Assessing adherence to recommended HIV Post Exposure Prophylaxis regimens prescribed to doctors working at the Free State Academic Complex in Bloemfontein, South Africa.

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I, Taahir Asmal, declare that the coursework that I herewith submit in a publishable manuscript format in fulfilment of the Master of Medicine Degree qualification (MMed Internal Medicine) at the University of the Free State is my independent work. I have not previously submitted it for a qualification at another institution of higher education.

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Signed on 20/05/2021

Contents

Abstract

Background

The prevalence of HIV infection in South Africa is one of the highest in the world and healthcare workers in this setting are particularly at risk of being infected through occupational exposures. All high-risk exposures to infective bodily fluids are considered as important, warranting the use of post exposure prophylaxis (PEP). This study determined adherence to PEP in doctors, regardless of specialty and rank.

Methods

A cross sectional study was conducted by distributing a structured anonymous questionnaire to doctors working in 3 teaching hospitals in central South Africa.

Results

A total of 233 of 400 distributed questionnaires were completed (response rate 58,2%) from 543 employed doctors across 3 different hospitals and over 16 specialties (coverage 42.9%). Almost all the respondents (84,7%) had at least one high risk exposure, with an average of 2,3 exposures per respondent. Most (49%) of the respondents were exposed when performing venesection. Majority (58%) thought that the exposure could have been avoided. Of those exposed, 83% used PEP at least once. Of those who took PEP, 56% stopped prematurely with 71% of them citing adverse side effects as the main reason. Workload impacted adherence negatively in at least 50% of respondents.

Conclusion

Majority of doctors had more than two occupational exposures. Adherence to PEP is generally poor. This is mainly due to the side effect profile of PEP regimens used at the time of the study. The recent widespread availability of better tolerated ART drugs and more tolerable regimens for PEP, may improve adherence.

Keywords

HIV – Human Immunodeficiency Virus

PEP – Post Exposure Prophylaxis

AIDS – Acquired immunodeficiency Syndrome

ART – Anti Retro Viral therapy

PMTCT – Prevention of Mother to Child Transmission

NSI – Needle Stick Injury

FS – Free State

UFS – University of the Free State

DOH – Department of Health

HCW – Healthcare Workers

RCT – Randomised Control Trial

UKZN – University of Kwa Zulu Natal

UAH – Universitas Academic Hospital

PH – Pelonomi Hospital

NDH – National District Hospital

NHLS – National Health Laboratory Service

HPCSA – Health Professions Council of South Africa

Abbreviations

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HPCSA – Health Professions Council of South Africa

SA – South Africa

PLWH – Persons living with HIV

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Chapter 1

Introduction

Healthcare workers are exposed to human immunodeficiency virus (HIV) positive patients daily and, especially in South Africa (SA), are at risk of exposure to the virus while carrying out their daily routines. South Africa has one of the highest prevalence of HIV infection in the world according to the United Nations HIV registry[1]. In 2019, approximately 7 million people were infected with HIV, with this being an underestimate as most of the data on this was obtained from pregnant females presenting for antenatal care; and registered patients who were following up at primary care and HIV clinics. Despite this, data obtained from the World Health Organisation's (WHO) country profile in 2019 estimates that 90% of patients who are infected know their status. They also estimate that 62% of persons living with HIV (PLWH) are on antiretroviral therapy (ART)[2]. The WHO also estimates that there was an improvement in the rate of viral suppression from 2016 to 2019 with an estimated 54% of those on ART being suppressed (HIV viral load < 1000).

The incidence of new HIV infections has been declining since the SA governments' national HIV program from 400 000 new infections in 2010 to approximately 250 000 in 2018[2]. The incidence of HIV infection is the third highest in the world, after Swaziland and Lesotho. Not surprisingly SA has the largest HIV treatment program in the world. The above statistics plotted against the census data of the total population, places the data into context - that an estimated 20% of the general population were HIV positive and just under half of these patients were virally suppressed[1,2]. This means that there were many patients who were HIV positive and virally unsuppressed who presented to healthcare facilities for primary, secondary or tertiary level for care.

Globally there were about 5000 new HIV infections daily with 64% of these infections in Sub-Saharan Africa. UNAIDS data suggest that there was an increase in the prevalence of HIV infected individuals in SA from 2015 to 2017 but a higher percentage of those infected with HIV are on antiretroviral therapy (ART)[1].

The impact of HIV infection, and resultant acquired immunodeficiency syndrome (AIDS), on the economy of a country, such as SA, is large and often underestimated. The use economic models may determine the financial loss to the gross domestic product (GDP) in hours worked per year, to estimate the amount lost in productivity but that underestimates the actual burden of the disease – as it not only affects the productivity of one generation, but due to the incidence being highest in the childbearing age group, it also affects the generation following those who are infected, i.e. their children – thus increasing the burden of disease on the health system with more patients presenting for care[3].

The burden of the disease on the healthcare system

With a high incidence rate of HIV infection of 4 per 1000, an alarming number of patients present to healthcare facilities, being newly diagnosed. These patients present in varying stages of the disease and in various clinical conditions, from seroconverting flu-like symptoms to the gravely ill HIV stage 4 patients with AIDS-defining

opportunistic or other contagious infections. They require multiple levels of support and expertise regarding their treatment and care, and often more than one medical discipline is involved. These newly diagnosed patients, not yet started on suppressive ART, are assumed to have high HIV viral loads. The other subset of patients that pose a major risk to healthcare workers are those on ART with unsuppressed viral loads – these patients who have failed first line therapy present a risk to transmit a potentially drug resistant virus to healthcare workers[3,4,5].

HIV and AIDS has radically impacted the practice of medicine in South Africa on many levels. Firstly, it drains a large number of resources, not only in treating HIV itself, but also in treating associated opportunistic co-infections related to immune suppression. Secondly, taking into consideration that a lot of the diseases associated with a poor socioeconomic status are infectious in nature, healthcare workers who deal with patients afflicted with such illnesses are exposed to a higher risk of getting infected[4,5,6].

The burden of HIV related illness is considerable, with its effects spread over a variety of manifestations involving most, if not all the disciplines in medicine. It is the researcher's opinion that dealing with a large patient load of an already sick general population with a relative shortage of doctors provides the ingredients to an inevitably high probability of being exposed to HIV through accidental injuries on duty[6].

The burden of the disease on the healthcare worker

A prospective cohort study in 1990 (before the advent of ART) conducted by Henderson et al concluded that the risk of HIV transmission after percutaneous exposure was 0,3%, with 0,09% risk of transmission after mucocutaneous exposures. If the exposure occurred on intact skin the risk was 0% (i.e. no reported cases)[8].

In the post-ART era, studies to quantify the risk of HIV seroconversion after an occupational exposure to the virus are unethical to conduct, and most of our data are obtained from occupational health reports and animal studies. It is unlikely that a study can or will be conducted to quantify the risk of transmission, but with more data collected and more research into the topic of post exposure prophylaxis in non-occupational setting; i.e. PMTCT, injection drug users, sex workers and sero-discordant couples, we may extrapolate the data to infer assumptions of healthcare worker risk[9].

There are a multitude of factors that contribute to these injuries being common, such as patient workload, availability of protective equipment, notwithstanding its use thereof, and hours worked/overworked. The grading of exposure in a risk category (i.e., high, and low risk) is omitted as this may delay the rapid initiation of HIV post-exposure prophylaxis (PEP)[8,9].

Current Guidelines

At the time of the study the recommended protocols were devised from the WHO guideline and the South African HIV Clinicians Society. They regarded exposure to the following fluids as infectious:

- Blood (or any blood-stained fluids)
- Genital secretions (incl. vaginal/penile secretions and ejaculate)
- Tissue fluids
- Body cavity fluids (including ascites, CSF, pericardial fluids etc)
- Breast milk

whereas non-infectious fluids included:

- Sweat
- Tears
- Saliva and sputum
- Urine and stool

The guidelines regarded all exposures to infective bodily fluid as a risk, regardless of type – previous risk stratification guidelines have made distinction between penetrating wounds, the type of needle involved etc. The rationale of this thinking is that in the South African setting, and given the prevalence of untreated HIV, all exposures must be regarded as high risk and treated initially; and to seek expert opinion later from occupational health or infectious disease physicians. Other considerations are the availability of the medication after exposure; how soon should the PEP be taken; and what medications to use[9,10].

ART medications differ in their mechanisms of action and will briefly be reviewed considering their various side effects[12,13]:

- The nucleotide and nucleoside reverse transcriptase inhibitors (NRTI's) and the non-nucleoside reverse transcriptase inhibitors (NNRTI's) work by blocking the conversion of viral ribonucleic acid (RNA) to deoxyribonucleic acid (DNA). They do this by binding to HIV reverse transcriptase (an enzyme found within the viral capsid), but they also bid to cellular DNA polymerase and mitochondrial pol-γ. This affects the functioning of these enzymes and results in hyperlactataemia and steatohepatitis. Other adverse effects of these drugs include hypersensitivity reactions that can be severe and life threatening.
- The protease inhibitors interfere with the function of HIV protease, resulting in non-functional viral proteins being produced. They also are mechanistically proven to cause endoplasmic reticulum stress in the (gastrointestinal tract) GIT cells with resultant severe symptoms arising there.

- Integrase inhibitors work by inhibiting the HIV integrase enzyme which is responsible for incorporating viral DNA into the hosts DNA. The effectivity of this drug is mostly on viral integrase and not on human enzymes and therefore are more tolerable drug than the other classes.

Data suggest that the most effective time to initiate PEP would be within two hours of the incident. This is important as it ensures that adequate levels of circulating drug are present to prevent viral integration into host cells. Interestingly, integrase inhibitors are recommended in these setting, and new regimens include integrase inhibitors as first line medication, although traditional regimens have not been proven inferior[9,10,11].

The use of starter packs to initiate PEP and then the subsequent prescription of the full course is disregarded in current guidelines. Now provision of the full month of treatment as soon as possible, preferably within 2 hours of exposure and the use of drugs with the best side effect profile is advocated. This is to ensure that the medication is taken as soon as possible, with the least chance of breaks in treatment availability - to boost compliance to the regimen, and to improve adherence to the full 28-day course. Animal studies have shown that taking PEP for 28 days consecutively confers maximum benefit and prevents HIV seroconversion[9,10,11].

The Southern African HIV Clinicians Society recommended using Tenofovir with the addition of Emtracitabine or Lamivudine (TDF+ETC/3TC) as a backbone, and the addition of the integrase inhibitor (I-Inh) Dolutegravir (DTG) as the preferred agent or a boosted protease inhibitor like Atazanavir/Ritonavir (ATZ/r) or the I-Inh Raltegravir (RAL) or if the person taking the PEP is pregnant. Alternatively, boosted Lopinavir/Ritonavir (LPV/r) or Efavirenz (EFV) may be used. They also recommended that starter packs should not be used and that a full month of medication should be provided at the first point of presentation. Follow up should done at 2 weeks, 6 weeks, and 3 months after exposure. The Occupational Health department at Universitas and Pelonomi hospitals' use a backbone of TDF+3TC with the addition of LPV/r[8].

A very interesting study by described adherence to a regimen of 3TC/Zidovudine(AZT) for 3 days, 3TC/AZT for 28 days and 3TC/AZT/LPV/r for 28 days. They found that all of the participants who took the 3 day course were adherent, and this was associated with a 70% reduction in the report of side effects. Adherence to 28 days of regimens containing 3TC/AZT and 3TC/AZT/LPV/r was 56% and 62% respectively. The frequency of adverse events in participants who completed the 3 days course was 28% vs 91 and 96% for the 28 day cohorts. Non-completion of the PEP regimen was higher in the groups who took the PEP for 28 days. The main reasons cited for the defaulting was intolerance to side effects (SE's).

Doctors in the public sector are also under enormous strain from the burden of patient numbers[7]. Due to these enormous stressors placed on them, adherence to a PEP regimen with many side effects may influence their adherence

and their productivity at work. For this reason, and others, the side effect profile of PEP should be as low as possible and support in terms of adherence must be readily available[11].

Literature Review

Research conducted in Southern Africa.

In a study conducted at the University of Kwa-Zulu Natal Gounden and Moodley (2000) reported that approximately 13% of participants had occupational exposures to HIV. 82% of those exposed took HIV PEP whilst 17% did not, citing the injury as trivial and not requiring PEP. They also found that 48% of participants discontinued PEP due to side effects[14].

Another study conducted by Karstaedt and Pantanowitz (2001) in Baragwanath Hospital in Gauteng (2001) reported that 69% of junior doctors in their internship had an exposure in the preceding year with 33% having an exposure to HIV infected blood. Only 64% of high-risk exposures were reported[15].

Kassa et al. (2016) conducted a similar study in three public hospitals in Botswana which described the occupational exposure and adherence to PEP in HCW's. A cross sectional survey was undertaken and found that 26% of respondents had significant exposures to potentially infective sources. Of them, only 37% reported the exposures and of those who reported an exposure, 69% received PEP with a 71% completion rate. Less than half of respondents were satisfied with their existing reporting systems[16].

A retrospective study conducted in Cape town by Papavarnavas et al (2017), reviewed all occupational health folders of healthcare workers after occupational HIV exposure, they found that many of the healthcare workers were lost to follow up. After analysing the data, they associated this loss to follow up with increasing age, and later initial presentation (i.e. those who presented to the occupational health department more than 24 hours after the incident)[17].

Aigbodion et al. (2019) studied a group of interns and found that 77% of respondents were exposed during their time as interns. The exposures occurred mostly during their internal medicine, surgical and obstetrics and gynaecology rotations[18].

Research in other African countries

Among lab workers in Nigeria, a study by Fadeyi et al (2011), described awareness and practice of safety precautions in HCW's when handling potential sources of infective fluids. The authors found that 41% of participants were unaware of the existence of basic safety precautions, and upon further review, 25% did not observe any safety precautions. Up to 50% of participants recapped needles and after exposure to potentially infected material, only 1,5% of participants would present to occupational health for PEP (even though 83% were willing to take PEP)[20].

International Studies

Research in developing countries

Internationally, studies in other high prevalence developing countries like India and Argentina, also reported similar rates of occupational exposures, with poor compliance to PEP[21,22].

A study by Halwani et al (2015), in Saudi Arabia described needle stick injuries in a 1000 bed tertiary hospital that serves 3 major cities. They found that most of exposures were caused by needles and that 64% of injuries occurred in the morning hours of duty. The presence of blood borne infections were known in only 51% of source patients[23].

A study in India by Swetharani KV (2016), et al described that 79% of participants recapped needles after use, almost 50% of participants reported exposures in the preceding year, and 70% of exposed participants did not report them. Almost 50% of participants did not use appropriate safety precautions before the exposure[24].

Aggarwal et al (2012), conducted a retrospective review of data of ongoing surveillance in a tertiary hospital. They described that most of the injuries on duty occurred in doctors (79%) and just over half of them were in their first year of practice. Over three quarters of the injuries were due to noncompliance with universal precautions and were possibly preventable. PEP was indicated in almost 100% of cases, with only 25% of the HCW's taking PEP within 2 hours of injury. Complete follow up was dismal and so was adherence to the full 28-day course[25].

Studies in developed countries

A study by Valin N et al (2016), described adherence rates to a new PEP regimen consisting of FTC/TDF/elvitegravir to be 92%. The adverse effects rates were 60% but were graded as mild-moderate and only 3 patients were switched to another regimen due to severe side effects. This shows that the medications used as part of the PEP regimen greatly influence adherence to a full course of therapy. Another conclusion can be made from this study from looking at their methodology – reminders were sent via text message to the participants and there was active case follow-up in terms of calling the participants regularly. This also contributed greatly to the adherence to PEP in these participants[26].

Critical appraisal of the research

Most studies done in South Africa focused on a specific group of doctors –

- Gounden et al focused-on obstetricians and gynaecologists
- Karstaedt et al focused-on interns only
- Aigbodion focused on interns only

- Papavarnavas focused on interns only

This may have influenced the data by inferring that the risk to all doctors are the same, regardless of the stage in their careers. This also may infer that doctors across specialties are exposed equally. This may introduce bias into the data presented, as Aigbodion et al demonstrated that interns had more exposures while rotating at specific specialties.

Fadeyi et al described the exposures and awareness of **laboratory** workers – people who work mostly with infective material – bodily fluids and blood. Their risk is assumed to be the highest amongst all healthcare workers. Rajkumari et al described exposures in **trauma** workers in a developing country. This also may skew the data obtained when relating this to all doctor exposures.

Our study intends to compare the exposures in all doctors, and if the data allows, to contrast the exposures in junior doctors as opposed to in senior doctors.

Valin et al described the tolerability of elvitegravir based regimens in their study group. They also had a novel way of reminding doctors of their appointments with occupational health. This study proved that an "active surveillance" approach to monitoring of drug tolerability and follow up in the study population influenced the adherence positively. Participants were given an appointment card when issued with the study drug which contained the details and telephone number of a healthcare staff member who would assist them should they develop side effects. Furthermore, when missing an appointment for follow up, they were called and rescheduled for the appointment. The method that they used to follow up the HCW's is relatively inexpensive considering the popularity of smart phones and the possibilities that lay ahead with this technology[27].

Although current data does not prove superiority of 2 versus 3 drug regimens, 3 drug regimens were shown to be superior in various settings, and this may be inferred in the occupational exposure setting. The factors that need to be considered are:

- Completion of the full 28-day course
- Side effect profile
- Ease of use
- Support system in place

With the ongoing changes to the ARV guidelines in South Africa, ART with better side effect profiles is becoming increasingly available and given the research data, it is the view of the author(s) that the results of this study will aid in strengthening guideline recommendations in motivating for better tolerated drugs for PEP.

Considering the above, guidelines need to keep the profile of the person being prescribed the PEP and should favour adherence to 28 days completion over superiority of regimen[11,26,27].

Hypothesis, Aims and Objectives

This research aimed to prove the hypothesis that doctors working in the Free State Academic Complex (FSAC) do not adhere to HIV PEP regimens prescribed to them, and this is in line with local and international studies done in this regard. The FSAC consists of 3 teaching hospitals within the district of Mangaung, a primary healthcare hospital, a secondary district hospital and a tertiary university complex hospital.

This study attempts to:

- Firstly, establish whether doctors adhere to current PEP prophylaxis guidelines, as set out by the Department of Health or local occupational health department of each hospital.
- Secondly, as the data allows, to ascertain why adherence may be poor to PEP as well as to describe the adherence in the study group.

This research with provide insight into the development of local guidelines with specific regard to PEP regimens and also assist in the targeting of vulnerable populations of healthcare workers for education.

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Chapter 2: Publishable Manuscript

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Adherence to HIV PEP Regimens Prescribed to Doctors working in the Free State Academic Complex

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Introduction

Healthcare workers (HCW's) are exposed to patients with human immunodeficiency virus (HIV) daily and are thus at risk of being infected while carrying out their daily routines. Patients who present to healthcare facilities in South Africa include those who have undiagnosed HIV infection while others who are known to be infected present for follow up care. Just over half (54%) of HIV infected patients who are known to be positive are virally suppressed (blood viral load less than 1000 copies per millilitre)[1,2]. These patients present in varying stages of the disease and in varying clinical conditions, from the flu-like illness of HIV seroconversion to patients with acquired immunodeficiency syndrome (AIDS) who are often co-infected with opportunistic infections (hepatitis B, tuberculosis, etc.). These patients require multiple levels of care from different disciplines, ranging from the clinical settings to the laboratory services[1,2].

Studies conducted in South Africa by Papavarnavas et al[3] (2001) and Aigbodion et al[4] (2019) have shown that the prevalence of occupational exposures to potentially infective material in junior doctors are high. A large proportion of healthcare workers will have one or more exposures in the course of their careers[3,4]. The risk of seroconversion after an occupational exposure to HIV is low – from 0,3% after a percutaneous exposure and 0,09% after a mucocutaneous exposure – but the data that supports these figures are scanty and prospective studies in this regard are not done for ethical reasons[5,6]. Available data regarding seroconversion after exposure, is extrapolated from the setting of non-occupational exposure (Prevention of mother to child transmission programs, pre-exposure prophylaxis programs and studies (PrEP), injection drug users, sex workers and sero-discordant couples)[5,6,7].

Adherence to post exposure prophylaxis (PEP) regimens prescribed to doctors have historically been low, as demonstrated in studies conducted locally and internationally[3,4,8,9,10,11,12]. Among the reasons for poor adherence in these studies included the poor tolerability of the PEP regimen used, increased workload of doctors and failure to follow up after being exposed. To prove that regimens with better drug tolerability have better adherence rates, studies by Valin et al[13] (2016) in the occupational setting and McAllister et al[14] (2017) in the non-occupational setting have shown good adherence with better tolerable drugs.

South Africa has a high prevalence of virally unsuppressed HIV positive patients, and thus the risk of being infected is substantial after *any* exposure. According to UNAIDS and WHO data of 2019, just over 50% of HIV infected patients in South Africa are virally suppressed[1,2].

The list of infective bodily fluids and general principles after exposure are found below[7,15].

- Fluids that are regarded as infective include – blood, genital secretions (including vaginal/penile secretions and ejaculate), tissue fluids, body cavity fluids (including ascites, cerebrospinal fluid, pericardial fluids, amniotic fluid) and breast milk. Non-infective material includes sweat, tears, saliva, urine, and stools.

- Risk profiling the exposure into high or low risk is discouraged as this may delay the initiation of PEP and given the possibility of the patient or the HCW unknowingly being in the window period, a consultation at the local occupational health department and full course of PEP is recommended to all regardless of the type of exposure.
- The most effective time to initiate PEP would be within the first two hours of being exposed. This ensures that there are adequate levels of circulating drug to prevent viral integration and replication in the host cell. Initial doses can be effective up to 72 hours after the exposure.
- The recommended Antiretroviral (ARV) combination is described by the WHO and the HIV clinician's society in their guidelines. Both guidelines are largely similar in their recommendations – suggesting a backbone of 2 nucleoside reverse transcriptase inhibitors (NRTI) combined with either an integrase inhibitor (II) or protease inhibitor (PI) as a third drug. This can be adjusted according to the tolerability of the regimen after considering contraindications to the prescription of any drug in the proposed regime.
- The HIV clinician's society also recommends that a full 28-day course be provided at the first point of contact and follow up should be 2, 6 and 12 weeks after exposure.

Studies have shown good tolerability to shorter courses with 2 active drugs, but these are scant and historically a 3 drug regimen is considered superior to a 2 drug regimen, provided that the full 28 day course is adhered to[16].

Previous studies conducted in South Africa focused on occupational exposures and adherence *in specific specialties* but did not describe adherence in doctors across all specialties and experience. Gounden et al[9] (2000) focused on the department of obstetrics and gynaecology, Kaerstad et al[10] (2001) and Aigbodion et al[4] (2019) focused primarily on medical interns at various healthcare facilities. These studies considered together, have shown that adherence is poor across all specialties and especially in junior doctors.

Similar research was conducted by Kassa et al[8] (2016) in Botswana, which included 3 state hospitals whose study population included all healthcare workers who were exposed to patients and their potentially infective biomedical waste. This included (among others), doctors, nurses, phlebotomists, counsellors, janitors, and waste handlers. Medical doctors constituted only a small subpopulation (6%) in this study.

The above studies found that the risk of exposure to potentially infected material in HCW's is high, but there is poor adherence to post-exposure PEP after an exposure occurred. The poor adherence included delays with initiation of PEP to defaulting the medications before 28 completed days, and loss to follow up.

The aim of this study was to determine whether doctors working in three teaching hospitals in central South Africa adhered to PEP regimens prescribed to them after exposure to infected and potentially infected sources. Furthermore, the authors intended to elucidate the main reasons for poor adherence. We identified the total exposures doctors had throughout their careers and the circumstances around the exposure(s).

Research methods and design

A cross-sectional study was performed by means of an anonymous structured questionnaire that was administered by the first author. The population of this study included all doctors working at a medical school with its teaching hospital complex consisting of three state-run hospitals namely Hospital A (tertiary care level), Hospital B (secondary care level) and Hospital C (primary care level). This study included all qualified medical doctors employed in the service of the three hospitals namely, interns, community service medical officers, medical officers, specialists in training (registrars) and specialists.

Data was collected between 1 October 2018 to 31 March 2019. Participants were recruited at their various departments during scheduled meetings and at their sites of work. After reading through the information document, completed questionnaires were placed in a box or envelope that was provided. The completed questionnaires were collected by the principal investigator. The aim was to recruit all doctors who worked in the 3-hospital complex, which at the time of data collection was reported to be 542 by the human resources (HR) department.

The questionnaire was in English. It consisted of 26 questions which focused on three areas: Demographic data, exposure data and information regarding PEP adherence. High risk exposures (percutaneous and mucocutaneous exposures) to infective bodily fluids were clearly described before enquiring about exposure to HIV infected material as only these exposures were considered as significant in the responses. For purpose of this study, adherence was considered as from the initial stat dose of ART to completion of the full course of 28 days.

We focused on the total number of exposures respondents had in their careers and the events following exposure. The questionnaire did not include circumstances around *each* exposure as it was evident after the pilot study that most respondents had more than 2 exposures.

Upon completion, all questionnaires were numbered, and the data was captured on Microsoft Excel which was then submitted to biostatistics and results were summarised by frequencies and percentages (categorical variables). The statistical program used was SAS version 9.4.

Ethical approval was obtained from the Health Sciences Research Ethics Committee (HSREC Protocol approval number **UFS-HSD2018/0018/2509**) of a higher education university in Central South Africa. The local Department of Health also approved the study (approval number **FS_201804_004**).

Results

There were 233 completed questionnaires of which 229 were processed fully with 4 questionnaires partially excluded from the results due to the responses in certain sections being inconsistent (e.g., respondents who indicated that they had an exposure initially but later indicated that they had no exposure in subsequent questions). The response rate was 58,2% since 400 questionnaires were distributed and 233 were returned by collecting the questionnaires from the departments 1 or 2 weeks after distribution. Initially 400 questionnaires were distributed and targeted as the authors were unaware of the total amount of doctors employed at each facility. This was due to late feedback from the HR departments of each hospital. The Free State Academic Complex (FSAC) had a total of 542 doctors across 3 different hospitals at the time of the study with 43% of all doctors completing the questionnaire.

Demographics

The majority (67,8%) of respondents were below 35 years of age and there was an equal distribution between males and females (49,8% and 50,2% respectively). The respondents varied in the stages of their careers ranging from interns to sub-specialists. Over half n=153 (65,6%) of respondents were practicing medicine for 6 years and longer (post qualification) of whom just under half n=70 (45,7%) were practicing for more than 11 years *(see table 1).*

Respondents varied in their respective specialities with interns and medical officers accounting for 32,2% of the population. These respondents were considered as general practitioners. Laboratory specialities made up 11,6% of the specialist population and included registrars and qualified consultants in laboratory haematology, chemical pathology, medical microbiology, virology and anatomical pathology. The clinical specialities accounted for the largest percentage of respondents which ranged across 15 specialities (see figure 1).

Table 1: Demographic data of participating doctors

Age	**n=233**
<35	158(67,8%)
>36	75(32,2%)
Gender	**n=233**
Males	116(49,8%)
Females	117(50,2%)
Professional registration	**n=233(%)**
Intern	46(19,7%)
Medical officer	29(12,5%)
Registrar	106(45,5%)
Specialist	52(22,3%)
Years in practice	**n=233**
<1	17(7,3%)
1-2	29(12,5%)
3-5	34(14,6%)
6-10	83(35,6%)
>11	70(30%)
Specialty	**n=233**
Laboratory	18(11,6%)
Clinical	137(56,2%)
General Practitioners	78(32,2%)

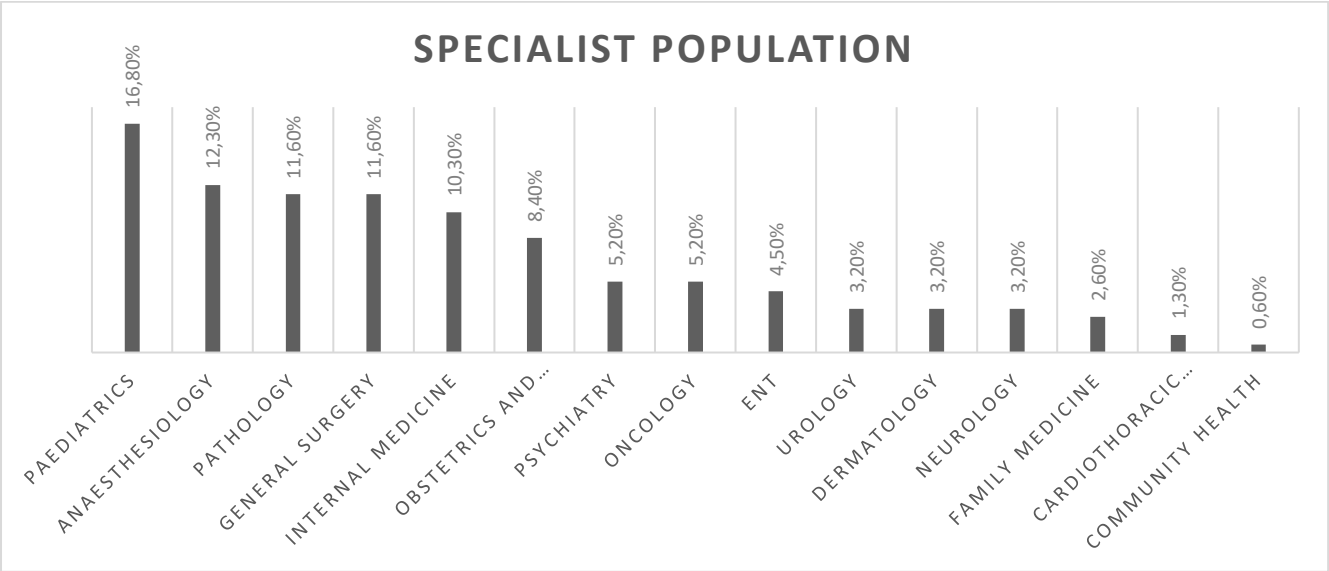

Figure 1: Distribution of specialty in terms of percentage

Exposure to HIV

Of the 229 respondents, 194 (84,7%) reported one or more exposures with a total of at least 453 exposures (more than 5 exposures were considered as 5). This translated to 2,3 exposures (with a range of 1-5) per respondent. Twenty-four (12,3%) respondents had more than 5 exposures and of these, only half had taken HIV PEP more than 5 times. Only 35 (15,3%) of respondents never had an exposure.

Ninety-five (49,0%) exposures occurred when performing venesection, 77 (40,0%) whilst performing a major operation and 48 (25,0%) while inserting an invasive line (e.g., central venous catheter insertion). Of those exposed, 110 (57,9%) respondents thought that the exposures could have been avoided on at least one occasion.

HIV PEP Prophylaxis

Of the respondents who had one or more exposure, 174 (90,7%) used PEP at least once. With regards to those who had 2 or more exposures, only 57 (45,6%) used PEP after *each* exposure. On occasion where respondents were exposed to infective fluids of patients *known* to be HIV positive, 33 (18,9%) elected not to take PEP. When respondents were exposed to patients with *unknown* HIV status, one in five (20,0%) elected not to take PEP. This contrasts with the 215 (93,0%) respondents who believe that HIV PEP is important after *every* exposure.

PEP was started within 2 hours in 66 (37,7%) of respondents after having an exposure; within 6 hours in 71 (40,6%) and after 6 hours in 38 (21,0%). The main reasons for delaying the initiation of PEP beyond 2 hours was a prohibitive

workload in 65 (59,6%), involvement in emergency procedure in 31 (28,4%) and unavailability of the protocol in 25 (23,0%).

In those who took PEP, 78 (45,0%) respondents took a regimen consisting of 3 or more tablets, 52 (30,1%) 2 tablets and 27 (15,6%) 1 tablet. The remaining 16 (9,2%) were unsure of how many tablets the regimen consisted of. A third, 56 (31,8%) could not recall what ART they used as PEP (the names of the medications). Of those who could recall, the most used NRTI's were Lamivudine 47 (26,7%), Tenofovir 44 (25,0%), Zidovudine 31 (17,6%) and Emtracitabine in 14 (8,0%) respondents. Of the NNRTI's the most used drug was Efavirenz in 10 (5,7%) participants, and 27 (15,3%) used Lopinavir boosted Ritonavir.

Fourteen (10%) respondents with multiple exposures never completed the full 28-day course after initiation after all exposures, 122 (87,1%) completed it after some but not all exposures and only 4 (2,9%) completed the course after *every* exposure.

Of the 176 (90,1%) respondents who took PEP, 153 (86,9%) experienced side effects. Ninety-eight (56%) respondents stopped PEP prematurely of which 70 (71,4%) cited severe side effects as the main reason. Other reasons for non-completion were the source patient tested negative 35 (35,7%), and 3 (3,1%) were influenced by a colleague to stop prematurely.

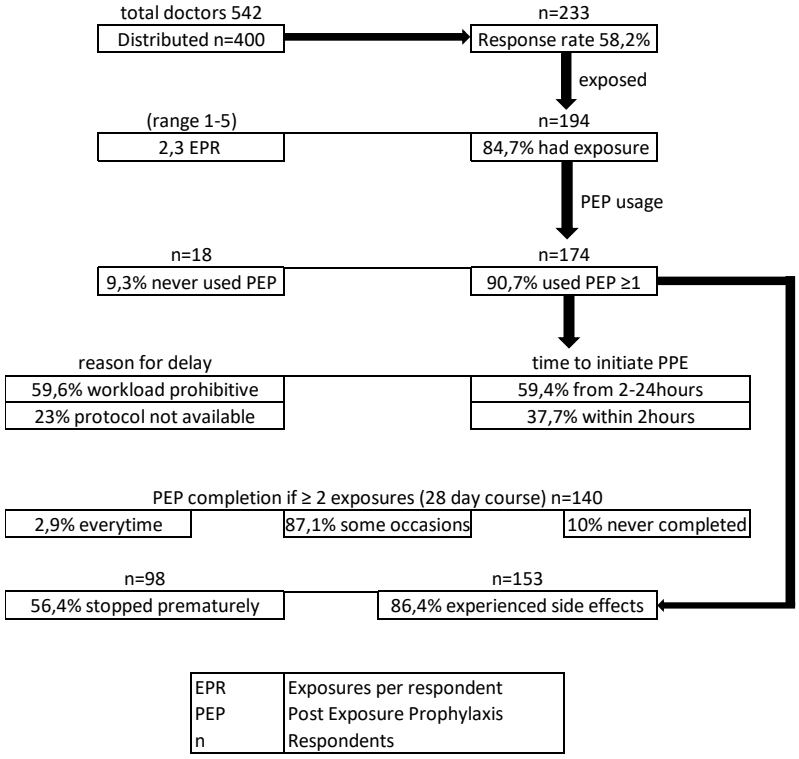

Figure 2: Exposures and PEP use

Respondents felt that workload adversely impacted adherence in 87 (49,4%) cases, and 97 (43,7%) thought that the protocol was not readily available. Twenty-one (9,5%) respondents felt afraid to report the incident to their senior or relevant authority and 162 (73,6%) felt that reporting to occupational health was too time consuming. See Figure 2 for quick facts regarding exposure and PEP use.

Discussion

Doctors working in the Free State Academic Complex did not adhere to HIV PEP regimens prescribed to them. The poor adherence began with initiating ART immediately after an exposure and extended to completion of the recommended 28-day protocol. Discussion with the occupational health department staff revealed that follow up is reported to be dismal at 6 weeks and worse at 3 months. Of note, at the time of the study, the routine prescribed ART regimen was 2 NRTI's and a PI, usually a combination of Tenofovir, Lamivudine and a combination pill of Lopinavir and ritonavir[17].

The above findings were in line with similar studies done internationally in Argentina, Botswana, Nigeria, India and in limited studies conducted locally in South Africa[3,4,8,9,10,11,12]. This study demonstrated that on average, a doctor was exposed more than once in their career.

Research by Kaerstad et al[10] (2014) surveyed all interns in Baragwanath and Johannesburg general hospitals' and found that 69% of interns had an exposure. In 2019, when Aigodien et al[4] (2019) conducted a similar study and found that 77,7% of interns had an exposure[8,9]. For the purposes of this study, junior doctors were considered as those who accumulated less than five years of post-graduate experience, and 81,8% of them had an exposure. When considering *all* respondents regardless of years of experience, a further increase to 86% was noted. This implies that most exposures occurred in the junior years of practice. Given the previous studies done on interns we can infer that most exposures occur during earlier years of practice with a plateauing rate of exposure as experience increases. With more time in practice, an exposure is likely to occur, but the incidence of high-risk exposures is less in the senior doctors.

There was a significant difference in the usage of PEP between junior and senior doctors, with as much as 10% more senior doctors using PEP after each exposure as compared to junior doctors. *Figure 4* demonstrates the largest area in the middle circle as the most exposures, whereas the smaller outer circle demonstrates less exposures in the more senior years.

The disparity in rate of exposure can be explained by senior doctors (which included professors and specialist consultants employed in the public sector) being in a more consultative role than in a service delivery role. It is not

surprising that 49% of respondents were exposed during venesection which is typically done by interns in the public sector.

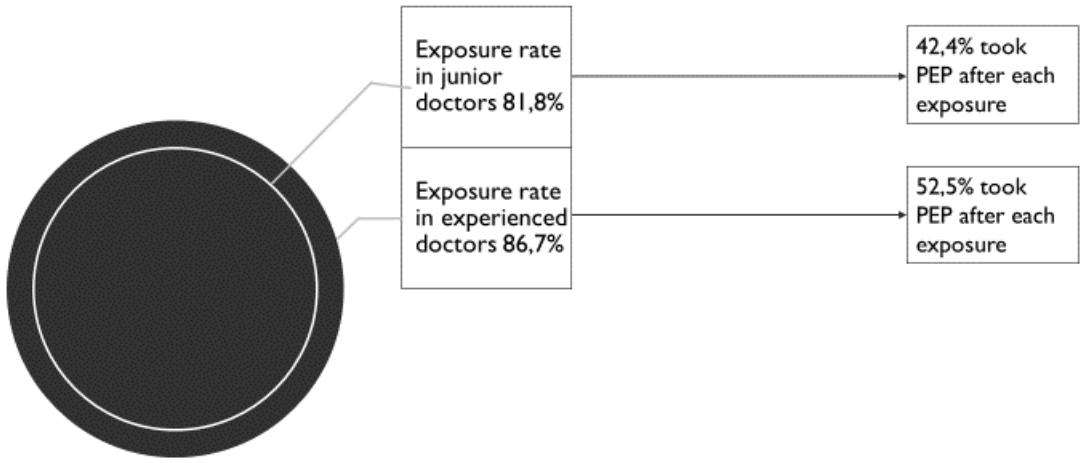

Figure 4: Exposures among interns, junior and experienced doctors

There is a large strain on the public health system with large workloads and a low doctor to patient ratio[18]. Due to workload, respondents who delayed PEP for longer than 2 hours after being exposed cited their workload to be prohibitive (49%) and furthermore almost 60% of respondents cited this as a major factor that impacted adherence.

In line with other studies, completion rates of PEP were dismal and the main reason for defaulting PEP was side effects. This finding was in line with international studies mentioned above. The most common regimen prescribed to doctors working in the public sector at the time of this study contained protease inhibitors, which is known to have a high side effect profile[17,21]. Aigbodion et al reported that most of the side effects reported in their study was gastrointestinal in nature and this is congruent with known side effects to protease inhibitors[21].

The use of better tolerable regimens that contain integrase inhibitors as opposed to protease inhibitors may improve adherence as demonstrated by Valin et al[13] (2016) in the occupational setting and Inciarte et al[21] (2017) in the non-occupational setting. It will be interesting to see how adherence improves after the recent roll out of the integrase inhibitors as part of the national ART schedule. McAllister et al[14] demonstrated that a dolutegravir regimen was well tolerated as PEP in the non-occupational setting, and this may also hold true for the occupational setting[13].

It is unclear whether a 2 two drug or a 3 drug regimen is more efficacious, but the former has been proven non inferior to the latter[7]. Of note, Tetteh et al[16] (2015) has shown that a shorter regimen has better adherence rates (3 days vs 28

days) and that side effect profile of the regimen became worse with longer courses, which ultimately negatively impacted adherence.

Due to the national roll-out of newer ART in 2019, Dolutegravir based regimens in particular, the review of adherence using these drugs make this a gap worth exploring for future studies.

This study administered the questionnaire to 42% of all doctors working in the Free Sate Academic Complex. This study looked at *all* the doctors at a given working complex- irrespective of speciality, stage of career; and of whether the respondent was in a clinical or a laboratory setting.

The study did not assess the circumstances around every exposure, and data surrounding every exposure is limited especially considering that on average, each respondent had 2,3 exposures with 12,3% of respondents having more than 5 exposures. This led to reporting bias as we did not determine when in their career the exposure occurred, the specific circumstances around each exposure, or how many respondents had PEP training. Other data that was lacking in this study was the ART regimen used after *each* exposure. This made it difficult to objectively determine which drugs were associated with the highest side effect profile.

Conclusion

In conclusion, doctors working in the FSAC do not adhere to universal PEP protocols recommended to them. They have multiple occupational exposures in their careers, especially during the junior year of work. They often do not initiate, nor do they complete PEP due to their workload, non-familiarity with protocols and intolerable side effects of regimens used at the time of the study. With targeted training, awareness campaigns and better tolerated regimens (Dolutegravir); adherence and completion rates of PEP after occupational exposure to HIV can be improved.

Acknowledgements

The authors would like to acknowledge Professor Sumaiya Adam for her insights in the final draft of this manuscript, her time, attention and advice, and Dr Claire Armor Barrett for her insights into the protocol and questionnaire design.

Competing interests

The authors have declared no competing interests in the publication of this study.

Author’s contributions

The first author completed this study as part of a master of medicine dissertation for postgraduate studies. The protocol, data collection and final draft of this article was done by the first author.

The second and last authors were the study supervisors and advised on the structure, amendments and final write up of this study.

The third author was the biostatistician involved in analysis of data, and made recommendations on the results and write up of the final draft of this study.

Funding information

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [TA], upon reasonable request.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Disclaimer

The views expressed in the submitted article are those of the authors and not an official position of the institution or funder.

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Appendices

Letter of approval from research ethics committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

11-Sep-2018

Dear **Dr Taahir Asmal**

Ethics Clearance: **Assessing adherence to established HIV post exposure prophylaxis regimens in doctors working in the public sector in Bloemfontein, South Africa. A multicentre study.**

Principal Investigator: **Dr Taahir Asmal**

Department: **Internal Medicine Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/0018/2509**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
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Permission from head of department

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[redacted]

18 December2017

Dr E le Grange
The Chairperson,
Ethics Committee' Faculty of Health Sciences
University of the Free State

Dear Dr Le Grange

I hereby give **Dr Asmal** (Internal medicine registrar) permission to conduct a multicenter study;

Title: Assessing adherence to established **HIV Post Exposure Prophylaxis** regiments in the public sector in Bloemfontein, namely **Universitas, Pelonomi and National** hospital.

Kind regards

.....
Dr TRP MOFOKENG : HOD
Dept of Internal Medicine

Dr TRP Mofokeng
BS(Lewis & Clark) USA, M.Med (Int) UFS
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Letter of approval from department of health

health
Department of Health
FREE STATE PROVINCE

08 May 2018

Dr T Asmal
Dept. of Internal Medicine
University of Free State

Dear Dr T Asmal

Subject: Assessing adherence to recommended HIV Post Exposure Prophylaxis regimens prescribed to doctors working at the Free State Health Complex in Bloemfontein, South Africa.

- Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participants must be obtained
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of National, Pelonomi, Universitas Hospital and National Hospital Gateway Clinic nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and no names will be used.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** khusemj@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 10/05/2018

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Study protocol

Assessing adherence to recommended HIV Post Exposure Prophylaxis regimens prescribed to doctors working at the Free State Health Complex in Bloemfontein, South Africa.

Researchers:

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General Words

HIV – Human Immunodeficiency Virus

PEP – Post Exposure Prophylaxis

AIDS – Acquired immunodeficiency Syndrome

ART – Anti Retro Viral therapy

PMTCT – Prevention of Mother to Child Transmission

NSI – Needle Stick Injury

FS – Free State

UFS – University of the Free State

DOH – Department of Health

HCW – Healthcare Workers

RCT – Randomised Control Trial

UKZN – University of Kwa Zulu Natal

UAH – Universitas Academic Hospital

PH – Pelonomi Hospital

NDH – National District Hospital

NHLS – National Health Laboratory Service

HPCSA – Health Professions Council of South Africa

Abbreviation of ARV Drugs:

(For the purposes of the completed report all ARV's are listed here, these abbreviations are not necessarily found in the content of this protocol)

3TC – Lamivudine

ABC – Abacavir

AZT – Zidovudine

ATZ – Atazanavir

d4t – Stavudine

DRV – Darunavir

ddC – zalcitabine

ddI – Didanosine

DTG – Dolutegravir

EFV – Efavirenz

ETR - Etravirine

FTC – Emtracitabine

IDV – Indinavir

LPV/r – Lopinavir with boosted Ritonavir

MVC – Miraviroc

NFV – Nelfinavir

NVP – Nevirapine

RAL – Raltegravir

RVP – Rilpivirine

SQV – Saquinavir

TDF – Tenofovir

Definitions:

Healthcare worker: All personnel involved in patient care, for the purposes of this study – All doctors working in the study hospitals. In this study, it will refer to doctors specifically. This includes specialists and general practitioners.

Virally unsuppressed: HIV viral load of >1000 copies/mL as monitored by NHLS assay (1)

Seroconversion: The process of the development of detectable HIV antibodies after being exposed to the HIV virus (1)

Occupational Exposure: In the context of HIV this includes any work-related exposure to infected material that would increase the risk of being infected with HIV.

Protocol in Layman terms

The population of healthcare workers (HCW) in South Africa are exposed to the Human Immunodeficiency Virus (HIV) daily, and as such, are one of the most at-risk populations of being infected with the virus as part of their occupation. This is through being in contact with patients in a high disease burden population as part of their daily jobs.

Some patients who have a high number of HIV circulating in their bloodstream (virally unsuppressed) which may be due to a multitude of reasons, present to our healthcare facilities for medical attention; and it is through carrying out medical procedures on these patients that HCW's are exposed.

HIV is transmitted through contact with bodily fluids containing the virus, and as such, invasive medical procedures carry the highest risk of transmission of the disease (this includes any procedure wherein the HCW will encounter bodily fluids of the patient). The highest risk is when the infected material/fluid comes into direct contact with any part of the HCW from which it may be easily absorbed into the bloodstream. An example of this is contamination of the mucous membranes (e.g. eyes, mouth, etc) or penetrating injuries through the skin (needle stick injuries from used needles).

Although the risk of being infected is low with most exposures, the risk may be practically abrogated with the use of antiretroviral therapy (ART), which in this context we call occupational post exposure prophylaxis (PEP). Due to the efficacy of ART that is available in South Africa, the only major **controllable** factors that contribute to a HCW seroconverting (becoming HIV positive after being exposed to the virus) are:

- Time of taking the stat (first/immediate) dose of medication
- Adherence to the full course of PEP (28 days)

Studies that aim to determine the risk of seroconverting to HIV positivity in a worker who was HIV negative are unethical and most of the data that we have comes from programmes already instituted e.g. Prevention of Mother to Child Transmission (PMTCT) that are used in HIV pregnant women presenting to hospitals for obstetric services. We therefore are not able to truly quantify the risk or seroconversion with and without PEP, and we are unable to truly risk stratify different exposures to lower or higher risk of becoming HIV positive.

Throughout the course of the author's study and practice of medicine, adherence to PEP was perceived to be dismal, due to poor tolerability, and occasionally the work load of the HCW which influences their presentation to occupational health departments of their respective facilities.

It is the hypothesis of the author that doctors do not adhere to PEP regimens as set out by the occupational health department, and I intend this as the rationale to undertake this study. I also hope to ascertain why adherence is poor and eventually make recommendations to the local healthcare facilities that may influence adherence.

This study will be conducted by means of a questionnaire. The questionnaires will be distributed by the author and research assistants to personnel working within public healthcare facilities in the Free State Health Complex

(Universitas, Pelonomi and National Hospitals) in Bloemfontein. The study population includes all doctors working in these facilities.

Defining the research problem

The burden of the disease on the population

Healthcare workers are exposed to HIV positive patients daily and, especially in South Africa, are thus at risk of direct exposure to the virus in vivo whilst carrying out their daily routines. South Africa has one of the highest prevalence of HIV infection in the world, according to statistics obtained from the United Nations HIV registry. Approximately 7 million people are infected with the HIV virus in South Africa, this being an underestimate, with most of the data on this obtained from pregnant females presenting for antenatal care, and registered patients who are following up at primary care and HIV clinics. Despite these alarming figures, only approximately 3.9 million patients are on antiretroviral therapy, and even less of these patients (3.2 million) are virally suppressed. The incidence of HIV infection is, the third highest in the world, after Swaziland and Lesotho. Despite having the largest HIV treatment program in the world, the above statistics plotted against the census data of the total population, paints a bleak picture that under 10% of the general population, that we know of, are HIV positive; and more appalling is that just under half of these patients are not on antiretroviral medication. This translates to there being many patients who are HIV positive and virally unsuppressed who present to our hospitals at a primary, secondary or tertiary level for care (2).

Globally there are about 5000 new HIV infections daily with 64% of these infections in Sub-Saharan Africa. UNAIDS data suggest that there is an increase in the prevalence of HIV infected individuals in South Africa from 2015 to 2017 but a higher percentage of those infected with HIV are on antiretroviral therapy (ART). Only 45% of patients on ART are virally suppressed (3).

The impact of HIV infection, and resultant acquired immunodeficiency syndrome (AIDS), on the economy of a country, such as South Africa, is large and often underestimated. One may use economic models to determine the financial loss in hours worked per year, to estimate the amount lost in productivity but that underestimates the actual burden of the disease. The burden of disease not only affects the productivity of one generation, but due to the incidence being highest in the child bearing age group, it affects the generation following those that are infected, i.e. their children – this increasing the burden of disease on the health system. Growing up in single parent households or as orphans of the state places immense pressure on the social welfare systems of a country and significantly impacts on the outcome of the child's future, often resulting in social disintegration and further burdening the healthcare system – directly, by making poor health choices and indirectly, by funnelling much needed resources into social grants. This vicious cycle perpetuates and eventually may lead to the moral, economic, social and physical degradation of a society; all of this eventually translates into increasing the burden on the healthcare system (4).

The burden of the disease on the healthcare system

An alarming number of patients present to healthcare facilities, being newly diagnosed with HIV. These patients present in varying stages of the disease and in various clinical conditions, from seroconverting flu-like symptoms to the gravely ill HIV stage 4 patients with AIDS-defining opportunistic or other contagious infections. They require multiple levels of support and expertise regarding their treatment and care, and often more than one medical discipline is involved. These newly diagnosed patients, not yet started on suppressive ART, are assumed to have high HIV viral loads. The other subset of patients that pose a major risk to healthcare workers are those on ART with unsuppressed viral loads – these failing patients present a high risk of transmission of a potentially drug resistant virus (4–6).

HIV and AIDS has radically impacted the practice of medicine in South Africa on many levels. Firstly, it drains a large amount of resources, not only in treating HIV itself, but also in treating associated opportunistic co-infections related to the immune suppression. Secondly, taking into consideration that a lot of the diseases associated with a poor socioeconomic status are infectious in nature, healthcare workers who deal with patients afflicted with such illnesses are at the highest risk of getting infected with HIV and the like (7).

The burden of HIV related illness is considerable, with its tentacles spread over a variety of manifestations involving most, if not all, of the disciplines in medicine. Some disciplines having a higher risk of exposure to HIV infected tissues and body fluids than others; e.g. General Surgery and Obstetrics as opposed to Radiology. It is the researcher's opinion that dealing with the large patient load of an already sick general population with a relative shortage of doctors provides the ingredients to an inevitably high probability of being exposed to HIV through accidental injuries on duty.

The burden of the disease on the healthcare worker

A prospective cohort study in 1990 (before the advent of ART) conducted by Henderson et al concluded that the risk of HIV transmission after percutaneous exposure was 0,3%, with 0,09% risk of transmission after mucocutaneous exposures. If the exposure occurred on intact skin the risk was 0% (i.e. no reported cases) (8).

In the post-ART era, studies to quantify the risk of HIV seroconversion after an occupational exposure to the virus are unethical to conduct, and most of our data are obtained from occupational health reports and animal studies. It is unlikely that a study can or will be conducted to quantify the risk of transmission, but with more data collected and more research into the topic of post exposure prophylaxis in non-occupational setting; i.e. PMTCT, injection drug users, sex workers and sero-discordant couples (homo and heterosexuals), we may extrapolate the data to infer assumptions of healthcare worker risk (9).

There are a multitude of factors that contribute to these injuries being common, such as patient work load, availability of protective equipment, notwithstanding its use thereof, and hours worked/overworked. The grading of exposure in a risk category (i.e. high and low risk) is omitted as this may delay the rapid initiation of HIV post-exposure prophylaxis (PEP) (8).

Current Guidelines

In their current guidelines for the management HIV PEP, The South African HIV Clinicians Society regards exposure to the following fluids as infectious (9):

- Blood (or any blood-stained fluids)
- Genital secretions (incl. vaginal/penile secretions and ejaculate)
- Tissue fluids
- Body cavity fluids (including ascites, CSF, pericardial fluids etc)
- Breast milk

whereas non-infectious fluids include:

- Sweat
- Tears

- Saliva and sputum
- Urine and stool

Current guidelines regard all infectious exposures as risky regardless of type; whether low or high risk – previous risk stratification guidelines have made distinction between penetrating wounds, the type of needle involved etc. The rationale of this thinking is that in the South African setting, and given the prevalence of untreated HIV, all exposures must be regarded as high risk and treated initially; with expert opinion to be sought later from occupational health or infectious disease physicians. Other considerations are the availability of the medication after exposure; how soon should the PEP be taken; and what medications to use (10–12).

Data suggest that the most effective time to initiate PEP would be within two hours of the incident. This is important as it ensures that adequate levels of circulating drug are present to prevent viral integration into host cells. Interestingly, integrase inhibitors are recommended in this light, and new regimens include integrase inhibitors as first line medication, although traditional regimens have not been proven inferior (1,10).

The use of starter packs to initiate PEP and then the subsequent prescription of the full course is disregarded in current guidelines. Now provision of the full month of treatment as soon as possible, preferably within 2 hours of exposure and the use of drugs with the best side effect profile is advocated. This is to ensure that the medication is taken as soon as possible, with the least chance of breaks in treatment availability - to boost compliance to the regimen, and to improve adherence to the full 28-day course. Animal studies have shown that taking PEP for 28 days consecutively confers maximum benefit and prevents HIV seroconversion (10,13).

The Southern African HIV Clinicians Society recommends using Tenofovir with the addition of Emtracitabine or Lamivudine (TDF+ETC/3TC) as a backbone, and the addition of the integrase inhibitor Raltegravir (RAL) as the preferred agent or the boosted protease inhibitor Atazanavir/Ritonavir (ATZ/r) if the person taking the PEP is pregnant. Alternatively, boosted Lopinavir/Ritonavir (LPV/r) or Efavirenz (EFV) may be used. It is also recommended that starter packs should not be used and that a full month of medication should be provided at the first point of presentation. Follow up should done at 2 weeks, 6 weeks and 3 months after exposure (1). The Occupational Health department at Universitas and Pelonomi hospitals' use a backbone of TDF+3TC with the addition of LPV/r.

The World Health Organization (WHO) guidelines are not dissimilar in their recommendation. The largest difference in regimens are found in guidelines of developed countries' recommendations. This is due to the availability of drugs in those countries that are somewhat 'novel' in developing countries (11).

Doctors, arguably, function on a high level and excellence is expected of their decisions; as these decisions influence the lives of patients drastically, sometimes being the very difference between life and death. Doctors in the public sector are also under enormous strain from the burden of patient numbers. Due to these enormous stressors placed on them, adherence to a PEP regimen with many side effects may influence their adherence and their productivity at work. For this reason, and others, the side effect profile of PEP should be as low as possible and support in terms of adherence must be readily available.

Literature Review

Research conducted in Southern Africa

In a study conducted at the University of Kwa-Zulu Natal Goundan and Moodley (2000) reported that approximately 13% of participants had occupational exposures to HIV. 82% of those exposed took HIV PEP whilst 17% did not, citing the injury as trivial and not requiring PEP. They also found that 48% of participants discontinued PEP due to side effects (14).

Another study conducted by Karstaedt and Pantanowitz (2001) in Baragwanath Hospital in Gauteng (2001) reported that 69% of junior doctors in their internship had an exposure in the preceding year with 33% having an exposure to HIV infected blood. Only 64% of high risk exposures were reported (15).

Kassa et al. (2016) conducted a similar study in three public hospitals in Botswana which described the occupational exposure and adherence to PEP in HCW's. A cross sectional survey was undertaken and found that 26% of respondents had significant exposures to potentially infective sources. Of them, only 37% reported the exposures and of those who reported an exposure, 69% received PEP with a 71% completion rate. Less than half of respondents were satisfied with their existing reporting systems (16).

A retrospective study conducted in Cape town by Papavarnavas et al (2017), reviewed all occupational health folders of healthcare workers after occupational HIV exposure, they found that many of the healthcare workers were lost to follow up. After analysing the data, they associated this loss to follow up with increasing age, and later initial presentation (i.e. those who presented to the occupational health department more than 24hours after the incident) (17).

Research in other African countries

Tetteh et al (2015), described adherence to a regimen of 3TC/AZT and 3TC/AZT/LPV/r, where they found that non-completion of the PEP regimen was 44% i.e. almost half of all exposed HCW's on the medications defaulted before 28 days. The main reasons cited for the defaulting was intolerance to side effects (SE's) (18).

Among lab workers in Nigeria, a study by Fadeyi et al (2011), described awareness and practice of safety precautions in HCW's when handling potential sources of infective fluids. The authors found that 41% of participants were unaware of the existence of basic safety precautions, and upon further review, 25% did not observe any safety precautions. Up to 50% of participants recapped needles and after exposure to potentially infected material, only 1,5% of participants would present to occupational health for PEP (even though 83% were willing to take PEP) (19).

International Studies

Research in developing countries

Internationally, studies in other high prevalence developing countries like India and Argentina, also reported similar rates of occupational exposures, with poor compliance to PEP. Due the ethical dilemmas associated with conducting randomized controlled trials (RCT's) to ascertain the rate of transmission after exposures we do not know the exact rate of transmission after a high risk occupational exposure (20–23).

A study by Halwani et al (2015), in Saudi Arabia described needle stick injuries in a 1000 bed tertiary hospital that serves 3 major cities. They found that most of exposures were caused by needles and that 64% of injuries occurred

in the morning hours of duty. The presence of blood borne infections were known in only 51% of source patients (24).

A study in India by Swetharani KV (2016), et al described that 79% of participants recapped needles after use, almost 50% of participants reported exposures in the preceding year, and 70% of exposed participants did not report them. Almost 50% of participants did not use appropriate safety precautions before the exposures (22).

Aggarwal et al (2012), conducted a retrospective review of data of ongoing surveillance in a tertiary hospital. They described that most of the injuries on duty occurred in doctors (79%) and just over half of them were in their first year of practice. Over three quarters of the injuries were due to noncompliance with universal precautions and were possibly preventable. PEP was indicated in almost 100% of cases, with only 25% of the HCW's taking PEP within 2 hours of injury. Complete follow up was dismal and so was adherence to the full 28-day course (23).

Studies in developed countries

A recent study a Valin N et al (2016), described adherence rates to a new PEP regimen consisting of FTC/TDF/elvitegravir to be 92%. The adverse effects rates were 60% but were graded as mild-moderate and only 3 patients were switched to another regimen due to severe side effects. This shows that the medications used as part of the PEP regimen greatly influence adherence to a full course of therapy. Another conclusion can be made from this study from looking at their methodology – reminders were sent via text message to the participants and there was active case follow-up in terms of calling the participants regularly. This also contributed greatly to the adherence to PEP in these participants (25).

Critical appraisal of the research

Most studies done in South Africa focused on a specific group of doctors –

- Gounden et al focused-on obstetricians and gynaecologists
- Karstaedt et al focused-on interns only

This may have influenced the data by inferring that the risk to all doctors are the same. This cannot be true as different specialities have different ways in which they manage patients. An example of this is that anaesthesiologists may not be exposed as much as obstetricians to blood borne pathogens, although they may be more exposed to respiratory droplet pathogens (14,15). Other studies like Fadeyi et al described the exposures and awareness of **laboratory** workers – people who work mostly with blood. Their risk is assumed to be the highest amongst all healthcare workers (19). Rajkumari et al described exposures in **trauma** workers in a developing country. This also may skew the data obtained when relating this to all doctor exposures (21).

Our study intends to compare the exposures across a multitude of disciplines.

Valin et al described the tolerability of elvitegravir based regimens in their study group. They also had a novel way of reminding doctors of their appointments with occupational health. This study proved that an "active surveillance" approach to monitoring of drug tolerability and follow up in the study population influenced the adherence positively. The method that they used to follow up the HCW's is relatively inexpensive considering the popularity of smart phones and online presence of many a HCW today (25).

With the ongoing changes to the ARV guidelines in South Africa, ARV's with a better side effect profile are becoming increasingly available and, given the research data, it is the view of the author that the results of this study will aid in strengthening guideline recommendations in motivating for better tolerated drugs for PEP.

Aim of this study

To describe the adherence of doctors working in the Free State Health Complex in Bloemfontein to prescribed HIV PEP regimens. This is a study to be conducted at 3 hospitals in the Free State province of South Africa.

Objectives of this study

This study attempts to:

- Firstly, establish whether doctors adhere to current PEP prophylaxis guidelines, as set out by the Department of Health or local occupational health department of each hospital
- Secondly, as the data allows, to ascertain why adherence may be poor to PEP.

This will allow the researcher to make recommendations to the relevant institutions on how to improve safety and adherence to PEP firstly on a local level what to do once exposure has occurred and make available the means of educating HCWs if there are any risks identified in their behaviours regarding the use of PEP.

Secondly in this light, this researcher also endeavours to assist in providing invaluable data to developers of HIV PEP guidelines nationally so that they take into consideration the target population and their behaviours, attitudes and the circumstances around exposures.

Methods

Study design

A descriptive cross-sectional study will be done by means of a questionnaire. Adherence to PEP as well as factors influencing adherence will also be asked of in the questionnaire.

Sample

The population aimed at in this study are all doctors working in Free State Academic Complex during the period of data collection – April to May 2018.

Other healthcare workers like nursing staff and auxiliary healthcare workers will not be included in the study due to time and personnel constraints.

Inclusion criteria

All doctors working in the following hospitals:

- Universitas Academic Hospital – approximately 250 employed doctors
- Pelonomi Regional Hospital – approximately 250 doctors
- National District Hospital – approximately 30 doctors

Exclusion criteria

All HCW's who are not registered with the HPCSA as a medical doctor, i.e. nurses, allied health professionals, hospital auxiliary staff, laundry personnel, Human Resources etc.

For the purposes of this study, doctors working in private facilities will be excluded from the study.

Research assistants and study supervisors will be excluded from participating.

Measurement

An anonymous self-administered questionnaire will be handed out to doctors working in the public hospitals in all medical departments in the Free State Academic Complex in Bloemfontein.

Doctors working in each discipline will be approached after their weekly departmental meetings and medical officers will be recruited from the different departments during work hours. Provision will be made for doctors who do not complete the questionnaire in the week provided, and those doctors will be given one week to complete the questionnaire. Interns doctors will be included in the study, they usually attend departmental meetings as they rotate and will asked to participate with the registrars, consultants and all other doctors working in that specific department.

Casualty officers and those medical officers not affiliated with any specific department will be recruited at their site of practice (e.g. casualties, theatres and wards).

The completed questionnaires will be inserted into a sealed box to try to ensure anonymity. The box will then be collected by the researcher a week after delivery.

The design of the questionnaire accommodates different sections which form part of what this study aims to describe, i.e. demographic information, exposure to HIV infected patients and adherence to post exposure prophylaxis.

Research assistants will be recruited from the current group of interns with a valid driving licence working in Bloemfontein. They will be given the option of being affiliated with the study by having their names mentioned as part of the researchers. They will be recruited by sending a text message to them informing them of the study and what is required with interested individuals to contact the main researcher. The function of the assistants will be to assist in administration of the questionnaires, data collection and entering the data sheet entry for biostatistics evaluation. A maximum of five interested assistants will be given the opportunity to be a part of the study. If none of the interns are interested in being a research assistant the main author will administer, collect completed questionnaires and do the data entry himself.

Bias

To counter information bias, all doctors will be intended research participants and at the beginning of the questionnaire the participant will be asked: Have you completed this questionnaire before? If they respond in the

affirmative, then the questionnaire will be discarded, and the data will not be used as this may over or underestimate the variables.

The healthy worker effect will be countered by approaching each department on days 2 weeks apart to maximise capture and minimise missed participation, i.e. doctors on leave, sick leave or absent for the meetings.

Pilot Study

A pilot study will be performed on the Department of Internal Medicine registrars during their weekly research meeting at the UFS to determine the questionnaire length (in average time to complete), to see if the questionnaire is appropriate at ascertaining the relevant information from the study population. The data from the pilot study will be used as part of the data if the pilot study confirms that the questionnaire is appropriate, and no changes need to be made.

Data Analysis

Department of Biostatistics (UFS) will assist the researcher with the analysis of data. Results will be summarized by frequencies and percentages (categorical variables) and means and standard deviations or percentiles (numerical variables).

Ethical considerations

Ethical considerations include anonymity and confidentiality of the results until the completed report/article is done. This will be actively implemented by the researcher by ensuring anonymity in the questionnaire, and keeping the completed questionnaires safe after data collection.

Ethically, enquiring about the HIV status of a respondent may lead some confidentiality issues, and may make some respondents uncomfortable in answering this. For this reason, this information will not be asked of the participants.

Approvals

This protocol will be submitted to the Health Science Research Ethics Committee (HSREC) of the UFS, for approval before commencement of the data collection. Permission will be asked from the provincial Department of Health – Free State once the HSREC of the UFS approves the protocol.

Privacy and Confidentiality

Efforts that are and will be made to ensure anonymity include:

- Participants will be asked to complete the questionnaire and place it in a box that will be provided to them. Most of the questionnaires will be filled out en-masse before or after their academic meetings.
- The participant will retain the information document, and no signature will be required as consent – The Questionnaire begins by informing the participants that they give consent to participate by completing the questionnaire.
- The questionnaire does not ask of any identifying details of any participant – except which discipline are they working/specializing in. This may narrow down the possibility of identifying the department of the participant and as part of the demographic the sex of the participant. There will be no active intention to identify participants on this basis.

- The completed questionnaires will be kept by the researcher after the data is collected in a safe place accessible only to the researcher and the HSREC should they require it for ethical consideration/reason.

Budget

Description	**Information**	**Total**
Stationary	Questionnaires, staples, pens	R 1 710,00
Travel		R 237,50
Free Pens	1 pen per questionnaire	R 5000,00
Proof reading and medical writer		R 250,00
Consumables	Grammar, language editor	R 200,00

Total **R 7 397,50**

The researcher will obtain the funds from the research fund from the Department of Internal Medicine, the Postgraduate Committee – School of Medicine research fund and the Discovery Foundation Academic Fellowship Awards fund. The responsibility of covering shortfall, if any, will be the responsibility of the main researcher – from his own equity. Detailed budget attached to addendum.

Timeline

OUTCOME	**TIMEFRAME**	**RESPONSIBILITY**
Protocol submission	Jan-April 2018	Researcher
Ethics evaluation	April-May 2018	Ethics Committee
Permissions	April-June 2018	HEAD DOH
Data Collection	July-August 2018	Researcher and assistants
Data Analysis	September-October 2018	Researcher and Biostatistics
Preparation of manuscript	October-December 2018	Researcher/Supervisor(s)
Submission to evaluators	January 2019	Researcher
Submission to Faculty forum	June/July 2019	Researcher

Publishing of data

The data will be published in a locally or internationally available journal should they accept the manuscript. Also, the researcher aims to present the findings at the next faculty research forum should it be accepted.

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INFORMATION DOCUMENT

UFS-HSD2018/0018/2509

Study title: Assessing adherence to established Human Immunodeficiency Virus (HIV) Post Exposure Prophylaxis (PEP) regiments in doctors working in the public sector in Bloemfontein, South Africa. A multicentre study.

I am doing research to describe the adherence, and factors influencing adherence to HIV PEP regimens offered at their respective facilities, and what influences adherence to these regimens.

This is an invitation to participate in this study.

What is involved in participation: Participation involves completion of an anonymous questionnaire that will be administered to you. This includes completion of the questionnaire to the best of your ability and as truthfully as possible.

Risks: This questionnaire is anonymous and at no point requires you to provide any identifying information on any of the pages. A pen will be provided to you to complete the questionnaire which may be kept by you after completion.

Benefits: The information provided to the researcher through this questionnaire will allow him to make recommendations to the facilities locally; and be used as a consideration when developing guidelines nationally for HIV PEP. This will benefit the participants in that it will enable your employer/occupational health department to provide you with the necessary support systems and the most effective HIV PEP with the least adverse effects that will ultimately boost compliance and effectivity.

Participation is voluntary, and refusal to participate will result in no punitive action or loss of benefits to which you are otherwise entitled. You may discontinue participation at any time and request that your incomplete/complete questionnaire be excluded from the study.

There are no costs payable by you to participate in this study.

Confidentiality: The questionnaire at no point requires you to provide any identifying information and anonymity is guaranteed. Once the questionnaire is complete the researcher/assistant will place it in a box.

The data will be analysed by the Biostatistics Department of the UFS and individual questionnaires may be inspected by the Health Sciences Ethics Committee of the UFS.

The report and results of this study will be published in locally and/or internationally available journals and may be requested from the researcher after the report is complete.

Thank you for your participation in this study.

Contact details of researcher:

Dr T Asmal

071 681 6881

t_asmal@yahoo.com

Contact details of the Secretariat and Chair of the Health Sciences Research Council of the UFS:

051 405 2812

Questionnaire

You have been asked to participate in a research study. Please note that by completing this questionnaire you are voluntarily agreeing to participate in this research study. You will remain anonymous and your data will be treated confidentially at all times. You may withdraw from this study at any given moment during the completion of the questionnaire. The results of the study may be published

Questionnaire	Please mark with X	DATE (DDMMYY)

A Demographics

1 Have you completed this survey before? (if yes do not proceed with the questionnaire and place incompleted in collection box)

	Y	N

2 What is your age?

16-25	26-30	31-35	36-40	41-45	46-

3 Gender

	Male	Female

4 What best describes your professional position as per your HPCSA registration? *

	Intern	Medical Officer	Registrar	Specialist

* If consultant the mark "Specialist". If Private General Paractioner then mark "Medical Officer".

5 For how many years have you been practicing medicine (years)?

	<1	1-2	3-5	6-10	>11

6 If Registrar or Specialist, what is your speciality or current discipline?

The following questions refer to exposures from patients who are HIV positive, or the status was unknown

7 From the list below, tick the options that are relevent to you, which you have been exposed to (index patient/s must be HIV positive or you did not know the HIV status of the patient)

I have had exposure via	intact skin	penetrating injury/broken skin	conjuctiva/ oral mucosa	Other
Blood contamination				
Saliva Contamination				
CSF contamination				
Urine/Faeces				
Body Cavity Fluids				
Amniotic Fluid				
Breast Milk				

An X in a grey box is regarded as a high risk exposure

8 How many high risk exposures have you had in the last 5 years? (this includes patients whose status you did not know)

	None	1-3	4-5	>6

9 What were you doing when the high risk exposure occurred? (in case of high risk exposure; may tick more than one)

Venesection	
Lumbar Puncture	
Minor Operative Procedures	
Major Operative Procedures	
Insertion of invasive/central lines	

10 In your opinion could the exposure have been avoided? (specific regard to high risk exposures)

Yes	No	Unsure

C Post Exposure Prophylaxis

11 Do you consider the use of HIV PEP to be important after every high risk exposure? (includes patients whose status you do not know)

Yes	No	Unsure

12 Have you ever taken HIV post exposure Prophylaxis?

Yes	No

13 Have you taken HIV PEP after EVERY exposure? (in case of more than one)

Yes	No	Not Applicable

14 If you did not know the status of the patient, did you take PEP until you found out? (after high risk exposure)

Yes	No	Not Applicable

15 Were there ever occasions where you knew that the patient was HIV positive and you did not take Post Exposure Prophylaxis?(after high risk exposure)

Yes	No

16 How soon after the exposure did you start HIV PEP?

Within 2 hours	
Within 6 hours	
Within 12 hours	
Within 24 hours	
>48 hours	

17 If >6 hours, what influenced the delay? (may choose more than one)

Protocol not readily available	
Workload prohibitive	
Support from Seniors/Colleagues	
Unavailable medication	
Involved in Emergency Procedure	
Other	

18 Did you complete the full duration of HIV PEP (30 days)? On all exposures

Yes	No

19 If you have taken HIV PEP, how many pills were you required to take? (if combination pills, state the amount of active drug used)

1	2	>3	Unsure

20 Which ARV's did you use for PEP? (all active drug[s] used; may use trade name if unsure)

21 Have you experienced any side effects to any of the HIV PEP medications?

Yes	No	Unsure

22 Have you EVER stopped HIV PEP prematurely (before 30 completed days)?

Yes	No

23 If yes to 35, what was the reason(s) for stopping HIV PEP prematurely? (may choose more than one)

Patient found to be negative	
Severe Side Effects	
Unavailability of drugs	
Protocol not readily available	
Influenced by colleague to stop	
Other	

24 If other, please state:

_____

_____

25 Did you feel that your workload impacted on your adherence to the PEP regimen?

_____

Yes	No	Unsure

26 Do you feel that your hospitals protocol is readily available and easy to follow after exposure?

Yes	No	Unsure

27 Do you feel afraid to report to any exposure to your senior on duty or to occupational health at your facility?

Yes	No

28 Do you feel that reporting to occupational health is too time consuming

Yes	No

29 Would you recommend to any of your colleagues that taking HIV PEP after exposure is not necessary?

Yes	No	Unsure

Thank you for taking the time to participate in this study.

Instructions to authors

Journal: Southern African Journal of Infectious Disease

From: https://sajid.co.za/index.php/sajid/pages/view/submission-guidelines#part_1

Title

The article's full title should contain a maximum of 95 characters (including spaces).

Abstract

The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of four paragraphs labelled Background, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction

The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design

This must address the following:

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- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
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Results

Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion

The discussion section should address the following four elements:

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- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
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Conclusion

Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements

Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

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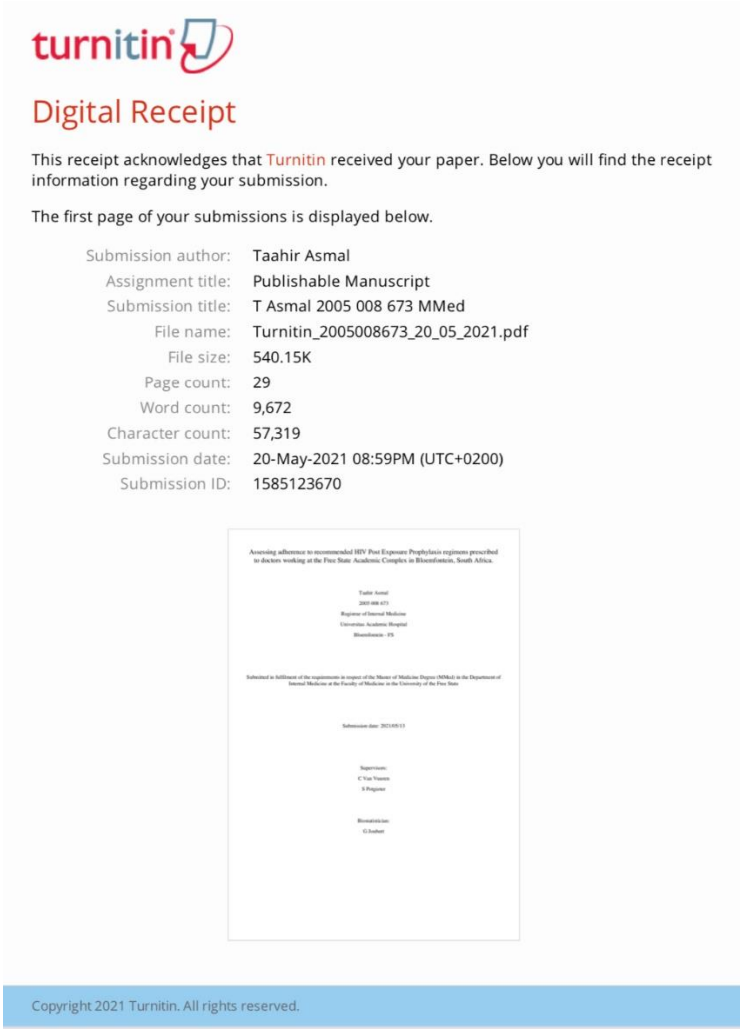

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