

**TIME-TO-EVENT ANALYSIS OF EFFECTIVENESS OF HIV POST-EXPOSURE
PROPHYLAXIS IN A NAIROBI SEX WORKERS COHORT**

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DECLARATION

I, Evelia Janet Musimbi, declare that this thesis is my own work. It has not been submitted in any form for any degree or diploma to any other University or Institution. Where information has been derived from other sources, it has been duly acknowledged.

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ABSTRACT

Background: The current overall HIV prevalence in Kenya is 4.8%, yet research on effectiveness of non-occupational Post-Exposure Prophylaxis (PEP) for HIV prevention is still patchy and consequent risks poorly understood.

Objective: To characterize the PEP real-world effectiveness and prospective sexual health risks among .

Methods: Data from sex workers aged ≥ 18 years prescribed PEP as from 2016 to 15th October 2018 were analyzed. A comparison group of non-PEP/non-Pre-Exposure Prophylaxis (PrEP) enrolled as from 2016 was used and random sample of 503 taken for comparative analysis in a ratio of 1:1. Sociodemographic comparison of profiles was done at baseline using a Chi-squared test. Kaplan-Meier cumulative event and hazard functions and Cox proportional hazards models were fitted, in analyses that included PrEP, for time-to-ARV initiation.

Results: There were 42.9% of 196 PEP users and 57.1% (comparison group) whose data were linked with baseline data. Chi-square test for differences resulted in statistical significance in age categories ($p=0.0027$) and in sex work duration ($p<0.001$) between the PEP and the Comparison group. There were 8 (0.64%) total HIV infections (ARV initiations), 6 (1.3%) from the Control group and 2 (0.64%) from Pre-Exposure Prophylaxis (PrEP) group. Five (3.1%) incident HIV-infection/ARV initiation among MSMW and 3 (0.28%) among FSW found. Men who have sex with men (MSMW) were at higher risk of HIV compared to female sex workers (FSW) with hazard ratio of 17.2 ($p<0.00001$). In total 52 (9.35%) sex workers had repeat PEP prescriptions with 90.3%, 8.4%, 1.1% and 0.2% having had 1,2,3 and 4 PEP episodes respectively. PEP recurrence rate was 8.6 per 100 person-months of follow up. There was HIV event-free survival in the PEP group. Univariable and multivariable Cox models yielded same results. Multiple pairwise log-rank test indicated presence of significant survival difference between PEP and Controls ($p\text{-value}=0.046$), insignificant differences between PEP and PrEP ($p=0.025$) and PrEP and Control group ($p=0.631$) and evidence of clinically significant results. Survival among PEP users was comparative better hence effective but not statistically significant at alpha 0.05.

Conclusions: There is evidence that PEP is effective when adherently taken and associated with event-free survival but this is not statistically significant. The underpin the potential need to scale up condom counseling and in formulating personalized risk scores for treatment as HIV prevention among the sex workers for behavioural risk change and more focus on MSM.

DEDICATION

I dedicate my dissertation work to my family. I express my sincere gratitude to my loving parents whose words of encouragement and push for tenacity ring in my brothers and sister have been with me in a special way through the entire period, my dear husband for his support throughout. I also dedicate this dissertation to my many friends, especially John Mutiso and Isaiah Akuku for helping me develop my statistical skills.

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LIST OF ABBREVIATIONS AND ACRONYMS

ART	Antiretroviral therapy
MSM	Men who have sex with men
MSMW	Men who have sex with men and women
PEP	Post-exposure prophylaxis
nPEP	Non-occupational post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
STI	Sexually transmitted infection
TasP	Treatment as prevention
WHO	World health organization
UoM	University of Manitoba
UoN	University of Nairobi
HIV	Human Immunodeficiency Syndrome
PLHIV	People living with HIV
PHDA	Partners in Health and Development in Africa
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immunodeficiency Disease Syndrome
HTC	HIV testing and counseling

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CHAPTER ONE

1. INTRODUCTION

This chapter gives an overview including motivation of the study as well as the current knowledge gaps. In Section 1.1, the background to the study is presented. The statement of the problem is presented in Section 1.1 and study justification and significance described in Section 1.2. Section 1.3 states the study objectives while Section 1.4 describes the assumptions of the study and Section 1.5 study limitations. Section 1.6 describes the organization of the subsequent chapters of the thesis.

1.0 Background

HIV/AIDS remains a key public health problem in Kenya. Post-exposure prophylaxis (PEP) is an emergency antiretroviral therapy (ART) to abort acquisition of HIV following occupational (Panlilio et al., 2005), intravenous drug use, or sexual high-risk exposures (Smith et al., 2005). However, the public health benefits of PEP will be determined by effectively targeting the most at-risk populations (MARPs) such as sex workers. PEP is therefore advised following sexual contact with a partner of unknown positive or known HIV status from a high-risk group.

Previous studies have shown that prompt initiation of ART following occupational (healthcare providers) and perinatal (immediately before and after birth) exposures to HIV can significantly decrease the risk of acquiring the virus (Cardo et al., 1997; Connor et al., 1994; Guay et al., 1999; Lindegren et al., 1999; Mitchell, Furegato, Hughes, Field, & Nardone, 2017; Shaffer et al., 1999; Wade et al., 1998; Wiktor et al., 1999). These evidence in occupational exposures are numerous and underscore its significance (Collaborators CDSCa, 1999; Gerberding, 2003; Tetteh et al., 2015) and have encouraged the use of PEP after sexual and/or non-occupational exposures (M. E. Roland et al., 2005) and consequently the importance in public health.

Since sexual contact is the most frequent route for new HIV infections (UNAIDS, 2018b) and accounts for at least three fourths of infections (UNAIDS/WHO, 1998; UNAIDS, 2010), prescription of PEP for non-occupational exposures becomes appropriate (Kahn et al., 2001), as viral acquisition across mucosal surfaces is the same for occupational and no-occupational exposures (Katz & Gerberding, 1997; Royce, Seña, Cates, & Cohen, 1997) but not without challenges.

The problem could possibly be an imprecise evaluation of HIV risk by sex workers/PWIDs arising from the unclear knowledge of HIV serostatus of the sources, hence delay in seeking PEP compared with perinatal or at healthcare providers level where the serostatus of the source is certain. Other concerns are on adherence, adverse PEP events (Sonder et al., 2010; Tetteh et al., 2015), refusal to have follow-up HIV test and the risk compensatory behaviours (Kahn et al., 2001).

All these underpins the fact that the effectiveness of PEP against HIV after sexual exposure is still indefinite and the potential clinical outcomes or risks of STIs not well known, especially at MARPs level and prevention strategies articulated. Besides, WHO approximates that more than a million new STIs are contracted every day or 357 million annually with either gonorrhoea, syphilis, chlamydia, and trichomoniasis (WHO, 2016) and that STIs such as syphilis can intensify the HIV risk of acquisition at least 3 times. STIs are thus pernicious contributors to the disease burden (Low & Broutet, 2017).

This limited evidence on the PEP effectiveness for sexual exposures has motivated this study to evaluate the PEP effectiveness, the future clinical outcomes related to the sexual risk-taking behaviours and assess whether adherence is related to these sexual risk-taking behaviours among a cohort of sex workers enrolled in the Sex Worker Outreach Project (SWOP)–Kenya.

Importantly, the care for individuals exposed to HIV involves four pathways: baseline assessment with testing, counseling and support, prescription of a full 28 days course of ART for PEP for maximum benefit and prevention of seroconversion, and follow-up with testing three months following exposure (WHO, 2014a). Essentially, studies on PEP use are therefore classically both observational and longitudinal by design. This makes SWOP–City useful in the study of the effectiveness of PEP while concurrently exploring population-based cohort facility-level design on PEP effectiveness for HIV prevention and the future risks related to its use.

SWOP–City, in itself is a dynamic cohort, and, more than 1,800 sex workers have accessed PEP at least once and reported condom failure in the past year (Personal communication 6/4/2018 with Joshua Kimani. MBChB, MPH, Dip(Int. Health), Clinical Research Director, UoM/UoN PHDA). A previous SWOP–City study on uptake reported about 4% had accessed PEP “more than once” (Izulla et al., 2016).

In longitudinal cohort studies (in-care) as the SWOP–City cohort, patients are often longitudinally evaluated and outcomes measured. The clinical and scientific interest lies in the prediction of the risk of such clinical events, for instance quantifying disease incidence, using either time-independent, time-dependent data or both, or determining the effectiveness of (bio)medical intervention. For the cohort, the incidence of these events is related to risk sets' differences (individuals with and without the event). The study focus is on analyses applied to incident HIV/STIs diagnoses.

The time-to-event analysis is suitable in determining the effectiveness of a particular treatment and in understanding the effect of biobehavioral factors (e.g., medication adherence) in health and diseases. In this study, the Kaplan–Meier method and Cox's Proportional Hazards (PH) model are fitted to study the probabilities of the events. The longitudinal follow-ups make time-to-event analysis method potent for analysis of PEP effectiveness due to the pervasive applicability of Cox PH of making full use of data in the real-time estimation of discrete incident HIV diagnosis and associated STIs.

In a Cox model framework, hazard ratios and pairwise survival differences were computed and a method of simple grouping and time zero for follow up being time after completion of PEP first course. The variable representing PEP exposure taken as dummy variable of (users=1 and nonusers=0) as described by (Zhou, Rahme, Abrahamowicz, & Pilote, 2005) and used to determine the PEP effectiveness from comparison groups as single time dependent variable. The event was time to ARV initiation.

1.1 Problem Statement

The HIV/AIDS has a devastating impact in Kenya which is one of the most affected countries in sub-Saharan Africa (AVERT, 2018). Current prevalence is 4.8 (UNAIDS, 2018a) and of the 1.6 million PLHIV in Kenya, more than half (53%) are unaware of their HIV status (Ng'ang'a et al., 2014). In Africa and more so in Kenya, HIV is mostly sexually transmitted and therefore affects all sections of the population i.e. children, teenagers, adult men and women, either through direct transmission or from a HIV-infected mother to a child during delivery or the nursing period (Keats et al., 2018; Kimani-Murage et al., 2014; Maina et al., 2014; Ng'ang'a et al., 2014).

MARPs such as sex workers, PWID, MSM are the most affected. Kenya's strategic direction is in the prevention of new infections (MoH/NACC, 2016). However, there is a lack of reliable epidemiological data on which to base the effectiveness of PEP that can enhance understanding of its utility and in turn lead to effective HIV prevention while developing sustainable strategies. Use of condom at last high-risk sex is just 43.9% among Kenyan adults aged 15–49 (UNAIDS, 2018a) and the repeat PEP use is a pointer of potential future risks of STIs, even so, inadequate research data to quantify the STIs associated with it.

There are factors that contribute to the incidence of new HIV infection and therefore the prevalence of disease. These include unawareness of ones' HIV status (Cherutich et al., 2012), not taking measures to prevent infection either before or after exposure to the disease especially using antiretroviral therapy, an infected mother not taking measures to prevent transmission of the virus to her child especially by not taking the antiretroviral therapy so as to lower the viral load (Inungu & Karl, 2006; Kembo, 2012; Sing & Patra, 2015; Todd et al., 2006).

New infections will have a burden on the economy as there will be a need for the government to invest more in providing free ART to those affected. For those who are not on treatment, there's a risk of spread of the same and increased burden to the healthcare system when they present with AIDS-related complications. Economically, the workforce is also reduced either due to morbidity or mortality due to the same (Dixon, McDonald, & Roberts, 2002; Inungu & Karl, 2006).

For those individuals that take preventive measures after exposure to HIV especially with use of antiretroviral therapy, whether for Post-Exposure Prophylaxis (PEP), Pre-Exposure Prophylaxis (PrEP) or Prevention of Mother-To-Child Transmission (PMTCT), the effectiveness of this is important so as to determine whether it is cost-effective to continue with the same or to devise new strategies.

While HIV risk exposures are preventable, it remains to impose severe impacts on individual and public health. However, PEP if ideally initiated very early (within 72 hours), for all individuals exposed and at high risk of acquiring HIV, and ideally within 72 hours and can be a useful tool in TasP (WHO, 2014b). Assessment of the relationship between adherence and sexual risk-taking needs to be done and is quite vital to the effectiveness of PEP intervention, trends of

uptake and quantification of prospective risks of STIs and comparative analysis of non-PEP users.

Previous research too has presented mixed results on the effectiveness of PEP against HIV after non-occupational exposure (M. E. Roland et al., 2005) and others available have mixed methodological quality. Hence, this study seeks to, using time-to-event methods, characterize and determine the effectiveness of post-exposure prophylaxis (PEP) and related clinical outcomes in SWOP–City cohort. Analysis of data arising from the cohort requires special methods as some observations may be censored when the event of interest hasn't occurred for all sex workers.

1.2 Study Justification and Significance

Pre-exposure prophylaxis may reduce an individual's risk of acquiring HIV (Tumarkin et al., 2018), on the other hand, it is still not entirely clear, given few studies, whether people at high risk of exposure to HIV are conferred sufficient protection if they use PEP. Since SWOP–City also rolled out PrEP, this study does comparative analysis with the non-PEP sex worker group, including the PrEP prescriptions.

It is also not definite whether current strategies for PEP after sexual exposures are satisfactorily specific. Utility of this study is found on the need to characterize PEP trends of usability and related risks among the sex workers and infer programmatic (cohort effects) and public health implications and the potential need to scale up PrEP given likely recurrent risks related to PEP and condom use information uptake or in formulating personalized risk scores for PrEP use for HIV.

PEP comprises of a 28-day course of ART provided within 72 hours prophylactically for a high-risk exposure (Smith et al., 2005). Conversely, a high proportion of exposed individuals stop both their prescribed 28-day PEP course for HIV before 15 days and follow-up testing for HIV before month 3 (Bentz et al., 2010) and its tolerability is often poor (Milinkovic et al., 2017). These worries associated with users' adherence have limited PEP prescription for the MARPs (Landovitz et al., 2012; Oldenburg, Bärnighausen, Harling, Mimiaga, & Mayer, 2014).

Assessment of whether PEP adherence is related to sexual risk-taking is important for the effectiveness of SWOP–City programme and in the identification of potential hotspots in the MARPs for HIV transmission that may diminish PEP potential protective benefits.

Few randomized controlled trials exist (e.g., Fätkenheuer et al., 2016; Milinkovic et al., 2017; Michelle E. Roland et al., 2011) have been conducted largely on tolerability, although additional evidence presented the benefits of PEP for HIV (Irvine et al., 2015) in nonhuman primate studies. But in humans few efficacy studies exist, and, while nested case-control studies have been done on health care providers following exposures from needle sticks (Cardo et al., 1997; Jain & Mayer, 2014) hardly any expressly on PEP following sexual exposure. This study fills the gaps in PEP for HIV literature and therefore could be a reference in the formulation of TasP policies in Kenya and elsewhere.

Although sex workers and/or MARPs (FSW, MSW, MSM, PWID/PWUD) may benefit from PEP, there may also be other clinical outcomes related with the high-risk behaviours such as STIs and HBV/HCV more common in MSM (Falade-Nwulia et al., 2015). This is the case since the rates of STIs are rising in some MARPs (Marrazzo, Dombrowski, & Mayer, 2018). This study quantifies the high-risks related with PEP usage and present the empirical evidence using both an observational and longitudinal cohort designs given the characteristic feature of SWOP–City of simultaneously being population-based cohort which can provide a thorough understanding of PEP protective benefits and related recurrent risks or otherwise and a further research to attempt to decrease the frequency of STIs in MARPs.

Apart from MARPs, this study, as aforesaid, seeks to characterize the PEP effectiveness and therefore useful for the general population’s consumption and countering the “where is the data (evidence)” narratives on potential protective benefits of PEP – if found. It can also be a source of information for basic research (biomedical science) in improving efficacy of the prophylaxis if need be. Similarly, this study can sufficiently provide information to future research agenda especially to clinical trialists in the design of randomized clinical trials in HIV TasP studies related to PrEP/PEP among others on considerations of inclusion of STI clinical outcomes as co-endpoints where it’s fitting.

More so, data on PEP utility are rare. This study uses the SWOP–Kenya data to provide knowledge for utility/uptake that is still weak in Kenya (Olsthoorn et al., 2015) and thus enabling PEP to become a critical tool for prevention of HIV among sex workers – and the general population. Similarly, analysis of risk-taking behaviours can further provide evidence for more interventions and psychosocial support linkage by SWOP–City and enhancement of operations with regard to the MARPs at policy levels.

SWOP–City is a unique longstanding observational cohort and analysis of its data may present statistical challenges and opportunities. The main challenge is different times of observations. However, opportunities abound in time-to-event analysis and estimation of proportion at-risk (free of event) at any time is feasible using Kaplan–Meier method combined with significance testing between the different sex worker groups via log-rank test as well as estimation of survival differences between them through hazard ratios. Covariate effects can be estimated too using Cox Proportional Hazards models.

An additional statistical challenge is in the repeat PEPs and/or recurrent STIs due to internal clustering of survival data–unobserved heterogeneity (Liu, 2014) from repeated events (Lin, Wei, Yang, & Ying, 2000) hence the potential use of frailty models and random coefficients models. However, this was not done given the nonoccurrence of STIs in the group.

1.3 Study Objectives

1.3.1 General Objective

To characterize and determine the effectiveness of non-occupational post-exposure prophylaxis (PEP) in SWOP–City cohort using time-to-event analysis.

1.3.2 Specific Objectives

- i) To assess the demographic characteristics, baseline sexual practices and risk behaviours for HIV
- ii) To compare the survival of the key populations specifically MSMW and FSW
- iii) To characterize the incidence of, and trends (patterns) for PEP episodes
- iv) To determine the effectiveness of PEP and compare with that of PrEP

1.4 Assumptions of the Study

Data was assumed missing completely at random (MCAR). Mechanisms of data missingness are categorized into three: MCAR, missing at random (MAR), and missing not at random (MNAR) (Little & Rubin, 2002). MCAR occurs when the missing data are unrelated to the unobserved and observed variables of the study, this means that the observed data is statistically representative of all sex workers' PEP experiences. In the Kaplan–Meier (KM) analyses, non-informative censoring is assumed, that is, sex workers who dropped out of the PEP ART did so because of reasons not associated to the programme (Campigotto & Weller, 2014; Ranganathan & Pramesh, 2012). Sex workers with missing data are not be modelled.

As a result of MCAR, it is assumed that the sex workers are comparable, and additional follow-up time in the earlier years adds no value to comparisons in the entire period. Sex workers are a risk set, only if they were at the time under observation and at risk for the event and that any censoring or drop-out is not related to the primary outcome or co-primary outcomes. This is useful since in KM estimator (Kaplan & Meier, 1958) and Cox proportional hazards model (Cox, 1992) for estimation of time-to-event regression models, where the risk set at a specific event time has all sex workers being observed and have not yet experienced the event of interest (Betensky & Mandel, 2015) when there are no delayed entries to the study.

This study also assumes that in the Cox Regression model, the proportional hazards assumption is valid across all the categories of age groups. Equally, it is assumed that sex workers with at least one STI diagnoses in the study period could be correlated due to some “unmeasured” biological changes attributable to these recurrent STIs, demonstrating the accumulating effects on the hazard of transition not measured or hard to quantify.

1.5 Organization of the thesis

This thesis is divided into 6 chapters, the first is this chapter, Introduction. This chapter presented an essential overview of PEP for HIV prevention and motivation for this study to enable the readers of this thesis to have sufficient knowledge to understand and follow the successive chapters. Chapter 2 reviews the existing literature of PEP and statistical methods for survival analysis. In Chapter 3, the SWOP–City data are explored and survival models applied in its analysis. In Chapter 4, results from the exploratory data analysis and survival models are presented. Chapter 5 presents the discussion of the results and how it compares with existing

empirical literature, directions for future research and provide conclusions of the thesis, public health implications and directions for future work.

CHAPTER TWO

2. LITERATURE REVIEW

2.0 Introduction

This chapter provides a literature review on HIV epidemiology in Kenya, PEP—uptake, adherence, and adherence counseling in relation to seroconversion and STI risks. The chapter is also concerned with the concepts and models, mostly Cox PH, for the analysis of time-to-event data, relevant to the analysis of SWOP–City data. In the programme, some sex workers repeatedly accessed PEP, there is a possibility of recurrence of STIs besides repeat PEP courses. In view of this, models for recurrent data are reviewed in this chapter for subsequent application in chapter 3.

2.1 Epidemiology of HIV in Kenya

By the end of 2017, a total of 36.9 million people were infected with HIV globally. The region most affected by this epidemic in Africa with Kenya, Mozambique and Uganda having the fourth-largest joint epidemic worldwide as at the year 2016 (UNAIDS, 2018b). In 2016, there were a total of 1.6 million PLHIV (AVERT, 2018; UNAIDS, 2018b).

HIV was first detected in Kenya in 1984 and the incidence increased through the years, whereby in the mid-90s, HIV was one of the major causes of morbidity and mortality in Kenya having a huge impact on the Kenyan economy and healthcare system (NACC, 2014a). The prevalence at 1996 was 10.5% of the general population but with improvement in the healthcare system and improved management of HIV, by 2015 the prevalence had reduced to 5.9% (AVERT, 2018).

The prevalence of HIV in 2016 was 5.4% which is a decline from 2015 (UNAIDS, 2017) estimates. In the same year, 36,000 deaths were reported to have been due to AIDS-related complications which is a decline from a previously reported 64,000 deaths due to the same in 2010. Of the infected, 64% of the adults, 65% of the children were on anti-retroviral treatment (AVERT, 2018; UNAIDS, 2017, 2018b). There were 62,000 reported new HIV infections.

Geographical location is a major factor in the prevalence of HIV with a range of 0.1% in Wajir county to 25.4% in Homa Bay county in Kenya (PEPFAR [U.S. President’s Emergency Plan for AIDS Relief], 2017).

There are certain groups that are also most affected by HIV in Kenya. These key populations are sex workers (both male and female), MSM, people who inject drugs (PWID) (IBBS, 2012; IOM, 2011; Musyoki et al., 2015).

About 3 years ago, studies reported that about 29% FSWs are living with HIV (MoH/NACC, 2016; Musyoki et al., 2015) although a pooled prevalence of 45.1% in FSW in comparison with 7.7% in female general population (Baral et al., 2012) was a little earlier reported. Among MSM about 18% (IOM, 2011; MoH/NACC, 2016; IBBS, 2012) was reported in both the year 2010 and 2011 and majority were in Mombasa and Nairobi (NACC, 2014a). MSM, mostly those in transactional sex, significantly contribute to the HIV epidemic in Kenya (McKinnon et al., 2014; Muraguri et al., 2015).

2.2 Post-Exposure Prophylaxis (PEP)

2.2.1 PEP Uptake

The uptake of post-exposure prophylaxis has been risen since its introduced and recommended for occupational and non-occupational exposures of HIV infection. Scientific publications exist on the uptake and effectiveness of PEP. A ten-year retrospective study done by Tissot et al. (2010) on non-occupational HIV exposures, found that there was a significant increase of PEP intake between 1998 and 2007.

Poynten et al. (2009)'s prospective analysis of nPEP use in relation to HIV infection and future HIV risk behaviours among homosexual men in Australia, found that above 70% of participants had previous information on nPEP and reported significant increase PEP uptake. However, Poynten et al. did not find a significant relationship between nPEP use and HIV risk behaviours. In a similar study done in Amsterdam, a modest increase of PEP uptake was observed after potential HIV exposure (Sonder et al., 2007), interestingly, about 75% of PEP requests were from MSM.

In Nairobi, Kenya, Izulla et al. (2016) reported 20 % of sex workers (n = 1119) asked for PEP at least once with close to 4% having accessed PEP more than once. The recurrent users were younger, with higher numbers of casual partners but had regular partners and highly likely to use condoms. In the Izulla et al.'s study, side effects, stigma, and lack of knowledge were the barriers to uptake of PEP.

2.2.2 Adherence to PEP, Adherence Counselling and HIV Seroconversion

WHO (2003) defined adherence as “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”. Within the context of PEP, incomplete adherence to the ART might raise the risk of seroconversion.

In a sample of 877 of HIV-negative people potentially exposed through sexual/injection drug use, Roland et al. (2005) reported seroconversion in 7 individuals and the possibility of “chemoprophylactic failure”. Roland et al. established that it is challenging to attribute the causes of seroconversion in non-occupational exposure due to increased likelihoods of subsequent exposures and that the effectiveness of PEP was somewhat indeterminate.

Malinverni et al. (2017)’s multivariate analysis for predictors of PEP adherence reported 66.4% completion rate of a 28-day treatment by participants. Malinverni et al. found that the use of PEP in previous occasions was associated with increased odds of PEP adherence. Also, MSM were more likely to adhere to PEP treatment as compared to the other groups with an odd of 1.4. In a similar study conducted by Thomas et al. (2015), 11 patients seroconverted within the follow-up time, and it was concluded that only a small proportion was as a result of PEP failure because of the continued high-risk behaviours already reported elsewhere (Gulholm, Jamani, Poynten, & Templeton, 2013; M. E. Roland et al., 2005; Tissot et al., 2010).

In a systematic review and meta-analytic study conducted by Oldenburg *et al.* (2014) on adherence of PEP, the overall adherence was found to be 78%. Among the 17 studies included, 3 were randomized, 9 prospective and 5 were retrospective. A high variance in pooled PEP adherence between the three categories was observed. Retrospective studies had the highest pooled adherence levels followed by randomized trials and then the prospective studies. According to Poynten et al. (2009) and Malinverni et al. (2017), men requesting for PEP had higher chances of seroconversion in their later days. This occurrence could be attributed to subsequent risky behaviours increases the likelihood of HIV exposure (Donnell et al., 2010).

Promising strategies for improving adherence to PEP are available. Supportive psychotherapy or counseling is an important component of PEP therapy (Grodesky, 1996). This may involve PEP adherence counseling tailored to address mental health stressors and/or psycho-social factors that may have negative impacts on the PEP adherence (Blashill, Ehlinger, Mayer, & Safren, 2015) and

in turn affect medication effectiveness. Likewise, in the SWOP–City, linkage to psychosocial support may influence PEP adherence positively and therefore act as an effect modifier.

2.2.3 Association with Sexually Transmitted Infections

Exposure to STIs will frequently co-exist with exposure to HIV by sexual routes (WHO, 2014a) hence provisions of PEP may also promote testing for other STIs (Kahn et al., 2001). Cohort studies have previously demonstrated that STIs are more likely to be diagnosed in MARPs (Mayer et al., 2014) including incident HBV (Falade-Nwulia et al., 2015) hence promoting HIV epidemics due to risky sexual practices. PEP prescriptions are associated with elevated risk of subsequently acquiring HIV/STIs (Mehta, Erbedding, Zenilman, & Rompalo, 2003).

Risky sexual behaviours are associated with increased STI counts (Fletcher, Rusow, Le, Landovitz, & Reback, 2013). Among sex workers, the high prevalence of STIs has been reported with trichomoniasis reaching prevalence above 20% and gonorrhoea above 5% (Grigoryan et al., 2013) with reinfection playing a huge role (Mehta et al., 2003). However, consistent and appropriate use of condoms can considerably decrease the risk of HIV/STIs (NACC, 2014b). Among determinants, STIs reinfection are age and sexual orientation (Hughes et al., 2001), In Kenya, Izulla et al. (2013) associated PEP use with gonorrhoea (6.9%), taking alcohol (84.3%), increased condom use (85.1%) and previous HIV testing (89.2%). Motives for accessing PEP were on client mistrust. PEP use is an indicator of future risks of HIV/STI. Izulla et al.'s results are quite consistent with Hladik et al. (2017)'s Kampala, Uganda study among FSW not accessing PEP but equally most-at-risk, in which case HIV infection was linked to low levels of education, lack of other jobs, gonorrhoea, genital ulcers, or any STI, gender-based violence, physical abuse and rape.

2.3 Methods for Time-to-event Analysis

2.3.1 Basic Concepts of Time-to-Event Analysis

The time-to-event analysis is an area of statistics is widely used in medical research and other fields as economics, social sciences and reliability studies in engineering to analyze and model time-to-event data. The time-to-event analysis considers the time between a fixed starting point (Bradburn, Clark, Love, & Altman, 2003), examples in medical research include duration between treatment administration and recovery, time to cancer diagnosis, cancer remission to relapse, time

to a terminating event – death etc. Time-to-event data are rarely normally distributed, however, are skewed and include typically several early events and comparatively few late events, hence special analysis methods are employable (Clark, Bradburn, Love, & Altman, 2003).

Censoring occurs when some information about individual survival time are available, but the survival time is not known exactly. occurs due to loss to follow-up in the study period, and withdrawal from the study for death or some other reason like adverse drug events.

Survival function $S(t)$ is the probability that an individual survives longer than some specified time t . If \mathbf{T} is a non-negative random variable signifying the waiting time until the event of interest occurs, $S(t)$ provides the probability that the random variable \mathbf{T} is beyond the specified time t . $S(t)$ is essential to time-event analysis and often expressed as a KM curve where the vertical drops in a specify an event.

Hazard function ($h(t)$) gives the instantaneous potential per unit time for the occurrence of the event of interest, conditional on the individual has survived up to time t . $h(t)$ is fairly a measure of risk. While the *Hazard Ratio* (HR) is the ratio of incidence rates—the HR is an estimate of the ratio of the hazard rate in one group to another. It's analogous to relative risk.

Generally, two regression models exist for the time-to-event data: semi-parametric model (Cox PH model) and parametric models accelerated failure time (AFT) models (Montaseri, Charati, & Espahbodi, 2016).

2.3.2 Parametric modeling

Typical parametric models include Weibull, exponential, and log-normal (Therneau & Grambsch, 2000). They are useful only if the parametric assumption exists and therefore a more powerful analysis may be done. Parametric AFT models are alternatives to the PH model (Wei, 1992). Different from the PH model described in section 2.3.4, the AFT method models survival times directly and produces a summary measure interpreted in respect of the survival curve (Hutton & Monaghan, 2002). The focus of this thesis is on Cox PH.

2.3.3 Nonparametric modeling

2.3.3.1 Kaplan-Meier Method

The probability of survival can be estimated from the survival times that were observed, for the censored and uncensored, by Kaplan and Meier (1958) – KM (product-limit) approach.

Suppose that the sex workers have k distinct events during the follow-up at distinctive times $t_1 < t_2 < \dots < t_k$, then at each event time t_j then there n_j sex workers at risk, that is, those that do not have the event of interest and uncensored before t_j . d_j is the number having the event at t_j . And since the events are assumed to occur independently of one another, the cumulative probability of survival is obtained by multiplying the probabilities from one interval to the next. That is, the probability of surviving at time t_j is got from $S(t_{j-1})$ and in terms of notation, the cumulative probability calculated as:

$$(2.1) \quad \hat{S}(t_j) = \prod_{j:t_j \leq t} \left(1 - \frac{d_j}{n_j}\right)$$

Where: \hat{S} = the estimated survival probability at time t : $P(>t)$. The risk set n_j at time t_j consists of the original sample minus all those who have been censored or had the event before t_j . d_j/n_j = gives the proportion that experienced the event at the event time t_j ; $1 - d_j/n_j$ is the proportion surviving the event time. Usually, $d_j = 1$ person, in cases where data are grouped in time intervals (e.g., everyone who had the event in the 2nd month). $\prod_{j:t_j \leq t}$ = multiplication of the survival probability of event time t with the probabilities of surviving all the prior event times.

The KM assumptions are that the survival probabilities are similar for all the individuals enrolled early and late, censoring is not related to prognosis and that the events occurred at the times indicated (Bland & Altman, 2004).

2.1.1.1 Comparing survival curves–Log-rank test and Wilcoxon test

In medical and epidemiological research, the survival experience of two or more groups of individuals is usually compared. Wilcoxon test proposed by Gehan (1965) and Breslow (1970) and the log-rank test suggested by Mantel (1966) and Cox (1972) are usually used in the comparison of survival curves.

The log-rank test is a version of chi-square (χ^2), considerably computed in a similar manner as the χ^2 statistic (Stevenson, 2009) and p-value obtained from the χ^2 table. It is used in the calculation of a test statistic for a null hypothesis that there is no difference between the groups in the probability of an event at any time point. And approximately χ^2 with one degree of freedom. It's based on the similar assumptions as the KM survival curve (Bland & Altman, 2004).

For KM curves, statistical significance may be the p -value obtained from the log-rank test or Wilcoxon test. However, as the log-rank test is purely a significance test, cannot give an estimate of the size of the (overall) difference between groups and a related confidence interval. Secondly, the KM method and the log-rank test cannot study many factors simultaneously, and therefore not used in the multivariable analysis.

Wilcoxon is a form of the log-rank test weighting strata by their sizes and gives more weight to earlier time points, hence more sensitive to differences at earlier time points. The log-rank test has most power for testing differences and frequently applied after checking for PH assumption validity—so is effective as a set-up for later Cox PH models, with Wilcoxon being the fallback approach if the PH assumption is unmet (Martinez & Naranjo, 2010).

2.3.4 Semi-Parametric modeling

2.3.4.1 Cox proportional hazards model

Cox PH relates several covariates or risk factors considered simultaneously, to survival time. The measure of effect is HR. It also allows for both continuous and categorical prognostic factors to be modelled. It models the shape of the $h(t)$ with an empirical part that is dependent on time and an exponential part dependent on the covariates (Laura Lee Johnson & Joanna H. Shih, 2012). Suppose a sex worker i at risk of an event after being followed for time t . The proportional hazard is shown as:

$$(2.2) \quad h_i(t) = h_0(t)e^{\beta_1 x_{i1} + \dots + \beta_k x_{ik}}$$

or

$$(2.3) \quad \log h_i(t) = \log h_0(t) + \beta_1 x_{i1} + \beta_2 x_{i2} + \dots + \beta_k x_{ik}$$

And compared with another j in a different group

$$(2.4) \quad HR_{i,j} = \frac{h_i(t)}{h_j(t)} = \frac{h_0(t)e^{\beta_1 x_{i1} + \dots + \beta_k x_{ik}}}{h_0(t)e^{\beta_1 x_{j1} + \dots + \beta_k x_{jk}}} = e^{\beta(x_{i1} - x_{j1}) + \dots + \beta(x_{ik} - x_{jk})}$$

It has a baseline $h_0(t)$ that is left unspecified however must be positive i.e the hazard when all the covariates are zero, a linear function of a set of k fixed covariates that is exponentiated and is equivalent to the relative risk. The $h(t)$ must be strictly parallel; this implies that the change in a prognostic factor/predictor leads to a proportional change of the hazard on a logarithmic scale.

This produces covariate-adjusted HRs independent of time. β is the logarithm of the HR between the two corresponding data subgroups for one binary predictor.

The Cox model is extendable to time-dependent covariates (Y. Xue & Schifano, 2017) such as adherence to PEP self-reported over time have a proportional effect on $h(t)$ over time. For this, the HR for two individuals with covariates $x_i(t)$ and $x_j(t)$ is:

$$(2.5) \quad HR_{i,j} = \frac{h_i(t)}{h_j(t)} = \frac{h_0(t)e^{\beta'x_i(t)}}{h_0(t)e^{\beta'x_j(t)}} = e^{\beta'(x_i(t)-x_j)}$$

2.3.4.2 Model Diagnostics for the Cox PH

The purpose of diagnostics is to ensure the PH assumption is met, checking for influential observations (outliers) and checking for suitability of the variables' functional forms (i.e., which variable to include in the model). Xue and Schifano (2017) discuss goodness-of-fit for the Cox model diagnostics largely based on residuals and earlier research by Hess (1995) on graphical techniques. Full details of these are found on Xue and Schifano (2017)'s article.

This study has categorical predictors and explores the utility of residual, deviance residuals for linearity testing and outliers, graphical methods to test PH assumption. PH assumption violation is solvable by stratification and adding time*covariate interactions (Borucka, 2014; Fox & Weisberg, 2002) as implemented by Tolosie and Sharma (2014).

2.3.4.3 Tests for Significance of Effect for the Cox Model and Interpretation

Often statistical task in the time-to-event analysis is modeling the covariate effect. The prognostic index is the key outcome from a Cox model (Royston & Altman, 2013). The significance of the effect of every covariate in the Cox PH model is typically checked by the Wald test, likelihood ratio test (LRT) and the score test (Belaskova & Fiserova, 2017; Tolosie & Sharma, 2014). The Wald statistic is frequently used in software packages, and the value (e.g., z in R software) from the Cox PH results corresponds to the ratio of each regression coefficient to its standard error. The Wald statistic evaluates whether the β coefficient of a given variable of an individual is statistically significantly different from a hypothetical individual having a prognostic index of 0.

In the model, the regression coefficients are the weights obtained from the linear predictor, where higher values (positive signs) show a higher hazard (i.e., the risk of failure) and worse

prognosis (Royston & Altman, 2013) for the individual in terms of the variable. The exponentiated coefficients are the HRs, which give the effect size of covariates. The overall statistical significance of the model is indicated by p-values from three asymptotically equivalent alternative tests (The Wald test, LRT and score log-rank statistics) which usually give the same results for large sample sizes. However, the LRT is preferable for its better behaviour for small sample sizes.

2.3.5 Modelling Repeated (Recurrent) Time-to-Event outcomes

Recurrent health problems are often encountered in medical and epidemiological studies, and maybe put into two categories: (a) continuous risk interval, which is suitable for discrete health problems where the first incidence doesn't rule out the likelihood of a second closely afterward (Guo, Gill, & Allore, 2008), and (b) discontinuous risk intervals such as for infections (e.g., Hughes et al., 2001) and hospital admissions. That is, when an individual has an STI s/he is not at risk of the second infection pending recovery from the initial infection, hence the period of infection needs to be removed from the risk set outcomes.

Due to the independence assumption of Cox PH, it can merely be applicable for time-to-event analysis of the first event only (Pandeya, Purdie, Green, & Williams, 2005) and this brings wastefulness in data use. Guo et al. (2008) discuss six models for analysis of such data based on Poisson regression, extended Cox and Frailty. An approach could be in modeling the number of events for each individual and fitting a negative binomial or Poisson models but Amorim and Cai (2015) contends that it's wasteful since information concerning the timing of events isn't utilized. A possibility could be in simple random coefficients model or simple frailty model (Ha, Jeong, & Lee, 2017).

For the recurrent STI diagnoses, it is possible to hypothesize that individuals who had repeated infections during the follow-up period share a common biological heterogeneity that can't be quantified (Wand & Ramjee, 2015). For instance, an "unobserved heterogeneity" can be incorporated in the analysis by jointly modelling HIV seroconversion with the recurrent STIs using random effects Cox regression similar to Wand and Ramjee approach.

2.4 Brief review of methods for analysis of drug effectiveness

As explained in their paper, Phadnis et al. (2014) on estimation of the medication effectiveness, the of assessment of medication effectiveness in literature is founded on calculation of a HR

comparing hazard of event for two groups, that is, those with or without medication/drug exposure. Cox proportional hazards model is useful in assessment of drug/treatment effect. Methods include simple group matching which includes a (single time point) fixed-in-time medication use (1 = users and 0 = nonusers) dummy variable (Zhou et al., 2005). The aforementioned two groups are then followed from the time of prescription (time for matching for nonusers) until the event occurs or to the end of study follow-up. Cox PH model can also be used through time-dependent exposure variable having 0 = for before use and 1 = for after medication use.

Medication effectiveness can also be modeled in a complete time-dependent Cox PH model approach by considering interactions between time-dependent covariates of medication status (current medication usage status – on versus off), the “proportion of cumulative exposure” to medication at a given point in time, and the “switching behaviour between taking and not taking” the medication by the patient as robustly described by Phadnis et al. (2014). Other methods, potentially for prophylaxes, include “the net effect of efficacy, adherence, and any change in sexual behavior” (e.g., McCormack et al., 2016). Often, measurement of event-free survival (EFS) in studies is a way of seeing how well a medication/treatment works.

CHAPTER THREE

3. METHODOLOGY

3.0 Introduction

This chapter presents the study context and setting, specifies the study design, the datasets motivating this thesis is presented and the sampling strategy described. The chapter also identifies the main study measures and variables and outlines analysis methodologies with a focus on the application of the Cox PH model to SWOP–City data. Due to statistical semantics arising from a lack of a unified approach in the statistical literature, analyses in this chapter were considered univariable in contrast to bivariate (e.g., Beymer et al., 2017) and multivariable (see Tsai, 2013, on achieving consensus on multivariable analyses).

3.1 Study Design and Data Source

This is a study from a well-established SWOP–City cohort using data collected retrospectively from sex workers’ clinical database for HIV prevention, Care and Treatment maintained by University of the Manitoba/University of Nairobi. SWOP–City has the strength of potentially being a standard longitudinal cohort design and observational design at the same time combined with population-based cohort facility-wise study of PEP/TasP and associated sexual risks and risk behaviours.

Inclusion criteria is data from HIV-negative sex workers/MARPs, aged ≥ 18 and having been prescribed PEP (≥ 1) from since roll up year to August 2018, active in sex work in the past 3 months, has at least one full sexual health screen (test for gonorrhoea, HIV, syphilis and chlamydia). For the comparative group, eligibility is HIV-negative sex workers/MARPs of no known history of PEP in the entire study period).

3.2 Sampling

There is an inter-relationship among sample size, effect size, significance level = $P(\text{Type I error})$ = the probability of detecting a significant effect when actually there is none, and Power = $1 - P(\text{Type II error})$ = probability of not observing a significant effect when truly there is an effect. The sample size was estimated for comparing HR using a formula from Shao, Chow, and Wang (2003) and Collett (2004):

(2.6)

$$n = \frac{(Z_{\alpha/2} + Z_{\beta/2})^2}{p_1 p_2 [\log(HR)]^2}$$

Where $Z_{\alpha/2}$ and $Z_{\beta/2}$ corresponds to the upper $\alpha/2$ and upper $\beta/2$ points of the standard normal (Z) distribution (or probit function). For a 2-sided type I error, α , β is the Type II error, and therefore $1 - \beta$ is the power, p is the event rate in the population, in which case $p_2 = 1 - p_1$, and hazard ratio, HR .

The current reported overall prevalence of HIV is 28% among cohort FSWs and at least 34% among the MSMW (UoM/UoN, 2018), giving a pooled prevalence of 31%. For the period under study, a 3.5% seroconversion rate was used and a 50% reduction in hazard of HIV for those taking PEP. The sample aim was to test covariates classifying half of the sex workers as low risk and the other half as high risk. The function was implemented in R, as in equation (2.6) to obtain the number of events for the whole sample:

```
hr=2.35 # Hazard ratio
hr0=1 # the assumed initial HR, HR before PEP intervention/Null hypothesis HR
pE=0.31 # the general probability of occurrence of the HIV
#event
pA=0.5 # the sample size proportions allocated to PEP group
alpha=0.05 # type I error
beta=0.20 # beta is 1-power
(n=((qnorm(1-alpha/2)+qnorm(1-beta))/(log(hr)-log(hr0)))^2/(pA*(1-pA)*pE))
ceiling(n) # number of events (nE)= 211, if all the cohort data in the period are used.
(Power=pnorm((log(hr)-log(hr0))*sqrt(n*pA*(1-pA)*pE)-qnorm(1-alpha/2)))
```

The total sample size, $N = \frac{n_E}{P_E} = \frac{139}{0.31} = 448$.

After adjusting for missing data resulting from data management, all the PEP data in the period was used ($N_1=503$), and this reduced to 470 after data management.

Simple Random Sampling (SRS) method was used to select 503 from comparison (non-PEP/PrEP) group:

```
# Simple random sampling the data
```



```
nonpep<- read.csv(file.choose())
sampled<-nonPEPpop[sample(nrow(nonPEPpop), 503), ]
write.csv(sampled, file = "sampleszed.csv")
```

This also reduced to 468 after data management. Since total number prescribed PrEP were few (397), it was cleaned and reduced to 314 and used for comparative analysis.

3.3 Variables and Measures

3.3.1 Sociodemographic and baseline covariates

Categorical age (18–25 years, 26–30 years, 31–35 years, 36–40, 41–45 and 45+ years). Marital status (single, married, divorced/separated/widowed), binary education (secondary or below, college or above). Binary key population type (FSW, MSMW).

Baseline covariates were: binary length of sex work (<mean, ≥mean), average casual clients (<mean, ≥mean), average regular clients (<mean, ≥mean). Sexual practices and risk behaviours: regular client vaginal sex (never, often, always), regular client oral sex (never, often, always), regular client anal sex (never, often, always), casual client vaginal sex (never, often, always), casual client oral sex (never, often, always), casual client anal sex (never, often, always), sex under alcohol influence (never, sometimes, mostly, always), use drugs (yes, no), condom (often use) frequency (always, sometimes, never), condom use consistency (yes, no).

3.3.2 Primary Outcome variable

The incident HIV ARV initiation of the sex workers was considered as the desired event. The event time was defined as the interval between first PEP prescription and an ARV initiation or censoring (time in months).

3.4 Ethical considerations and Data Management

3.4.1 Ethical considerations

Being a subset of a parent study within the UoM/UoN HIV prevention, care and treatment research programme, administrative permission to use the SWOP–City data was obtained from the PHDA. The study was presented for approval to the Ethical Review Committee of the Kenyatta National Hospital/UoN College of Health Sciences as part of UoM/UoN use of clinical database.

3.4.2 Data Management

As with programme data, multiple dataset files were encountered with varied subsets of observations. The files were appended, where applicable, using R `rbind()` or `append()` functions if they had similar variables and `merge()` and `dplyr` package `right`, `left`, `inner`, `outer`, `anti` and `semi` join functions used for inclusion of new variable to the rows using numeric unique identifiers.

The unique identifiers were of multiple alphanumeric types for the subsets of observations, where the numeric part was unique for all services, at enrollment, any type of clinic visit regardless of key population type. In order to facilitate efficient merge without loss of information, the alphanumeric was separated into characters and digits using `colsplit` function of the `reshape2` package: `colsplit(df$alphanumericcolumn, "(?<=\\p{L})(?=[\\d+])", c("char", "digit"))`. It's the numeric part was used for merging/joining the files.

File joins were done, initially, using all rows of a master file having types of service (ART, PrEP, PEP, OIs) and inconsistent observations—with clashing unique numeric identifiers—with the full register removed. To ensure that only data for sex workers prescribed PEP is included in the analysis, those prescribed PrEP or both prophylaxes courses at at least some point during the follow up were removed and carefully looking at the seroconversion in order not to exclude inappropriately.

For the comparison group, the data for non-PEP takers within the period were filtered out and corresponded to the period as from the year of the first PEP prescription in the PEP group (i.e, enrollment at the time of the first year of PEP among the PEP group). Rows (sex workers) with earlier than 2016 ARV initiation were excluded, the resulting data was cleaned and inconsistencies addressed by the PHDA team. A sample was drawn from this dataset as described in Section 3.2. Sex workers (rows of data) without HTC results but had enrollment earlier than June 2018 were removed due to the cohort recommended periodic three months HTC.

3.4 Data Analysis

R Core Team (2018) was used in the analysis of data. All predictors were assessed at baseline. Univariable Cox proportional hazards (Cox PH) models were used for predictor variables, as well as univariable Kaplan-Meier (KM) estimators with log-rank tests for predictor variables, were fitted baseline covariates.

The proportional hazards assumption was tested by comparing the KM plots with the predicted plots by time period (Therneau & Grambsch, 2000) and by deviance residuals. Multivariable Cox PH model was fitted for the predictor variables.

3.4.1 Exploratory Data Analysis

The number of PEP episodes in the SWOP–City, episodes by final HIV serostatus. Number of repeat PEP episodes broken into number with 2, 3, at least 4). The median PEP-to-PEP episode intervals among sex workers repeat episodes of PEPs from the time when roll up to August 2018 is provided in months, between 1st and 2nd PEP, and between subsequent episodes if available.

Proportions of sex workers given PEP by key population type, sex, stratified by age, key population type, those with at least 2 sexual health screens in the subsequent year and by sociodemographic data is provided.

Length of follow up is also be estimated using reverse KM (X. Xue et al., 2017) to describe the length of time SWOP–City observed the enrolled sex workers. The 95% confidence limits for median follow-up as well as interquartile range (IQR) was obtained (Appendix B.1 – R script). Reverse Kaplan-Meier is obtainable by reversing the indicator of the event (incident HIV) with the aim of the having primary outcome of interest beings censored instead.

3.4.2 Univariable Time-To-Event Analysis

3.4.2.1 Sociodemographic data at Baseline by Final HIV Serostatus

For sociodemographic differences and initial analyses, Pearson Chi-Square was used run to compare HIV/STIs frequencies by key population type this important is knowing whether to fit Cox PH stratified by sex or by key population type or general models. Initial trends analyses was done following French et al. (2012)’s pregnancy procedures and applied to PEP use since roll up to August 2018 (Appendix B.2 – R script).

3.4.3 Multivariable Time-To-Event Analysis

3.4.3.1 Incidence and trends (patterns) of repeat PEP

The frequency of repeat PEP was assessed per 100 person-years (FEM, 2018; Hilbe, 1993; Rothman, 2012). Similar to French et al. (2012)’s analyses, the numerator was the overall number of repeat PEP recorded covering second, third and successive PEPs while the

denominator was “time-at-risk of subsequent PEPs” determined as the sum of the time between the end date of each sex worker’s first PEP up to the end of the study period.

KM approach was used to find the probability of repeat PEP. Time-to-second PEP episode analyses were done while excluding subsequent episodes the since 2016 in the SWOP–City (Appendix B.7 – R script). Assessment of differences in time-between-event (PEP prescription periods) using the log-rank test.

Comparison of the characteristics of sex workers with one PEP episode with those having repeat episodes was done using Chi-Square test for trend (Koletsis & Pandis, 2016; The BMJ, 2017). Predictors associated with repeat episodes of PEP were subsequently be modelled using Cox PH.

3.4.4 Analysing the Effectiveness of PEP

Time-independent covariates such as sex, baseline age never change values over time while time-dependent can take different values over time.

As in equation (2.5), a Cox PH model for hazard comparisons related to getting treatment as opposed to not getting treatment can be specified by:

$$(2.7) \quad h(t|z) = h_0(t)e^{(\beta Z)}$$

where $Z = 1$ if the sex worker received PEP and 0 otherwise. Accordingly for sex workers who never received PEP, $h(t|z = 0) = h_0(t)$ and for sex workers who were prescribed PEP course $h(t|z = 1) = h_0(t)e^{(\beta Z)}$. All these enables computation of HR feasible for the incident HIV given by $HR = e^{(\beta)}$ understood as the hazard of incident HIV infection for sex workers on PEP becomes $e^{(\beta)}$ multiplied by the hazard of HIV-infection for those not on PEP.

Obviously, $\beta > 0$ indicates a harmful effect for the prophylaxis users and $\beta < 0$ denotes the treatment’s protective effect. Approximation of β is by maximization of the partial likelihood given by:

$$(2.8) \quad L_p(\beta) = \prod_{i=1}^m L_i = \prod_{i=1}^m \left(\frac{e^{\beta X_j}}{\sum_{j \in R(t_i)} e^{\beta X_j}} \right) \delta_j$$

Where, δ_j is the censoring variable (1=if event, 0 if censored) and $R(t_i)$ is the risk set at time t_i

In the time-independent Cox PH model in equation (2.9) where β_j is the j^{th} covariate's (X_j) parameter.

(2.9) $h(t, \mathbf{X}) = h_0(t) \exp(\sum_{j=1}^p \beta_j X_j)$; where covariates X_j are taken at baseline. The HR is dependent on covariates X_j, \dots, X_p but not on time. In the analysis of PEP effectiveness at baseline and assuming that the sex workers' sexual practices and risk behaviours would positively change along the follow-up time. A univariable Cox PH model of time-independent PEP status would be fit as:

(2.10) $h(t, \mathbf{X}) = h_0(t) \exp(\beta * MED)$; where MED – whether a sex worker had PEP or not (1 yes, 0 for no) at baseline. This cannot fit into the realities of the analysis of PEP effectiveness as the variable MED is time-varying and gets a value depending on the length of time the sex worker has been followed-up.

In the SWOP–City, for the period a sex worker was in the cohort, there were periods in which he/she was not on medication. Therefore, the medication status of ‘on PEP’ and ‘off PEP’ could be gathered during the follow up. The assumption of equation (2.9) can be relaxed to incorporate time-dependent covariates.

And given the use of Cox PH in this study, it can be taken that the effect of other demographic, sexual practices and risk behaviours has already been validly adjusted for, considering the assumptions of the model. A model with a time-dependent indicator of whether a sex worker was prescribed a PEP course at each point in time may be more suitable:

(3.1) $h(t, \mathbf{X}) = h_0(t) \exp(\beta * MED(t))$; where $MED(t) = 1$ Or 0

This study considered PEP users and non-PEP users in the analysis. Within the period under study, some sex workers requested PEP once while others repeatedly and others none at all. It is considered that the cohort of sex workers is at risk of HIV exposure. Given this, analysis of the effectiveness of PEP may possibly be centered on determining an HR comparing hazard of HIV infection for the two groups (i.e., with or without prophylaxis exposure) assessed at a single time-point in time.

It appears, however, that within this context of SWOP–City’s observational study of real-world PEP effectiveness, single time-dependent methods could unsuccessfully bring in subtle shades useful in the analysis of PEP effectiveness given the dynamics of PEP use, on-and-off use and non-use in the cohort and miss the real effect. It was therefore regarded in this thesis that PEP effectiveness is likely the effect of a time-dependent variable, that included present PEP status (“PEP on” in contrast to “PEP off”) which is a binary variable in the analysis coded as MED on = 1 or MED off = 0 for every time point the sex worker is on PEP or otherwise. This resulted into a single-time-dependent Cox model for beginning the time-to-event analysis. Covariates such as age group (AGE) and key population type (typePOP), that is, FSW and MSMW were added to have: MED, AGE, typePOP. The hazard was modeled as (3.2):

(3.2) $h(t) = h_0(t) \exp(\beta_1 * MED + \beta_2 * AGE + \beta_3 * typePOP)$. Where the variables’ descriptions are as already explained above.

In a framework, Phadnis et al. (2014) show that the Cox model of such a time-dependent covariate apparently demonstrates how changing patterns of medication exposure has an impact on its real-world effectiveness. Model (3.2) could be critical in understanding the HIV-preventive effectiveness of the PEP medication in a real-world setting. Ignoring time-varying inherent qualities of medication exposure or limiting the modeling to sub-components may omit the relations between outcome and exposure leading to aetiologically inappropriate inferences (Vacek, 1997) however in the SWOP–City the prophylaxis exposure is on and off – possibly on-demand PEP by the sex workers.

Vatcheva, Lee, McCormick, and Rahbar (2015) reaffirms Vacek (1997)’s views on effect modification that when there are synergistic effects, failing to factor in an interaction effect might lead to bias and results in misinterpretation, and in some cases to inappropriate policy or clinical decisions.

Model inference then is similarly done as in the Cox PH model with time-independent covariates shown in equation (2.8) and (2.9). The only distinction is that the $X'_{j,s}$ values changes at every risk set.

The aforementioned time-dependent covariate model could also be reached by use of transition models motivated by the real-world setting in the SWOP–City. The sex workers begin in a PEP-free state (1st state). The 2nd state is the only intermediate state where a sex worker begins taking

PEP and the 3rd is the incident HIV-infection state or censoring. For those not taking PEP, it is possible to move from 1st to 3rd state. This means that what transpires to a sex worker in a certain state is determined by only the fact that she/he is in that specific state and not on the history preceding it (Putter, Fiocco, & Geskus, 2007).

However, analyses of PEP effectiveness in this study were only based on equation (3.2) and significance testing done as reviewed in Chapter 2, Section 2.3.4.3..

The study used a single time-dependent analysis of effectiveness of medication status. A method of simple grouping from time zero for follow up being time after completion of PEP first course. The variable representing PEP exposure taken as dummy variable of (users=1 and nonusers=0) as described by (Zhou et al., 2005) and used to determine the PEP effectiveness from comparison groups. The event was time to ARV initiation.

```
##splitting time for long format to accommodate time-dependent covariate #library(survival)
idata1 <- read.csv(file.choose())
pepeff <- survSplit(data = idata1,
  cut = c(3, 6,9,12,15,18, 21,24,27,30,33,36), # vector of 3 months intervals of
timepoints to cut at
  end = "tstop", # character string with name of event time variable
  event = "event", # character string with name of censoring indicator
  start = "tstart",#character string with name of start time variable (created)
  id = "id", # character string with name of #new id variable to be created
  zero = 0, # used as start
  episode = "episode" # character string with name of new episode variable (optional)
)
write.csv(pepeff, file = "pepeff.csv")
```

CHAPTER FOUR

4. RESULTS

4.0 Introduction

In this Chapter, the results of all the analyses, longitudinal medication status are presented (Section 4.7). KM plots and Cox PH models are provided. Although medication status variable was later dropped due to infinite HR resulting from event-free survival. All analyses were done at 5% level of significance.

4.1 Descriptive Analyses

Given the change in documentation formats as from 2018, it was not possible to analyse the risk profiles due to lack of the “dates of exposures” for the preceding years. All the PEP were taken as stipulated (within 72 days).

4.2 Comparative analyses of sociodemographic, baseline sexual practices data and final HIV seroconversion status

The proportion of PEP users was 42.9 %. Chi-square test comparing sex workers prescribed PEP and a comparison group of non-treated sex workers (non-PEP/PrEP) showed that there was a statistically significant difference in proportions between FSW and MSMW $p < 0.001$ at 5% level of significance. Similarly, condom consistency, sex work duration in months and age were significant as shown in Table 1 below.

Table 1: Baseline demographic characteristics and Final HIV Serostatus

<i>N</i> = 196	PEP	Non-PEP/PrEP	<i>p</i> -value ¹
	42.9 %	57.1 %	
	Proportion [CI-95 %]		
Final HIV-serostatus	0 (0.0%)	3 (2.7%)	
Key population type			
FSW	71.8 [61.4, 80.2]	28.2 [19.8,38.6]	<0.001
MSMW	20.7 [14.2,29.2]	79.3 [70.8,85.8]	

¹ Tests for differences in proportions. Chi-square test for categorical variables to compare sex workers prescribed PEP and a comparison group of non-treated sex workers (non-PEP/PrEP).

<i>N</i> = 196	PEP	Non-PEP/PrEP	<i>p</i> -value ¹
	42.9 %	57.1 %	
	Proportion [CI-95 %]		
Age			
18–25	26.4 [17.6,37.6]	73.6 [62.4,82.4]	0.0027
26–30	56.0 [42.3,68.8]	44.0 [31.2,57.7]	
31–35	61.5 [45.9,75.1]	38.5 [24.9,54.1]	
36–40	31.8 [16.4,52.7]	68.2 [47.3,83.6]	
41–45	44.4 [18.9,73.3]	55.6 [26.7,81.1]	
45+	50.0 [15.0,85.0]	50.0 [15.0,85.0]	
Highest education level			
Secondary or below	48.2 [40.0,56.5]	51.8 [43.5,60.0]	0.06386
College or above	31.5 [20.7,44.7]	68.5 [55.3,79.3]	
Used condom last sex			
Yes	73.1 [62.3,81.7]	26.9 [18.3,37.7]	0.6942
No	1.0 [20.7,1.0]	0.0 [0.0,79.3]	
Condom frequency			
Always	77.1 [63.5,86.7]	22.9 [13.3,36.5]	0.6226
Sometimes	66.7 [48.8,80.8]	33.3 [19.2,51.2]	
Never	1.0 [20.7,1.0]	0.0 [0.0,79.3]	
Condom consistency			
Yes	48.5 [39.0,58.]	51.5 [41.9,61.0]	0.02259
No	32.5 [23.4,43.2]	67.5 [56.8,76.6]	
Sex work duration in months			
7 or below	61.4 [48.4,72.9]	38.6 [27.1,51.6]	<0.001

<i>N</i> = 196	PEP	Non-PEP/PrEP	<i>p</i> -value ¹
	42.9 %	57.1 %	
	Proportion [CI-95 %]		
7 or above	94.1 [73.0,99.0]	5.9 [1.0,27.0]	
Sex practices with casual clients			
Vaginal			
Always	72.4 [61.4,81.2]	27.6 [18.8,38.6]	0.4681
Never	1.0 [20.7,1.0]	0.0 [0.0,79.3]	
Sometimes	1.0 [43.9,1.0]	0.0 [0.0,56.1]	
Oral			
Always	1.0 [20.7,1.0]	0.0 [0.0,79.3]	0.6923
Never	73.0 [61.0,82.4]	27.0 [17.6,39.0]	
Sometimes	75.0 [50.5,89.8]	25.0 [10.2,49.5]	
Anal			
Always	74.0 [63.23,82.5]	26.0 [17.5,36.7]	0.5601
Sometimes	66.7 [20.8,94.0]	33.3 [6.1,79.2]	
Sex practices with regular clients			
Vaginal			
Always	73.0 [61.9,81.8]	27.0 [18.2,38.1]	0.2065
Never	1.0 [34.2,1.0]	0.0 [0.0,65.8]	
Sometimes	1.0 [43.9,1.0]	0.0 [0.0,56.1]	
Oral			
Always	1.0 [20.7,1.0]	0.0 [0.0,79.3]	0.1186
Never	73.3 [61.0,82.9]	26.7 [17.1,39.0]	
Sometimes	93.6 [82.8, 97.8]	6.4 [2.2,17.2]	

N = 196	PEP	Non-PEP/PrEP	p-value¹
	42.9 %	57.1 %	
	Proportion [CI-95 %]		
Anal	78.9 [70.5,85.5]	61.0 [57.9,64.0]	
Always	1.0 [20.7,1.0]	0.0 [0.0,79.3]	0.3199
Never	74.0 [63.3, 82.5]	26.0 [17.5,36.7]	
Sometimes	10.0 [20.7,1.0]	0.0 [0.0,79.3]	
Sex under alcohol influence			
Never	37.0 [26.8,48.5]	63.0 [51.5,73.2]	0.5098
Sometimes	47.3 [37.5,57.4]	52.7 [42.6,62.5]	
Most times	45.5 [21.3,72.0]	54.5 [28.0,78.7]	
Always	50.0 [23.7,76.3]	50.0 [23.7,76.3]	
Use drugs			
Yes	45.5 [33.0,58.5]	54.5 [41.5,67.0]	0.4552
No	41.5 [33.4,50.1]	58.5 [49.9,66.6]	

4.3 Comparing the survival of the FSW and MSMW key populations

4.3.1 Log rank test for difference in survival in FSW and MSMW

The log-rank test was used for comparing survival curves of FSW and MSMW. The null hypothesis in log-rank was that no difference exists in survival of FSW and MSMW key populations. Since the log-rank non-parametric test, survival distributional assumptions are not made. The test compares number of events observed in each key population to that which is expected if the survival curves of the two key populations were identical. The log rank statistic is approximately chi-square test statistic distributed.

Table 2: Log rank test for difference in survival

Strata	Number	Observed	Expected	$(O-E)^2/E$	$(O-E)^2/V$	p-value
FSW	1090	2	6.81	3.4	22.9	0.000002
MSMW	162	6	1.19	19.4	22.9	

The table above shows results from log-rank test for difference in survival. The given p-value of $p = 0.000002$ shows that the key populations differ significantly in terms of survival. FSW survive longer than the MSMW. Figure 1 in Section 4.3.2 below shows the overall cumulative event functions depicting the contribution of MSM on the survival distributions.

4.3.2 Graphical summaries of survival curves by key population type

Comparison by key population type – FSW and MSM. Given event-free survival in the PEP group, cumulative event and hazard functions were fitted as shown in Figures 1 and 2. The curves indicate that the MSMW were at a higher risk.

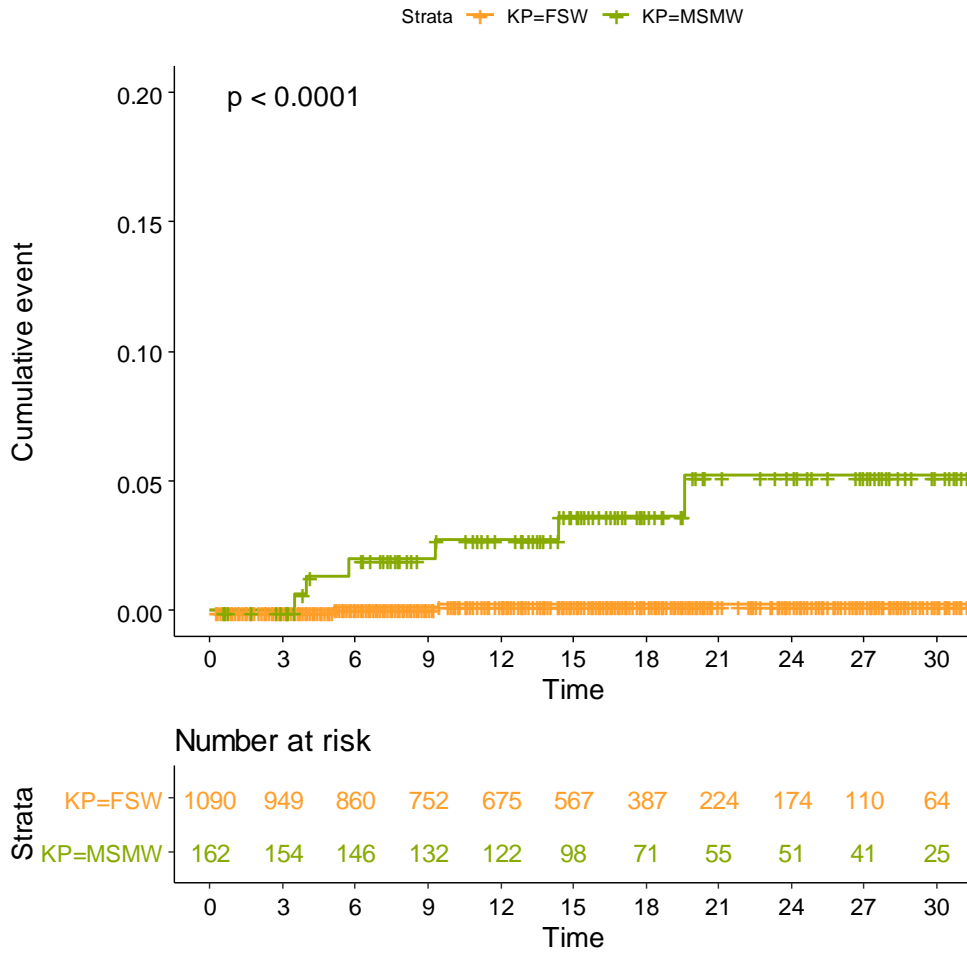


Figure 1: Kaplan Meier Curve for Cumulative Events by Key Population Type

The event for MSMW was higher compared with that of FSW.

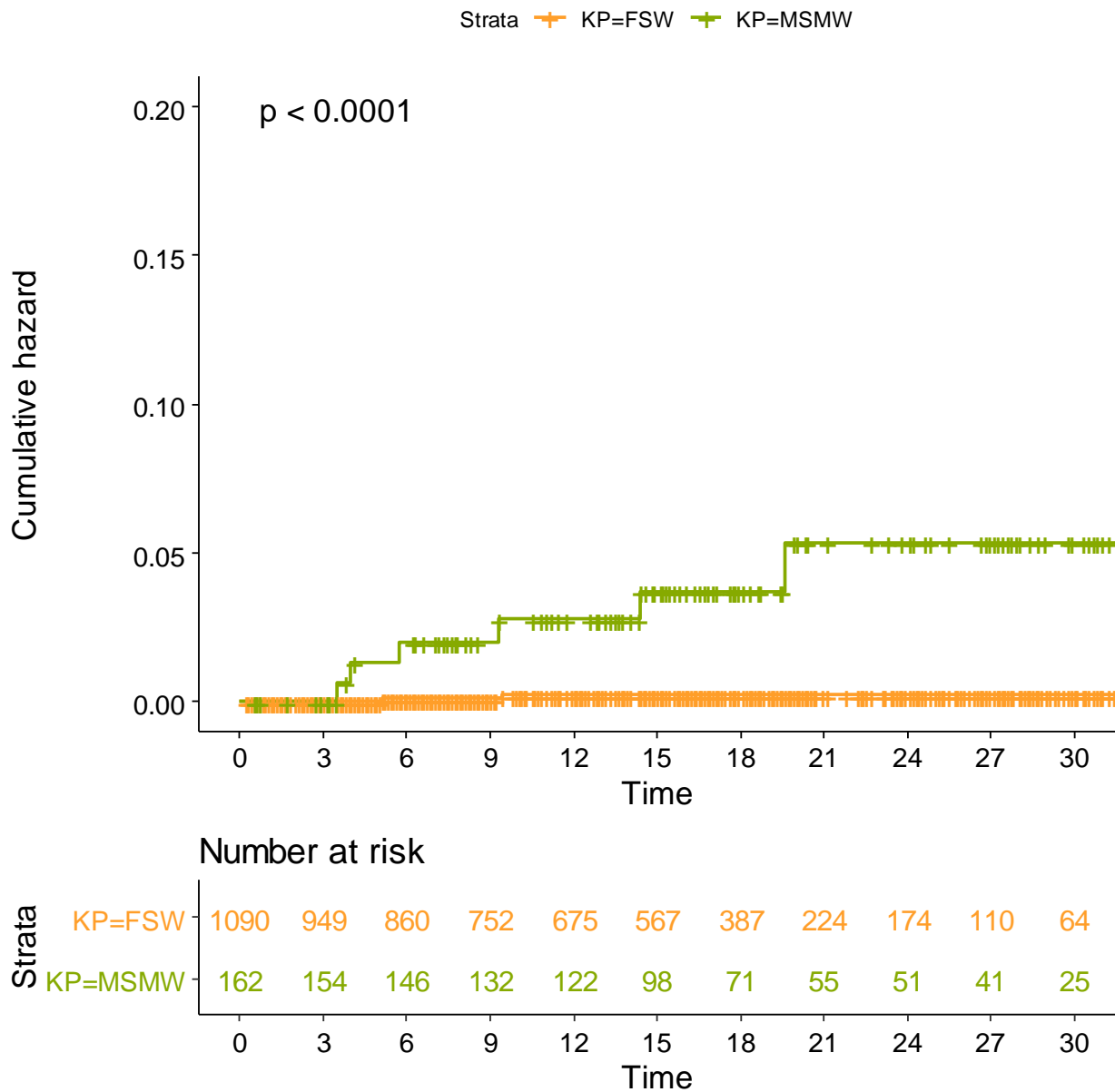


Figure 2: Cumulative Hazard by Key Population Type

4.4 The incidence of, and trends (patterns) for PEP episodes

In the period 2016 – 2018, 617 PEP prescriptions were made (records for follow up for 2016-2018 were looked at due to database challenges). Five hundred and thirty-four sex workers were at risk of a subsequent PEP at a total time at risk of subsequent PEP of 6188.3 months. There were 60 PEP repeats captured as of 15th October 2018 among sex workers who took a course in 2016, 2017 and 2018. However, the repeats were either for sex workers prescribed PEP in 2016

and 2017 or 2018 and with the repeats only made in 2018. In total 52 (9.35%) sex workers had repeat PEP prescriptions. The rate of repeat PEP was 8.6 per 100 person-months. The episodes are shown Figure 3 below.

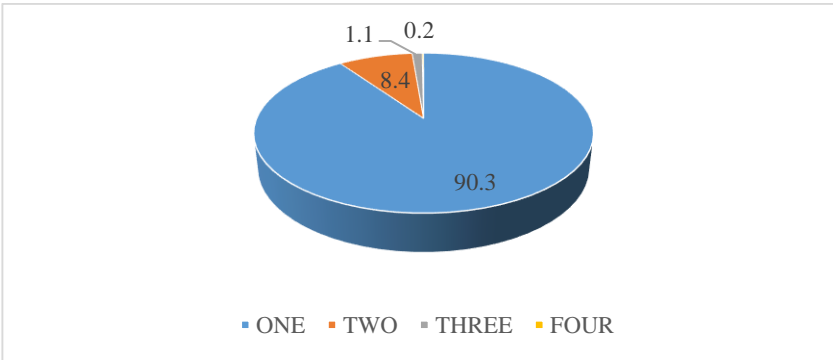


Figure 3: Pie chart for Proportion (%) of first and successive PEP courses from 2016-2018

Thirty-five MSMW and 581 FSW were prescribed PEP during the 2016 – 15th October 2018 according to the SKOP-City data. The month of July 2017 recorded the highest PEP prescriptions (54). Figure 4 below shows the monthly incidence from 2016 to mid-October 2018.

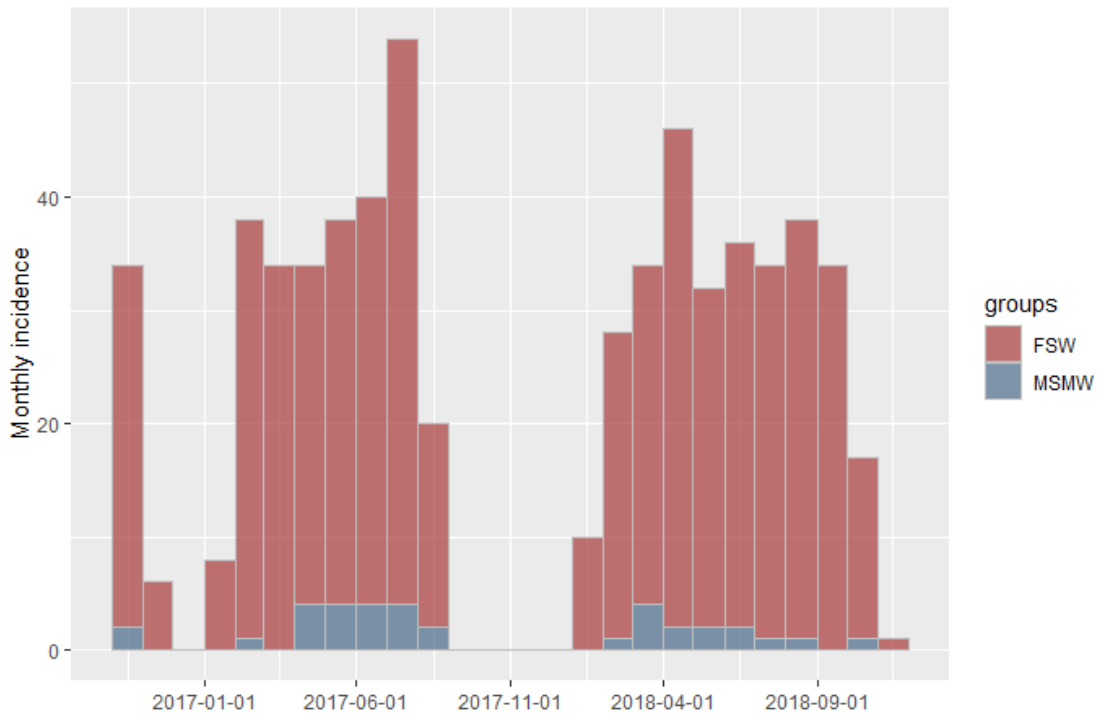


Figure 4: Monthly incidence of PEP by key population type

Due to their density, most of the PEP prescriptions were to the FSW. PEP users were relatively young and within the age category of 18-25 or 26-30 years as exemplified in Figure 5 below.

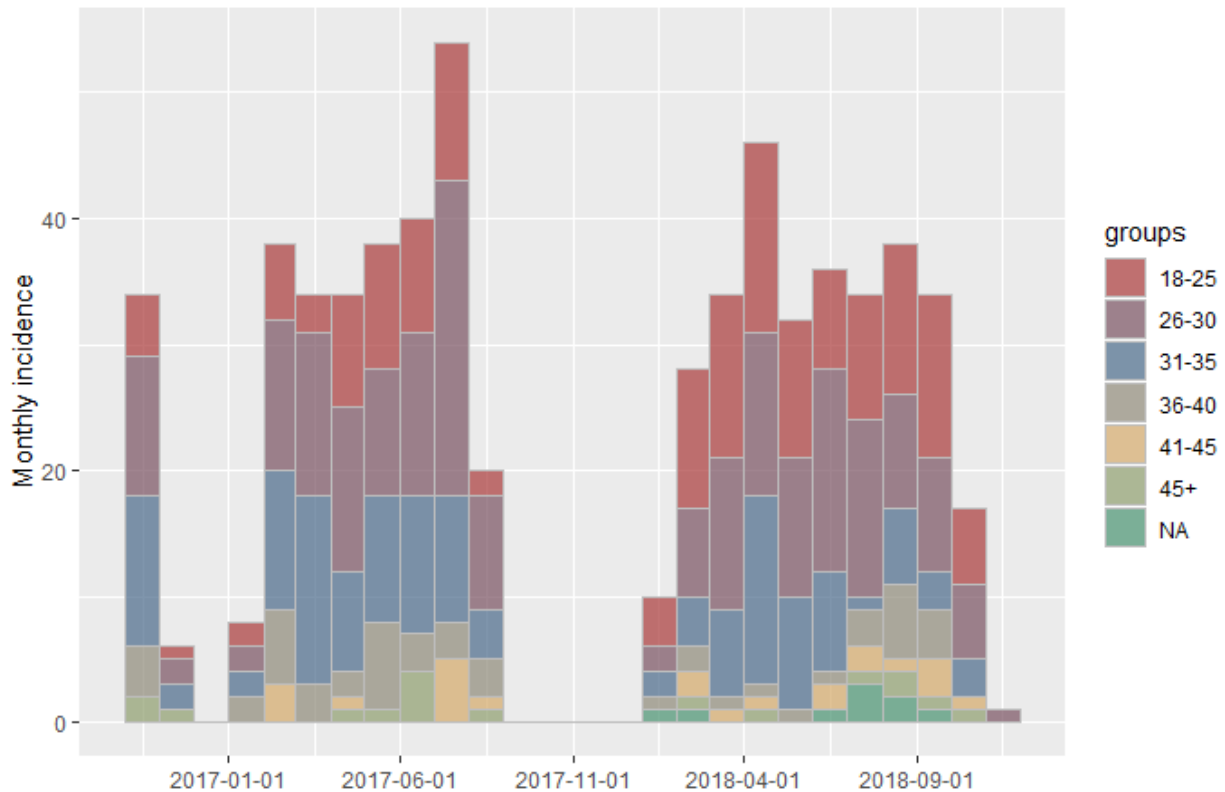


Figure 5: Monthly incidence of PEP by age groups

Figure 6 below shows the log-incidence over time for the year 2018. Using the 2018 PEP prescription data, the model reports a daily growth rate of 0.001016848. This means that the number of PEP prescriptions will increase steadily over time as shown by the line of best fit.

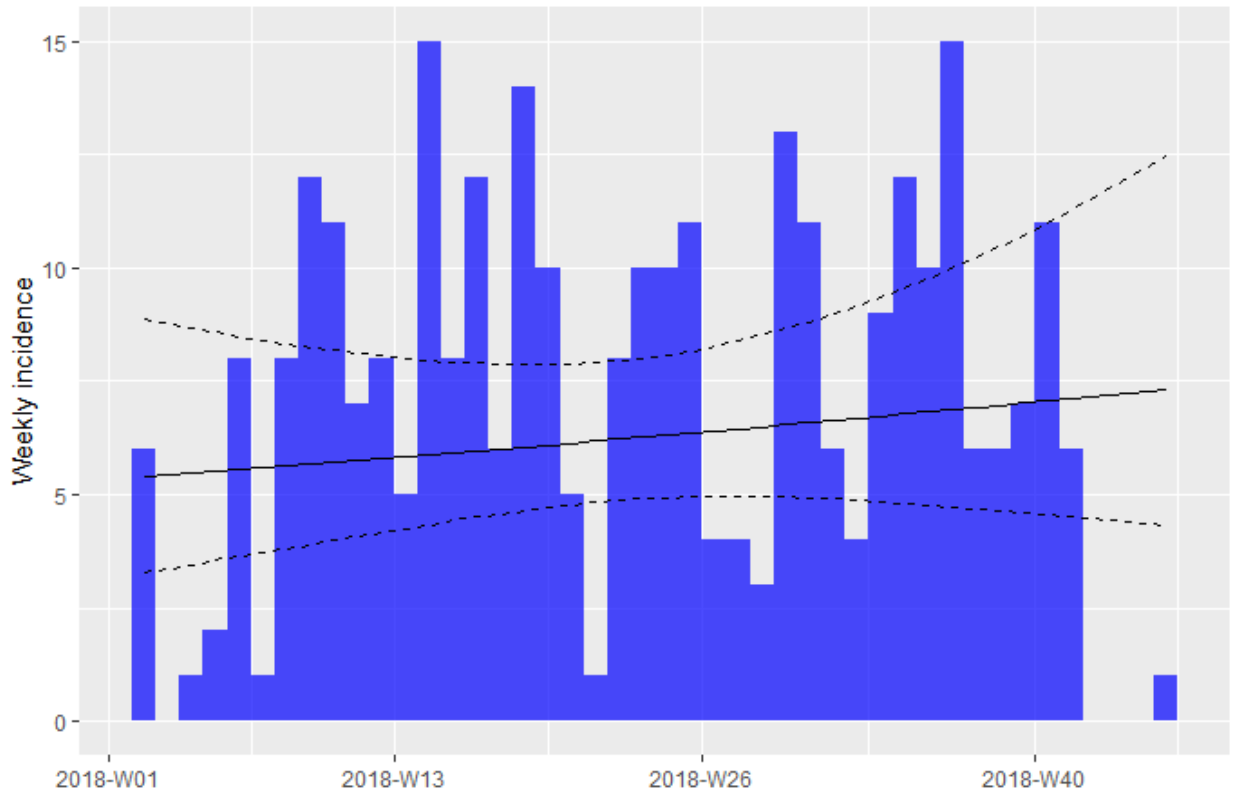


Figure 6: Weekly incidence of PEP, 3rd Jan 2018 - 15 Oct 2018 and regression of log-incidence of PEP over time

4.5 Results from Analyses of the effectiveness of PEP and comparison with PrEP

4.5.1 Results from testing for the proportional-hazards (PH) assumption

Table 3: Results from proportional hazard assumption test

	rho	chisq	p-value
MSMW	0.135	0.1710	0.67920
PEP	0.674	1.38×10^{-8}	0.99991
PrEP	0.765	7.77	0.00532
Global	NA	7.77	0.05101

The output Table 3 above, indicates that the test is not statistically significant every covariate.

The global significance test is not statistically significant too. Therefore, the proportional hazard

was assumed. (R scripts in the Appendix C). Figure 7 shows the graphs of scaled Schoenfeld residuals, for each covariate, plotted against the transformed time.

Global Schoenfeld Test p: 0.05101

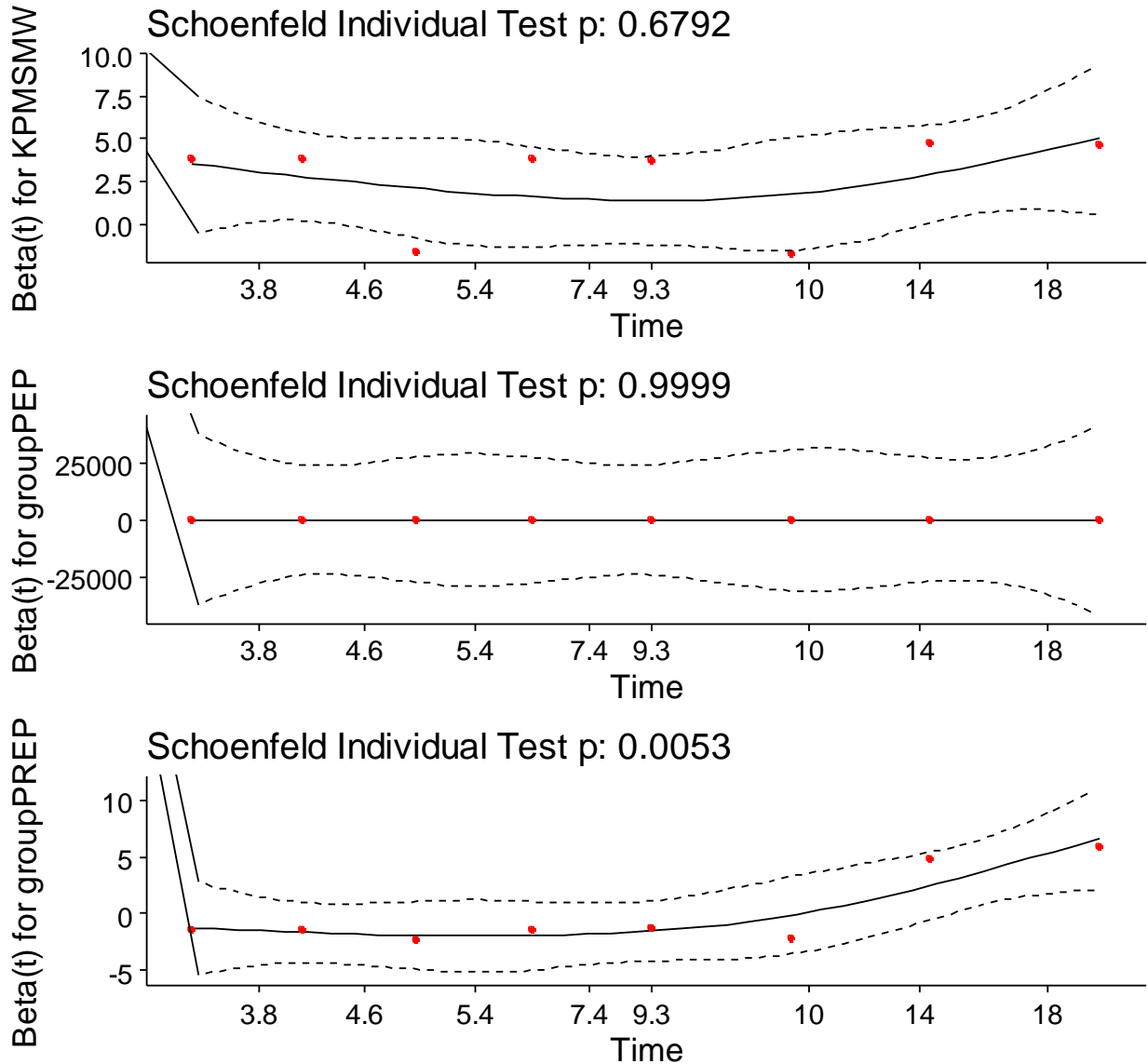


Figure 7: Graphical Model Diagnostics for the Cox PH

4.5.2 Univariable Analyses

MSMW were at a higher risk of HIV infection compared to FSW with HR of 17.2 shown in Table 4 below. Comparing PEP, PrEP and the controls as a reference, the HR for PrEP was 0.67 while that of PEP was very small. However, both were not statistically significant.

The results in Table 4 shows that HRs associated with the treatments compared with the control group. The exponentiated coefficients ($Exp(\beta_j)$) gives the covariate effect size. Being on PEP reduces the hazard by a factor of 0.000000007 and thus associated with good prognosis. Being on PEP is associated with good prognostic. Being on PrEP reduces the hazard by a factor of 0.672. However, Wald test was 0.23 on 2 degrees of freedom, $p=0.9$ suggesting highly insignificant results. The results were not statistically significant for PrEP too ($p=0.63$).

Table 4: Univariable Time-to-event Analyses of key population type

Covariate	β_j^2	$Exp(\beta_j)$	$SE^3(\beta_j)$	z	p-value
Treatment					
PEP	-18.8	0.000000007	5870	0.00	1.00
PrEP	-0.398	0.672	0.834	-0.48	0.63
Key population (FSW=reference)					
MSMW	2.848	17.248	0.817	3.49	0.00049

4.5.3 Multivariable Analyses

Subsequent multivariable analyses showed the same statistically not significant results as the univariable analyses as shown in Table 5. Age categories were not statistically significant.

Table 5: Multivariable Time-to-event Analyses

Covariate	β_j^4	$Exp(\beta_j)$	$SE^5(\beta_j)$	z	p-value
Age category					
18-25	3.22	24.9	521,000	0.00	1.00
26-30	-16.6	0.00000631	522,000	0.00	1.00

² β_j = the corresponding coefficients

³ SE = standard errors

⁴ β_j = the corresponding coefficients

⁵ SE = standard errors

Covariate	β_j^4	$Exp(\beta_j)$	$SE^5(\beta_j)$	z	p-value
31-35	2.31	10.1	521,000	0.00	1.00
36-40	2.47	11.8	521,000	0.00	1.00
41-45	-16.9	0.00000469	522,000	0.00	1.00
45+	-1.68	0.00000489	522,000	0.00	1.00
Key population (FSW=reference)					
MSMW	2.12	8.33	0.859	2.47	0.014
Treatment (Controls = reference)					
PEP	-1.86	0.000000819	8990	0.00	0.998
PrEP	3.22	1.38	0.852	0.38	0.706

4.5.4 Results from single factor time-dependent medication status of on and off

Along the follow up, there were sex workers who had recurrent PEP episodes. On fitting a single time-dependent covariate model of medication status along the follow up from the long format of data through survSplit function, there were similar results as of univariable model and multivariable model. Tests for global significance were all not statistically significant at alpha 0.05 as shown in the Table below. The logrank test (p=0.009) and likelihood ratio test (LRT) (p=0.03) were significant depicting global significance of the model fit. However, Wald test wasn't significant (p=0.9). These tests assess the null hypothesis that all of the β are 0. But looking at the standard error, it is so high because of there were no events in the PEP group.

Cox model regression coefficients are computed from events, based on the sex workers' values of the covariate of experiencing an event and the covariate values of all the sex workers still at risk at that a particular time. Without no events in the PEP group (the lowest-risk group of the 2 groups), there would no ability to compute the Cox model coefficient for the PEP group or its associated HR. Therefore, it appears that the LRT is still valid, but the interest is in calculation of

the HR from the model. Given this, HIV-event free survival curve was plotted to see the probabilities of survival of the groups.

Table 6: Solution to time-dependent analyses by follow up medication status

Covariate	β_j^6	$Exp(\beta_j)$	$SE^7(\beta_j)$	z	p-value
PEP	-10.12	4.03×10^{-5}	72.87	-0.139	0.89
MED	NA	NA	0.000	NA	NA
PEP:MED	NA	NA	0.000	NA	NA

The focus of event free survival (EFS) is on the event-free status (non-occurrence of events). In the Kaplan-Meier plot, the proportion estimates the proportion of sex workers who have not had the HIV endpoints and thus are not ARV initiated. In this scenario, the sex workers on PEP have a better survival chance without having had HIV and initiated on ARV. It was plotted inversely (1 - EFS Kaplan-Meier estimate), the survival curves can be interpreted as the estimated proportions of sex workers experiencing the event over time.

Figure 8⁸ shows the proportions of sex workers surviving. The median survival probability for sex workers within PEP is about 15 months while that within the comparison group is about 21 months.

⁶ β_j = the corresponding coefficients

⁷ SE = standard errors

⁸ Number for PEP = 470 and Comparison group = 468. They appear truncated at the beginning of the plotted graph

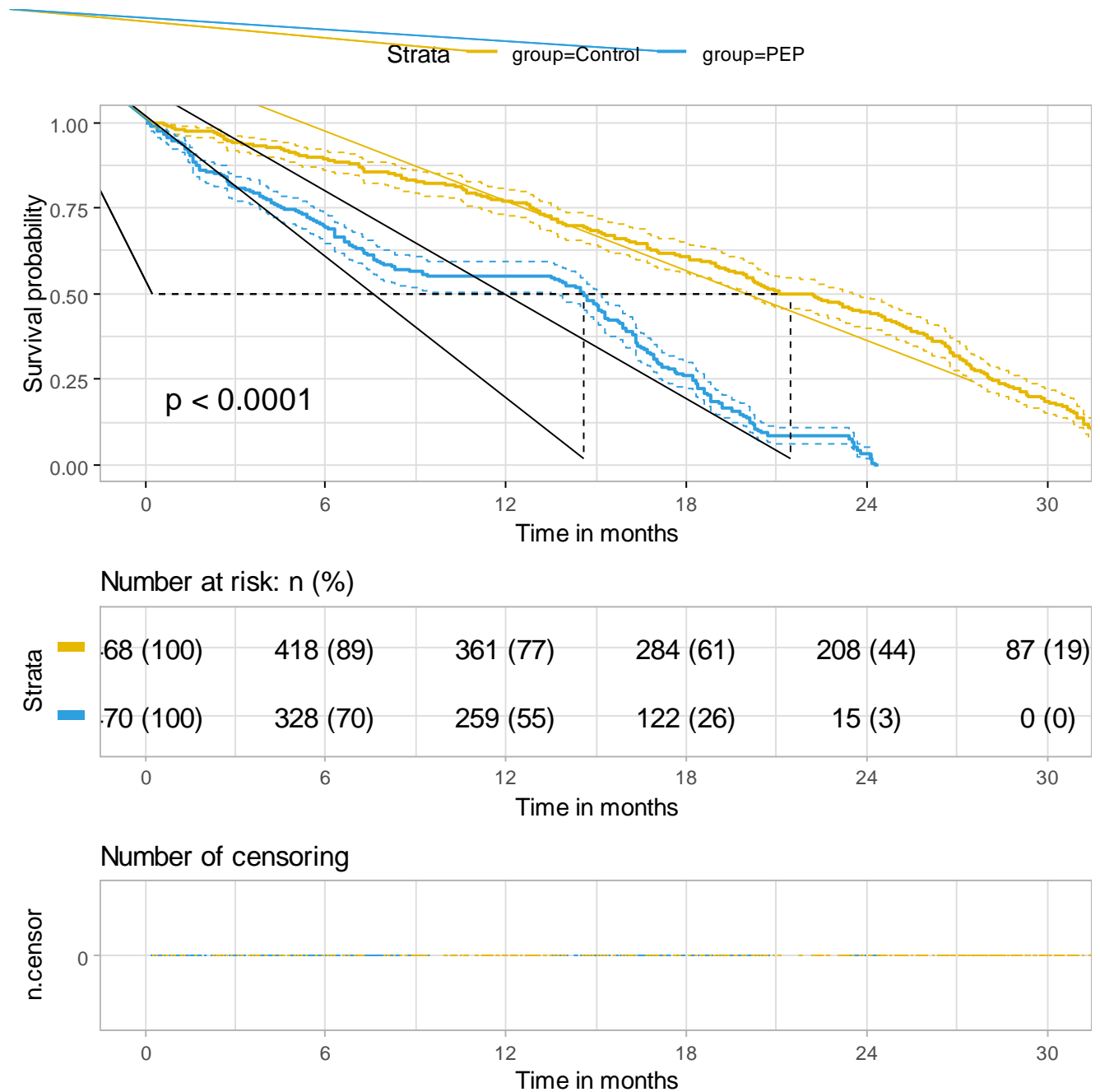


Figure 8: HIV event free survival

Table 7 shows the Cox model fit for HIV event free survival using the censored. Survival in PEP group is 2.106×10^{-9} better than the control group, however, this is not statistically significant at alpha 0.05.

Table 7: Cox Model for the censored

	β_j^9	$Exp(\beta_j)$	$SE^{10}(\beta_j)$	z	p-value
PEP	-19.98	2.106×10^{-9}	1.008×10^4	-0.002	0.998
Wald test					1
Log-rank					0.009
Likelihood ratio test					0.03

4.5.5 Pairwise comparisons of survival by treatment groups using Log-Rank test

Pairwise comparisons of treatments was performed using the log- rank test as executed by the *pairwise_survdiff* function in the R package *survminer* (Kassambara & Kosinski, 2018). The p-values were adjusted with the Hochberg (1995)'s method. The log-rank test was used for comparing multiple survival curves of PEP, PrEP and the control group (non-treatment). The null hypothesis was that there is no difference exists in survival for the sex workers who were prescribed PEP, PrEP and the those who never received any of the prophylaxis courses (control group). The log rank statistic is approximately chi-square test statistic distributed. The interest here was to conduct multiple comparison test comparing of every group with each other. *pairwise_survdiff* function returned a list the p values associated with the pairwise comparisons.

```
idata1<-read.csv(file.choose()) ##data on PEP, PrEP and Controls
# Pairwise survdiff
result <- pairwise_survdiff(Surv(tstop, event) ~ group,
  data = idata1)
result
```

Table 8: Pairwise comparisons of PEP, PrEP and Controls groups using Log-Rank test

	Control	PEP
PEP	0.046	–
PrEP	0.631	0.025

⁹ β_j = the corresponding coefficients

¹⁰ SE = standard errors

The pairwise log-rank test indicates that there is a significant difference between PEP and Controls with a p-value of 0.046 and between PEP and PrEP given the p-value of 0.025. The comparison test between PrEP and controls is not statistically significant as shown in table 8. The pairwise comparisons also give a Likelihood ratio test of 25.06 on 9 degrees of freedom, $p=0.003$. This suggests there exist a difference in survival among sex workers in PEP group but not in Controls. However, the log-rank doesn't show the direction of effect. Cumulative events (incidence) curves, as opposed to survival curves were plotted to show the cumulative probabilities of experiencing the event of interest.

4.5.6 Graphical summaries of survival curves by treatment groups

In terms of graphical comparison of treatment groups: PEP, PrEP and the comparison (the controls) and given event-free survival in the PEP group, cumulative event functions were fitted as shown in Figures 9 and 10.

At time 15 months, the cumulative survival probability was about 0.07 with 458 at risk. The plots were plotted as $1 - S(t)$. The plots show the proportion of the sex workers surviving past every subsequent interval.

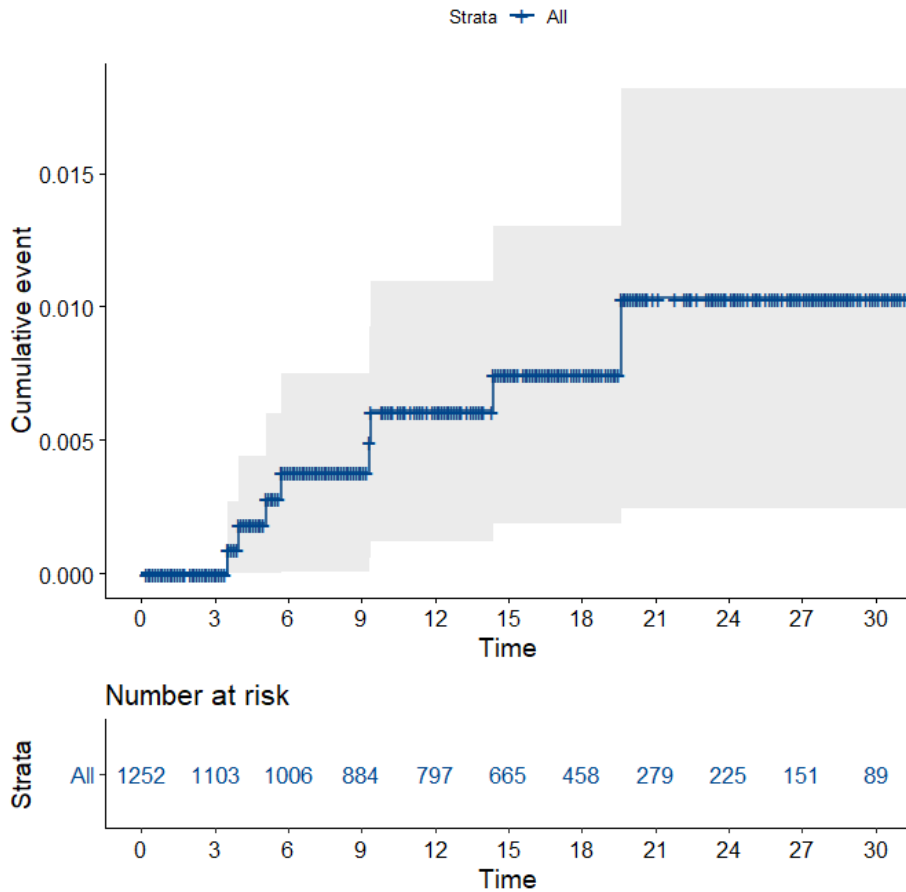
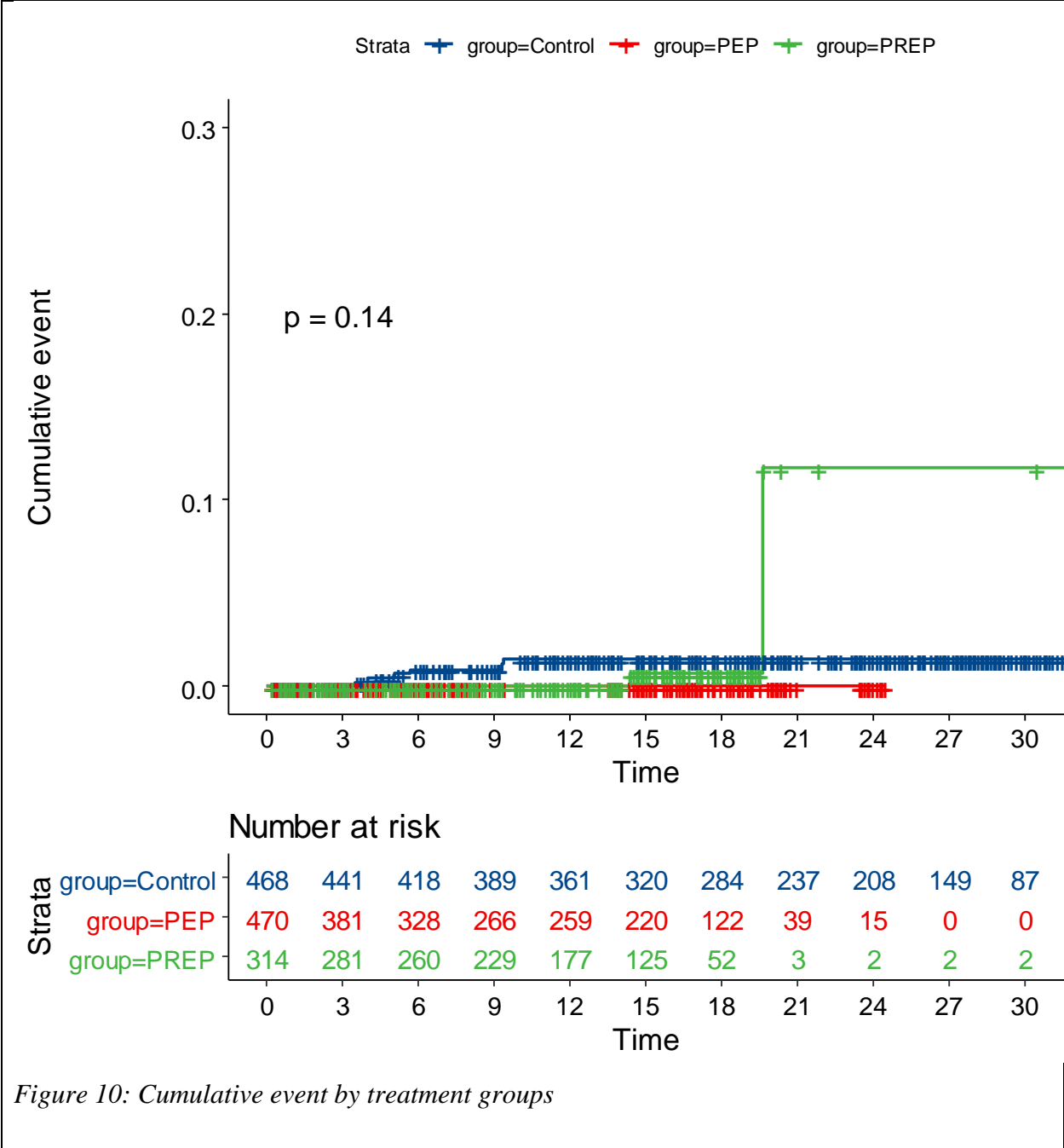


Figure 9: Cumulative event by all the treatment groups

Figure 10 below shows the cumulative events by treatment groups. The Cumulative events (incidence), or cumulative failure probability, was computed as $1-S_t$. The cumulative event probabilities for the PEP, PrEP and the comparison group are shown in the figure below. Although there is event free survival in the PEP group, survival in the comparison group is compares well with other treatment groups.



CHAPTER FIVE

5. DISCUSSION AND CONCLUSIONS

5.1 Discussions

This thesis determined the effectiveness of post-exposure prophylaxis after sexual exposure (PEP-SE) in SWOP–City cohort using time-to-event analysis. The results in Chapter 4 provide an evidence for the effectiveness of PEP but not statistically significant. This implies that there was generally a good PEP performance and no evidence of chemoprophylactic failure given completion of the PEP courses.

It is important to state that in this study MSMW had higher risks of HIV-exposure compared to FSWs. Test for differences using Chi-square in proportions by key population type among PEP and non-PEP showed a statistical difference in the proportions of FSW and MSMW. Equally, MSMWs were positively associated with HIV-infection accounting for up to 17 times that of FSWs. This outcome conforms with Bautista-arredondo, Servan-mori, Beynon, González, and Volkow (2015)'s study in which they found the existence of significant differences between women and men with reference to their sociodemographic and behavioural profiles.

Men are at higher risk of HIV infection due to their sexual behaviour. This study's results agree with that of Fletcher et al. (2013) that reported HIV high risk in MSM. This study also reports that PEP is effective in aborting HIV infection in the cohort. Among the PEP takers, there was no HIV-infection while two in PrEP and six non-prophylaxis group. PrEP had HR of 0.67 compared with the non-prophylaxis group. This study underscores the HIV-protective effect of PEP that has since been reported in Healthcare workers (Cardo et al., 1997; Connor et al., 1994; Guay et al., 1999; Lindegren et al., 1999; Mitchell et al., 2017; Shaffer et al., 1999; Wade et al., 1998; Wiktor et al., 1999).

It appears that PEP may well be associated with behaviour change in the cohort hence lack seroconversion. Such that those prescribed PEP have positive behaviour changes along the follow up hence prolonged survival periods. Comparatively, PrEP with the controls as a reference, the HR for PrEP was 0.67 while that of PEP to the non-prophylaxis was very small in statistical significant survival differences analysis by log-rank test. In essence log-rank test for difference in survival between PEP and non-prophylaxis overwhelmingly provided strong evidence (p-value of $p < 0.00001$) although the test doesn't give the direction of effect. However,

it could also be possible that the shorter period of follow up could have had an impact on the analyses presented here.

An overall survival differences analysis among the three groups of prophylaxis by pairwise log-rank test indicated that there is a significant difference between PEP and Controls with a p-value of 0.046 and between PEP and PrEP given the (p-value=0.025). The contrast test between PrEP and non-prophylaxis was not statistically significant (p=0.63). Lack of chemoprophylactic failure among those in PEP group is provides a clinically significant result for effectiveness, although statistical significance was not achieved.

5.2 Limitations

A with observational cohort studies, since the study used self-reported measures, recall, and social desirability biases could not be ruled out. It was also problematic since the sexual risk behaviours could have happened before or after the time of incident diagnosis of primary outcome or co-primary outcomes. Among the recent PEP users who had their first course, limited length of time 'at risk' was a problem. Individual regimens of PEP were not considered in the model. Nevertheless, the objective of the thesis was to empirically point out that, in real-world settings, PEP adherence and usage trends (on/off) are useful in the determination of PEP effectiveness.

5.3 Recommendations

The greatest recommendation from this study is the mobilization of uptake of PEP within the recommended 72 hours after exposure and adherence counselling. The sex-workers contribute largely to the spread of HIV within the country, and if this can be controlled at this level, then there will be a significant decline in the incidence of HIV in the country. This will, therefore, ease the burden on the country as a whole.

HIV is a global pandemic with Africa being the most affected region in the world and Kenya is one of the greatest hit regions in Africa as at the year 2016 (UNAIDS, 2018b). The prevalence of HIV in 2016 was 5.4% (UNAIDS, 2017). There is a need to reduce the spread of HIV, hence the incidence which will help ease the burden of the pandemic of the different sectors of the country, from health, to economic, social, psychological etc.

There should also be policies set-up to enable quick and easy access to PEP throughout the country especially for non-occupational exposures, the sexual contact is one of them. Additionally, given the HIV high-risk in MSM, more targeted sexual risk taking reductions is required in this key population.

5.4 Future research

Future studies would be needed to capture the real-world efficacy of individual classes of PEP regimens. Since this study used secondary data, the longitudinal or final sexual practices and risk behavior changes were not captured. Future studies may need to be designed with a view of collecting time-varying sexual risk behaviours in conjunction with adherence profiles. This would provide more understandings on risk compensatory behaviours and possibly factored in the determination of net efficacy that would be adjusted for sexual practices and risk behaviours.

Although poor recruitment and other factors may be an issue in randomized control trials (RCT), given no or few RCTs, future studies would also need to consider a pragmatic schedule, open-label RCTs among the Nairobi sex worker cohort to show in what way PEP would be utilized in standard medical practice to augment this study from an RCT focal point.

Transition Cox PH models may be considered in the analysis of PEP effectiveness in the future. It would be useful for future studies to incorporate time-dependent covariates such as cumulative proportion of months covered on medication, medication status together with the number of switches from medication status (on and off) given full data on recurrent PEP during the 3 month sequences of follow up. This would be important in isolating the treatment effects.

5.5 Conclusions

This study shows that PEP in HIV TasP following sexual exposures among the sex worker cohort, when taken as recommended within the 72 hours, is effective and may be associated with behavior change along the follow up. One characteristic of the sex workers who were on PEP is that they were all adherent to the treatment regimen and this could have contributed to the final outcomes. However, lack of adherence to PrEP as reported from the SWOP-City staff could have contributed to final results of 2 infections within the study but there could be competing risks (risky behaviours in the PrEP group), which could have contributed to the outcome. The 8 individuals who seroconverted provided a very small number which may not be adequate for modelling.

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APPENDICES

Appendix A: Ethical Approval Letter



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Ref. No.KNH/ERC/R/39

19th February 2018

Dr.Joshua Kimani
Co-Investigator
UNTID
College of Health Sciences
University of Nairobi

Dear Dr. Kimani

Re: Approval of Annual Renewal – Use of clinical care database by the University of Nairobi/University of Manitoba Research team to evaluate HIV prevention, care and treatment in Kenya (P258/09/2008)

Refer to your communication dated February 8, 2018.

This is to acknowledge receipt of the study progress report and hereby grant annual extension of approval for ethical research protocol P258/09/2008.

The approval dates are 18th February 2018 – 17th February 2019.

This approval is subject to compliance with the following requirements:

- a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
- b) All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH- UoN ERC before implementation.
- c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH- UoN ERC within 72 hours of notification.
- d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
- e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
- f) Clearance for export of biological specimens must be obtained from KNH- UoN-Ethics & Research Committee for each batch of shipment.

Protect to discover

- g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

Ensure that the ethical renewal is renewed timely as per KNH-UoN ERC requirements.

For more details consult the KNH- UoN ERC website <http://www.erc.uonbi.ac.ke>

Yours sincerely,



PROF. M.L. CHINDIA
SECRETARY, KNH-UON ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chairperson, KNH-UoN ERC

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Appendix B: R scripts for PEP incidence and trends

```
#####  
##### 4.4 The incidence of, and trends (patterns) for PEP episodes###  
#####  
  
library(ggplot2)  
  
library(incidence) install.packages("incidence")  
  
library(readxl) # install.packages("readxl")  
  
library(lubridate) #install.packages("tidyverse")  
  
library(lubridate) #or install.packages("lubridate")  
  
pep.i<-read_excel(file.choose())  
  
View(data$start_regimen_date)  
  
class(pep.i$start_regimen_date)  
  
head(pep.i$start_regimen_date)  
  
i <- incidence(pep.i$start_regimen_date)  
  
i  
  
plot(i)  
  
pep.i$start_regimen_date <- ymd(pep.i$start_regimen_date)  
  
i.7 <- incidence(pep.i$start_regimen_date, interval=7)  
  
plot(i.7)  
  
## bi-weekly  
  
i.14 <- incidence(pep.i$start_regimen_date, interval=14)  
  
plot(i.14, border = "white")  
  
## monthly
```

```

i.month <- incidence(pep.i$start_regimen_date, interval="month")

plot(i.month, border = "white")

i.month <- incidence(pep.i$start_regimen_date, interval="month", groups = pep.i$KP)

plot(i.month, stack = TRUE, border = "grey")

i.7.KP <- incidence(pep.i$start_regimen_date, interval = 7, groups = pep.i$KP)

i.7.KP

plot(i.7.KP, stack = TRUE, border = "grey")

i.month <- incidence(pep.i$start_regimen_date, interval="month", groups = pep.i$Ranks)

plot(i.month, stack = TRUE, border = "grey")

i.month.age <- incidence(pep.i$start_regimen_date, interval="month", groups = pep.i$AGE)

plot(i.month.age, stack = TRUE, border = "grey")

i.tail <- subset(i, from=as.Date("2018-01-03"))

i.tail

plot(i.tail)

plot(i.tail, border="white")

i.tail.7 <- subset(i.7, from=as.Date("2018-01-03"))

i.tail.7

plot(i.tail.7, border="white", groups = pep.i$AGE)

plot(i.tail.7, stack = TRUE, border = "grey",groups = pep.i$KP)

late.fit <- fit(i.tail.7)

late.fit

plot(late.fit)

plot(i.tail.7,fit=late.fit,color="blue")

```

```

best.fit <- fit_optim_split(i.tail.7)

best.fit

plot(i.tail.7, fit=best.fit$fit)

episodes<-read.csv(file.choose())

##PEP episodes

df <- data.frame(

  Episodes = c("One", "Two", "Three","Four"),

  Frequency = c(556, 52,7,1)

)

head(df)

bp<- ggplot(df, aes(x="", y=Frequency, fill=Episodes))+

  geom_bar(width = 1, stat = "identity")

bp

pie <- bp + coord_polar("y", start=0)

pie

```

Appendix C: Cox PH Model Diagnostics

```

library("survival")

library("survminer")

idata1<-read.csv(file.choose())

cox.res <- coxph(Surv(tstop, event) ~ KP + group, data = idata1)

cox.res

test.ph <- cox.zph(cox.res)

ggcoxzph(test.ph)

```

```
ggcoxdiagnostics(cox.res, type = "deviance",
                 linear.predictions = FALSE, ggtheme = theme_bw())
```

Appendix D: R Scripts for Effectiveness of PEP

```
#####  
#####Pairwise comparisons using Log-Rank test - PEP, PrEP and controls #####  
#####  
##  
library(survival)  
library(survminer)  
idata1<-read.csv(file.choose())  
Surv<-with(idata1, Surv(tstop, event))  
res1 <- pairwise_survdif(Surv(tstop, event) ~ group,  
                        data = idata1)  
res1  
#####Cox regression by group#####  
fit1<-coxph(formula = Surv(tstop, event) ~ group, data = idata1)  
summary(fit1)  
#####  
#  
###Fitting time dependent cox regression using on and off medication status####  
#####  
#  
##Some sex workers took PEP atleast once  
pepeff<-read.csv(file.choose()) ##data on PEP and Controls
```

```

attach(pepeff) ##or not

Surv<-with(pepeff, Surv(tstart,tstop,event))

fit1 <- coxph(Surv(tstart,tstop, event) ~ med, data = pepeff) ##Medication status alone

summary(fit1) ##infinite values

fit2 <- coxph(Surv(tstart, tstop, event) ~ group + med, data = pepeff)## run with treatment group

summary(fit2) ##std errors huge

fit3 <- coxph(Surv(tstart,tstop, event) ~ group*med, data = pepeff) ##interaction effect of
med*group

summary(fit3) ##effectiveness of PEP is based on fit3 ##NA for MED due to lack of events in
PEP group

#####

####HIV event free survival#####

#####

#####Calculating the EFS by disease

pepeff<-read.csv(file.choose()) ##data on PEP and Controls

attach(pepeff) ##or not

###

pepplusctrl$event <- factor(pepplusctrl$event, levels = c(0,1), labels = c("Censored","Event"))

summary(pepplusctrl$event)

###

pepplusctrl$event <- factor(pepplusctrl$event, levels = c(0,1), labels = c("Censored","Event"))

summary(pepplusctrl$event)

## Summary

```

```

summary(pepplusctrl)

##

## Cross table

addmargins(xtabs(data = pepplusctrl, ~ group + event))

pepplusctrl<-read.csv(file.choose())

Surv<-with(pepplusctrl, Surv(tstop, event))

## Calculate the EFS by disease

HEFS3x <- survfit(formula = Surv(tstop, event != "Censored") ~ group,
                 data = pepplusctrl,
                 type = "kaplan-meier",
                 error = "greenwood",
                 conf.type = "log-log")

## Numerical results

summary(HEFS3x, times = c(0,3,6,9,12,15,18,21,24,27,30,33,36))

## Plot Kaplan-Meier

plot(HEFS3)

library(survival)

library(survminer)

ggsurvplot(
  HEFS3,          # survfit object with calculated statistics.
  pval = TRUE,   # show p-value of log-rank test.
  conf.int = TRUE, # show confidence intervals for
  # point estimates of survival curves.

```

```

conf.int.style = "step", # customize style of confidence intervals

xlab = "Time in months", # customize X axis label.

break.time.by = 6, # break X axis in time intervals by 6 months.

ggtheme = theme_light(), # customize plot and risk table with a theme.

risk.table = "abs_pct", # absolute number and percentage at risk.

risk.table.y.text.col = T, # colour risk table text annotations.

risk.table.y.text = FALSE, # show bars instead of names in text annotations

# in legend of risk table.

surv.median.line = "hv", # add the median survival pointer.

palette =

  c("#E7B800", "#2E9FDF") # custom color palettes.

)

#####HIV Event-free survival (EFS)

###

pepplusctrl$event <- factor(pepplusctrl$event, levels = c(0,1), labels = c("Censored","Event"))

## Regression

model_cox <- coxph(formula = Surv(tstop, pepplusctrl$event != "Censored") ~ group,

  data = pepplusctrl,

  ties = c("efron","breslow","exact")[1])

summary(model_cox)

#####

```

Appendix E: R Scripts for survival probability – Graphical summaries

```
#####
```



```

# #computing survival probability by key population####
#####

library(prodlim) ##Install and load

library(survival) ##Install and load

library(Publish) ##Install and load

library(survminer)

i-data<-read.csv(file.choose())

Surv<-with(i-data, Surv(tstop,event))

idata<-read.csv(file.choose()) #Loading the data

fit_KP <- survfit(Surv(tstop, event) ~ KP, data = idata) #Compute survival curves

print(fit_KP)

summary(fit_KP) ##FSW/MSMW

# Plot cumulative events

ggsurvplot(fit_KP, conf.int = TRUE,

           palette = c("#FF9E29", "#86AA00"),

           risk.table = TRUE, risk.table.col = "strata",

           fun = "event")

# Plot the cumulative hazard function

ggsurvplot(fit_KP, conf.int = TRUE,

           palette = c("#FF9E29", "#86AA00"),

           risk.table = TRUE, risk.table.col = "strata",

           fun = "cumhaz")

##Survival curves with the treatment groups

```

```

require(survival)

fit2 <- survfit( Surv(tstop, event) ~ group,
  data = idata)

# Visualize: add p-value, changing y limits
# changing color using brewer palette

ggsurvplot(fit2, pval = TRUE,
  break.time.by = 3,
  risk.table = TRUE,
  risk.table.height = 0.5#Useful when you have multiple groups
)

##Survival curves for the PEP/PrEP and CTRLs
# Plotting cumulative events

ggsurvplot(fit2, conf.int = TRUE,
  palette = c("#FF9E29", "#86AA00"),
  risk.table = TRUE, risk.table.col = "strata",
  fun = "event")

# Plotting cumulative events

ggsurvplot(fit2, conf.int = TRUE,
  pval = TRUE,
  break.time.by = 3,
  palette = c("#FF9E29", "#2E9FDF", "#86AA00"),
  risk.table = TRUE, risk.table.col = "strata",
  fun = "event")

```

```
# Plotting cumulative events
```

```
ggsurvplot(fit2, conf.int = TRUE,  
           pval = TRUE,  
           break.time.by = 3,  
           palette = c("blue", "red", "green"),  
           risk.table = TRUE, risk.table.col = "strata",  
           fun = "event")
```

```
# Plotting the cumulative hazard function
```

```
ggsurvplot(fit2, conf.int = TRUE,  
           palette = c("#FF9E29", "#86AA00"),  
           risk.table = TRUE, risk.table.col = "strata",  
           fun = "cumhaz")
```