

## Original article

# A retrospective of occupational post-exposure prophylaxis against HIV infection in healthcare workers at King Chulalongkorn Memorial Hospital

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## Abstract

**Background:** Healthcare workers are at risk for exposure to diseases through direct contact with patients. A large number of newly registered antiretroviral drugs currently available, both in monotherapy and in combination formulations, has led to adjustments in clinical practice for human immunodeficiency virus (HIV) prophylaxis. Therefore, analysis of antiretroviral drug regimens used, to determine whether they meet clinical guidelines or not, is important to ensure safety for healthcare workers.

**Objective:** This study aimed to investigate the antiretroviral drug regimens received by healthcare workers.

**Methods:** Retrospective data were collected, from patients diagnosed by ICD-10 criteria from January 1, 2019 to December 31, 2022, by the researcher. The data from an electronic database, which was created specifically for research purpose, were screened and confidential.

**Results:** During the period between January 1, 2019 and December 31, 2022, at the emergency room, there were 121 visits from 106 healthcare workers, who had occupational accidents and requested antiretroviral therapy to prevent post-exposure HIV infection. In 116 of those visits, which represented 95.9%, physicians prescribed antiretroviral drugs no later than 72 hours after exposure, which was in line with clinical guidelines. Most of those who received antiretroviral drugs in 2019, 2020, and 2021 were prescribed rilpivirine + tenofovir disoproxil fumarate /emtricitabine. This regimen accounted for 77.2%, 82.2%, and 78.1% in each year, respectively. While for those who received antiretroviral drugs in 2022, the majority of them were prescribed dolutegravir + tenofovir disoproxil fumarate /emtricitabine, which represented 85.7%. Common adverse effects found from antiretroviral drugs were nausea, vomiting, jaundice, and facial numbness.

**Conclusion:** At King Chulalongkorn Memorial Hospital, occupational post-exposure prophylaxis prescriptions in healthcare workers were consistent with Thailand National Guidelines on HIV/AIDS diagnosis, treatment, and prevention.

**Keywords:** Accident, antiretroviral drugs, healthcare workers, occupational post-exposure prophylaxis against HIV infection.

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Received: July 6, 2023

Revised: September 20, 2023

Accepted: October 26, 2023

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Nowadays, there is an increasing number of HIV-infected patients seeking healthcare services in hospitals. The estimated numbers of people living with HIV in years 2000, 2005, 2010, 2015, 2016, 2017, and 2021 were 683,841; 555,808; 493,932; 437,700; 449,309; 439,610; and 520,000 individuals, respectively.<sup>(1-2)</sup> It can be observed that since the years 2015, 2016, 2017, and 2021, the number of patients has been on the rise. This puts healthcare workers as high-risk group due to their direct contact with service recipients, who may or may not be infected with HIV. Despite their highest level of self-protection by adhering to the safety precautions that treat all human blood and bodily fluids as if they were known to be infectious (standard precautions)<sup>(3,4)</sup>, there are still high risks of occupational transmission of HIV infection, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections for those healthcare workers who are not careful or fail to follow standard precautions.<sup>(5)</sup>

Standard precautions are intended to be applied to the care of all patients in all health-care settings, regardless of the suspected or confirmed presence of an infectious agent. These precautions constitute the primary strategy for infection prevention. They are based on the principle that all blood and other bodily fluids, secretions and excretions, excluding perspiration, may contain transmissible infectious agents. These precautions include: hand hygiene; the use of gloves, a gown, a mask, eye protection or a face shield, depending on the anticipated exposure, and safe injection practices. Also, equipment or items in the patient environment likely to have been contaminated with infectious bodily fluids must be handled appropriately to prevent transmission of infectious agents. Respiratory hygiene/cough etiquette could also be part of the set of standard precautions.<sup>(4)</sup>

Therefore, this study aimed to investigate the patterns of antiretroviral drug prescription in the Emergency Department of King Chulalongkorn Memorial Hospital for ensuring healthcare workers' safety. Moreover, analyzed data can help healthcare workers to concern about preventing infection.

## **Materials and methods**

### ***Study design***

This research was a retrospective study that collected data from electronic medical records of healthcare workers, who delivers care and services to the sick and ailing either directly or indirectly, who were treated at the emergency room,

King Chulalongkorn Memorial Hospital, Thai Red Cross Society, between January 1, 2019 to December 31, 2022, who received antiretroviral drugs for occupational post-exposure prophylaxis against HIV infection. There is no official workflow.

### ***Population and sample***

The population of interest in this study were healthcare workers who received antiretroviral therapy after occupational exposure at the emergency room, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, from January 1, 2019 to December 31 2022.

### ***Sample selection method***

#### ***Inclusion criteria***

Healthcare workers who had been subjected to occupational accidents, including those involving needle sticks, sharp objects, and exposure of patient's blood or body fluids to compromised skin or mucous membranes, at King Chulalongkorn Memorial Hospital, Thai Red Cross Society, from January 1, 2019 to December 31, 2022.

#### ***Exclusion criteria***

Healthcare workers whose information in the electronic medical records was incomplete.

#### ***Data collection tools***

Electronic medical records from King Chulalongkorn Memorial Hospital, Thai Red Cross Society, that had been identified with disease codes from the 10<sup>th</sup> revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). The disease codes used were: A) T81.2 Accidental puncture or laceration during a procedure, not elsewhere classified; B) Z57.8 Occupational exposure to other risk factors; C) Z57.9 Occupational exposure to unspecified risk factor; D) Z20.6 Contact with and (suspected) exposure to human immunodeficiency virus [HIV]; E) Z20.8 Contact with and (suspected) exposure to other communicable diseases; and F) Z11.3 Encounter for screening for infections with a predominantly sexual mode of transmission.

The medical record data has been converted and the patient's identifiable information had been masked, in order to protect the rights and personal information of the patients in accordance with the Personal Data Protection Act 2019. Microsoft Excel version 2019 program was utilized.

### **Research process**

This research followed a retrospective survey study design. The methodology steps were as follows: 1) Determined the topic and scope of the research; 2) Conducted a review of the literature and research on occupational post-exposure prophylaxis against HIV infection in healthcare workers; 3) Developed a research plan and designed data collection tools for retrospective data collection; 4) Wrote a research proposal; 5) Applied for research ethics approval; 6) Created a data collection form that included the needed information: patient's code number, ICD-10 disease code, list of medications used, dosages, duration of therapy, and routes of drug administration; 7) Collected retrospective data from electronic medical records of healthcare workers who received occupational post-exposure antiretroviral prophylaxis at King Chulalongkorn Memorial Hospital, Thai Red Cross Society, from January 1, 2019 to December 31, 2022. Patient information was concealed by conversion of hospital number (HN) to code number and data organization with a modified excel table that showed only antiretroviral use information; 8) Analyzed the characteristic of the sample using descriptive statistics: frequency distribution and percentage, to demonstrate the patterns of antiretroviral drug prescription in the Emergency Department at King Chulalongkorn Memorial Hospital, Thai Red Cross Society; and 9) Summarized the study results.

### **Statistical analysis**

This research utilized descriptive statistics and analyzed the data on categorical data, using the Microsoft Excel program. Frequency and percentage were applied to analyze the data distribution.

## **Results**

### **General information**

The study identified that 106 healthcare workers who received post-exposure prophylaxis against HIV infection made a total of 121 visits. Ninety-three of those healthcare workers made one visit. While 11 of them made two visits, and two made three visits. Their ages ranged between 16 to 48 years with an age average of 27 years. Among these visits, there were 71 made by females, 58.7%, and 50 visits made by males, 41.3%.

The study found that the number of occupational accidents that occurred in the years 2019, 2020, 2021, and 2022 are 37, 30, 24, and 30, respectively.

Classified by the type of healthcare workers who experienced occupational accidents, it was found that physicians had the highest number of accidents at 55 (45.5%). They were followed by nurses, who had 35 accidents (28.9%). Medical students had 15 accidents (12.4%). Nursing assistants had eight accidents (6.6%). Laboratory technicians had four accidents (3.3%), while dentists, medical technology students, nursing student, and orderlies had 1 accident (0.8%) each.

The most common type of accidents among these workers were hollow-bore needle punctures, which occurred 59 times (48.8%), followed by conjunctival /mucous membrane exposures at 25 times (20.7%), and solid needle punctures at 13 times (10.7%). Cuts from other sharp objects and non-intact skin exposures both occurred nine times (7.4%) each. Lastly, scalpel cuts occurred six times (5.0%).

The tests on the sources of blood or bodily fluids revealed 26 cases of anti-HIV negative results, which accounted for 21.5%, 36 cases of anti-HIV positive results (29.8%), and 59 cases of unknown status (48.8%).

The study found that, when sorted by the time interval between the prescription of antiretroviral drugs and the accident, those cases could be divided into five following groups: 108 cases (89.3%) received antiretroviral drugs within 24 hours; five cases (4.1%) received antiretroviral drugs within 25 - 48 hours; three cases (2.5%) received antiretroviral drugs within 49 - 72 hours; one case (0.9%) received antiretroviral drugs within more than 72 hours; and four cases (3.3%) did not receive antiretroviral drugs.

The recommendation from the Thailand National Guidelines that all healthcare workers who may have come into contact with HIV should consult a specialist physician, who has been appointed by the hospital as a consultant in case of occupational exposure, within 72 hours. In this study, healthcare workers received consultation with an infectious disease physician 109 times (90.1%), and did not seek consultation with an infectious disease physician 12 times (9.9%).

Laboratory tests are a necessary basis before initiating HIV post-exposure prophylaxis. Thailand national guidelines recommending testing for Anti-HIV, CBC, Cr, SGPT, HBsAg, and Anti-HCV. The study found that 90 cases were tested for all CBC, CR, SGPT, Anti-HIV, HBsAg, Anti-HBs, and Anti-HCV (77.0%). Twenty-one cases were tested for only Anti-HIV, HBsAg, Anti-HBs, and Anti-HCV (18.0%).

Two were tested for only Anti-HIV (1.7%). Four cases did not receive any laboratory testing (3.4%).

As for antiretroviral regimens, if the source of blood or bodily fluid has detectable viral load or no viral load test result, the Thailand National Guidelines on HIV/AIDS treatment and prevention 2017 recommend using an NRTI-based regimen in combination with rilpivirine (RPV) or protease inhibitors (PIs). However, Thailand National Guidelines on HIV Diagnosis, treatment, and prevention 2020/2021 and 2021/2022 recommend using an NRTI-based regimen in combination with dolutegravir (DTG). In the study, healthcare workers who received antiretroviral therapy in years between 2019 and 2021 were mostly on an NRTI-based regimen combined with rilpivirine, or to be more specific, rilpivirine in combination with tenofovir disoproxil/emtricitabine (TDF/FTC co-formulation tablets), which accounted for 77.2, 82.2, and 78.1% in each year respectively. While healthcare workers who received antiretroviral therapy in 2022 were mostly on an NRTI-based regimen combined with dolutegravir, namely dolutegravir in combination with tenofovir disoproxil/emtricitabine (TDF/FTC co-formulation tablets), which accounted for 85.7%, as shown in **Table 1**.

There were 117 cases of healthcare workers who receiving antiretroviral drugs after occupational accidents, and there were four cases that antiretroviral drugs were not prescribed. Among those who received the drugs, there were 54 cases of workers who completed the 4 week treatment and came to the 1 month follow-up visit; they represented 46.2%. There were 31 cases of healthcare workers who did not come to the follow-up visit but were tested for Anti-HIV; they accounted for 26.5%. There were 30 cases of workers who did not come to the follow-up visit and were not tested for Anti-HIV; they accounted for 25.6%.

The study found that from those healthcare workers who received antiretroviral drugs and came to the 1 month follow-up visit, 48 cases experienced no side effect from the antiretroviral drugs, which accounted for 88.9%. Four cases (7.4%) experienced mild side effects: nausea, vomiting, dizziness, and rash, which could be alleviated by drugs, and able to complete the 4 week treatment. Lastly, Two cases (3.7%) experienced severe side effects: jaundice and facial numbness, that required doctors to consider changing drug regimens.

**Table 1.** Numbers and percentages of the sample classified by antiretroviral regimen and year.

Antiretroviral regimen	Number of pills (day)	Number of cases			
		2019	2020	2021	2022
DTG/TDF/FTC	1				15
DTG+TDF/FTC	2 (1 + 1)	2	3	7	15
DTG+TDF+3TC	4 (1 + 1 + 2)	1			
DTG+DRV+RTV	4 (1 + 1 + 2)		1		
RAL+TDF/FTC	3 (2 + 1)	8	2		
RAL+TDF+3TC	5 (2 + 1 + 2)	1			
RPV+TDF/FTC	2 (1 + 1)	44	37	25	5
RPV+TDF+3TC	3 (1 + 1 + 1)		1		
TDF/FTC+3TC	2 (1 + 1)	1			
EVG/COBI/FTC/TAF	1		1		
<b>Total</b>		<b>57</b>	<b>45</b>	<b>32</b>	<b>35</b>

COBI, Cobicistat; DRV, Darunavir; DTG, Dolutegravir; EVG, Elvitegravir; FTC, Emtricitabine; RAL, Raltegravir, RPV, Rilpivirine; RTV, Ritonavir; TAF, Tenofovir alafenamide fumarate; TDF, Tenofovir disoproxil fumarate; 3TC, Lamivudine

## Discussion

Based on the retrospective data retrieval, it was found that among healthcare workers who had experienced occupational accidents and received antiretroviral treatment at the emergency room, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, from 2019 to 2022 the majority of them were women aged between 16 and 48 years, with an average age of 27 years. The majority of accidents involved physicians, followed by nurses and medical students, which were similar to results from studies conducted at Siriraj Hospital <sup>(6)</sup>, Ramathibodi Hospital <sup>(7)</sup>, and Trang Hospital <sup>(8)</sup>, from which, the healthcare workers involved were women and the majority of accidents happened to nurses, followed by physicians, and medical students.

In terms of annual incidence of occupational accidents, the numbers of accidents were similar across the board. In years 2019, 2020, 2021, and 2022, there were 37, 30, 24, and 30 accidents, respectively. The incidences rate is lower compared to results from studies conducted at Siriraj Hospital <sup>(6)</sup>, Ramathibodi Hospital <sup>(7)</sup>, and Trang Hospital. <sup>(8)</sup> These findings highlight the importance of investigating the causes of these accidents and implementing preventive measures to reduce the occurrence and achieve a decreasing trend in the future.

The most common type of accidents among healthcare workers was hollow-bore needle punctures, which aligned with the findings from studies conducted at Ramathibodi Hospital <sup>(7)</sup> and Trang Hospital. <sup>(8)</sup>

In this study, it was found that 29.8% of sources of blood or bodily fluids involved in the accidents had positive Anti-HIV status, while the studies at Ramathibodi Hospital and Trang Hospital reported percentages of 15.9% and 9.3%, respectively. This variation can be attributed to the difference in the prevalence of HIV infection in those specific areas.

Accidental exposures to blood or bodily fluids, needle punctures, and cuts from sharp objects, not only pose a risk of HIV infection, but also carry the potential for transmission of other blood-borne diseases such as HBV and HCV infections, which are chronic and incurable. Therefore, in order to ensure the maximum safety of healthcare workers who have experienced occupational accidents, testing for HBsAg, Anti-HBs, and Anti-HCV are essential. Furthermore, since antiretroviral drugs can cause adverse reactions, baseline laboratory tests should be performed to evaluate potential adverse reactions

before initiating antiretroviral treatment. These tests may include complete blood count (CBC), creatinine (Cr), and serum glutamic pyruvic transaminase (SGPT). However, in this study, it was observed that 3.5% of workers did not receive these essential laboratory services, and only 76.9% received comprehensive laboratory testing. Therefore, it is important to implement more stringent guidelines to ensure maximum safety of healthcare workers.

Guidelines on administering antiretroviral drugs to prevent HIV infection in healthcare workers following exposure to blood or bodily fluids have been derived from various sources, including animal experiments<sup>(9)</sup>, studies on reducing maternal to infant transmission<sup>(10)</sup>, and case reports across multiple studies. These findings have led to recommendations for the use of antiretroviral drugs for post-exposure prophylaxis in healthcare workers. Similar guidelines have been developed in Thailand<sup>(11)</sup>, The United States of America <sup>(12)</sup>, England <sup>(13)</sup>, and other European countries.<sup>(14)</sup> In case there is an indication for antiretroviral therapy, the drugs must be administered as soon as possible, ideally within 1 - 2 hours after exposure and no later than 72 hours after exposure. The study found that the majority of the workers (89.3%) had access to antiretroviral drugs within 24 hours after exposure, which was in accordance with both Thai and international clinical guidelines. Specifically, among 117 cases of healthcare workers receiving antiretroviral drugs, 108 cases (92.3%) received them within 24 hours, while 116 (99.2%) received them within 72 hours.

On choosing an appropriate antiretroviral regimen, Thailand National Guidelines on HIV/AIDS Diagnosis, treatment, and prevention recommend choosing regimen based on risk of HIV infection and information on the source of exposure. If the source of exposure is HIV-positive, viral load of the source and possibility of drug-resistant virus must be evaluated.<sup>(11)</sup> The study found that there were a total of 10 antiretroviral drug regimens that had been used at the emergency room, King Chulalongkorn Memorial Hospital. The most often used regimen was rilpivirine (RPV) 25 mg once daily in combination with tenofovir disoproxil fumarate (TDF) 300 mg/emtricitabine (FTC) 200 mg once daily (RPV+TDF/FTC), which had been prescribed 111 times out of 169 prescriptions, accounting for 65.7%. It was followed by dolutegravir (DTG) 50 mg once daily in combination with tenofovir disoproxil fumarate (TDF) 300 mg/Emtricitabine (FTC) 200 mg once daily

(DTG+TDF/FTC), which had been prescribed 27 times or 16.0% of 169 prescriptions, and DTG/TDF/FTC (co-formulation tablet) which had been prescribed 15 times or 8.9% of 169 prescriptions. The majority of workers were prescribed the antiretroviral regimen recommended in that particular year by the national guidelines from 2017<sup>(15)</sup>, 2020/2021<sup>(16)</sup>, and 2021/2022.<sup>(11)</sup> In 2019, when RPV+TDF/FTC was the recommended primary regimen, it was prescribed 44 times from 57 prescriptions (77.2%). While in 2020, when RPV+TDF/FTC was the recommended primary regimen, it was prescribed 37 times from 45 prescriptions (82.2%). In 2021, both RPV+TDF/FTC and DTG+TDF/FTC were recommended. Therefore, out of 32 antiretroviral drugs prescriptions, RPV+TDF/FTC was prescribed 25 times (78.1%) and DTG+TDF/FTC was prescribed 7 times (21.9%). While in 2022, when both DTG+TDF/FTC and DTG/TDF/FTC (co-formulation tablet) were recommended, out of 35 antiretroviral drug prescriptions, both DTG+TDF/FTC and DTG/TDF/FTC (co-formulation tablet) were prescribed 15 times (42.9%) each. In 2019 and 2020, prescriptions of raltegravir or dolutegravir in combination with NRTIs (TDF/FTC or TDF/3TC) were infrequent, since both raltegravir and dolutegravir were listed on Thailand National List of Essential Medicine as medicines used only for patients with specific needs. They were used mainly in cases where patients have developed resistance to primary and secondary regimens. Later, in 2021 and 2022, there was an increasing trend in prescriptions of dolutegravir in combination with TDF/FTC or TDF/3TC, which was in accordance with recommendations from Thailand National Guidelines on HIV/AIDS Diagnosis, Treatment, and Prevention 2021/2022. The antiretroviral regimen prescribed between 2019 and 2022 is the recommended choice.

A previous study reported that the use of single-tablet HIV regimens could improve patient adherence and completion rates to more than 90.0%.<sup>(17)</sup> King Chulalongkorn Memorial Hospital, Thai Red Cross Society, has begun selling DTG/TDF/FTC co-formulation tablets since June 2021. The study found that in 2021, there were no prescriptions of the co-formulation tablets. But in 2022, 42.9% of workers were prescribed the co-formulation tablets, which showed an increase in use of the co-formulation tablets when compared to 2021.

On completion rates, at 1 month follow-up visit after initiating therapy, it was found that only 46.2%

of the workers came to the follow-up visit, while 26.5% did not come to the follow-up visit but were tested for Anti-HIV, and 25.6% were not tested for Anti-HIV after taking antiretroviral drugs. The follow-up rate is lower compared to results from studies conducted at Siriraj Hospital<sup>(6)</sup>, Ramathibodi Hospital<sup>(7)</sup>, and Trang Hospital.<sup>(8)</sup> Therefore, physicians and emergency room pharmacists should emphasize the importance of the follow-up visit after 4 week antiretroviral treatment course completion and regular blood testing to ensure the safety of healthcare workers.

Adverse reactions to anti-HIV drugs are another crucial factor to consider. All antiretroviral drugs can cause side effects, particularly gastrointestinal side effects.<sup>(11)</sup> In this study, adverse reactions observed were nausea, vomiting, dizziness, and rash, which was consistent with the findings from studies conducted in Thailand at Ramathibodi Hospital<sup>(7)</sup> and Trang Hospital.<sup>(8)</sup> However, these adverse reactions can be alleviated by medication. The incidence of adverse events among healthcare workers who received anti-HIV drugs and attended follow-up visits at one month was 7.7%. In other words, adverse reactions were found in 4 out of 52 workers who attended follow-up visits. Two of those workers required change of drug regimen, one due to jaundice and the other due to right-sided facial numbness. When considering the antiretroviral regimen used, it was found that the worker with jaundice was initially prescribed atazanavir/ritonavir (ATV/r) 300/100 mg once daily in combination with tenofovir disoproxil fumarate (TDF) 300 mg/emtricitabine (FTC) 200 mg once daily (ATV/r+TDF/FTC), which was later changed by the physician to rilpivirine (RPV) 25 mg once daily in combination with tenofovir disoproxil fumarate (TDF) 300 mg/Emtricitabine (FTC) 200 mg once daily (RPV+TDF/FTC). At 1-month follow-up visit, no adverse reactions from antiretroviral drugs were found. The other worker with right-sided facial numbness was initially treated with a combination of raltegravir (RAL) 400 mg every 12 hours and tenofovir disoproxil fumarate (TDF) 300 mg/Emtricitabine (FTC) 200 mg once daily (RAL+TDF/FTC), which was subsequently changed by the physician to raltegravir (RAL) 400 mg every 12 hours in combination with tenofovir disoproxil fumarate (TDF) 300 mg and lamivudine (3TC) 300 mg once daily (RAL+TDF+3TC). At the scheduled 1 month follow-up, no adverse reactions from antiretroviral drugs were found.

The major issue concerning antiretroviral therapy in healthcare workers is the lack of awareness regarding the importance of the follow-up visit after completing the 4 week treatment. Out of 117 cases, 54 of them came to the 1 month follow-up visit, which accounted for 46.2%. While 61 from 117 did not come to the 1 month follow-up visit, which accounted for 52.1%. This necessitates the collaboration of the multidisciplinary team to encourage attending the follow-up visit so that the physician can assess the treatment outcomes.

The limitation of this study was its retrospective nature, which resulted in incomplete patient information. This incompleteness can be partly attributed to physicians at the emergency room documenting medical records using different ICD-10 codes, based on different diagnostic guidelines, which may differ from the data collected by the research team. Consequently, the number of healthcare workers receiving services at the emergency room, might be underestimated. Additionally, some workers might choose not to seek treatment due to knowledge that the source was HIV-negative. Therefore, further investigations are needed to gather more information.

## Conclusion

Healthcare workers who had occupational accidents and received antiretroviral treatment at the emergency room, King Chulalongkorn Memorial Hospital, Thai Red Cross Society, were given antiretroviral agents that were in line with recommendations from Thailand National Guidelines on HIV/AIDS diagnosis, treatment, and prevention. There is a shift towards prescribing single-tablet regimens, which is now becoming more common when compared to before 2022. This approach greatly improves adherence and completion rates. At the follow-up visit, after 4 week treatment completion, there was no HIV infection among those healthcare workers. The most common side effects from antiretroviral drugs were nausea, vomiting, jaundice, and facial numbness. One of the major issues was the lack of awareness among healthcare workers regarding the importance of follow-up laboratory testing after four weeks of antiretroviral therapy, which is necessary for physicians to evaluate the treatment progress. Therefore, physicians should educate workers on occupational accident prevention and emphasize the need for anti-HIV testing at one month after initiating antiretroviral therapy.

Pharmacists also play a vital role in advising workers to take their medications on time and regularly until their scheduled appointments, which will lead to the maximum safety for all healthcare workers.

## Acknowledgements

The authors would like to express our deepest gratitude to all subjects who were recruited in this study.

## Conflict of interest statement

Each of the authors has completed an ICMJE disclosure form. None of the authors declare any potential or actual relationship, activity, or interest related to the content of this article.

## Data sharing statement

All authors have completed and submitted the International Committee of Medical Journal Editors Uniform Disclosure Form for Potential Conflicts of Interest. None of the authors disclose any conflict of interest.

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