep 22nd 2020

6.1 ARTICLE

6.1.1 Abstract

Introduction

HIV prevention studies among women at high risk of HIV infection such as sex workers recommend urgently scaling-up targeted combination prevention interventions, particularly in sub-Saharan Africa. But there has been little attention given to how inconsistent exposure to combination prevention could affect subsequent HIV risk factors. We analysed longitudinal data consisting of repeated measures on individuals to investigate how the number of missed visits was associated with subsequent individual-level HIV risk factors, in a clinic cohort predominantly consisting of sex workers in Kampala, Uganda.

Methods

Participants were scheduled to attend a visit every three months at a dedicated clinic since April 2008. The association of the number of missed visits (none, 1-2, ≥3) between consecutively attended visits and subsequent HIV risk factors was assessed using random-effects logistic regression models (capturing within and between-individual effects) based on data up to August 2017. The outcomes were (i) presence of either syndromic sexually transmitted infections (STI) or laboratory-diagnosed active syphilis infection, (ii) daily alcohol use, and (iii) inconsistent condom use with paid sex in the past month.

Results

Of the 3084 HIV-negative women enrolled, 2206 (71.5%) had ≥1 follow-up visit with a total of 15,968 follow-up visits attended. Participants in 81.9% of the follow-up visits had attended the previous scheduled visit, 13.4% had missed 1-2 visit(s), and 4.7% had missed ≥3 visits. Within a given participant, the number of missed visits were associated with increased odds of STI detection (aOR=1.32, 95%CI:1.12-1.56 for 1-2 missed visits; aOR=1.79, 95%CI:1.33-2.41 for ≥3 missed visits compared with no missed visits; p-value<0.001) and of daily alcohol use (aOR=1.33, 95%CI: 1.03–1.71 for 1-2 missed visits; aOR=1.73, 95%CI: 1.06-2.82 for ≥3 missed visits; p-value=0.01), but not associated with inconsistent condom use with paid sex in the past month.

Conclusions

Participants were more likely to sustain their frequency of condom use with paid sex in the past month despite missing consecutive visits. However, missing visits might have delayed STI detection and treatment. Therefore, not only is it important to include STI management in a targeted package but routinely delivering that package to settings known for sex work may be necessary.

Key words

Missed clinic visits, clinic engagement, sexually transmitted infections, HIV risk behaviour, female sex workers, Uganda, sub-Saharan Africa

6.1.2 Introduction

In settings with inadequate HIV interventions in sub-Saharan Africa (SSA), mathematical models estimate between 58.3% and 88.9% of incident HIV cases acquired in the period of 2000-2020 to be directly and indirectly related to sex work[1].

Systematic and comprehensive reviews of HIV prevention interventions focused on female sex workers (FSWs) have suggested that interventions are most effective when combined to include biomedical, behavioural, and structural components tailored to local contexts[2,3]. These components are ultimately aimed at proximate determinants for HIV prevention, increasing protected sex (using condoms or PrEP), and reducing biological HIV susceptibility through sexually transmitted infections (STIs)[2-5]. Given the limited coverage of targeted combination HIV prevention, particularly in SSA, a common call to action has been to urgently scale-up effective interventions[6-8]. But consistent exposure of women at high risk of HIV infection to available HIV prevention services might be affected by several characteristics of sex work such as high mobility, stigma and discrimination in health care settings, harmful substance use, and low HIV risk perception[7-11].

In SSA, epidemiological studies of HIV prevention among FSWs have reported lower HIV incidence and prevalence among those who were more regularly exposed to HIV interventions than among those less regularly exposed[12-14]. But the pathways for this effect of intervention exposure frequency have not been clearly demonstrated. Other studies among FSWs which have evaluated whether individuals sustained sexual behaviours during, and approximately a year after, terminating clinic-based counselling and STI management have reported mixed findings[15,16]. According to the information-motivation-behavioural skills framework, we would expect individuals to sustain behavioural patterns over time if they are well-informed about HIV transmission and prevention, well-motivated to adopt behaviour, and have acquired behavioural skills[17].

To date, studies involving FSWs have not examined temporal associations between inconsistent exposure to combined HIV prevention and subsequent HIV risk factors (e.g. STI, daily alcohol use, and sexual behaviour). This paper investigates the association of the number of missed scheduled visits between successive visits attended and the subsequent proximate HIV risk determinants among women at high-risk of HIV infection (predominantly sex workers) attending a dedicated HIV prevention and treatment clinic in Kampala, Uganda. We consider three HIV risk determinants: (i) either syndromic or laboratory diagnosed STIs (ii) daily alcohol use (iii) inconsistent condom use with paid sex in the past month.

6.1.3 Methods

Study population and setting

The Good Health for Women Project is an ongoing HIV prevention and treatment programme established in April 2008 for women at high risk of HIV infection in Kampala, Uganda. The programme includes a dedicated study clinic. Full details on recruitment and enrolment have been published previously[18-20]. In brief, FSWs trained as peer-educators mobilised other FSWs and women employed in surrounding entertainment venues within locations frequented by sex workers. These women were invited to attend the clinic, where they were re-screened for eligibility and those who consented were enrolled if they self-reported receiving money, goods, or other favours in exchange for sex, or worked in surrounding entertainment facilities.

Consenting women who tested HIV-positive or HIV-negative at enrolment were enrolled into the clinic cohort in two waves. The first enrolment was between April 2008 and May 2009 (cohort 1) with follow-up visits scheduled once every three months. The second enrolment started in January 2013 (cohort 2) at an ongoing basis with identical follow-up procedures as cohort 1. This paper includes only HIV-negative participants enrolled by 1st May 2017 who last attended a follow-up visit on 29th August 2017. To encourage study retention, participants with upcoming visits within the following month were mobilised and attended group meetings held every two weeks. While participants who had missed at least two consecutive visits were contacted by phone or traced in their community through peer-educators and invited to attend the clinic on an agreed date.

Data collection and HIV intervention

At enrolment and follow-up visits, socio-demographic data, behavioural, reproductive health and clinical data including signs and symptoms of STIs, were recorded using standardized questionnaires by trained staff. Participants were tested for HIV at every visit and for syphilis every 6 months following the Uganda Ministry of Health guidelines[21].

Free sexual and reproductive health services (family planning services and antenatal care) and general health care for participants and their children aged<5 years were offered at the clinic. Each participant at every visit was offered a free combined prevention package, which included sexual health education, counselling on HIV prevention and harmful substance use, treated for diagnosed STIs, and given condoms. Nurse-counsellors also demonstrated the correct use of condoms in group sessions.

At every visit, the project staff emphasised specific HIV components of the prevention package depending on a participant's behavioural responses, test results for HIV and syphilis, and clinical outcomes including STI syndromic diagnosis. For example, participants who reported consistent condom use or non-drinkers were encouraged to maintain this behaviour, whereas inconsistent condom users or harmful drinkers were supported to acknowledge their behaviour and its possible consequences, and to take immediate steps to change behaviours. Participants were also given information on existing HIV prevention products and services such as post-exposure prophylaxis (PEP), and referred to providers when needed.

As part of the community mobilisation activities, quarterly meetings were held with members of the community advisory board which included representatives of study participants and of police, local council leaders, facility managers and owners.

Outcomes and main exposure

The three primary outcomes recorded at follow-up visits are:

(i) detection of an STI, derived from either presenting with abnormal vaginal discharge, genital ulcer disease syndrome, or pelvic inflammatory disease or presence of an active syphilis infection (Rapid Plasma Reagin titres≥1:8 and positive Treponema Pallidum Haemagglutination Assay). From 2008 to 2010, endocervical and vaginal swabs were used to detect *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, and Trichomonas vaginalis.

(ii) daily alcohol use was derived from two questions: “In the last 3 months, did you during a period of at least 2 weeks daily drink alcohol?” and “How often do you have a drink containing alcohol?”. Corresponding responses of either “Yes” or “4 or more times a week” were categorised as daily alcohol use.

(iii) inconsistent condom use with paid sex in the past month was based on responses from the following question: “During the last month, how often did you use a condom when you had sexual intercourse in exchange for money, goods or other favours?”. Consistent condom use was defined by responses of “always” while inconsistent condom use by “most of the time”, “sometimes” or “never”. Visits on which participants did not report paid sex in the past month were excluded from analysis where this visit captured the outcome.

The main exposure was defined by the number of missed scheduled visits between successive visits attended. A participant who attended the clinic during the window period of 14 days before and 76 days after the scheduled date was considered to have attended that scheduled visit, and missed a visit if otherwise. Missed visits were grouped into three categories: i) no missed visit(s), ii) 1-2 missed visits, iii) ≥3 missed visits.

Statistical analysis

Stata version 14 (StataCorp, 2015) was used for analysis. Separate analyses were performed for each of the three outcomes since a composite measure might have obscured the relationship of each with missing visits. To account for within-participant clustering, random-effects logistic regression models were fitted with a random effect for participant. Each model accounted for the effect of the outcome at the prior visit attended on the outcome at a subsequent visit (Figure 6.1) and a-priori for the cohort of enrolment (cohort 1 vs cohort 2), the sequentially scheduled visit number, and age. For the visit number, we tested for extra-linear variability using likelihood ratio tests (LRT) and graphically compared the fitted curves for each of the three outcomes over time from enrolment with corresponding observed trends, by cohort.

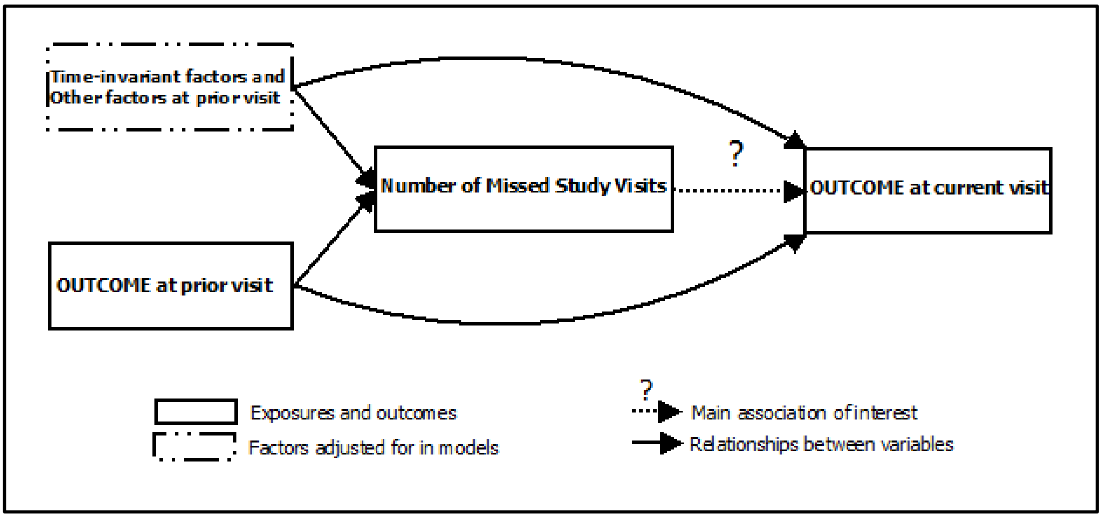


Figure 6.1: An illustration of the relationship for the number of missed study visits between successive visits attended and HIV risk determinants within a given participant.

Standard random-effects models assume that time-varying covariates are independent of individual-level residuals[22]. However, the missing visits may partly depend on individual-level characteristics, which might violate the assumption. One solution is to partition the effects for the missed visits variable into: (i) time-varying within-individual effects, (ii) time-invariant between-individual effects[23]. The between-individual effects were estimated by the coefficients for the proportion of times during the study that each participant missed 0, 1-2, and ≥3 visits. The within-individual effects were estimated by the coefficients for the difference between these participant-level proportions and corresponding visit-level dummy variables for the three missed visit categories (mean centring for each participant).

The difference of between-individual and within-individual effects enabled to assess whether participants who more regularly missed visits had a higher than average risk for a given HIV risk determinant than those who less regularly missed visits over the observation period. Further, the percentage of total variation in each risk determinant attributed to differences between participants was estimated as the ratio of between-participant variance to the total variance.

Variable selection

Time-varying variables that potentially confound the associations were examined first, which included socio-demographic characteristics, behavioural, substance use, reproductive, and detection of an STI. These were included in the models if there was a 10% relative change in partial coefficients for missed visits after inclusion. To avoid covariates on the causal pathway, time-varying covariates recorded at the prior visit were used in the model. For each outcome, missed visits were assessed for linearity and departures from linearity using LRTs.

Table 6.1: Shows the proportion with no follow-up visit, and odds ratios from simple and multivariable models for determinants of no follow-up visit among women enrolled into the GHWP between April 2008 and May 2017.

Characteristic at enrolment	Frequency distribution, n (column %)	Proportion with no follow-up visit, n (%)	Odds Ratio (95% CI) adjusted for cohort and age	p-value	Adjusted Odds Ratio (95% CI) for risk factors[1]	p-value
Total	3084	878 (28.5)				
SOCIO-DEMOGRAPHIC						
Cohort of enrolment						
Closed cohort	647 (21.0)	42 (6.5)	1	<0.001	1	<0.001
Open cohort	2437 (79.0)	836 (34.3)	7.71 (5.57-10.68)		6.59 (4.70-9.24)	
Age in years						
<24	1350 (44.6)	459 (34.0)	1	<0.001	1	<0.001
25-34	1306 (43.2)	321 (24.6)	0.62 (0.52-0.74)		0.77 (0.61-0.97)	
35+	368 (12.2)	69 (18.8)	0.40 (0.30-0.53)		0.44 (0.30-0.65)	
Number of children						
None	484 (16.2)	187 (38.6)	1	0.01	1	0.01
One	781 (26.1)	239 (30.6)	0.77 (0.60-0.99)		0.72 (0.53-0.96)	
At least 2	1730 (57.8)	407 (23.5)	0.66 (0.51-0.85)		0.63 (0.47-0.86)	
Where paying clients are recruited from						
Bar, club or restaurant	1396 (49.1)	356 (25.5)	1	<0.001	1	0.004
Street	775 (27.3)	291 (37.5)	1.51 (1.24-1.83)		1.37 (1.09-1.72)	
Several avenues	670 (23.6)	138 (20.6)	0.87 (0.69-1.09)		0.88 (0.68-1.13)	
Current contraceptive use						
none or other	1813 (63.6)	530 (29.2)	1	0.01	1	0.05
oral cc	205 (7.2)	34 (16.6)	0.57 (0.38-0.85)		0.58 (0.37-0.89)	
inject	696 (24.4)	180 (25.9)	0.84 (0.68-1.03)		0.85 (0.67-1.08)	
Pregnant	138 (4.8)	26 (18.8)	0.73 (0.46-1.16)		0.80 (0.48-1.34)	
Frequency of paid sex in the last 12 months at enrolment						
Less than once a week/None	400 (13.1)	125 (31.3)	1	<0.001	1	<0.001
At least once a week	945 (31.0)	210 (22.2)	0.63 (0.48-0.83)		0.46 (0.31-0.69)	
Daily	1703 (55.9)	522 (30.7)	0.90 (0.70-1.15)		0.56 (0.38-0.83)	

Condom use frequency with paid sex in the last month						
Inconsistent	1186 (41.1)	297 (25.0)	1	0.002	1	0.001
Consistent (always)	1366 (47.5)	396 (29.0)	1.39 (1.15-1.67)		1.34 (1.10-1.65)	
No paid sex	329 (11.4)	88 (26.7)	1.15 (0.86-1.54)		0.69 (0.43-1.09)	
Ever experienced gender-based violence[2]						
Never	1308 (59.3)	456 (34.9)	1	0.10	1	0.04
Ever	898 (40.7)	279 (31.1)	0.86 (0.71-1.03)		0.80 (0.65-0.99)	

[1]Adjusted for cohort of enrolment, Age in years, number of children, Where paying clients are recruited from, Current contraceptive use, Frequency of paid sex in the last 12 months at enrolment, Condom use frequency with paid sex in the last month.[2]Ever experienced violence only asked in cohort 2, so these are only cohort 2 participants

6.1.4 Results

Cohort and participant characteristics

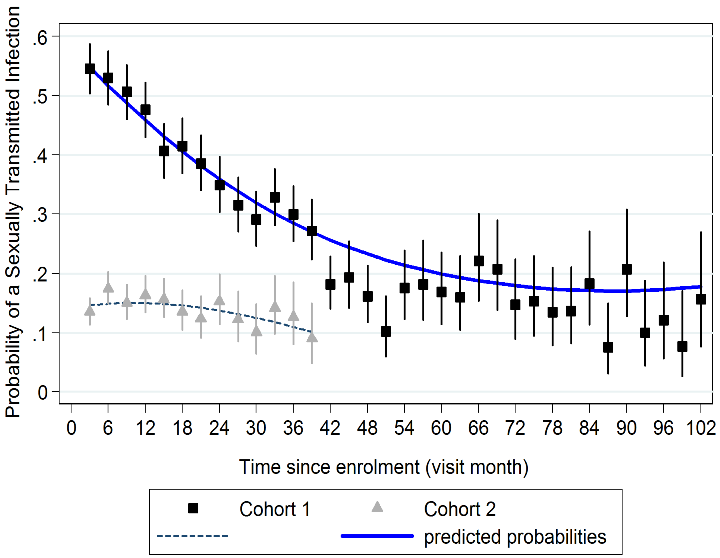
Between April 2008 and April 2017, 4915 women were enrolled into the clinic cohort. At enrolment, 35.7% (n=1715) of the participants tested HIV-positive. Of the 3084 HIV-negative participants, 2206 (71.5%) had ≥1 follow-up visit. The majority (94.9%) of the 878 participants without follow-up had been enrolled in cohort 2. Table 6.1 compares the characteristics for those with and without a follow-up visit, but adjusted comparisons are shown in the supplementary table C.1. Having no follow-up was independently associated with: cohort 2, being younger, having no children, not using contraceptives, street-based FSW, less frequent paid sex, never experienced gender-based violence and reporting consistent condom use. But we found no evidence for an association of loss to follow-up with being detected with an STI or reported daily alcohol use.

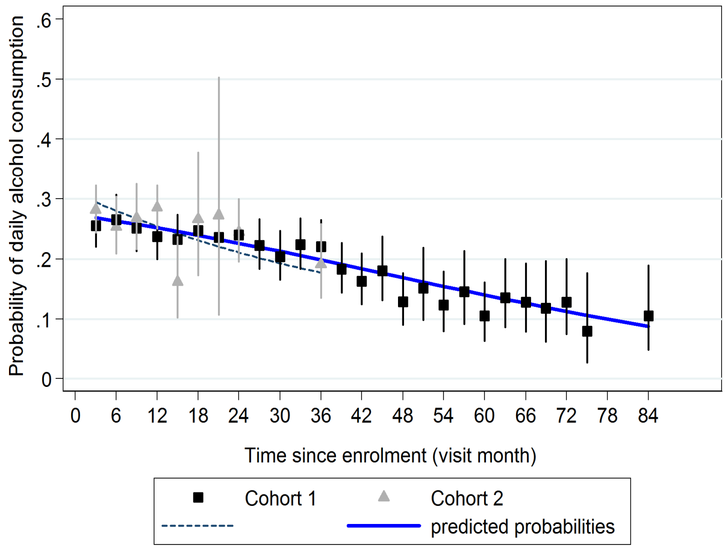
The findings that follow are among participants with ≥1 follow-up visit. At enrolment, the mean age was 26.7 years (standard deviation: 6.3). Most participants were widowed or divorced (63.3%), had ≥1 child (86.2%), and a substantial proportion had incomplete primary education level (41.1%). Most participants reported sex work to be their only source of income (56.5%) and usually recruited clients from established facilities like bars, night clubs, or restaurants (50.2%). Only 4.7% (n=106) reported having no paid sex in the last 12 months.

HIV risk determinants

At enrolment, cohort 2 participants reported higher sexual risk behaviour, and substance use (daily alcohol use and illicit drugs) than cohort 1 participants, but were more likely to have been tested for HIV within the last 6 months and less likely to have been detected with an STI.

Figure 6.2 shows the trends over time in STI detection, daily alcohol use, and inconsistent condom use with paid sex in the last month, by cohort. In cohort 1, the decline within the first 2 years of enrolment was steeper for STI detection (p-trend<0.001) than daily alcohol use (p-trend<0.001) and inconsistent condom use with paid sex in the last month (p-trend=0.51). The proportion reporting inconsistent condom use showed no substantial change over the first two years but declined thereafter (p-trend=0.003) appearing to stabilize at about 30%. In cohort 2, the decline in proportions was steeper for inconsistent condom use (p-trend=0.005) than daily alcohol use (p-trend=0.06) or STI detected (p-trend=0.38).





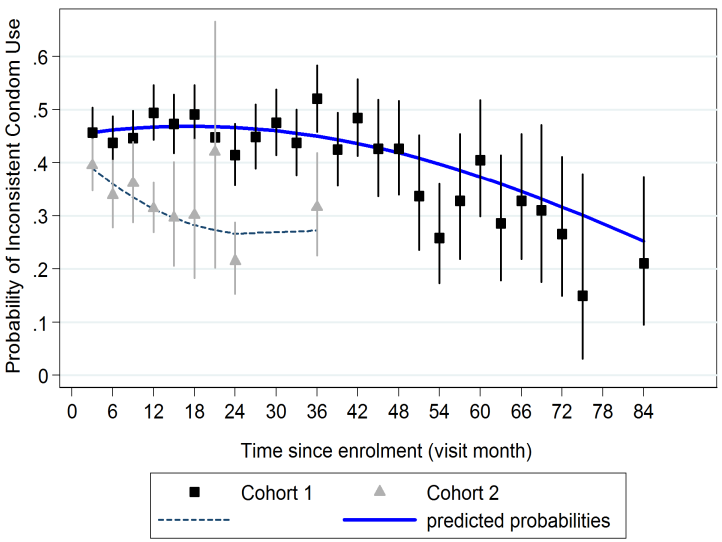


Figure 6.2: Estimated trends since enrolment for HIV risk determinants (presence of any Sexually Transmitted Infection, frequency of alcohol use, and frequency of condom use with paid sex in the last month) among HIV-negative participants

Table 6.2: Distribution for the number of visits missed, percentage of those visits with HIV risk determinants (Sexually Transmitted Infection, daily alcohol use, and inconsistent condom use with paid sex in the last month) and Odds ratio for risk determinants.

Characteristic	Follow-up visits attended	HIV risk outcomes: Presence of any Sexually Transmitted Infection (Yes versus No)			Alcohol consumption frequency (Daily Versus Non-daily)			Condom use frequency with paid sex in the last month (Inconsistent Versus consistent)		
		% of all reports	Odds Ratio[a] (95% CI)	P-value	% of all reports	Odds Ratio[a] (95% CI)	p-value	% of all reports	Odds Ratio[a] (95% CI)	p- value
Total	15,968	3680 (25.0)			2299 (21.8)			2894 (41.5)		
Number of visits missed between attendances†										
No missed visit	13080(81.9)	3128 (25.6)	1	<0.001	1966 (21.5)	1	0.001	2595 (41.9)	1	0.27
One/two missed visit(s)	2139(13.4)	423 (22.1)	1.37 (1.19-1.58)		256 (23.7)	1.34 (1.06-1.68)		246 (40.2)	1.03 (0.83-1.29)	
At least 3 missed visits	749 (4.7)	129 (22.5)	1.87 (1.47-2.38)		77 (25.3)	2.00 (1.30-3.09)		53 (30.8)	0.71 (0.47-1.09)	
Cohort of enrolment										
Cohort 1	9063 (56.7)	2804 (32.2)	1	<0.001	1654 (20.6)	1	0.37	2340 (44.0)	1	<0.001
Cohort 2	6905 (43.3)	876 (14.6)	0.17 (0.15-0.20)		645 (25.6)	1.17 (0.84-1.62)		554 (33.3)	0.48 (0.38-0.60)	
Age in years										
<24	6068 (38.1)	1618 (29.1)	1	0.004	759 (18.6)	1	<0.001	1130 (44.3)	1	0.13
25-34	7707 (48.4)	1703 (24.0)	0.82 (0.71-0.96)		1224 (23.7)	2.21 (1.55-3.17)		1460 (40.2)	0.79 (0.63-1.00)	
35+	2160 (13.6)	350 (17.6)	0.72 (0.57-0.90)		312 (24.4)	1.43 (0.84-2.42)		302 (38.0)	0.79 (0.55-1.13)	
Condom use frequency with paid sex in the last month†										
Inconsistent	4608 (29.3)	1207 (28.4)	1	0.26	946 (29.4)	1	<0.001	1603 (62.1)	1	<0.001
Consistent (always)	6392 (40.6)	1404 (23.8)	0.93 (0.83-1.04)		1023 (24.5)	0.90 (0.76-1.06)		906 (26.1)	0.43 (0.38-0.50)	
No paid sex	4727 (30.1)	1032 (23.9)	1.02 (0.90-1.17)		315 (10.2)	0.41 (0.33-0.51)		376 (41.7)	0.67 (0.55-0.81)	
Alcohol consumption frequency†*										
Non-drinker	5505 (34.7)	1193 (23.5)	1	0.52	110 (3.1)	1	<0.001	688 (38.2)	1	0.31
Non-daily drinker	6353 (40.0)	1534 (26.1)	0.99 (0.88-1.12)		672 (15.0)	5.15 (4.02-6.58)		1293 (41.1)	1.02 (0.85-1.22)	
Daily drinker	4024 (25.3)	930 (25.5)	1.07 (0.92-1.23)		1511 (60.6)	16.13 (12.34-21.08)		910 (45.0)	1.15 (0.93-1.42)	
Presence of Sexually Transmitted†*‡										
No STI	10870 (72.4)	1793 (18.1)	1	<0.001	1407 (20.7)	1	0.04	1704 (38.3)	1	0.001
With STI	4148 (27.6)	1761 (44.6)	1.55 (1.39-1.72)		808 (24.2)	1.19 (1.01-1.40)		1132 (48.9)	1.27 (1.10-1.46)	

[a]Using the random effects logistic regression model adjusted for cohort, the visit number (linear and quadratic), age, and previous outcomes. †Data obtained at follow-up visits, *Covariate at the previous visit showing the proportion of outcome at the following visit, ‡Presence of both STI symptoms from clinical examination and test results for STI for syphilis.

Visit attendance

Out of the 170 HIV seroconverters during observation, 54 women who tested HIV positive at their second visit to the clinic were excluded from analysis, whereas the data prior to the visit with an HIV-positive test result were included for the remaining 116 seroconverters. Thus, 2152 participants attended 15,968 (70.1%) follow-up visits out of 22,749 scheduled visits. Per person, the median number of visits attended was five (interquartile range (IQR): 3-11) while eight visits (IQR: 4-15) were scheduled. At least once during the study, 53.3% of participants missed 1-2 consecutive visits and 28% missed ≥3 consecutive visits.

Figure 6.3 shows patterns of missed visits between successive visits attended. In cohort 1, the percentage of participants attending visits consecutively was stable for the first 4 years of enrolment (until month 48), averaging 92.6% (95% CI: 91.6-93.5%). After year 4, this percentage decreased substantially to an average of 64.5% (95% CI: 62.1-66.8%). This later period coincides with cohort 2 enrolment, which had similar percentages attending visits consecutively: 63.6% (95% CI: 61.9-65.3%). Overall, participants in 81.9% of the 15,968 follow-up visits had attended consecutively, 13.4% had missed 1-2 visit(s), and 4.7% had missed ≥3 visits (Table 6.2).

Missing visits and HIV risk determinants

Table 6.3 and Table 6.4 show results from the crude and multivariable random-effects logistic regression models, respectively, for STI, reported daily alcohol use, and inconsistent condom use with paid sex in the last month.

The effect of missing visits on each of the three HIV risk determinants was not substantially changed with the multivariable model. In a given participant, the multivariable model shows that missing visits was associated with increased odds of STI detection at a subsequent visit (compared to “No missed visit”: aOR=1.32, 95%CI: 1.12–1.56 for 1-2 visits; aOR=1.79, 95%CI: 1.33-2.41 for ≥3 visits; p<0.001). Similarly, missing visits was associated with increased odds of daily alcohol use (aOR=1.33, 95%CI: 1.03–1.71 for 1-2 visits; aOR=1.73, 95%CI: 1.06-2.82 for ≥3 visits; p=0.01). There was no evidence for an association between missing visits and inconsistent condom use with paid sex in the last month at a subsequent visit (p=0.80).

When within and between-participants coefficients for missing visits were compared, we found no evidence that those who missed a higher proportion of visits during the study also had a higher tendency of being detected with an STI (p=0.24), reporting daily alcohol use (p=0.23), or reporting inconsistent condom use with paid sex (p=0.89), over and above the effect for missing visits. The higher proportion of total variance attributed to differences between participants for alcohol use (39.4%) and inconsistent condom use (28.4%) than that for STI detection (18.4%) might suggest that daily alcohol use and inconsistent condom use were more persistent within participants than STI detection.

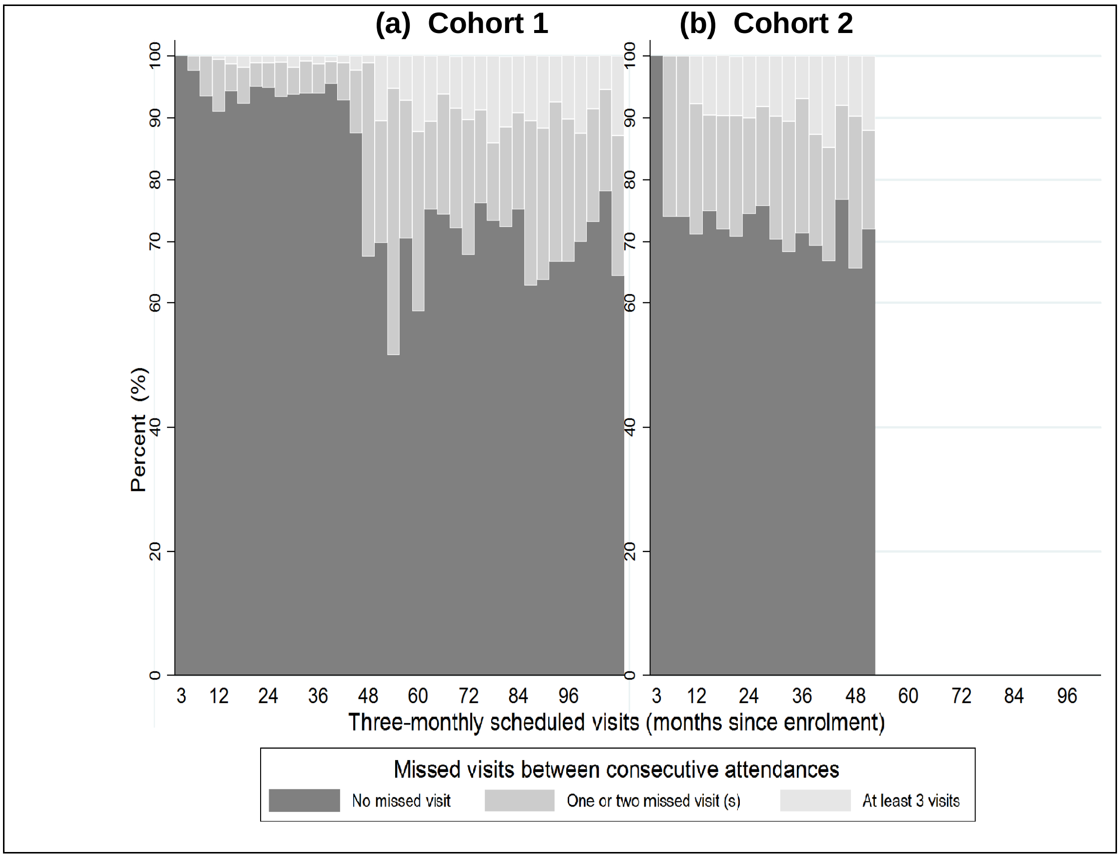


Figure 6.3: Distribution for the categories of the number of missed visits between successive visits attended, by the cohort of enrolment (cohort 1, cohort 2).

Table 6.3: Distribution of the number of follow-up visits attended, the percentage of follow-up visits with HIV risk outcomes (Sexually Transmitted Infection, frequency of alcohol consumption, and frequency of condom use with clients in the last month) and Odds ratio from the random-effects logistic model, among HIV-negative participants.

Characteristic	Follow-up visits attended	HIV risk outcomes: Presence of any Sexually Transmitted Infection (Yes versus No)			Alcohol consumption frequency (Daily Versus Non-daily)			Condom use frequency with paid sex in the last month (Inconsistent Versus consistent)		
	Number of visits	% of all reports	Odds Ratio[a] (95% CI)	P-value	% of all reports	Odds Ratio[a] (95% CI)	p-value	% of all reports	Odds Ratio[a] (95% CI)	p-value
Total	15,968	3680 (25.0)			2299 (21.8)			2894 (41.5)		
SOCIO-DEMOGRAPHIC										
Number of visits missed between attendances†										
No missed visit	13080 (81.9)	3128 (25.6)	1	<0.001	1966 (21.5)	1	0.001	2595 (41.9)	1	0.27
One/two missed visit(s)	2139 (13.4)	423 (22.1)	1.37 (1.19-1.58)		256 (23.7)	1.34 (1.06-1.68)		246 (40.2)	1.03 (0.83-1.29)	
At least 3 missed visits	749 (4.7)	129 (22.5)	1.87 (1.47-2.38)		77 (25.3)	2.00 (1.30-3.09)		53 (30.8)	0.71 (0.47-1.09)	
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Cohort 1	9063 (56.7)	2804 (32.2)	1	<0.001	1654 (20.6)	1	0.37	2340 (44.0)	1	<0.001
Cohort 2	6905 (43.3)	876 (14.6)	0.17 (0.15-0.20)		645 (25.6)	1.17 (0.84-1.62)		554 (33.3)	0.48 (0.38-0.60)	
Age in years										
<24	6068 (38.1)	1618 (29.1)	1	0.004	759 (18.6)	1	<0.001	1130 (44.3)	1	0.13
25-34	7707 (48.4)	1703 (24.0)	0.82 (0.71-0.96)		1224 (23.7)	2.21 (1.55-3.17)		1460 (40.2)	0.79 (0.63-1.00)	
35+	2160 (13.6)	350 (17.6)	0.72 (0.57-0.90)		312 (24.4)	1.43 (0.84-2.42)		302 (38.0)	0.79 (0.55-1.13)	
Condom use frequency with paid sex in the last month†										
Inconsistent	4608 (29.3)	1207 (28.4)	1	0.26	946 (29.4)	1	<0.001	1603 (62.1)	1	<0.001
Consistent (always)	6392 (40.6)	1404 (23.8)	0.93 (0.83-1.04)		1023 (24.5)	0.90 (0.76-1.06)		906 (26.1)	0.43 (0.38-0.50)	
No paid sex	4727 (30.1)	1032 (23.9)	1.02 (0.90-1.17)		315 (10.2)	0.41 (0.33-0.51)		376 (41.7)	0.67 (0.55-0.81)	
Alcohol consumption frequency†⁎										
Non-drinker	5505 (34.7)	1193 (23.5)	1	0.52	110 (3.1)	1	<0.001	688 (38.2)	1	0.31
Non-daily drinker	6353 (40.0)	1534 (26.1)	0.99 (0.88-1.12)		672 (15.0)	5.15 (4.02-6.58)		1293 (41.1)	1.02 (0.85-1.22)	
Daily drinker	4024 (25.3)	930 (25.5)	1.07 (0.92-1.23)		1511 (60.6)	16.13 (12.34-21.08)		910 (45.0)	1.15 (0.93-1.42)	
Presence of Sexually Transmitted†⁎‡										
No STI	10870 (72.4)	1793 (18.1)	1	<0.001	1407 (20.7)	1	0.04	1704 (38.3)	1	0.001
With STI	4148 (27.6)	1761 (44.6)	1.55 (1.39-1.72)		808 (24.2)	1.19 (1.01-1.40)		1132 (48.9)	1.27 (1.10-1.46)	

[a]Using the random effects logistic regression model adjusted for cohort, the visit number (linear and quadratic), age, and previous outcomes. †Data obtained at follow-up visits, ⁎Covariate at the previous visit showing the proportion of outcome at the following visit, ‡Presence of both STI symptoms from clinical examination and test results for STI for syphilis.

Table 6.4: Association between the number of missed study visits between successive visits attended and subsequent HIV risk determinants (presence of any Sexually Transmitted Infection, daily alcohol use, and inconsistent condom use with paid sex in the last month)

Characteristic	Presence of any Sexually Transmitted Infection (Yes Vs No)		Alcohol consumption frequency (Daily Vs Non-daily)		Condom use frequency with paid sex in the last month (Inconsistent Vs consistent)	
	Adjusted OR[a] (95% CI)	p-value	Adjusted OR[b] (95% CI)	p-value	Adjusted OR[c] (95% CI)	p-value
FIXED EFFECTS						
Number of missed study visits						
Within-participant effect						
Attended preceding visit (Reference)	1	<0.001	1	0.01	1	0.80
1-2 missed study visit(s)	1.32 (1.12-1.56)		1.33 (1.03-1.71)		1.06 (0.83-1.36)	
At least 3 missed study visits	1.79 (1.33-2.41)		1.73 (1.06-2.82)		0.90 (0.57-1.42)	
Between-participants effect[d]						
Attended preceding visit (Reference)	1	0.004	1	0.003	1	0.60
1-2 missed study visit(s)	1.83 (1.26-2.67)		4.13 (1.79-9.56)		0.80 (0.40-1.61)	
At least 3 missed study visits	1.57 (0.93-2.65)		0.87 (0.34-2.23)		0.76 (0.32-1.82)	
Unit increase in visit number (time since enrolment)						
Unit visit number	0.88 (0.86-0.90)	<0.001	0.97 (0.96-0.98)	<0.001	1.02 (0.99-1.06)	0.12
Unit quadratic visit number	1.002 (1.001-1.002)	<0.001			0.998 (0.997-0.999)	0.002
Age in years						
<24(Reference)	1	<0.001	1	0.01	1	0.32
25-34	0.80 (0.69-0.93)		1.46 (1.12-1.90)		0.85 (0.69-1.05)	
35+	0.65 (0.51-0.82)		0.98 (0.66-1.46)		0.85 (0.61-1.19)	
RANDOM EFFECTS						
Variance between participants	0.728		2.143		1.309	
% total variance attributed to differences between participants	18.1%		39.4%		28.5%	

[a]*Presence of any Sexually Transmitted Infection*, adjusted for: Presence of any Sexually Transmitted Infection, Cohort of enrolment, Unit visit, Unit quadratic visit, Age in years, Highest education level, Main source of income at follow-up, Place for usual recruitment of clients, Number of clients within last month, Alcohol consumption frequency at follow-up (lagged), Condom use frequency with clients in the last month; [b]*Alcohol consumption frequency (Daily Vs Non-daily)*, adjusted for: Alcohol consumption frequency at follow-up (lagged), Cohort of enrolment, Unit visit, Age in years, Main source of income at follow-up, Place for usual recruitment of clients, Number of clients within last month, Illicit drug use within last 3 months at follow-up, Current contraceptive use (lagged), Presence of any Sexually Transmitted Infection; [c]*Condom use frequency with paid sex in the last month (Inconsistent Vs consistent*), adjusted for: Condom use frequency with clients in the last month, Cohort of enrolment, Unit visit, Unit quadratic visit, Age in years, Marital status at follow-up, Number of clients within last month, Alcohol consumption frequency at follow-up (lagged). The difference between the coefficients for between-participants minus within-participants gives us the contextual effects over and above the visit-level effects: the p-value of contextual effects for STI diagnosis was p=0.24, for reported frequency of alcohol use p=0.23, and for reported frequency of condom use with clients in the last month p=0.89.

6.1.5 Discussion

To our knowledge, this is the first study to demonstrate how the duration for which a woman at high risk of HIV infection is not exposed to a combined prevention package is associated with HIV risk determinants. Missing visits were independently associated with increased risk of both STI detection and reported daily alcohol use at the subsequent visit, but not found to be associated with reported inconsistent condom use with paid sex in the last month.

Missing visits and STI detection

The strong evidence for an independent association of missing visits with subsequent STI detection in a given participant is consistent with findings from other epidemiogical studies that related the frequency of visit attendance with the prevalence of STIs among FSWs in SSA[13,14,24]. In these studies, FSWs who attended a lower proportion of study visits had a higher prevalence of STIs than those who attended a higher proportion of visits, but overall there was no sufficient evidence to support these differences perhaps because of low statistical power.

In our study, this association could be explained in two broad ways. Firstly, missing visits might have delayed the detection and treatment of STIs which medical personnel could have otherwise detected and prescribed appropriate treatment. A large observational study in Karnataka, India found that about one-fifth of all syndromically detected STIs were identified at clinic visits where the FSW had reported no STI symptoms[25]. Secondly, missing visits may have been underlined by other factors such as mobility, harmful alcohol use, acquisition of a new intimate partner, or stigma and social discrimination, which are characteristic of sex work and have been reported to inhibit utilisation of health services[7,9,10,26,27]. For example, in a subpopulation of participants who had missed at least 2 visits in this study and were contacted between October and December 2015, over half reported mobility as the main reason for missing visits. Further, participants in an earlier qualitative study nested in this cohort, reported moving to fishing communities for prolonged periods, which communities have been associated with elevated STIs and low condom use[28-30]. These observations underscore the need for regular screening and testing of STIs among women at high risk of HIV infection, which may include routinely delivering a prevention package with STI management to settings known for sex work.

Missing visits and daily alcohol use

We did not find published HIV prevention studies that had examined the association between missing visits and subsequent alcohol use among women at high risk of HIV infection in SSA with which to compare our findings. However, the positive association between missing visits and reported daily alcohol use at a subsequent visit may reflect the probable impact of the combined prevention package that includes risk reduction counselling. Brief interventions of alcohol harm reduction counselling were found to be effective in reducing drinking frequency in a systematic review of HIV prevention interventions among FSW in SSA[3]. In the current study, consecutively attending visits may have increased awareness of the dangers of harmful drinking and consequently, could have led to lower reported daily alcohol use[31]. Without consistent exposure, however, these intervention benefits might be precarious since daily alcohol use between visits within a given participant was found to more persistent than the other HIV risk determinants. This finding is consistent with the conclusion in a previous quantitative study in this clinic cohort of a high prevalence of persistent problem drinking[32].

Factors that underlie missed visits may also explain the positive association between missing visits and daily alcohol use. Qualitative studies within this clinic cohort have noted that participants used alcohol to cope with sex work-related challenges[33,34]. Therefore, they might be more likely to depend on alcohol to cope with additional challenges due to some of the factors mentioned earlier that underlie missed visits such as mobility.

Missing visits and inconsistent condom use

Given that we did not find an association between missing visits and inconsistent condom use with paid sex, condom use frequency within an individual might have been sustained between successive visits attended regardless of the number of missed visits. Despite the potential bias associated with self-reported sensitive information, this finding is consistent with the information-motivation-behavioural skills framework[17,35]. It is also consistent with results in a study among FSWs from Cote d'Ivoire which found similar proportions of participants reporting consistent condom use with clients by frequency of visits attended[14], and another in Kenya which suggested sustained individual sexual behaviours after 1 year of terminating routine clinic-based counselling and STI management[15]. Cross-sectional studies among FSWs have found a higher proportion of reported consistent condom use with clients among women who attended more education sessions in the past six months or among those who were contacted more often in the past month by study staff, but this study design is subject to many methodological limitations including selection bias[14,36].

Strengths and limitations

A key strength of this study was its longitudinal nature with long follow-up of up to 8 years, which enabled examining within-individual and between-individual effects. This within-between formulation of random-effects regression models and the large sample size enhanced our analysis. Conversely, key limitations include the presence of missing data and study attrition. Missing data occurred mainly as a result of programming errors in the electronic data capture system as it was rolled-out in January 2015. In 2015, the behavioural questionnaire was worst affected with up to 19.5% of the expected data identified as missing. Because of the programming errors missing data was considered to be missing completely at random. For attrition, some participants might have exited the study after a self-perception of low HIV risk, say, because they were accessing services elsewhere or following exit from sex work. While this might be expected to overestimate the effect of missing visits some of these participants might no longer be part of the target group. Lastly, our study does not carefully capture all the potential changes in outcomes in the period between visits, limiting a full understanding of the sustainability of the intervention.

Conclusion

In this setting, whereas consistent exposure to a combined prevention package is clearly needed among women at high risk, specific components within the package may require less emphasis than others after earlier sessions with service providers. For example, apart from targeted programmes ensuring that condoms are always available to women at high risk, consistently providing information on condoms and demonstrating condom use may be needed less after earlier sessions. However, not only should STI management be included in a targeted package provided at clinic facilities, it should be routinely delivered through mobile clinics to settings known for sex work so as to serve those unable or unwilling to attend clinic facilities.

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CHAPTER 7: DISCUSSION

7.1 Introduction

In this chapter, I summarise and synthesise the main findings from this thesis including a discussion of the strengths and limitations, significance and implications of the thesis findings for public health, practical applications and possible directions of future research.

7.2 Recap of the aim and objectives

In this thesis, I sought to examine the importance of regular exposure to a package of interventions to prevent HIV acquisition among women at high risk of HIV, which package included risk reduction counselling, STI management, and HIV testing.

The following objectives were addressed:

(i) Examined HIV incidence trends and proximate HIV risk determinants following enrolment into an HIV programme for women at high of HIV, in which individuals were scheduled to attend a dedicated study clinic once every three months.

(ii) Investigated the association between missed scheduled clinic visits (i.e. interrupted exposure to HIV prevention interventions) and subsequent HIV risk among HIV-negative women enrolled into the targeted HIV programme

(iii) Investigated the association between missed scheduled clinic visits and subsequent key proximate determinants of HIV risk among HIV-negative women enrolled into the targeted HIV programme.

7.3 Summary of key findings

7.3.1 Substantial decline in HIV incidence following enrolment

In examining HIV incidence, the interpretation of trends was affected by the approach used to assign the timing of seroconversion between the last negative and first positive test dates. The implausible fluctuations in HIV incidence patterns based on the mid-point approach were reduced when the random-point approach was applied to assign the timing of seroconversion. This finding is consistent with a simulation study which systematically evaluated the two approaches, and concluded that HIV incidence estimates based on the random-point approach were very similar to the actual rates, irrespective of the proportion of scheduled HIV testing dates that would be missed over the observation period[145]. Although the limitations of the mid-point approach have been highlighted in HIV incidence studies for population-based HIV surveillances with annual HIV testing, studies among high-risk women have commonly applied the mid-point approach despite high-risk women having a higher likelihood to miss scheduled visits due to barriers such as high mobility[145,146].

To assess the impact of cumulative loss of participants on HIV incidence, trends based on multiple imputation of the unobserved time-to-seroconversion for participants with attrition were compared to those without multiple imputation. HIV incidence estimates were likely overestimated using multiple imputation since imputation did not account for possibility of women exiting the cohort as a result of leaving sex work or adopting less risky behaviours. Based on the random-point approach without multiple imputation, HIV incidence substantially declined after enrolment into the programme. Among participants who were enrolled in 2008/2009 (cohort 1), HIV incidence reduced by 67% from 6.1 cases per 100 PYR (95% CI: 3.8-9.7) within the first 6 months of follow-up to 2.0 cases per 100 PYR (95% CI: 1.1-3.9) in the third year. Among those enrolled from January 2013 (cohort 2), incidence reduced by 53% from 3.8 cases per 100 PYR (95% CI: 2.6-5.5) within the first 6 months to 1.8 cases per 100 PYR (95% CI: 1.0-3.5) in the third year.

The decline in HIV incidence could be explained by two main factors whose effects are difficult to separate. Firstly, it is likely to be caused by the combination HIV prevention intervention offered through this targeted programme which included biomedical, behavioural and structural interventions. This is supported by evidence from systematic reviews of interventions to reduce HIV infection among FSWs in sub-Saharan Africa and other resource poor settings[74-77]. In particular, the following components included in the GHWP routine intervention package have been found to be effective in HIV prevention among FSWs: risk-reduction counselling, condom promotion, syndromic screening and treatment of STIs, HIV testing, and interventions to reduce harmful alcohol use[74-77,147]. Secondly, women with the most risk of HIV acquisition might have seroconverted early during follow-up, consequently contributing to lower incidence during the later period of follow-up. For example, women who seroconverted within the first 18 months of follow-up reported higher inconsistent condom use with paid sex in the last month at enrolment than those who remained HIV-free in the cohort for longer than 18 months ($p<0.001$), although there was no evidence of a difference in other behavioural and STI reports at enrolment by pre-18 months seroconverters and post-18 months women. Nonetheless, the changes in the proximate HIV risk determinants during follow-up can explain the reduced HIV incidence trends because of the strong correlation between incidence and the changes in the proportions of self-reported inconsistent condom use with paid sex in the last month, daily alcohol use and detected STIs.

Changes in contextual factors in this setting can also affect patterns of HIV incidence among high-risk women over time. For example, contextual changes might explain the lower HIV incidence within the first 6 months for participants in cohort 2 than in cohort 1. At enrolment, participants in the two cohorts had similar proportions of self-reported inconsistent condom use with paid sex in the last month and daily alcohol use, but the proportion with STIs detected was substantially lower for those in cohort 2 versus cohort 1. The effects of these individual-level factors on the risk of HIV acquisition can be modified by changes in the local epidemiological context of the population-level prevalence of HIV and other STIs, coverage of ART, proportion with viral load suppression and safe male circumcision, particularly among the men who pay for the sex. For example, exposure to HIV may have decreased during follow-up as HIV prevalence in Ugandan men was estimated to have decreased from 6.1% in 2011 to 4.3% (95% CI: 3.9%-4.7%) in 2016 (prevalence remained higher in urban areas with Kampala having 5.5% living with HIV in 2016)[36]. Similarly, there was a large increase in ART coverage (from 20% to 67%) and in the proportion of males who are circumcised (from 26% to 43%) between 2011 and 2016, respectively, which would suggest a reduction in HIV exposure at enrolment for those enrolled in cohort 2, compared to cohort 1.

Despite the rapid decline in HIV incidence following enrolment, the continued high HIV incidence during follow-up underscores the need for further strengthening of the HIV prevention programme. In cohort 1, HIV incidence levelled off at 2.0 cases per 100 PYR (95% CI: 1.1-3.9) at year 3 and 4 of follow-up (2011/2012), then rose steadily to 3.8 cases per 100 PYR (95% CI: 1.9-7.5) at year 8 (2016/2017). The data were consistent with no change in incidence between these two periods (age-adjusted p-value=0.15) but this may be due to lack of power, due to the loss-top-follow-up by year 8, which subsequently shrunk the cohort size and widened the confidence intervals. Nevertheless, the high HIV incidence even among participants with the longest follow-up in both cohorts still qualifies them as high risk according to UNAIDS (with 2.0 cases per 100 PYR)[148]. Further, their incidence is over 18 times the threshold incidence required for HIV elimination (0.1 per 100 PYR) as defined in a key modelling study used in the argument for HIV treatment as prevention[53].

The levelling off of HIV incidence in cohort 1 and low rate of incidence decline in cohort 2 correspond to the period with a high proportion of participants who missed scheduled clinic visits following the start of cohort 2. This observation suggests that participants may have been sub-optimally exposed to the combined HIV prevention package. Therefore, this thesis addressed the hypothesis that interrupting regular exposure (i.e. missing scheduled visits) to a combined HIV prevention package is associated with a higher risk of HIV acquisition among women with a high ongoing risk of HIV. Below, I summarise findings for the relationship of missing scheduled visits with subsequent HIV risk, and with proximate determinants of HIV risk.

7.3.2 Missing scheduled visits and increased subsequent HIV risk

This thesis found strong evidence that missing scheduled visits was associated with increased risk of HIV acquisition. As for estimating HIV incidence trends, the random-point approach was used to assign the timing of HIV seroconversion while examining the association between missing visits and HIV risk. As observed in chapter 6, the association found is consistent with results from previous epidemiological studies among FSWs in SSA, which reported a higher HIV incidence or prevalence among participants who attended fewer scheduled clinic visits or peer-education sessions over the study observation period[29,80,98,131]. In addition, the findings support the recommendations by WHO for high-risk women to have regular quarterly clinical contacts with HIV service providers for STI screening and HIV testing[149].

By considering time-varying patterns of missed visits (rather than the proportion of total visits attended), this thesis enabled a better understanding for the relationship between visit attendance and subsequent HIV risk, and permitted adjusting for time-varying individual-level characteristics. Previous cohort studies have presented incidence by the proportion of total visits attended, which is sub-optimal as an individual can vary their attendance of scheduled visits over the observation period[29,80,98]. Further, attendance of visits may be associated with the participant’s perceptions of HIV risk. A systematic review that examined determinants for using HIV counselling and testing services among FSWs in SSA highlighted risk perception resulting from previous behaviour as a common determinant[150]. For example, a participant can attend visits following a period self-perceived to be at high risk, and miss visits during times they self-perceive to be at low-risk or have exited sex work. The cumulative measure of visit attendance used in previous studies did not account for this variation within a participant over the observation period. Similarly, analysis of the proportion of total visits attended does not allow for adjustment for the influence of time-varying HIV risk determinants on the relationship between visit attendance and HIV incidence. As a result, the estimates for this relationship were subject to potential confounding which is overcome by using time-varying patterns of visit attendance.

Contrary to the finding of a positive association between missed visit attendance and subsequent HIV risk in this thesis, a cohort study among Kenyan FSWs showed that missed visits were associated with lower HIV risk. This study defined a time-varying measure of visit attendance based on the duration between successive visits but did not estimate proportions of missed visits[28]. The study found that a duration of more than 60 days between successive visits was associated with reduced HIV risk[28]. The different findings may be as a result of notable differences in the two cohorts. Firstly, the Kenyan cohort followed up participants monthly rather than once every three months as in the GHWP. Detailed reasons for missing scheduled visits were not collected in the Kenyan study, but reasons which deter study or clinic attendance of FSWs in other settings commonly include high mobility and the burdensome procedures[80,151]. It is plausible that when at low risk for HIV, participants might consider short intervals between scheduled visits (e.g. monthly visits) and the related research procedures as burdensome, and lead to a higher proportion of missed visits. Supporting this theory, the Kenyan study found that women who left the cohort were at a lower HIV risk than those who stayed[28]. This suggests that the Kenyan study might have underestimated HIV incidence associated with missed scheduled visits. To my knowledge, no studies have directly compared the effect of different frequencies of scheduling follow-up visits on HIV prevention and retention in retention in health services and research among high-risk women and this is an area for future research.

In the GHWP, the association between missed study visits and HIV incidence was not modified by the cohort in which participants were enrolled. The point estimate of association was stronger in cohort 2 than cohort 1 but there was no statistical evidence of effect modification. The weak point estimate in cohort 1 can be explained by the low proportion of cohort 1 participants who missed scheduled visits prior to initiation of cohort 2, which may be because transport cost refunds to participants during this early period encouraged visit attendance.

The influence of missed scheduled visits on subsequent HIV risk could be due to either changes in individual behavioural and biological risk determinants or concomitant changes in contextual factors irrespective of individual-level changes. Although data on changes in contextual factors between visits are difficult to obtain, these changes can be highlighted using data collected about reasons for missing visits and by examining changes in individual-level proximate determinants of HIV risk in this cohort. The changes in proximate HIV risk determinants between visits were assessed based on the repeated measures captured on individual behaviour, clinical and biological outcomes. In particular, I examined how missed scheduled visits during follow-up might have influenced individual-level changes in key proximate HIV risk determinants between visits, which in turn could explain the increased subsequent HIV risk. Examining these changes in proximate determinants can enable implementers of HIV programmes for high-risk women to better understand the utility for some components of targeted prevention during regular exposure, and pathways to intervene in order to optimise HIV prevention for high-risk women.

In the following section, I summarise findings for the association between missing scheduled visits and three key proximate determinants for HIV risk, which are highly prevalent among FSWs in SSA: detection of STI, daily alcohol use, and inconsistent condom use with paid sex in the last month[20,29,40,66,69,152].

7.3.3 Missed scheduled visits and changes in proximate determinants of HIV risk

There was a strong independent association of missing scheduled visits with having an STI detected and with increased reported daily alcohol use at the subsequent visit, but not with reported inconsistent condom use with paid sex in the last month. This analysis accounted for the between-participants effects of missing visits quantifying the propensity of a participant to miss visits. Comparing the within- and between-participant coefficients suggested no evidence that the participants who missed a higher proportion of visits during the study also tended to be detected with or report a determinant of HIV risk, over and above that for the effect for missing scheduled visits. This finding provides further confidence in the observed association between missing scheduled visits and each of the key HIV risk determinants for a given participant.

The finding showing no evidence for the association between missed scheduled visits and consistency of condom use with paid sex suggests that high-risk women are likely to have sustained their pattern of reported consistency of condom use with paid sex despite missing scheduled visits. Notwithstanding concerns about the accuracy of using reported condom use, this finding about the sustained reported consistency of condom use supports the information-motivation-behavioural skills conceptual model for behavioural change. According to this model, individuals can sustain patterns of HIV preventive behaviour if they are well informed about HIV prevention, are motivated to act, and acquire the necessary behavioural skills[141]. Although the level of prevention knowledge, motivation, and acquired skills were not directed recorded during the GHWP study, all participants had attended at least one visit with an intensive prevention package. As a result of this exposure to the programme, participants are likely to have acquired improved knowledge on HIV prevention, motivation, and some skills.

Studies with which to compare these findings on consistent condom use are scarce among high-risk women in SSA. The finding suggesting sustained patterns of reported consistent condom use with paid sex are consistent with results from an RCT among

542 FSWs attending once a month to a dedicated clinic in Cote d'Ivoire[80]. Participants were randomised to either a basic STD diagnosis and treatment strategy (including a gynaecological examination when symptomatic) or to an intensive strategy that included a gynaecological examination regardless of symptoms[80]. Of the 225 (42%) FSWs with at least one outcome (carried out every after 6 months), this trial showed similar proportions of reported consistent condom use with clients between FSWs who attended at least four out of five scheduled visits and those with less visits before their last outcome assessment, regardless of treatment arm..

Similarly, the sustainability of reported consistent condom use during missed scheduled visits in this thesis could also be compared with findings in studies which examined whether changes in consistent condom use were sustainable one year after the completion of RCTs. In an RCT for STI prevention among 172 FSW in Nairobi, Kenya, the frequency of reported consistent condom use with clients was sustained within individuals following the provision of free male condoms, community and clinic-based counselling, and STI management at monthly clinic visits. After trial completion, scaled-back community-based resources remained in place. A follow-up survey one year after the end of the RCT showed that reported consistent condom use with clients was sustained and in fact slightly increased[132]. In contrast, an earlier study among 966 high-risk women in Cameroon who received eight intensive, monthly counselling sessions about condoms and STI testing and treatment found that participants were substantially less likely to report consistent condoms use at the follow-up survey than during the RCT after a similar timeframe of one year[133].

In a similar way, the combination of acquired skills and community-level activities might explain the likely sustainability of consistent condom use frequency among participants in this thesis despite missing scheduled visits. Twice a week, the GHWP offered outreach HIV counselling and testing in addition to distributing free condoms to venues and locations where sex work takes place supported by peer-educators. Participants might also have accessed services including HIV counselling and testing, and access to free condoms from other providers of HIV prevention and treatment services to key populations. The most notably is the Most at Risk Populations programme (MARP) initiated in 2008 as a model clinic under the Ugandan Ministry of Health[153]. The MARP initiative is peer-supported with condom outlets in locations associated with sex work but other services such as HIV testing, STI screening and treatment are offered at a dedicated clinic located at the Mulago national referral hospital in Kampala. In fact, the existence of similar programmes may partly explain why a higher proportion of participants enrolled in cohort 2 reported a higher proportion of consistent condom use and to have tested for HIV within the last 6 months at enrolment than those enrolled in cohort 1.

Despite not directly assessing individual-level changes in condom use by intervention exposure over time, other studies have suggested a positive association between the amount of intervention exposure and reported condom use with clients[98,131]. In a survey among FSWs covered by the IMPACT project in Kenya, the authors found a positive relationship between the reported number of peer-education sessions in the past six months and reported consistent condom use with clients[131]. At the time of the survey, the IMPACT project had been providing peer-mediated interventions for about 5 years, which included individualised and weekly-group peer sessions at homes of FSWs or a drop-in centre.

In contrast to the findings of reported condom use, the positive association of missed scheduled visits with STI and daily alcohol use do not fit the information-motivation-behavioural skills model despite the relationship between these HIV risk determinants. Among FSWs, the risk determinants are hierarchically inter-related in that alcohol misuse among other factors such as gender-based violence, financial incentives for condomless sex or poverty can hinder consistent condom use[49,68,152]. In particular, alcohol misuse reduces the ability of women at high risk of HIV exposure to negotiate and correctly use condoms[69,152], and harmful drinkers have also reported experiencing increased risk of sexual and physical violence, which limits their consistent use of condoms[49,68,152]. In turn, the correct and consistent use of condoms reduces the risk of STI acquisition in addition to preventing unintended pregnancies[79]. While condomless sex with an infected sexual partner directly increases the risk of HIV acquisition for FSWs, coinfection with STIs increases their biological HIV susceptibility[60,61,79]. Thus, the findings for risk determinants in this thesis suggest effect modification by the infectiousness of sexual partners since the sustained patterns of condom use with paid sex associated with missed visits was not accompanied by sustainability in STIs. The infectiousness of sexual partners can be as a result of the different epidemiological contexts where participants solicit for sex when they miss visits and when they attend, or the type of sexual partners (occasional versus regular)[124,154-156]. These plausible underlying modifiers are discussed further in section 7.5 but first, I discuss individual-level pathways between missing scheduled visits and HIV risk in the following section.

7.4 Pathways between visit attendance and HIV risk at the individual-level

The combined prevention package in the GHWP study can be thought of as having a joint effect on HIV prevention by targeting different underlying determinants (such as hazardous alcohol abuse) and proximate determinants (such as inconsistent condom use and STIs) along the pathway towards HIV infection, which in turn affect the biological determinants of HIV acquisition. According to the proximate-determinants conceptual framework for HIV infection proposed by Boerma and Weir, there are three direct biological mechanisms for HIV acquisition, as is generally true for infectious diseases: (i) exposure of a susceptible person to an infected person, (ii) efficiency of HIV transmission to a susceptible person given exposure to an infected person, and (iii) duration of HIV infectivity of the infected person (i.e. duration not on ART)[51]. The three biological mechanisms are related by the general equation for infectious disease transmission referred to as the reproductive number, R_0. R_0 is the product of the three mechanisms: the rate of exposure of a susceptible person, the efficiency of HIV transmission and the duration of HIV infectivity[157]. Presence of an STI and inconsistent condom use are proximate determinants of the efficiency of HIV transmission (mechanism ii above) as they increase the efficiency of transmission from an HIV-infected partner to an HIV-negative FSW. The effect of a change in one biological mechanism on HIV risk depends on the extent of influence of the other remaining mechanisms on HIV infection. For example, the effect of sustained condom use with paid sex or increase in STIs (mechanism ii) during interruptions of visit attendance might depend on other factors such as the likelihood of being exposed to a partner living with HIV (mechanism i) and whether the infected sexual partners are likely to be effectively on ART treatment (mechanism iii). Therefore, the changes at any of the three biological mechanisms can explain the association of missing visits and increased subsequent HIV risk.

Although the biological mechanisms were not directly captured in the GHWP study, they are jointly influenced by changes in proximate HIV risk determinants and in epidemiological contexts such as prevalence of HIV or STI in the general population from which participants solicit sexual partners. Given that missing visits was associated with a higher risk of STI detection at a subsequent visit, untreated STIs might explain the increased HIV infection when high-risk women miss visits. While free condoms are usually distributed in sex work venues, services for screening and treatment of STIs are typically not easily accessible to FSWs in this setting despite a high burden of STIs[40,57,158-162]. In a recent cross-sectional study conducted between July and October 2018 among 441 FSWs across the 4 regions of Uganda, only 26.5% reported to have tested for syphilis at least twice in the prior 12 months[161]. Previous studies within this cohort and other settings among high-risk women have reported that the presence of an STI was associated with at least a twofold increase in HIV risk[29,158,163]. Although ulcerative STIs are more likely to facilitate HIV transmission, non-ulcerative STIs have also been shown to increase HIV risk[20,164]. This increased HIV risk has been explained in diverse ways including the negative influence of STIs on: vagina flora, genital and rectal mucosal barriers, local CD4 positive cells, and cytokines[158,165-167].

Despite depending on weak evidence, intervention studies which include clinic-based STI management have consistently argued for the importance of STIs in explaining the higher HIV infection among FSWs with infrequent attendance of clinic visits[80,82,98,131]. For example, the authors in the cohort study of FSWs in Cote d'Ivoire also argued that a lower STI rates among regular clinic visit attenders (attended ≥4 out of 5 scheduled visits) than among irregular attenders explained the relatively lower incidence rate among regular attenders[80]. However, there can be an over-representation of HIV infection and STIs among irregular attenders if they are intrinsically more high-risk women than the regular attenders. This thesis provides strong evidence suggesting that untreated STIs is a key risk determinant accounting for the association of missing visits and increased HIV risk. The assessment of individual-level changes in proximate determinants allowed for a better understanding of this key pathway.

The regular attendance of study visits is likely to have facilitated early detection and treatment of STIs among participants, hence reducing HIV risk. On the contrary, missing of visits could lead to a failure to detect or treat STIs, which would have been otherwise detected by the medical personnel and treated at the clinic. The importance of regular visits to a clinic providing screening and treatment of STIs in detecting STIs among FSWs has been demonstrated within a large observational study in Karnataka, India[144]. In this Indian study of 2705 FSWs, 18% of all syndromically detected STIs were identified at clinic visits where the respondent had reported no STI symptoms. Therefore, it is critical for high-risk women to be regularly exposed to HIV interventions that include STI screening and treatment, given that it is typically difficult to achieve 100% condom use and the shortcomings with other prevention modalities.

7.5 Underlying factors influencing visit attendance and HIV risk

7.5.1 Mobility

In the GHWP, missing scheduled visits is also likely a marker for changes in the underlying determinants of HIV infection including mobility, stigma and social discrimination. In addition to delayed STI treatment caused by missing visits, these underlying factors might explain the increased detection of STIs despite the sustained reported consistent condom use with clients during missed visits. Although it is difficult to longitudinally capture changes in underlying determinants, data on reasons for missing visits in a subgroup of participants who missed at least two study visits and findings from previous studies in this cohort are informative[47,151,162]. For example, of the 342 HIV-negative women who missed at least 2 consecutive visits and were contacted between October and December 2015 in this thesis, 49.0% reported the main reason for missing visits related to mobility such as travelling or relocation. Other reasons reported included getting married or being asked to stop attending by a sexual partner (10.5%), facility-related delays (2.9%), fear of medical procedures (17.8%), and concerns about transport costs (4.7%) or time costs (9.9%). In addition, poor accessibility of the clinic might be of concern for some participants who missed visits. In a cross-sectional study of 874 participants who attended the study clinic between 2017 and January 2018, a high proportion (40%) reported the clinic to be poorly accessible and of which 69% reported high transport costs[162].

Consistent with mobility as the key reason reported in this thesis for missing visits, a sub-study among 644 young participants aged 15-24 years reported that 31% moved across a minimum of 4 work venues within 18 months of follow-up where venues were located using Google maps[151]. While the work venues were concentrated within and near Kampala including the fishing communities, they also spanned across towns within and outside of Uganda[151]. This observation is in line with results from the cross-sectional study referenced earlier among 441 FSWs across Uganda that reported 25.1% to have moved regularly across many towns in and outside of Uganda[161].

Within the GHWP study, the core reason reported for the high mobility in the sub-study of young participants was financial[151]. Participants who interrupted their visit attendance as a result of mobility are likely to be exposed to HIV-positive sexual partners if they acquired clients from settings associated with a higher prevalence of STIs or HIV, and high risk behaviour. And if they fail to consistently use condoms, they are then likely to be at a high risk of HIV acquisition. While mobility among high-risk women remains to be better understood, qualitative studies nested in the GHWP have reported that some participants usually travelled for extended periods in search of clients including to fishing communities where there is high HIV prevalence and high-risk behaviours among people in these communities[47,168-172]. For example, a cross-sectional sero-behavioural survey of 46 fishing communities around Lake Victoria conducted in August 2010 estimated an HIV prevalence of 20.4% (95%CI: 15.6-25.2) among men, which is over three times higher than that of Kampala men[171]. This is likely to affect HIV risk among those who missed visits, in line with findings from a systematic review of 68 epidemiological studies examining key sexual risk factors for HIV infection in SSA, which concluded that the effect of multiple partners, paid sex, or STIs on HIV risk was larger in settings with a high background prevalence than in those with low background prevalence[173].

7.5.2 Stigma and social discrimination

Missing visits might also be correlated with stigma and fear for social discrimination, which are commonly experienced by FSWs globally and can inhibit uptake of health services[20,50,122,150,174,175]. While dedicated facilities facilitate the utilisation of services targeted to women at high risk of HIV exposure, those who were reluctant to be identified as FSWs due to sex-work stigma might have been less willing to regularly attend a clinic perceived to serve sex workers. This is supported by findings from a respondent-driven sample of 2387 FSWs in six sites within Zimbabwe which found that women who were reluctant to self-identify as FSWs were less likely to attend services despite having similar HIV risk factors as those who identified as FSWs[22].

In the GHWP study, an example of stigma and social discrimination is reflected by the noticeable proportion of participants who reported getting married or being stopped by a partner as their main reason for missing visits among the subgroup of participants who had missed at least two consecutive visits. These participants might have feared causing suspicions of infidelity by their intimate partner and to cause relationship strain by regularly attending study visits. This concern of the role of intimate partners in the utilisation of HIV interventions has been raised elsewhere[154,176]. For example, in a clinical trial of microbicide gel (HPTN 035), women with new partners were less likely to use the intervention consistently and subsequently, had a higher HIV incidence than those who did not change partners[154]. In addition, qualitative studies among FSWs have reported that many of the new intimate relationships are initially encounters with clients that transition into regular sexual partnerships[30,31,47,54,177]. In the GHWP study, there is also some evidence to suggest that these partners might be high-risk usually with multiple partners[31,54] and one study in Benin among male partners to high-risk women has reported a higher HIV prevalence in regular (16.1%) than non-regular partners (8.5%)[178]. Therefore, alternative HIV interventions are required to reach such high-risk women inhibited to attend services due to stigma in addition to offering complementary biomedical interventions such as PrEP, given that they are less likely to use condoms with intimate partners.

7.5.3 Alcohol consumption

Excessive alcohol use might have been an important pathway for the association of missing visits and increased HIV risk. While qualitative studies have reported that women at high risk of HIV exposure commonly use alcohol to cope with the stress and stigma associated with their work, excessive alcohol use could affect various aspects of their life including inhibiting the utilisation of health services and cognitive function such as decision-making[30,65]. As a result, these could increase high-risk sexual behaviour, the risk for experiencing sexual violence, in turn perhaps increasing the risk for STIs which might remain untreated and subsequently, increase HIV infection[30,65,69]. In the GHWP, participants received alcohol reduction counselling at the visits they attended and might have gained improved awareness of the risks associated with harmful drinking when alcohol questionnaires were administered. Missing visits also meant that participants missed contact with the trained nurse-counsellors for support in maintaining healthy drinking habits. Given that all the participants had at least a previous contact with the clinic, it is unlikely that social desirability bias might have had a considerable impact on the independent association of missing visits and increased reporting of daily alcohol use at the subsequent visit.

7.6 Strengths and limitations

7.6.1 Strengths

This thesis had several strengths that should be noted. Notably, all participants who attended a given visit received the intervention package given that there was a clinic attendance system to follow. A given participant attended all services from risk reduction counselling, HIV testing, to clinical examination for STIs and pregnancy. Therefore, attendance was synonymous to receiving the intervention package while missing of a visit meant that the participant missed the intervention package at the clinic as well. However, it is possible that participants who missed visits could also receive some of the components from other service providers, particularly HIV testing services offered during moonlight outreach and other services from private clinics.

Secondly, the data in the GHWP study were collected prospectively which enabled examining the temporal relationships between missing scheduled visits and subsequent outcomes of HIV risk and risk determinants. Examining temporal relationships is very informative since it accounts for individual changes during observation that would otherwise be lost with a cumulative measure of missed scheduled visits. In addition, the study was strengthen by the long period of observation of up to 8 years and the large sample of 2206 HIV-negative high-risk women with at least one follow-up visit.

Thirdly, there was a clear eligibility criteria for high-risk women to be recruited into the programme, where the mobilisation team supported by peer educators recruited individuals from their work venues and trained nurse-counsellors rescreened for eligibility at the study clinic. The study also recruited the vulnerable women who were reluctant to self-identify as sex workers but had similar HIV risk factors as those who identified as FSW.

Another key strength of this thesis is that the study represents clinic visit attendance in a dedicated program for women at high risk of HIV although visits were scheduled for every three months. The high retention of participants in the GHWP study is likely a combination of factors including the positive attitude of study staff who were trained to deliver services to sex workers in a non-judgemental manner. In addition, the high quality services in the GHWP study might have encouraged clinic service utilisation and about three-quarters reported that they were satisfied with the clinic services in a sample of 874 participants interviewed between October 2017 and January 2018[162].

The research component incorporated into the HIV programme allowed for quality data to be collected at each study visit. It was possible to triangulate individual-level programme data from different sources at the clinic allowing for data checking and cleaning. This enabled identifying opportunities for strengthening the programme data in real-time. Despite some changes over time in the data collection tools to reduce the amount of data collected at a given visit, the comparability of variables across visits were not affected. Lastly, explicitly modelling both the proportion of times a participant misses visits during the study and missing of visits using the random-effects model enabled assessing whether participants who generally tended to miss visits also tended to be the most-at-risk participants.

7.6.2 Limitations

There were several potential limitations that could affect the validity of these findings. First, study is subject to different sources of selection bias particularly since data was based on a clinical cohort. While women at high risk of HIV exposure were enrolled after screening, participants might have not been eligible for all the time in follow-up because of changes in their characteristics. Given that participants can exit and re-enter the target population, metrics such as whether a participant reported paid sex in the last month cannot sufficiently define eligibility during follow-up because they do not represent all the changes since the last attended visit. Therefore, including women who were no longer part of the target population in the analysis might have underestimated the effect of missing visits since these participants are likely to also intermittently attend visits. On the contrary, there might have been an over-representation of HIV risk or HIV risk determinants among participants missing visits if participants who had missed visits selectively returned for a subsequent visit only after suspecting a recent high-risk exposure, or to access treatment for a suspected STI. However, this potential selection bias is likely to have been reduced because the study actively traced participants who had missed at least two visits, in addition to other study activities for improving retention. As described earlier, these activities included peer-educators actively mobilising participants to attend follow-up visits and holding of group meetings at the clinic with participants who had scheduled visits within the following month. In particular, peer-educator outreach visits have been shown to be associated with an increased probability for FSWs to attend the study clinic and attending the clinic earlier in the Karnataka study among FSWs in India[144]. Although I allowed for selection effects by adjusting for the measurements at the preceding visit that a given participant attended, these measurements do not necessarily reflect all the potential changes in risk in the duration between successive visits.

Secondly, whereas the long duration of the clinic cohort was important to investigate the research objectives, it is subject to potential period effects as a result of multiple changes in study procedures and characteristics at the population level. For example, the underlying processes for HIV infection are likely to have been affected by the removal of transport refund to participants at the start of cohort 2, which led to more missed visits. At the population level, underlying processes may have been affected by changes in the epidemiological context over the duration of the study in factors such as the population-level prevalence of HIV and other STIs, coverage of ART, proportion with viral load suppression and safe male circumcision, particularly among the men who pay for the sex. Despite the difficulty in adequately accounting for the multiple sources of period effects in this observational study, I adjusted for a cohort indicator variable (cohort 1 and cohort 2) as a proxy for period effects.

Thirdly, it is difficult to reliably measure condom use because of self-reporting biases. Participants are likely to give socially-desirable responses regardless of the number of missed study visits because of factors such as the social distance between interviewer and respondent, and a perceived sense that an undesirable response could invite judgement[179]. This likely weakened the observed associations between missed visits and self-reported outcomes. However, the study staff made efforts for participants to feel comfortable in the clinic environment and for them to build trust with study staff. The practices in this study including the same gender administering questionnaires to the women, building rapport and trust, and the repeated interviews have been found to enable participants to open up and reveal sensitive information[179,180].

7.7 Generalisability of findings

The finding in this thesis on the association between interruption of exposure to HIV interventions and HIV risk may not necessarily be generalizable to women who sell sex for money or goods in Uganda or SSA. This is because the underlying factors which affect the risk of HIV and STIs vary in different regions, contexts and categories of high-risk women[173]. However, the sub-optimal attendance of HIV services observed in this thesis might be generalizable to the wider Ugandan women who sell sex for money or goods and those in other settings. Consistent with the GHWP study, a cross-sectional study of FSWs across Uganda reported high mobility with one-quarter stating that they moved regularly in search of clients across many towns in Uganda and outside of Uganda[161]. Despite interrupting intervention exposure, participants in Kampala might have sustained patterns of reported consistent condom use with paid sex because of an easier access to condoms given that condoms are commonly distributed in sex work venues. Sustaining consistent condom use might be difficult in settings where FSWs find it difficult to access condoms such as in one setting in northern Uganda[181]. The finding on increased STIs detection following the interruption of intervention exposure may apply to various settings across SSA, given the high STI rates among FSWs and that services for STIs screening and treatment are typically only available at clinic facilities[20,161].

More generally, the characteristics of participants attending the GHWP study are comparable to those of FSWs recruited into a respondent-driven sampling survey in Kampala[158], suggesting generalizability of our findings. While the women at high risk of HIV exposure in sex work settings vary in their social and economic status, the participants attending this current clinical cohort operate mainly from low socio-economic settings and usually have limited economic options[47]. These women are likely more vulnerable to sex work related HIV risk factors than those in a higher social-economic status and consequently, at a substantially higher risk for HIV exposure. In this study, the participants might have been mainly attracted to attend the study clinic because of the availability of free health services offered in a non-judgemental environment. To better understand non-response, however, it might have been helpful to collect detailed data on the characteristics of all women invited to attend the clinic. In contrast to women in a lower social-economic status, those in a higher social-economic status are likely more empowered to consistently use condoms, could access private health services for treatment of STIs and could afford modern HIV prevention methods such as PREP. Hence, these findings may not be applicable to women at high risk of HIV exposure in the higher social-economic status. However, the generalizability of the findings in this thesis across different contexts needs to be verified.

7.8 Significance and Implications

Globally, the benefits of early initiation and adherence to ART have often been emphasised over prevention, leading to substantial progress towards the 90-90-90 targets for HIV diagnosis, treatment and viral supression[182]. Compared to the general population, however, related progress remains slow among high-risk women in Uganda and some other settings[119,121,125,183]. In Uganda, 45.5% of FSWs living with HIV reported knowing their serostatus, 37.8% reported to be on ART, and 35.2% had viral suppression in the most recently available respondent-driven sampling survey conducted between April and December 2012[121]. As with HIV treatment, the findings in this thesis suggest that the impact of HIV prevention programmes targeting women with ongoing substantial risk could be improved further if programmes ensure that these women are frequently and consistently exposed to combined prevention services.

Systematic reviews for HIV prevention interventions among FSWs involving studies from SSA have indicated a broad range of interventions that can be effective, particularly when the behavioural, biomedical, and structural components are concurrently implemented[74,76,77]. The common themes for translating this evidence into public health impact have included calls to implement, scale-up and expand options in HIV programming for people at high risk of HIV exposure in different epidemiological contexts[7,14,24,73]. In addition, there is growing interest regarding how these effective combination HIV prevention interventions can be delivered to populations at high risk, including understanding the extent to which these populations interact with HIV services[116,119,129,184,185]. Recent epidemiological studies among FSWs across different settings have reported that FSWs are sub-optimally exposed to HIV prevention services, with exposure commonly measured as the proportion who had an HIV test in the last 6 months[119,129,185]. This thesis contributes to the HIV prevention literature by using data from multiple visits to a dedicated clinic for women at high risk of HIV exposure to demonstrate that inconsistent exposure to combined HIV prevention package is likely to reduce the potential impact of targeted HIV programming. Thus, targeted HIV programmes could further accelerate declines in new HIV infections among women at high risk, their sexual partners and the general population if programmes integrate monitoring the extent of exposure of high-risk women to HIV services and efforts to facilitate consistent exposure as key programme components.

7.8.1 Practical implications and lessons

Routinely monitor and foster individual engagement with HIV services

The benefits of regularly attending prevention services are important for the individual's long-term health but also epidemiologically, the health of individuals could aid averting potential onward HIV transmission to sexual partners, and in turn, to other secondary transmissions[14]. In this thesis, the finding showing that missing scheduled visits was associated with increased HIV risk underscores the need for routine monitoring of how the individual high-risk women engage with effective HIV services. This finding also supports the need this thesis demonstrates why the recent Uganda Ministry of Health guidelines on HIV testing for key populations are critical, as they recommend that they be retested once every three months through health facilities and community approaches[186]. For both approaches, targeted HIV programmes need to routinely capture how consistently women at high risk are exposed to health services and promote their regular attendance to services. These women could be motivated to regularly attend services through programmes efforts that improve the demand of and adherence to HIV services such as fostering appropriate risk perception, sufficiently making use of peers and social networks, and articulating the benefits of consistent exposure to HIV services[117,187,188]. Engagement with HIV prevention services is also an important entry point for HIV treatment programs[189,190]

Boosting intervention exposure through meeting broader health and social needs

Targeted HIV prevention programmes are likely to further boost regular service attendance if they offer a range of integrated services which meet the broader health and social needs of the women at high risk of HIV infection. Among other services, this programme integrated services that included syndromic STI management, risk reduction counselling, provision of modern contraceptives and antenatal care services as well as offering free medical care for the participants and their children under 5 years. As a result, findings showed that participants were more likely to attend subsequent visits if they had been detected with an STI, were receiving modern contraceptives, reported alcohol problem or had more children. In addition, a substantial proportion (76%) of participants who attended the study clinic between October 2017 to January 2018 reported being satisfied with the clinic services, perhaps because of the integrated free services offered in a non-judgemental way[191]. Globally, such integrated sexual health interventions were also found to be highly cost-effective in a systematic review that assessed economic evidence on sexual and reproductive health interventions for sex workers, with more cost-saving resulting from high HIV prevalence and numbers of partners per sex work[192]. Therefore, HIV programmes need to identify specific needs for women at high risk of HIV infection and provide tailored services that meet these needs as an enabler for regular exposure to HIV services.

Routinely monitor and evaluate acceptability of intervention components

Some of the barriers to consistent intervention exposure which participants reported in this study underscore the need for continuous monitoring and evaluation of targeted HIV programmes so as to improve programme delivery and participant engagement over time. For example, about 18% of the participants who missed at least two scheduled visits reported the fear of the speculum examination as the main reason for missing. The implication for this observation is that programmes need to routinely assess acceptability and communicate benefits for specific procedures in the delivery of HIV services so as to facilitate individual choices, in addition to regularly conducting refresher training for staff to be more non-judgemental while offering services targeting women at high risk of HIV exposure.

Regularly screen and treat STIs

The finding that having an STI was likely an important proximate determinant for increased HIV risk when participants missed scheduled visits underscores the need for ensuring routine screening and treatment for STIs. STI management can be easily integrated with other facility-based clinic services for key populations, but are rarely included in outreach service packages. Targeted services offered through outreach could overcome some of the barriers to regular exposure to facility-based services such as lack of transportation costs[32,191], poor accessibility of the clinic[191], work demands[193], and social stigma[193,194] and could facilitate attendance at health facilities[117,129,144]. This HIV programme had both components of facility-based and outreach services, but outreach services were limited to distributing condoms and offering voluntary counselling and testing for HIV. Women who only attend the outreach are likely to miss out on a wider range of services available at the clinic facility including earlier detection and treatment of STIs. However, the feasibility and effectiveness of mobile STI screening and treatment for sex workers unable to attend static clinic facilities has been demonstrated in other settings[25,195]. For example, in Peru mobile teams of health workers visited mapped sex work venues to provide a multicomponent intervention that included STI screening through obtaining vaginal swabs and subsequently delivering test results and free treatment the following week[195].

Notwithstanding the benefit for high-risk women to consistently attend services at the clinic facility, integrating STI management into the basic service package offered during venue-based outreach or mobile clinics could facilitate earlier detection and treatment of STIs for people unable to routinely attend the facility-based services. A mobile clinic is being piloted in Kampala to offer HIV services to high-risk women in active sex work venues[151].

Controlling the risk of HIV within intimate or regular partners

Given the negative influence of sexual partners on HIV service attendance, targeted HIV programmes for high-risk women should not only focus on the prevention needs of the individual but also consider tailoring interventions to suit the individual's relationship dynamics. For example, the difficulty for high-risk women to consistently negotiate condom use within relationships particularly with intimate partners underscores the urgent need for biomedical interventions such as PrEP to be widely available as an important option. Uganda has recently started rolling out PrEP particularly for key populations and only an estimated 3000 people are recorded to have received PrEP by March 2018[8]. Given that evidence has shown that efficacy of PrEP is correlated with level of adherence, the effective use of PrEP would still require regular contact of FSWs with the service providers even if long-acting PrEP were available to address the inconvenience of daily pills and pill-related stigma[91].

In addition, programmes should carefully consider strategies for communicating the risk of HIV acquisition and transmission including negotiating of condom use within intimate relationships for high-risk women. Other ways for HIV control within intimate relationships may include offering HIV self-test kits to high-risk women, which can promote couple testing. For example, a small study among 280 HIV negative women (of which 102 were FSWs) accessing reproductive health services in Kenya found that 83% of FSWs offered self-test kits reported that the kits were also used by primary partners[196]. This observation suggests that distributing HIV self-test kits to high-risk women could encourage their intimate or regular sexual partners to also test for HIV and subsequently, take the necessary measures to prevent HIV transmission. However, both PrEP and HIV self-testing need to be integrated into the primary HIV prevention interventions, and sexual and reproductive health services, which can be offered through mobile clinics to reach high-risk women unable to attend the static clinic facilities.

Mitigating the negative effects of mobility

Despite FSWs often being mobile, there remains limited guidance on how to mitigate the negative effects of mobility and how to address the prevention and treatment needs of those who are mobile. As discussed earlier, not only does the high mobility interrupt consistent exposure to accessible services such as treatment of STIs, but also changing behaviours during mobility and changing epidemiological contexts could modify subsequent risks of STIs and HIV infection[197]. As such, HIV programmes need to tailor HIV services that carefully consider the mobility patterns for FSWs, and to map out locations in which FSWs seek for clients. Within the GHWP, a sub-study among young participants aged 15-24 years has demonstrated the use of google maps to locate sex work venues in and outside Uganda that a given participant frequented within the past 18 months[151]. Consequently, the use mobile clinics can be implemented in the active sex work locations or use referral clinic vouchers to encourage attendance of HIV services by mobile FSWs. Although a cluster-randomized controlled trial showed that the use of clinic vouchers to redeem HIV self-testing kits from providers reached fewer FSWs than the distribution of kits by fellow FSWs[198], the voucher system to access key HIV services could be important for highly mobile high-risk women.

Another way to reduce the negative effects on HIV risk associated with mobility could be to ensure that HIV programming for FSWs is accessible across places, perhaps through a community-led national scale up of services as was the case for Sisters with a Voice programme in Zimbabwe[183]. In addition, the often much overlap between sex work and other sexual networks in the general population calls for intensifying HIV prevention and treatment efforts in geographical places and populations common with sex work. For example, the overlap of fishing communities and sex work in Uganda implies that increased community uptake and coverage of circumcision, HIV testing, and ART among men in these communities could substantially impact on the HIV risk associated with mobile sex work[37].

7.8.2 Implication for estimating the timing of HIV seroconversion

The findings after comparing HIV incidence trends using different approaches in this thesis resonate with evidence that challenges the use of mid-point approach to infer the timing of the HIV infection, specifically when participants regularly missed scheduled visits[145,146]. In the simulation study which systematically evaluated the mid-point approach, the approach showed HIV incidence to falsely increase at the start of observation period then decrease towards the end of the observation period[145]. This systematic bias became more apparent as the proportion of missed HIV tests during the study period were increased. While a similar incidence trend pattern as the above bias was observed among women enrolled in cohort 2, this was not the case among those enrolled in cohort 1.

In cohort 1, women regularly attended scheduled visits mainly because of knowing that they would be given transport refund until refunding was stopped at the introduction of cohort 2. Hence, estimates of incidence patterns based on the mid-point were likely less biased during the period with regular visit attendance but perhaps more biased once transport refund was stopped in cohort 1.

Overall, while Vandormael and colleagues suggested that the amount of bias using the mid-point approach might have been dependent on the proportion of missed HIV tests[145], the current findings suggest that, beyond that, the median length of interval between the last negative and first positive tests for seroconverters could explain the amount of potential bias. Therefore, where this median seroconversion interval is widened as a result of missed scheduled visits then other methods with less restrictive assumptions about the timing of seroconversion than the mid-point must be applied. A number of methods exist within the survival analysis framework but the random-point approach is a more intuitive in estimating incidence rates[145,199-202].

7.8.3 Future research

The data on study visit attendance at the clinical cohort provided a unique opportunity to improve our understanding in the delivery of combination HIV prevention programmes among women at high risk of HIV infection. This thesis demonstrates that women at high risk of HIV infection need regular and consistent exposure to targeted HIV interventions. In addition, it emphasises STI management as a critical component of targeted combined HIV prevention packages offered at clinic facilities and perhaps, in outreach services to reach those unable to consistently attend facilities. However, improving the delivery of targeted interventions requires a better understanding of the underlying pathways through which inconsistent exposure to targeted HIV programming might have an effect on subsequent HIV risk factors and actual HIV risk. In this study, data were not available on the various contextual factors likely to be concomitant or consequent to missing scheduled visits.

To develop more effective interventions, future research should incorporate data on the socio-structural contexts during the period between service exposure including the measurement of mobility, the relevance of social influences on attendance of health facilities and other specific reasons for inconsistent exposure to services. This study could also be strengthened by obtaining data on the level of exposure to outreach services including HIV testing, utilisation of condoms supplied in entertainment places, the extent participants accessed similar services from elsewhere and extent of high risk HIV exposures in the period between service attendances.

Data recording and reporting in future work could also be extended in other ways. Firstly, the mobilisation team in this study recorded some data on the reasons for consecutively missing at least two scheduled visits, but these data could not be linked to the individual-specific data collected at clinic visits. Linking these data could increase their usefulness by relating the reasons for missing visit(s) to a given participant’s service attendance over time and impact of active follow-up through phone contacts and community tracing on subsequent attendance.

A key criticism for previous studies that explored targeted programme attendance and HIV incidence was the failure to adjust for confounders. While I adjusted for socio-demographic and behavioural characteristics in this study, some important key confounders may not have been considered. Some of these key variables include participants' duration in sex work for those involved in sex work and indicators for social influence. Future studies should examine the confounding effect of these key factors, where possible, because these factors are known to be associated with HIV infection and use of HIV services.

7.9 Conclusion

Globally, the remarkable progress in HIV testing, treatment, and viral suppression without an accompanying sufficient reduction in new infections underscores an urgent need for strengthening primary HIV prevention. Primary HIV prevention and treatment is becoming increasingly important among key populations and their sexual partners, particularly among those with high rates of partner change able to sustain HIV transmission. In high HIV prevalence settings, scaling-up effective HIV services might not be sufficient to sustain declines in HIV acquisition without additionally ensuring that high-risk women are regularly exposed to combination prevention packages.

This thesis has shown that high-risk women are at an increased risk of HIV acquisition when they interrupt their regular exposure to a package of complementary multiple interventions. Therefore, interruptions in regular intervention exposure can reduce the effectiveness of HIV prevention services among high-risk women. Whereas ensuring adequate exposure could maximise the potential impact of HIV programming for high-risk women. Accordingly, HIV programmes need to routinely monitor the exposure to combined prevention packages for individual women with a high ongoing HIV risk and actively facilitate them to regularly attend effective intervention packages.

HIV programmes can facilitate regular exposure to and use of HIV services among high-risk women by providing peer-supported, user-friendly, and integrated services which meet their broader health and social needs. In the GHWP clinic, regular exposure to the HIV prevention package was facilitated by offering supportive services that included sexual and reproductive health care, antenatal care, and primary health care for the women and their children aged 5 years and below. Therefore, providers of HIV services need to strengthen and integrate supportive services, and train health professionals to be non-discriminatory towards high-risk women.

HIV packages which incorporate complementary multiple interventions are necessary in preventing HIV acquisition among high-risk women. These packages have the benefit of influencing one or more proximate HIV risk determinants given the challenges of reaching optimal use with each intervention modality. Despite this thesis suggesting that high-risk women sustained reported consistency of condom use with paid sex after an interruption in regular exposure, there was an increased risk of detecting STIs and reporting daily alcohol use during the same period. This observation underscores the importance of actively facilitating high-risk women to regularly attend complementary interventions including those for STIs and alcohol use.

The allocation of resources for the mix of interventions in a prevention package can be guided by understanding individual-level changes in the key proximate risk determinants with regular exposure. There may be limited utility of some intervention components with regular exposure, whereas others may consistently be required. This thesis suggests that HIV programmes in high prevalence settings need to regularly screen and treat STIs among high-risk women and consistently implement interventions to prevent harmful use of alcohol over time. Contrary, some intervention components focusing on condom use such as condom demonstration may be of limited utility during regular exposure once high-risk women acquire behavioural skills although consistent condom use needs to be emphasised. Therefore, HIV programmes can better redirect resources towards other key components of the interventions to accelerate reductions in HIV risk.

HIV programmes need to also implement combination HIV packages that consider underlying barriers to regular intervention exposure among high-risk women. The delivery of HIV services can be tailored to better suit socio-structural barriers such as mobility, influence of intimate partners on routine exposure and consistent use of interventions, and the fear of being seen at the clinic facilities. For these high-risk women unable to regularly attend services at health facilities, HIV programmes could adopt innovative ways to deliver and facilitate regular exposure to combination intervention packages, perhaps using mobile clinics, referral clinic vouchers, or even leveraging technology.

The difficulty of determining changes in contextual factors during interruptions in intervention exposure limits the interpretation of findings in this thesis and warrants further investigation. In addition, there is need to determine how frequently high-risk women should be exposed to combination HIV prevention packages in different epidemiological settings, i.e whether monthly, once every three months or semi-annual exposure to prevention packages is optimal.

CHAPTER 8: REFERENCES

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APPENDICES

Appendix A: Ethical Approvals

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LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Mr Ivan Kasamba
LSHTM

29 June 2017

Dear Ivan,

Study Title: Influence of attendance at a clinic service for high-risk women on HIV prevention and treatment outcomes: a longitudinal study in Kampala, Uganda

LSHTM Ethics Ref: 14341

Thank you for your application for the above research project which has now been considered by the Observational Committee via Chair's Action.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	HCT_WOM_Vs 3.0	15/01/2013	3.0
Protocol / Proposal	Alcohol WOM_Vs 1.0	19/03/2015	1.0
Protocol / Proposal	SOC DEM__WOM_Vs 4.0	05/11/2015	4.0
Protocol / Proposal	RH_WOM_Vs 4.0	05/11/2015	4.0
Protocol / Proposal	STI_Vs 4.0	05/11/2015	4.0
Local Approval	GHWP UNCST Approval to 2019	18/05/2016	version 1.0
Local Approval	GHWP Study UVRI REC App of study cont to 2017	10/11/2016	version 1.0
Investigator CV	CV_Ivan_Kasamba	23/06/2017	v1.0
Protocol / Proposal	Proposal_Ivan_Kasamba	24/06/2017	Version 3.0

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

At the end of the study, the CI or delegate must notify the committee using the End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk.

Further information is available at: www.lshtm.ac.uk/ethics.

Yours sincerely,

[redacted]

Professor John DH Porter
Chair

Uganda National Council for Science and Technology
(Established by Act of Parliament of the Republic of Uganda)

Our Ref: HS 364 **18th May 2016**

Dr. Anatoli Kamali
Principal Investigator
MRC/UVRI Uganda
Research Unit on AIDS
Entebbe

Re: Good Health for Women Project (GHWP)- Studies on the epidemiology and prevention of HIV and other disease in a cohort of women involved in high risk sexual behaviour and their male regular partners in Kampala.

This is to inform you that on **2nd March 2016**, Uganda National Council for Science and Technology (UNCST) reviewed the Progress report and application for renewal and approved the continuation of the above study.

UNCST granted continuing approval valid until **7th November 2019**. If however, it is necessary to continue with the study beyond the expiry date, a request for continuation should be made to the Executive Secretary, UNCST.

Yours sincerely,

[redacted]

Hellen .N. Opolot
for: Executive Secretary
UGANDA NATIONAL COUNCIL FOR SCIENCE AND TECHNOLOGY

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Uganda National Health Research Organisation

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REPUBLIC OF UGANDA

Our Ref: GC/127/16/11/30
Your Ref: MRCU/16/0910

November 10th, 2016

Dr. Anatoli Kamali,

RE: UVRI REC review of progress report titled **"The Good Health for Women Project (GHWP) - studies on the epidemiology and prevention of HIV and other diseases in a cohort of women involved in high risk sexual behavior and their male regular partners in Kampala."**

Thank you for submitting your progress report for the above study dated October 5th, 2016, received on 6th October 2016 to the UVRI Research Ethics Committee (REC).

This is to inform you that after review of your report, UVRI REC continuation approval has been granted for you to continue with this study for another one year up to 7th October, 2017.

At that time, REC would expect you to submit a progress report and request for renewal, prior to the expiry date, to allow timely review.

Yours sincerely,

[redacted]

Dr. Jonathan Kayondo
For Chair, UVRI REC
C.C Secretary, UVRI REC

Appendix B: Data Collection Tools

Appendix C: Additional Data Analysis Results

Supplementary Table C.1: Shows distribution of enrolment characteristics, proportion with no follow-up visit, and odds ratios from simple and multivariable models for risk factors for having no follow-up visit among women enrolled into the Good Health for Women Project (GHWP) between April 2008 and May 2017.

Characteristic at enrolment	Frequency distribution, n (column %)	Proportion with no follow-up visit, n (%)	Odds Ratio (95% CI) adjusted for cohort and age	p-value (LRT)	Adjusted Odds Ratio (95% CI) for risk factors	p-value (LRT)
Total	3084	878 (28.5)				
SOCIO-DEMOGRAPHIC						
Cohort of enrolment						
Closed cohort	647 (21.0)	42 (6.5)	1	<0.001	1	<0.001
Open cohort	2437 (79.0)	836 (34.3)	7.71 (5.57-10.68)		6.59 (4.70-9.24)	
Age in years						
<24	1350 (44.6)	459 (34.0)	1	<0.001	1	<0.001
25-34	1306 (43.2)	321 (24.6)	0.62 (0.52-0.74)		0.77 (0.61-0.97)	
35+	368 (12.2)	69 (18.8)	0.40 (0.30-0.53)		0.44 (0.30-0.65)	
Highest education level at enrolment						
Less than primary	1191 (41.5)	328 (27.5)	1	0.15		
Completed Primary to incomplete Ordinary level	1221 (42.5)	330 (27.0)	0.91 (0.75-1.10)			
Completed Secondary Ordinary level and above	460 (16.0)	123 (26.7)	0.78 (0.60-1.01)			
Marital status*						
Widowed/divorced	1864 (61.5)	483 (25.9)	1	0.11		
Currently married	215 (7.1)	67 (31.2)	1.33 (0.96-1.84)			
Never married	950 (31.4)	296 (31.2)	0.91 (0.75-1.12)			
Number of children*						
None	484 (16.2)	187 (38.6)	1	0.01	1	0.01
One	781 (26.1)	239 (30.6)	0.77 (0.60-0.99)		0.72 (0.53-0.96)	
At least 2	1730 (57.8)	407 (23.5)	0.66 (0.51-0.85)		0.63 (0.47-0.86)	
Source of income*						
Sex work alone	1750 (58.1)	523 (29.9)	1	0.01		
Sex work and other job	1118 (37.1)	275 (24.6)	0.75 (0.63-0.90)			
No sex work	145 (4.8)	43 (29.7)	0.88 (0.60-1.30)			
Where paying clients are recruited from						
Bar, club or restaurant	1396 (49.1)	356 (25.5)	1	<0.001	1	0.004
Street	775 (27.3)	291 (37.5)	1.51 (1.24-1.83)		1.37 (1.09-1.72)	
Several avenues	670 (23.6)	138 (20.6)	0.87 (0.69-1.09)		0.88 (0.68-1.13)	

REPRODUCTIVE HEALTH						
Pregnancy*						
Not pregnant	2858 (95.4)	811 (28.4)	1	0.25		
Pregnant	138 (4.6)	26 (18.8)	0.76 (0.48-1.21)			
Current contraceptive use*						
none or other	1813 (63.6)	530 (29.2)	1	0.01	1	0.05
oral cc	205 (7.2)	34 (16.6)	0.57 (0.38-0.85)		0.58 (0.37-0.89)	
inject	696 (24.4)	180 (25.9)	0.84 (0.68-1.03)		0.85 (0.67-1.08)	
Pregnant	138 (4.8)	26 (18.8)	0.73 (0.46-1.16)		0.80 (0.48-1.34)	
BEHAVIOURAL CHARACTERISTICS						
Frequency of paid sex in the last 12 months at enrolment						
Less than once a week/None	400 (13.1)	125 (31.3)	1	<0.001	1	<0.001
At least once a week	945 (31.0)	210 (22.2)	0.63 (0.48-0.83)		0.46 (0.31-0.69)	
Daily	1703 (55.9)	522 (30.7)	0.90 (0.70-1.15)		0.56 (0.38-0.83)	
Number of sexual partners*						
<5	753 (26.3)	190 (25.2)	1	0.87		
5-19	671 (23.4)	169 (25.2)	1.05 (0.82-1.35)			
Atleast 20	1442 (50.3)	420 (29.1)	1.06 (0.86-1.30)			
Number of men the participant had paid sex with in last month*						
<5	789 (27.6)	203 (25.7)	1	0.98		
5-19	650 (22.7)	162 (24.9)	0.98 (0.76-1.26)			
At least 20 or cannot remember	1420 (49.7)	411 (28.9)	0.99 (0.80-1.21)			
Condom use frequency with paid sex in the last month*						
Inconsistent	1183 (41.1)	296 (25.0)	1	0.002	1	0.001
Consistent (always)	1366 (47.5)	397 (29.1)	1.39 (1.15-1.67)		1.34 (1.10-1.65)	
No paid sex	329 (11.4)	88 (26.7)	1.15 (0.86-1.54)		0.69 (0.43-1.09)	
Alcohol consumption frequency*						
Non-drinker	691 (23.4)	203 (29.4)	1	0.27		
Non-daily drinker	1218 (41.2)	327 (26.8)	0.97 (0.77-1.20)			
Daily drinker	1047 (35.4)	284 (27.1)	0.85 (0.68-1.06)			
Binge drinking in last 3 months*						
Non drinker	690 (23.1)	201 (29.1)	1	0.28		
No binging	721 (24.1)	164 (22.7)	1.06 (0.82-1.37)			

Binged	1576 (52.8)	465 (29.5)	0.90 (0.73-1.10)	
Illicit drug use in last 3 months*				
Not used drugs in last 3 months	2075 (72.4)	562 (27.1)	1	0.36
Non-daily drug user	187 (6.5)	58 (31.0)	1.14 (0.81-1.60)	
Daily drug user	603 (21.0)	159 (26.4)	0.89 (0.72-1.10)	
HIV TESTING HISTORY				
>1 year ago or never	990 (33.1)	202 (20.4)	1	0.07
7-12 months ago	404 (13.5)	95 (23.5)	0.96 (0.72-1.28)	
<6 months ago	1599 (53.4)	535 (33.5)	1.21 (0.99-1.48)	
SEXUALLY TRANSMITTED INFECTIONS (STIs)§*				
No STI	1941 (65.8)	592 (30.5)	1	0.89
With STI	1008 (34.2)	221 (21.9)	0.99 (0.81-1.20)	

§STI variable was a composite variable combining data on STI symptoms from clinical examination and test results for STI for syphilis. *Data collected at enrolment and follow-up study visits.

Supplementary Table C.2: Factors associated with the odds of being in higher categories of missed study visits (MSV) than in lower categories using two-level random-effects ordered logistic regressions.

Characteristic	[1]Model 1: Odds Ratio (95% CI)	p-value (LRT)	Model 2: Adjusted Odds Ratio (95% CI)	p-value (LRT)
SOCIO-DEMOGRAPHIC				
Cohort of enrolment				
Cohort 1 (Closed cohort)	1	<0.001	1	<0.001
Cohort 2 (Open cohort)	2.39 (2.13-2.68)		3.40 (2.93-3.95)	
Age in years				
<25	1	0.001†	1	0.42
25-34	1.22 (1.08-1.37)		1.10 (0.96-1.26)	
At least 35	1.26 (1.07-1.48)		1.08 (0.89-1.31)	
Years of follow-up				
First 2 years of follow-up	1	<0.001	1	<0.001
Post 2 years follow-up	2.42 (2.17-2.70)		2.37 (2.10-2.66)	
With a stable sexual partner*				
Yes	1	0.21		
No	0.93 (0.83-1.04)			
Highest education level				
Less than primary	1	0.04	1	0.02
Completed Primary to incomplete ordinary level	1.15 (1.02-1.30)		1.15 (1.00-1.33)	
Completed Secondary ordinary level above	0.99 (0.84-1.17)		0.89 (0.73-1.09)	
Marital status*				
Widowed/divorced	1	<0.001		
Currently married	1.28 (1.13-1.46)			
Never married	0.93 (0.81-1.07)			
Number of children*				
None	1	0.09		
One	0.95 (0.78-1.15)			
At least 2	1.10 (0.92-1.33)			
Source of income*				
Sex work alone	1	<0.001		
Sex work and other job	0.99 (0.89-1.10)			
No sex work	1.37 (1.18-1.60)			
Where paying clients are recruited from				
Bar, club or restaurant	1	<0.001	1	<0.001
Street	1.39 (1.19-1.62)		1.52 (1.27-1.82)	
Several avenues	1.12 (0.99-1.28)		1.13 (0.98-1.32)	
REPRODUCTIVE HEALTH				
Current contraceptive use*				
none or other	1	<0.001		
oral cc	0.86 (0.73-1.02)			
inject	0.93 (0.83-1.03)			
Pregnant	1.41 (1.18-1.69)			
Pregnancy*				
Not pregnant	1	<0.001	1	<0.001
Pregnant	1.43 (1.20-1.72)		1.60 (1.33-1.94)	

BEHAVIOURAL CHARACTERISTICS				
Number of sexual partners*				
<5	1	0.001		
5-19	0.80 (0.71-0.91)			
At least 20 or cannot remember	0.88 (0.78-0.99)			
Number of clients in the last month*				
<5	1	0.001		
5-19	0.80 (0.71-0.91)			
At least 20 or cannot remember	0.88 (0.78-0.99)			
Condom use frequency with clients in the last month*				
Inconsistent	1	<0.001	1	0.001
Consistent (always)	1.02 (0.92-1.14)		0.98 (0.87-1.11)	
No paid sex	1.40 (1.24-1.58)		1.23 (1.07-1.42)	
Alcohol consumption frequency*				
Non-drinker	1	<0.001†	1	0.05
Non-daily drinker	0.98 (0.87-1.09)		1.07 (0.95-1.22)	
Daily drinker	0.78 (0.68-0.89)		0.91 (0.78-1.06)	
Binge drinking in last 3 months*				
Non-drinker	1	<0.001		
No binging	0.71 (0.62-0.80)			
Binged	1.08 (0.96-1.21)			
Illicit drug use in last 3 months*				
No	1	0.15	1	0.01
Yes	1.09 (0.97-1.22)		1.23 (1.08-1.40)	
SEXUALLY TRANSMITTED INFECTIONS (STIs)*§				
No STI	1	<0.001	1	<0.001
With STI	0.71 (0.64-0.79)		0.79 (0.70-0.89)	

[1]The outcome is a three-level categorical variable (No missed visit, 1-2 missed scheduled visits, ≥3 missed scheduled visits). [1]Model 1, adjusted for cohort of enrolment and age at previous attendance. Model 2, adjusted for cohort of enrolment, age at previous attendance, years of follow-up, education level, Where paying clients are recruited from, pregnancy status, Condom use frequency with clients in the last month at follow-up, Alcohol consumption frequency at follow-up, Illicit drug use in last 3 months at follow-up, Sexually Transmitted Infections (STI). † p-value for trend. The Odds Ratios are proportional odds interpreted as the odds of being in higher categories of MSV [i.e (i) ≥3 or (ii) 1-2 or ≥3]than in lower categories[(i)no MSV or 1-2, or (ii) no MSV, respectively]. §STI variable was a composite variable combining data on STI symptoms from clinical examination and test results for STI for syphilis. *Data collected at enrolment and follow-up study visits.

Supplementary Table C.3: Association of HIV seroconversion with the number of missed visits between consecutively attended visits using the Cox regression model, by cohort of enrolment.

	Cohort 1			*Cohort 2*		
Characteristic	New HIV cases/pyr (Rate/100 pyr)	Adjusted Hazard Ratio (95% CI)	p-value (LRT)	New HIV cases/PYR (rate/100 PYR)	Adjusted Hazard Ratio (95% CI)	p-value (LRT)
SOCIO-DEMOGRAPHIC						
Number of visits missed between attendances			0.45			0.002
No missed visit	53 /1886 (2.8)	1		28 /1220 (2.3)	1	
One/two missed visit(s)	18 /542 (3.3)	1.30 (0.73-2.32)		20 /708 (2.8)	1.62 (0.88-2.97)	
At least 3 missed visits	22 /574 (3.8)	1.41 (0.80-2.51)		29 /607 (4.8)	2.81 (1.61-4.91)	
Age in years			0.27			0.12
<25	30 /774 (3.8)	1		23 /788 (3.0)	1	
25-34	51 /1706 (3.0)	0.74 (0.45-1.20)		41 /1250 (3.3)	1.04 (0.60-1.79)	
At least 35	12 /524 (2.4)	0.57 (0.27-1.19)		13 /470 (2.7)	1.18 (0.57-2.44)	
With a stable sexual partner*			0.12			0.01
Yes	71 /2437 (2.9)	1		42 /1522 (2.8)	1	
No	22 /566 (3.9)	1.53 (0.89-2.61)		35 /645 (5.4)	2.04 (1.25-3.33)	
Highest education level at enrolment			0.07			0.48
Incomplete primary level	43 /1336 (3.2)	1		31 /1025 (3.0)	1	
Completed Primary to incomplete O level	41 /1300 (3.2)	1.05 (0.68-1.63)		29 /968 (3.0)	1.16 (0.68-1.97)	
Completed Secondary O'level above	9 /368 (2.4)	0.94 (0.45-1.94)		16 /425 (3.8)	1.50 (0.79-2.86)	
Recruitment of clients*			0.03			0.10
Bar, club or restaurant	46 /1608 (2.9)	1		30 /1109 (2.7)	1	
Street	20 /354 (5.7)	2.05 (1.18-3.56)		26 /534 (4.9)	1.80 (1.02-3.19)	
Several avenues	27 /964 (2.8)	0.92 (0.56-1.49)		21 /669 (3.1)	1.02 (0.57-1.81)	
REPRODUCTIVE HEALTH						
Current contraceptive use*			0.001			0.09
none or other	55 /1641 (3.4)	1		45 /1519 (3.0)	1	
oral cc	7 /348 (2.0)	0.60 (0.27-1.34)		5 /177 (2.8)	0.87 (0.34-2.23)	
inject	30 /725 (4.1)	1.25 (0.79-1.96)		26 /653 (4.0)	1.46 (0.88-2.40)	
Pregnant	1 /289 (0.3)	0.09 (0.01-0.69)		1 /107 (0.9)	0.24 (0.03-1.75)	

BEHAVIOURAL CHARACTERISTICS						
Number of men the participant had paid sex within last month*			0.24			0.23
<5	55 /1883 (2.9)	1		24 /933 (2.6)	1	
5-19	14 /554 (2.5)	0.58 (0.30-1.11)		13 /535 (2.4)	0.84 (0.40-1.76)	
At least 20 or cannot remember	24 /567 (4.2)	0.82 (0.46-1.49)		36 /955 (3.8)	1.07 (0.57-1.99)	
Condom use frequency with paid sex in the last month*			0.27			0.001
Inconsistent	32 /827 (3.9)	1		40 /788 (5.1)	1	
Consistent (always)	34 /1120 (3.0)	0.66 (0.40-1.11)		21 /1102 (1.9)	0.36 (0.21-0.64)	
No paid sex	27 /1056 (2.6)	0.71 (0.39-1.31)		16 /545 (2.9)	0.83 (0.40-1.69)	
Alcohol consumption frequency*			0.03			0.44
Non-drinker	24 /1137 (2.1)	1		25 /733 (3.4)	1	
Non-daily drinker	42 /1249 (3.4)	1.69 (0.99-2.88)		26 /953 (2.7)	0.72 (0.40-1.31)	
Daily drinker	27 /617 (4.4)	2.21 (1.20-4.08)		26 /800 (3.2)	0.79 (0.43-1.46)	
SEXUALLY TRANSMITTED INFECTIONS (STIs)*§			0.14			0.17
No STI	51 /1991 (2.6)	1		58 /2042 (2.8)	1	
With STI	42 /1012 (4.1)	1.40 (0.89-2.20)		19 /459 (4.1)	1.06 (0.60-1.86)	

§STI variable was a composite variable combining data on STI symptoms from clinical examination and test results for STI for syphilis. *Data collected at enrolment and follow-up study visits.