Special article

Croatian Recommendations for Dialysis of HIV-Positive Patients

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Abstract

Human immunodeficiency virus (HIV) infection may be associated with renal impairment since about 0.4% of all HIV-positive patients develop end-stage renal disease. The share of patients with HIV infection in hemodialysis centers throughout the world ranges from 0.3% to as high as 38%. In Croatia, renal replacement therapy was needed by 1% of all the HIV-positive patients from 1985 until the end of 2014. Healthcare professionals (HP) should be aware of the risks of occupational exposure to blood-borne infections in their daily work. Performing dialysis in HIV-positive patients increases the risk of exposure to HIV during the extracorporeal circulation of the infected blood. However, post-exposure prophylaxis (PEP) with effective antiretroviral drugs significantly reduces the risk of infection after occupational exposure. On behalf of the Croatian Society of Nephrology, Dialysis and Transplantation, the authors of this paper have proposed recommendations for the management of HIV-positive patients on dialysis, which aim to prevent the transmission of HIV among patients and HPs. The important recommendations include the following:

1. When the need arises, it is necessary to provide HIV-positive patients with dialysis in the vicinity of their place of residence.
2. HIV-positive patients should be dialyzed with a separate hemodialysis machine in an isolated area. Alternatively, they can be dialyzed in an area for the hemodialysis of HCV-positive and/or HBV-positive patients.
3. Specialized and trained personnel should be provided during the hemodialysis procedure, together with strict compliance with the standard precautions for the prevention of blood-borne infections.
4. There should be a good and prompt cooperation with the National Referral Center for HIV infection.

Keywords: human immunodeficiency virus, HIV, dialysis, recommendations, blood transmitted infection, exposure, prevention

Introduction

When the disease caused by the human immunodeficiency virus (HIV) is left untreated, it generally progresses inexorably in all infected persons, from asymptomatic infection to the condition of complete destruction of the immune system, resulting in acquired immunodeficiency syndrome (AIDS) [1]. However, today, thanks to antiretroviral therapy (ART), HIV infection has become a chronic condition that can be successfully managed long-term [2-4]. Some observational studies have suggested that persons infected with HIV can live nearly as long as non-infected persons [5,6]. Owing to the prolonged life expectancy of persons infected with HIV, there has been an increase in the chronic diseases and complications associated with the treatment of HIV and the drugs used to manage HIV diseases, including acute and/or chronic renal disease [7]. In HIV-infected persons, kidney damage may occur as a result of the direct effects of the virus, such as HIV-associated nephropathy (HIVAN), as well as indirect effects of HIV, including complications of immunodeficiency caused by HIV, secondary (oppor-
tunistic) infections and side effects from the treatment of these conditions, i.e., nephrotoxic drugs. Chronic renal failure is associated with common risk factors, such as age, hypertension and diabetes, but also with certain antiretroviral drugs (tenofovir, indinavir and others) [8].

Epidemiology of Renal Failure in Persons Infected with HIV

Croatia, with an annual rate of new HIV diagnoses of 10-20/1,000,000 inhabitants, is among the countries with the lowest prevalence rates. According to the HIV/AIDS Registry of the Croatian National Institute of Public Health, from 1985, when the first cases of HIV infection were recorded in Croatia, to the end of 2014, a total of 1,194 HIV-positive individuals have been registered. Possible factors responsible for an increased risk of developing acute/chronic renal failure (ARF/CRF) are advanced age, female sex, diabetes, hypertension, intravenous drug abuse, certain coinfections (hepatitis B virus, hepatitis C virus), low CD4 T-lymphocyte count, the use of some antiretroviral drugs, a history of renal impairment and high HIV viral load. Numerous studies have already demonstrated that the use of antiretroviral drugs and suppression of the viral load can improve kidney function and reduce proteinuria, thereby indicating that HIV has a nephrotoxic effect. This is particularly evident in Afro-Americans, for whom the risk for CRF is nearly three times higher than for Caucasians [9].

In a large study involving over 35,000 patients, 0.4% of them developed stage 4 or 5 renal failure (GFR <30 ml/min or dialysis or transplant), with an incidence rate of 0.67/1,000 person years of follow-up (PYFU) [8]. In a cross-sectional multicenter EuroSIDA survey, the prevalence of end-stage renal disease (ESRD) was 0.5% [10], and an observational cohort study conducted in Great Britain showed a 3.8-fold increase in ESRD among the black HIV-positive patients in the cohort during the 12-year study period [11]. The percentage of patients infected with HIV in dialysis centers around the world ranges from 0.3% to as high as 38% [12]. From 1985 to 1999 the percentage of dialysis centers providing care to HIV-positive patients in the United States increased from 11% to 39% [13].

Methods for Treating Chronic Renal Failure in HIV-infected Patients

For HIV-infected patients who develop severe renal impairment, whether acute or chronic, replacement of renal function is necessary. They can be treated with hemodialysis (HD), peritoneal dialysis (PD), and may be candidates for kidney transplantation [12-14]. In the aforementioned EuroSIDA survey, out of 122 patients with ESRD, 96 received dialysis and 26 renal transplant. The most frequent causes of ESRD were HIV-associated nephropathy and other glomerulonephritis [10]. The advantages and disadvantages of each form of dialysis in HIV-infected patients are presented in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1. Advantages and disadvantages of dialysis in patients with HIV-infection</th>
<th>adapted from 11,14,15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>METHOD</strong></td>
<td><strong>ADVANTAGES</strong></td>
</tr>
<tr>
<td></td>
<td>- Transmission of the virus by dialysis machines has not been confirmed*</td>
</tr>
<tr>
<td></td>
<td>- Lowering of the viral load in the blood during the procedure</td>
</tr>
<tr>
<td>HEMODIALYSIS</td>
<td>- Higher risk of HCV-infection for patients</td>
</tr>
<tr>
<td></td>
<td>- Higher frequency of contacts with patients’ blood, higher risk of infection transmission to personnel</td>
</tr>
<tr>
<td></td>
<td>- Higher costs</td>
</tr>
<tr>
<td></td>
<td>- Possibility of viral replication in the dialysate**</td>
</tr>
<tr>
<td></td>
<td>- Higher incidence of peritonitis (due to opportunistic microorganisms)</td>
</tr>
<tr>
<td><strong>PERITONEAL DIALYSIS</strong></td>
<td>- Less risk of infection transmission to personnel</td>
</tr>
<tr>
<td></td>
<td>- Lower costs</td>
</tr>
</tbody>
</table>

*The size of the HIV virion is about 105 nm and the pores of the dialyzer are 1-7 nm. Viral RNA is not detectable in the dialysate.

**Peritoneal dialysate is less contagious than blood but the virus can replicate in the dialysate: up to 7 days at room temperature and up to 2 days in empty lines.

Additional shortcomings of PD are the loss of protein into the dialysate in already asthenic patients, cognitive motor dysfunction in advanced HIV diseases and reduced patient compliance [14,15]. Priority should be given to HD and transplantation when possible. The observational cohort study conducted in Great Britain showed that the 5-year survival of patients infected with HIV who had received transplants was similar to that of patients infected with HIV who were receiving dialysis and on the transplant list (85% and 89%, respectively). The good transplant results of this group of patients should be placed in the context of a young patient population, relatively short period of monitoring and, most importantly, the exclusion of patients with contraindications for transplantation, among whom survival is significantly limited. Patients infected with HIV have a markedly higher rate of kidney rejection in the first post-transplant year in comparison to transplant patients not.
infected with HIV: 31-48% vs. 12-24%, probably associated with HIV-modulated immune response and less exposure to immunosuppressants, together with highly active antiretroviral therapy [11].

**Prevention of HIV Transmission in Dialysis Centers**

Healthcare personnel should be aware of the risk of occupational exposure to blood-borne pathogens in their daily duties. Therefore, they should be expected to fully comply with the standard precautions to prevent exposure to blood, other bodily fluids and tissues potentially containing HIV and other blood-borne pathogens [16,17]. Administration of dialysis to patients infected with HIV increases the risk of sharps injuries, particularly needles-ticks. The risk of seroconversion after a needlestick involving exposure to the blood of a HIV-positive patient is 0.3%, while the risks for hepatitis B and C are considerably higher, 2% for HCV and 6-30% for HBV [16,18-20].

HIV, like HBV and HCV, does not pass through intact skin and the airborne transmission of this virus has not been confirmed. Contacts via broken skin, blood splashes on the mucous membranes and other forms of mucocutaneous incidents rarely result in seroconversion and infection [16]. In a retrospective study by Cardo et al. [19], the risk factors increasing the transmission of HIV infection after percutaneous exposure were deep injury, injury with a device that was visibly contaminated with blood, injury with a device that had previously been placed in the source patient’s vein and the death of the source patient two months after the percutaneous incident. These factors are probably surrogate markers of viral inoculum. Although low titer viremia may mean lower inoculum, it does not entirely exclude the possibility of the transmission of HIV infection because the viral load does not include the intracellular HIV. Transmission of HIV infection from source patients with undetectable HIV levels in the blood has been documented [20].

The first case of the transmission of HIV infection from a patient to a healthcare worker occurred in 1984 [21]. In 1987, the US Centers for Disease Control and Prevention (CDC) issued Recommendations for Prevention of HIV Transmission in Healthcare Settings and for other blood-borne pathogens, in which the concept of universal precautions was introduced [22]. According to these recommendations, the blood and bodily fluids of every patient are potentially infectious and should be treated as such. The CDC recommends compliance with the recommendations for control and prevention of blood-borne infections issued by the United States Occupational Safety and Health Administration (OSHA). These recommendations are regularly updated and revised according to information from recent studies and are readily available in printed or electronic form via the CDC website [22, 23]. From 1984 to 1999, 57 healthcare workers in the United States acquired HIV infection occupationally, most often from needlestick incidents (84%). From 1999 to the end of 2013, owing to compliance with the CDC recommendations, only one healthcare worker acquired HIV infection occupationally (a laboratory technician from a needle puncture while working with a live HIV culture) [24]. In dialysis units, there have been no reported cases of the transmission of HIV among patients in the United States but cases were reported in Argentina (two dialysis centers), Columbia and Egypt [25]. Post-exposure prophylaxis (PEP) significantly reduces the risk of infection and is, therefore, justified whenever possible [19,20,26].

**Experiences of Other Countries in the Management of Kidney Failure in Persons Infected with HIV**

The international guidelines are largely based on the recommendations of the CDC, with certain particularities related to the dialysis centers, equipment and type of dialyzer.

The European Best Practice Guidelines for the Prevention and Management of HBV, HCV and HIV in Hemodialysis Patients recommend the suitable implementation of the standard precautions for protection from the transmission of infectious agents, which has achieved a very low risk of infection transmission. It is necessary to screen for the presence of individual pathogens (HBV, HCV and HIV) in all patients included in a dialysis program for the first time or when are transferred from other dialysis centers, having obtained the patients’ prior informed consent. The isolation of patients infected with HIV in a separate area and the use of special dialysis machines for them are not recommended. The principles for the prevention of the transmission of HBV infection are also sufficient for the prevention of the transmission of HIV [27].

The most common errors in the protocol for infection control that can lead to the transmission of infection are the reuse of dialyzers, blood lines and the same needles for different patients; the use of contaminated multidose heparin vials and the use of ineffective disinfectant (benzalkonium chloride) [28].

The recommendations of the Infectious Diseases Society of America state that dialysis is safe for healthcare workers and patients if the recommendations of the CDC for the prevention and control of infection are strictly followed. Vascular access for dialysis (the placement of endovenous catheters and the creation of arteriovenous fistulae) should be provided for all patients, including those infected with HIV [29].

On the other hand, in some countries, such as the Republic of South Africa, in addition to the implementation of the standard precautions and annual screening for the causes of infectious diseases in all dialysis patients, it is recommended that patients infected with HIV should be dialyzed in separate areas or rooms, although it is not insisted on the use of dedicated machines [30].

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Croatian Recommendations for the Dialysis of HIV-Positive Patients

At the meeting of the Board of the Croatian Society for Nephrology, Dialysis and Transplantation (HDNDT) on January 25, 2013, it was decided to prepare Recommendations for the Prevention of HIV Infection in Patients on Dialysis and Healthcare Workers, in cooperation with infectious disease specialists from the Dr. Fran Mihaljevic University Hospital for Infectious Diseases in Zagreb, the Croatian Referral Center for the Diagnosis and Treatment of HIV Infection. The first version of the recommendations was published on the website of the Croatian Society for Nephrology, Dialysis and Transplantation in April 2014, for the purpose of public debate. Until now, HIV-positive patients have been receiving acute dialysis at the Dr. Fran Mihaljevic University Hospital for Infectious Diseases, University Hospital Center in Zagreb, and the University Hospital Center in Split, while chronic hemodialysis, in addition to the Dr. Fran Mihaljevic University Hospital for Infectious Diseases and University Hospital Center in Zagreb (since 2003) is also provided at the Sibenik General Hospital (2013-2015). It may be expected that the need will arise to provide dialysis to patients with HIV in other centers. Therefore, the Croatian Society for Nephrology, Dialysis and Transplantation has proposed Recommendations for the Dialysis of HIV-Positive Patients, with the goal of preventing the transmission of HIV infection among patients and healthcare personnel.

Based on current knowledge, literature and the authors’ experience, on behalf of the Croatian Society for Nephrology, Dialysis and Transplantation, recommendations have been made for the dialysis of HIV-positive patients, based on the level and degree of evidence in the guidelines presented/cited in Tables 2 and 3 [31].

Table 2. Level of Evidence in the Guidelines [adapted from 31]

<table>
<thead>
<tr>
<th>LEVEL OF IMPACT</th>
<th>ON PATIENTS</th>
<th>IMPACT OF THE GUIDELINES</th>
<th>ON PHYSICIANS</th>
<th>ON DECISIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVEL 1</td>
<td>The majority of patients would like to receive the recommended therapy.</td>
<td>The recommendations should be applied to the majority of patients.</td>
<td>The guidelines can be the basis for the recommended application.</td>
<td></td>
</tr>
<tr>
<td>Level 1</td>
<td>We recommend</td>
<td>LEVEL 2</td>
<td>A large number of patients would like to receive the recommended therapy.</td>
<td>Various options can be applied; an individualized approach is required.</td>
</tr>
<tr>
<td>LEVEL 2</td>
<td>We advise</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Level of Evidence in the Guidelines [adapted from 31]

<table>
<thead>
<tr>
<th>LEVEL OF IMPACT</th>
<th>QUALITY OF EVIDENCE</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High</td>
<td>We are convinced that the actual impact is very close to that of the estimated impact.</td>
</tr>
<tr>
<td>B</td>
<td>Medium</td>
<td>The actual impact is close to the estimated impact but there are possible discrepancies.</td>
</tr>
<tr>
<td>C</td>
<td>Low</td>
<td>The actual impact could be different from the estimated impact.</td>
</tr>
<tr>
<td>D</td>
<td>Very Low</td>
<td>The estimated impact is uncertain, probably far from the actual impact.</td>
</tr>
</tbody>
</table>

Recommendations

- When the need arises, it is necessary to provide HIV-positive patient with dialysis in the vicinity of his/her place of residence (1A).

Commentary

- Renal function is impaired in over 30% of persons infected with HIV [29].
- HIV-positive persons who exhibit the following should be referred to a nephrologist:
  - a significant decrease in the glomerular filtration rate (GFR), >25%, compared to the previous value,
  - GFR <60 ml/min/1.73 m² with albuminuria >300 mg/24 hours, hematuria, elevated arterial pressure and
  - GFR <30 ml/min/1.73 m² (1C).
- This group of patients should be provided with vascular access for hemodialysis, optimally a native arteriovenous fistula [32] (1B).
- It is necessary to determine the viral status of all patients included in a hemodialysis program and all patients transferred from other centers for hemodialysis, including HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, anti-HCV, anti-HIV, and HBV DNA screening for all anti-HBc total (IgG/IgM) and/or anti-HBe positive patients (1A).
- The viral status of all patients on hemodialysis should be checked every six months (1C).
Commentary on recommendations 2 and 3

- It is necessary to diagnose persons infected with HIV early, in order to initiate antiretroviral therapy and reduce the incidence of opportunistic infections. Early ART would also lower the risk of HIV transmission and HIV-associated non-AIDS (HANA) conditions as it lowers the risk of opportunistic infections. However, when the CDC guidelines are strictly followed, the risk of HIV transmission is practically negligible [27]. Therefore, the recommendation of the European Renal Best Practice is to determine anti-HIV at the beginning of dialysis treatment and when patients are to be transferred from one to another dialysis center, although this is not necessary every six months [33,34]. The Croatian Society for Nephrology, Dialysis and Transplantation considers that this opinion by the ERBP working group on Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for preventing infection transmission in hemodialysis units should be adapted to Croatian conditions. Since we believe that there is room for improvement in the implementation of CDC guidelines in dialysis centers and reduction of nosocomial transmission, and are prompted by our own experiences with a large proportion of HCV-positive patients 15 years ago, we recommend the monitoring of the viral status of hemodialysis patients every six months.

- In HIV-positive patients, it is necessary to quantify the viral load (HIV RNA) every six months or more often, as needed (1C).

Commentary

- HIV viremia should be determined once a year according to the infectious diseases recommendations (1A). However, due to the increased risk of nosocomial transmission of HIV owing to extracorporeal circulation during the hemodialysis procedure, we believe that it is necessary to determine the HIV viremia of HIV-positive patients on hemodialysis every six months. In cases of patient noncompliance and suspected irregular intake of therapy (that increases the possibility of developing antiretroviral-drug-resistant HIV), which can result in increased viremia and contagiousness, HIV viremia should be determined immediately.

- HIV-positive patients should be dialyzed with a separate hemodialysis machine (in addition to providing a backup machine in the event of breakdown) in an isolated area. Alternatively, they can be dialyzed in an area for hemodialysis of HCV-positive and/or HBV-positive patients (1B).

- Although the KDIGO guidelines, opinion of the ERBP, and recommendations of the Infectious Disease Society of America do not endorse separate hemodialysis machines for HIV-positive patients (Level B of evidence for separate machines, Level C for an isolated area [27-29]), cases of the transmission of HIV among patients in the dialysis centers of developing countries have been recorded due to failure to comply with the CDC guidelines [35,36]. Therefore, our recommendation is that the dialysis of HIV-positive patients should be conducted using separate dialysis machines in isolated areas.

- In the case of coinfection with HBV, hemodialysis should be performed in a HBV-positive area, and in the case of coinfection with HCV, in a HCV-positive area.

- HIV-positive patients should be vaccinated against HBV and HAV (1A).

- Trained personnel should be provided during the hemodialysis procedure (medical technician/nurse, cleaning staff), together with strict compliance with the general measures for the prevention of blood-borne infections (1A).

Commentary

- The standard precautions for protection from pathogens are based on the principle that blood, bodily fluids, excretions (except perspiration) and mucous membranes can contain transmissible infectious agents. These precautions are designed to protect patients and healthcare personnel, and include hand hygiene, the use of adequate protection (gloves, masks, goggles and aseptic techniques in order to reduce patient exposure to microorganisms), procedures for sharps/infectious waste, spilled blood and bedding; routine cleaning of the hospital environment and the immunization of personnel. These measures should be especially carefully implemented in dialysis centers, owing to extracorporeal circulation during the HD procedure (1C).

- Nevertheless, we cannot be certain that all these measures will be implemented in their entirety [37].

- Acute hemodialysis should be performed in separate areas of intensive care units on continuous dialysis/hemofiltration machines (with the dialysis solution and dialysate in a closed system) or hemodialysis machines with a reservoir containing prepared solution for hemodialysis (Genius) (1B).

- Blood and other specimens from HIV-positive patients in institutions, the Department of Public Health or other public health institutions should be transported in leak-proof PVC containers with well fitted lids and labeled "B20". Specimens sent outside an institution should be conveyed by me-
tical transport, not by public transportation or mail, in additional packaging (small wooden boxes).

- There should be good and prompt cooperation with the National Referral Center of the Ministry of Health for the Diagnosis and Treatment of HIV Infection (contact telephone 2826 227 or 2826 206, e-mail: bfm@bfm.hr) for rapid diagnosis and professional assistance in case PEP is needed. In the event of a needlestick involving the blood of a HIV-positive patient, PEP should begin as soon as possible, preferably within 24 hours, but no later than 72 hours after the incident, and continue for four weeks. Highly active antiretroviral therapy (HAART) should be adjusted according to the therapy being received by the HIV-positive patient in consultation with the attending infectious disease specialist at the Dr. Fran Mihalićević University Hospital for Infectious Diseases [17] (1A).

Conclusion

HIV is an important public health problem, which poses challenges to experts and healthcare personnel in cases of renal failure and the management of renal replacement therapy. The majority of these patients are on hemodialysis, while a significantly smaller number are on peritoneal dialysis or have received transplants. Healthcare personnel should be aware of the risk of occupational exposure to blood-borne infection in their daily work, and are expected to comply with all the measures that can prevent their exposure to blood, other bodily fluids and tissues that may contain potentially blood-borne infectious pathogens. The dialysis procedure for HIV-positive patients characterized by the extracorporeal circulation of blood presents a risk for inoculating the virus in the event of a needlestick incident, although the seroconversion risk after needlestick injuries is 0.3%, while the risks of seroconversion for hepatitis B and C are significantly higher: 2% for HCV and as high as 6-30% for HBV. Postexposure prophylaxis with antiretroviral therapy for four weeks significantly lowers the risk of seroconversion even further.

Conflict of interest statement. None declared.

References