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Current Recommendations on the Workup and Post-exposure Prophylaxis for HIV, HBV, and HCV in Healthcare Workers

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Opinion statement

Hepatitis B, hepatitis C, and HIV are the most commonly acquired infections related to occupational exposure in the health care setting. Measures to reduce the risk of transmission in health care workers (HCW) include primary prevention and post-exposure prophylaxis (PEP). Primary prevention essentially includes the adoption of standard precautions to avoid percutaneous or mucocutaneous injuries and hepatitis B vaccination. PEP varies according to both the source patient and HCW serologic status. So far PEP is not approved for hepatitis C. The post-exposure management for hepatitis B will depend on the vaccination and immune status of the HCW. Immune HCW do not need prophylaxis. For non-immune HCW, prophylaxis includes hepatitis B vaccination and immune globulin within 7 days of the exposure. HIV-exposed HCW should initiate prophylaxis as soon as possible, using three drugs regardless of the type of exposure risk. New regimens including integrase inhibitors and protease inhibitors have improved HCW adherence to PEP. Timely reporting any exposure remains a challenge and is a priority for an adequate work up and management. HCW frequently do not recognize high-risk exposures and do not seek post exposure prophylactic management. Multidisciplinary efforts are still needed to improve HCW awareness and adherence to PEP.

Introduction

Hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV) are the three main blood-borne infections associated with occupational exposure in the health-care and laboratory setting [1, 2], and represent a significant burden to HCW.

An estimated 385,000 percutaneous injuries (PI) occur annually in the United States of America [3]. The incidence of PI per 100,000 inpatient-days has been calculated as 2.43 in nurses, 0.23 in medical doctors, and 0.2 for technicians [4]. The average number of sharp object injuries ranges from 0.18 to 2.53 per HCW per year in the USA [5]. In 2000, a model including 14 geographical regions estimated 16,000 HCV infections, 66,000 HBV infections, and 1000 HIV infections had occurred in health care workers worldwide in that year. The proportion of infections attributable to percutaneous injuries was 39%, 37%, and 4.4% for HCV, HBV, and HIV respectively [5]. The prevalence of HBV infection in HCW has been estimated to be 10 times higher than the general population in non-vaccinated individuals [6].

The average risk of transmission after a PI from an infected source is 0.3% for HIV [7, 8], and ranges from 1.8 to 10% for HCV according to different studies [8–10]. HBV is highly infectious; the virus has been demonstrated to survive for more than 7 days in environmental surfaces, even in the absence of visible blood. The probability of infection is much higher and depends on the expression of hepatitis B e antigen (HBeAg). The risk of clinical hepatitis and seroconversion is 22-31% and 37-62%, if the source patient is HBeAg positive, compared to 1-6% and 23-37% if the source patient is HBeAg negative [6]. This is due to the high viral load present in the blood of patients positive for HBeAg (10^7 – 10^9 virions/mL) [11]. The risk of transmission is increased in developing countries, both because the prevalence of infection in the general population is usually higher and due to a lower rate of vaccination coverage among HCW against HBV [12].

Besides the morbidity and mortality associated with these infectious diseases, PI also generate medical and lost productivity costs. In 2004, the estimated total annual cost for needle-stick injuries in the healthcare industry was 107.3 million of which 96% resulted from testing and prophylaxis and 4% from treating long-term infections [13].

Preventive measures and standard precautions are the most important strategies to reduce occupational blood-borne infection in HCW. The risk of acquisition of HBV infection has declined effectively since the introduction of immunization to all HCW (1982); in the United States the number of HBV infections among HCW declined from 17,000 in 1983 to 263 in 2010 [14•]. Vaccination is the most important measure to prevent HBV infection [6]. PEP use for HIV has been recommended for occupational exposure since the late 1980s [15]. In 1997, the CDC published the first case-control study showing the benefits of zidovudine use as PEP in exposed HCW [16]. PEP has reduced significantly the incidence of occupationally acquired blood-borne infections. Since 1985, the National HIV Surveillance System has recorded 58 confirmed and 150 possible occupationally acquired HIV infections. Only one case of occupational HIV infection has been reported since 1999 [17, 18]. This is probably the result of a better implementation of preventive strategies as well as PEP. There is currently no recommended PEP for HCV. So far no data support the use of antivirals for PEP in HCV, but options for treating acute HCV infection are arising and effective [19–21].

HCWs perception is also an important factor for effective PEP. They seem to underestimate the risk of exposure. PI reporting and PEP coverage tend to be low among medical personnel [22–24]. Lack of knowledge is the most common reason for not reporting (41.6%) [23]. This has important consequences since reporting PI is critical to adopt measures such as PEP to prevent infections.

This article provides a brief description of preventive measures and PEP related to occupational exposure to the three more common blood-borne infections and comments briefly on HCW's perception and knowledge of PEP.

Prevention and early management

Prevention

Primary prevention remains the most important strategy for averting occupationally acquired blood-borne infection. This includes the use of

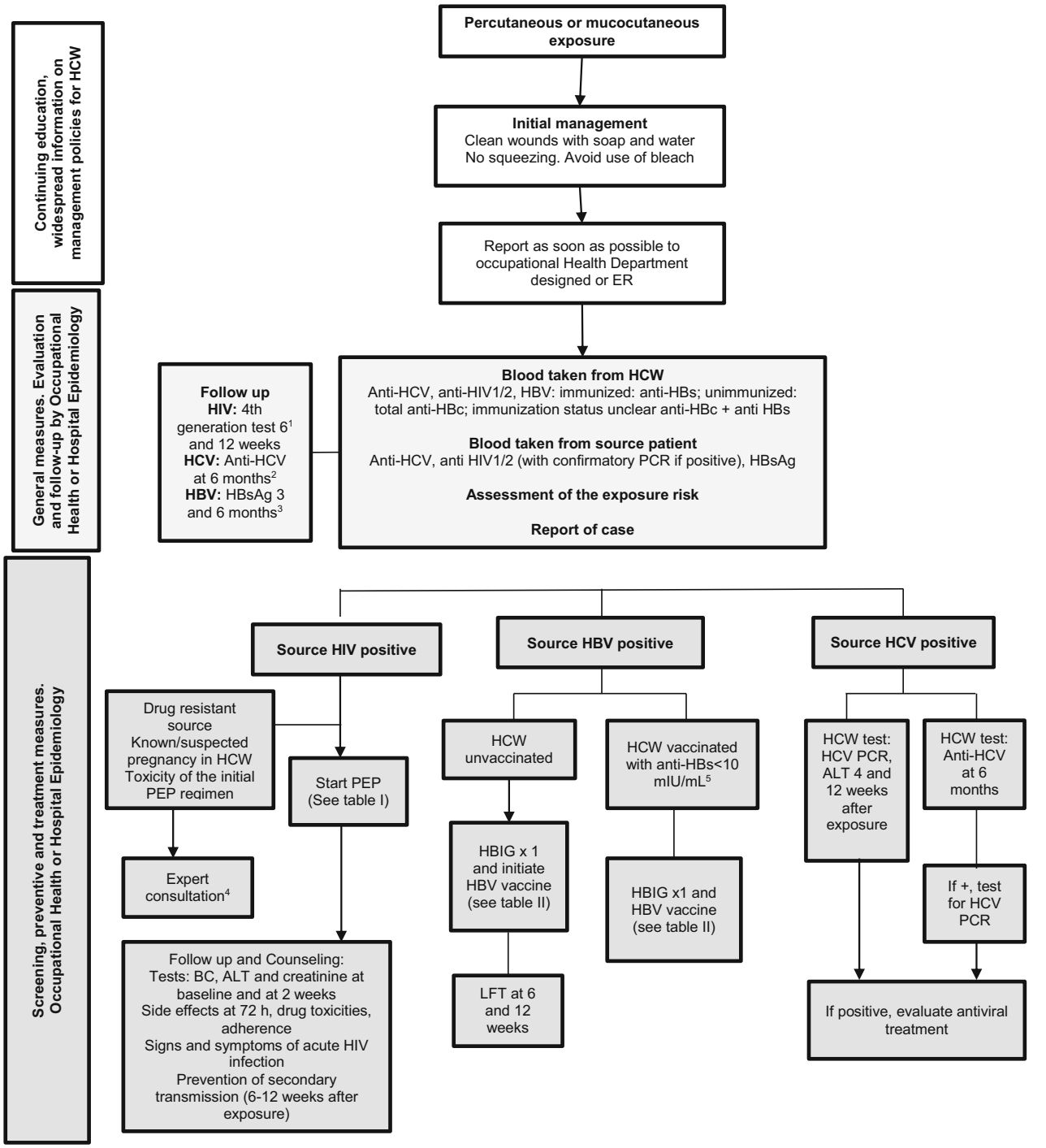
safe medical devices, personal protective equipment and adequate work practices, as well as immunity to preventable diseases [3, 25, 26]. However, low compliance with personal protective equipment has been reported as a frequent cause of percutaneous injuries or mucocutaneous exposure [4, 27]. The adoption of local regulations and policies supports and promotes safety in the workplace and reduces blood-borne pathogen associated infections [11]. Education and regular training of staff are low-cost measures that should be adopted more rigorously to improve compliance to standard precautions [3, 28]. Surveillance programs should be established in every workplace, including a comprehensive plan to prevent the transmission of occupationally acquired infections with PEP provision as needed [8].

HBV vaccine is an effective and safe vaccine that consists of three doses of a recombinant hepatitis B surface antigen (HBsAg) protein at 0, 1, and 6 month interval. Post-vaccination seroprotection is attained in approximately 92% of HCW aged < 40 years and 84% of those aged > 40 years [6]. All HCW should know their immune response to vaccination. For first time immunized HCW, an anti-HBs (antibodies against surface antigen of HBV) quantitative titer should be obtained 1 to 2 months after the third dose of the vaccine. Immunocompetent HCW with titers ≥10 mIU/mL are considered immune for life and no further testing is needed. Prospective studies have suggested that protection against acute and chronic HBV infection persists for more than 20 years among immunocompetent HBV vaccine responders [29]. However, since anti-HBs decrease over time, the recommendation is that every HCW is tested for anti-HBs upon hire. Those with <10 mIU/mL should receive three additional doses and be tested again for anti-HBs, 1 to 2 months after [14•]. A cumulative response rate of 69% has been estimated among initial non-responders after 6 doses [6]. Non-responders to revaccination (six doses) should be carefully advised to report any exposure of risk to evaluate the need for hepatitis B immune globulin (HBIG).

Early management

Every health care setting should have clear and standard protocols for post-exposure management. Protocols should be widely distributed among HCW, and continuous medical education should be done periodically to assure accurate information on the know-how. The instance to contact in case of exposure should be clearly identified. Any percutaneous or mucocutaneous exposure should receive immediate management. This includes immediate cleansing of the injury site with soap and water. Exposed membranes should be flushed with water, avoiding the use of bleach and other agents. Squeezing the wound is not recommended [8], neither is testing needles or other sharp objects [30]. After cleaning the wound, the HCW should report the injury to the health service in charge of occupational health. The report must include details of the exposure to assess the risk.

Figure 1 shows the steps of the work up after a percutaneous or mucocutaneous exposure. Baseline evaluation includes testing the source patient and the exposed HCW. Testing includes HIV antibodies, HBsAg, and HCV antibodies. Counseling to the HCW should include the risk of blood-borne infection according to the exposure and the risk of transmission to others. The exposed person should avoid donating plasma or other corporal fluids during the follow up period. Specific recommendations for HIV, HBV, and HVC will be reviewed in the next sections.



ER: emergency department. LFT: Liver function test. CBC: cell blood count. ALT: alanine aminotransferase. PCR: Polymerase Chain Reaction

1. If HIV is not a fourth generation test, perform last test at 6 months
2. Depend of strategy implemented: (PCR HCV or Anti-HCV)
3. HBsAg may be a false positive if test within 2 weeks of Hepatitis B vaccine
4. Expert consultation should not delay PEP
5. Vaccinated HCW with anti-HBs ≥ 10mIU/mL do not need further treatment

Fig. 1. Work up and post-exposure management for HIV, HBV, and HCB in health care workers. Adapted from [6–8, 31].

HIV postexposure prophylaxis

Testing the exposed HCW

All individuals exposed and potential candidates for PEP should be tested for HIV (ELISA) and be negative to receive PEP. Options for HIV tests include HIV rapid test kits, fourth generation HIV tests that include p24 antigen and conventional HIV antibody tests. The use of fourth generation HIV tests shortens the window period around 5 days compared to the other tests [17].

Testing the source patient

The source patient should be tested for HIV, HBV, and HCV. If the source patient reports high risk factors for HIV in the last 6 weeks, a viral load should be done. Otherwise, one negative HIV test is enough to rule out the need for PEP. In general, consented testing should be done. If the source patient does not accept testing, unconsented testing can be done under special circumstances and with adequate advice [32].

If the source patient has previously been diagnosed HIV positive, antiretroviral use history, failures and last viral loads should be obtained, to choose the best antiretroviral (ARV) options for PEP. This should be done without delaying PEP initiation. If the source patient is currently taking ARV and has a suppressed viral load, CDC guidelines recommend that PEP should be offered anyway, considering the viral load only reflects cell-free virus in peripheral blood and that HIV persists in latently infected cells [7]. On the contrary, UK guidelines do not recommend PEP in those circumstances, considering it has been proven that HIV suppression reduces transmission risk in many studies and the risk remains but extremely low [33, 34].

Indications for PEP

PEP is recommended for all individuals with a history of percutaneous, mucosal or non-intact skin exposures to potentially infected blood, bloody fluids or other potentially infectious fluids such as semen; vaginal secretions; breast milk; and cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids [7, 8]. PEP should be started immediately after reporting the injury, ideally in the first 2 hours of exposure. Although the interval of time for which PEP is effective is not clear, recommendations are to initiate prophylaxis within 36-72 hours of the exposure [7, 8]. The first dose of PEP should be administered before the source patient test results are available, and stopped if they are negative. If the source is unknown, the probability for HIV infection in the source and the risk of transmission should be evaluated on an individual basis to decide the need for PEP.

Choosing PEP

To ease protocols and improve uptake and adherence, current guidelines no longer recommend risk stratification of the exposure to choose a PEP regimen. The current proposal is to use three drugs in every case according to the CDC [7, 8]. WHO guidelines consider that three drugs are preferred but two drugs could be an acceptable option when three drugs are not available or concern over toxicity exists (this is mainly for limited resources countries) [35].

Table 1 represents the different regimens recommended by international organisms. In general, the recommended backbone is tenofovir with emtricitabine or lamivudine, which have demonstrated less toxicity compared to zidovudine [7, 8, 36]. The preferred third drug now includes an integrase inhibitor (tenofovir, emtricitabine, and raltegravir), due to lower side effects, improved safety and tolerability of the drug. However, cost can be a limitation for this regimen, which is why WHO guidelines still recommend a PI such as atazanavir or lopinavir boosted with ritonavir as the third component [35, 36]. Efavirenz is still considered as an alternative regimen in the WHO guidelines, however concern has risen regarding associated adverse effects (mainly neurological). A systematic review conducted by the WHO comparing different regimens for PEP showed higher completion rates and lower adverse effects with raltegravir as the third drug, compared to protease inhibitors. In that systematic review no studies using efavirenz as a third drug were included [36]. Many studies have analyzed factors associated with non-completion in HCW. Efavirenz as part of the regimen has been associated with increased failures to complete the 4 weeks of treatment [37]. If the HCW is pregnant, efavirenz should be avoided.

ARV prophylaxis can be provided as a starter pack (for the first 72 hours) to ensure the exposed individual comes back for follow up, assess tolerance, improve adherence, complete testing, and counseling. Prescribing the whole 28-day treatment from the beginning is also accepted [35].

When choosing a regimen it is important to consider the probability for the virus to be resistant, and the tolerability and adherence of the HCW. If the source patient is known to be HIV positive then a history of ARV and any resistance pattern has to be obtained. If a genotype was done, it should be used to choose the best regimen for the HCW. PEP should be administrated for 4 weeks.

Follow up

First contact after starting ARV should be at 72 hours to evaluate signs and symptoms of toxicity. Regular follow up with the HCW is important to improve adherence. Side effects of drugs are a common reason for them to stop PEP.

Table 1. Post exposure prophylaxis regimens recommended for HIV [8, 17, 35]

	Recommended regimens	Alternative regimens	Comments
Backbone	Truvada (Tenofovir 300 mg +Emtricitabine 200 mg) qd	Tenofovir 300 mg+ lamivudine 300 mg qd	Tenofovir + emtricitabine/lamivudine have showed better completion rates and lower adverse events.
3rd drug	Raltegravir 400 mg bid Dolutegravir 50 mg qd Darunavir 800 mg/ritonavir 100 mg qd Atazanavir 300 mg/ritonavir 100 mg qd Lopinavir 400 mg/ritonavir 100 mg bid	Efavirenz 600 mg qd	Limited availability of integrase inhibitors and darunavir in developing countries Discontinuation rates of atazanavir due to jaundice Discontinuation of lopinavir due to gastrointestinal toxicity Central nervous system adverse events related to efavirenz

Serologic follow up should be done at 6 weeks, 12 weeks, and 6 months. CDC guidelines recommend last testing at 4 months if a 4th generation test is performed. The exception is if the source patient is co-infected with hepatitis C, in this case serologic testing should go up to 12 months since seroconversion can be delayed. The use of condoms is recommended while taking PEP and until serologic testing at 12 weeks is negative. If the HCW is breastfeeding, recommendation should be to avoid breast-feeding for 12 weeks.

HBV post exposure management

Testing the exposed HCW

HCW who are documented vaccine responders (known anti-HBS ≥ 10 mIU/mL after ≥3 doses of the vaccine) do not need any post exposure prophylaxis. Those with an unknown or incomplete history of HBV vaccination and those who are documented non-responders (anti-HBS <10 mIU/mL after 6 doses of the vaccine) should be tested to rule out HBV infection with total anti-HBc (antibodies against core antigen) and HBsAg.

Testing the source patient

If the source patient is HBsAg positive or untested or unidentifiable, PEP should be initiated with HBV vaccine and HBV immune globulin as soon as possible (ideally in the first 24 hours of exposure) and no later than one week after [1, 6]. If the source patient is HBsAg negative, the HCW should be tested for immunity against vaccine and complete or reinitiate vaccination as needed (see Table 2). The CDC does not recommend testing for immunity to HCW with incomplete vaccination because anti-HBs ≥10 mIU/mL as a correlate of vaccine induced

Table 2. Post exposure management of HBV according to immune status of the HCW and serology of the source patient [6, 30]

Vaccination status of HCW	Source HBsAg positive	Source HBsAg negative
Not vaccinated	HBIG 1 dose and initiate vaccination	Initiate vaccination
Incompletely vaccinated or does not recall a complete schedule	HBIG 1 dose and complete vaccination and follow standard protocol to test for anti-HBs	Complete vaccination and follow standard protocol to test for vaccine response[3]
Vaccinated with an unknown anti-HBs titer	If anti-HBs ≥ 10 mIU/mL: no action needed If anti-HBs < 10 mIU/mL: HBIG 1 dose + initiate standard revaccination	If anti-HBs ≥ 10 mIU/mL – no action needed If anti-HBs < 10 mIU/mL –initiate revaccination and test for anti-HBs[3]
Non-responder to primary schedule of HBV vaccine	HBIG 1 dose + initiate standard revaccination	Initiate revaccination and test for vaccine response[3]
Non-responder to 2 complete schedules of HBV vaccine	HBIG 2 doses, ASAP and after 1 month [2]	No action needed
Vaccine responder[1]	No action needed	No action needed

ASAP- As soon as possible
[1]Vaccine responder is defined as anti-HBs ≥ 10 mIU/mL
[2]HBIG is administered intramuscularly, up to seven days after the exposure
[3] If HBIG is used, anti-HBs should be tested 4-6 months after to avoid false positive results

protection has only been determined for persons who have completed an approved vaccination series.

PEP options

HBIG provides passive anti-HBs, with temporary protection. It is obtained from human plasma known to have high titer of anti-HBs. For non-responders to the vaccine, this is the main method of protection after HBV exposure (see Table 2). The dose recommended for adults is 0.06 mL/kg, the route of administration is intramuscular. Anaphylactic reactions, although rare, may occur. In the occupational settings, multiple doses of HBIG, starting within one week of exposure to HBsAg positive blood provides approximately 75% of protection [6].

However, the current recommendations for HBV PEP are not always available in developing countries. HBIG can be expensive and there is a need for other ways of prevention. Nucleotide analogues (NAs) are widely and successfully used to treat patients with HBV and HIV infection and their efficacy for PEP is being explored. Two studies report anti-HBV NAs containing regimens reduced incident HBV infections in HIV positive patients [38, 39]. Another study described the prevention of viremia in an animal model (Chinese woodchuck) inoculated with a virus similar to HBV who were treated with entecavir and/or a DNA vaccine targeting woodchuck hepatitis virus [40]. Further clinical studies are needed to confirm the efficacy of NAs-based HBV PEP in HCW. So far these are not recommended [6].

Follow up

HCW should be tested for HBsAg at 3 and 6 months from the exposure.

HCV post exposure management

There is no PEP currently recommended for HCV. Hence, compliance to standard precautions remains the cornerstone of preventing occupational exposure to HCV [8, 17].

Testing the exposed HCW

Baseline workup in the exposed HCW includes HCV antibodies, liver function tests, and HVC RNA if antibodies are positive, and should be performed within 48 hours of exposure to evaluate preexisting HCV infection. The exposed HCW that is anti-HCV positive should be managed as chronic HCV infection.

Testing the source patient

The source patient should be tested for HCV antibodies. If the source patient is anti-HCV positive, it is consistent with a presumptive HCV infection and an HCV RNA test should be performed to confirm current infection. Positive HCV antibodies could also be present due to a past HCV infection or a false positive result.

Follow up

All anti-HCV negative HCW exposed to a source with positive HCV antibodies (with or without HCV RNA positive) should be followed up with liver function

tests and HCV RNA test at week 4 and 12; liver function tests and HCV antibodies at week 24 [8]. If the source patient is HCV antibody negative and suspected to have a recent exposure to HCV, a HCV RNA test should be performed.

So far, the use of PEP for hepatitis C is not recommended. PEP has been studied without clear positive results [41••]. IFN given after PI has been unsuccessful [10, 42]. A pilot study examined the efficacy of 4 weeks of weekly peginterferon (PegIFN) administered to 44 of 51 enrolled healthcare personnel following NSI to HCV-positive sources [42]. No cases of HCV transmission occurred in any of the healthcare personnel, including 162 who did not enroll in the study. The recent development of direct-acting antivirals (DAAs) raises the question about new possible effective regimens for PEP. So far DAAs are approved for chronic hepatitis C treatment. Considering an overall low rate of HCV transmission by PI and the high cost of DAAs, evidence to support prophylaxis against hepatitis C in healthcare workers is still low [19, 42].

Others recommend treating the HCV infection before it progresses to chronic HCV [20]. INF therapy after detection of repeatedly positive HCV-RNA assays in the exposed healthcare worker seems a good option considering the cumulative evidence that treating an acute HCV infection is more successful than a chronic HCV infection. However, watchful waiting is also recommended, considering that 20–40% of patients who develop acute HCV will spontaneously clear their infection. In this case, recommendation is no intervention and close monitoring for 3–4 months to document persistent viremia before treatment [43]. The urgency of treating acute infections may be reduced with the notable success of oral DAAs in chronic infections [21, 44].

Health care workers perception of PEP

Underreporting of occupational exposure is frequent among HCW and trainees. Reasons for underreporting include lack of knowledge, lack of time, and estimation that the risk of transmission is low, among others [24]. Studies in highly endemic settings have reported low percentages of training in medical students and nurses [45, 46] with high percentages of PI exposure. In a cross sectional study done in Cambodia among medical students less than half of the students reporting an exposure had been tested for HIV. Only 5% took PEP [46]. Knowledge about PEP in HCW is lacking. Inadequate information in developing countries goes up to 84% of HCW surveyed and lack of PEP use up to 82% [47, 48].

Awareness of the hospital policies regarding PEP improves knowledge on PEP, and would probably improve PEP uptake. Hence, policy communication and education should be a target to improve reporting and uptake of PEP [31]. Implementation of PEP helplines has also improved the implementation of PEP programs [49].

Conclusions

Occupational exposure to HCV, HBV, and HIV represent a significant burden to HCW. The reduction of transmission risk requires adequate prevention and timely post-exposure management. Post exposure prophylaxis has significantly reduced incident infections. Prophylaxis options for HIV have improved, with

new regimens favoring lower toxicity and better adherence. Immune globulin and vaccination are recommended for hepatitis B exposure. Vaccination is an effective and safe tool for prevention of hepatitis B infection, however low coverage is still an issue in HCW. In both hepatitis B and HIV prophylaxis, optimal management might be limited by high costs of treatment (immune globulin and new antiretrovirals), and can be an issue in limited resources countries. The benefit of the use of antivirals for hepatitis B and C prophylaxis is still not confirmed. No prophylaxis has been approved for hepatitis C. Other challenges that remain are underreporting of exposures and low uptake of PEP, mostly due to HCW unawareness of exposure risk. Increased efforts are needed to improve HCW awareness and compliance to existing preventive tools, through education, promotion of reporting, and better implementation of clear protocols in health care settings.

Compliance with Ethical Standards

Conflict of Interest
Alexandra Martin-Onraët, Grace Salazar-Tamayo, and Carolina Perez-Jimenez declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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