Factors Associated with Loss to Follow-up After Occupational HIV Exposure among Health Care Workers Attending the Groote Schuur Hospital Occupational Health Clinic

NECTARIOS SOPHOCLES PAPAVARNAVAS

PPVNEC001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

Master of Medicine (MMed) in Medicine

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of Submission: 15/06/2017

Supervisor: Prof G Maartens

Department of Medicine

University of Cape Town

Table of Contents

Abstract 6
Background 6
Methods 6
Results 6
Discussion 6
Conclusion 7
Acknowledgements *8*
Dedication *8*
List of tables and figures *9*
Acronyms and abbreviations *10*
Glossary of terms *11*

Chapter 1: background and literature review 12
Background 13
Introduction *13*
Global burden *13*
Background to HIV post-exposure prophylaxis *13*
Efficacy of PEP *14*
History of PEP *15*
Literature review 15
Objectives of literature review: *15*
Literature search strategy: *16*
Attendance to visits *16*
Variables and relationship to loss to follow-up *18*
Underreporting *21*
Future areas of research *21*
Conclusion *22*
References 23

Chapter 2: Publication ready manuscript 35
Abstract 37
Background *37*
Methods *37*
Results *37*
Conclusion *38*
Background 39
Methods 40
Study setting *40*
Study design *40*
Outcomes *41*
Data collection *41*
Study population *41*
Inclusion criteria *41*
Exclusion criteria *42*
Sample size estimation *42*
Statistical analysis *42*
Results 43
Discussion 44
Conclusion 46
Declarations 46

References 47
Chapter 3: Appendices 56
Protocol 57
Published article 77
Instructions for authors (AIDS Research and Therapy)–abbreviated 85
DPTC approval 94
Ethics approval 96

Declaration

I, NS Papavarnavas, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 14/08/2017

ABSTRACT

Background

There is limited data on factors associated with loss to follow-up (LTFU) of health care workers (HCWs) following occupational exposure to HIV, and most studies were conducted in an era when poorly tolerated antiretrovirals (ART) like zidovudine were used.

Methods

A retrospective cohort study was conducted of HCWs attending a referral hospital's Occupational Health Clinic (OHC) in Cape Town, South Africa, for post-exposure prophylaxis (PEP) during a period when tenofovir (TDF) was available. Data was obtained from an existing database maintained by the OHC.

Our primary outcome was to identify factors associated with LTFU at the 3-month visit, with secondary outcomes evaluating factors associated with LTFU at the 6-week and 6-months visits. We selected 7 variables a priori for our logistic regression model and ensured there were at least 10 outcome events per variable to minimize bias.

Results

Two hundred and ninety-three folders were evaluated for descriptive analysis. LTFU worsened with successive visits: 36% at 6 weeks, 60% at 3 months, and 72% at 6 months. In multivariate analysis at the 3-month visit LTFU was associated with age (adjusted odds ratio (aOR), 0.6 per 10-year increase [95% CI, 0.5 to 0.9]), HCW category of doctor (aOR 2.7 [95% CI, 1.3 to 5.5]), and time from exposure to receiving PEP of more than 24 hours (aOR 5.9 [95% CI, 1.3 to 26.9]).

Discussion

Our finding that LTFU increases with successive visits is consistent with other studies. It is believed higher LTFU in younger HCWs may be related to the greater change and instability they experience in their younger years.

Doctors are more likely to be LTFU than other HCWs which could be related to concerns of confidentiality in performing HIV testing at their facility. Additionally, doctors may be making their own assessments of the risk of exposure. Lastly, doctors may be submitting their own blood samples for HIV testing instead of attending the OHC.

One study showed longer time from exposure to receiving PEP was not associated with attendance of visits, but we showed this did influence LTFU at the 3-month visit. This could be explained by HCWs who present after 24 hours having a perceived lower benefit from PEP.

Newer studies have shown that completion of PEP is based on the tolerability of ART and not on whether dual or triple therapy are used. This could explain why in our cohort there was no correlation between type of ART and LTFU.

There is literature to support increased attendance of follow-up visits by contacting HCWs by telephone or mail. Furthermore, the WHO has recently advised the final follow-up visit to be at 3 months rather than 6 months. We suspect with fewer visits, there may be less LTFU.

Conclusion

We identified factors associated with LTFU of HCWs after occupational HIV exposure, which could be used to target interventions to improve follow-up.

Acknowledgements

Special thanks to my supervisor Prof Gary Maartens for his continued support, leadership, patience and inspiration. A big thank you to Mrs Kathryn Manning for assistance with data analysis and preparation of the manuscript. This MMed would not have been possible without permission and assistance from Ms Milah Govender, Dr Fahd Conrad and their health care team. I am grateful for the time and effort the health care workers in the Occupational Health Clinic have put in to maintain the database. Furthermore, a special thanks to the librarians at the University of Cape Town for their teaching and assistance with literature searching.

Dedication

I would like to dedicate my protocol to my father Lakis, my mother Dee, and to my friends Prabash and Lynelle for all their continued support and encouragement.

List of tables and figures

Table 1. Articles identified from various databases 31

Figure 1. PRISMA flow diagram 32

Table 2. Studies looking at post-exposure prophylaxis across the globe 33

Figure 2. Occupational Health Clinic Protocol 34

Figure 3. Flow chart illustrating data set of health care workers chosen for analysis 51

Table 3: Baseline characteristics and follow-up of 293 health care workers with occupational exposure 52

Table 4: Variables associated with loss to follow-up at 3 months 53

Table 5: Variables associated with loss to follow-up at 6 weeks and 6 months 54

Figure 4. Percentage Loss to follow-up (LTFU) by number of visits of various health care worker categories 55

Acronyms and abbreviations

ART:	antiretroviral therapy
ATV/r:	atazanavir/ritonavir
CDC:	Centre for Disease Control and Prevention
GSH:	Groote Schuur Hospital
F/u:	follow-up
HIV:	Human Immunodeficiency Virus
HCW:	health care worker
LPV/r:	lopinavir/ritonavir
LTFU:	lost to follow-up
MeSH:	medical subject headings
ND:	not documented
PCS:	prospective cohort study
PEP:	post-exposure prophylaxis
RAL:	raltegravir
RCS:	retrospective cohort study

SIV:	Simian Immunodeficiency Virus
TDF:	tenofovir disoproxil fumarate
USA:	United States of America
WHO:	World Health Organization

Glossary of terms

Health care worker: all persons who work in a health care facility whom may be exposed to: infectious body fluids and tissue materials, or whom may come into contact with contaminated supplies, environmental surfaces or equipment. (1)

Source: the patient from whom the health care worker was exposed to.

Post-exposure prophylaxis: represents the use of antiretrovirals for the prevention of HIV infection in those exposed to a potential HIV source. (2)

Mucocutaneous exposure: exposure of infectious material to non-intact skin, or mucus membranes. (3)

Percutaneous exposure: is an exposure to infectious material with a needle, or sharp object. (3)

Seroconversion: the period in time in which HIV-antibodies begin to develop to circulating HIV. (4)

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

Background

Introduction

Health care workers are at risk of developing infectious diseases from being exposed to occupational infectious material, with PEP as an important means of preventing HIV seroconversion among HCWs exposed to the virus. There are many other infectious diseases that HCWs are exposed to, but in this literature review we will concentrate on HIV only. Anecdotally a large proportion of HCWs are LTFU at various visits. We hope to understand the factors that are associated with LTFU and the interventions that could decrease LTFU.

Global burden

HIV is a worldwide problem with 2.1 million new HIV infections reported in 2015, bringing the total number of people living with HIV to around 36 million. (5) South Africa currently has 7.03 million people living with HIV which equates to 12.7% of the population. (6) Furthermore, a study performed in a district hospital in Cape Town, South Africa, described 60% of their admissions were from HIV seropositive patients. (7) We can probably assume that a large proportion of these HIV infected individuals' will at some point in their lives come into contact with HCWs.

The World Health Organization (WHO) in 2002 estimated 3 million occupational HIV percutaneous exposures occur among 35 million HCWs annually, with 90% of exposures occurring in resource limited settings. Furthermore, it is estimated that worldwide 500 HCW HIV seroconversions occur on an annual basis. (8) These estimates are far smaller in developed countries. (1)

Background to HIV post-exposure prophylaxis

Immunological understanding of HIV is important in order to appreciate the importance of PEP. It is believed the administration of PEP will hinder HIV replication and thus prevent the development of systemic infection. The dendritic cells of the mucosa are the initial site for HIV-infection and in a primate model with Simian

Immunodeficiency Virus (SIV) infection the virus remains in the dendritic cells for 24 hours before migrating to the regional lymph nodes for presentation to the T-lymphocytes. (9, 10) After the regional lymph nodes are infected, dissemination into peripheral blood occurs within 5 days. (10) PEP is able to target the above steps, in order to prevent infection of the T-lymphocytes by HIV, and furthermore allow time for the immune system to develop cellular immunity against HIV. (11)

Efficacy of PEP

Animal models have shed light onto the importance of adherence to PEP. An animal model by Tsai et al, (12) demonstrated that sub-optimal duration of treatment and delay in initiating treatment are associated with PEP failure. This experiment, involving macaque monkeys inoculated with SIV, illustrated 100% efficacy if PEP was started within 24 hours; 50% efficacy if started after 48 hours, and 25% efficacy if started after 72 hours. Furthermore, if PEP was given within 24 hours, but only continued for 3 days, all of the monkeys seroconverted; if 10 days of treatment was given, half seroconverted; while if a full 28-day regimen was prescribed, all macaques were protected. (11, 12) This is clinically relevant in educating HCWs of the importance of beginning PEP as soon as possible and to ensure adherence to PEP is maintained for the full 28 days. A more recent study, (13) involving rhesus monkeys infected with SIV, and ART begun at different time points of 3,7,10 and 14 days, illustrated concerning findings that have implications for ART in PEP. Monkeys infected at day 3 had no detectable viraemia, but infection of lymphoid tissue was noted in all 4 monkeys after 3 days post inoculation with SIV. This illustrates that early seeding of the virus into lymphoid tissue can occur in the absence of viraemia. However, one needs to take into account these studies are based on animal models with SIV infection. Furthermore, studies of this nature will probably never be performed on humans due to ethical considerations.

A study by Cardo et al, (14) illustrated zidovudine monotherapy was 81% effective in preventing occupational HIV seroconversion. However, one needs to take into account the study was a case-control retrospective study with small numbers of HCWs. (11) Furthermore, with the role out of more ART into the general population,

exposure to resistant virus is becoming a reality and the need to prescribe individualized ART regimens is essential. (15) Additionally, there are case reports of occupational HIV infection due to resistant HIV, even after ART was prescribed to HCWs. (16-18)

History of PEP

PEP has come a long way since the since the 1980's. Initially, the PEP regimen of choice included monotherapy, zidovudine 100 mg four-hourly. However, the Centre for Disease Control and Prevention (CDC) only recommended the use of PEP in 1996. (1, 19) Currently, countries worldwide are using dual or triple ART for PEP, but the literature to support its use in occupational exposures is lacking. (20) However, prevention-of-mother-to-child-transmission studies have demonstrated superiority when using triple ART when compared with monotherapy ART. (21)

Data from the United States of America (USA) between 1985 and 2013 showed 57 cases of confirmed HIV seroconversion among HCWs and a further 138 potential cases. (22) The last reported case of HIV seroconversion in the USA was in 2008, in which a laboratory worker developed HIV after working with an HIV-live-culture. Before 2008, the last reported case was in 1999. The decrease in number of HIV seroconversion can be attributed to: increased uptake of universal standard precautions instituted in 1995, increased PEP utilization, and training to reduce exposure to infectious material. (1)

Literature review

Objectives of literature review:

We aimed to identify factors associated with LTFU among HCWs who are exposed to HIV infection in the occupational setting. This literature review will look at the following factors: age, sex, HCW category, type of exposure, source patient HIV status, type of ART, and time from exposure to receiving PEP.

Literature search strategy:

Articles only in English were considered. The following keywords and medical subject headings (MeSH) terms were utilized as part of the search strategy in: Pubmed, EBSCO Host (CINAHL, Academic Search Premier, African-wide Information, and Medline), Scopus, and Cochrane Library:

- (HIV OR Human Immunodeficiency Virus) AND exposure
  AND
- post-exposure prophylaxis OR postexposure prophylaxis OR post exposure prophylaxis
  AND
- Health personnel OR health care workers OR health care providers
  AND
- Lost to follow up OR loss to follow up OR lost to follow-up OR loss to follow-up OR adherence OR patient compliance OR attendance OR follow up
  NOT
- pre-exposure

Table 1 illustrates articles identified from the various databases. Furthermore, figure 1 illustrates the number of studies included and excluded from the literature review.

Attendance to visits

Attendance of HCWs to follow-up visits after occupational exposure to HIV has been highly variable, ranging from 0 to 98.9% in observational studies, table 2. (23-33) One study,(26) showed increased attendance to follow-up visits at the 6-month visit compared to the 3-month visit. This could be explained by the perception that HCWs may see the 6-month visit as more important compared with the 3-month, in ruling out HIV seroconversion. However, other studies have shown attendance of visits decreases with time. (24, 28, 29, 32)

We could only identify three studies that included more than 10 HCWs in their cohort that evaluated factors associated with attendance to follow-up, with inconsistency in the findings. (25, 32, 33)

Variables and relationship to loss to follow-up

We hypothesized the following variables would be associated with LTFU: age, sex, type of HCW, type of exposure, source patient's HIV status, type of ART, and time from exposure to receiving PEP.

Age

Studies have shown the majority of occupational exposures to infectious materials occur in younger HCWs who are in their twenties to thirties. (26, 29, 31, 33-35) This is probably related to a large proportion of HCWs being students or doctors, who are in their first year of practice, and are probably inexperienced and more likely to be involved in occupational exposures. (27, 29, 36, 37) Furthermore, it has been noted that younger patients are more likely to be LTFU, (38-40) which may be related to the greater change and instability they experience in their younger years. (41) Taking into account the above literature we postulated that young HCWs would be more likely to be LTFU.

Sex

There is little in the literature indicating which sex is more likely to be LTFU with occupational HIV exposure. Escudero et al (32) showed women were more likely to attend follow-up visits compared with men. Hence, we postulated men to be more likely to be LTFU.

Category of health care worker

Students and doctors are often involved in invasive medical procedures which places them at risk of being exposed to infectious material. (27, 29, 31, 37) One study, (26) looked at category of HCW and showed: 32% of doctors, and 28% of interns did not attend the 3-month follow-up visit, but that nurses were more likely to attend follow-up visits. However, it is difficult to interpret the data, because the number of nurses in the study was small. This is in contrast to Gutierrez et al (25) who showed cleaning personnel were more likely to be LTFU. Again, it is difficult to interpret the data, because there were only 2 groups in the study: 'Cleaning personnel' and 'Other

HCWs'. Two other studies, (32, 33) found type of HCW category did not influence attendance to follow-up.

We postulated LTFU would be greater in doctors because of a number of factors. First, the ease with which doctors can submit their own blood samples for HIV testing instead of attending the OHC. One study, (42) showed a large proportion of HCWs obtained HIV testing outside of the facility where they worked. Reason cited for the above finding, was concerns surrounding confidentiality of testing for HIV at the facility. Second, doctors may be making their own assessment of the severity of the exposure and may deem it unnecessary to follow-up. (43)

Type of exposure

Not all exposures carry the same risk of acquiring HIV. Risk differs depending on the type of exposure: hollow-bore, solid sharp or mucocutaneous. Risk of HIV seroconversion after percutaneous exposure is estimated to be around 0.23% with no PEP. (44, 45) However, there are a number factors associated with a greater risk of acquiring HIV after percutaneous exposure: increased depth of injury, hollow bore needle, higher source patient's HIV viral load, increased inoculum, a device previously inserted into the source patient's artery or vein, and the absence of personal protection use such as gloves. (46, 47) Gloves have been shown to decrease blood volume transmission by 46-86%. (46) Risk due to mucocutaneous exposure is thought to be extremely low. (44) Other sources have evaluated the risk to be around 0.03%. (11, 48) Percutaneous exposure to HIV has an incidence of around 70 to 97%, while mucocutaneous exposure is around 3 to 8%. (33, 35, 36, 49) One study, (26) showed follow-up increased in those with more severe exposures. However, Escudero et al, (32) showed this had no influence. We postulated that those exposed to more severe exposures would be less likely to be LTFU, due to increased possibility of HIV seroconversion.

HIV source status

Literature surrounding HIV source status and occupational exposure is conflicting, with one study showing source HIV status was not related to attendance of follow-

up visits, (25) while another showed positive serological status was associated with improved follow-up. (32) One would expect HCWs exposed to an HIV seropositive source would be less likely to be LTFU compared to those where the source patient's status is unknown, because of the real risk of contracting HIV from a seropositive source. Additionally, there is literature suggesting transmitted drug resistant HIV is increasing in South Africa. (50) It is unknown what the implications of exposure to drug resistant HIV would have on LTFU.

Antiretroviral therapy regimen

It has been shown that HIV seronegative HCWs suffer more side effects than HIV seropositive patients on the same regimen. (51) One study showed ART use for PEP was associated with a six times increased risk of side effects and eight times increased chance of discontinuing therapy when compared to HIV seropositive patients. (52) There are a number of studies which report that dual therapy is better tolerated than triple therapy. (53, 54) However, many of these studies include ART that are no longer used, due to their side effect profiles. Newer studies have shown that completion of PEP is based on the tolerability of ART and not on whether dual or triple therapy are used. (48, 55) Furthermore, one study, (56) found that raltegravir (RAL), used as the third agent in PEP, was better tolerated than lopinavir/ritonavir (LPV/r). In well-resourced areas RAL is the third drug of choice in PEP regimens due to its favourable tolerability profile. (57) To the best of our knowledge there are no studies looking at the effect of ART on occupational PEP with regard to LTFU. We aimed to evaluate the effect dual and triple therapy would have on LTFU.

During the study period the Department of Health South African national guidelines for PEP recommended the use of TDF and emtricitabine for exposures presenting within 72 hours. The policy of adding a third antiretroviral (usually a boosted protease inhibitor) was changed during the study period: initially this was added only for high risk exposures, but subsequently this was added for all exposures. Figure 2 shows the protocol followed by the OHC.

Time of exposure to receiving PEP

PEP is rarely prescribed to those that present after 72 hours, because of poor efficacy. (12) However, most HCW present within the first few hours of exposure, allowing the difficult decision of when to prescribe ART to those late presenters to be uncommon occurrence. (27, 42) One would expect, HCWs seeking medical intervention earlier are likely to have better insight into the benefits of PEP, resulting in improved follow-up. However, a study by Escudero et al (32) showed time from exposure to receiving PEP did not influence attendance of visits.

Underreporting

Underreporting may affect the true incidence of the number of exposures and hence may affect the above aforementioned variables. Underreporting of exposures ranges from 35% to 78%. The causes of underreporting are due to the following: exposure being perceived as low risk for transmission of HIV, lack of knowledge of severity of exposure, fear of testing seropositive for HIV, concerns surrounding the confidentiality of HIV testing at the facility, HCWs being unaware of facilities available for reporting, lack of support from the hospital, unwillingness to take ART, inconvenience of follow-up and time constraints such as the procedure of reporting the exposure is time consuming. (29, 37, 42, 43, 58-62)

Future areas of research

Some HCWs may experience severe distress and fear of seroconverting after being exposed to infectious material, which may result in less LTFU, while others may feel a few days of ART will be adequate to prevent seroconversion, which may result in greater LTFU. These different circumstances necessitate adequate counselling. This may include counselling regarding exposure risk, coping mechanisms, donation of organs or blood, breastfeeding, use of condoms, and the risks and benefits of PEP. (48) Unfortunately with busy clinics, one may not spend adequate time on counselling. This may be improved by developing protocols with checklists to confirm that all of the above factors are discussed with the HCW, as this could potentially affect LTFU.

There is currently little literature looking at the methods of decreasing LTFU in HCWs who present for PEP. However, Escudero et al (32) implemented a protocol in which the HCWs were contacted by telephone or mail. They showed attendance increased from 33.2% to 54%. Another study, (29) suggested increasing awareness through advertising of occupational health facilities and active tracing of those HCWs that are LTFU. One study, (60) suggested adherence to follow-up could be improved with fewer follow-up visits. The WHO has recently advised the final follow-up visit should be at 3 months instead of 6 months. (63) Furthermore, Gaines et al (64) suggested the last follow-up visit should be at 6 weeks if laboratory 4th generation HIV ELISA tests are used, and 8 weeks if 4th generation rapid HIV tests are used. A case report from 1990 describes a HCW who tested HIV seropositive after occupational exposure between eight to nine months. (65) However, 4th generation HIV ELISA tests were not available in the 1990's, meaning our new generation tests are more likely to identify HIV earlier.

We will advise making the final follow-up visit at 3 months. Furthermore, in the era of smart phones, one can set reminders to phones to attend visits. Furthermore, computerized text messages can be sent to HCWs reminding them of their upcoming visit. Studies will need to be performed to see if the above methods lead to decreased LTFU.

Conclusion

Post exposure prophylaxis treatment regimens have significantly improved with time, but concerns regarding management such as high rates of LTFU have been neglected and is an area that requires particular attention. There is little data looking at the factors surrounding LTFU, and the data identified have been inconsistent. It is hoped that this retrospective cohort study will shed light on these factors so as to identify targeted interventions to decrease LFTU.

References

(Vancouver style)

1. Joyce MP, Kuhar D, Brooks JT. Notes from the field: occupationally acquired HIV infection among health care workers - United States, 1985-2013. MMWR Morb Mortal Wkly Rep. 2015;63(53):1245-6.
2. Moorhouse M, Bekker LG, Black V, Conradie F, Harley B, Howell P, et al. Guideline on the management of occupational and non-occupational exposure to the human immunodeficiency virus and recommendations for post-exposure prophylaxis: 2015 update S Afr J HIV Med. 2016;16(1):1-14.
3. Centers for Disease Control and Prevention [internet]. Infection, Frequently Asked Questions - Bloodborne Pathogens — Occupational Exposure. https://www.cdc.gov/oralhealth/infectioncontrol/faq/bloodborne_exposures.htm. Accessed 22 Feb 2017.
4. Cohen MS, Gay CL, Busch MP, Hecht FM. The detection of acute HIV infection. J Infect Dis. 2010;202 Suppl 2:S270-7.
5. United Nations Program on HIV/AIDS. Global AIDS Update.Switzerland, United Nations Program on HIV/AIDS. 2016. http://www.who.int/hiv/pub/arv/global-aids-update-2016-pub/en/. Accessed 21 Jun 2016.
6. Statistics South Africa. Statistical release, mid-year population estimates 2016. http://www.statssa.gov.za/?page_id=1854&PPN=P0302 (2016). Accessed 22 Jan 2017.
7. Meintjes G, Kerkhoff AD, Burton R, Schutz C, Boulle A, Van Wyk G, et al. HIV-Related Medical Admissions to a South African District Hospital Remain Frequent Despite Effective Antiretroviral Therapy Scale-Up. Medicine (Baltimore). 2015;94(50):e2269.
8. World Health Organization. The world health report 2002, chapter 4: reducing risks, promoting healthy life. http://www.who.int/whr/2002/chapter4/en/index8.html (2002). Accessed 21 Mar 2016
9. Blauvelt A. The role of skin dendritic cells in the initiation of human immunodeficiency virus infection. The American journal of medicine. 1997;102(5):16-20.

10. Spira AI, Marx PA, Patterson BK, Mahoney J, Koup RA, Wolinsky SM, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. J Exp Med. 1996;183(1):215-25.
11. Beekmann SE, Henderson DK. Prevention of human immunodeficiency virus and AIDS: postexposure prophylaxis (including health care workers). Infect Dis Clin North Am. 2014;28(4):601-13.
12. Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofberger N, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol. 1998;72(5):4265-73.
13. Whitney JB, Hill AL, Sanisetty S, Penaloza-MacMaster P, Liu J, Shetty M, et al. Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys. Nature. 2014;512(7512):74-7.
14. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med. 1997;337(21):1485-90.
15. Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated US Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep. 2005 Sep 30;54(RR-9):1-7.
16. Beltrami EM, Luo CC, de la Torre N, Cardo DM. Transmission of drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. Infect Control Hosp Epidemiol. 2002;23(6):345-8.
17. Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. J Infect. 2001;43(1):12-5.
18. Lopez-Lopes GI, Coelho LP, Hornke L, Volpato AP, Lopercio AP, Cabral GB, et al. Transmission of a multidrug-resistant HIV-1 from an occupational exposure, in Sao Paulo, Brazil. AIDS. 2015;29(12):1580-3.
19. Polder JA, Bell DM, Baker E, Castro K, Chamberland M, Curran J, et al. Public Health Service Statement on Management of Occupational Exposure to

Human Immunodeficiency Virus, Including Considerations Regarding Zidovudine Postexposure Use. MMWR Morb Mortal Wkly Rep. 1990;39(RR-1):1-14.
20. Siegfried N, Beanland RL, Ford N, Mayer KH. Formulating the Future Research Agenda for Postexposure Prophylaxis for HIV: Methodological Challenges and Potential Approaches. Clin Infect Dis. 2015;60 Suppl 3:S205-11.
21. de Vincenzi I. Triple antiretroviral compared with zidovudine and single-dose nevirapine prophylaxis during pregnancy and breastfeeding for prevention of mother-to-child transmission of HIV-1 (Kesho Bora study): a randomised controlled trial. Lancet Infect Dis. 2011;11(3):171-80.
22. Do AN, Ciesielski CA, Metler RP, Hammett TA, Li J, Fleming PL. Occupationally acquired human immunodeficiency virus (HIV) infection: national case surveillance data during 20 years of the HIV epidemic in the United States. Infect Control Hosp Epidemiol. 2003;24(2):86-96 11p.
23. de la Tribonniere X, Dufresne MD, Alfandari S, Fontier C, Sobazek A, Valette M, et al. Tolerance, compliance and psychological consequences of post-exposure prophylaxis in health-care workers. Int J STD AIDS. 1998;9(10):591-4.
24. Pungpapong S, Phanuphak P, Pungpapong K, Ruxrungtham K. The risk of occupational HIV exposure among Thai healthcare workers. Southeast Asian J Trop Med Public Health. 1999;30(3):496-503.
25. Gutierrez EB, Heloísa Lopes M, Shikanai Yasuda MA. Accidental exposure to biological material in healthcare workers at a university hospital: Evaluation and follow-up of 404 cases. Scand J Infect Dis. 2005;37(4):295-300.
26. Maiphetlho L. An Analysis of Needle-stick and Splash Exposures Among Health Care Worker and Students at Groote Schuur Hospital: 2001-2005. University of Cape Town. 2008. http://open.uct.ac.za/handle/11427/3422. Accessed 16 Dec 2016.
27. Jayanth ST, Kirupakaran H, Brahmadathan KN, Gnanaraj L, Kang G. Needle stick injuries in a tertiary care hospital. Indian J Med Microbiol. 2009;27(1):44-7.
28. Siika AM, Nyandiko WM, Mwangi A, Waxman M, Sidle JE, Kimaiyo SN, et al. The structure and outcomes of a HIV postexposure prophylaxis program in a high HIV prevalence setup in western Kenya. J Acquir Immune Defic Syndr. 2009;51(1):47-53.
29. van der Maaten GC, Nyirenda M, Beadsworth MJ, Chitani A, Allain T, van Oosterhout JJ. Post exposure prophylaxis of HIV transmission after occupational

injuries in Queen Elizabeth Central Hospital, Blantyre, Malawi, 2003 - 2008. Malawi Med J. 2010;22(1):15-9.

30. Olowookere SA, Fatiregun AA. Human immunodeficiency virus postexposure prophylaxis at Ibadan, Nigeria. J Int Assoc Physicians AIDS Care (Chic). 2010;9(3):187-90.

31. Onyedum CC, Chukwuka C, Iyoke CA, Omotola OF. HIV postexposure prophylaxis (PEP) in a nigerian tertiary health institution. J Int Assoc Physicians AIDS Care (Chic). 2011;10(3):171-5.

32. Escudero DV, Furtado GH, Medeiros EA. Healthcare worker adherence to follow-up after occupational exposure to blood and body fluids at a teaching hospital in Brazil. Ann Occup Hyg. 2015;59(5):566-71.

33. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Outcomes of a postexposure prophylaxis program at the Korle-Bu Teaching Hospital in Ghana: a retrospective cohort study. Journal of the International Association of Providers of AIDS Care. 2015;14(6):544-52.

34. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Adverse events and adherence to HIV post-exposure prophylaxis: a cohort study at the Korle-Bu Teaching Hospital in Accra, Ghana. BMC Public Health. 2015;15:573.

35. Sin WW, Lin AW, Chan KC, Wong KH. Management of health care workers following occupational exposure to hepatitis B, hepatitis C, and human immunodeficiency virus. Hong Kong Med J. 2016;22(5):472-7.

36. Aggarwal V, Seth A, Chandra J, Gupta R, Kumar P, Dutta AK. Occupational exposure to human immunodeficiency virus in health care providers: a retrospective analysis. Indian J Community Med. 2012;37(1):45-9.

37. Karstaedt AS, Pantanowitz L. Occupational exposure of interns to blood in an area of high HIV seroprevalence. S Afr Med J. 2001;91(1):57-61.

38. Milne V, Kearns R, Harrison A. Patient age, ethnicity and waiting times determine the likelihood of non-attendance at a first specialist rheumatology assessment. Int J Rheum Dis. 2014;17(1):19-25.

39. Corfield L, Schizas A, Noorani A, Williams A. Non-attendance at the colorectal clinic: a prospective audit. Ann R Coll Surg Engl. 2008;90(5):377-80.

40. Hynes L, Byrne M, Dinneen SF, McGuire BE, O'Donnell M, Mc Sharry J. Barriers and facilitators associated with attendance at hospital diabetes clinics among

young adults (15-30 years) with type 1 diabetes mellitus: a systematic review. Pediatr Diabetes. 2016;17(7):509-18.

41. Arnett JJ. Emerging adulthood. A theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469-80.

42. Kassa G, Selenic D, Lahuerta M, Gaolathe T, Liu Y, Letang G, et al. Occupational exposure to bloodborne pathogens among health care workers in Botswana: Reporting and utilization of postexposure prophylaxis. Am J Infect Control. 2016 Aug;44(8):879-85.

43. Elmiyeh B, Whitaker IS, James MJ, Chahal CA, Galea A, Alshafi K. Needle-stick injuries in the National Health Service: a culture of silence. J R Soc Med. 2004;97(7):326-7.

44. Centers for Disease Control and Prevention. Occupational HIV transmission and prevention among health care workers. 2015. http://www.cdc.gov/hiv/workplace/occupational.html. Accessed 17 Mar 2016.

45. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014;28(10):1509-19.

46. Mast ST, Woolwine JD, Gerberding JL. Efficacy of gloves in reducing blood volumes transferred during simulated needlestick injury. J Infect Dis. 1993;168(6):1589-92.

47. Update: provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV. MMWR Morb Mortal Wkly Rep. 1996;45(22):468-80.

48. Henderson DK. Management of needlestick injuries: a house officer who has a needlestick. JAMA. 2012;307(1):75-84.

49. Serdar T, Derek L, Unic A, Marijancevic D, Markovic D, Primorac A, et al. Occupational exposures in healthcare workers in University Hospital Dubrava-10 year follow-up study. Cent Eur J Public Health. 2013;21(3):150-4.

50. Manasa J, Danaviah S, Lessells R, Elshareef M, Tanser F, Wilkinson E, et al. Increasing HIV-1 Drug Resistance Between 2010 and 2012 in Adults Participating in Population-Based HIV Surveillance in Rural KwaZulu-Natal, South Africa. AIDS Res Hum Retroviruses. 2016;32(8):763-9.

51. Cai J, Xiao J, Zhang Q. Side effects and tolerability of post-exposure prophylaxis with zidovudine, lamivudine, and lopinavir/ritonavir: a comparative study with HIV/AIDS patients. Chin Med J. 2013;127(14):2632-6.

52. Quirino T, Niero F, Ricci E, Pusterla L, Carradori S, Gabbuti A, et al. HAART tolerability: post-exposure prophylaxis in healthcare workers versus treatment in HIV-infected patients. Antivir Ther. 2000;5(3):195-7.
53. Puro V. Post-exposure prophylaxis for HIV infection. Italian Registry of Post-Exposure Prophylaxis. Lancet. 2000;355(9214):1556-7.
54. Bassett IV, Freedberg KA, Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. Clin Infect Dis. 2004;39(3):395-401.
55. McAllister J, Read P, McNulty A, Tong WW, Ingersoll A, Carr A. Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence. HIV Med. 2014;15(1):13-22.
56. Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus raltegravir each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. J Antimicrob Chemother. 2016;71(7):1987-93.
57. Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis. 2015;60 Suppl 3:S170-6.
58. Voide C, Darling KE, Kenfak-Foguena A, Erard V, Cavassini M, Lazor-Blanchet C. Underreporting of needlestick and sharps injuries among healthcare workers in a Swiss University Hospital. Swiss Med Wkly. 2012;142:w13523.
59. Rajkumari N, Thanbuana BT, John NV, Gunjiyal J, Mathur P, Misra MC. A prospective look at the burden of sharps injuries and splashes among trauma health care workers in developing countries: true picture or tip of iceberg. Injury. 2014;45(9):1470-8.
60. Schmid K, Schwager C, Drexler H. Needlestick injuries and other occupational exposures to body fluids amongst employees and medical students of a German university: incidence and follow-up. J Hosp Infect. 2007;65(2):124-30.
61. Chauvin A, Hutin A, Leredu T, Plaisance P, Pateron D, Yordanov Y. Accidental blood exposures among emergency medicine residents and young physicians in France: a national survey. Intern Emerg Med. 2017;12(2):221-7.

62. Lin C, Li L, Wu Z, Wu S, Jia M. Occupational exposure to HIV among health care providers: a qualitative study in Yunnan, China. J Int Assoc Physicians AIDS Care (Chic). 2008;7(1):35-41.
63. World Health Organization. Guidelines on Post-Exposure Prophylaxis for HIV and the Use of Co-Trimoxazole Prophylaxis for HIV-Related Infections Among Adults, Adolescents and Children: Recommendations for a Public Health Approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization. http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en/ (2014). Accessed 17 Sept 2016.
64. Gaines H, Albert J, Axelsson M, Berglund T, Gisslen M, Sonnerborg A, et al. Six-week follow-up after HIV-1 exposure: a position statement from the Public Health Agency of Sweden and the Swedish Reference Group for Antiviral Therapy. Infect Dis (London). 2016;48(2):93-8.
65. Ridzon R, Gallagher K, Ciesielski C, Ginsberg MB, Robertson BJ, Luo CC, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needle-stick injury. N Engl J Med. 1997;336(13):919-22.
66. Miceli M, Herrera F, Temporiti E, Li D, Vila A, Bonvehi P. Adherence to an occupational blood borne pathogens exposure management program among healthcare workers and other groups at risk in Argentina. Braz J Infect Dis. 2005;9(6):454-8.
67. Erhabor O, Ejele OA, Nwauche CA. Epidemiology and management of occupational exposure to blood borne viral infections in a resource poor setting: the case for availability of post exposure prophylaxis. Niger J Clin Pract. 2007;10(2):100-4.
68. Ko NY, Yeh SH, Tsay SL, Pan SM, Feng MC, Chiang MC, et al. Adherence to management after occupational exposure to bloodborne pathogen among health care workers in Taiwan. Am J Infect Control. 2009;37(7):609-11.
69. Davanzo E, Frasson C, Morandin M, Trevisan A. Occupational blood and body fluid exposure of university health care workers. Am J Infect Control. 2008;36(10):753-6.
70. Ko N, Yeh S, Tsay S, Ma H, Chen C, Pan S, et al. Intention to comply with post-exposure management among nurses exposed to blood and body fluids in

Taiwan: application of the theory of planned behaviour. J Hosp Infect. 2011;77(4):321-6.

71. Mehta A, Rodrigues C, Singhal T, Lopes N, D'Souza N, Sathe K, et al. Interventions to reduce needle stick injuries at a tertiary care centre. Indian J Med Microbiol. 2010;28(1):17-20.

72. Grime PR, Ris L, Binns C, Carruthers JR, Williams S. Pan-Thames survey of occupational exposure to HIV and the use of post-exposure prophylaxis in 71 NHS trusts. J Infect. 2001;42(1):27-32.

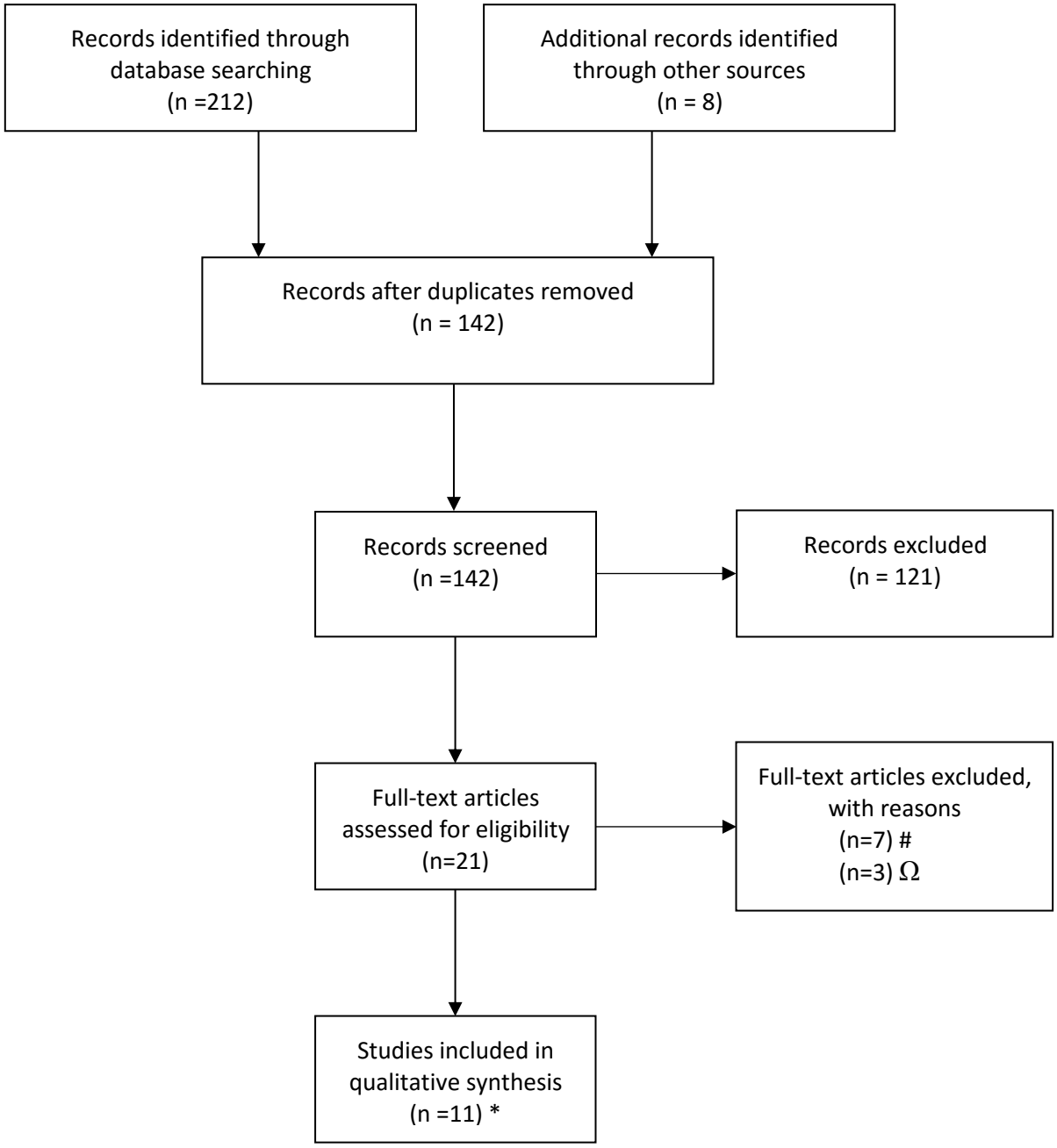
73. Van Oosterhout JJG, Nyirenda M, Beadsworth MBJ, Kanyangalika JK, Kumwenda JJ, Zijlstra EE. Challenges in HIV post-exposure prophylaxis for occupational injuries in a large teaching hospital in Malawi. Trop Doct. 2007;37(1):4-6.

Table 1. Articles identified from various databases		
Database searched	**Results#**	**Used***
Pubmed	92	9
Scopus	62	4
EBSCO host	46	0
Cochrane	12	0
Total	212	13

#Articles identified from the various databases.
*Articles used after screening for: duplicates and articles that were not pertinent to the study.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA flow diagram: Available from http://prisma-statement.org/



Articles with less than 10 HCWs exposed to HIV seropositive source, references: (59, 66-71)
Ω Articles with insufficient data looking at loss to follow-up, references: (60, 72, 73)
*Studies included are illustrated in table 2.

Table 2. Illustrating various studies that looked at post-exposure prophylaxis across the globe, including: sample size, study design, and their respective follow-up periods

Year	Site of study	Reference	Sample size (n)	Study design	6-week f/u (%)	3-month f/u (%)	6-month f/u (%)	Overall f/u (%)
2015	Ghana	(33)	289	RCS	87	75	62	ND
2015	Brazil#	(32)	612	PCS	ND	43.5	36.6	33.2 to 54*
2011	Nigeria ❑	(31)	105	RCS	ND	ND	ND	0
2010	Nigeria ❑	(30)	48	RCS	ND	ND	83.7	ND
2010	Malawi	(29)	162	RCS	ND	6.3	1.9	ND
2009	Kenya	(28)	91	RCS	32	ND	12	ND
2009	India	(27)	296	RCS	ND	ND	ND	98.9
2008	South Africa	(26)	441	RCS	ND	17	45	ND
2005	Brazil◉	(25)	57	RCS	ND	ND	ND	67
1999	Thailand	(24)	175	PCS	ND	65	63	ND
1998	France	(23)	16	RCS	ND	ND	ND	94

Abbreviations: f/u: follow-up, ND: not documented, RC: retrospective cohort study, PC: prospective cohort study.

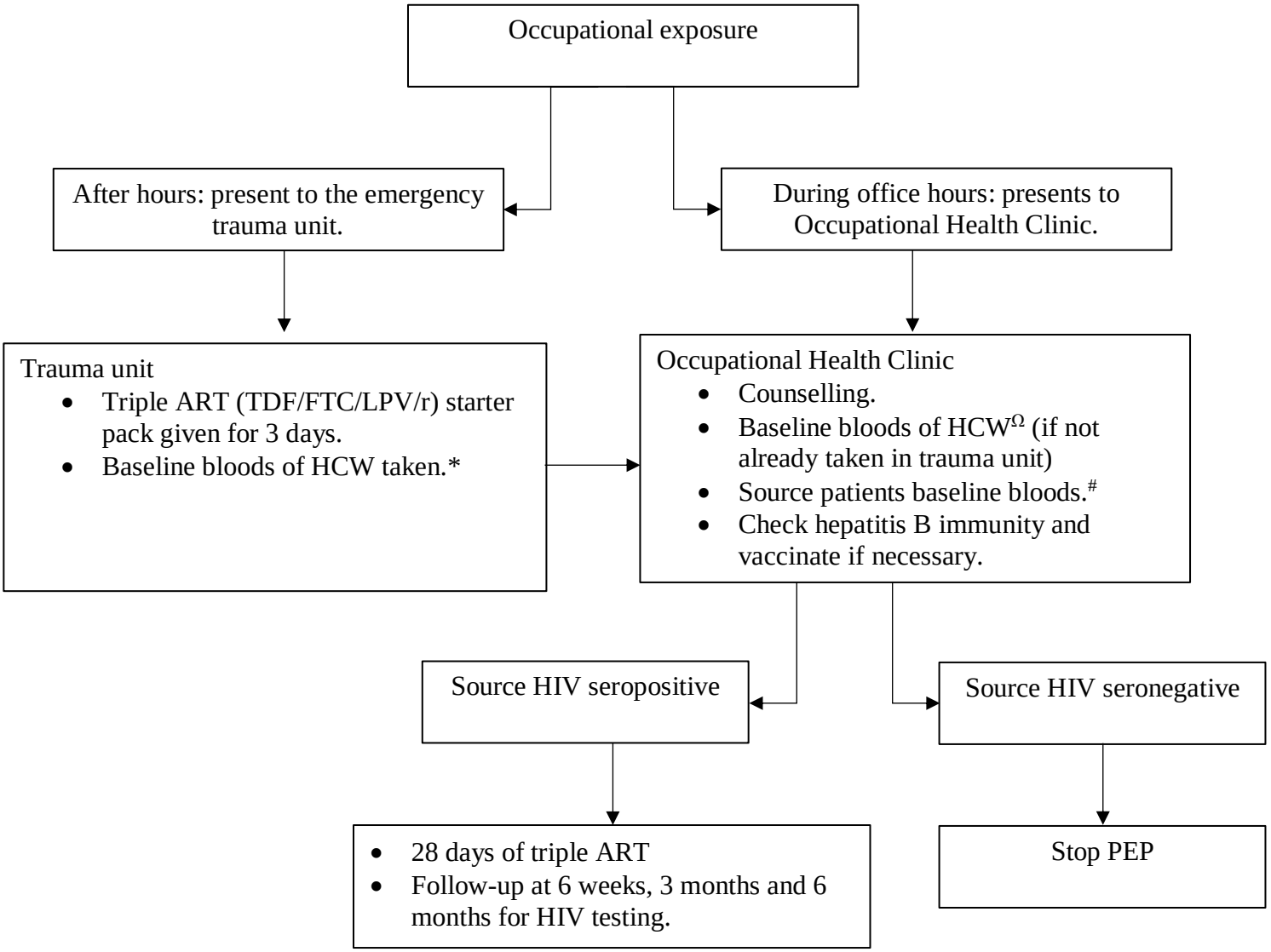
#Included those exposed to HIV, Hepatitis B virus, and Hepatitis C virus.

*Before and after the implementation of telephonic and mail reminders to health care workers of their upcoming visits.

❑Combination of post-exposure prophylaxis and non-occupational post-exposure prophylaxis cases.

◉Includes health care workers exposed to both HIV positive and unknown sources.

Figure 2. Occupational Health Clinic Protocol for health care workers exposed to potentially infectious material[$]



[$]Adapted from "The management and treatment of hospital staff who have been accidentally exposed to blood or body fluids," with permission from the Occupational Health Clinic.

*Baseline bloods include: 4th generation Roche COBAS HIV-1/2 Combo automated test with a confirmatory Siemens Integral 4th generation ELISA, Hepatitis B antibody titre, Hepatitis C antibody, full blood count, creatinine, and alanine aminotransferase.

ΩHCW: Health care worker.

#Source patients baseline bloods include: Hepatitis sAg, Hepatitis C antibody, HIV (if not already known), and in cases where the source is known to be HIV positive a CD4 and viral load are taken.

CHAPTER 2: PUBLICATION READY MANUSCRIPT

Factors Associated with Loss to Follow-up After Occupational HIV Exposure in Cape Town, South Africa: a Retrospective Cohort Study

Nectarios Sophocles Papavarnavas[1], Kathryn Manning[2], Fahd Conrad[3], Milah Govender[4], Gary Maartens[5]

[1]NP: Department of Medicine, Old Main Building, J – Floor, Groote Schuur Hospital, Observatory, Cape Town, South Africa, 7925

taripapas@yahoo.com

[2]KM: Department of Medicine, Old Main Building, J – Floor, Groote Schuur Hospital, Observatory, Cape Town, South Africa, 7925

kathryn.manning@uct.ac.za

[3]FC: Floor E11A, Management Suite, Groote Schuur Hospital, Main Road, Observatory, Cape Town, South Africa, 7925

Fahd.Conrad@westerncape.gov.za

[4]MG: Quality and Safety Unit, Groote Schuur Hospital, Main Road, Observatory, Cape Town, South Africa, 7925

miladevi.govender@westerncape.gov.za

Corresponding author: [5]GM: Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa 7925

gary.maartens@uct.ac.za

Factors Associated with Loss to Follow-up After Occupational HIV Exposure in Cape Town, South Africa: a Retrospective Cohort Study

Nectarios Sophocles Papavarnavas[1], Kathryn Manning[1], Fahd Conrad[2], Milah Govender[3], Gary Maartens[4]

Abstract

Background

There is limited data on factors associated with loss to follow-up (LTFU) of health care workers (HCWs) following occupational exposure to HIV, and most studies were conducted in an era when poorly tolerated antiretrovirals like zidovudine were used.

Methods

A retrospective cohort study was conducted of HCWs attending a referral hospital's Occupational Health Clinic in Cape Town, South Africa for post-exposure prophylaxis (PEP) during a period when tenofovir was available. Our primary outcome was LTFU at the 3-month visit. We selected 7 variables a priori for our logistic regression model and ensured there were at least 10 outcome events per variable to minimize bias.

Results

Two hundred and ninety-three folders were evaluated for descriptive analysis. LTFU worsened with successive visits: 36% at 6 weeks, 60% at 3 months, and 72% at 6 months. In multivariate analysis at the 3-month visit LTFU was associated with age (adjusted odds ratio (aOR), 0.6 per 10-year increase [95% CI, 0.5 to 0.9]), HCW category of doctor (aOR 2.7 [95% CI, 1.3 to 5.5]), and time from exposure to receiving PEP of more than 24 hours (aOR 5.9 [95% CI, 1.3 to 26.9]).

Conclusion

We identified factors associated with LTFU of HCWs after occupational HIV exposure, which could be used to target interventions to improve follow-up.

Keywords: loss to follow-up, post exposure prophylaxis, health care workers, HIV.

Word count: 3811

[4]Correspondence: gary.maartens@uct.ac.za
Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa
Full list of authors information is at end of article

Background

The World Health Organization (WHO) estimates 3 million occupational Human Immunodeficiency Virus (HIV) percutaneous exposures occur among 35 million healthcare workers (HCWs) annually, with 90% of exposures occurring in resource limited settings. [1] HCWs exposed to potentially infectious material from a source patient with HIV infection, or unknown HIV status, are offered post-exposure prophylaxis (PEP) if this is appropriate, and attend several follow-up visits for PEP toxicity monitoring and exclusion of HIV infection. Although HIV seroconversion following occupational exposure is uncommon, early diagnosis is critical as treatment of early HIV infection reduces the risk of HIV transmission and has direct benefits for the individual by reducing morbidity and mortality. [2, 3]

Attendance of HCWs to follow-up visits after occupational exposure to HIV has been highly variable, ranging from 0 to 98.9% in observational studies. [4-13] A literature search yielded three studies that evaluated factors associated with attendance to follow-up. [6, 12, 13] Two studies found that the type of HCW category did not influence attendance to follow-up, [12, 13] but one study found that HCW category did influence attendance to follow-up. [6] One study identified being exposed to an HIV seropositive source increased attendance to follow-up, [13] but another found this had no effect. [6] One study [13] reported that type of exposure and time to reporting did not influence attendance to follow-up; and women had better attendance to follow-up than men. [13] Sample size calculations were not reported in any of these three studies. Furthermore, many of the PEP regimens used in these studies included poorly tolerated antiretroviral drugs. A recent systematic review reported that tenofovir disoproxil fumarate (TDF) based PEP was better tolerated with higher completion rates than zidovudine based PEP, which used to be the standard of care. [14] The WHO now recommends the use of TDF as part of the backbone for PEP regimens. [15]

We aimed to evaluate factors associated with loss to follow-up (LTFU) following occupational exposure to HIV in a referral hospital in Cape Town, South Africa, where the HIV prevalence is 12.7%. [16] We conducted our study in a period when we

switched to TDF based PEP, and ensured we had sufficient power to determine variables associated with LTFU.

Methods

Study setting

Data was collected from the Occupational Health Clinic (OHC) of Groote Schuur Hospital, a referral hospital in Cape Town, South Africa. HCWs who have significant occupational HIV exposure are started on PEP if they present within 72 hours of the exposure. During the study period the South African national guidelines for PEP recommended the use of TDF and emtricitabine for exposures presenting within 72 hours. The policy of adding a 3rd antiretroviral (usually a boosted protease inhibitor) was changed during the study period: initially this was added only for high risk exposures, but subsequently this was added for all exposures. HCWs are counselled about the risks of HIV, the need to document HIV testing for possible compensation, and potential adverse drug reactions to PEP. HIV status of the HCW was determined at baseline using 4th generation Roche COBAS HIV-1/2 Combo automated test with a confirmatory Siemens Integral 4th generation ELISA. PEP was discontinued in HCWs who tested HIV seropositive at baseline. HIV testing was repeated at week 6 (when HCWs were informed that HIV tests may be false negative), and months 3 and 6 after the exposure. Confidentiality of HCWs is protected by keeping all files in the OHC and not in the general records department; only OHC clinic staff are able to access the files.

Study design

We conducted a retrospective cohort review to identify the factors associated with LTFU in HCWs following occupational HIV exposure. The OHC maintains an electronic database of all visits related to HCW occupational HIV exposures. We collected data from the database and additional data from folders between January 2013 and September 2015. Twenty-nine additional folders were obtained in 2012, but were unfortunately collected in alphabetical order and not according to time as completed

between 2013 and 2015. This being an oversight by the MMed candidate. However, we do not believe this oversight affected the results of the study.

Outcomes

The primary outcome was the proportion of HCWs LTFU at the 3-month visit, which is the key follow-up date to determine if HIV seroconversion has occurred, in keeping with the WHO guidelines. [15] Secondary outcomes were the proportion of HCWs LTFU at the 6-week and 6-month visits.

Data collection

Data collection at the OHC is collated from an "Occupational Health Clinic Percutaneous Inoculation Report" form. The data are collected each time the HCW presents for follow-up or when contacted by telephone. This form is completed by the occupational health worker on duty, who is either the nurse or doctor. Once 6 months have lapsed since the last visit, the data collected are recorded in an electronic database using Microsoft Excel and HCW folders are then archived in the clinic.

Study population

Inclusion criteria

HCWs were categorized into three groups: 'Doctors', 'Students' (e.g. medical, allied health, and nursing students) and 'Allied Health Professionals' (e.g. nursing, physiotherapists, occupational therapists, administrative clerks, pharmacists, and emergency medical services). HCWs were included if they were exposed to potentially infectious material from patients who are HIV-infected or HIV status unknown and attended the OHC. The following materials were deemed to be potentially infectious: pleural, pericardial, peritoneal, cerebrospinal, synovial fluid, amniotic fluid, and blood. [17]

Exclusion criteria

Exclusion criteria were: HCW tested HIV seropositive at baseline; exposed to a HIV seronegative source; those who requested follow-up at a private doctor or who went back to their own training institutions, such as elective students; multiple exposures within the 6-month follow-up period; exposures deemed to be from non-infectious material. [17]

Sample size estimation

We selected seven variables a priori for inclusion into our model based on our review of the literature: age at exposure, sex, HCW category, type of exposure, source patient HIV status, dual or triple antiretroviral therapy (ART), and time from exposure to time of receiving PEP. Assuming 25% LTFU at 3 months, [12] we required a sample size of 280 to ensure a minimum of 10 outcome events per variable, which are needed to improve precision and minimize bias in logistic regression models [18].

Statistical analysis

All statistical analysis was performed using Stata (Version 13.1; Stata Corp, College Station, Texas, USA). Descriptive statistics were used to characterize the total sample, and results were expressed as median (interquartile range) for non-normally distributed continuous variables, and frequencies and percentages for categorical variables.

We used separate multivariable logistic regression models for each time point to identify factors associated with LTFU at the 3-month, 6-week, and 6-month follow-up visits. The full model approach was utilized using a priori selected variables in order to ensure decreased risk of selection bias and overfitting. [19] This approach allows multiple epidemiological variables to be assessed independently while controlling effects of other variables. [20] Univariate analysis was used to estimate crude odds ratios (ORs) and 95% confidence intervals (95% CIs), while multivariable logistic regression provided adjusted estimates for odds of LTFU at each time point.

Odds ratios were presented with 95% CIs and a level of $p<0.05$ was considered statically significant.

Results

Two hundred and sixty-four folders were obtained between January 2013 and September 2015, with an additional 29 folders collected according to alphabetical order in 2012. There was incomplete data on 12 HCWs who were included in the descriptive analysis but excluded from the univariate and multivariate analysis as shown in figure 3.

The characteristics of the 293 patients from our cohort are shown in table 3. The dual nucleotide/nucleoside reverse transcriptase inhibitors used in PEP were TDF (97%), zidovudine (2%), and stavudine (1%); all of which were combined with either lamivudine or emtricitabine. The third agent used in 210 HCWs who were given triple ART was: lopinavir/ritonavir (82%), atazanavir/ritonavir (13%), raltegravir (4%), and efavirenz (1%).

LTFU at the various visits were: 36% at 6 weeks, 60% at 3 months, and 72% at 6 months (table 3). The univariate and multivariate analysis of variables associated with LTFU at the 3-month visit are shown in table 4. In the multivariate analysis, significant risk factors associated with LTFU were: younger age, HCW category of doctor, and time from exposure to receiving PEP of more than 24 hours. The multivariate analysis of variables associated with LTFU at the 6-week and 6-month follow-up visits are shown in table 5. Variables associated with LTFU at the 6-week visit were: male sex and HCW category of doctor. Variables associated with LTFU at the 6-month visit were similar to the 3-month visit: younger age, HCW category of doctor, and time from exposure to receiving PEP of more than 24 hours.

LTFU by category of HCW at the various visits is shown in figure 4, with doctors having the highest proportion LTFU.

Discussion

We showed that LFTU of HCWs after occupational HIV exposure was high and increased with successive visits. Younger age, the HCW category doctor, and time from exposure to receiving PEP of more than 24 hours were associated with LTFU at the 3-month visit, which was our primary endpoint. Men were more likely to be LTFU at the 6-week visit than women. These findings could be used to target interventions designed to improve follow-up.

Our finding that LTFU increases with successive visits is consistent with other studies. [9, 12, 13] We found that younger age was a significant risk factor for LTFU, which is in keeping with other studies. [21-23] The higher LTFU in younger HCWs may be related to the greater change and instability they experience in their younger years. [24] Men tended to be more likely to be LTFU in our study, which is similar to the findings of Escurdero et al. [13]

The majority (207 out of 281) of HCWs in our study were doctors and students. Doctors and students are often involved in invasive medical procedures, which places them at risk of being exposed to infectious material. [7, 9, 11, 25] Furthermore, students and doctors with less than a year's experience, are prone to occupational exposure because of their inexperience. [7, 9, 26] We found that doctors are more likely to be LTFU than other HCW categories. This could be explained by the ease with which doctors can submit their own blood samples for HIV testing instead of attending the OHC. One study, [27] showed a large proportion of HCWs obtained HIV testing outside of the facility where they worked, which they suggested was due to concern surrounding the confidentiality of HIV testing at the facility. Furthermore, doctors may be making their own assessment of the severity of the exposure and may deem it unnecessary to follow-up. [28] In contrast to our findings of increased LTFU in doctors, Gutierrez et al [6] showed cleaning personnel were more likely to be LTFU. Two other studies found type of HCW category did not influence attendance to follow-up. [12, 13]

Longer time from exposure to receiving PEP at the 3-month visit was positively associated with LTFU. This could be explained by HCWs who present after 24 hours having a perceived lower benefit from PEP. However, type of exposure and source patient HIV status, which are associated with risk of HIV acquisition, were not associated with LTFU in our cohort. Escudero et al [13] also found that type of exposure was not related to attendance to follow-up. Findings from studies that assessed the effect of the source patient's HIV status on LTFU are contradictory, with one study reporting no effect, [6] while another found positive serological status was associated with improved follow-up. [13]

There are a number of studies which reported that dual ART regimens are better tolerated than triple regimens. [29, 30] However, many of these studies include ART that are no longer used due to toxicity. Newer studies have shown that completion of PEP is based on the tolerability of ART and not on whether dual or triple therapy are used. [31, 32] This could explain why in our cohort there was no correlation between type of ART used and LTFU.

There were several limitations of our study. First, the retrospective cohort design is inherently prone to bias. However, the data was captured by OHC staff on a standard form and we had very little missing data. Second, although we found that time from exposure to receiving PEP was associated with LTFU, the 95% CIs were wide due to the small sample size of HCWs with delayed presentation. Third, we did not explore associations between years of HCW experience and exposure as we did not have this data. Other researchers have reported an association between years of experience and the incidence of occupational exposures. [7, 9, 25] Finally, Groote Schuur Hospital is a tertiary facility with referrals from other hospitals that fall under the University of Cape Town, so our findings may not be generalizable to other settings such as district hospitals.

We have identified factors associated with LTFU, which could be used to target interventions to decrease LTFU. In one study, [13] contacting HCWs by telephone or mail improved attendance to follow-up from 33% to 54%. Schmid et al [33] suggested attendance to follow-up could be improved with fewer follow-up visits. The WHO has

recently advised the final follow-up visit should be at 3 months rather than 6 months. [15] Furthermore, it has been suggested that the last follow-up visit should be at 6 weeks if laboratory 4th generation HIV ELISA tests are utilized, and 8 weeks if 4th generation rapid HIV tests are utilized. [34] Lastly van der Maaten et al, [9] suggested increasing awareness of the availability of PEP through campaigns.

Conclusion

We have identified factors associated with LTFU of HCWs after occupational HIV exposure. Future research should identify measures to improve attendance to follow-up, which could be targeted at doctors, younger HCWs, and HCWs with delayed presentation.

Abbreviations
ART: antiretroviral therapy; CIs: Confidence intervals; HCW: health care worker; HIV: Human Immunodeficiency Virus; LTFU: loss to follow-up; OHC: occupational health clinic; ORs: odds ratios; PEP: post exposure prophylaxis; TDF: tenofovir disoproxil fumarate; WHO: World Health Organization.

Declarations

Ethics approval
Ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town.

Consent for publication
'Not applicable.'

Availability of data and material
Data sets are available from the corresponding author on reasonable request.

Competing interests
The authors declare they have no competing interests.

Funding
GM received partial support from the National Research Foundation of South Africa (grant reference number 85810).

Author contributions
NP and GM designed the study, wrote the proposal, analyzed the data, and prepared the manuscript. KM was involved in proposal writing, statistical analysis, and manuscript preparation. NP, FC and MG were involved in data collection.

Acknowledgements
'Not applicable.'

Authors' details
[4]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa. [1]Department of Medicine, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa. [2]Trauma and Emergency Unit, Groote Schuur Hospital, Cape Town, South Africa. [3]Quality and Safety Unit, Groote Schuur Hospital, Cape Town, South Africa.

References

(Vancouver style)
1. World Health Organization. The world health report 2002, chapter 4: reducing risks, promoting healthy life. http://www.who.int/whr/2002/chapter4/en/index8.html (2002). Accessed 21 Mar 2016
2. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493-505.
3. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795-807.
4. de la Tribonniere X, Dufresne MD, Alfandari S, Fontier C, Sobazek A, Valette M, et al. Tolerance, compliance and psychological consequences of post-exposure prophylaxis in health-care workers. Int J STD AIDS. 1998;9(10):591-4.

5. Pungpapong S, Phanuphak P, Pungpapong K, Ruxrungtham K. The risk of occupational HIV exposure among Thai healthcare workers. Southeast Asian J Trop Med Public Health. 1999;30(3):496-503.

6. Gutierrez EB, Heloísa Lopes M, Shikanai Yasuda MA. Accidental exposure to biological material in healthcare workers at a university hospital: Evaluation and follow-up of 404 cases. Scand J Infect Dis. 2005;37(4):295-300.

7. Jayanth ST, Kirupakaran H, Brahmadathan KN, Gnanaraj L, Kang G. Needle stick injuries in a tertiary care hospital. Indian J Med Microbiol. 2009;27(1):44-7.

8. Siika AM, Nyandiko WM, Mwangi A, Waxman M, Sidle JE, Kimaiyo SN, et al. The structure and outcomes of a HIV postexposure prophylaxis program in a high HIV prevalence setup in western Kenya. J Acquir Immune Defic Syndr. 2009;51(1):47-53.

9. van der Maaten GC, Nyirenda M, Beadsworth MJ, Chitani A, Allain T, van Oosterhout JJ. Post exposure prophylaxis of HIV transmission after occupational injuries in Queen Elizabeth Central Hospital, Blantyre, Malawi, 2003 - 2008. Malawi Med J. 2010;22(1):15-9.

10. Olowookere SA, Fatiregun AA. Human immunodeficiency virus postexposure prophylaxis at Ibadan, Nigeria. J Int Assoc Physicians AIDS Care (Chic). 2010;9(3):187-90.

11. Onyedum CC, Chukwuka C, Iyoke CA, Omotola OF. HIV postexposure prophylaxis (PEP) in a nigerian tertiary health institution. J Int Assoc Physicians AIDS Care (Chic). 2011;10(3):171-5.

12. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Outcomes of a Postexposure Prophylaxis Program at the Korle-Bu Teaching Hospital in Ghana: A Retrospective Cohort Study. Journal of the International Association of Providers of AIDS Care. 2015;14(6):544-52.

13. Escudero DV, Furtado GH, Medeiros EA. Healthcare worker adherence to follow-up after occupational exposure to blood and body fluids at a teaching hospital in Brazil. Ann Occup Hyg. 2015;59(5):566-71.

14. Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis. 2015;60 Suppl 3:S170-6.

15. World Health Organization. Guidelines on Post-Exposure Prophylaxis for HIV and the Use of Co-Trimoxazole Prophylaxis for HIV-Related Infections Among Adults, Adolescents and Children: Recommendations for a Public Health Approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization. http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en/ (2014). Accessed 17 Sept 2016.

16. Statistics South Africa. Statistical release, mid-year population estimates 2016. http://www.statssa.gov.za/?page_id=1854&PPN=P0302 (2016). Accessed 22 Jan 2017.

17. Centers for Disease Control. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep. 1988;37(24):377.

18. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.

19. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012;98(9):683-90.

20. Stoltzfus JC. Logistic regression: a brief primer. Acad Emerg Med. 2011;18(10):1099-104.

21. Corfield L, Schizas A, Noorani A, Williams A. Non-attendance at the colorectal clinic: a prospective audit. Ann R Coll Surg Engl. 2008;90(5):377-80.

22. Milne V, Kearns R, Harrison A. Patient age, ethnicity and waiting times determine the likelihood of non-attendance at a first specialist rheumatology assessment. Int J Rheum Dis. 2014;17(1):19-25.

23. Hynes L, Byrne M, Dinneen SF, McGuire BE, O'Donnell M, Mc Sharry J. Barriers and facilitators associated with attendance at hospital diabetes clinics among young adults (15-30 years) with type 1 diabetes mellitus: a systematic review. Pediatr Diabetes. 2016;17(7):509-18.

24. Arnett JJ. Emerging adulthood. A theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469-80.

25. Karstaedt AS, Pantanowitz L. Occupational exposure of interns to blood in an area of high HIV seroprevalence. S Afr Med J. 2001;91(1):57-61.

26. Aggarwal V, Seth A, Chandra J, Gupta R, Kumar P, Dutta AK. Occupational exposure to human immunodeficiency virus in health care providers: a retrospective analysis. Indian J Community Med. 2012;37(1):45-9.

27. Kassa G, Selenic D, Lahuerta M, Gaolathe T, Liu Y, Letang G, et al. Occupational exposure to bloodborne pathogens among health care workers in Botswana: Reporting and utilization of postexposure prophylaxis. Am J Infect Control. 2016 Aug;44(8):879-85.

28. Elmiyeh B, Whitaker IS, James MJ, Chahal CA, Galea A, Alshafi K. Needle-stick injuries in the National Health Service: a culture of silence. J R Soc Med. 2004;97(7):326-7.

29. Puro V. Post-exposure prophylaxis for HIV infection. Italian Registry of Post-Exposure Prophylaxis. Lancet. 2000;355(9214):1556-7.

30. Bassett IV, Freedberg KA, Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. Clin Infect Dis. 2004;39(3):395-401.

31. Henderson DK. Management of needlestick injuries: a house officer who has a needlestick. JAMA. 2012;307(1):75-84.

32. McAllister J, Read P, McNulty A, Tong WW, Ingersoll A, Carr A. Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence. HIV Med. 2014;15(1):13-22.

33. Schmid K, Schwager C, Drexler H. Needlestick injuries and other occupational exposures to body fluids amongst employees and medical students of a German university: incidence and follow-up. J Hosp Infect. 2007;65(2):124-30.

34. Gaines H, Albert J, Axelsson M, Berglund T, Gisslen M, Sonnerborg A, et al. Six-week follow-up after HIV-1 exposure: a position statement from the Public Health Agency of Sweden and the Swedish Reference Group for Antiviral Therapy. Infect Dis (London). 2016;48(2):93-8.

Figure 3. Flow chart illustrating data set of health care workers chosen for analysis

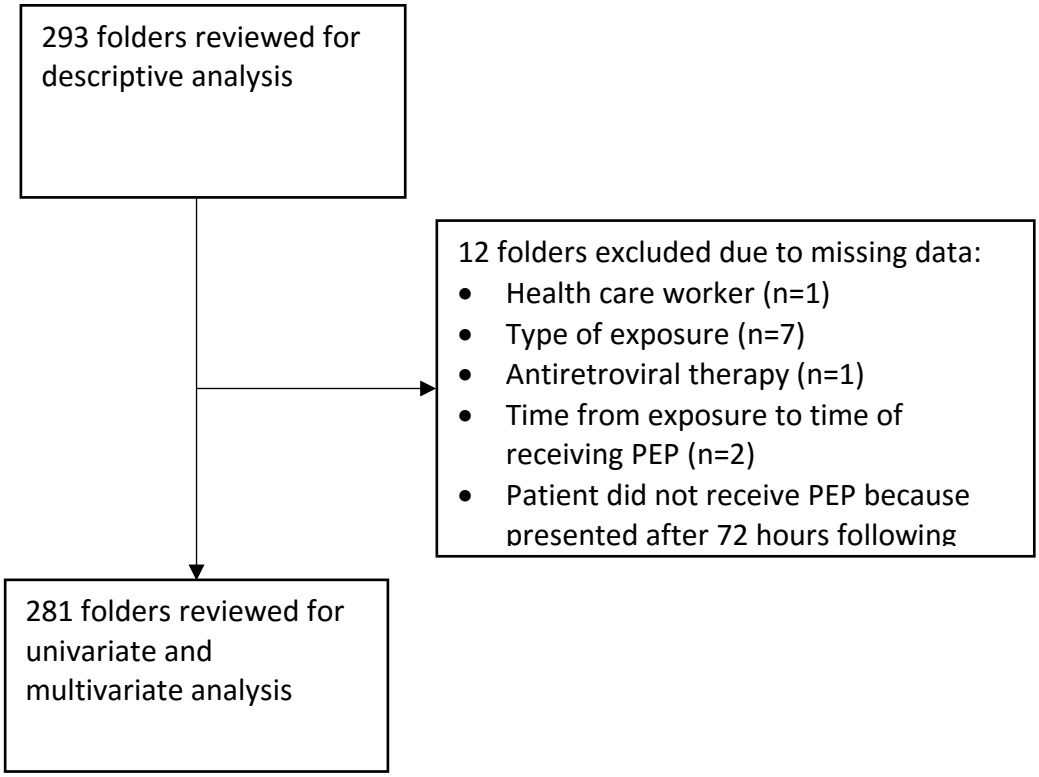


Table 3: Baseline characteristics and follow-up of 293 health care workers with occupational exposure

Variable	Sample (n)
Age, median (IQR)	28 (24-35)
Sex	
Women	197 (67%)
Men	96 (33%)
Health care worker *	
Allied Health Professional	85 (29%)
Doctor	100 (34%)
Student	107 (37%)
Type of exposure#	
Hollow-bore	137 (48%)
Mucocutaneous	86 (30%)
Solid sharp	63 (22%)
Source patient HIV status	
Positive	246 (84%)
Unknown	47 (16%)
Antiretroviral ⌘⊙	
Dual	81 (28%)
Triple	210 (72%)
Time from exposure to receiving PEP**	
<24 hours	268 (92%)
24-48 hours	17 (6%)
48-72hours	1 (0.3%)
>72hours	4 (1.4%)
Loss to follow-up❑	
6 week	100 (36%)
3 month	169 (60%)
6 month	203 (72%)

Number with missing data: *n=1, #n=7, ⌘n=1, **n=2, ❑n=12

⊙One Health care worker did not receive PEP because presented too late

Table 4: Variables associated with loss to follow-up at 3 months

Variables	Unadjusted OR (95% CI)	P-value	Adjusted OR (95%CI)	P-value
Age (per 10-year increase)	0.7 (0.5 to 0.9)	0.003	0.6 (0.5 to 0.9)	0.011
Sex				
Women *				
Men	1.4 (0.8 to 2.4)	0.190	1.4 (0.8 to 2.5)	0.262
Health care worker				
Allied Health Professional*				
Doctor	2.9 (1.6 to 5.4)	0.001	2.7 (1.3 to 5.5)	0.006
Student	2.0 (1.1 to 3.6)	0.022	1.2 (0.6 to 2.6)	0.584
Type of exposure				
Hollow-bore *				
Mucocutaneous	1.6 (0.9 to 2.9)	0.095	1.1 (0.6 to 2.2)	0.707
Solid sharp	1.3 (0.7 to 2.4)	0.377	1.0 (0.5 to 1.9)	0.948
Source patient HIV status				
Positive	0.9 (0.4 to 1.8)	0.742	0.5 (0.2 to 1.1)	0.074
Unknown*				
Antiretroviral				
Dual	1.4 (0.8 to 2.3)	0.250	1.5 (0.8 to 2.8)	0.228
Triple *				
Time from exposure to receiving PEP				
<24 hours *				
>24hours	3.0 (1.0 to 9.2)	0.052	5.9 (1.3 to 26.9)	0.023

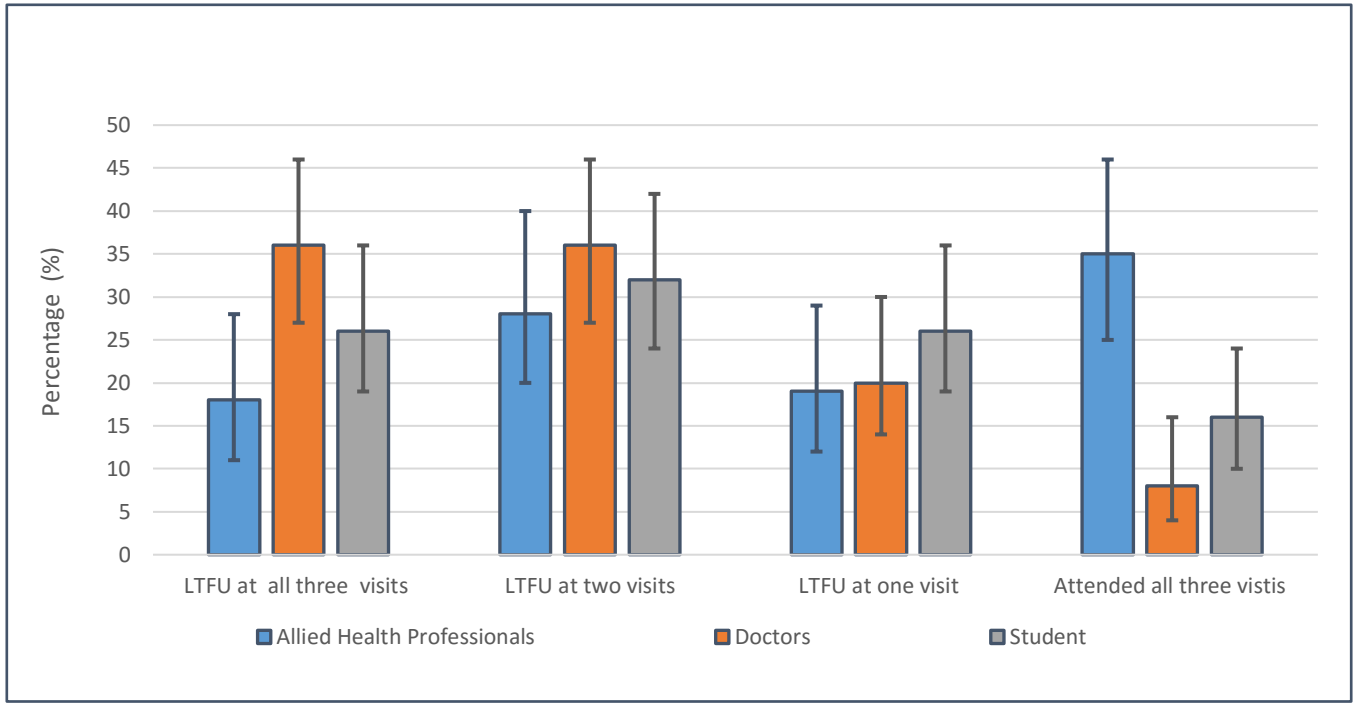
*Reference category

Table 5: Variables associated with loss to follow-up at 6 weeks and 6 months

Variables	6-week Adjusted OR	P-value	6-month Adjusted OR	P-value
Age (per 10-year increase)	1.0 (0.7 to 1.3)	0.764	0.6 (0.5 to 0.9)	0.010
Sex				
Women *				
Men	1.8 (1.1 to 3.2)	0.027	1.8 (0.9 to 3.4)	0.082
Health care worker				
Allied Health Professional *				
Doctor	2.1 (1.1 to 4.4)	0.034	2.1 (1.0 to 4.5)	0.049
Student	1.1 (0.5 to 2.5)	0.750	1.3 (0.6 to 2.9)	0.532
Type of exposure				
Hollow-bore *				
Mucocutaneous	1.0 (0.5 to 1.9)	0.988	1.2 (0.6 to 2.5)	0.659
Solid sharp	1.1 (0.5 to 2.1)	0.857	1.1 (0.5 to 2.4)	0.728
Source patient HIV status				
Positive	1.0 (0.5 to 2.2)	0.952	0.7 (0.3 to 1.7)	0.489
Unknown*				
Antiretroviral				
Dual	1.2 (0.6 to 2.3)	0.544	0.7 (0.4 to 1.4)	0.333
Triple *				
Time from exposure to receiving PEP				
<24 hours *				
>24hours	1.3 (0.5 to 3.4)	0.552	7.8 (1.0 to 61)	0.049

*Reference category

Figure 4. Percentage Loss to follow-up (LTFU) by number of visits of various health care worker categories (visits were scheduled at 6 weeks, 3 months, and 6 months). Error bars are shown



CHAPTER 3: APPENDICES

Protocol

University of Cape Town

Faculty of Health Sciences

Factors Associated with Loss to Follow-up After Occupational HIV Exposure among Health Care Workers Attending the Groote Schuur Hospital Occupational Health Clinic

Master of Medicine (Internal Medicine)

Dr Nectarios Sophocles Papavarnavas

PPVNEC001

Contact details:

Address:

4 Wellington Mews

Wellington Avenue

Wynberg

Cape Town

7800

Mobile number: 082 807 1968

Email: taripapas@yahoo.com

Supervisor: Prof G Maartens

Statistical analyst: Mrs K Manning

Occupational Health panel: Dr F Conrad, Sr M Chetty, Ms M Govender

Date: 25 April 2016

EXECUTIVE SUMMARY:

Anecdotally follow-up rates among health care workers after occupational exposure to Human Immunodeficiency Virus are poor. Identifying factors associated with poor follow-up could result in interventions to improve follow-up, such as enhanced counselling and reminders. The aim of this retrospective cohort study is to explore factors associated with loss to follow-up at the key 3-month visit using multivariate logistic regression. Secondary outcomes include loss to follow-up at the 6-week and 6-month visits. Data will be extracted from an existing database maintained by the Occupational Health Clinic of Groote Schuur Hospital, with missing data obtained from files maintained in the clinic. Data will be collected using Microsoft Excel. All patient identifiers will be kept completely confidential and only aggregate data will be reported.

TABLE OF CONTENTS

Glossary of abbreviations....4

Background....5

Hypothesis, study aims and objectives....8

Hypotheses....8
Study aims....8
Study objectives....8

Methods....9

Study Design....9
Study setting....9
Study population....9
Sampling....10
Measurements....10
Sample size....12
Data collection....12
Confidentiality....12
Quality assurance....13

Data analysis....13

Ethics....14

Timing....14

Action plan....15

Budget....16

Reporting of results....16

References....16

GLOSSARY OF ABBREVIATIONS

ART	Antiretroviral therapy
HIV	Human Immunodeficiency Virus
HCW	Health care worker
LTFU	loss to follow-up
MMed	Maters of medicine
PEP	Post-exposure prophylaxis
Source	The patient from whom the exposure occurred.

BACKGROUND

According to the 2015 statistics of South Africa, the population was estimated to be 54.96 million, of whom 6.19 million are living with Human Immunodeficiency Virus (HIV). This equates to 11.2% of South Africa's population living with HIV, of whom a large proportion will at some time in their lives come into contact with Health care workers (HCWs). (1)

The World Health Organization estimates 3 million HIV percutaneous exposures occur among 35 million HCWs annually, 90% of these exposures occur in resource limited settings and it is estimated that 500 occupational related HIV infections occur each year. (2) This is in stark contrast to developed countries where estimates are far smaller. (3)

USA data, on occupational exposures, from 1985 to 2013 illustrated 58 confirmed cases and 150 possible cases of HIV seroconversion. However, since 1999 there has been only one confirmed case in 2008 of HIV seroconversion in a laboratory worker who sustained a percutaneous injury while working with live HIV culture. The decrease in number of cases can be attributed to the increased uptake of universal standard precautions instituted into the "standard precautions" in 1995; increased post-exposure prophylaxis (PEP) utilization, and training to reduce sharp exposures and other injuries. (3)

PEP has come a long way from the 1980's where single dose 100mg four hourly Zidovudine was used compared to the current gold standard of triple therapy either used once or twice daily. (4) There are no controlled data on the efficacy of PEP, and it is assumed that combination PEP will be superior to monotherapy, as is the case for prevention of mother-to-child transmission. A retrospective case control study by Cardo et al (5) showed an 81% reduction in occupational transmission of HIV when HCWs are given PEP with Zidovudine monotherapy. A recent article (6) showed there is little evidence to support the optimal number of drugs needed to prevent seroconversion among HCWs.

Risk of HIV seroconversion after percutaneous exposure is 0.23% with no PEP. (7, 8) However, there are a number factors associated with a greater risk of acquiring HIV

after occupational exposure: increased depth of the injury, hollow bore needle, higher source patient's HIV viral load, increased inoculum, device previously inserted into the source patient's artery or vein, and absence of glove use. (9, 10) Gloves have been shown to decrease blood volume transmission by 46-86%. (9) Risk due to mucosal splash injury or non-intact skin is thought to be extremely low. (7) Other sources have evaluated the risk to be around 0.03%. (11) Percutaneous exposure to HIV is more common than mucosal splash exposure as shown in a number of studies. (12-14) To the best of our knowledge, there is currently no literature to indicate whether HCWs follow-up attendance after occupational HIV exposure is affected by the nature of the exposure. We believe HCWs may be less inclined to attend follow-up after lower risk exposures.

Unfortunately, the estimates of the number of exposures of HIV to HCWs is believed to be under-reported due to time constraints among HCWs. (15) A number of studies have shown that doctors are less likely to report injuries due to: work pressure, time constraints, and better understanding of risks involved in exposure compared to other HCWs. (15, 16)

Adherence to PEP needs to be stressed among HCWs, as animal models have shown suboptimal duration of therapy and delay in starting PEP are associated with PEP failure. In a study by Tsai et al (17) protection of macaque monkeys against Simian Immunodeficiency Virus was optimal if treatment of PEP was started within 24 hours; if treatment was started after 48 hours it was 50% effective, and if started after 72 hours it was only 25% effective. Furthermore, if PEP was given within 24 hours but only continued for 3 days, all of the monkeys seroconverted; if 10 days of treatment was given, half seroconverted; while if a full 28-day regimen was prescribed, all macaques were protected. (17, 18) The above information illustrates the need for optimal adherence and correct length of treatment to protect HCWs from HIV.

HIV seronegative HCWs suffer more side effects than HIV seropositive patients on the same regimen. (19) One study (20) showed antiretroviral therapy (ART) use for PEP was associated with 6 times increased risk of side effects and 8 times higher chance of discontinuing therapy when compared to HIV seropositive patients. There

are a number of studies which reported that 2-drug regimens were better tolerated than 3-drug regimens. (21, 22) However, many of these studies include antiretrovirals that are no longer used due to toxicity. Newer studies have shown that completion of PEP is based on the tolerability of ART prescribed and not on whether triple or dual therapy is used. (23)

To the best of our knowledge, there is no data on lost to follow-up (LTFU) in occupational PEP with 2 versus 3-drug regimens. In the Occupational Health Clinic lopinavir/ritonavir or atazanavir/ritonavir were used as the third agent and not raltegravir, due to cost considerations. One study (24) found that raltegravir, used as the third agent in PEP, was better tolerated than lopinavir/ritonavir. In well-resourced areas raltegravir is the third drug of choice in PEP regimens due to its favourable tolerability profile. (25)

A study of adherence to ART among HIV infected patients in South Africa showed women were significantly more likely to adhere to treatment compared to men. (26) However, data with regard to ART adherence is conflicting; a systematic review by Nicastri et al,(27) found women were less likely to adhere to ART compared to men, but many of these studies were performed in first world settings.

Two small studies in Nigeria, of people with both occupational and non-occupational exposure, reported 50% attendance within 24 hours of exposure in the first study, (28) and 100% attendance within 72 hours in the second study. (29) In both studies, men presented earlier than women for PEP. Failure to present within 24 hours of exposure was thought to be related to lack of awareness and following non-occupational exposures. (28) While another study of occupational HIV exposure demonstrated 80% attendance within 24 hours of exposure. (30)

There is currently a paucity in the literature of factors associated with LTFU after starting PEP. Studies that have evaluated this, have yielded highly variable results, with attendance ranging from 0% to 98.9%. (28-31) A study by Tetteh et al (30) described attendance of 87%, 75% and 62% at 6 weeks, 3 months and 6 months respectively. Unfortunately, the only factor they described with regards to attendance of follow-up visits was category of HCW, in-which they found no

statistically significant difference between the various categories of HCWs. A number of studies reporting attendance to follow-up did not asses the epidemiological factors surrounding attendance to follow-up. (28, 29, 31)

As illustrated above there is little literature on factors surrounding LTFU among HCWs. It is hoped that this Master of medicine (MMed) dissertation will identify and explore these factors. If HCWs are identified at high risk for LTFU, then additional counselling and other measures (e.g. text messaging) could be implemented to improve follow-up.

HYPOTHESIS, STUDY AIMS AND OBJECTIVES

HYPOTHESES

We hypothesize that identifiable variables related to the exposed HCW; the nature of the occupational exposure, and/or the type of PEP will be associated with LTFU. Furthermore, we hypothesize attendance will decrease with time.

STUDY AIMS

To explore factors related to LTFU after occupational HIV exposure at the Occupational Health Clinic of Groote Schuur Hospital primarily at 3 months, and secondarily at 6 weeks and 6 months.

STUDY OBJECTIVES

1. To describe the epidemiology of HIV exposures among HCWs who received PEP at the Occupational Health Clinic.
2. To describe the proportion of HCWs attending follow-up visits at 6 weeks, 3 and 6 months.
3. To determine predictors of LTFU visits at 6 weeks, 3 and 6 months using multivariable logistic regression.

Methods

Study Design

Retrospective cohort study.

Study setting

Groote Schuur Hospital Occupational Health Clinic.

Study population

Inclusion criteria

- HCWs (including healthcare professional students) with a significant occupational exposure to potentially infectious material from patients' who are HIV-infected or HIV status unknown, and who attended the Groote Schuur Hospital Occupational Health Clinic. The following are deemed to be infectious: pleural, pericardial, peritoneal, cerebrospinal, synovial fluid, amniotic fluid and blood. (32)

Exclusion criteria

- HCWs exposed to a HIV negative source.
- Exposure deemed to be from non-infectious material. The following are not considered infectious unless visibly stained with blood: faeces, sputum, nasal secretions, urine, sweat, tears and vomitus. (32)
- HCWs who tested HIV seropositive or "Unknown" HIV result at time of exposure.
- Non-occupational exposures.
- HCWs who requested follow-up at a private doctor or who went back to their own training institutions, such as in elective students.
- HCWs with multiple injuries with overlapping time points, as these HCWs may be less likely to be LTFU due to multiple injuries, and increased risk of HIV seroconversion, in the specified 6-month time period.

Sampling

Data will be collected using the Microsoft Excel spreadsheet in use by the Occupational Health Clinic. The study period will look retrospectively from September 2015 until 240 HCWs fulfilling the inclusion criteria are evaluated (see sample size below).

HCWs are seen at first presentation and then followed up after 6 weeks, 3 months and 6 months. The window for each of the three follow-up visits are:

- ≥4 to ≤10 weeks for the 6-week follow-up visit.
- >10 to ≤20 weeks for the 3-month follow-up visit.
- >20 to ≤32 weeks for the 6-month follow-up visit.

Measurements

Primary outcome

Since currently used HIV antibody tests detect HIV infection within 3 months of exposure, even allowing for a possible delay in seroconversion due to PEP, we will describe the proportion of HCWs LTFU at the 3-month visit. (33, 34)

Secondary outcome

Our secondary outcome will be the proportion of HCWs LTFU at the 6 week and 6-month visits.

Variables for logistic regression

The full model approach will be utilized; as a priori selected variables will be included in the multivariable analysis. Predictors that have been assessed not to contribute to the outcomes in the multivariable analysis have be withdrawn. This is to ensure decreased risk of selection bias and overfitting. (35)

A multivariable logistic regression model will be developed with 6 variables identified below for both primary and the secondary outcomes. (36) We have chosen a multivariable logistic regression model because this will allow us to look at multiple epidemiological variables and independently look at each one while controlling the

effects of others. This will allow us to determine our outcomes of attendance at the various appointments and the independent epidemiological variables related to it. (37)

The following variables have been chosen:

1. *Sex:* we postulate that women will have less LTFU compared to men, in keeping with the better ART adherence among women in Southern Africa. (26)
2. *Age:* Younger HCWs are more likely to be LTFU, which may be related to more chaotic lifestyles younger individuals experience. (38)
3. *HCW category:* doctors are expected to have the highest proportion of LTFU. (15, 16) The following HCW categories will be used for analyses:
    - *Doctors*: interns, medical officers, registrars and consultants.
    - *Students*: medical, nursing, allied health and pharmaceutical.
    - *Allied health*: physiotherapist, radiographer, social worker, dietician, speech therapist, audiologist, occupational therapist, pharmacist, enrolled nurse, enrolled nurse assistant and registered nurse.
    - *Other*: recipients in support services, engineering, sterilization, clerical, emergency services, forensic pathology laboratory services and *undefined* where a category could not be identified.
4. *Type of exposure:* HCWs with higher risk exposures, as defined in the background section, are less likely to be LTFU.
5. *Length of time from exposure to receiving PEP:* HCWs seeking medical intervention earlier are likely to have more insight into the benefits of PEP, which could result in less LTFU.
6. *PEP regimen:* HCWs placed on dual therapy are less likely to be LTFU, because they are less likely to experience side effects as compared to HCWs on triple therapy.

SAMPLE SIZE

The study by Tetteh et al (30) described follow up attendance of 75% at 3 months. Our primary end point is LTFU at 3-months.

According to a logistic regression analysis model by Peduzzi et al: (36) 10 events per variable are needed to improve precision. As we have identified 6 variables potentially associated with LTFU, we need 60 outcomes. Assuming 25% LTFU at 3 months, we need a sample size of 240. However, if during the study, attendance of the 3-month follow-up is seen to be more than 75%, we will adjust our sample size accordingly. If follow-up is noted to be lower than 75% at 3 months, we'll keep the sample size unchanged as this will increase our power.

DATA COLLECTION

Data will be collected from the Occupational Health Clinic in Groote Schuur Hospital. Data has already been collated on an "Occupational Health Clinic Percutaneous Inoculation Report" form. The data is collected each time the HCW presents for follow-up or when telephonically contacted. The form is completed by the occupational health worker on duty, which is either the sister in charge or doctor on duty. 6 months after the last visit, namely the 6-month appointment, the data collated from the folders are placed in an electronic database and stored in the clinic.

Data will be extracted from the "Occupational Health Clinic Percutaneous Inoculation Report" form and electronic database. All forms will be kept confidential and will not be removed from the clinic. If data is missing from forms, files will be requested from records for completion of the study spreadsheet. All information surrounding recipients and source patients shall be kept confidential. This will be ensured by a password protected laptop, and back-ups on an encrypted USB flash drive and password protected Dropbox application. The researchers will keep all passwords safe and shall not be shared with any other HCWs.

CONFIDENTIALITY

A unique identifying number will be issued to each HCWs in-place of their name and hospital number. A separate spreadsheet, will be kept with the unique identifier

number correlating to the name and hospital number of the HCW. The spreadsheet with the unique identifier number and personal information will be deleted once all data has been collected.

QUALITY ASSURANCE

Quality assurance will be ensured by using the Microsoft Excel spreadsheet from the Occupational Health Clinic electronic database. There will be only one person involved in data collection which will be the MMed candidate and therefore no training is needed for extraction of data. Quality control will be ensured by seeking help from a statistician with regard to using software to prevent double entries from occurring in the electronic database as well as assimilation of data into flow diagrams, tables and charts. (39)

DATA ANALYSIS

Data will be captured using Microsoft Excel.

Adjusted odds ratios will be presented together with 95% confidence intervals in order to determine the precision of estimates. A level of $p<0.05$ will be considered statistically significant where appropriate.

Descriptive statistics will be used to characterize the total sample and compare results between those who attended the follow-up visits versus non-attendance.

Continuous variables will be tested for normality using histograms and exploratory analysis, and expressed using means (standard deviations) or medians (interquartile ranges) depending on their distributions, while categorical variables will be expressed as frequencies and percentages.

Group comparisons of continuous variables will be analyzed using either parametric tests (two-sample t-test) or non-parametric tests (Mann-Whitney U test) depending on the distribution. Chi-square test or Fisher's Exact tests will be used to test for associations between categorical variables. Depending on the nature of two continuous variables, a Pearson's or Spearman's correlation will be used to describe

the direction and strength of the relationship.

All statistical analysis will be performed using Stata (Version 13.1; Stata Corp, College Station, Texas, USA).

ETHICS

- Clearance from the Human Research Ethics Committee of the University of Cape Town will be obtained for permission to extract data from the electronic database, forms in the Occupational Health Clinic as well as access files from records if not all information is available from the forms and electronic database.
- As stated in "Methods" all information will be kept safe through password protected laptop, encrypted USB flash drive and password protected Dropbox application. HCW data will be deleted once all data has been collected, so as to ensure the data cannot be traced back to the HCW.
- The benefits of the study will include understanding of the epidemiological factors surrounding LTFU of PEP and to explore possible methods to ensure better follow-up.
- Neither Prof Maartens or myself have any conflicts of interest or ties with the Occupational Health Clinic.

TIMING

- The study will run retrospectively from September of 2015.
- Protocol will be submitted to the Postgraduate Committee in April 2016.
- Ethics submission will be in May 2016.
- Data analysis will be completed in July 2016.
- Manuscript preparation and completion will be accomplished by 30th of March 2017 for submission for publication.

ACTION PLAN

ACTIONS	RESPONSIBLE	TIME	Accomplished	BUDGET
Literature study	NS Papavarnavas & G Maartens	February2016-March 2017	Y/N	Not applicable
Ethical aspects	NS Papavarnavas & G Maartens	April 2016	Y/N	Not applicable
Funding	NS Papavarnavas			Not applicable
Specimen collection & determination	NS Papavarnavas	May 2016	Y/N	Not applicable
Statistical analysis	NS Papavarnavas & K Manning	July 2016	Y/N	Not applicable
Publication preparation	NS Papavarnavas & G Maartens	March 2017	Y/N	If online journal is selected then UCT research office will be approached to cover publication costs

The principal investigator and researcher will meet on a regular basis to discuss the MMed as well as to ensure the specific dates are adhered to in the "Action Plan."

BUDGET

- Any unforeseen costs incurred during the study will be funded by the MMed candidate.

REPORTING OF RESULTS

Results will be tabulated, graphed and designed in flow diagrams. Access to the information will be firstly distributed to the relevant members assisting in the study as well as Occupational Health Clinic. Finally, all data will be shared with the Health Science Faculty of the University of Cape Town and will be published in a relevant journal.

REFERENCES

(Vancouver style)

1. Statistics South Africa. Statistical release, mid-year population estimates 2015. http://www.statssa.gov.za/?page_id=1854&PPN=P0302. Accessed 16 Mar 2016. 2015.
2. World Health Organization. The world health report 2002, chapter 4: reducing risks, promoting healthy life. http://www.who.int/whr/2002/chapter4/en/index8.html (2002). Accessed 21 Mar 2016
3. Joyce MP, Kuhar D, Brooks JT. Notes from the field: occupationally acquired HIV infection among health care workers - United States, 1985-2013. MMWR Morb Mortal Wkly Rep. 2015;63(53):1245-6.
4. Polder JA, Bell DM, Baker E, Castro K, Chamberland M, Curran J, et al. Public Health Service Statement on Management of Occupational Exposure to Human Immunodeficiency Virus, Including Considerations Regarding Zidovudine Postexposure Use. MMWR Morb Mortal Wkly Rep. 1990;39(RR-1):1-14.
5. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med. 1997;337(21):1485-90.
6. Siegfried N, Beanland RL, Ford N, Mayer KH. Formulating the Future Research Agenda for Postexposure Prophylaxis for HIV: Methodological Challenges and Potential Approaches. Clin Infect Dis. 2015;60 Suppl 3:S205-11.
7. Centers for Disease Control and Prevention. Occupational HIV transmission and prevention among health care workers. 2015. http://www.cdc.gov/hiv/workplace/occupational.html. Accessed 17 Mar 2016.
8. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014;28(10):1509-19.

9. Mast ST, Woolwine JD, Gerberding JL. Efficacy of gloves in reducing blood volumes transferred during simulated needlestick injury. J Infect Dis. 1993;168(6):1589-92.

10. Update: provisional Public Health Service recommendations for chemoprophylaxis after occupational exposure to HIV. MMWR Morb Mortal Wkly Rep. 1996;45(22):468-80.

11. Henderson DK. Management of needlestick injuries: a house officer who has a needlestick. JAMA. 2012;307(1):75-84.

12. Karstaedt AS, Pantanowitz L. Occupational exposure of interns to blood in an area of high HIV seroprevalence. S Afr Med J. 2001;91(1):57-61.

13. Serdar T, Derek L, Unic A, Marijancevic D, Markovic D, Primorac A, et al. Occupational exposures in healthcare workers in University Hospital Dubrava-10 year follow-up study. Cent Eur J Public Health. 2013;21(3):150-4.

14. Aggarwal V, Seth A, Chandra J, Gupta R, Kumar P, Dutta AK. Occupational exposure to human immunodeficiency virus in health care providers: a retrospective analysis. Indian J Community Med. 2012;37(1):45-9.

15. Stringer B, Infante-Rivard C, Hanley JA. Effectiveness of the hands-free technique in reducing operating theatre injuries. Occup Environ Med. 2002;59(10):703-7.

16. Elmiyeh B, Whitaker IS, James MJ, Chahal CA, Galea A, Alshafi K. Needle-stick injuries in the National Health Service: a culture of silence. J R Soc Med. 2004;97(7):326-7.

17. Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, Bischofberger N, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol. 1998;72(5):4265-73.

18. Beekmann SE, Henderson DK. Prevention of human immunodeficiency virus and AIDS: postexposure prophylaxis (including health care workers). Infect Dis Clin North Am. 2014;28(4):601-13.

19. Cai J, Xiao J, Zhang Q. Side effects and tolerability of post-exposure prophylaxis with zidovudine, lamivudine, and lopinavir/ritonavir: a comparative study with HIV/AIDS patients. Chin Med J. 2013;127(14):2632-6.

20. Quirino T, Niero F, Ricci E, Pusterla L, Carradori S, Gabbuti A, et al. HAART tolerability: post-exposure prophylaxis in healthcare workers versus treatment in HIV-infected patients. Antivir Ther. 2000;5(3):195-7.

21. Puro V. Post-exposure prophylaxis for HIV infection. Italian Registry of Post-Exposure Prophylaxis. Lancet. 2000;355(9214):1556-7.

22. Bassett IV, Freedberg KA, Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. Clin Infect Dis. 2004;39(3):395-401.

23. McAllister J, Read P, McNulty A, Tong WW, Ingersoll A, Carr A. Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence. HIV Med. 2014;15(1):13-22.

24. Leal L, Leon A, Torres B, Inciarte A, Lucero C, Mallolas J, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus raltegravir each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. J Antimicrob Chemother. 2016;71(7):1987-93.

25. Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis. 2015;60 Suppl 3:S170-6.

26. Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr. 2006;43(1):78-84.

27. Nicastri E, Leone S, Angeletti C, Palmisano L, Sarmati L, Chiesi A, et al. Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. J Antimicrob Chemother. 2007;60(4):724-32.

28. Onyedum CC, Chukwuka C, Iyoke CA, Omotola OF. HIV postexposure prophylaxis (PEP) in a nigerian tertiary health institution. J Int Assoc Physicians AIDS Care (Chic). 2011;10(3):171-5.

29. Olowookere SA, Fatiregun AA. Human immunodeficiency virus postexposure prophylaxis at Ibadan, Nigeria. J Int Assoc Physicians AIDS Care (Chic). 2010;9(3):187-90.

30. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Outcomes of a postexposure prophylaxis program at the Korle-Bu Teaching Hospital in Ghana: a retrospective cohort study. Journal of the International Association of Providers of AIDS Care. 2015;14(6):544-52.

31. Jayanth ST, Kirupakaran H, Brahmadathan KN, Gnanaraj L, Kang G. Needle stick injuries in a tertiary care hospital. Indian J Med Microbiol. 2009;27(1):44-7.

32. Centers for Disease Control. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep. 1988;37(24):377.

33. Moorhouse M, Bekker LG, Black V, Conradie F, Harley B, Howell P, et al. Guideline on the management of occupational and non-occupational exposure to the human immunodeficiency virus and recommendations for post-exposure prophylaxis: 2015 update S Afr J HIV Med. 2016;16(1):1-14.

34. World Health Organization. Guidelines on Post-Exposure Prophylaxis for HIV and the Use of Co-Trimoxazole Prophylaxis for HIV-Related Infections Among Adults, Adolescents and Children: Recommendations for a Public Health Approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization. http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en/ (2014). Accessed 17 Sept 2016.

35. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012;98(9):683-90.

36. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.

37. Stoltzfus JC. Logistic regression: a brief primer. Acad Emerg Med. 2011;18(10):1099-104.

38. Hynes L, Byrne M, Dinneen SF, McGuire BE, O'Donnell M, Mc Sharry J. Barriers and facilitators associated with attendance at hospital diabetes clinics among young adults (15-30 years) with type 1 diabetes mellitus: a systematic review. Pediatr Diabetes. 2016;17(7):509-18.

39. Whitney CW, Lind BK, Wahl PW. Quality assurance and quality control in longitudinal studies. Epidemiol Rev. 1998;20(1):71-80.

Published article

Papavarnavas *et al. AIDS Res Ther (2017) 14:23*
DOI 10.1186/s12981-017-0149-8

AIDS Research and Therapy

RESEARCH Open Access

Factors associated with loss to follow-up after occupational HIV exposure in Cape Town, South Africa: a retrospective cohort study

Nectarios Sophocles Papavarnavas[1], Kathryn Manning[1], Fahd Conrad[2], Milah Govender[3] and Gary Maartens[4*]

Abstract

Background: There is limited data on factors associated with loss to follow-up (LTFU) of health care workers (HCWs) following occupational exposure to HIV, and most studies were conducted in an era when poorly tolerated antiretrovirals like zidovudine were used.

Methods: A retrospective cohort study was conducted of HCWs attending a referral hospital's Occupational Health Clinic in Cape Town, South Africa for post-exposure prophylaxis (PEP) during a period when tenofovir was available. Our primary outcome was LTFU at the 3-month visit. We selected seven variables a priori for our logistic regression model and ensured there were at least 10 outcome events per variable to minimize bias.

Results: Two hundred and ninety-three folders were evaluated for descriptive analysis. LTFU worsened with successive visits: 36% at 6 weeks, 60% at 3 months, and 72% at 6 months. In multivariate analysis at the 3-month visit LTFU was associated with age (adjusted odds ratio (aOR), 0.6 per 10-year increase [95% CI, 0.5–0.9]), HCW category of doctor (aOR 2.7 [95% CI, 1.3–5.5]), and time from exposure to receiving PEP of more than 24 h (aOR 5.9 [95% CI, 1.3–26.9]).

Conclusion: We identified factors associated with LTFU of HCWs after occupational HIV exposure, which could be used to target interventions to improve follow-up.

Keywords: Loss to follow-up, Post exposure prophylaxis, Health care workers, HIV

Background

The World Health Organization (WHO) estimates 3 million occupational human immunodeficiency virus (HIV) percutaneous exposures occur among 35 million healthcare workers (HCWs) annually, with 90% of exposures occurring in resource limited settings [1]. HCWs exposed to potentially infectious material from a source patient with HIV infection, or unknown HIV status, are offered post-exposure prophylaxis (PEP) if this is appropriate, and attend several follow-up visits for PEP toxicity monitoring and exclusion of HIV infection. Although HIV seroconversion following occupational exposure is uncommon, early diagnosis is critical as treatment of early HIV infection reduces the risk of HIV transmission and has direct benefits for the individual by reducing morbidity and mortality [2, 3].

Attendance of HCWs to follow-up visits after occupational exposure to HIV has been highly variable, ranging from 0 to 98.9% in observational studies [4–13]. A literature search yielded three studies that evaluated factors associated with attendance to follow-up [6, 12, 13]. Two studies found that the type of HCW category did not influence attendance to follow-up, [12, 13] but one study found that HCW category did influence attendance to follow-up [6]. One study identified being exposed to an HIV seropositive source increased attendance to follow-up, [13] but another found this had no effect [6]. One study [13] reported that type of exposure and time to reporting did not influence attendance to follow-up; and women had better attendance to follow-up than men [13]. Sample size calculations were not reported in any of these three studies. Furthermore, many of the PEP

*Correspondence: gary.maartens@uct.ac.za
[4] Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town 7925, South Africa
Full list of author information is available at the end of the article

regimens used in these studies included poorly tolerated antiretroviral drugs. A recent systematic review reported that tenofovir disoproxil fumarate (TDF) based PEP was better tolerated with higher completion rates than zidovudine based PEP, which used to be the standard of care [14]. The WHO now recommends the use of TDF as part of the backbone for PEP regimens [15].

We aimed to evaluate factors associated with loss to follow-up (LTFU) following occupational exposure to HIV in a referral hospital in Cape Town, South Africa, where the HIV prevalence is 12.7% [16]. We conducted our study in a period when we switched to TDF based PEP, and ensured we had sufficient power to determine variables associated with LTFU.

Methods

Study setting

Data was collected from the Occupational Health Clinic (OHC) of Groote Schuur Hospital, a referral hospital in Cape Town, South Africa. HCWs who have significant occupational HIV exposure are started on PEP if they present within 72 h of the exposure. During the study period the South African national guidelines for PEP recommended the use of TDF and emtricitabine for exposures presenting within 72 h. The policy of adding a 3rd antiretroviral (usually a boosted protease inhibitor) was changed during the study period: initially this was added only for high risk exposures, but subsequently this was added for all exposures. HCWs are counselled about the risks of HIV, the need to document HIV testing for possible compensation, and potential adverse drug reactions to PEP. HIV status of the HCW was determined at baseline using 4th generation Roche COBAS HIV-1/2 Combo automated test with a confirmatory Siemens Integral 4th generation ELISA. PEP was discontinued in HCWs who tested HIV seropositive at baseline. HIV testing was repeated at week 6 (when HCWs were informed that HIV tests may be false negative), and months 3 and 6 after the exposure. Confidentiality of HCWs is protected by keeping all files in the OHC and not in the general records department; only OHC clinic staff are able to access the files.

Study design

We conducted a retrospective cohort review to identify the factors associated with LTFU in HCWs following occupational HIV exposure. The OHC maintains an electronic database of all visits related to HCW occupational HIV exposures. We collected data from the database and additional data from folders between January 2013 and September 2015, with 29 additional folders obtained in 2012.

Outcomes

The primary outcome was the proportion of HCWs LTFU at the 3-month visit, which is the key follow-up date to determine if HIV seroconversion has occurred, in keeping with the WHO guidelines [15]. Secondary outcomes were the proportion of HCWs LTFU at the 6-week and 6-month visits.

Data collection

Data collection at the OHC is collated from an "Occupational Health Clinic Percutaneous Inoculation Report" form. The data are collected each time the HCW presents for follow-up or when contacted by telephone. This form is completed by the occupational health worker on duty, who is either the nurse or doctor. Once 6 months have lapsed since the last visit, the data collected are recorded in an electronic database using Microsoft Excel and HCW folders are then archived in the clinic.

Study population

Inclusion criteria

HCWs were categorized into three groups: 'Doctors', 'Students' and 'Allied Health Professionals' (e.g. nursing, physiotherapists, occupational therapists, administrative clerks, pharmacists, and emergency medical services). HCWs were included if they were exposed to potentially infectious material from patients who are HIV-infected or HIV status unknown and attended the OHC. The following materials were deemed to be potentially infectious: pleural, pericardial, peritoneal, cerebrospinal, synovial fluid, amniotic fluid, and blood [17].

Exclusion criteria

Exclusion criteria were: HCW tested HIV seropositive at baseline; exposed to a HIV seronegative source; those who requested follow-up at a private doctor or who went back to their own training institutions, such as elective students; multiple exposures within the 6-month follow-up period; exposures deemed to be from non-infectious material [17].

Sample size estimation

We selected seven variables a priori for inclusion into our model based on our review of the literature: age at exposure, sex, HCW category, type of exposure, source patient HIV status, dual or triple antiretroviral therapy (ART), and time from exposure to time of receiving PEP. Assuming 25% LTFU at 3 months, [12] we required a sample size of 280 to ensure a minimum of 10 outcome events per variable, which are needed to improve precision and minimize bias in logistic regression models [18].

Statistical analysis

All statistical analysis was performed using Stata (Version 13.1; Stata Corp, College Station, Texas, USA). Descriptive statistics were used to characterize the total sample, and results were expressed as median (interquartile range) for non-normally distributed continuous variables, and frequencies and percentages for categorical variables.

We used separate multivariable logistic regression models for each time point to identify factors associated with LTFU at the 3-month, 6-week, and 6-month follow-up visits. The full model approach was utilized using a priori selected variables in order to ensure decreased risk of selection bias and overfitting [19]. This approach allows multiple epidemiological variables to be assessed independently while controlling effects of other variables [20]. Univariate analysis was used to estimate crude odds ratios (ORs) and 95% confidence intervals (95% CIs), while multivariable logistic regression provided adjusted estimates for odds of LTFU at each time point. Odds ratios were presented with 95% CIs and a level of $P < 0.05$ was considered statically significant.

Results

Two hundred and sixty-four folders were obtained between January 2013 and September 2015, with an additional 29 folders collected according to alphabetical order in 2012. There was incomplete data on 12 HCWs who were included in the descriptive analysis but excluded from the univariate and multivariate analysis as shown in Fig. 1.

The characteristics of the 293 patients from our cohort are shown in Table 1. The dual nucleotide/nucleoside reverse transcriptase inhibitors used in PEP were TDF (97%), zidovudine (2%), and stavudine (1%); all of which were combined with either lamivudine or emtricitabine. The third agent used in 210 HCWs who were given triple ART was lopinavir/ritonavir (82%), atazanavir/ritonavir (13%), raltegravir (4%), and efavirenz (1%).

LTFU at the various visits were: 36% at 6 weeks, 60% at 3 months, and 72% at 6 months (Table 1). The univariate and multivariate analysis of variables associated with LTFU at the 3-month visit are shown in Table 2. In the multivariate analysis, significant risk factors associated with LTFU were: younger age, HCW category of doctor, and time from exposure to receiving PEP of more than 24 h. The multivariate analysis of variables associated with LTFU at the 6-week and 6-month follow-up visits are shown in Table 3. Variables associated with LTFU at the 6-week visit were: male sex and HCW category of doctor. Variables associated with LTFU at the 6-month visit were similar to the 3-month visit: younger age, HCW category of doctor, and time from exposure to receiving PEP of more than 24 h.

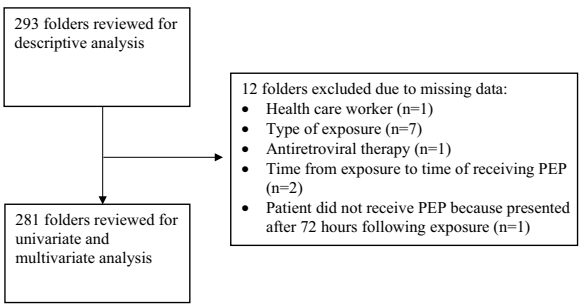


Fig. 1 Flow chart illustrating data set of health care workers chosen for analysis

Table 1 Baseline characteristics and follow-up of 293 health care workers with occupational exposure

Variable	Sample (n)
Age, median (IQR)	28 (24–35)
Sex	
Women	197 (67%)
Men	96 (33%)
Health care worker[a]	
Allied health professional	85 (29%)
Doctor	100 (34%)
Student	107 (37%)
Type of exposure[b]	
Hollow-bore	137 (48%)
Mucocutaneous	86 (30%)
Solid sharp	63 (22%)
Source patient HIV status	
Positive	246 (84%)
Unknown	47 (16%)
Antiretroviral[c,f]	
Dual	81 (28%)
Triple	210 (72%)
Time from exposure to receiving PEP[d] (h)	
<24	268 (92%)
24–48	17 (6%)
48–72	1 (0.3%)
>72	4 (1.4%)
Loss to follow-up[e]	
6 weeks	100 (36%)
3 months	169 (60%)
6 months	203 (72%)

Number with missing data: [a] n = 1, [b] n = 7, [c] n = 1, [d] n = 2, [e] n = 12

[f] One health care worker did not receive PEP because presented too late

LTFU by category of HCW at the various visits is shown in Fig. 2, with doctors having the highest proportion LTFU.

Table 2 Variables associated with loss to follow-up at 3 months

Variables	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age (per 10-year increase)	0.7 (0.5–0.9)	0.003	0.6 (0.5–0.9)	0.011
Sex				
Women [a]				
Men	1.4 (0.8–2.4)	0.190	1.4 (0.8–2.5)	0.262
Health care worker				
Allied health professional[a]				
Doctor	2.9 (1.6–5.4)	0.001	2.7 (1.3–5.5)	0.006
Student	2.0 (1.1–3.6)	0.022	1.2 (0.6–2.6)	0.584
Type of exposure				
Hollow-bore[a]				
Mucocutaneous	1.6 (0.9–2.9)	0.095	1.1 (0.6–2.2)	0.707
Solid sharp	1.3 (0.7–2.4)	0.377	1.0 (0.5–1.9)	0.948
Source patient HIV status				
Positive	0.9 (0.4–1.8)	0.742	0.5 (0.2–1.1)	0.074
Unknown[a]				
Antiretroviral				
Dual	1.4 (0.8–2.3)	0.250	1.5 (0.8–2.8)	0.228
Triple[a]				
Time from exposure to receiving PEP (h)				
<24[a]				
>24	3.0 (1.0–9.2)	0.052	5.9 (1.3–26.9)	0.023

[a] Reference category

Discussion

We showed that LFTU of HCWs after occupational HIV exposure was high and increased with successive visits. Younger age, the HCW category doctor, and time from exposure to receiving PEP of more than 24 h were associated with LTFU at the 3-month visit, which was our primary endpoint. Men were more likely to be LTFU at the 6-week visit than women. These findings could be used to target interventions designed to improve follow-up.

Our finding that LTFU increases with successive visits is consistent with other studies [9, 12, 13]. We found that younger age was a significant risk factor for LTFU, which is in keeping with other studies [21–23]. The higher LTFU in younger HCWs may be related to the greater change and instability they experience in their younger years [24]. Men tended to be more likely to be LTFU in our study, which is similar to the findings of Escurdero et al. [13].

The majority (207 out of 281) of HCWs in our study were doctors and students. Doctors and students are often involved in invasive medical procedures, which places them at risk of being exposed to infectious material [7, 9, 11, 25]. Furthermore, students and doctors with less than a year's experience, are prone to occupational exposure because of their inexperience [7, 9, 26]. We found that doctors are more likely to be LTFU than other HCW categories. This could be explained by the ease with which doctors can submit their own blood samples for HIV testing instead of attending the OHC. One study, [27] showed a large proportion of HCWs obtained HIV testing outside of the facility where they worked, which they suggested was due to concern surrounding the confidentiality of HIV testing at the facility. Furthermore, doctors may be making their own assessment of the severity of the exposure and may deem it unnecessary to follow-up [28]. In contrast to our findings of increased LTFU in doctors, Gutierrez et al. [6] showed cleaning personnel were more likely to be LTFU. Two other studies found type of HCW category did not influence attendance to follow-up [12, 13].

Longer time from exposure to receiving PEP at the 3-month visit was positively associated with LTFU. This could be explained by HCWs who present after 24 h having a perceived lower benefit from PEP. However, type of exposure and source patient HIV status, which are associated with risk of HIV acquisition, were not associated with LTFU in our cohort.

Escudero et al. [13] also found that type of exposure was not related to attendance to follow-up. Findings from studies that assessed the effect of the source patient's HIV status on LTFU are contradictory, with one study reporting no effect, [6] while another found positive serological status was associated with improved follow up [13].

Table 3 Variables associated with loss to follow-up at 6 weeks and 6 months

Variables	6-week		6-month	
	Adjusted OR	P value	Adjusted OR	P value
Age (per 10-year increase)	1.0 (0.7–1.3)	0.764	0.6 (0.5–0.9)	0.010
Sex				
Women[a]				
Men	1.8 (1.1–3.2)	0.027	1.8 (0.9–3.4)	0.082
Health care worker				
Allied health professional[a]				
Doctor	2.1 (1.1–4.4)	0.034	2.1 (1.0–4.5)	0.049
Student	1.1 (0.5–2.5)	0.750	1.3 (0.6–2.9)	0.532
Type of exposure				
Hollow-bore[a]				
Mucocutaneous	1.0 (0.5–1.9)	0.988	1.2 (0.6–2.5)	0.659
Solid sharp	1.1 (0.5–2.1)	0.857	1.1 (0.5–2.4)	0.728
Source patient HIV status				
Positive	1.0 (0.5–2.2)	0.952	0.7 (0.3–1.7)	0.489
Unknown[a]				
Antiretroviral				
Dual	1.2 (0.6–2.3)	0.544	0.7 (0.4–1.4)	0.333
Triple[a]				
Time from exposure to receiving PEP (h)				
<24[a]				
>24	1.3 (0.5–3.4)	0.552	7.8 (1.0–61)	0.049

[a] Reference category

There are a number of studies which reported that dual ART regimens are better tolerated than triple regimens [29, 30]. However, many of these studies include ART that are no longer used due to toxicity. Newer studies have shown that completion of PEP is based on the tolerability of ART and not on whether dual or triple therapy are used [31, 32]. This could explain why in our cohort there was no correlation between type of ART used and LTFU.

There were several limitations of our study. First, the retrospective cohort design is inherently prone to bias. However, the data was captured by OHC staff on a standard form and we had very little missing data. Second, although we found that time from exposure to receiving PEP was associated with LTFU, the 95% CIs were wide due to the small sample size of HCWs with delayed presentation. Third, we did not explore associations between years of HCW experience and exposure as we did not have this data. Other researchers have reported an association between years of experience and the incidence of occupational exposures [7, 9, 25]. Finally, Groote Schuur Hospital is a tertiary facility with referrals from other hospitals that fall under the University of Cape Town, so our findings may not be generalizable to other settings such as district hospitals.

We have identified factors associated with LTFU, which could be used to target interventions to decrease LTFU. In one study, [13] contacting HCWs by telephone or mail improved attendance to follow-up from 33 to 54%. Schmid et al. [33] suggested attendance to follow-up could be improved with fewer follow-up visits. The WHO has recently advised the final follow-up visit should be at 3 months rather than 6 months [15]. Furthermore, it has been suggested that the last follow-up visit should be at 6 weeks if laboratory 4th generation HIV ELISA tests are utilized, and 8 weeks if 4th generation rapid HIV tests are utilized [34]. Lastly van der Maaten et al. [9] suggested increasing awareness of the availability of PEP through campaigns.

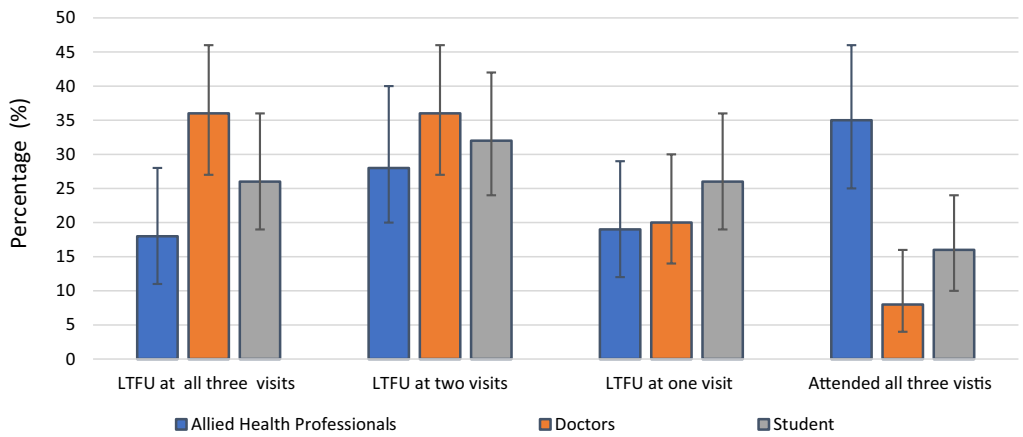


Fig. 2 Percentage loss to follow-up (LTFU) by number of visits of various health care worker categories (visits were scheduled at 6 weeks, 3 months, and 6 months). *Error bars* are shown

Conclusion

We have identified factors associated with LTFU of HCWs after occupational HIV exposure. Future research should identify measures to improve attendance to follow-up, which could be targeted at doctors, younger HCWs, and HCWs with delayed presentation.

Abbreviations

ART: antiretroviral therapy; CIs: confidence intervals; HCW: health care worker; HIV: human immunodeficiency virus; LTFU: loss to follow-up; OHC: Occupational Health Clinic; ORs: odds ratios; PEP: post exposure prophylaxis; TDF: tenofovir disoproxil fumarate; WHO: World Health Organization.

Authors' contributions

NP and GM designed the study, wrote the proposal, analyzed the data, and prepared the manuscript. KM was involved in proposal writing, statistical analysis, and manuscript preparation. NP, FC and MG were involved in data collection. All authors read and approved the final manuscript.

Author details

[1] Department of Medicine, Old Main Building, J-Floor, Groote Schuur Hospital, University of Cape Town, Observatory, Cape Town 7925, South Africa. [2] Trauma and Emergency Unit, Floor E11A, Management Suite, Groote Schuur Hospital, Main Road, Observatory, Cape Town 7925, South Africa. [3] Quality and Safety Unit, Groote Schuur Hospital, Main Road, Observatory, Cape Town 7925, South Africa. [4] Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town 7925, South Africa.

Acknowledgements

Not applicable.

Competing interests

The authors declare they have no competing interests.

Availability of data and materials

Data sets are available from the corresponding author on reasonable request.

Ethics approval

Ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town.

Funding

GM received partial support from the National Research Foundation of South Africa (Grant Reference Number 85810).

Publisher's Note

Received: 21 March 2017 Accepted: 13 April 2017
Published online: 21 April 2017

References

1. World Health Organization. The world health report 2002, chapter 4: reducing risks, promoting healthy life. http://www.who.int/whr/2002/chapter4/en/index8.html. Accessed 21 Mar 2016.
2. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365(6):493–505.
3. Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015;373(9):795–807.
4. de la Tribonniere X, Dufresne MD, Alfandari S, Fontier C, Sobazek A, Valette M, et al. Tolerance, compliance and psychological consequences of post-exposure prophylaxis in health-care workers. Int J STD AIDS. 1998;9(10):591–4.
5. Pungpapong S, Phanuphak P, Pungpapong K, Ruxrungtham K. The risk of occupational HIV exposure among Thai healthcare workers. Southeast Asian J Trop Med Public Health. 1999;30(3):496–503.
6. Gutierrez EB, Heloísa Lopes M, Shikanai Yasuda MA. Accidental exposure to biological material in healthcare workers at a university hospital: evaluation and follow-up of 404 cases. Scand J Infect Dis. 2005;37(4):295–300.
7. Jayanth ST, Kirupakaran H, Brahmadathan KN, Gnanaraj L, Kang G. Needle stick injuries in a tertiary care hospital. Indian J Med Microbiol. 2009;27(1):44–7.
8. Siika AM, Nyandiko WM, Mwangi A, Waxman M, Sidle JE, Kimaiyo SN, et al. The structure and outcomes of a HIV postexposure prophylaxis program in a high HIV prevalence setup in western Kenya. J Acquir Immune Defic Syndr. 2009;51(1):47–53.
9. van der Maaten GC, Nyirenda M, Beadsworth MJ, Chitani A, Allain T, van Oosterhout JJ. Post exposure prophylaxis of HIV transmission after occupational injuries in Queen Elizabeth Central Hospital, Blantyre, Malawi, 2003–2008. Malawi Med J. 2010;22(1):15–9.
10. Olowookere SA, Fatiregun AA. Human immunodeficiency virus postexposure prophylaxis at Ibadan, Nigeria. J Int Assoc Phys AIDS Care (Chic). 2010;9(3):187–90.
11. Onyedum CC, Chukwuka C, Iyoke CA, Omotola OF. HIV postexposure prophylaxis (PEP) in a Nigerian tertiary health institution. J Int Assoc Phys AIDS Care (Chic). 2011;10(3):171–5.
12. Tetteh RA, Nartey ET, Lartey M, Mantel-Teeuwisse AK, Leufkens HG, Nortey PA, et al. Outcomes of a postexposure prophylaxis program at the Korle-Bu Teaching Hospital in Ghana: a retrospective cohort study. J Int Assoc Provid AIDS Care. 2015;14(6):544–52.
13. Escudero DV, Furtado GH, Medeiros EA. Healthcare worker adherence to follow-up after occupational exposure to blood and body fluids at a teaching hospital in Brazil. Ann Occup Hyg. 2015;59(5):566–71.
14. Ford N, Shubber Z, Calmy A, Irvine C, Rapparini C, Ajose O, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis. 2015;60(Suppl 3):S170–6.
15. World Health Organization. Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach: December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. http://www.who.int/hiv/pub/guidelines/arv2013/arvs-2013upplement_dec2014/en. Accessed 17 Sep 2016.
16. Statistics South Africa. Statistical release, mid-year population estimates 2016. http://www.statssa.gov.za/?page_id=1854&PPN=P0302. Accessed 22 Jan 2017.
17. Centers for Disease Control. Update: universal precautions for prevention of transmission of human immunodeficiency virus, hepatitis B virus, and other bloodborne pathogens in health-care settings. MMWR Morb Mortal Wkly Rep. 1988;37(24):377.
18. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373–9.
19. Moons KG, Kengne AP, Woodward M, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: I. Development, internal validation, and assessing the incremental value of a new (bio)marker. Heart. 2012;98(9):683–90.
20. Stoltzfus JC. Logistic regression: a brief primer. Acad Emerg Med. 2011;18(10):1099–104.
21. Corfield L, Schizas A, Noorani A, Williams A. Non-attendance at the colorectal clinic: a prospective audit. Ann R Coll Surg Engl. 2008;90(5):377–80.
22. Milne V, Kearns R, Harrison A. Patient age, ethnicity and waiting times determine the likelihood of non-attendance at a first specialist rheumatology assessment. Int J Rheum Dis. 2014;17(1):19–25.
23. Hynes L, Byrne M, Dinneen SF, McGuire BE, O'Donnell M, Mc Sharry J. Barriers and facilitators associated with attendance at hospital diabetes clinics among young adults (15–30 years) with type 1 diabetes mellitus: a systematic review. Pediatr Diabetes. 2016;17(7):509–18.

24. Arnett JJ. Emerging adulthood. A theory of development from the late teens through the twenties. Am Psychol. 2000;55(5):469–80.
25. Karstaedt AS, Pantanowitz L. Occupational exposure of interns to blood in an area of high HIV seroprevalence. S Afr Med J. 2001;91(1):57–61.
26. Aggarwal V, Seth A, Chandra J, Gupta R, Kumar P, Dutta AK. Occupational exposure to human immunodeficiency virus in health care providers: a retrospective analysis. Indian J Commun Med. 2012;37(1):45–9.
27. Kassa G, Selenic D, Lahuerta M, Gaolathe T, Liu Y, Letang G, et al. Occupational exposure to bloodborne pathogens among health care workers in Botswana: reporting and utilization of postexposure prophylaxis. Am J Infect Control. 2016;44(8):879–85.
28. Elmiyeh B, Whitaker IS, James MJ, Chahal CA, Galea A, Alshafi K. Needlestick injuries in the National Health Service: a culture of silence. J R Soc Med. 2004;97(7):326–7.
29. Puro V. Post-exposure prophylaxis for HIV infection. Ital Regist Post Expo Prophyl. Lancet. 2000;355(9214):1556–7.
30. Bassett IV, Freedberg KA, Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. Clin Infect Dis. 2004;39(3):395–401.
31. Henderson DK. Management of needlestick injuries: a house officer who has a needlestick. JAMA. 2012;307(1):75–84.
32. McAllister J, Read P, McNulty A, Tong WW, Ingersoll A, Carr A. Raltegravir–emtricitabine–tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence. HIV Med. 2014;15(1):13–22.
33. Schmid K, Schwager C, Drexler H. Needlestick injuries and other occupational exposures to body fluids amongst employees and medical students of a German university: incidence and follow-up. J Hosp Infect. 2007;65(2):124–30.
34. Gaines H, Albert J, Axelsson M, Berglund T, Gisslen M, Sonnerborg A, et al. Six-week follow-up after HIV-1 exposure: a position statement from the Public Health Agency of Sweden and the Swedish Reference Group for Antiviral Therapy. Infect Dis (Lond). 2016;48(2):93–8.

Instructions for authors (AIDS Research and Therapy)–abbreviated

Instructions for authors (AIDS Research and Therapy)–abbreviated

For full instructions please click on the following URL: https://aidsrestherapy.biomedcentral.com/submission-guidelines

Preparing you manuscript:

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
- non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
- if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Ethics approval and consent to participate

Manuscripts reporting studies involving human participants, human data or human tissue must:

- include a statement on ethics approval and consent (even where the need for approval was waived)

- include the name of the ethics committee that approved the study and the committee's reference number if appropriate

If your manuscript does not report on or involve the use of any animal or human data or tissue, please state "Not applicable" in this section.

Consent for publication

If your manuscript does not contain data from any individual person, please state "Not applicable" in this section.

Availability of data and materials

All manuscripts must include an 'Availability of data and materials' statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study. By data we mean the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article. We recognise it is not always possible to share research data publicly, for instance when individual privacy could be compromised, and in such instances data availability should still be stated in the manuscript along with any conditions for access.

Competing interests

All financial and non-financial competing interests must be declared in this section.

Please use the authors initials to refer to each author's competing interests in this section.

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section.

Please use initials to refer to each author's contribution in this section.

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

If you do not have anyone to acknowledge, please write "Not applicable" in this section.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

References

All references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text, followed by any in tables or legends.

The reference numbers must be finalized and the reference list fully formatted before submission.

What should be cited?

Only articles, clinical trial registration records and abstracts that have been published or are in press, or are available through public e-print/preprint servers, may be cited.

Unpublished abstracts, unpublished data and personal communications should not be included in the reference list, but may be included in the text and referred to as "unpublished observations" or "personal communications" giving the names of the involved researchers. Obtaining permission to quote personal communications and unpublished data from the cited colleagues is the responsibility of the author. Footnotes are not allowed, but endnotes are permitted. Journal abbreviations follow Index Medicus/MEDLINE.

Any in press articles cited within the references and necessary for the reviewers' assessment of the manuscript should be made available if requested by the editorial office.

Preparing main manuscript text

- Use double line spacing
- Include line and page numbering
- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF
- Do not use page breaks in your manuscript

Style and language

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood.

Please note that the use of a language editing service is not a requirement for publication in the journal and does not imply or guarantee that the article will be selected for peer review or accepted.

Preparing figures

When preparing figures, please follow the formatting instructions below.

- Figures should be provided as separate files, not embedded in the main manuscript file.
- Each figure of a manuscript should be submitted as a single file that fits on a single page in portrait format.
- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.
- Individual figure files should not exceed 10 MB. If a suitable format is chosen, this file size is adequate for extremely high quality figures.

Preparing tables

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.
- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.
- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.
- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.
- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.
- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.
- Color and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained in a table legend.
- Commas should not be used to indicate numerical values.

Preparing additional files

As the length and quantity of data is not restricted for many article types, authors can provide datasets, tables, movies, or other information as additional files.

DPTC approval

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
E-mail : Bernadette.Eick@westerncape.gov.za

Professor G. Maartens
Pharmacology Division
K-Floor – Old Main Building

E-mail: Gary.Maartens@uct.ac.za / taripapas@yahoo.com

Dear Professor Maartens

RESEARCH PROJECT: Factors Affecting Loss To Follow-Up After Occupational HIV Exposure Among Health Care Workers Attending The Groote Schuur Hospital Occupation Health Clinic (MMed Candidate Dr N. S. Papavardavas)

Your recent letter to the hospital refers.

You are hereby granted permission to proceed with your research and is valid until **30th May 2017**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary may be used.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please introduce yourself to the person in charge of an area before commencing.
f) Please discuss the study with the HOD before commencing.
g) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
h) Confidentiality must be maintained at all times.
i) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
j) **Once research is complete, please submit a copy of the publication or report.**

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 20 May 2016
BE/vms
C.C. Mr L. Naidoo, Professor E. Weimann

G46 Management Suite, Old Main Building,
Observatory 7925

Private Bag X,
Observatory, 7935

Tel: +27 21 404 6288 fax: +27 21 404 6125

www.capegateway.go.v.za

Ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 May 2016

HREC REF: 283/2016

Prof G Maartens
Pharmacology Division
K Floor
Old Main Building

Dear Prof Maartens

PROJECT TITLE: FACTORS AFFECTING LOSS TO FOLLOW-UP AFTER OCCUPATIONAL HIV EXPOSURE AMONG HEALTH CARE WORKERS ATTENDING THE GROOTE SCHUUR HOSPITAL OCCUPATIONAL HEALTH CLINIC (MMed candidate- Dr NS Papavarnavas)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study. This is subject to approval from Occupational Health Clinic at GSH and institutional approval.

Approval is granted for one year until the 30th May 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student Dr NS Papavarnavas is involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC 283/2016