CASE
REPORT

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Adverse effects of antiretroviral prophylaxis after occupational exposure to HIV

Efeitos adversos da profilaxia antirretroviral após exposição ocupacional ao HIV

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ABSTRACT | Occupational exposure to biological materials involving risk of human immunodeficiency virus (HIV) transmission is a medical emergency. Post-exposure prophylaxis (PEP) should be started early and administered for 28 days. Since July 2015, the Brazilian Ministry of Health recommends the combined use of three antiretroviral drugs for PEP, which are less toxic and better tolerated than the ones previously used. Nevertheless, almost half of the exposed individuals under PEP exhibit adverse effects, which are usually mild and self-limited. The most frequent adverse events are gastrointestinal disorders, asthenia, headache and dizziness. However, more severe events have been reported, and the rate of non-completion of prophylaxis remains high. In 2017, the Brazilian Ministry of Health modified the first-line PEP regimen involving replacement of the third antiretroviral drug. The present article reports a case of toxicity associated with PEP following an occupational accident involving exposure to HIV infected biological material. In addition, we review the potential adverse effects of antiretroviral drugs included in the prophylactic regimens recommended by the Brazilian Ministry of Health and discuss measures occupational physicians should adopt vis-à-vis these complications.

Keywords | occupational exposure; post-exposure prophylaxis; drug-related side effects and adverse reactions; antiretroviral agents.

RESUMO | A exposição ocupacional a material biológico com risco de transmissão do vírus da imunodeficiência humana (HIV) constitui uma emergência médica. A profilaxia pós-exposição (PEP) deve ser iniciada precocemente e mantida por 28 dias. Desde julho de 2015, o Ministério da Saúde passou a recomendar o uso combinado de três drogas antirretrovirais para a PEP, menos tóxicas e melhor toleradas do que as usadas anteriormente. Apesar disso, quase metade dos expostos em uso da PEP apresenta efeitos adversos. Geralmente, eles são leves e autolimitados. Os mais comuns são alterações gastrointestinais, astenia, cefaleia e tontura. Entretanto, eventos mais graves já foram observados e a taxa de interrupção da profilaxia permanece elevada. Em 2017, o Ministério da Saúde modificou o esquema de primeira linha da PEP, substituindo o terceiro antirretroviral. Esse artigo relata um caso de toxicidade associada ao uso da PEP após exposição ocupacional a material biológico contaminado pelo HIV, traz a revisão dos potenciais efeitos adversos das drogas antirretrovirais que compõem o esquema profilático preconizado pelo Ministério da Saúde e discute a conduta do médico do trabalho diante dessas complicações.

Palavras-chave | exposição ocupacional; profilaxia pós-exposição; efeitos colaterais e reações adversas relacionados a medicamentos; antirretrovirais.

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INTRODUCTION

A total of 47,292 cases of work accidents involving exposure to biological materials were reported in 2014 in Brazil[1], however, the actual number might be much larger. When this type of accident occurs, the risk of transmission of the human immunodeficiency virus (HIV) and need of post-exposure prophylaxis (PEP) should be assessed. For this purpose, four aspects should be taken into consideration: type of biological material involved in the accident, type of exposure, time elapsed from accident to onset of care delivery and serological status of the exposed individual[2,3].

The average risk of HIV transmission after occupational percutaneous exposure to infected blood was estimated as 0.3%[4]. According to the study published in 1997 by Cardo et al.[5], use of zidovudine (AZT) was associated with 81% reduction of the risk of infection with HIV following occupational percutaneous exposure. Several prophylactic regimens were suggested thereafter. In Brazil, the guidelines formulated by the Ministry of Health (MH) in 2015 recommended the use of a combination of three antiretroviral drugs for prophylaxis of infection with HIV following exposure, both occupational or not. This regimen comprised two nucleoside analog reverse transcriptase inhibitors, tenofovir (TDF) and lamivudine (3TC), and one ritonavir (RTV)-boosted protease inhibitor, atazanavir (ATV/r)[2]. In 2017, MH published new "Clinical Protocol and Therapeutic Guidelines for Post-Exposure Prophylaxis against Risk of Infection with HIV, STI and Viral Hepatitis," currently in force, which introduced changes in the first-line regimen. ATV/r was replaced by dolutegravir (DTG), an integrase inhibitor[3]. The duration of prophylaxis is still 28 days, and should be started within the first 72 hours after exposure. Early onset and four-week treatment are crucial to ensure a higher efficacy of intervention[2,3].

The choice of the drugs included in the regimen recommended by MH was based on studies of antiretroviral therapy and pre- and post-exposure prophylaxis, mainly considering the risk of adverse effects and of discontinuation, in addition to dosage, cost and availability of antiretroviral drugs within the Unified Health System. Although compared to the 2015 protocol these drugs are less toxic and better tolerated, all antiretroviral agents might cause adverse effects and develop drug interactions. The most frequent adverse effects are usually mild and transient, but there are also reports of severe events in association with use of the drugs included in the aforementioned regimen[2,3].

The first-line regimen currently recommended (TDF+3TC+DTG) is associated with a smaller number of adverse effects and drug interactions, which contributes to improve adherence and clinical management. The previous regimen including ATV/r remains as an alternative option when DTG cannot be used[3].

The aims of the present study were, based on the report of a case of HIV PEP toxicity, to review the most common, and also the most severe adverse effects associated with use of the PEP regimen recommended by MH, and to discuss the behavior of occupational doctors vis-à-vis such complications. The present case report was approved by the research ethics committee of José de Alencar Gomes da Silva National Cancer Institute and authorized by the involved patient by signing an informed consent form.

CASE DESCRIPTION

A 33-year-old female nurse pricked her finger with the needle she used to puncture the vein of a patient at the hospital emergency department where she works. She was provided immediate care, on which occasion the following laboratory tests were performed: complete blood count (CBC), blood sugar, urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), rapid HIV test, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV). All the tests yielded normal results and the serologic tests were negative. Relative to the source-patient, the rapid HIV test was positive, and infection with HIV was later confirmed by means of immunoassay and Western Blot. PEP was thus started with the regimen recommended by MH at the time of the accident: TDF 300 mg/day, 3TC 300 mg/day and ATV/r 300/100 mg day for 28 days. On the second day of treatment, she presented nausea and vomiting. On day four, she sought the institutional workers' health service complaining of ill feeling, fatigue,

nausea, moderate itch and jaundice. She cried much along the consultation, said she was afraid of seroconversion, and that she felt ill at ease with how the other staff members looked at her as a function of the symptoms she had developed after the onset of antiretroviral medication, jaundice in particular. The following laboratory tests were then performed: CBC, urea, creatinine, AST, ALT, alkaline phosphatase, gamma-glutamyltransferase (GGT) and total bilirubin and fractions. The only abnormal finding was unconjugated hyperbilirubinemia (5.77 mg/dL). On these grounds, the nurse was granted a 10-day leave and referred to the psychology staff of the institutional workers' health service. A specialist in HIV was consulted as to the need to make changes into the PEP regimen. However, the regimen remained the same, and the nurse was subjected to weekly clinical and laboratory monitoring. On day 18, she still complained of ill feeling, fatigue, nausea, bloated stomach and jaundice. The indirect bilirubin was still elevated (5.88 mg/dL). The sick leave was extended for further 19 days. She completed the 28-day PEP with no changes in the regimen, despite the persistence of ill feeling and nausea. These symptoms disappeared once the drugs were discontinued. The indirect bilirubin levels returned to normal (0.38 mg/dL) 11 days after the end of PEP. None of the other laboratory tests yielded abnormal results. HIV serology remained negative 30 and 90 days after exposure. The nurse received care from the psychology staff all along the PEP follow-up period.

DISCUSSION

The first to do in the case of occupational exposure to any biological material is to assess the risk of HIV transmission and the indication of antiretroviral prophylaxis based on the analysis of four aspects:

- type of biological material involved;
- type of exposure;
- time elapsed from accident to care delivery;
- serological status of the exposed individual on the first assessment[2,3].

In the case reported here, the worker was exposed to the patient's blood, which as is known, is an infecting biological material involved in HIV transmission. Other biological materials also representing risk factors are sperm, vaginal fluids, serous membrane fluid, amniotic fluid, cerebrospinal fluid, synovial fluid and breast milk. In the present case, exposure occurred per percutaneous route, on the occasion the nurse's finger was pricked by the needle she used for venipuncture. This type, as well as exposure involving contact with mucous membranes, non-intact skin and bites with blood, is associated with risk of HIV transmission. Therefore, these two aspects already sufficed to characterize occupational exposure to risk of infection with HIV. The worker was provided immediate care at the emergency department of the hospital where she works. This condition is a medical urgency, because when indicated, PEP should be started as early as possible to ensure the efficacy of intervention. The maximum interval from exposure to onset of PEP is 72 hours. After this period, antiretroviral prophylaxis brings no benefits. On the first assessment, also the rapid HIV test was performed; since the result was negative, PEP was indicated. PEP is not indicated when the rapid HIV test is positive. When the results are discordant or non-valid, the decision to start or not PEP should be made together with the exposed individual, and more specific diagnostic tests should be performed[2,3].

When the serological status of the source-patient is known, this information contributes to the decision on the indication of PEP. However, the rapid HIV test cannot be always performed, while the treatment of exposed individuals cannot be delayed, nor be conditioned to the results of the test. In the case reported here, the rapid HIV test was performed for the source-patient, and the positive result obtained corroborated the decision to start PEP[2,3].

More than 50% of the individuals subjected to antiretroviral prophylaxis develops adverse effects. Therefore, it is essential for occupational physicians, especially the ones who work at health care services, to recognize such effects, keep up-to-date in regard to the national guidelines for occupational PEP and be able to explain the aims of PEP to workers, so that the latter rigorously comply with the medication dosage and schedule and the prescribed duration of prophylaxis for it to attain the expected efficacy[3].

Gastrointestinal complaints, such as diarrhea, nausea, vomiting, abdominal discomfort or pain and flatulence are the most frequent adverse effects. They might appear soon after the onset of PEP, as in the case reported here: the worker began complaining of nausea and vomiting on the second day of use. Nausea remained for the full duration of PEP. Another complaint was bloated stomach. Other quite common adverse effects include symptoms such as fatigue, asthenia, headache and dizziness, among others. In the case reported here, the worker complained of ill feeling and fatigue. As a rule, these symptoms have mild-to-moderate intensity and are self-limited, as in the case reported here. For this reason, only symptomatic medication should be recommended as per need. The rate of antiretroviral discontinuation due to adverse events found in studies on PEP varied from 11.7 to 21%[6-8]. Abnormal findings on laboratory tests are usually rare, discrete and transient[3]. Occupational physicians should follow up exposed workers in order to detect these so common adverse effects and reinforce the need to adhere to the regimen in use to ensure the efficacy of prophylaxis.

In the case reported here, the exposed worker exhibited unconjugated hyperbilirubinemia and jaundice starting on PEP day 4. This adverse event was the greatest source of distress for her, due to fear of developing a more serious condition and also to her colleagues' reactions. ATV — included in the first-line PEP regimen used at the time of the accident — was the cause of unconjugated hyperbilirubinemia and jaundice through inhibition of the UGT1A1 enzyme. In one study on antiretroviral therapy, 44% of the patients who received ATV exhibited grade 3–4 hyperbilirubinemia (more than 2.5 times the upper limit of normal) and 5% grade 2–4 jaundice[9]. In a study on PEP with TDF/3TC/ATV/r, hyperbilirubinemia was detected in 87% of the cases and jaundice in 66%, but only two participants discontinued prophylaxis for this reason[10]. In another study on PEP including ATV, jaundice occurred in 16% of the cases[8]. While it affects the external appearance of patients, eventually causing apprehension and even discontinuation of prophylaxis, hyperbilirubinemia is reversible and is not associated with hepatocellular toxicity[8,9]. A part of the task of occupational physicians is to reassure exposed workers about the reversibility of this condition, reinforce the relevance of completing the four-week regimen and to perform clinical and laboratory assessments more often than recommended in the MH guidelines. In the case reported here, the worker performed weekly visits until the end of PEP and the reversion of the adverse effects, and then 30 and 90 days after the accident for anti-HIV testing, as recommended by MH[2,3].

Another significant effect caused by both exposure to HIV and the reaction to antiretroviral drugs used for PEP is the occurrence of mental and emotional disorders in the exposed individuals, including despair, impaired concentration and irritability. In the case reported here, the worker developed depressive mood, fear of becoming ill and fear of the colleagues' opinion following the appearance of jaundice. The psychological impact of occupational exposure to HIV should not be underestimated, as it might induce dysfunction in the personal and professional life of workers, even when seroconversion does not occur. It might also cause psychological disorders, eventually persistent and severe, such as chronic posttraumatic stress disorder. Occupational physicians should pay attention to the possible development of these disorders, and psychosocial support should be an essential component of the care provided during the follow up of exposed health care professionals, as occurred in the case reported here[2,11].

Although rare, more severe adverse events are associated with antiretroviral medication and deserve to be emphasized. Occupational physicians should be aware of the potential nephrotoxicity of TDF, especially among workers with previous kidney disease or risk factors such as poorly controlled arterial hypertension, long history of diabetes or use of potentially nephrotoxic drugs. In such cases, it is recommended for occupational physicians to consult with a specialist about the need to replace TDF. Although the two studies on tolerance to PEP including TDF did not find elevation of the creatinine levels among the exposed individuals[6,7], there is a report of acute kidney failure and Fanconi syndrome in a previously healthy individual 16 days after the onset of PEP including TDF and a RTV-boosted protease inhibitor[12].

Also the risk of severe acute exacerbation of hepatitis at the end of PEP including TDF and 3TC should be considered when exposed workers are infected with the hepatitis B virus. However, the onset of PEP should not be delayed when the serological status of the exposed

worker is unknown. Once the result of the hepatitis B serological test becomes available, occupational physicians should refer infected workers for follow up at a reference service[2,3].

ATV and TDF might be associated with skin toxicity. Severe cases of Stevens-Johnson syndrome and erythema multiforme following use of ATV for antiretroviral therapy were documented. However, the cases of exanthema associated with prophylaxis using TDF and ATV were benign and reverted following the discontinuation of drugs[7,13]. Once again, the task of occupational physicians is to reassure workers and orient them to complete PEP.

Use of ATV for antiretroviral therapy was associated with first-degree atrioventricular block[14]. Although there are no reports of cardiac toxicity among patients subjected to prophylaxis including ATV, it is recommended to orient and monitor workers with previous conduction disorders or concomitantly using medication likely to prolong the PR interval, such as beta blockers, calcium channel blockers and digoxin, for treatment of bradyarrhythmia symptoms.

In regard to more complex cases, in which exposed workers exhibit severe intolerance to the PEP regimen, severe comorbidities, risk of drug interactions or the source-patient is suspected of being infected with drug-resistant HIV, occupational physicians should consult with specialists[2].

Chart 1 summarizes the orientations for occupational physicians vis-à-vis the complications of prophylaxis after occupational exposure to HIV based on the current recommendations formulated by MH.

Chart 1. Orientations for occupational physicians relative to complications of post-exposure prophylaxis, Rio de Janeiro, 2017.

Adverse events	Measures	Rationale
Gastrointestinal disorders, such as diarrhea, nausea, vomiting, abdominal discomfort or pain and flatulence	Do not interrupt prophylaxis Prescribe symptomatic medication as per need	Usually mild and self-limited symptoms
General symptoms, such as fatigue, asthenia, headache and dizziness	Do not interrupt prophylaxis Prescribe symptomatic medication as per need	Usually mild and self-limited symptoms
Unconjugated hyperbilirubinemia and jaundice	Do not interrupt prophylaxis Weekly clinical-laboratory follow up	Not associated with hepatocellular toxicity Reversible after the end of prophylaxis
Mental and emotional disorders	Offer psychosocial support until the end of follow up	Might cause dysfunction in personal and professional life Might be severe and persistent
Nephrotoxicity	Workers with previous kidney disease or significant risk factors: consult with a specialist and consider replacing TDF Occurrence of severe nephrotoxicity: consult with a specialist	TDF has a potential for nephrotoxicity, which is however rare when used for prophylaxis
Acute severe exacerbation of hepatitis among individuals infected with the hepatitis B virus	Start first-line regimen Refer workers with positive hepatitis B virus serology to a reference service	Potential risk for liver flare following TDF and 3TC discontinuation among individuals infected with the hepatitis B virus
Skin disorders	Do not interrupt prophylaxis	Usually benign exanthema Improvement after the end of prophylaxis
Heart conduction disorders	Orient and monitor workers with previous conduction disorders or concomitantly using drugs likely to prolong the PR interval for treatment of bradyarrhythmia symptoms under use of ATV Occurrence of AVB: consult with a specialist	Potential risk of AVB

TDF: tenofovir; ATV: atazanavir; AVB: atrioventricular block; 3TC: lamivudine.
Source: Guidelines for post-exposure prophylaxis formulated by the Ministry of Health in 2015 and 2017.

REFERENCES

1. Departamento Intersindical de Estatística e Estudos Socioeconômicos. Anuário da saúde do trabalhador. São Paulo: Departamento Intersindical de Estatística e Estudos Socioeconômicos; 2016.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Profilaxia Antirretroviral Pós-Exposição de Risco à Infecção pelo HIV. Brasília: Ministério da Saúde; 2015.
3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Profilaxia Pós-Exposição (PEP) de Risco à Infecção pelo HIV, IST e Hepatites Virais. Brasília: Ministério da Saúde; 2017.
4. Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med. 1997;102(5 Suppl. 2):9-15. https://doi.org/10.1016/S0002-9343(97)89441-7
5. Cardo DM, Culver DH, Ciesielski CA, Srivastana PU, Marcus R, Abiteboul B, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med. 1997;337(21):1485-90. https://doi.org/10.1056/NEJM199711203372101
6. Mayer KH, Mimiaga MJ, Cohen D, Grasso C, Bill R, Van Derwark R, et al. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (NPEP) in a Boston Community Health Center. J Acquir Immune Defic Syndr. 2008;47(4):494-9. https://doi.org/10.1097/QAI.0b013e318162afcb
7. Tosini W, Muller P, Prazuck T, Benandelmoumen G, Peyrouse E, Christian B, et al. Tolerability of HIV postexposure prophylaxis with tenofovir/emtricitabine and lopinavir/ritonavir tablet formulation. AIDS. 2010;24(15):2375-80. https://doi.org/10.1097/QAD.0b013e32833dfad1
8. Diaz-Brito V, León A, Knobel H, Peraire J, Domingo P, Clotet B, et al. Post-exposure prophylaxis for HIV infection: a clinical trial comparing lopinavir/ritonavir versus atazanavir each with zidovudine/lamivudine. Antiviral Therapy. 2012;17:337-46. https://doi.org/10.3851/IMP1955
9. McDonald C, Uy J, Hu W, Wirtz V, Juethner S, Butcher D, et al. Clinical Significance of Hyperbilirubinemia Among HIV-1-Infected Patients Treated with Atazanavir/Ritonavir Through 96 Weeks in the CASTLE Study. AIDS Patient Care STDs. 2012;26(5):259-64. https://doi.org/10.1089/apc.2011.0092
10. Burty C, Prazuck C, Truchetet F, Christian B, Penalba C, Salmon-Ceron D, et al. Tolerability of Two Different Combinations of Antiretroviral Drugs Including Tenofovir Used in Occupational and Nonoccupational Postexposure Prophylaxis for HIV. AIDS Patient Care STDs. 2010;24(1):1-3. https://doi.org/10.1089/apc.2009.0263
11. Worthington MG, Ross JJ, Bergeron EK. Posttraumatic Stress Disorder After Occupational HIV Exposure: Two Cases and a Literature Review. Infect Control Hosp Epidemiol. 2006;27(2):215-7. https://doi.org/10.1086/501155
12. Penot P, Gosset C, Verine J, Molina JM. Tenofovir disoproxil fumarate-induced Fanconi's syndrome during HIV postexposure prophylaxis. AIDS. 2016;30(8):1311-3. https://doi.org/10.1097/QAD.0000000000001054
13. Swamy VHT, Mothi SN, Sudheer AP, Srirama B, Kumar AP. Atazanavir/Ritonavir Induced Maculopapular Rash in Post Exposure Prophylaxis - A Case Report. Int J Pharma Res Health Sci. 2016;4(5):1433-4. https://doi.org/10.21276/ijprhs.2016.05.18
14. Busti AJ, Tsikouris JP, Peeters MJ, Das SR, Canham RM, Abdullah SM, et al. A prospective evaluation of the effect of atazanavir on the QTc interval and QTc dispersion in HIV-positive patients. HIV Med. 2006;7:317-22. https://doi.org/10.1111/j.1468-1293.2006.00382.x

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